Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;376:125-35. DOI: 10.1056/NEJMoa1607427

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

STUDY PROTOCOL

TITLE	A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.
STUDY	Phase III
PROTOCOL N°	AAA-III-01/FINAL version 1.0
EudraCT N°	2011-005049-11
DATE	November 14th, 2011
SPONSOR	Advanced Accelerator Applications SA 20 rue Diesel 01630 Saint Genis Pouilly France Tel: +33450993070 www.adacap.com / info@adacap.com

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GOOD CLINICAL PRACTICE AND CONFIDENTIALITY STATEMENT

This trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

PROTOCOL SYNPOSIS

Clinical Study Protocol Synopsis		
Version date	November 14th, 2011	Version FINAL version 1.0
Study number	AAA-III-01	Clinical phase III
EudraCT number	2011-005049-11	Drug substance ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
Title of the study	A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.	
Study centres	Centres in EU and USA (approximately 28 EU sites and 13 USA sites)	
Sponsor	Advanced Accelerated Applications SA	
Indication	Patients with inoperable, progressive, OctreoScan® positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours), who are treated with 20 mg or 30 mg Octreotide LAR every 3-4 weeks at a fixed dose for at least 12 weeks prior to enrolment in the study.	
Objectives	**Primary objective:** • To compare Progression Free Survival (PFS) after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria), somatostatin receptor positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours). **Secondary objective(s):** • To compare the Objective Response Rate (ORR) between the two study arms; • To compare the Overall Survival (OS) between the two study arms; • To compare the Time to Tumour Progression (TTP) between the two study arms; • To evaluate the safety and tolerability of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; • To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire; • To explore the correlation of toxicity outcomes and administered radiation doses corrected for body weight and body surface area; • To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine; • To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients;	

	• To explore the correlation of clinical efficacy outcomes with OctreoScan® tumour uptake score; • To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP).
Study design	A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study. In this study, treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) will be compared to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, somatostatin receptor positive, histologically proven midgut carcinoid tumours; these patients should be progressive under Octreotide LAR. In case patients in either arm experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections are allowed. Objective tumour response in both arms will be assessed every 12±1 weeks from the first treatment date according to RECIST Criteria. The baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date. Patients will be evaluated for safety and tolerability in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm as indicated in Table 1 and Table 2, respectively (see pages 10-13).
Treatment	**^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm:** • 30 mg Octreotide LAR treatment for symptom control will continue until the end of study, unless the patient progresses or dies; • Treatment will consist of a cumulative dose of 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; • Four administrations of 7.4 GBq (200 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; • Concomitant amino acids will be given with each administration for kidney protection; • ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be administered at 8±1-week intervals, which can be extended up to 16 weeks to accommodate resolving acute toxicity (see Dose Modifying Toxicity (DMT) below); in case patients experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections are allowed. **Octreotide LAR arm:** • 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) until the end of the study, unless the patient progresses or dies (see Dose Modifying Toxicity (DMT) below); • In case patients experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections are allowed.
Dose modifying toxicity	According to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0, DMT is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other

	Grade 3 or 4 toxicity possibly related to study drug and regardless of its duration. 1. **If the patients experiences DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy**, the subsequent treatments of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. After resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient goes off-study. If the DMT event does not reoccur, the next treatment is at full dose. 2. **If the patient experiences DMT with the increased dose Octreotide LAR**, the dose will be adjusted to the previous well-tolerated dose, to be increased again with the next treatment to 60 mg.
Study duration	32 months total: 14 months recruitment and 18 months treatment and assessments until the End of Study. Long-term toxicities suspected in relationship to the study drug (included haematology, biochemistry, urine analyses), PFS (based on local assessments), OS data will be collected every 6 months for 3 years after the End of Study (phone contact or visit at site).
Planned number of patients	200 patients (considering the drop-out rate, 100 patients per treatment group will be randomly assigned to open-label treatment).
Inclusion criteria	1. Presence of inoperable (curative intent) at enrolment time, histologically proven, midgut carcinoid tumour. 2. Ki67 index ≤ 20%. 3. Patients on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to enrolment in the study. 4. Patients ≥18 years of age. 5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 (Appendix 2) evidenced with CT scans/MRI obtained within 3 years from enrolment; previous images must be centrally evaluated to confirm the disease progression under previous therapy: for the purpose of determining disease progression the oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan should be one that was performed while the patient was on a fixed dose of Sandostatin LAR. 6. Confirmed presence of somatostatin receptors on all technically evaluable tumour lesions documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to enrolment in the study. 7. The tumour uptake observed using OctreoScan® must be ≥ normal liver uptake observed on planar imaging (Appendices 5 and 6). 8. Karnofsky Performance Score (KPS) ≥60

	9. Presence of at least 1 measurable site of disease.
Exclusion criteria	1. Serum creatinine >150 µmol/L or 1.7 mg/dL, or a measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) of <50 mL/min. 2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <$2x10^9$/L ($2000/mm^3$); platelets <$75x10^9$/L ($75x10^3/mm^3$). 3. Total bilirubin >3 x ULN. 4. Serum albumin ≤3.0 g/dL unless prothrombin time is within the normal range. 5. Pregnancy (see protocol Appendix 7). 6. For female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel) as defined in Appendix 7. 7. Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to enrolment in the study. 8. Peptide receptor radionuclide therapy (PRRT) at any time prior to enrolment in the study. 9. Targeted surgery, radiotherapy (external beam), chemotherapy, embolization, interferons, mTOR-inhibitors or other investigational therapy within 12 weeks prior to enrolment in the study. 10. Known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks, prior to enrolment in the study. Patients with a history of brain metastases must have a head CT with contrast to document stable disease prior to enrolment in the study. 11. Uncontrolled congestive heart failure (NYHA II, III, IV). 12. Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN. 13. Any patient who has both OctreoScan® positive and negative tumours. 14. Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, unless the tumour uptake observed by OctreoScan® imaging during continued Octreotide treatment is at least as high as normal liver uptake observed by planar imaging (Appendices 5 and 6). 15. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study.

	16. Prior external beam radiation therapy to more than 25% of the bone marrow. 17. Urinary incontinence. 18. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years. 19. Patients who have not provided a signed an informed consent form to participate in the study, obtained prior to the start of any protocol related activities.
End of Study	The End of Study is defined as the moment that the last enrolled patient has completed 72 weeks of assessments (unless early termination) after the patient's first treatment in either arm of the study.
Long-term follow-up after End of Study	Long-term toxicity to critical organs (bone marrow and kidney) suspected in relationship to the study drug (including haematology, biochemistry, urine analyses) will be monitored every 6 months for 3 years after the End of Study. PFS (based on local assessments) and OS data will be recorded every 6 months for 3 years after the End of Study. Phone contacts or visits at site can be performed during the 3 years follow-up after end of the study.
Treatment	
Form/dosing route	A ready-to-use radioactive liquid solution for intravenous infusion.
Investigational drug	[Lutetium-177]-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic(2-7)disulfide. Abbreviated: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
Dosage	In total 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administered in four equally divided doses.
Duration of treatment	Four administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (each treatment 7.4 GBq (200 mCi)) at 8±1-week intervals, which can be extended to 16 weeks for resolving acute toxicity. Patients are scheduled to continue to receive study treatment until any of the following occurs: 1. Unacceptable toxicity; 2. Progressive disease as determined by RECIST Criteria; 3. Inability or unwillingness of the patient to comply with study procedures; 4. Patient withdrawing consent to participate.
Assessments (see accompanying Visit Schedules)	
Efficacy	Objective CT/MRI tumour assessment in both arms will be performed every 12±1 weeks from the first treatment date until End of Study.

Safety	Safety assessments will be performed 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and every 12±1 weeks from the first treatment date in both study arms. Long-term toxicity to critical organs suspected in relationship to the study drug will be monitored every 6 months for 3 years after the End of Study.
Overall Survival	OS will be calculated from randomization until the day of death due to any cause; OS will not be censored if a patient receives other anti-tumour treatments after study medication. Survival data will be recorded at the End of Study, and every 6 months for 3 years after the End of Study.
Statistical methods	
Sample size	POWER Procedure Log-Rank Test for Two Survival Curves (SAS 9.2) based on the following assumptions: Median PFS for group 1 (Octreotide LAR): 14 months Median PFS for group 2 (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate): 30 months Nominal Power: 90% Alpha: 0.05 Accrual period: 0 months (patients enrolled over 14 month period but follow-up for each patients is fixed at 72 weeks) Follow-up period: 18 months (72 weeks) Based on the above median PFS assumptions, a sample size of 162 patients in total with an expected number of 75 events is obtained. Controlling for a drop-out rate of approximately 20% a total of 200 patients (100 patients per treatment group) will be randomized and treated. This sample size also provides the availability of sufficient safety data.
Stratification before randomization	1. Centre 2. OctreoScan® tumour uptake score (Grade 2, 3 and 4); see Appendix 5 3. The length of time that patients have been on the most recent constant dose of Octreotide prior to enrolment (≤6 and >6 months).
Statistical Analysis	The primary efficacy variable of this study is PFS. The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method, and the log-rank test will be used to compare the PFS between the two treatment groups. The secondary efficacy variables are: Objective Response Rate (ORR), Time to Tumour Progression (TTP) and OS. Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups will be compared by Fisher's exact test. OS and TTP will be similarly analyzed as the primary efficacy variable.

	Survival curves will be compared by the log-rank test. The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of PFS, TTP, and OS at any time point (i.e.: S1=S2), against the two sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2). The comparison of ORR by Fisher's exact test investigates the null hypothesis that the two treatment group proportions are equal (i.e.: p1=p2) against the two sided alternative hypothesis that the two treatment group proportions are not equal (i.e.: p1≠p2).

Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm

Visit	Eligibility	Baseline	Treatments / Assessments																						EOS[6]	FOLLOW-UP[7]
Week		Week -3	0	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	76	Every 6-months for 3-years
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																									
OctreoScan®	< 24 weeks																									
Histology and Ki67[1]	x																									
Diagnosis and Extent of Cancer	x																									
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																									
Demographic Data	x																									
Relevant Medical History		x																								
Prior Therapy for Carcinoid Tumour	x	x																								
Confirmation of Eligibility and Randomization		▼																								
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Cardiac Ejection Fraction		(x)[4]																								
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x												x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x	x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x					x					x			x			x			x			x		
Hematology[2]	x	x		x	x		x	x		x	x		x		x			x			x			x	x	x
Blood Chemistry[2]	x	x		x	x		x	x		x	x		x		x			x			x			x	x	x
Urinalysis[2]	x	x		x	x		x	x		x	x		x		x			x			x			x	x	x
Pregnacy test[2]		x			x			x			x															
Serum CgA[1]		x					x				x				x			x			x			x		
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy		----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	
Adverse Events[5]		----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x
Survival Information		----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----

Refer to Protocol Section 6 for further details on Visits Assessments

Table 1 Footnotes

⬇ TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 4 administrations at 8±1-week intervals
⬇ TREATMENT: 30 mg Sandostatin® LAR Depot injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion
Last Sandostatin® LAR Depot injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date
IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)
[1]Centrally evaluated until End Of Study
Disease progression at inclusion to be confirmed centrally: the oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan should be one that was performed while the patient was on a fixed dose of Sandostatin LAR
RECIST Disease Assessment during the 3 years follow-up will be performed locally
[2]Tests included in the local laboratory assessments:
- Haematology: WBC with differential, Platelets, Hb, MCV
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb, fT4
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein by dipstick test, 5-HIAA, Pregnancy test (the latter at baseline for female of childbearing potential and during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy within 7 days prior to each treatment)
- At baseline it is preferable that laboratory tests will be performed within 2 weeks before treatment administration
- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4 weeks after each treatment. Then every 12±1 weeks
- If a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured
[3]During the study, symptoms will be recorded in the e-CRF according to patient diary notes
[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterium №-11)
[5]AEs/SAEs will be reported from signing the informed consent form onwards until end of study. During the long-term 3 year follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer
[6]EOS = End of Study Visit for each patient
[7]Patient must be contacted every 6 months up to 3 years after the end of the study (phone contacts or visits at Site)
Laboratory assessments (haematology, biochemistry, urinalysis), SAEs suspected in relationship to the study drug, progression free survival (local evaluation) and overall survival data will be reported
----▶ Information to be collected during the entire study

Table 2: Visit Schedule: Octreotide LAR Arm

Visit	Eligibility	Baseline	Treatment																		EOS[5]	FOLLOW-UP[6]
Week		Week -3	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	6-month for 3 yrs
Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇		
Informed Consent	x																						
OctreoScan®	< 24 weeks																						
Histology and Ki67[1]	x																						
Diagnosis and Extent of Cancer	x																						
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																						
Demographic Data	x																						
Relevant Medical History		x																					
Prior Therapy for Carcinoid Tumour	x	x																					
Confirmation of Eligibility and Randomization		▼																					
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																					
ECG		x	x		x		x		x													x	
Physical Exam and Vital Signs		x				x			x			x			x			x			x	x	
Karnofsky Performance Status	x	x				x			x			x			x			x			x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x		
Hematology[2]	x	x				x			x			x			x			x			x	x	x
Blood Chemistry[2]	x	x				x			x			x			x			x			x	x	x
Urinalysis[2]	x	x				x			x			x			x			x			x	x	x
Pregnancy Test		x																					
Serum CgA[1]		x				x			x			x			x			x			x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	▶	
Adverse Events	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	▶	
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x
Survival Information	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	▶

Refer to Protocol Section 6 for further details on Visits Assessments

Table 2 Footnotes

⬇TREATMENT: 60 mg 4-week interval Octreotide LAR Depot injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1]Centrally evaluated until End Of Study

Disease progression at inclusion to be confirmed centrally: the oldest CT/MRI scan must not be older than 3 years, and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan, should be one that was performed while the patient was on a fixed dose of Sandostatin LAR.

RECIST Disease Assessment during the 3 year follow-up will be performed locally

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb, fT4
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein by dipstick test, 5-HIAA, Pregnancy test (the latter only at baseline for female of childbearing potential)

[3]During the study symptoms will be recorded in the e-CRF according patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterium №-11)

[5]EOS= End of Study Visit for each patient

[6]Patient must be contacted every 6 months up to 3 years after the end of the study (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), progression free survival (local evaluation) and overall survival data will be reported

-----▶ Information to be collected during entire the study

INVESTIGATOR APPROVAL SIGNATURE PAGE

Protocol N°AAA III-01 / FINAL version 1.0, November 14th, 2011

1. I have carefully read this protocol entitled "**A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours**", and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Ethics Committee and that all administrative requirements of the governing body of the institution will be complied with fully.
3. I confirm that I will conduct the study in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and FDA requirements as specified in Title 21, Code of Federal Regulations, Part 50, 54, 56, 312 and the provisions of the Helsinki Declaration (Appendix 1); copies of these documents have been given to me by the Sponsor.
4. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines, and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents.
5. Informed written consent will be obtained from all participating patients in accordance with institutional and ICH Guidelines for Good Clinical Practice.
6. I will enrol patients who meet the protocol criteria for entry and who can be followed up in accordance with this protocol.
7. I understand that my signature on each completed Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
8. I understand that the information presented in this study protocol is confidential and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration/European Medicines Agency, European Competent Authorities and Ethic Committees.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

_____

Affiliation

SPONSOR APPROVAL SIGNATURE PAGE

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Name		Date

	Pgalletti
	Signature

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APPENDIX 18 – STAGING OF MIDGUT CARCINOIDS BY TNM CRITERIA **165**

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LIST OF ABBREVIATIONS

5-HIAA	5-Hydroxyindoleacetic Acid
^{90}Y	Yttrium-90
^{111}In	Indium-111
^{177}Lu	Lutetium-177
AAA	Advanced Accelerator Applications
ADME	Absorbtion, distribution, metabolism, elimination
AE	Adverse event
AP	Alkaline Phosphatase
ALAT/ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
ASAT/AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CgA	Chromogranin-A
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Dose Modifying Toxicity
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DTPA	Diethylene Triamine Pentaacetic Acid
EC	Ethics Committee
ECG	Electrocardiogram
E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumour Society
EORTC	European Organization for Research and Treatment of Cancer
Erasmus MC	Erasmus Medical Centre, Rotterdam, NL
FAS	Full Analysis Set
FDA	Food and Drug Administration
fT4	Free Thyroxine
FSH	Follicle Stimulating Hormone
γ-GT	Gamma-Glutamyl Transferase
GBq	Giga Becquerel (Bq = unit of radioactivity)
GCP	Good Clinical Practice
GHS	Global Health Status
GEP	Gastro-Entero-Pancreatic
GFR	Glomerular Filtration rate
GlycoHb	Glycosylated Haemoglobin
GMP	Good Manufacturing Practice
Gy	Gray (unit of radiation exposure; equal to 100 rad)
H	Hours
Hb	Haemoglobin
HPF	High-Power Field (microscopic exam)
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ID	Identification (Number)
IDMC	Independent Data Monitoring Committee
I.M.	Intramuscular
IMPD	Investigational Medicinal Product Dossier
IRC	Independent Review Committee
IRB	Institutional Review Board

IWRS	Interactive Web-Based Response System
KPS	Karnofsky Performance Score
LAR	Long Acting Release
LDH	Lactic Dehydrogenase
LPF	Low-Power Field (microscopic exam)
MBq	Mega Becquerel (Bq = unit of radioactivity)
MCi	MilliCurie (unit of radioactivity; 1 mCi = 37 MBq)
MCV	Mean Corpuscular Volume (red blood cells)
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Millimole
MRI	Magnetic Resonance Imaging
MST	Median Survival Time
NaCl	Sodium Chloride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (USA)
NET	Neuroendocrine Tumour
NIH	National Institute of Health (USA)
NYHA	New York Heart Association
ORR	Obective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDEC	Poorly Differentiated Endocrine Carcinoma
PFS	Progression Free Survival
PLT	Platelets
PPS	Per Protocol Set
PK	Pharmacokinetics
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
QoL	Quality of Life
QC	Quality Control
QP	Qualified Person
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RSE	Radiation Stability Enhancer
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAF	Safety Set (SAF
S.C.	Subcutaneous
SD	Stable Disease
SNM	Society of Nuclear Medicine
SOP	Standard Operating Procedures
Sstr2	Somatostatin Receptor Subtype 2
SWOG	South West Oncology Group
ULN	Upper Limit of Normal (according to local laboratory normal values)
VIPoma	VIP Producing Tumour
VIP	Vasoactive Intestinal Peptide
WBC	White Blood Cells
WDEC	Well-differentiated Endocrine Carcinoma
WDET	Well-differentiated Endocrine Tumour
WHO	World Health Organization
WMA	World Medical Association

1- INTRODUCTION

1.1 Background

Gastro-entero-pancreatic neuroendocrine tumours (GEPNETs) are rare neoplasms that arise from neuroendocrine cells throughout the body. Most are more indolent than other epithelial malignancies; however, they can be aggressive and resistant to therapy (Yao J et al., 2008b). Symptomatic GEPNETs are often metastasized at diagnosis (Chamberlain RS et al., 2000; Öberg K, 2004, 2010). Neuroendocrine tumour hepatic metastases may lead to liver dysfunction but are often associated with a long deteriorating disease course, in many cases with debilitating clinical symptoms, either due to hormonal overproduction or to large tumour burden.

The typical symptoms of carcinoid syndrome include flushing (80%), diarrhoea (70%), abdominal pain (40%), valvular heart disease (30–40%), telangiectasia (25%), wheezing (15%) and pellagra-like skin lesions (5%). Carcinoid heart disease is characterized by plaque-like fibrous endocardial thickening that classically involves the right side of the heart, occurring in 50-70% of patients with carcinoid syndrome. Haemodynamically significant heart disease is observed in about 5-10% of patients (Caplin ME et al, 1998; Kulke MH and Mayer RJ, 1999, Öberg K, 2004).

In this protocol, a midgut carcinoid tumour is defined as a tumour arising from neuroendocrine cells located in the midgut (i.e., jejunum, ileum, appendix). Sixty six percent of carcinoid tumours arise in the midgut; the small bowel being the most common site, followed by the appendix (Clark et al., 2009).

The primary treatment for carcinoid tumours is surgery with curative intent. However, only a minority of the patients with GEPNETs can be cured by surgery (Öberg K, 2000). In inoperable disease, external beam radiation therapy or chemotherapy are not particularly effective (Cheng PNM et al., 1999; Bukowski RM et al., 1994; Andreyev HJN et al., 1995; Neijt JP et al., 1995; Ritzel U et al., 1995; Ansell SM et al., 2001; Kouvaraki MA et al., 2004; Sun W et al., 2005; Ducreux MP et al., 2006; Bajetta E et al., 2007). Consequently, there are few if any approved treatment options with significant efficacy for patients with advanced disease. Well-differentiated carcinoid tumours express somatostatin receptors, in particular subtype 2 (sstr2), in high abundance. Somatostatin derivatives, such as Octreotide are used to treat symptoms of hormonal overproduction, and to a lesser extent these have a cytostatic effect (Öberg K, 2000, 2002; Rinke A et al., 2009), apart from stabilization.

1.2 Peptide Receptor Radionuclide Therapy

Tumour-targeted peptide receptor radionuclide therapy (PRRT) is under clinical evaluation since 1992 for GEPNETs expressing somatostatin receptors. Initial results have been obtained with ^{111}In-DTPA^{0}-Octreotide, but more promising results were obtained from Novartis and/or Investigator sponsored phase I/II studies with ^{90}Y-DOTA^{0}-Tyr^{3}-Octreotide and, in particular, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (De Jong M et al., 2002; Valkema R et al., 2002, 2006; Waldherr C et al., 2001; Paganelli G et al., 2001; Bodei L et al., 2008, 2009, 2010, 2011; Kwekkeboom DJ et al., 2003, 2005, 2008; Forrer F et al., 2007, 2009; Menda Y et al., 2010)

DOTA^{0}-Tyr^{3}-Octreotide (Octreotide) and DOTA^{0}-Tyr^{3}-Octreotate (Octreotate) consist of a somatostatin peptide analogue, coupled with a metal-ion complexing moiety (DOTA). They can be labelled with the beta-emitters Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu). By targeting somatostatin receptor positive tumours (as imaged by OctreoScan®, Mallinckrodt/Covidien), a tumouricidal radiation dose is delivered. ^{90}Y is a high-energy beta-emitter with a maximum tissue penetration of

12 mm and a physical half-life of 64.1 hours (h). ^{177}Lu is a medium-energy beta-emitter with a maximum tissue penetration of 2 mm and a physical half-life of 6.7 days. It also emits medium and low-energy gamma radiation, which can be used for imaging and dosimetry. Octreotate and Octreotide bind with high-affinity to somatostatin receptors (especially sstr2) and retain both their binding properties and physiological function when complexed with ^{90}Y or ^{177}Lu (Reubi JC et al., 2000).

Studies in patients on biodistribution, excretion, and organ and tumour dosimetry have been performed using ^{111}In-DTPA-Pentetreotide (OctreoScan®, Covidien), ^{86}Y-DOTA^{0}-Tyr^{3}-Octreotide, and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Cremonesi M et al., 1999; Krenning E et al., 1992; Kwekkeboom DJ et al., 1999, 2001; Rosch F et al., 1999; Barone R et al., 2005; Wehrmann C et al., 2007; Bodei L et al., 2008; Forrer F et al., 2009; Sandström M et al., 2009; Garkavaij M et al., 2010; Claringbold PG et al., 2011; Bodei L et al., 2011). Comparisons between ^{86}Y-DOTA^{0}-Tyr^{3}-Octreotide and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the one hand, and OctreoScan® on the other, showed that the uptake in physiological target organs (liver, spleen and kidneys) is not significantly different, whereas uptake in sstr2 expressing NETs is about 2 times higher for ^{86}Y-DOTA^{0}-Tyr^{3}-Octreotide (Barone R et al., 2008) and 3 to 4 times higher for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Kwekkeboom DJ et al., 2001) when compared to OctreoScan® tumour uptake. This advantage is slightly offset by a higher radiation dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the bone marrow (Forrer F et al., 2009).

There is a rapid urinary clearance of radiolabelled Octreotide and Octreotate from the circulation, which gives these radiopharmaceuticals a major advantage over radiolabelled antibodies which provide another way for cell targeted delivery of radiation. Antibodies have long plasma half-lives (several days), that result in high levels of whole-body irradiation. However, because of the absorbed radiation dose to the kidneys, therapy with radiolabelled (ß-particle emission) somatostatin analogues is not recommended in patients whose creatinine clearance is less than 50 mL/min. A mean decrease in creatinine clearance by 30%, as observed in some patients treated with ^{90}Y-DOTA^{0}-Tyr^{3}-Octreotide, could leave these patients in need of dialysis (Cybulla M et al., 2001).

Concomitant administration of amino acids reduces renal radioactivity uptake without altering tumour uptake (Kwekkeboom DJ et al., 2001). This phenomenon of protection ("blocking" renal tubular uptake of proteins, or peptides, by amino acid infusion) is similar to that demonstrated in humans using OctreoScan® or endogenous proteins (Hammond PJ et al., 1993; Rolleman EJ et al., 2003). Cationic amino acids appear to be responsible for the effect since physiological solutions containing only lysine and arginine are able to provide protection equivalent to more complex formulations.

1.3 Risk-Benefit Assessment

1.3.1 Treatment Options

GEPNETs constitute a life-threatening disease, and functioning GEPNETs are associated with debilitating clinical symptoms.

- Streptozocin (Zanosar®, Sicor Pharmaceuticals / Pfizer, a chemotherapeutic drug) was approved in the US for treating progressive metastatic pancreatic islet cell cancer in 1982. To the best of our knowledge, Streptozocin is only registered in France for treatment of insulinoma and metastasized carcinoid tumour, and therefore not widely available in EU Member States.

- Sunitinib (Sutent®, Pfizer, a multi-targeted receptor tyrosine kinase (RTK) inhibitor) has been approved in the US for treatment of renal cell carcinoma and gastrointestinal stromal tumour, but not for any GEPNET indication. In the EU, it was approved in November 2010 for treatment of adults with unresectable or metastatic, progressive well-differentiated pancreatic neuroendocrine tumours.
- Everolimus (Afinitor® Tablets, Novartis Pharmaceuticals Corporation, an oral inhibitor of mammalian target of rapamycin (mTOR)) has been approved in the US for treatment of progressive neuroendocrine tumors of pancreatic origin, but not for any other GEPNET indication. Approval for the same indication in Europe is presumed to be pending.

1.3.2 Efficacy of Sandostatin® LAR

Except for Sandostatin® LAR Depot, medications registered for the treatment of GEPNETs are restricted to those of pancreatic origin (see Section 1.3.1). Therefore these agents are only beneficial to a small subset of GEPNET patients. In the case of Sandostatin® LAR Depot, the drug is registered in EU countries (but not in the US) "to treat neuroendocrine tumours located in the gut" (Appendix 4). The drug has been shown to provide a modest increase in progression free survival in patients with progressive, mid-gut carcinoid tumours (Rinke A et al., 2009). Sandostatin® LAR and Octreotide acetate (daily s.c.) are registered for transient relief of the debilitating symptoms associated with carcinoid syndrome or caused by other types of functioning GEPNETs (Appendix 4).

1.3.3 ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Phase I/II Study Data

615 subjects were treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with concomitant amino acid infusion in an Investigator sponsored Phase I/II study at the Erasmus Medical Center (Erasmus MC) between January 2000 and March 2007. As a result of the unmet medical need, the patients population enrolled was heterogeneous including various somatostatin receptor positive tumour types; the majority consisted of GEPNETs, including carcinoid tumours and pancreatic isle cell tumours, but patients with melanoma, thyroid tumours and non-small cell lung carcinomas, among others, were also included. The standard treatment for the enrolled patients was 4 administration of 7.4 Gbq (200 mCi) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Follow-up monitoring for all enrolled patients continued beyond treatment until a patient was lost to follow-up, patient death or for a maximum of 10 years, whichever occurred first. Long-term follow-up has been performed for 367 Dutch patients. Nearly all the 248 patients from outside the Netherlands were lost to follow-up within 1 year post treatment.

The Erasmus MC phase I/II study has been conducted according to the ethical principles of GCP, however, it was an Investigator Initiated trial. A retrospective, independent verification of the source data, and a statistical analysis of the study results have been conducted by a contract CRO to support the initiation of the present phase III study.

1.3.3.1 Safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

All enrolled 615 subjects were included in the Safety analyses of the independent data review, which consisted of all subjects who entered the trial and received at least one dose of trial medication.

Acute adverse effects occurring within 24 h after the administration of the radiopharmaceutical were nausea (25% of administrations), vomiting (10%) and abdominal discomfort or pain (10%).

13% of the subjects experienced one or more severe events suspected to be related to the study drug.

Six patients were hospitalized within 2 days of the administration because of hormone-related crises (de Keizer B et al, 2008). All recovered after supportive care.

Three patients presented with serious liver toxicity, two of them had diffuse liver metastases, one had liver cirrhosis. In one patient liver functions deteriorated in the weeks following the first administration. The patient died of hepatic failure after 6 weeks. Because this patient experienced a similar deterioration due to rapid tumour growth after previous courses of chemotherapy, the liver failure after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment was considered more likely tumour growth–related rather than radiation induced. A second patient, who had multiple liver metastases, had temporary increases in serum ALAT (ALT), ASAT (AST), and bilirubin concentrations. This condition resolved without causative treatment and resumed treatment at half dose, uneventfully. The third patient, a 76 years old man suffering from liver cirrhosis, developed hyperbilirubinemia after the second administration of 200 mCi and passed away 3 weeks from treatment. In general, liver parameters in the whole population did not show a clear trend towards worsening under treatment.

There were two cases of renal insufficiency with suspected relationship with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. This relative benign profile was confirmed both by serum/urine analyses performed during the study. The evaluation of the dosimetry data collected on all treated patients indicated that there was no correlation between creatinine clearance loss per year and the administered activity.

Haematological toxicity was experienced by 12.8% of the whole population.

Myelodysplastic Syndrome (MDS) suspected to be related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate occurred in five patients. MDS was diagnosed 1 to 3 years after treatment.

Acute Myeloid Leukemia (AML) occurred in two patients, both suspected to be treatment related. One of these patients, with a pancreatic gastrinoma, had previously received extensive chemotherapy, fractionated radiation therapy, and a liver transplant prior to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octerotate. This patient was diagnosed with AML, 30 months after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The other patient, with a gastrinoma metastasized to the liver, and no prior therapy, developed MDS (as mentioned above), 33 months post treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octerotate. Nine months later (42 months post treatment) the patient developed AML and died soon thereafter.

A subanalysis of the hematological data has been conducted on the 367 Dutch patients for whom a longer follow-up was available, leading to the following results:

- Leucopoenia CTC grade 3-4 occurred in 4.1% of patients (26.7% of them already had a CTC grade 1 toxicity at baseline and 33.3% of the subjects received prior Chemotherapy or Radionuclide therapy or Radiotherapy). The nadir was experienced during treatments 1-2 by 28.3% of cases, during treatments 3-4 by 52.2% of cases and during follow-up for the rest (especially between months 3 and 6);

- Anaemia CTC grade 3-4 occurred in 4.9% of patients (66.7% of them already had a CTC grade 1 toxicity at baseline, 11.1% had a CTC grade 2-3 toxicity at baseline, 44.4% received prior Chemotherapy or Radionuclide therapy or Radiotherapy and 11.1% experienced Hb toxicity after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate re-treatments exceeding the cumulative 800 mCi dose). The nadir

was experienced during treatments 1-2 in 15.2% of cases, during treatments 3-4 in 41.3% of cases and during follow-up for the rest (especially between months 3 and 6);

- Thrombocytopenia CTC grade 3-4 occurred in 7.3% of patients (7.4 % of them already had a CTC grade 1 toxicity at baseline, 40.7% received prior Chemotherapy or Radionuclide therapy or Radiotherapy and 7.4% experienced the PLT toxicity after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate re-treatments exceeding the 800 mCi dose). The nadir was experienced during treatments 1-2 in 15.2% of cases, during treatments 3-4 in 56.5% of cases and during follow-up for the rest (especially between months 12 and 24).

- Pancytopenia was observed in 8.2% of cases. As general rule, an event was classified as Pancytopenia when a reduction in the number of red and white blood cells, as well as platelets, occurred concomitantly; at least one out of these three parameters (Haemoglobin, White Blood Cells and Platelets) was CTC Grade 3-4, while the other two parameters were CTC Grade ≥1. In 80% of the pancytopenia cases, at least one of the three parameters was already CTC Grade ≥1 at baseline, 6.7% of the patients experienced pancytopenia after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate re-treatments exceeding the cumulative 800 mCi dose, and 27.7% of the subjects had received Chemotherapy or Radionuclide therapy or Radiotherapy prior to enrolment in the Study.

The haematological toxicity nadir was observed in the 74.5% of cases during treatment, the rest during the follow-up period. Although classified as suspected to be treatment related, it can't be excluded that the decrease in the laboratory parameters observed during the follow-up period may at least partially be due to a concomitant deterioration of patients condition or disease progression.

1.3.3.2 Efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

Efficacy endpoints of the phase I/II Erasmus MC data have been independently evaluated on the Full Analysis Set (FAS), consisting of 405 subjects with diagnosed GEPNETs, who had an OctreoScan® tumour uptake score ≥ Grade 2 and at least one valid primary efficacy variable on active treatment, showing the following results according to modified SWOG Criteria (note standard SWOG Criteria does not include minor responses):

- Objective tumour response (complete response (CR) + partial response (PR) + minor response (MR is defined as a tumour diameter decrease of 25% to 50%, Kwekkeboom DJ et al., 2005) in the overall GEPNET FAS population was 59.3% (95% CI; 54.30-64.09%); in the subgroup of 157 Dutch carcinoid tumour patients the objective tumour response was 61.2% (95% CI; 53.05 - 68.81%);
- Time to progression (TTP) from start of treatment in the overall GEPNET FAS population was 1164 days (38 months) with a 95% CI of 1014-1357 days (33.3-44.6 months);
- Median PFS from start of treatment in the overall GEPNET FAS population was 904 days (30 months) with a 95% CI of 813-994 days (26.7-32.7 months);
- Median OS from start of treatment in the overall GEPNET FAS population was: 1501 days (49 months) with a 95% CI of 1375-1667 days (45.2-54.8 months).

Special attention was paid to patients with the same diagnosis as proposed for this phase III trial. A subset of 51 subjects with the diagnosis carcinoid midgut with progressive disease at study entry was independently re-assessed.

Median PFS of these subjects was:

- 1375 days (45 months) 95% CI 678-1732 days (22-57 months) according to RECIST Criteria, Version 1.1.

- 1174 days (39 months) 95% CI 560-1732 days (18-57 months) according to SWOG Criteria.

Global Health Status (GHS) Quality of Life (QoL), Karnofsky Performance Score (KPS) and clinical symptoms before and after therapy have also been analyzed, as important endpoints of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy. QoL, KPS, and clinical symptoms improved and there was no significant decrease in QoL in patients, who had no symptoms before therapy. In patients who had suboptimal scores for GHS/QoL or symptoms before therapy, a clinically significant improvement was demonstrated (Teunissen JJ et al., 2004).

These results are in agreement with a recent publication of the Erasmus MC group (Khan S et al., 2011) on the phase I/II data, on a sample of 265 out of 282 Dutch patients with metastatic inoperable GEPNETs or bronchial NET, who completed the QoL questionnaire (EORTC QLQ-C30).

These results indicate that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy not only reduces tumours and prolongs overall survival but also improves the patients' self-assessed QoL.

2- STUDY OBJECTIVES

2.1 Primary Objective

- To compare Progression Free Survival (PFS) after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria Version 1.1, Eisenhauer EA et al., 2009; Appendix 2), somatostatin receptor positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours).

2.2 Secondary Objectives

Secondary objective(s):

- To compare the Objective Response Rate (ORR) between the two study arms;
- To compare the Overall Survival (OS) between the two study arms;
- To compare the Time to Tumour Progression (TTP) between the two study arms;
- To evaluate the safety and tolerability of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate;
- To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire (Appendix 3);
- To explore the correlation of toxicity outcomes and administered radiation doses corrected for body weight and body surface area;
- To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;
- To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients;
- To explore the correlation of clinical efficacy outcomes with OctreoScan® tumour uptake score;
- To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP).

3- STUDY DESIGN

3.1 Study Outline

This is a multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

Key criteria for enrolment in the study are; i) histologically proven midgut carcinoid tumours; ii) all documented tumours are somatostatin receptor positive tumours based on OctreoScan® scintigraphy within 24 weeks prior to enrolment in the study; iii) the patient is at a fixed dose of 20 mg or 30 mg Octreotide at 3-4 weeks intervals for least 12 weeks prior to enrolment in the study; and iv) has progressive disease as confirmed by RECIST Criteria; for the purpose of determining disease status the oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date.

Patients who have signed the informed consent form (ICF) and are eligible for study participation according to the inclusion and exclusion criteria will be randomly assigned to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm or the Octreotide LAR arm in an equal ratio (1:1). Baseline evaluations will be performed 2 weeks prior to their first treatment (Treatment Day 1). Patients will be evaluated for the safety, tolerability, and renal excretion pharmacokinetics (the latter only in a subset of 20 patients in pre-identified centres) in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm in Table 1 and Table 2, respectively.

Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a cumulative dose of 29.6 GBq (800 mCi), which provides a safe radiation dose to the critical organs, the bone marrow and the kidneys (Bodei L et al., 2010, 2011; Kwekkeboom DJ et al., 2008). Concomitant amino acids will be given with each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration for kidney protection. Also, in addition to the treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, the patients will receive supportive care with cold Octreotide (Section 5.2.1.1) for the overall 72 weeks of therapy, unless the patient progresses or dies.

If a patient experiences a Dose Modifying Toxicity (DMT) during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. After resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient goes off-study. If the DMT event does not re-occur, the next treatment is at full dose.

Patients in the comparator arm will receive 60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) intramuscular (i.m.) injections every 4 weeks for the overall 72 weeks of therapy, unless the patient progresses or dies. If the patient experiences toxicity with the increased dose, the dose will be adjusted to the previous well-tolerated dose, to be increased again with the next treatment to 60 mg.

Objective tumour assessment in both arms will be performed every 12±1 weeks from the first treatment date until the End of Study, unless the patient progresses or dies. Patients that are RECIST progressive are treatment failures and are out of the study.

If patients in either arm experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections are allowed.

Details on the timing of the administration of study medication and assessments are provided in the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm in Table 1 and Table 2, respectively (see pages 10-13).

3.2 End of Study

The End of Study is defined as the moment that the last enrolled patient has completed 76 weeks of assessments (unless early termination) after the patient's first treatment in either arm of the study.

The End of Study (EOS) for each patient is defined as the completion of 76 weeks of assessments after the patients's first treatment, unless the patient progresses or dies.

3.3 Study Design Rationale

This study is the first controlled comparative study with a radiolabelled versus non-radioactive somatostatin analogue. In this study safety and efficacy of treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate versus Octreotide LAR will be investigated in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

The chosen regimen for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm with a cumulative dose of 29.6 GBq (800 mCi), divided into 4 administrations, is identical to the regimen used in the Erasmus MC Phase I/II study. In this study, kidney dosimetry was scheduled after the third treatment in all the enrolled patients. The dosimetry evaluation was conducted on 408 out of 615 patients who had quantifiable kidney uptake. The follow-up results of kidney function parameters confirmed that the fourth treatment could be safely administered, even in the instance of some patient exceeding the 23 Gy kidney threshold. In patients for whom kidney dosimetry could not be performed, a fixed dose of 29.6 GBq (800 mCi) was administered without any deleterious effect on kidney function in any patient. This is consistent with the previous publication of Kwekkeboom DJ et al. (2008).

Patients in the comparator arm will receive 60 mg Octreotide LAR for 72 weeks from start of treatment (unless early termination). The dose is supported by the report that 30% of carcinoid tumour patients receive >30 mg (Anthony LB et al., 2004). In current clinical practice, it is likely that even a higher percentage of patients receive >30 mg of Octreotide LAR (Joseph S et al., 2010). 4-Week interval injections of 60 mg Octreotide LAR is a higher dose than the 4-week interval injections with 20 mg or 30 mg, which is presently the registered dose for relief of symptoms associated with functional GEPNETs, such as midgut carcinoid tumour (Sandostatin® LAR Depot prescribing information; see Appendix 4 for adverse events). With this type of treatment, the majority of symptomatic patients show an improvement in QoL, and most patients obtain temporary stable disease based on CT scans, although tumour regression rarely occurs (Faiss S et al., 2003; Rinke A et al., 2009; Ludlam W et al., 2011; Anthony L et al., 2011). Furthermore the patients in the present study must have confirmed metastatic progressive disease carcinoid tumours and also receiving 20-30 mg Octreotide LAR (or somatostatin analogue equivalent) to be eligible for enrolment. Therefore, if Sandostatin® LAR Depot is to be administered as an anti-tumour drug to patients that have already failed treatment (confirmed PFS at 20-30 mg Octreotide LAR), then a higher dose is required. Consequently, a 60 mg, 4-week interval dose is proposed for the control (best standard of care) arm of the present phase III study.

3.3.1 Substudy Design Rationale

A 20 patient Dosimetry, Pharmacokinetics, and ECG study will be performed in 2-3 selected sites. This is a substudy of the present phase III clinical trial, and will be performed on patients who have been randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm.

See section 6.6 for further details on sub-study procedures; in addition, a study manual of the substudy will be provided to participating sites.

3.3.1.1 Primary Objective:

- Calculate whole body and organ radiation dosimetry of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to determine the dose to critical organs (e.g., kidney and bone marrow) and correlate with findings of the Erasmus MC Phase I/II Clinical study.

3.3.1.2 Secondary Objectives:

- Define the pharmacokinetic profile (ADME) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate;
- Correlate safety, dosimetry, and pharmacokinetic data obtain in this study with the Erasmus MC phase I/II Clinical study to confirm previous findings;
- Evaluate cardiac safety: determine the acute electrophysiological changes during treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (through 24-hour continuous ECG recording via 12-lead Holter machine).

3.3.1.3 Eligibility

Any patient enrolled in the present phase III study who has been randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm is eligible to participate in the Dosimetry, Pharmacokinetics and ECG substudy.

Voluntary informed consent has to be given by every patient in order to be screened for sub-study eligibility and prior to the initiation of any sub-study-related procedures.

Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm

Visit	Eligibility	Baseline	Treatments / Assessments																						EOS[6]	FOLLOW-UP[7]
Week		Week -3	0	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	76	Every 6-months for 3-years
Therapy			↓↓			↓↓			↓↓			↓↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																									
OctreoScan®	< 24 weeks																									
Histology and Ki67[1]	x																									
Diagnosis and Extent of Cancer	x																									
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																									
Demographic Data	x																									
Relevant Medical History		x																								
Prior Therapy for Carcinoid Tumour	x	x																								
Confirmation of Eligibility and Randomization		▼																								
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Cardiac Ejection Fraction		(x)[4]																								
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x													x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x	x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x					x					x			x			x			x			x		
Hematology[2]	x	x		x	x		x	x		x	x		x		x			x			x			x	x	x
Blood Chemistry[2]	x	x		x	x		x	x		x	x		x		x			x			x			x	x	x
Urinalysis[2]	x	x		x	x		x	x		x	x		x		x			x			x			x	x	x
Pregnacy test[2]		x			x			x			x															
Serum CgA[1]		x					x				x				x			x			x			x		
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy		----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	
Adverse Events[5]		----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x
Survival Information		----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------

Refer to Protocol Section 6 for further details on Visits Assessments

Table 1 Footnotes

⬇ TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 4 administrations at 8±1-week intervals

↓ TREATMENT: 30 mg Sandostatin® LAR Depot injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion

Last Sandostatin® LAR Depot injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)

[1]Centrally evaluated until End Of Study

Disease progression at inclusion to be confirmed centrally: the oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan, should be one that was performed while the patient was on a fixed dose of Sandostatin LAR.

RECIST Disease Assessment during the 3 years follow-up will be performed locally

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb, fT4
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein by dipstick test, 5-HIAA, Pregnancy test (the latter at baseline for female of childbearing potential and during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy within 7 days prior to each treatment)
  - At baseline it is preferable that laboratory tests will be performed within 2 weeks before treatment administration
  - During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4 weeks after each treatment. Then every 12±1 weeks
  - If a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured

[3]During the study, symptoms will be recorded in the e-CRF according to patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterium №-11)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until end of study. During the long-term 3 year follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]EOS = End of Study Visit for each patients

[7]Patient must be contacted every 6 months up to 3 years after the end of the study (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), SAEs suspected in relationship to the study drug, progression free survival (local evaluation) and overall survival data will be reported

----▶ Information to be collected during the entire study

Table 2: Visit Schedule: Octreotide LAR Arm

Visit	Eligibility	Baseline	Treatment																			EOS[5]	FOLLOW-UP[6]
Week		Week -3	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	6-month for 3 yrs
Therapy			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																						
OctreoScan®	< 24 weeks																						
Histology and Ki67[1]	x																						
Diagnosis and Extent of Cancer	x																						
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																						
Demographic Data	x																						
Relevant Medical History		x																					
Prior Therapy for Carcinoid Tumour	x	x																					
Confirmation of Eligibility and Randomization		▼																					
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																					
ECG		x	x		x		x		x													x	
Physical Exam and Vital Signs		x				x			x			x			x			x			x	x	
Karnofsky Performance Status	x	x				x			x			x			x			x			x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x		
Hematology[2]	x	x				x			x			x			x			x			x	x	x
Blood Chemistry[2]	x	x				x			x			x			x			x			x	x	x
Urinalysis[2]	x	x				x			x			x			x			x			x	x	x
Pregnancy Test		x																					
Serum CgA[1]		x				x			x			x			x			x			x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→	
Adverse Events	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→	
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x
Survival Information	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→

Refer to Protocol Section 6 for further details on Visits Assessments

Table 2 Footnotes

⬇TREATMENT: 60 mg 4-week interval Octreotide LAR Depot injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1]Centrally evaluated until End Of Study

Disease progression at inclusion to be confirmed centrally: the oldest CT/MRI scan must not be older than 3 years, and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan, should be one that was performed while the patient was on a fixed dose of Sandostatin LAR

RECIST Disease Assessment during the 3 year follow-up will be performed locally

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb, fT4
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein by dipstick test, 5-HIAA, Pregnancy test (the latter only at baseline for female of childbearing potential)

[3]During the study symptoms will be recorded in the e-CRF according patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterium №-11)

[5]EOS= End of Study Visit in each subject

[6]Patient must be contacted every 6 months up to 3 years after the end of the study (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), progression free survival (local evaluation) and overall survival data will be reported

- - - - -▶ Information to be collected during entire the study

4- SELECTION OF STUDY POPULATION

4.1 Inclusion and Exclusion Criteria at Baseline

A total of 200 patients (100 patients per treatment group) will be randomly assigned to open-label treatment.

In order to assure a balanced study design, randomization will be stratified by centre, OctreoScan® tumour uptake score (Grade 2, 3 and 4), and length of time that patients have been on the most recent constant dose of Octreotide prior to enrolment (≤6 and >6 months).

4.1.1 Inclusion Criteria at Baseline

1. Presence of inoperable (curative intent) at enrolment time, histologically proven, midgut carcinoid tumour.
2. Ki67 index ≤ 20%.
3. Patients on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to enrolment in the study.
4. Patients ≥18 years of age.
5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 (Appendix 2) evidenced with CT scans/MRI within 3 years from enrolment; previous images must be centrally evaluated to confirm the disease progression under previous therapy: for the purpose of determining disease status the oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan should be one that was performed while the patient was on a fixed dose of Sandostatin LAR.
6. Confirmed presence of somatostatin receptors on all technically evaluable tumour lesions documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to enrolment in the study.
7. The tumour uptake observed using OctreoScan® should be ≥ normal liver uptake observed on planar imaging (Appendices 5 and 6).
8. Karnofsky Performance Score (KPS) ≥60
9. Presence of at least 1 measurable site of disease.

4.1.2 Exclusion Criteria at Baseline

1. Serum creatinine >150 µmol/L or 1.7 mg/dL, or a measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) of <50 mL/min.
2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <$2x10^9$/L (2000/mm^3); platelets <$75x10^9$/L ($75x10^3$/mm^3).
3. Total bilirubin >3 x ULN.
4. Serum albumin ≤3.0 g/dL unless prothrombin time is within the normal range.
5. Pregnancy (see protocol Appendix 7).

6. For female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel) as defined in Appendix 7.
7. Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to enrolment in the study.
8. Peptide receptor radionuclide therapy (PRRT) at any time prior to enrolment in the study.
9. Targeted surgery, radiotherapy (external beam), chemotherapy, embolization, interferons, mTOR-inhibitors or other investigational therapy within 12 weeks prior to enrolment in the study.
10. Known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks, prior to enrolment in the study. Patients with a history of brain metastases must have a head CT with contrast to document stable disease prior to enrolment in the study.
11. Uncontrolled congestive heart failure (NYHA II, III, IV).
12. Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN.
13. Any patient who has both OctreoScan® positive and negative tumours.
14. Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, unless the tumour uptake observed by OctreoScan® imaging during continued Octreotide treatment is at least as high as normal liver uptake observed by planar imaging (Appendices 5 and 6).
15. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study.
16. Prior external beam radiation therapy to more than 25% of the bone marrow.
17. Urinary incontinence.
18. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
19. Patients who have not provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities.

4.2 Inclusion and Exclusion Criteria Subsequent Treatments

4.2.1 Inclusion Criteria Subsequent Treatments

1. Serum creatinine ≤150 µmol/L or 1.7 mg/dL, or a measured creatinine clearance (or measured GFR) of ≥50 mL/min. Should a 40% increase over the baseline serum creatinine value occur during the course of treatment**,** with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockroft's method, patients must also have a measured creatinine clearance (or GFR) performed, unless resolved within 16 weeks.

2. Hb concentration ≥5.0 mmol/L (≥8.0 g/dL); WBC ≥2x10^9/L (2000/mm^3); platelets ≥75x10^9/L (75x10^3/mm^3).
3. Total bilirubin ≤3 x ULN.
4. Serum albumin >3.0 g/dL, or serum albumin ≤3.0 g/dL, but normal prothrombin time.
5. KPS ≥60.

4.2.2 Exclusion Criteria Subsequent Treatments

All exclusion criteria for baseline apply to all subsequent treatments, except for criteria 7 and 8.

4.3 Screening Failures

For patients not considered eligible after the screening period, the reason for not being eligible must be documented. No additional assessments are needed.

4.4 Discontinuation Criteria for Individual Patients

A "withdrawal" is a patient who is enrolled into the study, but who prematurely terminated the treatment or follow-up period for any reason.

The patient is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. It is also possible that the Sponsor or the Competent Authorities request termination of the study if there are concerns about conduct or safety:

A patient <u>may</u> be withdrawn from the study if:

1. A serious adverse event (SAE) occurs. The final decision will be made by the Investigator following consultation with the Sponsor.
2. The patient fails to comply with the dosing, evaluations, or other requirements of the study.
3. The patient starts treatment with one of the medications listed as disallowed (see Protocol section 5.6). The final decision to withdraw a patient who starts treatment with disallowed medication will be made by Investigator following consultation with the Sponsor.

A patient <u>must</u> be withdrawn from the study if:

1. The Investigator considers it, for safety reasons, to be in the best interest of the patient.
2. The patient withdraws his/her consent.
3. The patient is pregnant.

The date, time, and reason for discontinuation must be documented in the e-CRF. All patients who prematurely withdraw from the study will be asked to have a CT/MRI evaluation of their disease, except in case of pregnancy).

If a patient withdraws from the study for any reason, the Investigator must determine the primary reason for the withdrawal and record this information in the e-CRF.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show 'due diligence' by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

4.5 Dropouts and Replacements

For the purpose of this study, an "enrolled patient" is a patient who has signed the ICF and is then randomized to participate in a study arm after verification of all inclusion/exclusion criteria.

A "screening failure" is a patient who has signed the ICF, but who does not meet all selection criteria and has not received any study medication as part of this protocol. A screening failure is not counted as an enrolled patient. However, a patient who has signed the ICF and has received study medication as part of this protocol, but who is (later) found not to meet all selection criteria, is considered a "protocol violator".

Patients, who are randomized to a treatment arm but who terminate the study prematurely before receiving study medication will be replaced as necessary.

In general, recruitment and inclusion of patients is aimed at having a sufficient number of patients for the evaluation of the primary endpoint, and also at providing sufficient data for the safety profile. During the conduct of the study the screening failure rate and the dropout rate will be closely monitored. Further intervention in the study might be necessary and recruiting and replacement strategies may be adapted accordingly.

4.6 Prohibition and Restrictions

The patient must be willing to adhere to the prohibitions and restrictions during the course of the study as stated in the ICF, including the Patient Information Sheet.

5- STUDY MEDICATION AND TREATMENT

5.1 Description of Study Medication

The investigational drug product ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be provided by the Sponsor. The Sponsor will also provide/reimburse the amino acid solution for infusion as well as the Sandostatin® LAR Depot according to local regulations.

Granisterin, Ondansetron, Tropisetron, short-acting Sandostatin® or any other supportive care medication must be obtained through the hospital pharmacy.

5.1.1. Investigational Drug Product: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radiopharmaceutical solution for infusion supplied as a ready-to-use product. No manipulation of the product in needed at the clinical site. The only Quality Control (QC) tests that must be performed at the clinical site are; 1) confirm correct product certificate; 2) determine total radioactivity; 3) confirm visual appearance. Since ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is manufactured in centralized GMP facilities, the majority of required QC tests are performed before product shipment. A batch release certificate of the product will be sent to the investigational centres. This batch release certificate is provided by the Qualified Person (QP) of the manufacturing site to ensure that the product is suitable for administration and that it meets the specifications indicated in the Investigational Medicinal Product Dossier (IMPD).

The product is manufactured and supplied to the clinical sites in monodose vials. One vial, for one administration, contains 7.4 GBq (200 mCi) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at calibration time (the time of infusion) in a formulation solution of 22 to 25 mL. The variability of the volume depends on the time between the calibration date and the production date. The product will be shipped and calibrated for use at 24h or 48h after production in a centralized GMP facility. The calibration time of a dose depends on the distance from the manufacturing facility to the clinical sites. A radioactivity dose of 7.4 GBq (±5%) is specified at the time of infusion.

Chemical-physical properties of each dose are listed in Table 3 below.

Table 3: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Infusion Solution Composition.

Component	Composition (one vial)	Function
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	7.4 GBq / 200 mCi	Active Pharmaceutical Ingredient
X-DOTA^{0}-Tyr^{3}-Octreotate	10 µg/mL	Total peptide content
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	4.57 µg/mL*	Active Pharmaceutical Ingredient
DOTA^{0}-Tyr^{3}-Octreotate	5.92 µg/mL*	Active Pharmaceutical Ingredient Precursor
Volume	From 22-25 mL	
Specific Activity (GBq/Total peptide)	53 GBq/µmol (at EOP)*	
Radioconcentration	370 MBq/mL (at EOP)	
Other Constituents/Excipients	mg/mL	
Acetic Acid	0.48*	pH adjuster
Sodium Acetate	0.66*	pH adjuster
Gentisic Acid	0.63*	Radiation Stability Enhancer
Ascorbic Acid	2.80	Radiation Stability Enhancer
DTPA	0.05	Masking Agent

NaCl Water for Injection	6.85 -	Blood isotonic solution Solvent

*Values calculated assuming ^{177}Lu specific activity of 740 GBq/mg at labelling time and a mean synthesis yield of 80% and radiochemical purity ≥97%.

Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a cumulative dose of 29.6 GBq (800 mCi) with the dosing equally divided among 4 administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at 8±1-weeks intervals.

Additional information on the study drug preparation, radioprotection notes and recommendations for treated patients are provided in Appendices 14, 15 and 16.

5.1.1.1 Concomitant Treatment: 30 mg Sandostatin® LAR Depot

30 mg Sandostatin® LAR Depot is administered the day after each administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, according to the schedule in Section 5.7.2. Once completed the four treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients will continue the 4-week interval administrations of 30 mg Sandostatin® LAR Depot until End of Study (at 76 weeks from enrolment according to the schedule in Table 1) unless the patient progresses or dies before.

Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in a single-use kit containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

5.1.1.2 Concomitant Infusion with Amino Acid Solution

There are a number of studies published which demonstrate that commercial and custom made amino acid solutions reduce the kidney retention of radiolabeled somatostatin analogs in humans. Researchers at the Erasmus MC have directly demonstrated the benefit of 2.5% lysine/arginine in 1L solution in blocking kidney retention of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreoate. The 2.5% lysine and arginine solution is somewhat better tolerated, with vomiting occurring more often in patients co-infused with commercial amino acid solutions, but in both cases the side effects are mild and transient.

A number of groups have used commercial amino acid solutions instead of the custom lysine/arginine formulation developed at the Erasmus MC. Based on the published reports, solutions which contain a total amount of lysine and arginine of up to 24 g each in 1 to 2L would be expected to be the most effective in blocking renal uptake. Nevertheless, amino acid solution containing smaller amount of lysine and arginine (such as found in AminoSyn II 7%) are also reported to be effective. Solutions containing greater than 24g lysine and 24 g arginine may pose a risk of inducing elevated serum potassium levels. The specifications of the recommended formulation of an amino acid solution for co-infusion therapy are listed in Table 4.

Table 4: Specifications of the Recommended Amino Acid Solution for Co-Infusion.

Component	**Specification**	**Function**
Lysine	≥18 g, ≤24g	Renal protection
Arginine	≥18g, ≤24g	Renal protection
Saline or other suitable diluent	<2L ± 25%	Osmolarity (<1050 mOsmol), solvent
All other amino acids	No Specification	Inert nutrients

Some examples of commercial solutions that would meet or exceed these specifications (with grams lysine and arginine, and total infusion volume noted) are listed below, in order of preference:

1. Aminosyn II 15% (23.6 g lysine, 22.9 g arginine, in 1.5L)
2. Aminosyn II 10% (21.0 g lysine, 20.4 g arginine, in 2L)
3. VAMIN-18 (18 g lysine, 22.6 g arginine in 2L)

In the present study patients randomized in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm will receive a concomitant commercially available, locally approved parenteral amino acid infusion, which supplies ≥36 g of lysine + arginine in ≤2 L (≤1050 mOsm/L). Eligible solutions must have the highest amount of lysine and arginine (of up to 24 g each) among the commercially available products in order to ensure adequate renal protection.

In the case of Aminosyn II 15% the administration volume must be adjusted to 2 L through dilution with saline solution (see Appendix 8).

5.1.2 Comparative Drug: 60 mg Sandostatin® LAR Depot

In the control arm patients will receive administrations of Sandostatin® LAR Depot 60 mg at 4-week intervals until week 72 (according to the schedule in Table 2), unless the patient progresses or dies before.

Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

5.1.3 Rescue Medication: Short-acting Sandostatin®

Subcutaneous, short-acting Sandostatin® (Octreotide Acetate solution, Novartis; Octreotide short-acting) injections may be indicated for control of symptoms (i.e. diarrhoea and flushing) in patients in both study arms, in accordance with the manufacturer's prescribing information. Short-acting Sandostatin® for symptom control is administered by the patient at their discretion. Patients will be asked to record rescue medication administrations on a paper diary.

5.2 Packaging and Labelling

All medications used in this study, except the investigational drug product, are commercially available.

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be prepared, packaged, labelled, and released under the responsibility of Advanced Accelerated Application´s Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations. Instructions for shipment, storage and handling of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Solution of Infusion are provided in Appendix 16.

5.3 Handling of Study Medication

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and Sandostatin® LAR Depot must be administered at the investigational site. Short-acting Octreotide is self-administered by the patient.

The study medication must be stored, handled and administered only by qualified/authorized personnel and must be prepared in accordance with pharmaceutical quality requirements, and radiation safety regulations for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Drug inventory and accountability records for the study medication and rescue medication, as well as drug returns by the patient, will be kept by the Investigator/Pharmacist, and must be documented throughout the study. Returned supplies should not be distributed again, not even to the same patient. The Investigator will not supply investigative study medication to any person, except the patients in this study.

On ongoing basis the Investigator/Pharmacist agrees to conduct a study medication supply inventory and to record the results of this inventory on the study Medication Accountability Record. It must be possible to reconcile delivery records with those of used and unused medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the responsible person at the clinical site.

Used and unused study medication and packaging provided by Sponsor must be returned at the End of Study or upon expiration, except for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, which will be locally discarded. The return of all study medication will be documented appropriately.

5.4 Medication Prior to the Study

Patients must be on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to enrolment in the study.

5.5 Medication During the Study

The patient may not receive any other systemic therapy for the treatment of GEPNET (chemotherapeutic, biologic, or any investigational agent) other than ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and/or short-acting Octreotide and/or Sandostatin® LAR Depot during the study period. Localized therapy such as surgery or external beam irradiation may be performed on additional site(s), provided that it does not affect treatment response assessment.

5.6 Stratification and Randomization

For all patients who have signed the ICF, a screening number will be assigned in chronological order starting with the lowest number available on site. Patients will be identified by a unique patient identification number (Patient ID No.) composed of the centre number (four digits) and the screening number (three digits).

After the screening period, eligible patients will be randomly assigned in an equal ratio (1:1) to one of the two study groups for treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (plus best supportive care 30 mg Sandostatin® LAR Depot) or high dose (60 mg) Sandostatin® LAR Depot. The e-CRF will assign a unique randomization number to the patient, which will be used to link the patient to a treatment arm.

Randomization will be stratified according to centre, OctreoScan® tumour uptake score (Grade 2, 3 and 4), length of time that patients have been on the most recent constant dose of Octreotide prior to enrolment (≤6 and >6 months), according to a biased coin design (Appendix 17).

The details of the procedure to obtain the patient randomization number will be described in the Investigator's Manual.

5.7 Administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

5.7.1 Patient Preparation

There is no need for the patients to fast before treatment.

5.7.2 Administration Schedule

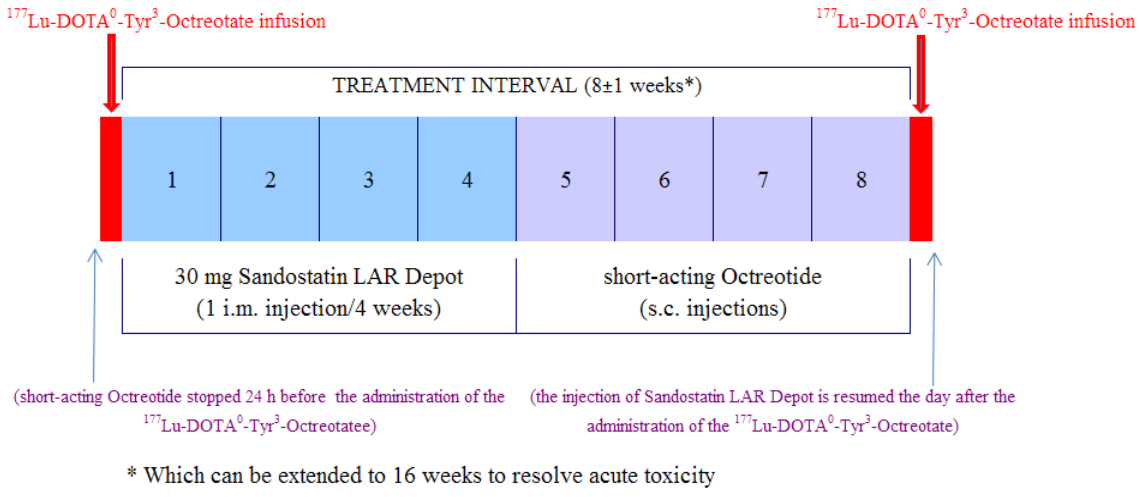
Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a cumulative dose of 29.6 GBq (800 mCi) with the dosing divided among 4 administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at 8±1-week intervals or up to 16 weeks to accommodate resolving acute toxicity (see Section 5.7.3).

In addition to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients will receive 30 mg Sandostatin® LAR Depot, until the End of Study, unless the patient progresses or dies. Before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment:

1. The last Sandostatin® LAR Depot injection must be administered on the day after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date (during this period short-acting Octreotide s.c. injections are allowed).
2. Short-acting Octreotide is not allowed during the 24 h before the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date, unless this is clinically impossible. Short-acting Octreotide can only be continued if the tumour uptake on the OctreoScan® during continued somatostatin analogue medication is $\geq$ liver uptake (Exclusion Criterion 14 (Sections 4.1.2 and 4.2.2) and Appendix 5).
3. Treatment with 30 mg Sandostatin® LAR Depot can be resumed the day after the administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

The scheme for supportive treatment with 30 mg Sandostatin® LAR Depot is schematically presented in Figure 1.

Figure 1: Concomitant Supportive Treatment with 30 mg Sandostatin® LAR Depot in the ^{177}Lu-DOTA^{0}-Tyr^{3} Octreotate Arm.



* Which can be extended to 16 weeks to resolve acute toxicity

On the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, and before the infusion with amino acids is started, an intravenous bolus of Granisetron (3 mg), or Ondansetron (8 mg), or Tropisetron (5 mg) is

given. In case nausea or vomiting occurs despite this medication, patients can be treated with other anti-emetic drugs at the discretion of the physician.

The amino acid solution and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (22-25 mL) are administered in parallel by peripheral vein infusion in one arm at a constant infusion rate through pumps or any other infusion system. The infusion with amino acids starts 30 minutes before the start of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion, and continues for a total of 4 h. During amino acid infusion patient is allowed to void.

Infusion rates are listed in Table 5 and see Appendix 8 for the infusion system scheme.

Table 5: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm Administration Schedule.

Preparation	**Starting Time (h)**	**Infusion Rate (ml/h)**	**Duration (h)**
Granisetron 3 mg (or alternative)	0	Bolus	-
Amino Acids: 2 L solution	0	500	4
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate[1]	0.5	50	0.5
Saline solution	1.0	50	0.5

[1] ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be infused directly into the line. The line must be flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

5.7.3 Dose Modifying Toxicity

In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm, dose modifying toxicity (DMT), according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE), is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity possibly related to study drug and regardless of its duration. Lymphocytopenia and liver enzyme toxicities (ALAT (ALT), ASAT (AST) and AP) will not be used to define a DMT.

If a patient experiences a DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration.

After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient goes off-study. If the DMT event does not reoccur, the next treatment is at full dose.

The scheme for dose modification after toxicity in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm is schematically presented in Figure 2.

5.7.4 Patient Release and Radioprotection Precautions

Following administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients should remain at the clinical site for an additional 4 to 5 hours in an area with suitable radiation shielding to protect others from unnecessary exposure (see Appendix 14). At the time of release, patients are given written instructions (Appendix 15) which outline the precautions the patient must take to minimize radiation exposure to people around them.

5.8 Administration of 30 mg Sandostatin® LAR Depot in ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm

30 mg Sandostatin® LAR Depot (Octreotide LAR) should be given as an i.m. injection in accordance with the product prescribing instructions for a single-use kit, containing a 5-ml vial of 10 mg, 20 mg, or 30 mg strength. See for further details on the administration schedule Section 5.7.2 and Figure 1.

5.9 Administration of 60 mg Sandostatin® LAR Depot in Comparator Arm

5.9.1 Patient Preparation

There are no specific requirements.

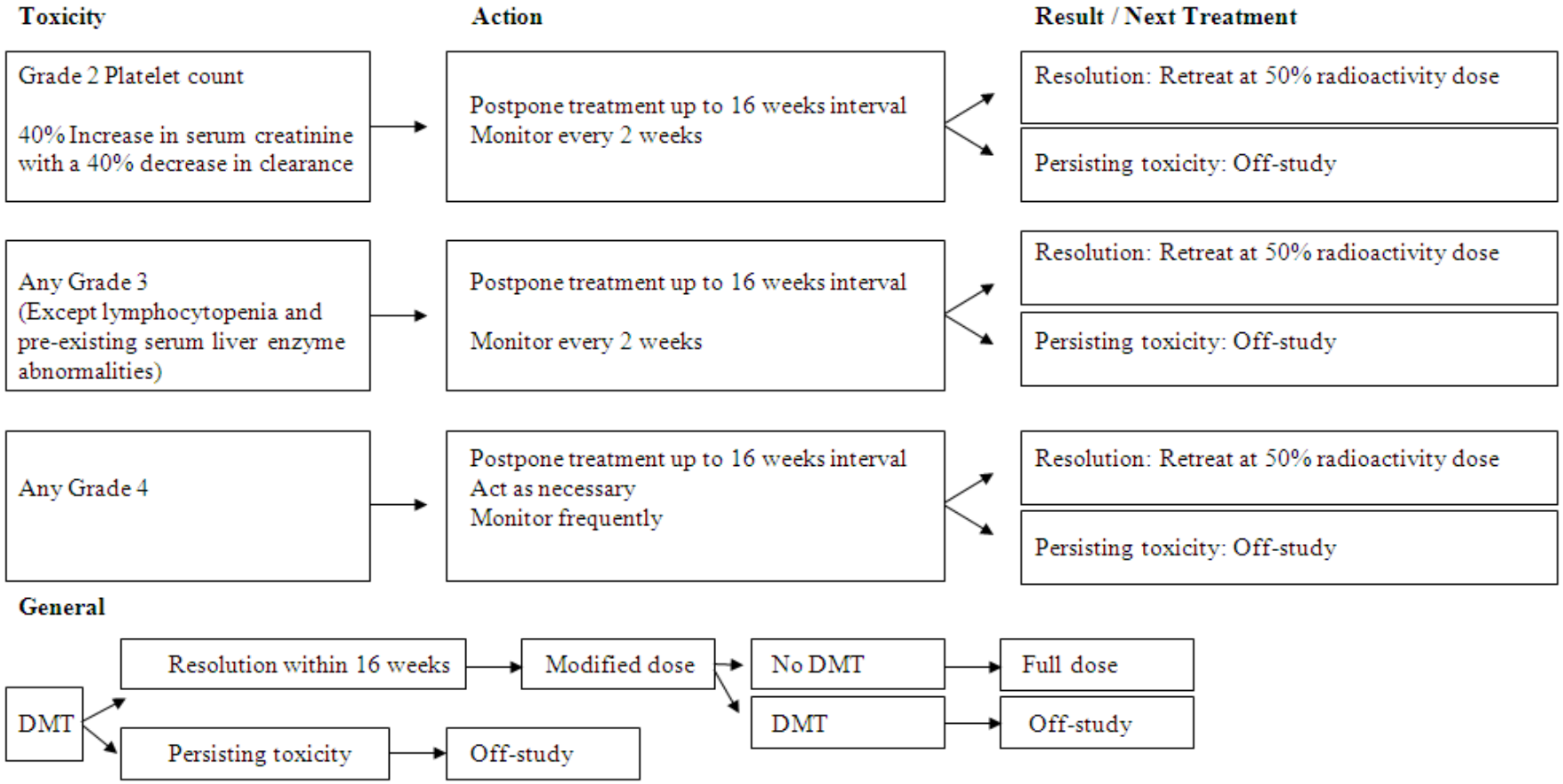
5.9.2 Administration Schedule

60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) should be given as i.m. concurrent injections once every 4 weeks for a period of 72 weeks. Each of these injections should be administered in accordance with the product prescribing instructions for single-use kits, containing 5-ml vials of either 10 mg, 20 mg, or 30 mg strength.

5.9.3 Dose Modifying Toxicity

In the treatment arm with Sandostatin® LAR Depot, a dose adjustment scheme will be applied in case of Grade 3 or 4 toxicity, especially in case of severe abdominal symptoms, and hypoglycaemia. If a patient experiences a DMT during Sandostatin® LAR Depot treatment, the subsequent treatment dose will be reduced to the previous well-tolerated dose and then at the next treatment, the dose will be increased again to 60 mg Sandostatin® LAR Depot.

Figure 2: Dose Modifying Schemes for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm.



6- ASSESSMENTS

Patients will be evaluated for safety and tolerability in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm as indicated in Table 1 and Table 2, respectively (variations of ±1 week in the visits schedule are allowed).

The assessments listed in Table 6 will be performed centrally. Procedures for centralized evaluations will be detailed in the Laboratory Manuals provided to each participating site.

Table 6: Centrally Performed Assessments.

Assessment	Material to be Delivered	Time-point	Section
Proven midgut carcinoid tumour diagnosis. *Centralized diagnosis confirmation is requested before randomization.*	Specimen of primary tumour or liver metastases	Screening	6.1.1.1
Immunohistochemical staining for CgA, synaptophysine and Ki67. *Centralized confirmation of Ki67 index ≤ 20% is requested before randomization. The central laboratory will also evaluate CgA and synaptophysine.*	Specimen of primary tumour or liver metastases	Screening	6.1.1.2
OctreoScan® tumour uptake in documented lesions. *Centralized confirmation of tumour uptake at least as high as normal liver uptake observed on planar imaging (Appendices 5 and 6) is requested before randomization.*	(Existing) OctreoScans *The OctreoScans® obtained within 24 weeks of enrolment will be accepted for inclusion only if the patient has not received other treatments for the indication in that time frame.*	Screening	6.1.4
Progression of disease according to RECIST Criteria. *Centralized confirmation of tumour progression according to RECIST is requested before randomization.*	(Existing) CT/MRI scans *The oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date.* *The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan, should be one that was performed while the patient was on a fixed dose of Sandostatin LAR.*	Screening	6.1.5
Objective tumour response according to RECIST Criteria. *Tumour response according to RECIST is re-evaluated centrally during the study.*	CT/MRI scans	Every 12 weeks	6.3.1
Serum CgA.	Blood sample	Every 12 weeks	6.5.2.2

Table 7: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm – 12-Week Efficacy and Safety Assessments Visit Schedule

		Minimum Assessments							EOS
	Screening	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Week		**-3**	**12**	**24**	**36**	**48**	**60**	**72**	**76**
Procedure									
Informed Consent		X							
OctreoScan®	< 24 wks								
Histology and Ki67									
CT/MRI		< 4 wks							
Demographic Data	X								
Relevant Medical History		X							
Prior Carcinoid Tumour Therapy	X	X							
Randomization (Eligibility)		X							
Octreotide LAR 30 mg			X	X	XXX	XXX	XXX	XXX	
Diary Delivery (symptoms and rescue medication)	X		X	X	X	X	X	X	
Relevant Medical History		X							
Cancer Related Symptoms		X							
Diagnosis and Extent of Cancer	X								
Cardiac Ejection Fraction		X							
ECG		X							X
Physical Exam		X	X	X	X	X	X	X	X
Karnofsky Performance	X	X	X	X	X	X	X	X	
Quality of Life		X	X	X	X	X	X	X	
Haemotology	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Prior/Concomitant Rescue Therapy (report in diary)	< 12 wks	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X
Disease Assessment RECIST (CT/MRI)	< 12 wks		X	X	X	X	X	X	
Survival Data		X	X	X	X	X	X	X	X

All enrolled patients in either arm have assessments conducted at 12-week intervals from the start of treatment up to 76 weeks (EOS, unless early termination). The 12-week interval assessments are incorporated in the treatment / assessment schedules shown in Figures 1 and 2. The specific 12-week interval assessments for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments are independly shown in Table 7, without the treatment specific assessments that are performed 2 week before and 4 weeks after treatment.

6.1 Demographics and Baseline Characteristics

Each patient's date of birth, sex, race, weight, height and relevant baseline characteristics will be recorded in the e-CRF.

6.1.1 Diagnosis and Extent of Cancer

A patient's history relating to his/her disease, including primary diagnosis, date of diagnosis, as well as disease status at study entry, will be collected. This includes the date of first diagnosis of midgut carcinoid tumour and the date of the first presence of metastases with specification of the metastatic site(s). For the determination of the stage of disease, TNM criteria will be used (Rindi G et al, 2007; Appendix 18).

6.1.1.1 Histology

All patients are required to have central histological confirmation of midgut carcinoid tumours in accordance with WHO classification and ENETS grading and staging guidelines (Rindi G et al., 2011), based on surgery/biopsy specimens of the primary tumour or liver metastases and assessed by immunohistochemical staining for CgA, synaptofysine and Ki67 (for the latter see Section 6.1.1.2). It would be preferable that samples were fixated in formalin and embedded in paraffin within two days of resection. If this fixation procedure has been undertaken, immuno-reaction will remain in the paraffin blocks at an adequate level for analysis.

It is not required to repeat the biopsy at study entry if a previous tumour sample is available for central review (samples embedded in paraffin, should be stable for up to 30 years, provided that the samples have been fixated appropriately in formalin prior to paraffin embedding).

For operating details and quality certificates see the Laboratory Assessment Manual.

6.1.1.2 Ki67

All patients are required to have central assessment of the Ki67 proliferation index based on surgery/biopsy specimens of the primary tumour or liver metastases and assessed by the microscopy and immunohistochemical staining.

Ki67 must be $\leq$20% for a patient to be eligible.

For operating details see the Laboratory Assessment Manual.

6.1.2 Cancer Related Symptoms

Each patient will be provided with a diary to record symptoms experienced and rescue medication (short-acting Octreotide s.c. injections) taken during the study.

6.1.3 Prior Antineoplastic Medications / Radiotherapy / Surgery

Information pertaining to any chemotherapy, hormonal therapy, immunotherapy, radiation, or surgery the patient has previously received will be documented.

6.1.4 OctreoScan® Tumour Uptake in Documented Lesions and Tumour Uptake Score

All patients are required to have OctreoScan® scintigraphy performed within 24 weeks prior to enrolment in the study, according to ENETS Consensus Guidelines (Kwekkeboom DJ et al., 2009) (Appendix 6).

Individual tumour uptake and extent (as per Appendix 5) will be determined on existing scans and/or scans that are retrieved from the investigational site through central, IRC (Independent Review Committee) assessment; confirmation of OctreoScan® tumour uptake in documented lesions and the OctreoScan® tumour uptake score will be documented.

OctreoScan® images obtained within 24 weeks of enrolment will be accepted for inclusion only if the patient has not received other treatments for the indication in that time frame.

Operating details and quality certificates are specified in the OctreoScan® Assessment Manual.

6.1.5 Progressive Disease According to RECIST Criteria

All patients are required to have progressive disease at the time of inclusion according to RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009; Appendix 2) confirmed by central laboratory. The oldest CT/MRI scan used to determine disease progression must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date. The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan, should be one that was performed while the patient was on a fixed dose of Sandostatin LAR.

For CT imaging at entry, a triphasic and contrast enhanced study should be performed with a slice distance of 5 mm or less, and continuous slices (Appendix 9).

Progressive disease assessment will be based on existing CT/MRI scans and/or scans that are retrieved from the investigational site. Central, blinded, real-time IRC (Independent Review Committee) assessment will be employed for an independent re-evaluation of progressive disease. Information will be collected pertaining to measurable, evaluable, or non-evaluable disease at baseline.

Patients with progressive disease will be accepted for inclusion only if the patient has been on a fixed dose of 20 mg or 30 mg Octreotide at 3-4 weeks intervals for 12 weeks prior to enrolment in the study.

Operating details and quality certificates are specified in the CT/MRI Assessment Manual.

6.2 Prior/Concomitant Medications

All medications taken at the time of start of screening through the End of Study are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.

6.3 Efficacy Assessment

6.3.1 Progression Free Survival

The primary efficacy endpoint is PFS as measured by objective tumour response, which is determined by RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009; Appendix 2).

Triphasic CT imaging is the preferred modality over MRI for determining objective tumour response (Appendix 10).

The tumour diameters of indicator lesions used for response assessment should be measured in the closest position to that used for the baseline CT or MRI assessment (it is recommended that for each patient identical acquisition and reconstruction protocols be used at all time-points).

Central, blinded, real-time IRC (Independent Review Committee) assessment will be employed for determining progressive disease. Changes from start of treatment will be assessed every 12±1 week after the first treatment date until the End of Study, unless the patient progresses or dies.

Additional PFS data will be collected up to 3 years after the End of Study based on local assessments.

Operating details and quality certificates are specified in the CT/MRI Assessment Manual.

6.3.2 Objective Response Rate

Objective Response Rate (ORR) will be calculated as the proportion of patients with tumour size reduction of a predefined amount (the sum of partial responses (PR) plus complete responses (CR)) and for a minimum time period. Response duration will be calculated from the time of initial response until documented tumour progression.

6.3.3 Overall Survival

Overall Survival (OS) will be calculated from start of study treatment until the day of death due to any cause; OS will not be censored if a patient receives other anti-tumour treatments after study medication.

Survival data will be collected at the End of Study and up to 3 years after the End of Study.

6.4 Quality of Life

The impact of treatment on health related QoL will be assessed using the EORTC QLQ-G.I.NET21 questionnaire (Appendix 3), which will be filled in by the patient prior to know CT scan/MRI result. Changes from baseline will be assessed every 12±1 week after the first treatment date until the end of study, unless the patient progresses or dies. The EORTC QLQ-G.I.NET21 questionnaire is a module for carcinoid/neuroendocrine tumours. This module comprises questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

Outcomes for both study arms will be collected and evaluated in relation to objective tumour response, KPS, and other parameters of clinical relevance.

Forms in Country-specific languages will be provided by the Sponsor.

6.5 Safety and Tolerability

6.5.1 Adverse Events

All adverse events (AEs), whether or not spontaneously reported by the patient, will be recorded starting from the signing of the ICF until the last study-related visit. Definitions and reporting procedures are outlined in Section 8.

6.5.2 Laboratory Assessments

The laboratory assessments require that blood samples for haematology and blood chemistry, and a urine sample for urinalysis are taken, as listed in Table 8. Laboratory assessments will be performed at the investigational site, except for the evaluation of serum CgA.

At Screening: all patients will have screening laboratory assessments including haematology, blood chemistry and urinalysis (see Table 8): this assessment can be combined with baseline evaluation if sampling is within 3 weeks (preferably 2 weeks in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) before the first treatment date.

During the Study:

- In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: within 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment. Blood tests performed 4 weeks after any treatment cannot serve as baseline values for the next treatment. A wash out period is required between treatments. Patients are not eligible for their next treatment until a minimum of 7 weeks has passed since the last administration of study drug (maximum 16 weeks). Throughout the study, laboratory assessments will be performed every 12±1 weeks (see Visit Schedule in Table 1).
- In the 60 mg Sandostatin® LAR Depot arm: throughout the study laboratory assessments will be performed every 12±1 weeks (see Visit Schedule in Table 2).

In the event of a significant laboratory abnormality, or if clinical or laboratory evidence of toxicity occurs, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value redresses. Appropriate remedial measures should be taken and the response recorded.

All safety laboratory results must be evaluated by the Investigator before administration of study medication.

Any clinically relevant change from baseline onwards, will be recorded on the Adverse Event page of the e-CRF.

Table 8: Laboratory Assessments.

Haematology	**Blood Chemistry**	**Urinalysis[3]**
• WBC with differential[1] • Platelets[1] • Hb[1] • MCV	• BUN • Serum creatinine[2] • Creatinine Clearance • Uric acid • Albumin • Total bilirubin[2] • AP • AST/ASAT • ALT/ALAT • Gamma-GT • Sodium • Potassium • LDH • CgA (centralized assessment) • GlycoHb • fT4	• RBC/hpf • WBC/hpf • Casts/lpf • Protein by dipstick test • 5-HIAA • Pregnancy test • *(if applicable)*

[1]Patients must meet the criteria for Hb, WBC, and platelets, as defined in the inclusion criteria, at baseline and before each subsequent treatment. If the patient cannot be retreated due to haematological abnormalities, the evaluation must be repeated at least once weekly until re-treatment.

[2]Patients must meet the criteria for serum creatinine and total bilirubin as defined in the inclusion criteria at baseline and before every re-treatment. As entry criterion, patients must have a serum creatinine level ≤150 µmol/L (1.7 mg/dL), or a measured creatinine clearance of ≥50 mL/min (through two 24-h urine collections). During the course of the study, the creatinine clearance will be calculated every 12±1 weeks according to the Cockcroft-Gault formula. If in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured in these collections. If the measured urinary creatinine clearance is ≤40% treatment can continue.

[3]Total urinary protein and other urinary measurements should be repeated by dip-stick test at follow-up visits every 12±1 weeks.

The Cockcroft-Gault formula allows this estimation based on the occurrence of creatininemia, and correlating patient muscular mass (and so the consequent creatinine production) to weight, sex and age:

*Est. Creatinine Clearance = [[140 - age(yr)]*weight (kg)]/[72*serum Cr(**mg/dL**)]*
(multiply by 0.85 for women)
or
*Est. Creatinine Clearance = [[140-age(yr)]*weight (kg)]/[48816* serum Cr(**mmol/L**)]*
(multiply by 0.85 for women)

During the Long-term Follow-up: In both study arms laboratory assessments will be performed every 6 months for 3 years after the End of Study. The Safety Assessment Schedule for the 3 year follow-up visits is shown in Table 9.

Table 9: Long-Term Follow-Up Visits Safety Assessments Schedule

	Assessments						
Months	**EOS**	**6**	**12**	**18**	**24**	**30**	**36**
Procedure							
Haematology	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Disease Assessment RECIST (CT/MRI) – Local assessment		X	X	X	X	X	X
Survival Data	X	X	X	X	X	X	X

6.5.3 Pregnancy Test

Women and men should not procreate until six months after the end of their last treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Due to the CT scans foreseen during the study (every 12±1 weeks), woman should not procreate until the End of Study.

A pregnancy test must be performed at baseline and within 7 days prior to each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment for every female patient of childbearing potential (Section 8.9 and Appendix 7).

6.5.4 Cardiac Ejection Fraction

Patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterium №-11. Patients with history of congestive heart failure who don't violate the above exclusion criteria will undergo an evaluation of their cardiac ejection fraction prior to baseline, preferably via gated equilibrium radionuclide ventriculography. The results from an earlier study (not exceeding 30 days) may substitute the evaluation at the discretion of the Investigator, if no clinical worsening is noted. It is recommended that the patient's measured cardiac ejection fraction is ≥ 40% before randomization.

6.5.5 ECG

ECGs will be recorded at baseline, immediately after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment procedure (following the completion of amino acid infusion) and at the End of Study to measure the different ECG intervals (RR, PR, QRS, and a more extended QT evaluation according to ICH E14, and heart rate (HR)). ECGs will be taken also in the 60 mg Sandostatin® LAR Depot arm at same time points, according to Table 2 schedule.

A single ECG will be taken supine, after 5 minutes rest, and not immediately after a meal. The parameters will be measured as a mean value of minimally 3 beats.

The Investigator/local cardiologist will note in the source documents (and in the e-CRF) whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs results and the different EGC intervals measurements. Relevant abnormalities at baseline will be recorded in the Medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

6.5.6 Physical Examination and Vital Signs

Physical examinations will be performed by the Investigator, or qualified designee. All body systems will be examined and any relevant findings will be documented in the source documents and CRF. Physical examinations should include heart rate, blood pressure and weight measurement (height will only be measured at baseline). Blood pressure and pulse rate will be performed after the patient rests for 5 minute. For each patient, all blood pressure recordings shall be made using the same type of instrument (i.e., manual BP recording vs. automatic digital vital signs monitor) on the same arm.

Significant findings that are present prior to baseline will be recorded in the Medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

6.5.7 Karnofsky Performance Score

KPS forms must be completed by a medical professional at each treatment and follow-up visit, and before any current clinical information is given to the patient (Appendix 13).

6.5.8 Study Visits and Assessments

Eligibility visit

Prior to any study activities, patient will be asked to read and sign an ICF that has been approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and which complies with regulatory requirements. Once the ICF has been signed the patient enters the eligibility screening period.

The following patient data will be assessed for both treatment arms:

- Confirm that the patient has signed ICF and obtain patient demographic data
- Determine body weight (for calculation of creatinine clearance)

- Provide OctreoScan® image for central evaluation (positive OctreoScan® image should have been documented within 24 weeks prior to enrolment in the study)
- Provide histological sample of the primary tumour or liver metastases for central confirmation of diagnosis (Histology and Ki67)
- Report cancer lesions and TNM staging (local assessment), and submit CT/MRI documentation for a central confirmation of progressive disease and evaluation of extent of disease (for the purpose of determining disease progression the oldest CT/MRI should not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date). The CT scan/MRI scan that is to be compared to the baseline CT scan/MRI scan, should be one that was performed while the patient was on a fixed dose of Sandostatin LAR.
- Document prior therapy for carcinoid tumour
- Assess Karnofsky performance score
- Deliver patient diary to record cancer-related symptoms experienced from eligibility to week 1
- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, PLTs, Hb, Mean Corpuscolar Volume (MCV)
    - biochemistry: blood urea nitrogen (BUN), serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate Aminotransferase (AST/ASAT), Alanine Aminotransferase (ALT/ALAT), gamma-Glutamyl Transferase (γ-GT), sodium, potassium, Lactic Dehydrogenase (LDH), glycosylated haemoglobin (glycoHb), free Thyroxine (fT4)
    - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-hydroxy-indoleacetic acid (5-HIAA)

Baseline visit

The baseline visit should occur about 3 weeks before the first study treatment to confirm patient eligibility (based on all inclusion and exclusion criteria, including those evaluated centrally). Baseline checks will enable randomization and the release of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the study subjects in this arm.

The following patient data will assessed for both treatment arms:

- Document relevant past medical history, and current medical conditions not related to the diagnosis of carcinoid tumour
- Document other therapies for concomitant diseases
- Assess ejection fraction in subjects with history of congestive heart failure
- Perform ECG
- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate), body weight, height
- Assess Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)

- Perform laboratory tests (local assessment. NB: screening and baseline lab evaluations can be combined if sampling is within 3 weeks before the first treatment date):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula or measured through two 24-h urine collections, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb, fT4, sodium, potassium
  - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
  - urinary pregnancy test (women of childbearing potential),
- Collect sample for central evaluation of CgA

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm

Visits during treatment / exams to be performed during the treatment period, per treatment arm.

Safety assessments will be performed 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment (see section 6.5.2).

The ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment / assessment schedule shown in Table 1 is idealized in the sense that all ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments occur at defined 8-week interval. In the event that the intervals are less than or greater then the defined 8-week interval, the investigator will need to ensure that the correct safety assessments before and after each treatment have been conducted (safety assessments must be performed 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, see section 6.5.2 for further details).

Importantly, if the scheduled 12-week assessment were to overlap with one of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment visits, then the 12-week assessment can not be performed at that time. However, it is critical that the 12-week assessment be conduct within the ±1-week window shown in Table 7. The 12-week assessment visit should be combined with the assessment visit that occurs two week before or four weeks after treatment if the 12-week safety and efficacy assessment would be within ± 1 week of its scheduled time, or the treatment schedule may be adjust ±1-week. See Table 7 and Table 10 for the listing of assessments that are required for pre- and post treatment, and at the 12-week intervals for safety and efficacy assessments.

Table 10: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm – Safety Assessment and Treatment Visit Schedule

	Treatment 1 Visits			**Treatment 2 Visits**			**Treatment 3 Visits**			**Treatment 4 Visits**		
	Baseline Visit	Visit T1B	Visit T1C	Visit T2A	Visit T2B	Visit T2C	Visit T3A	Visit T3B	Visit T3C	Visit T4A	Visit T4B	Visit T4C
Week	**- 3**	**0**	**4**	**6**	**8**	**12**	**14**	**16**	**20**	**22**	**24**	**28**
Procedure												
^{177}Lu-DOTA^{0}-Ty^{3}-Octreotate Treatment		X			X			X			X	
ECG	X	X			X			X			X	
Physical Exam	X			X			X			X		
Karnofsky Performance	X			X			X			X		
Quality of Life	X											
Haematology	X		X	X		X	X		X	X		X
Blood Chemistry	X		X	X		X	X		X	X		X
Urinalysis	X		X	X		X	X		X	X		X
Pregnancy Test	X			X			X			X		
Concomitant Rescue Therapy	X		X	X			X			X		
Adverse Events	X		X	X		X	X		X	X		X
Creatinine Clearance	X											

At all visits (in addition to exams at specific visits):

At all visits (in addition to exams at specific visits):

- Document concomitant therapy
- Document adverse events
- Deliver patient diary for the collection of cancer-related symptoms and rescue medication (except at weeks 7, 15, 23)
- Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary (except at weeks 7, 15, 23)
- Report survival information

Week 0 – 8 – 16

- Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate + 30 mg Octreotide LAR Depot
- ECG (at the end of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)

Week 4 – 20 - 28

- (only week 28) Treatment with 30 mg Octreotide LAR Depot
- Determine body weight (for calculation of creatinine clearance)
- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections if a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb, fT4
    - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA

Week 6 – 14 – 22

- Perform physical examination and record vital signs (systolic, diastolic blood pressure; pulse rate), body weight
- Determine Karnofsky performance score
- Perform laboratory tests (local assessment; within 2 weeks of the treatment date):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections if a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb, fT4

- urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
- urinary pregnancy test: only in women of childbearing potential
- collect sample for central evaluation of CgA (only week 23)

Week 12 – 36 – 48 – 60 – 72

- (except week 12) Treatment with 30 mg Octreotide LAR Depot
- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Determine Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections if a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb, fT4, sodium, potassium
  - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
- Collect sample for central evaluation of CgA
- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

Week 24

- Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate + 30 mg Octreotide LAR Depot
- ECG (at the end of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

Week 32 – 40 – 44 – 52 – 56 – 64 – 68

- Treatment with 30 mg Octreotide LAR Depot

Week 76 (EOS)

- Perform final physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections if a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a

concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb, fT4

- urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA

- Record cancer-related symptoms and rescue medication (through data reported in the patient's diary)
- Perform ECG

Follow-up visits (every 6-months for 3 years) after (EOS)

- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb, fT4
  - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
- Document serious adverse events suspected to be related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
- Report survival information
- Collect information on tumour progression (local assessment)

The Safety Assessment Schedule for the 3 year follow-up visits is shown in Table 9.

Octreotide LAR arm

At all visits (in addition to exams at specific visits):

- Document concomitant therapy
- Document adverse events
- Report survival information
- Deliver patient diary for the collection of cancer-related symptoms and rescue medication
- Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary
- Treatment with 60 mg Octreotide LAR Depot

Week 0 – 8 – 16

- Perform ECG

Week 12 – 36 – 48 – 60 – 72

- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Determine Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Perform laboratory tests (local assessment):

- haematology: WBC with differential count, platelets, haemoglobin, MCV
- biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb, fT4, sodium, potassium
- urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA

- Collect sample for central evaluation of CgA
- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

Week 24

- Perform ECG
- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Determine Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb, fT4, sodium, potassium
  - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
- Collect sample for central evaluation of CgA
- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

Week 76 (EOS)

- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections if a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb, fT4
  - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
- Record cancer-related symptoms and rescue medication (through data reported in the patient's diary)
- Perform ECG

Follow-up visits (every 6-months for 3 years)

- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb, fT4
    - urinalysis: RBC/hpf, WBC/hpf, casts/lpf, protein by dipstick test, 5-HIAA
- Record survival information
- Record information on tumour progression (local assessment)

The Safety Assessment Schedule for the 3 year follow-up visits is shown in Table 9.

6.6 Dosimetry, Pharmacokinetics and ECG

A Dosimetry, Pharmacokinetics and ECG substudy will be performed in 20 patients at 2-3 selected Sites performing full body (planar) and 3D SPECT scans on the day of the first 177Lu-DOTA0-Tyr3-Octreotate administration. Blood and urine samples will be collected at different intervals after the first ^{177}Lu-DOTA^{0}-Tyr^{3}-administration. All patients included in the substudy will undergo a 24-hour continuous ECG recording via a 12-lead Holter machine.

Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and 168 h (or within 156-168 h). The time point ranges indicated in brackets are to be considered if the specific timepoint is not feasible.

3D SPECT scans will be performed at 24 h and 48 h in the upper abdomen (comprising kidneys, liver and spleen) and, if deemed necessary based on the outcome of the planar imaging, also in different regions.

Blood samples (whole blood) will be collected from each patient just before administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapeutic dose from the opposite arm of drug infusion and then at the following time-points:

two time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 64 and 72 h (Day 4), 160 and 168 h (Day 8).

A urine sample will be collected within 24 h prior to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration, preferable just prior to the infusion of study drug (0 h sample) to achieve bladder emptying before study drug administration. Quantitative urine collections will be obtained for the periods 0-1 h (immediately post start infusion to 1 h post start infusion), 1 h – 4 h, 4 h – 16 h, and 16 h – 48 h post start infusion (Appendix 10). The rate and extent of elimination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be determined by analyzing the actual and cumulative percent injected dose (radioactivity) in the sequential, quantitative urine collections.

Radioactivity in blood and urine will be measured at the investigational site, with a COBRA-Packard auto-gamma counting system (Packard, Meriden, Conn., USA). In addition, a 10 mL aliquot will be withdrawn from each urine collection sample. Urine samples will be processed and further analyzed

by HPLC according to validated procedures in order to examine the chemical status of the radionuclide in urine.

A 24-hour continuous ECG recording via 12-lead Holter machine will be performed on the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Data recording will start two hours prior to the start of the amino acid infusion, will continue during the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and will continue after completion of the treatment procedure for a total of 24 hours.

Data obtained will be analyzed to determine whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Relevant abnormalities at baseline will be recorded in the Medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

Data from continuous recording over the 24-hour period will be analyzed to evaluate the effects of the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate electrocardiographic parameters and their relationship with drug plasma concentrations.

Descriptive statistics (N, mean, median, minimum, maximum, 95% confidence interval for the mean, etc.) of the observed values as well as for the changes from baseline value will be created. Frequency tabulations with values within, below or above the normal ranges will be made.

ECG parameters will include heart rate (HR), RR interval, PR interval, QRS width and QT interval.

QT intervals will be corrected for heart rate. ECG results will be evaluated by means of descriptive statistics (mean, median, 95% confidence interval for mean, etc.) and frequency tabulations.

Graphical presentations might be created to facilitate the interpretation.

6.6.1 Dosimetry of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

An extensive dosimetry analysis will be performed in 20 patients enrolled at selected clinical sites. The substudy will require planar and 3-D SPECT imaging, and will also include urine collection and blood sampling.

According to the MIRD scheme, the radiation dose to a target organ is the sum of the self-dose from this organ and the cross doses from all other target organs. In order to calculate the radiation dose to the various target organs the amount of radioactivity present in the source organs must be measured. The radioactivity uptake in each organ is determined at various time points. This uptake defines the kinetics of the radiopharmaceutical. By integrating the kinetic curve, the number of interactions from each source organ per injected activity dose is obtained, and this is the so-called residence time.

DATA ACQUISITION

Equipment

1. A gamma-camera with medium energy collimator. Energy window setting at 208 keV (20%).

2. Well counter with multichannel analyzer or gamma counter to determine ^{177}Lu activity in blood and urine samples.

3. A dose calibrator to measure the activity in the reference source and the injected activity.

Timing of measurements

The uptake of peptides in liver, spleen and kidneys occurs almost immediately. Based on previous experience (Phase I/II Erasmus study) the proposed measurement points are at approximately 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and 168 h (or within 156-168 h) after administration.

Performing the measurements

1. Conjugate view counting

Quantification of the ^{177}Lu radioactivity will be performed by using 180° opposed planar images (typically Anterior and Posterior views) in combination with transmission data through the subject and a system calibration factor (Siegel, 1999).

a. Determine the transmission factor $\Im$ ($= e^{-\mu} e^{t}$)

For abdominal uptakes the attenuation correction is considerable and should be performed. The $\mu e/\rho$ for the 208 keV window of ^{177}Lu may be determined by counting a point source during e.g. 5 minutes. This measurement must be repeated with several thicknesses of absorbing material with unit density. (In a narrow beam geometry the average tissue μ_e/ρ(208 keV) = 0.134 cm^2/g [2]). The patient thickness (t) at the Region Of Interest (ROI) in the abdomen is determined on a CT scan or measured with a ruler.

b. Determine the system calibration factor C

The calibration factor C (count rate per MBq ^{177}Lu) is measured by counting a known activity reference standard (usually 37-74 MBq ^{177}Lu, or 0.5-1% of the injected activity; measured in the dose calibrator). Count this standard in air for 3 minutes.

c. Acquire anterior and posterior planar views

Patient measurements are performed with a medium energy collimator and the 208 keV peak is used. The posterior and anterior views can be made as static planar images for a fixed time.

d. Determine the anterior IA and posterior IP count rates

Regions of interest (ROI) are drawn around the liver, kidneys and spleen both in the anterior and posterior views. Subtraction of the background can be performed by drawing a background ROI adjacent to the source ROI. Normalize the background count rate IADJ to the same area in the source ROIs IA and IP. The background correction factor F is determined by:

$F \cong 1 - \frac{I_{ADJ}}{I_A}\left(1 - \frac{t_j}{t}\right)$, with t_j the source thickness. When ROI shows large overlap by other source organs, like e.g. in the right kidney ROI with overlapping liver, ROIs should be drawn over both the non-overlapped regions of each organ to estimate the background.

e. Determine the absolute activity A

The absolute activity in each source region is calculated by the following equation: $A = F\sqrt{\frac{I_A I_P}{\Im}} \times \frac{f}{C}$. The source region attenuation factor f can usually be approximated by unity for smaller organs. For larger source thickness t_j, f is defined by: $f = \frac{\mu_j t_j / 2}{\sinh(\mu_j t_j / 2)}$. As for example the calculation for the liver is very time consuming and the fact that for some patients a CT may not be available, a hollow liver phantom filled with the same activity as in the reference standard ^{177}Lu in a container filled with water can be used to calculate f. For the kidneys infusion bottles of 150 cc were used.

In alternative to the calibration based method described above, another method based on relative calibration is proposed for the quantification of the ^{177}Lu radioactivity (Cremonesi, 2007). The conjugate-view technique will be applied to anterior and posterior images after background, scatter, attenuation, and physical decay corrections. Counts in whole-body images will be normalized at the first image, scanning the patient with 100% of the injected activity (Cremonesi 2006) subtracted by the percent of injected activity eliminated in the urine before the first image acquisition.

2. Blood and urine sample counting (see Appendix 10 and 11)

a. Urine sample counting

The majority of the infused ^{177}Lu-DOTA^0-Tyr^3-Octreotate is excreted via the kidneys into the urine. Urine will be collected at the following time intervals:

0-1 h, 1-4 h, 4-16 h, 16-48 h post ^{177}Lu-DOTA^0-Tyr^3-Octreotate administration.

Samples of the urine collected are counted in the well- or gamma counter and compared to the count rate from a reference of the injected dose. The total radioactivity excreted at each time point as percentage of the injected dose can be calculated and used for determination of the total body distribution of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, as well as urinary bladder residence time.

b. Blood sample counting

Blood samples will be taken just before administration of the therapeutic dose and at the following time-points: 2 time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h,

then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 64 and 72 h (Day 4), 160 and 168 h (Day 8).

The blood samples will be counted in the well- or gamma counter and compared to the count rate from a representative percentage of the injected activity inside the same counter.

3. Data analysis and radiation dosimetry calculations

The number of decays (NDs) per unit injected activity —mathematically equivalent to the quantity of residence time (Stabin MG et al., 2005)—will be calculated from multiexponential fits to the time–activity curves for spleen, kidneys, liver, testes, and remainder of body.

The time–activity curve for blood will be evaluated with rescaling for the individual blood mass based on patient sex, weight, and height. The ND in the red marrow (ND_{RM}) will be derived from the blood-based method (Cremonesi M et al., 2006, Forrer F et al., 2009): $ND_{RM} = ND_{blood} \cdot m_{RM} / m_{blood}$, where m_{RM} and m_{blood} are the individual red marrow and blood masses, and ND_{blood} is the ND in the blood. The red marrow mass will be derived assuming a fixed ratio of red marrow to blood mass (male, 1120/5000; female, 1300/3500). The total absorbed dose to red marrow will be extrapolated from the blood curve. Absorbed doses to target organs will be calculated by entering the ND values for all the source organs in the OLINDA/EXM software and adjusting the doses reported by the software for individual weight and organ masses for kidneys, liver, spleen (determined from CT), and red marrow.

Whenever possible and for comparison purposes only, the patient specific red marrow mass will be also derived based the individual volume of the lumbar vertebrae L2, L3, L4 (V_{L2-L4}) estimated from CT images Ferrer L et al., 2010), according to the equation: $m_{RM} = 6.7\% \, V_{L2-L4}$.

The dose to the red marrow will be then rescaled with the red marrow mass determined from the L2-L4 methods and compared with the previous one derived by proportionality with the blood volume.

Some more details on pharmacokinetic and radiation dosimetry calculations are given below.

a. Pharmacokinetic profile

1. Determine the time-activity curves in the source organs by either numerical fitting of exponential curves to the data or by compartmental modeling to all organ uptake, blood and excretion data. A general code for numerical and compartmental modeling is the SAAM II software (http://www.saam.com) (Cobelli C et al., 1998).

2. Integrate the time-activity curve in each source region to determine the cumulated activity Ã [in MBq.h]. For a typical result of step 1: a bi-esponential curve $A_{organ} = A_1 e^{-\lambda 1 t} + A_2 e^{-\lambda 1 t}$ the cumulated activity is:

$\tilde{A}_{organ} = \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}$, with λ_p the physical decay constant of ^{177}Lu.

3. The quotient of Ã and the injected activity IA yields the residence time $\tau = \tilde{A}/IA$ [in h].

   a. The bi-exponential clearance pattern is assumed to apply.

   b. If step 1 was not successful, numerical integration by the trapezoid method can be used. Linear extrapolation to t = 0 can be performed by assuming A(0) = A(4).

4. Determine the fraction of administered activity that is excreted by the urinal pathway. Perform a numerical fit of a bi-exponential curve with a curve-fitting program like SAAM II to the urinary data to determine the fractions and elimination rates in the subsequent clearance stages.

$$A_{Urine}(t) = A_0 - A_1 e^{-\lambda_1 t} - A_2 e^{-\lambda_2 t}$$

The cumulated activity in the total body $\tilde{A}_{TB}$ and residence time τ_{TB} is derived from the urine excretion curve by:

$$\tilde{A}_{TB} = \frac{A_0 - A_1 - A_2}{\lambda_p} + \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}, \quad \tau_{TB} = \frac{\tilde{A}_{TB}}{IA}$$

The cumulated activity in the total body is needed for the calculation of the cumulated activity in the remainder of the body (source contribution to the bone marrow dose) and the clearance stages are needed for the calculation of the bladder residence time. The residence time for the remainder of the body is calculated by subtraction of the sum of the residence times in all known source organs from the total body residence time:

$$\tau_{remainder} = \tau_{TB} - \sum_{source.organ.i} \tau_i$$

b. Radiation dosimetry calculation

Data for ^{177}Lu are available in the OLINDA/EXM (Stabin MG et al., 2005) software package. Alternatively, the S-factors can be also taken from the Radiation Dose Assessment Resource (RADAR) site (http://www.doseinfo-radar.com/RADARphan.html). By using these S-factors and the residence times for the source organs, the radiation dose to all target organs can be calculated.

4. Result reporting and documentation

a. Therapy administration and camera settings

1. Record the date, time and activity of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administered

2. Express the radioactivity uptake in the organs as a percentage of the activity administered and in relation to the time after administration

3. Record patient body thickness at each ROI and source to skin distance, when the conjugate view method fails.

b. Pharmacokinetics

1. Blood curve

   i. Indicate date, time, activity and volume of each blood sample

   ii. Record the results of the exponential curve fitting to the blood data

2. Urinary clearance pattern

   i. Indicate date, time, activity and volume of each urine sample as well as the total collected urine volume at each time interval

   ii. Record the results of the exponential curve fitting to the urine data

   iii. Total body residence time derived from urinary excretion curve

3. Radioactivity uptake in organs

   i. Indicate date, time and count rate in ROI over organs, background and reference source

   ii. Record the results for the conjugate view quantification as percentage of the injected activity at each time point

   iii. Record the results of the exponential curve fitting to the organ uptake

c. Dosimetry results

Prepare dosimetry table output showing the organ doses per injected activity for the reference phantom.

7- STATISTICAL METHODS

The statistical analysis of the present study will be performed in accordance with the principles stated in the Consensus-Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonisation (ICH). The data of the study will be analyzed when the database is discrepancy free and hard locked.

7.1 Sample Size

Currently, there is only one published clinical trial that provides source data on ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate's effect on a treated patient population with midgut carcinoid tumours. In the Erasmus MC phase I/II study ("A phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with somatostatin receptor positive tumours") an objective tumour response rate of 23% (CR + PR according to SWOG Criteria at 3 to 4 months after the last treatment) was determined in patients treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. This is based on an analysis in 188 patients with carcinoid tumours (Kwekkeboom DJ et al., 2008).

Recently a retrospective, independent verification of the Erasmus MC phase I/II study source data and a statistical analysis of the study results have been conducted by a contract CRO to support the initiation of the present phase III study. Within this study, an analysis of a subgroup of 51 patients with midgut carcinoid tumours that had progressive disease within 12 months before entering the study (notably similar to the population in the present phase III Study), a median PFS of 45 months with a 95% CI of 22-57 months was observed. However, because this subgroup size is small, the median PFS has a large confidence interval (95% CI of 22-57 months).

Additionally, when considering the second arm (Octreotide LAR) of the present phase III study, there are only two sets of relevant data for patients with midgut carcinoid tumours treated with Octreotide LAR available in literature: the PROMID study (Rinke A et al., 2009), which recently reported a median PFS of 14 months, and the RADIANT-2 study (Pavel M et al., data presented at the 8th Annual ENETS Conference, 9–11 March 2011, Lisbon, Portugal) reported a median PFS of 11 months. In the PROMID study, patients with midgut carcinoid tumours were enrolled in a double blinded randomized two armed trial. Patients in the control arm received a placebo, and patients in the treatment arm received 30 mg Octreotide LAR (Rinke A et al., 2009). In the RADIANT-2 study, patients with carcinoid tumours (diverse sites) were randomized for treatment in two comparator arms (Yao J et al., 2008). In one arm, patients received 30 mg Octreotide LAR alone, and in the other arm patients received Octreotide LAR plus Everolimus (Afinitor®). For the purpose of calculating sample size for the present phase III study, the results of the PROMID study were deemed to be the most applicable. This study was performed using a similar patient group (progressive midgut carcinoid tumours at enrolment) whereas the RADIANT-2 study was not restricted to midgut carcinoid tumours. The PROMID study however, was conducted as a fully double-blinded clinical trial, and it would be expected that such a study would not be significantly impacted by high patient dropout rates; rather the likely decision point for a patient to participate in such a study would be before enrolment – thus low impact on the trial for either dropout or intent to treat issues.

The median PFS of 45 months for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the subgroup of 51 patients with midgut carcinoid tumours that had progressive disease within 12 months before entering the Erasmus MC phase I/II study is associated with a high degree of uncertainty based on the wide 95% CI for the median PFS of 22-57 months. Furthermore, as the Erasmus MC phase I/II study has been conducted by a single center with specially trained investigators of high expertise, it can be assumed that survival times might be higher than might be observed in an average study site. This has to be considered in the present multi-national, multi-center study.

Therefore, the assumption that the median PFS for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm could be 45 months might be too optimistic with regards to the expected composition of study centers. In order to account for that, a median PFS of 30 months is chosen (which is obtained by calculating the mean of the median PFS of 45 months for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm for the subgroup of 51 patients mentioned above and of the median of 14 months for the Octreotide LAR, i.e. (45 months +14 months)/2 ≈30 months). This would still constitute a clinical relevant improvement in PFS compared to the control group (Octreotide LAR).

Based on the above median PFS assumptions, an estimate of 162 patients was determined according to the following conditions:

- 81 patients per arm
- ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: median PFS of 30 months
- Octreotide LAR: median PFS of 14 months (PROMID study)
- Significance level 5% two sided (or 2.5% one-sided), power 90%
- Accrual period: 0 months (patient enrolment occurs over 14 months, but treatment is fixed at 72 weeks).
- Follow-up period: 18 months (corresponding to the length of treatment period)

An accrual period of 0 months results from the fact that the primary variable (PFS) will be investigated for all patients during the same study period (= follow-up period) of 18 months.

Based on these conditions, a total number of 75 events are expected.

As stated above, there are limitations in the data currently available to confirm the accuracy of the sample size calculations, based on the primary endpoint assumptions. The present phase III study is different from the source data studies. With respect to the PROMID and RADIANT-2 studies, both studies were double-blinded. In the PROMID study the control arm was a true placebo. With respect to the Erasmus MC phase I/II trial, patients enrolled in the study were assured to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment.

In order to ensure an adequately sized clinical trial it is necessary to have a realistic estimate for dropout rates. In the PROMID study the dropout rate was predicted to be 10% before the start of the study. At the interim analysis (Rinke A et al., 2009), 9 patients (21%) out of 42 patients in the Octreotide LAR treatment arm had withdrawn from the study. Four of the dropouts were because of withdrawal of consent, and five were because of adverse events. This contrasts with the dropout of only 3 patients in the placebo arm (2 – withdrawn consent, 1 – switched treatment). Since the patients were unaware of what treatment they received, one can expect the dropout rate of the Octreotide LAR arm to be a lower limit for the present phase III study, because there will be additional dropouts due to patient 'treatment awareness'. In addition, the treatment arm of the current phase III trial will have a much longer time span of follow-up and time to progression, meaning that virtually all of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treated patients will need to complete at least a full year follow-up, because very few will have progression during this period. Consequently, dropout rates (and intent to treat penalties) could also be expected to be high in this arm. For these reasons the study is planned to account for approximately 20% dropouts.

Therefore, controlling for a drop-out rate of approximately 20%, a total of 200 patients will be randomized and treated (100 patients in each treatment group).

The overall event rate in the trial will be monitored to assess the extent to which the trial is achieving the design assumptions. This could be undertaken by the Trial Management Group, blind to the treatment under which each event occurs. The determination of this overall event rate could trigger potential modfications to the trial design during the trial.

7.2 Populations in the Analysis

Before the database is locked and statistical analysis of study is initiated, all problematic cases where evaluability remains unclear will be *scrutinized* by a Data Review Committee. The data review committee will consist of the biostatistician assigned to the study, and the study manager of the CRO responsible for the execution of the study along with the responsible persons within the Sponsor. Other persons may be invited.

For analysis of study results, the following patient populations have been defined:

Full Analysis Set (FAS): consists of all patients randomized. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

Safety Set (SAF): consists of all randomized patients, who received at least one dose of study drug. Patients will be analyzed according to treatment received.

Per Protocol Set (PPS): consists of all randomized patients, who had no major protocol violations. The PPS will be identified prior to database lock. Major protocol deviations refer to deviations that potentially impact efficacy analysis materially, such as not following important inclusion/exclusion criteria (e.g. incorrect diagnoses), taking wrong study medication, etc.

The FAS will be used for all analyses of efficacy, demographics and baseline characteristics. The PPS will be used for the per-protocol analyses of primary objective and key secondary variables. The safety set will be used for all safety analyses.

7.3 Demographics and Other Patient Characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for the FAS and the PPS. The summary of demographics will also be provided for the safety set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. All background and demographic data will be listed in detail.

7.4 Previous and Concomitant Medication

Previous and concomitant medications will be coded using World Health Organization (WHO) dictionary. Type and incidence of previous and concomitant medications will be tabulated (generic terms).

7.5 Analysis of Efficacy

All inferential statistics will be interpreted at the 5% 2-sided level. The primary objective will be tested confirmatorily. All other efficacy variables will only be evaluated exploratorily, i.e. all reported p-values for all other efficacy variables will only be interpreted in an exploratory sense.

7.5.1 Primary Objective

The primary efficacy variable of this study is Progression Free Survival (PFS). PFS is defined as the time from start of study treatment to documented progression according to RECIST Criteria or death due to any cause, as evaluated by the Independent Review Committee, within 76 weeks of start of study treatment. Patients, who drop out due to toxicity and who therefore cannot receive the full treatment are included as having disease progression. If a patient has no progression and has not died, the patient will be regarded as censored in the context of a time to event analysis at the date of last adequate tumour assessment.

The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method, and the log-rank test will be used to compare the PFS between the two treatment groups. The primary efficacy analysis will be conducted for the FAS. In addition, the primary efficacy variable will be analyzed for the PPS.

7.5.2 Secondary Objectives

The secondary efficacy variables are: Objective Response Rate (ORR), Time to Tumour Progression (TTP) and Overall Survival (OS). These key secondary efficacy variables will be reported using the FAS and PPS.

ORR is defined in section 6.3.2. For patients who start another anti-cancer therapy (including surgery for cancer), the ORR will be calculated based on assessments prior to the start of new therapy only. Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups will be compared by Fisher's exact test.

TTP is defined as the time (number of days) from start of study treatment to objective tumour progression. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date).

OS is defined as the time from the date of start of study treatment to the date of death due to any cause or the date of last contact (censored observation) at the date of data cut-off.

OS and TTP will be similarly analyzed as the primary efficacy variable.

Survival curves will be compared by the log rank test. The null hypothesis will be investigated that the survival experience in the two groups is the same, i.e., there is no difference between the treatment groups in the probability of PFS, TTP, and OS at any time point (i.e.: $S_1=S_2$), against the two sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: $S_1 \neq S_2$).

The comparison of response rates by Fisher's exact test investigates the null hypothesis that the two treatment group proportions are equal (i.e.: $p_1=p_2$) against the two sided alternative hypothesis that the two treatment group proportions are not equal (i.e.: $p_1 \neq p_2$).

The following correlation analyses will be performed:

- the correlation of toxicity outcomes with body weight and body surface area;
- the correlation of clinical efficacy outcomes (ORR, PFS, OS, TTP) with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;
- the correlation of clinical efficacy outcomes (ORR, PFS, OS, TTP) with OctreoScan® tumour uptake score;

- the correlation of clinical outcome (ORR, PFS, OS, TTP) with serum levels of Alkaline Phosphatase (AP);
- Outcomes for both treatment groups will be evaluated in relation to objective tumour response, KPS, and other parameters of clinical relevance.

For this purpose the correlation coefficient according to Pearson and the correlation coefficient according to Spearman are calculated depending on the respective type of the respective variable.

Statistical analysis will be coordinated by the responsible CRO biostatistician. A detailed SAP giving more details of the analysis and presentation of the results that are outlined here will be finalized before the database is locked. Any deviations from the Statistical Analysis Plan will be justified in the Study Report.

Health related QoL will be assessed using the EORTC QLQ-G.I.NET21 questionnaire (Appendix 3), which will be filled in by the patient. Changes from baseline will be assessed every 12±1 week after the first treatment date until the End of Study, patient's progression or death. The impact of treatment on health related QoL will be assessed by comparison of the changes from baseline by means of Wilcoxon's rank sum test on an alpha-level of 5%.

7.6 Safety

The statistical analysis of safety data will be mainly descriptive in nature.

7.6.1 Adverse Events

All original AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ classes and preferred terms will be used in the analyses.

Type and incidence of AEs, as well as severity and relatedness to the study medication will be recorded and notified appropriately. Special attention will be given to those patients who prematurely discontinue the study or the study medication due to an AE, or who experience a severe AE or an SAE. The investigator and the monitor will ensure that information on serious adverse events immediately notified with a SAE form are consistent with information on the same event contained in the e-CRF and in the source documents.

The number and percentage of patients with at least one AE will be determined, overall and separately for both treatment groups. The rate of patients with at least one AE is compared between the two treatment groups using Fisher's exact test on an α-level of 5%.

These analyses will be performed additionally for AEs leading to premature discontinuation and for serious adverse events.

Summary statistics will also be provided according to the intensity and the causality assessment (i.e. relationship to study medication). Frequencies and percentages will be provided for all categories. Percentages are based on the number of AE episodes, i.e. the number of AE forms filled in, and not on the number of symptoms, as one AE might be coded with more than one code.

A summary of adverse events will be given according to the primary system organ class (SOC) and preferred term (PT). Frequencies and percentages will be given overall and by treatment group in separate columns for SOC followed by those for PT in alphabetical order. All AE symptoms are taken into account for calculations.

Based on the preferred term, additionally an overview will be given for the most frequent AEs according to the intensity and the causality assessment to the study medication. Frequencies of

symptoms will be presented in descending order and will be determined for each PT together with the associated frequencies of categories. The number and percentage of patients with an AE of the respective PT will be given as well.

7.6.2 Laboratory Tests

Descriptive statistics including shift tables will be generated for all laboratory tests performed (haematology, blood chemistry, and urinalysis), i.e. the actual values and the changes from pre-treatment by cross-tabulations (with classes for below, within, and above normal range).

Abnormal laboratory test results will be tabulated.

7.6.3 Vital Signs and ECG

The normal ranges for the vital signs are as follows:

- Pulse rate: 40 – 100 bpm
- Systolic blood pressure (SBP): 100 – 150 mmHg
- Diastolic blood pressure (DBP): 45 – 90 mmHg

Descriptive statistics (N, mean, median, minimum, maximum, 95% confidence interval for the mean, etc.) of the observed values as well as for the changes from baseline value will be created. Frequency tabulations with values within, below or above the normal ranges will be made.

ECG parameters will include heart rate (HR), RR interval, PR interval, QRS width and QT interval.

QT intervals will be corrected for heart rate. ECG results will also be evaluated by means of descriptive statistics (mean, median, 95% confidence interval for the mean, etc.) and frequency tabulations.

Graphical presentations might be created to facilitate the interpretation.

7.6.4 Physical Examination

Physical examination results will be tabulated; abnormalities will be listed.

7.6.5 Karnofsky Performance Score

Descriptive statistics for KPS of the observed values as well as for the changes from baseline will be created.

7.7 Dosimetry

Descriptive statistics for the dosimetry parameters will be created (for further details please refer to section 6.6.1).

7.8 Pharmacokinetics

A separate PK analysis plan and a separate report will be created for the PK data.

7.9 Interim Analysis

Not applicable. There are no interim analyses planned for this study.

7.10 Other Analysis

Study termination reasons will be tabulated.

Protocol deviations will be tabulated.

7.11 Handling of Missing Data, Outliers, Visit Window and Other Information

Details on visit windows, analysis phases and how to deal with missing data will be specified in the Statistical Analysis Plan.

8- ADVERSE EVENTS AND OTHER SAFETY ASPECTS

8.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a patient and which does not necessarily have a causal relationship with the study medication. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a study medication, whether or not causally related to the study medication. Symptoms of the underlying diseases are not considered AEs, except a significant change as assessed by the Investigator.

AEs will be reported from signing the ICF onwards until end of study. If the information of an untoward medical occurrence is collected before starting the intake of study medication, this information will be listed as a pre-treatment AE during statistical analysis.

During the 3-year long-term follow-up of the patient, the Investigator must report only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the Sponsor Safety Officer.

8.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;

  Note: "life-threatening" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly or birth defect;
- Requires in-patient hospitalisation or leads to prolongation of hospitalisation, with the exception of elective pre-planned hospitalisations.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for severe allergic reactions that do not result in hospitalisation.

If a patient becomes pregnant during treatment, this should be reported as if it were an SAE to the Sponsor Safety Officer.

The Investigator must report all SAEs by sending a completed SAE Reporting Form to the Safety Officer designee within 24 h of becoming aware of the event.

8.3 Criteria for Causal Relationship to the Clinical Study Medication

The investigator should indicate the probable cause of the specific SAE in the appropriate section(s) of the SAE Reporting Form:

Possible Causes of the Serious Adverse Event	
Check off all that apply	**Specify**
Pre-existing / underlying disease ❑	
Study treatment ❑	
Other treatment ❑	
Protocol-related procedure ❑	
Other (e.g., accident, new / intercurrent illness) ❑	

8.4 Criteria for Defining the Severity of an Adverse Event

National Cancer Institute Common Terminology for Adverse Events (CTCAE), Version 4.0 (Appendix 12) will be used for determining the severity of adverse events.

8.5 Investigator Reporting Requirements

Throughout the study, the study staff will question the patient in a non-directive way as to the occurrence of AEs. The patient will also be instructed upon signing the ICF to contact the Investigator to report any study medication or non-study medication-related adverse or unusual event that occurs during participation to the study.

The study staff will record all these events in the patient's medical records and e-CRF, whether observed by the Investigator, the investigational staff, or spontaneously reported by the patient.

The Investigator will provide a complete description of the event in standard medical terminology, the date of onset and termination, severity, relationship to the study medication, action taken regarding the study medication, any treatment given, the outcome, and whether or not the event is considered an SAE. If known, the Investigator should report the underlying illness or disorder rather than the individual signs and symptoms.

8.6 Reporting of Serious Adverse Events

In the case of an SAE, the Investigator must immediately (within 24 h of awareness or at the earliest possible time point) complete the SAE section of the e-CRF, reporting all information that is required by the Regulatory Authorities and contact the delegated Safety Officer designee, if needed. The name and contact details of the delegated Safety Officer designee will be available in the Investigator File (and will be updated when needed).

The minimum information required for immediate reporting is the event description, the Subject ID, the study medication concerned, and the identifiable reporter (Investigator or designee). Even if not all the facts are known, an initial report should be made. The Investigator must provide follow-up

information as soon as possible. If requested by the delegated Safety Officer designee, documents relevant to the diagnosis, treatment, and course of the event must be submitted (e.g. technical investigation reports, histology findings, hospital discharge documents). All documents must be blinded with respect to the patient's name.

When the Investigator determines that there is not more information likely to be available, a final report should be provided.

The Sponsor or delegated CRO will assume responsibility for appropriate reporting of AEs to the competent authorities and Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB) according to local laws and regulations.

SAEs will be recorded once the patient has provided written consent to participate in the study. The collection of SAE information will continue to be reported by the Investigator for each patient until 3 years after the end of the study only if the SAE is related to the product.

Deaths due to progression of the underlying midgut carcinoid tumours are considered SAEs and must be reported to the sponsor as detailed above. Nonetheless, the deaths occurring in the wake of a documented progression of the underlying cancer shall not be reported to the competent authorities and Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB).

8.7 Adverse Events of Special Interest

In addition to the Serious Adverse Events defined above, a set of potential risks deserve special attention even if they do not fulfill any of the seriousness criteria. These non-serious adverse events of special interest (AESI) occurring in patients enrolled in the investigational arm should equally be reported to the clinical trial's pharmacovigilance department for safety analysis so long as they occur during the 52-weeks after the 4th administration of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate. The following domains of pathology have transpired from ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate treatment and AESIs related to these categories should be reported to pharmacovigilance if so deemed by Investigators.

- **Hematotoxicity**: The main critical organ of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate treatment is the marrow. Significant hematotoxicity, defined as Grade 2 or higher thrombocytopenia, or Grade 3 or 4 of any other hematotoxicity (anaemia, leuko-/neutropenia) are considered dose-modifying toxicities in the study and should be reported as AESIs when not strictly fulfilling the criteria of serious adverse events. Haematological toxicities to be considered AESIs should not be limited to the CTCAE-defined Grades specified above but should be expanded to include hematotoxicities regardless of severity if accompanied by clinical consequences, i.e., infections in the presence of leuko-/neutro-/lymphopenia, hemorrhages / purpuric lesions under thrombocytopenia that is not explained by another coagulation disorder, dyspnea / fatigue in the presence of anaemia not otherwise explained by the underlying carcinoid syndrome or other co-morbidity).
- **Secondary haematological malignancies**: such as MDS and acute myeloid leukemia, should be reported in every case, either as SAEs or AESIs. Given their delayed latency of onset, their period of detection and follow-up should be as long as possible, i.e., at least covering 3 years counted from the end of the 48-weeks of the scheduled follow-up.
- **Nephrotoxicity**: Since ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate is cleared through the kidneys and reabsorbed by the kidneys, the kidneys have always been considered the ''critical organs''. An infusion of amino acid is used for kidneys protection by inhibition of tubular reabsorption

of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate. Pursuant to these risk minimization efforts and in addition to the criteria of dose-modifying toxicities and criteria of inclusion (at baseline and before subsequent treatments) pertinent to renal function measurements, renal and urinary tract toxicities should be considered AESIs. Investigators are encouraged to report, e.g., renal failure (ranging from significantly reduced measured or estimated creatinine clearance to clinically overt renal failure other than that of obvious non-IMP-induced origin), suspected radiation nephropathy of any type, such as radiation-induced thrombotic microangiopathy (manifested with, e.g., proteinuria, hypertension, edema, anaemia, decrease serum haptoglobin), or general symptoms and signs of acute radiation toxicity (e.g., increased frequency and urgency of urination, nocturia, dysuria, bladder spasm, bladder obstruction, genitourinary ulceration or necrosis).

- **Cardiovascular events**: In line with the objectives of planned safety pharmacology studies, the potential effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on blood pressure, heart rate, electrocardiogram changes justify reporting as AESIs all significant departures of these parameters from the pre-treatment baseline if they occur within reasonable propinquity of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate administration in the judgment of the Investigator. Likewise, clinically manifest and/or consequences of hypo-/hypertension, arrhythmias, cardiac conduction disturbances, and other cardiac pathologies evidenced by objective findings / changes on electrocardiogram or echocardiography should also be considered for AESIs reporting.

8.8 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterised. An assessment should be made at the last study-related visit for each patient. Certain long-term AEs cannot be followed until resolution within the settings of this protocol. In these cases follow-up will be the responsibility of the treating physician.

Since it is unpredictable how long such a follow-up might take, data from this follow-up generated after the patient's last study-related visit will be recorded by the Investigator. Full details regarding this follow-up will be described in the Clinical Study Report, if necessary.

If during AE follow-up the case has progressed to the level of "SAE", or if a new SAE is observed whose relationship to the study medication could not be ruled out, the situation must be reported immediately by the Investigator becoming aware of the information (considering that the "date of SAE onset" is the date of the first manifestations of that AE).

8.9 Procedure in Case of Pregnancy

Prior to clinical study enrolment, women of childbearing potential (see Appendix 7 for definition) must be advised of the importance of avoiding pregnancy until six months after the end of the last treatment and the potential risk factors for an unintentional pregnancy. Due to the CT scans foreseen during the study (every 12±1 weeks), woman should not procreate until the End of Study. The patient must sign an ICF documenting this discussion. During the clinical study, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual period).

If a patient or Investigator suspects that the patient may be pregnant prior to study medication administration, the study medication must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the patient must not receive study medication and must not be enrolled in the clinical study. If pregnancy is suspected while the patient is receiving study medication, the study medication must immediately be withheld if it can be done safely until the result of pregnancy testing is known. If pregnancy is confirmed, the Investigator must immediately terminate the patient from the study but follow the patient to determine the outcome. The study medication must be permanently discontinued if this can be done safely. If study medication is to be discontinued, it should be done in an appropriate manner and the patient must be withdrawn from the clinical study.

The Investigator must report any pregnancy associated with investigational product exposure including conceptions occurring until 6 months after the last study medication administration. The report should be carried out within 24 hours of pregnancy confirmation by sending a completed Pregnancy Reporting Form to the Safety Officer.

Appropriate pregnancy follow-up procedures should be considered if indicated. The Investigator must report follow-ups within 24 hours of the receipt of any new information on the course of the pregnancy, including perinatal and neonatal outcome, by sending a completed Pregnancy Reporting Form to the Safety Officer.

When the outcome of the pregnancy, delivery, and newborn fulfil the criteria of SAEs [e.g., spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried foetus)], the Investigator should respond in accordance with the reporting procedure for SAEs described in section 8.6. Additional information regarding the outcome of pregnancy (which is categorised as an SAE) is mentioned below.

Death of a newborn within 1 month after birth should be reported as an SAE regardless of its relationship with the study medication.

If an infant dies more than 1 month after birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as reasonably related by the Investigator.

In case of a delivery of a living newborn, the newborn's condition is evaluated at birth. The miscarried foetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

Every case of pregnancy requires expedited reporting by the Sponsor to the competent authorities and Independent Ethics Committee(s)/ Institutional Review Board(s) (IEC/IRB).

8.10 New Safety Information Affecting the Conduct of the Study

When new information, including "Dear Doctor Letters" but not limited to that, necessary for conducting the clinical study properly will lead to a protocol amendment, the Sponsor should inform all Investigators involved in the clinical study, the head of the study site, ethics committees, and Regulatory Authorities of such information, and when needed, should amend the patient information.

9- TERMINATION OF THE STUDY

Early termination of the study can occur in the following cases:

- When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the Investigator and applicable authorities.
- The Sponsor reserves the right to discontinue the study at any time for failure to meet expected enrolment goals.

Termination of a study site:

- If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor of the discontinuation and the reason for it.

10- OPERATIONAL, ETHICAL, AND ADMINISTRATIVE CONSIDERATIONS

10.1 Data Quality Control

10.1.1 Data Collection, Review, and Clarification

10.1.1.1 Data collection

The study will be monitored by the Sponsor or a designee according to the current SOP for the monitoring of studies.

Shortly before the study starts, the Study Monitor will meet with the Investigator and Investigational Staff involved reviewing the procedures regarding study conduct and recording of data in the e-CRF. During the study, the Investigator will permit the Study Monitor to verify coherence of recorded data in the e-CRF and the progress of the study at the centre as frequently as necessary. The Investigator will make the electronic data screens available, provide missing or corrected data, and sign the e-CRFs. Key data transcribed into the e-CRF will be reviewed against the source documents. Personal information will be treated as strictly confidential and will not be made publicly available. Any inconsistency between the source data and the data recorded in the e-CRF will be corrected.

Clinical data will be captured via Electronic Data Capture (EDC) using the HyperSuite-Hypernet XMR® system, a electronic CRF (e-CRF). The Investigator site staff will enter and edit the data via a secure network, with secure access features (userid, password). The study paper questionnaire EORTC QLQ-G.I.NET21 will be completed directly by the patient at the investigator's site. The Investigator will provide to insert into a specific form of the e-CRF the questionnaire's answers for each patient.

The Sponsor will ensure that appropriate Quality Control (QC) steps are included in the different clinical processes to adequately protect the study patients and the quality of the study data.

An independent Quality Assurance (QA) department, Regulatory Authorities and/or IECs/IRBs may review this study. This implies that auditors/inspectors have the right to inspect the study centre(s) at any time during and/or after completion of the study and have access to source documents, including the patient's file. By participating in this study, the Investigator(s) agree(s) to this requirement.

For any data transfer, measures will be undertaken to protect patient data handed over against disclosure to unauthorised third parties and patient confidentiality will be maintained at all times.

10.1.1.2 Data Review

All data relating to the study must be recorded in the e-CRFs provided by the Sponsor or designated CRO. These e-CRFs should always reflect the latest observations on the patient's participation in the study. Therefore, e-CRFs are to be completed as soon as possible after (or during) the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the study determinations are completed by the same individual who made the initial ones at baseline. The Investigator must verify that all data entries in the e-CRFs are accurate and correct. At the end of each visit he must approve the data using an electronic signature. This approval is used to confirm the accuracy of the data recorded. The electronic case report form must be kept current to reflect patient status at each phase during the course of the trial.

The monitor will review the e-CRFs and evaluate them for completeness and consistency. The e-CRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the e-CRFs. Once clinical e-CRF data have been

submitted, corrections of the data fields will be audit trailed, meaning that the reason for change, as well as the name of the person performing the change will be logged together with the date and time. Roles and rights of the site personnel responsible for entering the date into the e-CRF will be determined in advance.

10.1.1.3 Data Clarification

If corrections to an e-CRF are needed, the responsible monitor or data manager will raise a query in the electronic data capture application. The appropriate investigational staff will answer queries sent to the Investigator. This will be audit-trailed by the e-CRF application.

10.1.2 Study Documents

10.1.2.1. Source Documents

Source data must be available at the study centre to document the existence of the study patients and substantiate the integrity of the study data collected. They must include the original documents relating to the study, as well as the medical treatment and medical history documentation of the patient.

The source medical records should at least include the following information for each patient:

- Patient identification (name, date of birth, gender);
- Documentation of eligibility criteria, i.e. medical and medication history, physical examination, and confirmation of diagnosis, including pathology assessment report;
- Participation in study (including study number);
- Study discussed, signed and dated ICF;
- Dates of all visits;
- Pathology, laboratory and Specialist's (e.g., ECG, dosimetry, pharmacokinetics) reports;
- Images/scans (e.g., OctreoScan® and CT/MRI) and reports;
- Patient QoL questionnaires;
- Documentation that protocol-specific procedures were performed;
- Randomization number (if applicable), study medication start and end dates;
- Dispensation and return of study medication;
- Record of all AEs and other safety parameters;
- Record of all previous and concomitant therapies;
- Date of study completion or reason for early discontinuation (if applicable).

The following documents are considered as source documents as well: patient diaries, nurse records, and worksheets.

The author of an entry in the source documents must be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the e-CRF are consistent with the original source data.

10.1.3 Clinical Study Monitoring

The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that patients' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and ICH GCP, and that the data reported by the Investigator or designee are accurate, complete, and verifiable with the source documents. The Sponsor or delegated CRO is responsible for assigning (a) Clinical Study Monitor(s), who will monitor the study in accordance with the monitoring guidelines. A copy of their Monitoring Log will be obtained at the study close-out visits.

10.1.4 Direct Access to Source Data/Documents

The Investigator and the study centre must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IEC(s)/IRB(s) and/or relevant Regulatory Authorities. They must provide all study-related records, as well as source documents to these instances when they are requested to. The confidentiality of the patient's identity shall be well protected and consistent with local and national regulations when the source documents are patient to direct access.

10.1.5 Data Management

Data management activities will be coordinated by the CRO under supervision of the Sponsor.

Final review of the clinical data will be executed by Data-Management staff. The Data manager will generate queries for the clarification of unclear / missing / inconsistent data. The errors found will be assessed by the Data Manager of the study and Investigators will be involved in resolving them. All changes to the database will be automatically recorded in an audit trail file. All changes will be requested from the Investigator through the EDC system. If a change is necessary once the Investigator has no further access to the database, a query will be sent to the Investigator for confirmation of the change. The Investigator's signature is required to show he/she agrees with the change that was made. The process of data-entry and data-cleaning for all patients starts when the study is still in the phase of 'treatment / follow-up' and should be completed soon after the completion of the study. After all corrections to the data are made, the database will be "locked" and no data can be changed without adequate documentation.

Copies of the electronic CRF together with all data changes made will be supplied to the Investigator at the end of the trial. The Investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract. At the End of Study, a copy of all data-sets will be provided to the Sponsor on electronic support.

All study-specific processes and definitions will be described in the Data Management Plan. Coding of AEs and Medical History terms will be performed using MedDRA; previous and concomitant medication will be coded using WHO codes.

10.2 Ethics and Protection of Patient Confidentiality

10.2.1 Ethical Conduct of Clinical Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki (Appendix 1), GCP, ICH guidelines, and the applicable laws and regulations.

ICH-GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting study activities that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of the patients are

protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the study data are credible.

The Investigator and all study staff will conduct the study in compliance with the IEC/IRB approved version of this protocol. The protocol, ICF, any information provided to the patient, recruitment advertisements, and any amendments to these items will have IEC/IRB approval prior to their use in the study. Voluntary informed consent will be given by every patient in order to be screened for study eligibility and prior to the initiation of any study-related procedures. The informed consent process must meet all applicable local laws. The rights, safety, and well-being of the patient is the most important consideration and prevails over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities.

10.2.2 Authorities

The protocol, name, and study centre of the Investigators, the votes of the IEC(s)/IRB(s), as well as other locally required documents will be submitted to the Health Authorities of the participating countries, according to local requirements for review and approval before the beginning of the study. The Health Authorities will be informed about the end of the study. Individual patient medical information obtained as a result of this study is considered.

10.2.3 Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such information may only be given to a third party after approval of the patient, to the patient's general practitioner or to other appropriate medical personnel responsible for the patient's well-being.

The Sponsor, its board members, and its personnel shall not disclose any confidential information on patients obtained during the performance of their duties in the study without justifiable reasons.

All individuals and organisations involved in conducting the study and/or processing the study data, must pay very careful attention to protect the patients' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a patient (e.g. name or address). These details shall be processed in accordance with the applicable local and regional laws.

10.2.4 Patient Information/Written Informed Consent

According to ICH GCP (CPMP/ICH135/95) the patient must give consent to participate in the study, only after being fully informed by the Investigator of the nature, significance, and implications of the study, as well as to the associated risks involved. Such meetings must be carried out on an individual basis, and adapted to the educational background and previous knowledge of the patient. Participation to this meeting will be documented in the patient's file.

The patient will be instructed by the Investigator that the consent for study participation can be withdrawn at any time, without justifying a reason, and that no disadvantageous consequences will follow regarding further medical treatment. The Investigator shall ask for the reason of premature termination without violating the patient's rights (ICH GCP Definition 4.3.4).

Furthermore, the patient must be informed about insurance coverage and the corresponding patient obligations (see Patient Information). **The ICF must be personally dated and signed in duplicate by both the Investigator and the patient.** The patient receives 1 of the 2 original documents of the patient information and consent form **signed and dated** by both Investigator and the patient.

The other original of the signed ICF will be retained by the Investigator in the Investigator's File, who will confirm the patient's consent in the e-CRF. The patient will only be included in the study after written consent is given.

Furthermore, it is recommended that the Investigator inform the patient's general practitioner of his/her participation in the study, provided that the patient has a general practitioner and the patient agrees to disclose this information.

10.2.5 Patient Cards

After signing an ICF for participation in the study, each patient is given a patient card, which indicates the contact details of the Investigator (e.g. stamp with telephone number), the patient's Subject ID, as well as the medication number. The patient shall carry this card with him/her during participation in the study so that the Investigator may be contacted in case of emergency.

10.3 Administration

10.3.1 Arrangement for Use of Information and Publication of Clinical Study Data

All information regarding the investigational product under study in the outlined protocol and Sponsor's operations, such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by the Sponsor and not previously published, are considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes including publications and presentations without the Sponsor's written consent.

It is understood by the Investigator that the information developed during the conduct of this study is considered confidential and will be used by the Sponsor for the development of the specified investigational medication. This information may be disclosed as deemed necessary by the Sponsor to other Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this study and to ensure complete and thorough analysis, the Investigator is obligated to provide the Sponsor with complete test results and all data developed in this study, and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

Any publication or public presentation of the results of this study must be according to the Sponsor's standards. The first publication is multicentre and coordinated by the Sponsor. The Investigator agrees that before he/she publishes any results of this study, he/she shall send the draft manuscripts and copies of the information to be presented to the Sponsor at least 30 working days before submission to a publisher or presentation. The Sponsor reserves the right to review these materials before submission for publication or presentation. This is not intended to restrict or hinder publication or presentation but instead to allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator(s).

10.3.2 Documents and Records Related to the Clinical Study

The Investigator must retain e-CRFs and source documents of all enrolled patients (i.e. all patients who gave consent to be screened for the study), study medication disposition, and other documents required by regulation, in his/her possession or in an accessible area for at least 15 years after the completion of this study, or at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, if required by the

applicable regulatory requirements. The Sponsor will notify the Investigator when the records no longer need to be kept.

The Investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the Investigator relocate or dispose any study documents before obtaining the Sponsor's written approval.

If it becomes necessary for the Sponsor or the appropriate Regulatory Authority to review any documentation relating to this study, the Investigator must permit, with the approval of the patient, access to such reports.

Any difficulty in archiving and storage of clinical study documents must be discussed with the study monitor prior to the initiation of the study.

The data and information collected during this study will be reported in Study Report(s) by the Sponsor. In accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for study reports, a coordinating Investigator will review and sign the Study Report(s) for this study. The signing coordinating Investigator will be selected by the Sponsor from the Investigators who participate in this study, based on the level of participation, the significant level of clinical research, and adherence to the clinical study protocol.

10.3.3 Protocol Amendment and/or Revision

Any changes to the study, which arise after approval of the protocol, must be documented as protocol amendments and/or revisions. Depending on the nature of the amendment and/or revision, either IEC/IRB approval or notification is required. The changes will become effective only after the approval of the Sponsor, the Competent Authority, and the IEC/IRB (if applicable).

10.3.4 Qualification of the Investigators

The Investigator(s) should be qualified by education, language, training, and experience to assume responsibility for the proper conduct of the study. He/she should meet all qualifications specified by the applicable regulatory requirements and should provide evidence of such qualifications through an up-to-date curriculum vitae (Principal as well as all other Investigators) and/or other relevant documentation requested.

The Investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, the current Investigator's Brochure, the product information, and other information sources provided by the Sponsor.

The Investigator should be aware of, and should comply with, ICH-GCP and the applicable regulatory requirements.

The Investigator should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

10.4 Finance and Insurance

The disclosed financial interest of the Investigator must be reported prior to enrolment of the first patient into the study, following study centre completion, and 1 year following study completion. The Investigator should promptly update this information if any relevant changes occur during this period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of his/her participation to the study. For any Investigator(s) leaving the site prior to study completion, an Investigator Financial Disclosure Form should be obtained at the end of his/her participation.

10.4.1 Insurance of Patients and Others

The Sponsor has covered this study by means of insurance according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number, and the sum insured are provided in the Investigator's File.

10.4.2 Investigator Indemnity

The Sponsor shall be liable towards the patients in accordance with the provisions of the Clinical Study Law. Notwithstanding the foregoing; the Sponsor does not, however, agree to indemnify, defend, or hold the Investigator harmless against liability, damage, loss, cost or expense (including reasonable attorney's fees and expenses), including liabilities arising out of or in connection with claims of any nature by third parties, including, without limitation, in respect of bodily injury or death, arising out of or in connection with the negligence, wrongful acts or omissions or wilful misconduct of the Investigator, the Institution, or its affiliates.

Including but not limited to:

- The making of unauthorised representations and warranties concerning the study medication or the study;
- The failure to obtain a signed ICF;
- Non-compliance with applicable rules or regulations;
- Failure to conduct the study in accordance with this protocol.

A condition of this indemnity obligation is that, whenever the Investigator has information from which it may be reasonably concluded that an incident of bodily injury, sickness, disease, or death has occurred, the Investigator must immediately notice the Sponsor of all pertinent data surrounding any such incident, and, in the event a claim is made or a suit is brought, the Investigator will assist the Sponsor and cooperate in gathering information with respect to the time, place, and circumstances, and in obtaining the names and addresses of the injured parties and available witnesses.

The Investigator shall not, except at his/her own cost, voluntarily make any payment or incur any expense in connection with any such claim or suit withot the prior written consent of the Sponsor.

11- QUALITY ASSURANCE

The Sponsor or delegated CRO is implementing and maintaining QA and QC systems with written SOPs to ensure that studies are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or designee may arrange to inspect or audit the study at any or all study centres. The auditor is independent from the clinical monitoring and project management team at the Sponsor's site. The audit may include on-site review of regulatory documents, e-CRFs and source documents. The auditors will have direct access to these documents.

12- CLINICAL STUDY ORGANISATION

12.1 Independent Data Safety Monitoring Board

An Independent Data Monitoring Committee (IDMC) will evaluate safety throughout the study. The IDMC will be independent from the Sponsor, specific agents of the Sponsor, Investigators, and any other study oversight bodies. They will advise the Sponsor, Investigators and investigational sites regarding the continuing safety of study patients and the patients yet to be recruited to the study as well as maintaining validity and scientific merit of the study, The IDMC will review ongoing examinations of safety data and promptly give recommendations to continue, continue with modification, or terminate the study.

The IDMC monitoring plan will be provided as a separate charter.

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14- APPENDICES

Appendix 1 – Helsinki Declaration

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative.

If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix 2 – RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009)

The complete criteria are included in the published RECIST document (Eisenhauer EA et al., 2009), also available at http://www.eortc.be). A summary is provided below.

A2.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

A2.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix 9 on imaging guidance).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

A2.1.2 Non-measurable

Non-measurable are all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

A3.2 Specifications by Methods of Measurements

A3.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before first treatment.

A3.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-

ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix 9 for more details.

CT, MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. As is described in Appendix 9, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in Appendix 9.

***Ultrasound*:**

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix 9). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy:

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers:

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, Histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

A4.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In trials where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

A4.2 Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Figure 3 of Appendix 9.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement (see also the example in Figure 4 in Appendix 9). All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3 Response Criteria

4.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2. Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a

normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions. Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report themas being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm. Lesions that split or coalesce on treatment. As noted in Appendix 9, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see section 4.6 below). Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

4.5. Frequency of Tumour Re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how

often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently.

For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6 Confirmatory measurement/duration of response

4.6.1 Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies (see the paper by Bogaerts et al. in this Special Issue10). However, in all other circumstances, i.e. in randomized studies (phase II or III) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different trials and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Overview of renewed RECIST Criteria, Version 1.1.

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]
		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Appendix 3 – EORTC Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:			**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Did you have hot flushes?		1	2	3	4
32.	Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33.	Did you have night sweats?		1	2	3	4
34.	Did you have abdominal discomfort?		1	2	3	4
35.	Did you have a bloated feeling in your abdomen?		1	2	3	4
36.	Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37.	Have you had acid indigestion or heartburn?		1	2	3	4
38.	Have you had difficulties with eating?		1	2	3	4
39.	Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40.	Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41.	Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42.	Were you concerned about disruption of home life?		1	2	3	4
43.	Have you worried about your health in the future?		1	2	3	4
44.	How distressing has your illness or treatment been to those close to you?		1	2	3	4
45.	Has weight loss been a problem for you?		1	2	3	4
46.	Has weight gain been a problem for you?		1	2	3	4
47.	Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48.	Have you had aches or pains in your muscles or bones?		1	2	3	4
49.	Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:						
50.	Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51.	Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

Appendix 4 – Sandostatin® LAR Depot (Patient Information Leaflet, Novartis Pharmaceuticals UK Ltd)

SANDOSTATIN® LAR® 10, 20 and 30 mg powder and solvent for suspension for injection

(octreotide)

Note: Doctors and other health professionals involved in the administration of Sandostatin LAR please consult the Summary of Product Characteristics (SmPC) and the administration instructions following Section 6 of this leaflet.

Patient Information Leaflet

This medicine will be referred to as Sandostatin LAR in this leaflet.

What you need to know about Sandostatin LAR

Your doctor has decided that you need this medicine to help treat your condition.
Please read this leaflet carefully before you start to have your medicine. It contains important information. Keep the leaflet in a safe place because you may want to read it again.
If you have any other questions, or if there is something you don't understand, please ask your doctor or nurse.
This medicine has been prescribed for you. Never give it to someone else. It may not be the right medicine for them even if their symptoms seem to be the same as yours.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Sandostatin LAR is and what it's used for

Sandostatin LAR is a long-acting injection, often called a 'depot' injection because the active ingredient is released into the body slowly. This means that you don't have to have an injection every day. Sandostatin LAR contains the active ingredient octreotide (as the acetate). Octreotide is a synthetic form of the natural hormone, somatostatin. It helps stop the release of some hormones, including growth hormone, in the body.

Sandostatin LAR can be used for three conditions.

1. <u>To treat acromegaly</u>

Acromegaly is a condition where the body produces too much growth hormone. The level of growth hormone controls the growth of tissues, organs and bones. Too much hormone means the size of bones and tissues, especially in the hands and feet, is larger than normal. The symptoms of acromegaly include headache, excessive perspiration, numb hands and feet, tiredness, and joint pain. In most cases, the overproduction of growth hormone is caused by an enlargement in the pituitary gland (a pituitary adenoma).

Sandostatin LAR is used to treat people with acromegaly;

- when daily treatment with Sandostatin injection given subcutaneously (under the skin) has been proved to be satisfactory; (Switching to Sandostatin LAR means that the injections will be much less frequent.)
- when other types of treatment for acromegaly (surgery or radiotherapy) are not suitable or haven't worked;
- after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective;
- before surgery on the pituitary gland.

2. <u>To relieve stomach or bowel symptoms associated with certain tumours known as 'gastroenteropancreatic' tumours (rare tumours of the stomach, bowels or pancreas)</u>

Overproduction of specific hormones and other related natural substances can be caused by some rare conditions of the stomach, bowels or pancreas. This upsets the natural hormonal balance of the body, and results in a variety of symptoms, such as flushing, diarrhoea, low blood pressure, rash, and weight loss. Treatment with Sandostatin LAR helps to control these symptoms. It is generally given to people who have already responded well to treatment with daily Sandostatin injections.

3. <u>To treat neuroendocrine tumours located in the gut (e.g. appendix, small intestine or colon)</u>

Neuroendocrine tumours are rare tumours which can be found in different parts of the body. Sandostatin LAR is also used to control the growth of these tumours, when they are located in the gut.

2. Things to consider before you are given Sandostatin LAR

Some people MUST NOT be given Sandostatin LAR. Talk to your doctor if:

- You think you may be allergic to octreotide or to any of the other ingredients of Sandostatin LAR. (These are listed at the end of the leaflet).
- You are breastfeeding.

You should also ask yourself these questions before having Sandostatin LAR:

- Are you pregnant ?
- Do you have diabetes?
- Do you have thyroid problems, or have you had a disease which may have affected your thyroid?
- Do you have any problems with your liver, or have you had a disease which may have affected your liver?
- Have you ever suffered from gallstones or other stomach problems?
- Do you have a history of Vitamin B12 deficiency?

If the answer to any of these questions is YES, tell your doctor or nurse because Sandostatin LAR might not be the right medicine for you.

Are you taking other medicines?

Sandostatin interacts with a large number of other medicines. Tell your doctor or nurse if you are taking any of the following:
Insulin, or other drugs for diabetes
Ciclosporin
Cimetidine
Bromocriptine

Medicines to control blood pressure (beta-blockers or calcium channel blockers) or agents to control fluid and electrolyte balance (diuretics)
Medicines metabolised by the liver for example carbamazepine, digoxin and warfarin and terfenadine.
Always tell your doctor or pharmacist about all the medicines you are taking. *This means medicines you have bought yourself as well as medicines on prescription from your doctor.*

Will there be any problems with driving or using machinery?
No problems have been reported.

Other special warnings

- Your doctor may want to give you a check up from time to time while you are being treated with Sandostatin LAR.
- Growth hormone secreting pituitary tumours may sometimes expand and cause problems. Tell your doctor if you experience any problems with your eyes or sight.
- Tell your doctor if your stomach or bowel problems get worse.
- There is very little experience of using Sandostatin LAR in children.
- Sandostatin LAR should only be used during pregnancy if clearly needed. Tell your doctor if you are pregnant or want to become pregnant.
- Women of child bearing potential must use an effective contraceptive method during treatment with Sandostatin LAR.

3. Taking Sandostatin LAR

Your doctor will work out the correct dose for you.

If you receive Sandostatin LAR for the treatment of acromegaly, or for the relief of symptoms of gastropancreatic tumours, the starting dose is usually 20 mg Sandostatin LAR, which is given at 4-week intervals. After about the first 3 months of treatment with Sandostatin LAR, your doctor will probably want to reassess your treatment. This may involve measuring the levels of growth hormone or other hormones in your blood. Depending on these results, and on how you are feeling, the dose of Sandostatin LAR may need to be changed. The dose given in each injection can be reduced to 10 mg or, if the treatment is not fully effective, it can be increased to 30 mg. After the most suitable dose for you has been found, your doctor will probably want to reassess your treatment about every 6 months.

Sandostatin LAR must be injected into the gluteal muscles in your buttocks. For repeat injections the doctor or nurse will use the left and right buttocks alternately.

If you have had no problems with Sandostatin injected subcutaneously, you can immediately be changed over to Sandostatin LAR. If you haven't had Sandostatin before, the doctor will give you a test dose to see how you react, before switching to Sandostatin LAR, if appropriate.

Depending on why you are having Sandostatin LAR, you may need to continue having subcutaneous Sandostatin for about two weeks after your first injection of Sandostatin LAR until it becomes fully effective. You might also occasionally need to use subcutaneous Sandostation as well when your symptoms are troublesome.

When Sandostatin LAR is being used prior to surgery on the pituitary gland, you must have the last dose at least 3 to 4 weeks before the surgery.

If you receive Sandostatin LAR for the treatment of neuroendocrine tumours located in the gut, the usual dose is 30mg at 4-week intervals. Your doctor will decide how long you should be treated with Sandostatin LAR.

Ask your doctor or pharmacist if you are unsure about how much medicine you are being given or how often you are being given it.

What if you forget a dose?
If you forget to go for your appointment for your injection, you should contact your doctor as soon as possible to arrange another appointment.

What if you have had too much? (Overdose)
If you think you have been given the wrong dose talk to the nurse or doctor.

4. Possible side effects

Most people who are prescribed Sandostatin LAR benefit from taking it, but a few can be upset by it. If you are receiving this medicine on a long term basis then you will go to hospital from time to time to have regular check-ups.

Some side effects can be serious
Tell your doctor immediately if you notice that:
- Your face becomes flushed or swollen or you develop spots or a rash
- Your chest feels tight, you become short of breath or wheezy
- You feel faint, possibly as a result of a fall in blood pressure.

These might be the result of an allergic reaction.

If you develop any of the following see your doctor immediately:
- Prolonged/troublesome bloating of the stomach with pain
- Nausea/vomiting associated with drowsiness
- Feeling restless or giddy
- Yellowing of skin or the whites of your eyes
- Acute pancreatitis (sudden, severe pains in the lower stomach). This may happen within the first few hours or days of treatment and resolves itself upon drug withdrawal.

These other side effects have been reported in clinical trials:

Up to 1 in 10 people have experienced:
- Local pain at the site of the injection
- Stomach ache, nausea, wind, diarrhoea or constipation
- Headache
- Changes in blood sugar levels (Hyperglycaemia)
- Gallstones.

Up to 1 in 100 people have experienced:
- Slow heart beat
- Hair loss
- Itching
- Rash
- Shortness of breath

- Dizziness
- Loss of appetite
- Changes in blood sugar levels (Hypoglycaemia)
- Impaired glucose tolerance
- Stomach discomfort after a meal
- Vomiting
- Bloated stomach
- Loose faeces (stools)
- Discolouration of faeces
- Fat in your faeces (pale and fatty loose stools)
- Inflammation of the gallbladder
- Biliary sludge
- Yellow skin and eyes
- Abnormal liver function test results
- Changes in activity of the thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight, tiredness, feeling cold or sweating too much, anxiety or swelling at the front of the neck.

Up to 1 in 1,000 people have experienced:

- Dehydration
- Fast heart beat.

Patients taking Sandostatin have reported experiencing the following additional side effects:

- Anaphylaxis (a type of allergic reaction which causes difficulty in breathing or dizziness), allergy/hypersensitivity reactions
- Itchy rash
- Inflammation of the pancreas
- Liver inflammation (hepatitis); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine
- Irregular heart beat
- Liver dysfunction.

If any of the symptoms become troublesome, or if you notice anything else not mentioned here, please go and see your doctor. He/she may want to give you a different medicine.

5. How to store Sandostatin LAR

Keep all medicines out of the reach and sight of children.

Sandostatin LAR should be stored in the fridge (between 2°C and 8°C). Keep in the original packaging to protect it from light. Sandostatin LAR can be kept below 25°C on the day of injection, but it must be kept in the outer carton to protect it from light. The suspension must only be prepared immediately before injection.

Do not use Sandostatin LAR after the expiry date which is printed on the outside of the pack.

6. Further information

Sandostatin LAR contains the active ingredient octreotide (as octreotide acetate) in a powder (microspheres) for suspension for injection. The powder also contains the inactive ingredients poly(DL-lactide-co-glycolide) and mannitol. The powder is white to off-white in colour.

Before it can be used, the powder must be suspended in a special liquid (vehicle), which is provided in a pre-filled syringe. This liquid consists of sodium carboxymethylcellulose, mannitol and sterile water. The liquid is clear and colourless.

Once the powder has been mixed with the liquid to be used for suspending the powder, Sandostatin LAR suspension contains less than 1mmol (23mg) of sodium per dose i.e. essentially sodium free.

Sandostatin LAR is supplied in a kit which contains

- one 5 ml glass vial containing either 10, 20, or 30 mg octreotide powder (as the acetate),
- one syringe containing 2.5 mL of the liquid to be used for suspending the powder,
- two needles [40 mm (1.5 inch), 19 gauge].

The product licence holder is Novartis Pharmaceuticals UK Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, England.

Manufacturer responsible for batch release Novartis Pharmaceuticals UK Ltd, Wimblehurst Road, Horsham, West Sussex RH12 5AB, England.

This leaflet was revised in July 2011.

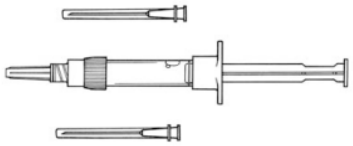
If you would like any more information, or would like the leaflet in a different format, please contact Medical Information at Novartis Pharmaceuticals UK Ltd, telephone number 01276 698370.

For the Medical and Pharmaceutical Professions

Instructions for intramuscular injection of Sandostatin LAR:

FOR DEEP INTRAGLUTEAL INJECTION ONLY
Content:

One vial containing
Sandostatin LAR

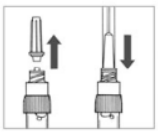


One prefilled syringe containing vehicle solution
+ two needles

Follow the instructions below carefully to ensure complete saturation of the powder and its uniform suspension before i.m. injection.

Sandostatin LAR suspension must only be prepared **immediately** before administration. Sandostatin LAR should only be administered by a trained health professional.

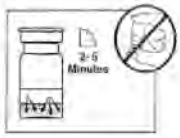
Allow the Sandostatin LAR vial and the vehicle syringe to reach room temperature.
Remove the cap from vial containing Sandostatin LAR. Ensure that the powder is settled at the bottom of the vial by lightly tapping the vial.



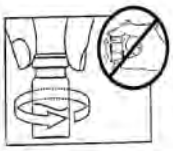
Remove the cap from the vehicle syringe.
Attach one of the supplied needles to the vehicle syringe.

Disinfect the rubber stopper of the vial with an alcohol swab.
Insert the needle through the centre of the rubber stopper of the Sandostatin LAR vial.

Without disturbing the Sandostatin LAR powder, gently inject all the vehicle into the vial by running the vehicle down the inside wall of the vial. **Do not inject the vehicle directly into the powder.** Withdraw the needle from the vial.

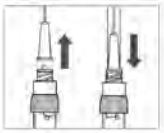


Do not disturb the vial until the vehicle has totally wetted the Sandostatin LAR powder (at least 2-5 minutes). **Without inverting the vial** check the powder on the walls and bottom of the vial. If dry spots exist, allow undisturbed wetting to continue. At this stage, prepare the patient for injection.



Once complete wetting has occurred, the vial should be moderately swirled for about 30 to 60 seconds until a uniform milky suspension is achieved. **Do not vigorously shake the vial** as this may cause the suspension to flocculate, making it unusable.

Immediately re-insert the needle through the rubber stopper and then, with the bevel down and the vial tipped at approximately 45 degree angle, slowly draw the contents of the vial into the syringe. **Do not invert the vial** when filling the syringe as this may affect the amount withdrawn.
It is normal for a small amount of suspension to remain on the walls and bottom of the vial. This is a calculated overfill.



Immediately change the needle (supplied).

Administration must occur immediately after the suspension has been prepared. Gently invert the syringe as needed to maintain a uniform suspension. Eliminate air from syringe.

Disinfect the injection site with an alcohol swab.
Insert needle into right or left gluteus and draw back to ensure that no blood vessel has been penetrated. Inject slowly i.m. by deep intragluteal injection with steady pressure. If the needle blocks, attach a new needle of the same diameter [1.1 mm, 19 gauge].

Sandostatin LAR must be given only by deep intragluteal injection, never i.v. If a blood vessel has been penetrated, attach a new needle and select another injection site.

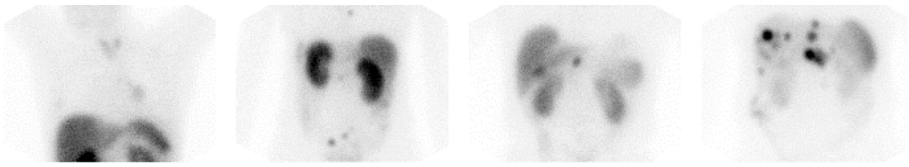
Appendix 5 – OctreoScan® Tumour Uptake and Extent of Tumour Burden Scales

The Tumour Uptake and the Extent of Tumour Burden scores are based soley on the planar images obtained at 24 hours after administration of OctreoScan® according to the Tumour Scoring methods described below. Planar image acquisition is to be performed according to the technical protocol specificed in Appendix 6 - Part 1.

Tumour Scoring

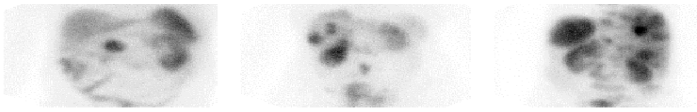
The intensity of Tumour Uptake and the Extent of Tumour Burden is to be scored according to simple scaling systems.

The Tumour Uptake score is determined by comparing the uptake of OctreoScan® (24 hour planar scintigrams) in the selected tumour to the uptake observed in the liver according to the following examples:



Tumour Uptake:	1) < Liver	2) ≈ Liver	3) > Liver	4) Very intense
Grade OctreoScan®:	(Excluded)			(>>Kidneys, spleen)

The Extent of Tumour Burden score is determined by assessing the number of OctreoScan® positive tumours and is scored according to following examples and descriptions:



Tumour Burden score OctreoScan®:	Limited	Moderate	Extensive

Limited: Up to 5 sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen).

Moderate: Multiple metastatic lesions in up to 2 parts of the body, neither qualifying for limited nor for extensive.

Extensive: Many tumour sites in ≥ 2 parts of the body, usually a combination of extensive liver and lymph node involvement or diffuse skeletal metastases; diffuse liver metastases with limited abdominal involvement does not qualify.

Appendix 6 - Part 1 - OctreoScan® Planar Imaging Protocol (ENETS Guidelines)

ENETS Guidelines

Neuroendocrinology 2009;90:184–189
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ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Somatostatin Receptor Imaging with ^{111}In-Pentetreotide

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Introduction

The purpose of this guideline is to assist nuclear medicine practitioners in performing, interpreting, and reporting the results of somatostatin receptor scintigraphy with ^{111}In-pentetreotide. It is not this guideline's aim to give recommendations on the use of PET tracers for somatostatin receptor imaging (SRI). The reason for this is that valid comparisons between state of the art SRI with ^{111}In-pentetreotide and these newer PET imaging methods are lacking, and that these newer methods have not been fully validated. Besides, because of the local production of PET radiopharmaceuticals and the diversity of peptide analogs that are applied, each with a different affinity profile and therefore potentially a different biodistribution and a different tumor detection sensitivity, it is virtually impossible to make guidelines for the application of these PET radiopharmaceuticals. The general recommendations on patient preparation and image interpretation, however, do apply. This guideline is adapted from the procedure guideline for somatostatin receptor scintigraphy with ^{111}In-pentetreotide, published by the Society of Nuclear Medicine [1]. ^{99m}Tc-Depreotide (Neotect®) is another commercially available somatostatin analog that has been approved specifically for the detection of lung cancer in patients with pulmonary nodules [2]. Because of the relatively high abdominal background and the impossibility of performing delayed imaging due to the short half-life of the tracer, it is less suited for the detection of abdominal neuroendocrine tumors [3]. Somatostatin is a regulatory peptide widely distributed in the human body, in particular in the central and peripheral nervous system, in the endocrine glands, in the immune system as well as in the gastrointestinal tract. In all these tissues, somatostatin action is mediated through membrane-bound receptors, of which five have been cloned (sst1–sst5) [4].They all belong to the family of G-protein-coupled receptors. Only sst2, sst5 and, to some extent, sst3 have a high affinity for the commercially available synthetic octapeptide octreotide [5].Somatostatin receptors are expressed in several normal human tissues, including brain, pituitary, gastrointestinal tract, pancreas, thyroid, spleen, kidney, immune cells, vessels and peripheral nervous system [6–9]. Somatostatin receptors have been identified in vitro in a large number of human neoplasias. A high incidence and density of somatostatin receptors are found in particular in neuroendocrine tumors, such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer and small cell lung carcinoma [10].Tumors of the nervous system including meningioma, neuroblastoma and medulloblastoma also very often express a high density of somatostatin receptors. But also tumors not known to classically originate from endocrine or neural cells, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma and gastric cancer can express somatostatin receptors. In the majority of these tumors, the sst2 receptor subtype is predominantly expressed, although low amounts of other somatostatin receptor subtypes may be concomitantly

present [11].It should also be emphasized that selected non-tumoral lesions may express somatostatin receptors. For instance, active granulomas in sarcoidosis express somatostatin receptors on epithelioid cells [12] and inflamed joints in active rheumatoid arthritis express somatostatin receptors, preferentially located in the proliferating synovial vessels [13].The expression of somatostatin receptor is therefore not specific for tumoral pathologies.

Imaging Results in Neuroendocrine and Other Tumors

Imaging results in tumors and other diseases are listed and subdivided according to reported sensitivity of SRI in table 1.

Normal Scintigraphic Findings and Artifacts

Normal scintigraphic features include visualization of the thyroid, spleen, liver, and kidneys, and the pituitary in some of the patients. Also, the urinary bladder and bowel are usually visualized to variable degrees. The visualization of the pituitary, thyroid, and spleen is due to receptor binding. Uptake in the kidneys is for the most part due to re-absorption of the radiolabeled peptide in the renal tubular cells after glomerular filtration. There is predominant renal clearance of the somatostatin analog, although hepatobiliary clearance into the bowel also occurs, necessitating the use of laxatives in order to facilitate the interpretation of abdominal images. False-positive results of SRI have been reported. In virtually all cases the term 'false-positive' is a misnomer because somatostatin receptor-positive lesions that are not related to the pathology for which the investigation is performed, are present. Many of these have been reviewed by Gibril et al. [46].The most common of these are listed in table 2 (which is not exhaustive). Diminished uptake in the spleen due to ongoing treatment with (unlabeled) octreotide may occur, which may be accompanied by a lower liver uptake. In case of hepatic metastases, this phenomenon may be misinterpreted as a better uptake in liver metastases. during octreotide treatment, the uptake of [^{111} In-DTPA^{0}]-octreotide in somatostatin receptor-positive tumors is also diminished. This may lead to a lower detection rate of somatostatin receptor-positive lesions, although there are also literature reports of improved tumor-to-background ratio after pretreatment with nonradioactive octreotide. A number of causes for a potential false-negative study interpretation are given in table 3.

Table 1. Sensitivity of SRI using pentetreotide

High sensitivity

- Pituitary tumors [14]
- GEPNETs
  - Gastrinomas [15, 16]
  - Nonfunctioning endocrine pancreatic tumors [17, 18]
  - Functioning endocrine pancreatic tumors except insulinomas [17, 18]
  - Carcinoids [19–22]
- Paragangliomas [23–25]
- Small cell lung cancer [26–29]
- Meningiomas [30, 31]
- Sarcoidosis and other granulomatous diseases [12, 32]
- Graves' disease and Graves' ophthalmopathy [33, 34]

Intermediate sensitivity

- Insulinomas [17, 35]
- Medullary thyroid carcinoma [36–38]
- Differentiated thyroid carcinoma (including Hurthle cell carcinoma) [39–41]
- Breast cancer [42]
- Lymphoma (NHL, HL) [43, 44]
- Pheochromocytoma [45]
- Astrocytoma [31]

High sensitivity = Detection rate >75%; intermediate sensitivity = detection rate 40–75%. Sensitivity is either patient- or lesionbased. GEPNET = Gastroenteropancreatic neuroendocrine tumor; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma

Common Indications

- Detection and localization of a variety of neuroendocrine and other tumors and their metastases
- Staging patients with neuroendocrine tumors
- Follow-up of patients with known disease to evaluate potential recurrence
- Selection of patients with metastatic tumors for peptide receptor radionuclide therapy and prediction of the effect of peptide receptor radionuclide therapy

Procedure

Patient Preparation

- When appropriate and clinically feasible, therapy with short-acting somatostatin analogs should be discontinued for 24 h before ^{111}In-pentetreotide administration. Such therapy can be resumed the day after injection of the radiopharmaceutical. Long-acting preparations should preferably be stopped 5–6 weeks before the study, and patients should be switched to shortacting formulations up to 1 day before the study. In follow-up studies, it may be more convenient to plan the injection of the radiopharmaceutical just before a new administration of the long-acting formulation is due. The reader should be aware that in such a condition, tumor and spleen uptake may be diminished due to receptor occupancy
- To reduce radiation exposure, patients should be well hydrated before and for at least 1 day after injection
- Laxatives are advised, especially when the abdomen is the area of interest. A mild oral laxative may be administered in the evening before injection and in the evening after injection. The need for bowel preparation should be assessed on an individual basis and laxatives should not be used in patients with active diarrhoea
- There is no need for fasting prior to the investigation
- The feasibility of the investigation in patients on hemodialysis (with imaging after dialysis) should be discussed with local nephrologists and radiation protection experts

Precautions

- In patients suspected of having insulinoma, an intravenous infusion of glucose should be available because of the potential for inducing severe hypoglycemia
- ^{111}In-pentetreotide should not be injected into intravenous lines for or together with solutions for total parenteral nutrition
- The usual precautions and considerations for nuclear medicine investigations in pregnant or breastfeeding women apply

Information Pertinent to Performing the Procedure

- A relevant history of the type of suspected or known primary tumor, its hormonal activity, the results of other imaging studies (CT or MRI), laboratory results (tumor markers), history of recent surgery, chemotherapy, radiation therapy, and octreotide therapy should be obtained

Table 2. Pitfalls and causes of potential misinterpretation of positive results

Radiation pneumonitis
Accessory spleen
Focal collection of stools
Surgical scar tissue
Gallbladder uptake
Nodular goiter
Ventral hernia
Bacterial pneumonia
Respiratory infections
Common cold (nasal uptake)
Cerebrovascular accident
Concomitant granulomatous disease
Diffuse breast uptake
Adrenal uptake

	Urine contamination
	Concomitant second primary tumor

Table 3. Causes of potential misinterpretation of negative results

	Presence of unlabeled somatostatin, either because of octreotide therapy or resulting from production of somatostatin by the tumor itself, may lower tumor detectability.
	Different somatostatin receptor subtypes have different affinities for the radioligand; variable tumor differentiation and receptor expression also influence tumor detectability. This may be important especially in patients with insulinomas and medullary thyroid carcinomas.
	Liver metastases of neuroendocrine tumors may appear iso-intense because of a similar degree of tracer accumulation by the normal liver. Correlation with anatomic imaging and/or SPECT imaging may be helpful

Radiopharmaceutical

- ^{111}In-pentetreotide is a [^{111}In-DTPA^{0}] conjugate of octreotide, a somatostatin analog (OctreoScan). The recommended administered activity is 185–222 MBq (5–6 mCi) in adults and 5 MBq/kg (0.14 mCi/kg) in children. The amount of pentetreotide injected is 10–20 μg; this dose is not expected to have a clinically significant pharmacologic effect. ^{111}In-pentetreotide is cleared rapidly from the blood. Excretion is almost entirely through the kidneys (50% of the injected dose is recovered in the urine by 6 h, 85% within 24 h). Hepatobiliary excretion is only about 2% of the administered dose
- The effective dose equivalent is 0.054 mSv/MBq. For a full patient dose of 222 MBq this is 12 mSv
- Before the administration of ^{111}In-pentetreotide, the labeling yield of the radiopharmaceutical should be tested according to the manufacturer's instructions
- The radiopharmaceutical should be used within 6 h of preparation
- ^{111}In-pentetreotide should be inspected visually before administration. Preparations containing particulate matter or color should not be administered

Image Acquisition

- Patients should void before imaging
- Images are acquired at 4 and 24 h or 24 and 48 h after injection. The 48-hour images may be needed when there is significant bowel activity at 24 h, which may potentially obscure lesions. Four-hour images may be obtained to enable evaluation before appearance of activity in the gut, but since the tumor-to-background ratio is lower at 4 h than at 24 and 48 h, some lesions may be missed at 4 h
- Planar images are acquired using a large-field-of-view gamma camera fitted with a medium-energy collimator. Symmetrical 20% energy windows are centered over both photopeaks of ^{111}In (173 and 247 keV) and the data from both windows are added. Planar localized images of the head, chest, abdomen, pelvis, and, if needed, the extremities can be acquired for 10–15 min/image. For whole-body images using a dual-head camera, acquisition should be for a minimum of 30 min (head to upper femurs) and longer for the entire body (e.g., a speed of up to 3 cm/min has been suggested) in a single pass. Since cervical lymph node metastases may be missed on the whole-body images, additional planar localized images of the head and neck, including lateral views, are suggested
- SPECT imaging of the appropriate regions, as indicated based on the clinical history, should be performed preferably with a multi-detector gamma camera. Early and delayed SPECT (i.e. 4 and 24 h after injection) may be helpful in distinguishing bowel activity from pathological lesions. If only one SPECT acquisition is obtained, acquisition at 24 h is preferred because of a higher target-to-background ratio. Although imaging systems may vary, an example of potentially useful acquisition parameters for a multi-detector system are the following: 3° angular sampling, 128x128 matrix, 360° rotation, 20–30 s/stop

Interpretation Criteria

- When possible, images should be evaluated in conjunction or fused with relevant anatomic images e.g., CT or MRI)
- The optimal time interval to localize tumors is 24 h after injection or later. At 4 h the background activity may be high. Nevertheless, early images may be important for comparison and evaluation of abdominal activity imaged at 24 h
- Knowledge of normal tissue accumulation of ^{111}In-pentetreotide is important for study interpretation. This radiotracer is seen in the pituitary, thyroid, liver, spleen, kidneys, bladder, and occasionally the gallbladder. Intestinal activity is usually not present at 4 h, but may be present at 24 h; images at 48 h may be necessary to clarify abdominal activity

Reporting

- In addition to the general information to be provided in each nuclear medicine report, it is suggested that the report contain the following information
- *Indication:* Results of laboratory tests (e.g., neuroendocrine tumor markers if applicable) or results of other imaging studies as well as other relevant history (known tumor and its type, recent radiation therapy, and chemotherapy)
- *Relevant medications:* For example, octreotide therapy and, when stopped, chemotherapy and/or laxatives, if given
- *Procedure description:* Timing of imaging relative to radiopharmaceutical administration; areas imaged; whether SPECT was performed and, if so, its timing and body areas included
- *Study limitations:* The referring physician may be reminded that some tumors may lack somatostatin receptors or the appropriate receptor subtypes and, therefore, may not be detected. The differential diagnosis should consider the many potential causes for a false-positive study, as listed in table 2

List of Participants

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

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Appendix 6 – Part 2 – OctreoScan® Summary of Product Characteristics

QUALITATIVE AND QUANTITATIVE COMPOSITION

OctreoScan is supplied as two vials which cannot be used separately.

1 vial 4920/A with 1.1 ml solution contains at activity reference time: (^{111}In) Indium(III)chloride 122 MBq

1 vial 4920/B contains:
Pentetreotide 10 µg

After reconstitution and labelling the solution contains ^{111}In-pentetreotide.

Physical characteristics of ^{111}In:
^{111}In is cyclotron produced and decays with a half-life of 2.83 days to stable cadmium.
Emission characteristics:
γ-rays 172 keV (90 % abundance)
γ-rays 247 keV (94 % abundance)
X-rays 23-26 keV

Radionuclidic purity: ^{111}In ≥ 99%, other γ-emitting nuclides ≤ 0.1%.
^{114m}In: max. 500 Bq per 1 MBq of ^{111}In at activity reference time/date.
Half-life of ^{114m}In: 49.51 days
For excipients see section 6.1.

PHARMACEUTICAL FORM

Vial A: Radiopharmaceutical precursor.
Vial B: Powder for solution for injection.
Vial A is a glass vial shielded with lead, containing a clear and colourless solution.
Vial B is a glass vial with grey rubber stopper and an aluminium crimp cap with orange flip off. It contains a white lyophilised powder.

CLINICAL PARTICULARS

Therapeutic indications

^{111}In pentetreotide specifically binds to receptors for somatostatin.
OctreoScan is indicated for use as adjunct in the diagnosis and management of receptor bearing gastro-entero-pancreatic neuroendocrine (GEP) tumours and carcinoid tumours, by aiding in their localisation. Tumours which do not bear receptors will not be visualised.

In a number of patients suffering from GEP or carcinoid tumours the receptor density is insufficient to allow visualisation with OctreoScan. Notably in approximately 50% of patients suffering from insulinoma the tumour can not be visualised.

Posology and method of administration

The dose for planar scintigraphy is 110 MBq in one single intravenous injection. Careful administration is necessary to avoid paravasal deposition of activity. For single photon emission tomography the dose depends on the available equipment. In general, an activity dose of 110 to 220 MBq in one single intravenous injection should be sufficient. No special dosage regimen for elderly patients is required.

There is limited experience on administrations in paediatric patients, but the activity to be administered in a child should be a fraction of the adult activity calculated from the bodyweight according to the following table (Paediatric Task Group, European Association of Nuclear Medicine).

3 kg = 0.1	4 kg = 0.14	6 kg = 0.19	8 kg = 0.23	10 kg = 0.27
12 kg = 0.32	14 kg = 0.36	16 kg = 0.40	18 kg = 0.44	20 kg = 0.46
22 kg = 0.50	24 kg = 0.53	26 kg = 0.56	28 kg = 0.58	30 kg = 0.62
32 kg = 0.65	34 kg = 0.68	36 kg = 0.71	38 kg = 0.73	40 kg = 0.76
42 kg = 0.78	44 kg = 0.80	46 kg = 0.82	48 kg = 0.85	50 kg = 0.88
52-54 kg = 0.90	56-58 kg = 0.92	60-62 kg = 0.96	64-66 kg = 0.98	68 kg = 0.99

Scintigraphy takes place approx. 24 hours after administration. When activity in the abdomen is observed at 24 hours which cannot be interpreted with certainty as uptake in tumour or activity in bowel

contents, scintigraphy should be repeated at 48 hours. In some cases, scintigraphy after 4 hours gives acceptable results. Physiologic uptake occurs in spleen, liver, kidneys and bladder. Thyroid, pituitary and intestines are visible in most patients.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
No specific contraindications have been identified.
For use during pregnancy and lactation see below.

Special warnings and special precautions for use

Because of the potential hazard of the ionizing radiation ^{111}In-pentetreotide should not be used in children under 18 years of age, unless the value of the expected clinical information is considered to outweigh the possible damage from radiation.

Administration of a laxative is necessary in patients not suffering from diarrhoea, to differentiate stationary activity accumulations in lesions in, or adjacent to, the intestinal tract from moving accumulations in the bowel contents.

In patients with significant renal failure administration of ^{111}In-pentetreotide is not advisable because the reduced or absent function of the principal route of excretion will lead to delivery of an increased radiation dose (E.D.E. 1.9E-01 mSv/MBq). Administration should be considered only when the possible damage from radiation is outweighed by the potential diagnostic information. Interpretable scintigrams may be obtained after haemodialysis during which the high background activity can at least partially be removed. Prior to dialysis images are non-diagnostic because of activity in the circulation. After dialysis a higher than usual uptake in liver, spleen and intestinal tract, and a higher than usual activity in circulation, were observed.

^{111}In-pentetreotide not bound to receptors, and non-peptide bound ^{111}In, are rapidly eliminated through the kidneys. To enhance the process of excretion, in order to reduce background noise and to reduce the radiation dose to kidneys and bladder, a liberal fluid intake (at least 2 litres) is required for 2 or 3 days following administration.

In diabetic patients, receiving high doses of insulin, the administration of pentetreotide may cause paradoxical hypoglycaemia via a temporary inhibition of glucagon secretion.

Regarding patients on octreotide therapy it is recommended to withdraw this therapy temporarily to avoid a possible blockade of somatostatin receptors. This recommendation is given on empirical grounds, the absolute need for such measure has not been demonstrated. In some patients the withdrawal of therapy might be not tolerated and may cause rebound effects. This is notably the case in insulinoma patients, where the danger of sudden hypoglycaemia must be considered, and in patients suffering from the carcinoid syndrome.

If the clinician responsible for the patients therapeutic management considers withdrawal of octreotide therapy tolerable a three days withdrawal period is recommended.

Positive scintigraphy with ^{111}In-pentetreotide reflects the presence of an increased density of tissue somatostatin receptors rather than a malignant disease. Furthermore positive uptake is not specific for GEP- and carcinoid-tumours. Positive scintigraphic results require evaluation of the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. An increase in somatostatin receptor density can also occur in the following pathological conditions: tumours arising from tissue embryologically derived from the neural crest, (paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas), tumours of the pituitary gland, endocrine neoplasms of the lungs (small-cell carcinoma), meningiomas, mamma-carcinomas, lympho-proliferative disease (Hodgkin's disease, non-Hodgkin lymphomas), and the possibility of uptake in areas of lymphocyte concentrations (subacute inflammations) must be considered.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Therefore, radiation protection precautions in accordance with national regulations must be taken.

Interaction with other medicinal products and other forms of interaction

No drug interactions have been reported to date.

Pregnancy and lactation

There is no experience with the use of OctreoScan in pregnant women. When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation have to be considered.

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. The administration of the maximal diagnostic activity of 220 MBq to the patient results in an absorbed dose to the uterus of 8.6 mGy. In this dose range lethal effects and the induction of malformations, growth retardations and functional disorders are not to be expected; however the risk for the induction of cancer and hereditary defects may be increased.Therefore, OctreoScan should not be used during pregnancy unless clearly necessary.

It is not known whether ^{111}In pentetreotide is excreted into the breast milk. Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If administration during lactation is considered necessary, breast feeding has to be discontinued and the expressed milk has to be discarded.

Effects on the ability to drive and use machines

^{111}In-pentetreotide does not affect the ability to drive or to use machines.

Undesirable effects

Adverse effects attributable to the administration of OctreoScan are uncommon (>1/1000, <1/100). Specific effects have not been observed.

The symptoms reported are suggestive of vasovagal reactions or of anaphylactoid drug effects.

The withdrawal of octreotide therapy as a preparatory step to scintigraphy might provoke severe adverse effects, generally of the nature of a return of the symptoms seen before this therapy was started.

Exposure to ionising radiation can lead to cancer or development of hereditary defects. As most diagnostic nuclear medicine investigations involve levels of radiation less than 20 mSv (effective dose), these adverse events can be expected with a low probability. However, with this product when performing SPECT this level might be exceeded. The EDE in a 70 kg individual with normal renal function is maximally 26 mSv. The higher dose may be justified under some clinical circumstances.

This product contains no excipients that have a recognised action or effect, or knowledge of which is important for safe and effective use of the product.

Overdose

The pharmaceutical form (monodose injection) makes inadvertent overdosing improbable. The renal elimination of ^{111}In-pentetreotide, not bound to receptors, and of non-peptide bound ^{111}In can be enhanced by administration of fluids.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals for tumour detection.
ATC: V09I B 01.

OctreoScan attaches to somatostatin receptors in tissues where, as consequence of disease, the cell-surfaces contain these receptors in a more than physiologic density. In individual patients, where the disease did not lead to an increased receptor density, scintigraphy will not be successful.

In carcinoid and GEP-tumours the prevalence of increased receptor density in the tumour-tissue in general is rather high.

Only limited studies of pharmacodynamic effects have been performed. The in vitro biological activity is approximately 30% of the biological activity of natural somatostatin. The in vivo biological activity, measured in rats, is less than that of equal amounts of octreotide. Intravenous administration of 20 µg of pentetreotide resulted in some patients in a measurable but very limited decrease of serum gastrin and serum glucagon levels of less than 24 hours duration.

Pharmacokinetic properties

Approximately 80% (resp. 90%) of intravenously administered radiolabelled pentetreotide is eliminated through the urinary system in 24 (resp. 48) hours. ^{111}In-pentetreotide is taken up by the following organs:

liver (approx. 2% at 24 hours) and spleen (approx. 2.5% at 24 hours). Uptake in thyroid and pituitary occurs but not reproducibly. The uptake in kidneys is partly a reflection of ongoing elimination through the urine and partly due to delayed excretion by the kidney. The elimination via the gallbladder and subsequently the faeces is approx. 2% of the administered activity dose in patients with normal intestinal function.

Up to 6 hours post-administration radioactivity in urine is predominantly intact ^{111}In-pentetreotide. Thereafter, increasing amounts of non-peptide-bound activity are excreted.

Preclinical safety data

Preclinical safety testing did not yield remarkable findings. No testing has been done on carcinogenic potential nor of the influence of pentetreotide on fertility or on embryotoxicity.

Radiation dosimetry

The following radiation dosimetry are calculated according to the MIRD system. The data are given in ICRP publication 80 in 1999.

"According to the biokinetic model described in ICRP 80 intravenously injected 111In-pentreotide is assumed to be immediately taken up in liver, spleen, kidneys and thyroid, while the rest is assumed to be homogeneously distributed in the remainder of the body. The experimentally found retention data is best described by mono- or bi-exponential functions. The biokinetic data come from patients with carcinoid tumours and endocrine tumours in the GI-tract. Uptake in tumour tissue present in any given organ may therefore be included in the published organ uptake values. The main route of excretion is via the kidneys and less than 2 % is excreted in faeces. An observed excretion of 85 % via urine after 24 h fits well with the model. The small excretion via the GI tract is not included in the model, since its contribution to the absorbed dose in normal circumstances is negligible."

Organ(s)	F_s	$T_{1/2}$	a	$\bar{A}_s/A_0$
Liver	0.06	2 h	0.40	2.59 h
		2.5 d	0.30	
		70 d	0.30	
Spleen	0.05	2.5 d	1.00	2.30 h
Kidney	0.06	2.5 d	1.00	2.76 h
Thyroid	0.001	2.5 d	1.00	2.76 min
Other organs and tissues	0.829	3 h	0.90	6.90 h
		2.5 d		
Bladder	1.00			
Adults and 15 years				1.63 h
10 years				1.40 h
5 years and 1 year				54.3 min

F_s	fractional distribution to organ or tissue
$T_{1/2}$	biological half-time for uptake or elimination
a	fraction of F_s taken up or eliminated with the corresponding half-time. A minus sign indicates uptake.
$\bar{A}_s/A_0$	cumulated activity in organ or tissue per unit of administered activity

Absorbed dose per unit activity administered (mGy/MBq)

Organ	Adult	15 Years	10 Years	5 Years	1 Year
Adrenals	5.8E-02	7.5E-02	1.2E-01	1.7E-01	3.0E-01
Bladder	2.0E-01	2.5E-01	3.1E-01	4.6E-01	8.2E-01
Bone surfaces	2.7E-02	3.4E-02	5.0E-02	7.6E-02	1.5E-01
Brain	9.6E-03	1.2E-02	2.0E-02	3.3E-02	5.8E-02
Breast	1.2E-02	1.5E-02	2.3E-02	3.7E-02	6.8E-02
Gall bladder	5.2E-02	6.3E-02	9.2E-02	1.4E-01	2.2E-01
GI- tract					
Stomach	4.3E-02	5.0E-02	7.8E-02	1.1E-01	1.8E-01
SI	2.9E-02	3.8E-02	5.9E-02	9.1E-02	1.6E-01
Colon	2.9E-02	3.6E-02	5.5E-02	8.9E-02	1.5E-02
(ULI	3.0E-02	3.7E-02	5.8E-02	9.4E-02	1.6E-01)
(LLI	2.7E-02	3.4E-02	5.0E-02	7.6E-02	1.3E-01)
Heart	2.5E-02	3.2E-02	4.9E-02	7.1E-02	1.3E-01
Kidneys	4.1E-01	4.9E-01	6.7E-01	9.6E-01	1.6E+00
Liver	1.0E-01	1.3E-01	2.0E-01	2.7E-01	4.8E-01
Lungs	2.3E-02	3.0E-02	4.4E-02	6.8E-02	1.2E-01
Muscles	2.0E-02	2.6E-02	3.8E-02	5.7E-02	1.1E-01
Oesophagus	1.4E-02	1.9E-02	2.8E-02	4.4E-02	7.8E-02
Ovaries	2.7E-02	3.5E-02	5.1E-02	8.1E-02	1.4E-01
Pancreas	7.2E-02	8.8E-02	1.3E-01	2.0E-01	3.2E-01
Red marrow	2.2E-02	2.7E-02	3.9E-02	5.3E-02	8.7E-02
Skin	1.1E-02	1.3E-02	2.1E-02	3.3E-02	6.2E-02
Spleen	5.7E-01	7.9E-01	1.2E+00	1.8E+00	3.1E+00
Testes	1.7E-02	2.3E-02	3.5E-02	5.5E-02	1.0E-01
Thymus	1.4E-02	1.9E-02	2.8E-02	4.4E-02	7.8E-02
Thyroid	7.6E-02	1.2E-01	1.8E-01	3.7E-01	6.9E-01
Uterus	3.9E-02	4.9E-02	7.1E-02	1.1E-01	1.9E-01
Remaining organs	2.3E-02	2.8E-02	4.2E-02	6.3E-02	1.1E-01
Effective dose per unit administered (mSv/MBq)	**5.4E-02**	**7.1E-02**	**1.0E-01**	**1.6E-01**	**2.8E-01**

For an administered maximal recommended activity of 220 MBq the effective dose is 12 mSv (in an adult of 70 kg).

PHARMACEUTICAL PARTICULARS

List of excipients

Vial 4920/A
Hydrochloric acid
water for injections
Ferric Chloride Hexahydrate

Vial 4920/B
Sodium citrate dihydrate
citric acid monohydrate
inositol
gentisic acid
After reconstitution and labelling the pH of the aqueous solution is 3.8-4.3. The ready to use solution does not contain a preservative agent.

Incompatibilities

Major incompatibilities: not known. After reconstitution and labelling OctreoScan may be diluted with 0.9% sodium chloride solution. Do not mix the injectate with any other solution in order to avoid possible incompatibilities.

Shelf life

Vial A and by consequence vial B of OctreoScan expire 24 hours after the activity reference time/date of the ^{111}In. Activity reference time/date and expiry time/date are both stated on the label on the shielding (sealed container) and appear in the documents that accompany each shipment. After reconstitution and labelling the solution must be used within 6 hours.

Special precautions for storage

The vials A and B are to be stored below 25 °C. Storage should take place in accordance with national regulations for radioactive materials. Store the ready to use solution below 25°C during the prescribed shelf life.

Nature and contents of container

Both 10 ml vials comply with the requirements for glass Type I, Ph.Eur. The vial containing pentetreotide is closed with a butylrubber stopper. The vial containing 111In-indium chloride is closed with a teflon-coated butylrubber stopper. Both vials are sealed with an aluminium crimp cap. OctreoScan is supplied as one pack containing two vials that cannot be used separately, one of which has a lead shielding. Both vials are packed in a closed, folded tin. Enclosed in the tin is a Sterican Luer Lock 0.90 x 70 mm / 20 G x 2 4/5 needle to be used for the labeling procedure.

Instructions for use/handling

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides.
This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

Instructions for labelling

1 Add the contents of vial A (^{111}In-chloride) to vial B (lyophilised pentetreotide) to obtain the product Indium (^{111}In) pentetreotide; only the Sterican (0.90 x 70) needle supplied with the shipped patient dose should be used to remove the indium chloride from its vial
2 Observe an incubation period of 30 minutes following the reconstitution
3 The preparation may be diluted with 2-3 ml of 0.9% sodium chloride solution if a larger volume is desired for easier handling in the syringe
4 The solution must be clear and colourless, this can be checked behind a lead wall containing a lead glass window. If the solution does not comply it should be discarded.
5 Use a tiny sample of this (diluted or not) volume for the quality control, which is described in the following paragraph
6 The solution is ready for use.

N.B.: FOR THE RECONSTITUTION DO NOT USE ANY OTHER ^{111}IN-CHLORIDE SOLUTION THAN THE ONE SUPPLIED IN THE SAME CONTAINER THAT HOLDS THE LYOPHILISED PENTETREOTIDE

Instructions for quality control

Analysis of ^{111}In-bound peptides versus ^{111}In-bound non-peptide compounds may be done on silicagel impregnated glass fiber strips (ITLC SG by GELMAN, cat.nr.61885). Prepare a thoroughly dried strip, approx. 10 cm long and 2.5 cm wide by marking a starting line at 2 cm, with additional marks at 6 and 9 cm. Apply 5 to 10 µl of the reconstituted and labelled solution to the starting line and develop in freshly prepared sodium citrate solution 0.1M, adjusted with HCl to pH 5. In approximately 2-3 min the front will have reached the 9 cm mark. Cut the strip at the 6 cm mark and measure the activity of both halves.

Non-peptide bound ^{111}In moves with the front. Requirement: The lower end of the chromatogram should contain ≥ 98% of the applied activity.

Instructions for waste disposal

Unused ^{111}In activity or unused OctreoScan should be allowed to decay until the activity has dropped to such a low level that, according to local
regulations, it is no longer considered radioactive. Then it may be disposed of as harmless waste. Unused vials with lyophilized pentetreotide may be disposed of as harmless waste.

Waste must be disposed of according to national regulations for radioactive material.

Appendix 7 – Precautions for Pregnancy

Men and women should not procreate until six months after the date of their last treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Due to the CT scans foreseen during the study (every 12±1 weeks), woman should not procreate until the end of the study.

It is noteworthy that β-HCG may be secreted by a small percentage of NETs, such that, in addition to being a pregnancy marker it also is a tumour marker. Consequently, NET female patients with positive β-HCG at baseline can be eligible to enter the study and receive treatment if pregnancy can be excluded by lack of expected doubling of β-HCG. Normally in pregnant subjects β-HCG doubles every 2 days during the first 4 weeks of pregnancy and every 3 ½ days by weeks 6 to 7.

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral ovariectomy) or is not postmenopausal (defined as amenorrhoea >24 consecutive months, and for women on hormone replacement therapy, only with a documented plasma follicle-stimulating hormone level >35 mIU/mL). Even women who are using oral, implanted or injected contraceptive hormones, an IUD, or barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, are practicing abstinence or where the partner is sterile (e.g. vasectomy) should be considered to be of childbearing potential. Postmenopausal women who have fertilised eggs implanted are also considered to be of childbearing potential.

Acceptable methods of contraception may include total abstinence at the discretion of the Investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensures compliance. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 6 months after investigational drug discontinuation.

All women of childbearing potential must use a double-barrier method of birth control or practice continuous abstinence from heterosexual contact throughout the study and for six months after the end of the last treatment.

Appendix 8 – ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Administration and Amino Acid Co-Infusion Scheme; Examples of Infusion Methods

Granisetron 3 mg is injected intravenously. The amino acid solution and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (22-25 mL) are administered in parallel by peripheral vein infusion in one arm at a constant infusion rate. The infusion with amino acids starts 30 minutes before the start of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion, and runs for a total of 4 h. The infusion is performed through pumps or any other infusion system. Table 11 shows the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration with amino acid co-infusion scheme.

Table 11: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate[1] Administration and Amino Acid Co-Infusion Schemes.

Preparation	Starting Time (h)	Infusion Rate (ml/h)	Duration (h)
Granisetron 3 mg (or alternative)	0	Bolus	-
Amino Acids: 2 L solution	0	500	4
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate[1]	0.5	50	0.5
Saline solution*	1.0	50	0.5

[1] ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be infused directly into the line. The line must be flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Examples of Infusion Methods

Example 1: Two Pumps Method

Two infusion pumps (pump 1 and pump 2) infuse the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and amino acids solution. A standard infusion set is connected to each pump and allows the infusion of the two pharmaceuticals products (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and amino acid solution) independently one each other.

The infusion set consists of:

1- a pre-filled, sterile container (glass bottle) of physiological solution that permit the fluid to flow one drop at a time, making it easy to see the flow rate (and also reducing air bubbles);

2- a long sterile tube with a clamp to regulate or stop the flow;

3- connectors to allow "piggybacking" of another infusion set onto the same line. This second line is connected to the amino acids solution bottle (pump 1) and to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate vial (pump 2).

By means of a 3 way cock another sterile tube guarantees the connection of the tube coming from the physiological solution bottle and the tube coming from the second bottle (amino acid solution in the case of the pump 1 or ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in the case of pump 2) to the device (the infusion pump) that allows precise control over the flow rate and total amount of products delivered. The confluence of the two fluids that flows into the l vein infusion tube is allowed by another cock.

A scheme of the pumps infusion method is shown in Figure 1.

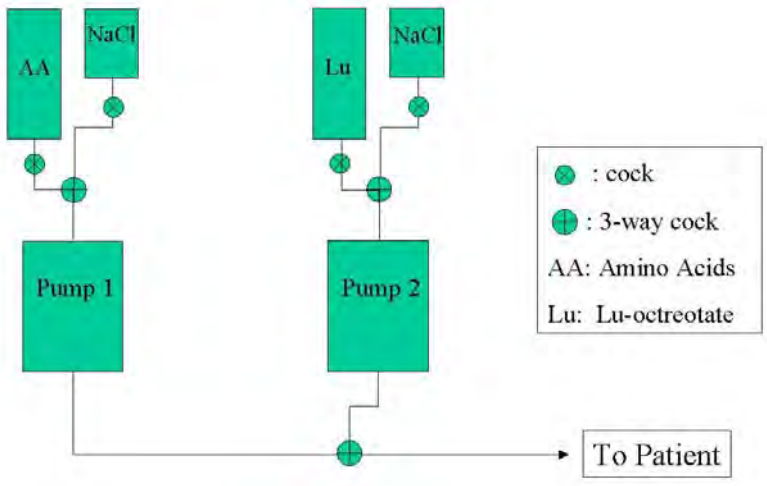


Figure 1: Two Pumps Infusion Method.

Example 2: Flebo Infusion Method

The flebo infusion method is schematically presented in Figure 2. It consists of a container for a vial of radiopharmaceutical made of polymethyl methacrylate with a cavity capable of containing the vial of radiopharmaceutical, and of a lid screwed onto the receptacle for closing the container, said lid presenting a central through-hole. A set, in combination with this container with the vial of radiopharmaceutical, consisting of a bottle of saline solution and two infusion catheters, enhances the radioprotection during the infusion of a radiopharmaceutical in an infusion operation.

In an infusion operation, saline bottle **4** is conventionally suspended in a cradle **7** attached to a stand **8**, equipped with a support shelf **9**. The first infusion catheter is inserted with the first needle **50** in the cap of bottle **4**, while the second needle **52** is inserted, via flared portion **27** and central through-hole **26** of lid **2**, into the cap of radiopharmaceutical vial **3** in such a way as not to be immersed in the pharmaceutical.

The second infusion catheter **6** also has its first needle **60** inserted via flared portion **27** and through-hole **26** of lid **2**, into the cap of the vial of radiopharmaceutical, whereas the second needle **62** is inserted in the brachial vein B of a patient. The first needle **60** is long enough to touch the bottom of the vial of radiopharmaceutical, where it must be held in place for the complete extraction of the radiopharmaceutical, as shown in Figure 2B.

The provision of flow via the bottle of saline solution **4**, the first infusion catheter **5**, vial **3** in container **1-2**, and the second infusion catheter **6** allows the radiopharmaceutical to be delivered by gravity. The saline solution is fed from bottle **4** into radiopharmaceutical vial **3** with flow regulation by means of flow-regulator **51**. The influx of saline brings about an increase in pressure in

radiopharmaceutical vial **3** which has its entire contents aspirated by the second infusion catheter **6**, the flow rate of which is regulated by flow-regulator **61**. (See US Patent 7842023)

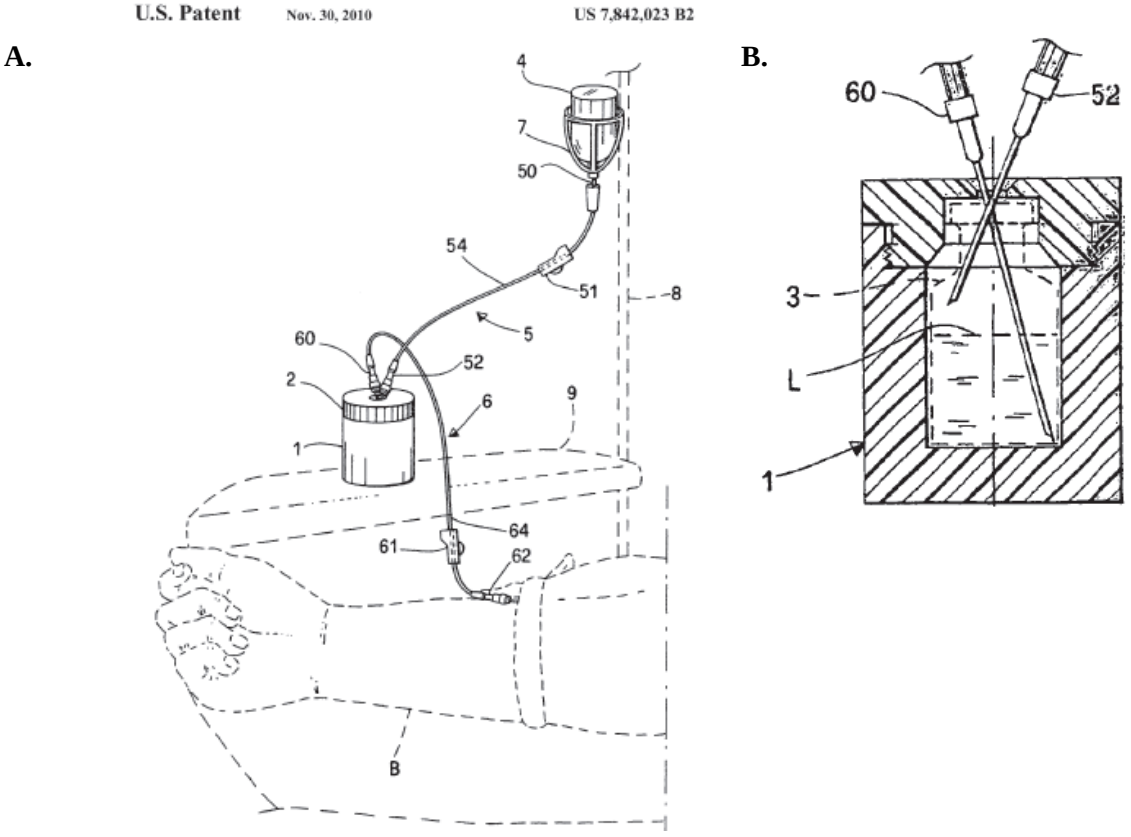


Figure 2: **Flebo Infusion Method (A) Showing Operations Details (B).**

From US Patent *No.* US 7842023

Appendix 9 – CT and MRI Imaging Protocols

The imaging protocols are performed according to Revised RECIST Criteria, Version 1.1 (Eisenhauer EA et. al., 2009, Appendix 2).

CT is the preferred imaging modality for assessing RECIST Criteria. The use of MRI should be limited to additional investigation uses only (such as liver studies). In the event that MRI is used for RECIST Criteria analysis, it must be used throughout the relevant study period, using the same acquisition protocol including that used at inclusion and baseline.

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

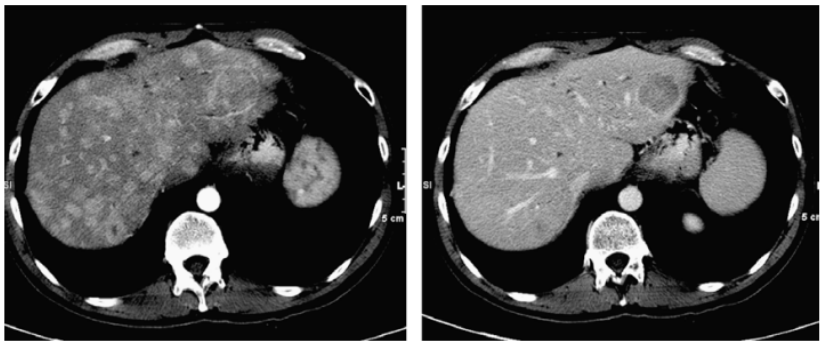


Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

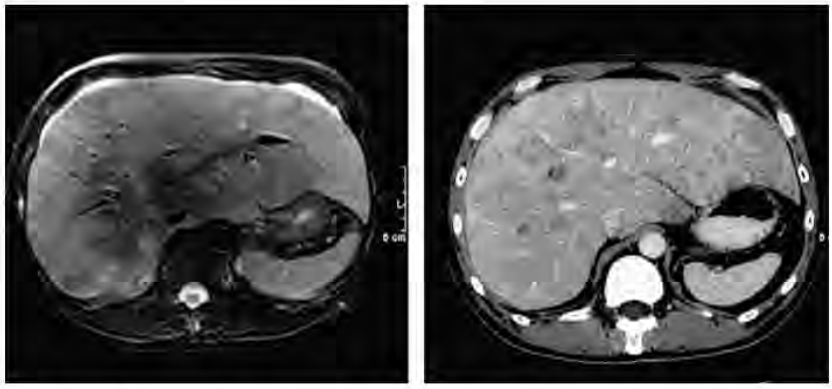


Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials.*

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

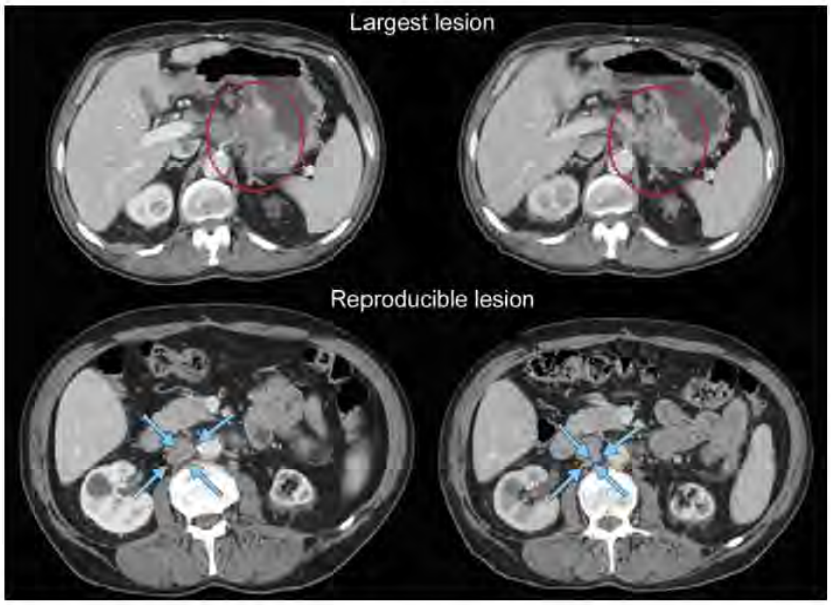


Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

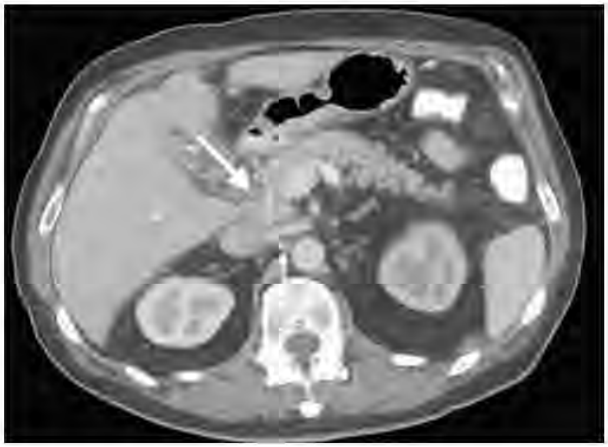


Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

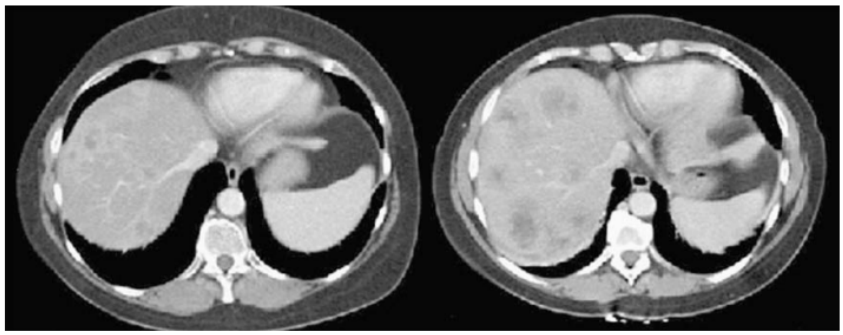


Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

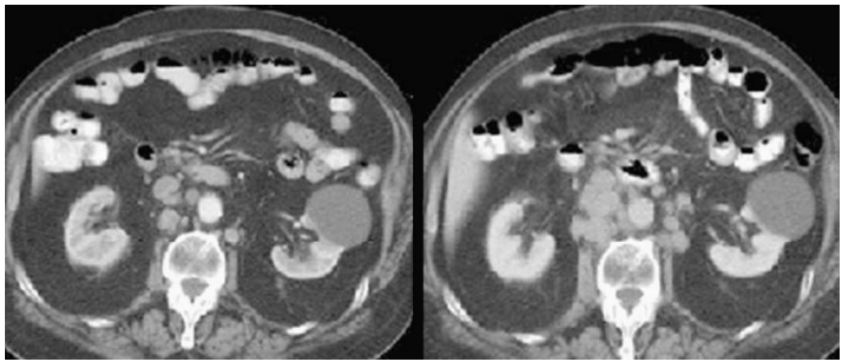


Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Apper ently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(continued on next page)

continued

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

Appendix 10 – Dosimetry and Pharmacokinetics Study: Manual for Procurement, Storage and Handling of Blood and Urine Samples

Blood samples (1 mL) will be collected in heparanized tubes just before administration of the therapeutic dose and then at the following time intervals:

two time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 64 and 72 h (Day 4), 160 and 168 h (Day 8)

The blood samples will be counted with a COBRA-Packard auto-gamma counting system (Packard, Meriden, Conn., USA).

A urine sample will be collected within 24 h prior to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration, preferable just prior to the infusion of study drug (0 h sample) to achieve bladder emptying before study drug administration. Quantitative urine collections will be obtained for the periods 0-1 h (immediately post start infusion to 1 h post start infusion), 1 h – 4 h, 4 h – 16 h, and 16 h – 48 h post start infusion.

Quantitative urine collection samples will be weighed and 1 mL of each of them will be counted with a COBRA-Packard auto-gamma counting system (Packard, Meriden, Conn., USA).
Moreover, a 10 mL aliquot will be withdrawn from each urine collection sample. Urine samples will be processed and further analyzed by HPLC according to validated procedures in order to examine the chemical status of the radionuclide in urine.

The collection of biological samples (blood and urine) will be recorded in the time-schedule template shown in Appendix 11.

Appendix 11 – Dosimetry and Pharmacokinetics Study: Time Schedule for Biological Samples

Patient ID: _____

weight: _____kg; height:_____cm; Haematocrit:_____%

Date of injection_____ time: _____

Administered activity (background corrected) _____GBq

BLOOD SAMPLES - 1 ml/sample			**URINE COLLECTION - COMPLETE**		
n.	**Time**	**date**	**n.**	**Time interval**	**date**
1	Before treatment	Day 1	1	Before treatment	Day 1
2	Half infusion	Day 1	2	Up to 1 h p.i. (before image n.1)	Day 1
3	End of infusion	Day 1	3	From 1h p.i. (after image n.1) → 4 h	Day 1
4	20 min p.i.	Day 1	4	16 h p.i. → 48 h p.i. (before image n.4)	Day 2-3
5	40 min p.i.	Day 1			
6	1 h p.i.	Day 1			
7	2 h p.i.	Day 1			
8	4 h p.i.	Day 1			
9	8 h p.i.	Day 1			
10	16 h p.i.	Day 2			
11	24 h p.i.	Day 2			
12	40 h p.i.	Day 3			
13	48 h p.i.	Day 3			
14	64 h p.i.	Day 4			
15	72 h p.i.	Day 4			
16	160 h p.i.	Day 8			
17	168 h p.i.	Day 8			

URINE COLLECTION: Please ask the patient to void their bladder BEFORE the acquisition of each scintigraphic image, especially within the first 24 h post injection, when the activity elimination rate is high.

Appendix 12 – National Cancer Institute Common Terminology Criteria for Adverse Events

This is an extract of the whole document. For the complete CTCAE guide, version 4.0, please refer to the following website: *http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf*

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.					
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node.					
Spleen disorder	Incidental findings (e.g., Howell-Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the spleen.					
Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach.					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents.					
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

Appendix 13 – Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 14 – Radioprotection Precautions for Patients Treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

1- Technical Data

The principle characteristics of lutetium-177 (^{177}Lu) are specified in Table 1 (from *Les principales caractéristiques du 177 lutetium (^{177}Lu)* and *Guide Pratique Radionucléides & Radioprotection*, D. Delacroix, J.P. Guerre, P. Leblanc, EDP Sciences, 2004).

Table 1: Emissions of ^{177}Lu

$^{177}_{71}$Lu — *Période : 6,71 jours* — *Activité massique : 4,07.10^{15} Bq.g^{-1}* — *Groupe de risque : 4*

Lutétium - 177

Principales émissions

	Gamma / X		Beta (Emax)		Electrons		Alpha	
	E (keV)	%	E (keV)	%	E (keV)	%	E (keV)	%
E1	55	5	208	11	6	9		
E2	113	6	384	9	48	5		
E3	208	11	497	79	110	9		
% omis		5		< 1		4		

Seuils d'exemption

Quantité en Bq	1.10^{7}
Concentration en Bq.g^{-1}	1.10^{3}

Transport (Bq)

A1	3.10^{13}
A2	7.10^{11}

^{177}Lu is generally produced using enriched ^{176}Lu placed in a reactor, following a reaction of the type [^{176}Lu n,γ ^{177}Lu]. This reaction results the production of a small amount of ^{177}Lu meta-stable (^{177m}Lu) which varies according to sources between 10^{-5} and 4×10^{-4} per MBq of ^{177}Lu produced. The characteristics of this radionuclide are given in Table 2.

Table 2: Emissions of ^{177m}Lu

Période : 160,4 jours — *Activité massique : 1,69.10^{14} Bq.g^{-1}* — *Groupe de risque : 3** — $^{177m}_{71}$Lu/$^{177}_{71}$Lu

Descendant : Embr. = 0,215 ; T = 6,71 jours

Lutétium - 177m / Lutétium - 177

Principales émissions

	Gamma / X		Beta (Emax)		Electrons		Alpha	
	E (keV)	%	E (keV)	%	E (keV)	%	E (keV)	%
E1	328	18	152	79	5	60		
E2	379	28	384	2	45	51		
E3	419	20	497	17	95	41		
% omis		450		12		60		

Seuils d'exemption

Quantité en Bq	-
Concentration en Bq.g^{-1}	-

Transport (Bq)

A1	-
A2	-

2- Recommendations

Based on radiation exposure calculations employing whole body clearance data (Wehrmann C et al, 2007) and exposure rates at one meter at 24 h (7,5 ± 3,6 µSv/h, Dpt. of Nucl. Med. Erasmus MC Rotterdam), patients may be treated on an outpatient basis for an administration of 7.4 GBq of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. As a precaution, it is recommended that patients be kept in radiation isolation for a period of 4 – 5 hours following administration, and be allowed to urinate during that time, and before release. This precaution is deemed prudent because this is the method of elimination (approximately 50% by urination within the first 6 hours; Kwekkeboom et al, 2001). At the time of release, the patient is given written instructions which summarize the precautions to take, in order to keep the exposure to others below regulatory limits.

Appendix 15 – Recommended Preacautions for Patients Treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera)

You have received treatment with a radioactive medicine. The therapeutic benefit of this medicine is due to the presence of the radioactivity. After each of your treatments you must follow certain precautions to minimize exposure or contamination of radioactivity to the people around you.

It is known that the health risks of this medicine are low because of its physical and radiopharmaceutical properties and its metabolic properties. Nevertheless, the following rules will ensure a high level of safety. They are the result of many years of experience in the use of radioactivity in medicine, and they include recommendations by international organizations.

1- General rule

You must avoid close contact with people who live with you, and should try to keep a distance of at least one meter for 7-days after you receive Lutathera.

2- Use of toilets

Toilets must be used in a seated position, even for men. It is absolutely necessary to use toilet paper each time. It is equally important to wash your hands to avoid contaminating the door handles. It is strongly recommended to move your bowels every day and use a laxative if you need help. Furthermore, empty your bladder (urinate) every hour or so on the day you received treatment and for day after. Follow your doctor's advice on how much fluid to drink.

3- Contact with children (less than 10 years old)

Because of the high sensitivity of children to radioactivity, it is strongly advised to limit contact to them to less than 15 minutes for each day while keeping a distance of at least 1-2 meters. It is strongly recommended that there be no contact with children who are less than 10 years old for 7-days after the administration of Lutathera.

4- The spouse and people in the family circle

It is strongly advised to sleep in separate beds at a distance of at least 1 meter. Embraces and sexual activity are not advised for eight days after the administration of Lutathera.

5- Seniors

Older people are less sensitive to radioactivity (between 3 and 10 times less than a middle-aged person). Therefore, the previous recommendations can be followed with a little more flexibility in the presence of the elderly.

6- Contact with pregnant women

Contact with pregnant women should follow the same restrictions recommended for children less than 10 years old.

7- Breastfeeding

Breastfeeding should be stopped because it is not compatible with a treatment using a radioactive product.

8- Pregnancy

Pregnancy must be excluded before the start of treatment. Any woman who has missed a period must be assumed to be pregnant until proven otherwise and alternative therapies which do not involve ionizing radiation must be then considered.

There is a potential risk that ionizing radiation by Lutathera could cause toxic effects on female and male gonads. Due to the nature of the compound, women of child-bearing potential, as well as males, must abstain from procreation (using effective contraceptive measures) during and up to 6 months after treatment with Lutathera.

9- People who need extra assistance

People who are confined to the bed or have reduced mobility will preferably receive assistance by a care provider. It is recommended that when providing assistance in the bathroom, the care provider wear disposable gloves for 2-3 days after administration. In the case of the use of special medical equipment such as catheters, colostomy bags bedpan, water nozzle, or anything that could be contaminated by your body fluids they must be emptied immediately in the toilet and then cleaned. If anyone helps you clean up vomit, blood, urine, or stool they should wear plastic gloves; the gloves should then be put in the specified trash plastic bag.

10- Dishes and bathroom accessories

For the first two days after your treatment wipes and/or toilet paper must be flushed down the toilet. Always wash your hands well after using the toilet.

It is strongly recommended to shower every day for at least the first 7 days after your treatment.

Try to flush any tissues or any other items that contain anything from your body, such as blood, urine and faeces down the toilet (at least for two days after the therapy). Items that cannot be flushed, such as menstrual pads and bandages, must be placed in specified plastic trash bags.

Wash your underwear, pyjamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of others in your household. Wash your items two or three times; use a standard washing machine; you do not need to use bleach and do not need extra rinses.

11- Trash recommendations

Keep the specified plastic trash bags separate from other trash; keep the bags away from children and animals.

A member of the Study Staff will tell you how and when to get rid of the specified plastic trash bag; you may be asked to bring the bag back to your treatment facility, or, after 70 days, the bag may be removed as other trash bags.

12- Professional activities

Lutathera could affect your ability to drive and to use machines, as dizziness has been reported as a common side effect.

If there is a risk of frequent contact and being in close vicinity to the public and/or with children, the activity must be temporarily suspended.

13- Use of public transportation

For short trips (less than 30 minutes), the precautions are minimum. If you ride with someone else, confirm she is not pregnant, and maintain a distance of >1 meter (use the back seat on opposite side of the driver). If you are able to do so, it is best to drive yourself.

14- Public activities

Avoid assisting in shows or public meetings which could expose third-parties for more than 30 minutes in the first week after your treatment.

Ask Your Doctor or a member of the Study Staff when:

- It will be safe to eat out, go shopping and attend events such as religious services, parties and movies;
- You will be able to return to work and to care for or teach others;
- It would be safe to donate blood;
- Special or longer distance travel is possible (Note: For up to 3 months or more following radioactive treatment you may set off radiation detectors at: national borders, airports, bus and train stations, tunnels, bridges, trash collection sites and even your place of employment); a member of your Study Staff will issue you a letter or card describing the therapy and the phone number of a person knowledgeable about your treatment (usually at the treating facility) in case local law enforcement agents need to check on this information; you should keep the letter or card containing the information with you whenever you are travelling for at least 3 months.

15- Hospitalization

In the case that an unplanned hospitalization occurs, it is important to notify your doctor.

16- Domesticated animals

The lifespan of domesticated animals is much less than that of humans. Therefore, the effect of the radioactivity is less. It is not necessary to take any particular precautions. But do not sleep with pets (ask your doctor for how long) since your secretions may be carried away by the pet.

17- Emergency Care

You will get an information card or letter at the time of your treatment that will show the date, type and amount of radioactivity that you were treated with; carry this card with you at all times for at least 3 months following your treatment.

If you are in a traffic accident or any other medical emergency and require medical assistance during the first week after your treatment, you should show this card to the medical providers to let them know about the date and dose of your radioactive treatment.

18- Important information for patients on risks of radiation

Radiation exposure to others should always be As Low As Reasonably Achievable, a goal often abbreviated as ALARA. If you follow the above advice, the radiation from you to others is likely to be less than what they receive from radiation in nature over a year's time.

Please phone us if:

- you have any questions, and particularly if
- any of the above instructions cannot be followed and/or if
- you see anything that may have accidentally or unavoidably increased exposure of others to radiation.

19- Recommended Precautions after Lutathera treatments

		mCi (MBq) administered			
		200 (7400)	200 (7400)	200 (7400)	200 (7400)
		Precaution Days			
Night-time restrictions					
	Sleep in a separate (1 meter separation) bed from adults for days shown	8	8	8	8
	Sleep in a separate bedroom from pregnant partners, infants, or children for days shown	15	15	15	15
Day-time restrictions					
	You may return to work after days shown	8	8	8	8
	Maximize your distance (1 meter) from children and pregnant women for days shown.	8	8	8	8
	Avoid extended time in public places for days shown	8	8	8	8

Appendix 16 – Instructions for Shipment, Storage and Handling of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) Solution for Infusion

NAME OF THE MEDICINAL PRODUCT

Lutathera 7400 MBq, radiopharmaceutical solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lutathera is supplied as ready for use radiopharmaceutical solution for infusion.

A vial contains 7400 MBq of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with a maximum specific activity of 48 GBq/umol at calibration time in a formulation solution with a concentration of 370 MBq at production time.

PHARMACEUTICAL FORM

Sterile Solution for infusion.

Clear, colorless or slightly yellow solution.

PHARMACEUTICAL COMPONENTS

List of excipients

Acetic Acid

Sodium Acetate

Gentisic Acid

Ascorbic Acid

DTPA

NaCl

Water for Injection

Shelf life

72 hours after production (to be used within three working? days).

Special precautions for storage

Store below 25°C.

Store in the original package for radioprotection purposes.

The product must be stored according to national regulations concerning radioactive products.

Nature and contents of container

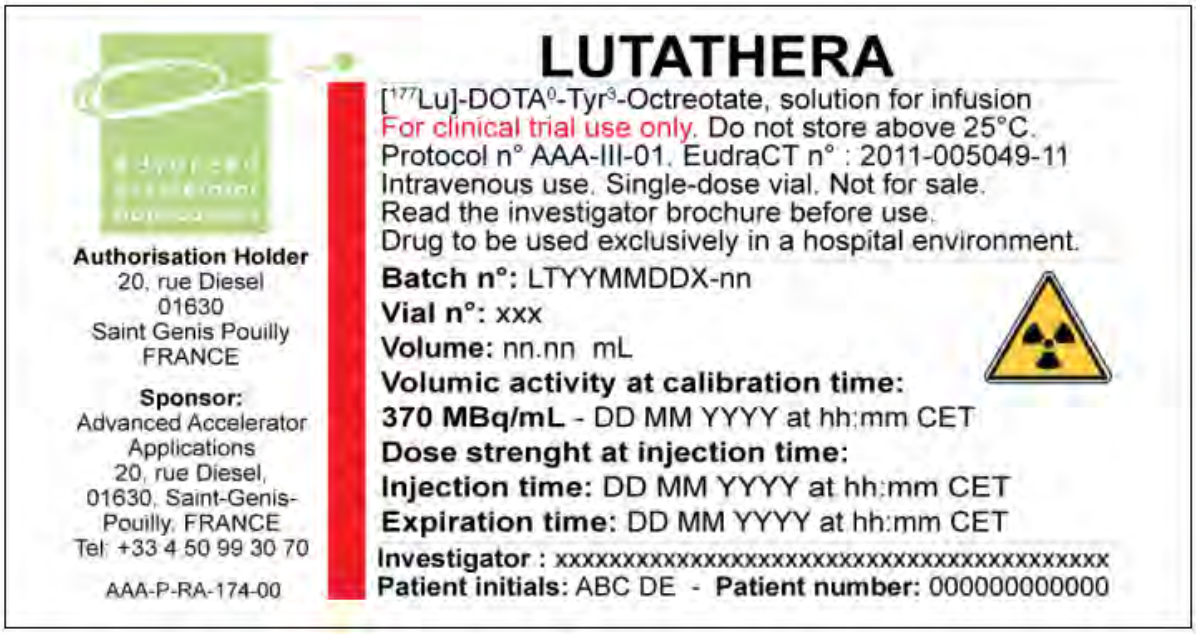
A 30 mL vial, colourless Type I glass, closed by a rubber stopper and sealed by an aluminum cap. One vial contains 22 to 25 mL of solution. The vial is inserted into a lead shielded container protected by a plastic sealed container closed in a Type A package (according to the Accord Dangereuses Route agreement or ADR).

Type A container

Plastic container

Lead container inserted in the plastic container.

The Type A container, the sealed Plastic container, the Lead container inset in the plastic container, and the 30 ml vial are all labeled with the product information. The labels are compliant with the annex 13 of Current GMP regulations. An example of the label is shown below.



Special precautions for disposal and other handling

The administration of radiopharmaceuticals creates risks for other people from external radiation or contamination from spills of urine, vomit, etc. Radiation protection precautions must be taken according to national regulations.

Radioactive waste disposal must be according to relevant national and international regulations.

The disposal of any unused product must be according to local requirements as well as applicable national requirements.

INSTRUCTIONS FOR THE USE OF Lutathera (7400 MBq)

Lutathera is delivered in monodose vials.

The integrity of the Lutathera package must be inspected before use and the product vial total radioactivity measured using a dose calibrator (or activimeter). The residual radioactivity in the vial should be determined after the product is administered.

The activimeter or dose calibrator must be periodically calibrated by means of a standard source of Lu-177. If this procedure is not in place at the clinical site, Advanced Accelerator Applications will provide a calibration protocol and will ship a source of Lu-177 to perform the calibration.

Lutathera does not need to be manipulated before administration because it is delivered as a ready to use monodose vial.

The vials must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle. The filled syringe in then connected to the infusion system.

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

Disposal of radioactive waste must be according to relevant national and international regulations.

A product batch release certificate will be sent to each center receiving the product. The manufacturing site's Qualified Person provides a product batch release certificate to the clinical site to guarantee that the product is suitable for injection and that it meets the specifications indicated in the Investigation Medicinal Product Dossier (IMPD). The product is not to be used before the site has received the release certificate. The product is not to be used if the site is notified that the product batch has not been released for use, or if the product batch has been recalled because of fabrication defects.

Lutathera must not be used after the expiry date which is stated on the label of the outer package.

Product receipt, tracking and administration data will be recorded using a informatics system provided by the CRO. In the event that the product is not administered for any reason, AAA will be notified, and a disposal verification record will be provided.

Quality Control of Lutathera

Minimum Quality Control is needed at the site, before the administration of Lutathera. The site will confirm that the product received has the correct release certificate. The results will be recorded. Additionally, the site's measurement of total radioactivity and product administration data (start and stop time, and residual radioactivity not administered) will also be recorded.

Lutathera storage requirements

Lutathera must be stored at a temperature below 25°C (77° F) but not lower than 3 °C (37.4 °F), in its original package for radioprotection purposes, according to national regulations concerning radioactive products.

Shelf life: 72 hours after production (to be used within three working days).

The disposal of any unused product or waste material must be according to local and national requirements.

Further information

The clinical site must request the required Lutathera dose for each patient at least 10 days before the scheduled treatment. A product order must be placed with AAA through the informatics system provided to each Investigator by the CRO. The administration date of the product for each patient should not be confirmed until the clinical site has received both an order confirmation and a production dose confirmation from AAA. The scheduled date of treatment must be accepted by AAA so that the Manfacturer's Production Planning matches patient treatment schedules.

Appendix 17 – Randomization Procedure of Patients after Enrolment.

Patient randomization will be performed according to a centralizedbiased coin design procedure, stratifying for the following factors; 1) centre; 2) OctreoScan® tumour uptake score (Grade 2, 3 and 4); and 4) length of time that a patient has been on the most recent constant dose of Octreotide prior to enrolment (≤6 and > 6 months). Approximately 28 European centres and 13 USA centres are expected to participate in the trial.

The rationale for the using this randomization procedure can be summarized as follows:

1. The study is unblinded; the centralized assignment to treatment arm upon the request of the Investigator at the time of enrolment of each patient ensures that the assignment of patients is not biased by knowledge of the next treatment in the random order.
2. The complexity of the disease means that a number of factors may influence the final outcome. The importance of each of these factors is likely to vary from centre to centre, the net effect being between-centre variability.
3. Randomization in blocks of patients could create problems because of the small number of patients in each treatment arm within each centre and stratum. The size of the randomization blocks presents opposing statistical problems. If the blocksize is too large, and there are unused assignments within blocks, there could be an imbalance in the overall assignments. If the block size is small then the probability of selection bias increases, which is of particular concern in an open trial such as the present phase III trial.
4. The above considerations favour the choice of an adaptive treatment assignment procedure (Pocock SJ et al., 1975). Among the various methods proposed, the biased coin design proposed by Pocock and Simon has been selected, since it can provide a fair balance within strata without being completely deterministic.

Details

The randomisation procedure for the present study takes into consideration that patients are sequentially enrolled, and each in turn requires assignment to a treatment arm. In the present phase III clinical trial there are N=2 treatment arms and M=3 factors (strata):

1. Centre (n_1=41 levels);
2. OctreoScan® tumour uptake score (n_2=3 levels);
3. The length of time that patients have been on the most recent constant dose of Octreotide prior to enrolment (n_3=2 levels);

for which treatment arm balance is required, the number of levels of these factors being n_1 , n_2 and n_3.

The procedure will be described by considering an arbitrary point during the trial. At such a point x_{ijk} be the number of patients with level j of factor i who have been assigned treatment k for j=1, 2,… ,n_i ; i=1, 2, 3; k=1, 2. Consider the next patient entering the trial. Let ,r_1, r_2, r_3 be the levels of factors 1, 2 and 3 for this patient. The choice of treatment for this new patient is determined in the following manner. For each treatment k one considers the new $\{x_{ijl}\}$, denoted $\{x^k_{ijl}\}$, that would arise if the treatment were assigned to the patient. This is achieved by adding one onto $\{x_{ir_il}\}$ for i=1, 2, 3. That is, define:

$$x_{ij_l}^{k} = x_{ijl} \qquad for\ j \neq r_i \quad or \quad l \neq k$$

$$x_{ir_i k}^{k} = x_{ir_i k} + 1$$

Where the superscript k refers to the particular treatment under consideration. Then, if treatment k were assigned to the next patient, $d_{ik} = range\left\{x_{ir_i l}^{k}\right\}$ for r_1, r_2, r_3 would be the resultant "lack of imbalance" among treatment assignments for patients with level r_i of factor i.

Let $G_k = \sum_{i=1}^{3} d_{ik}$ for k=1,2. Then G_k represents the "total amount of imbalance" in the treatment numbers which would exist at all the factor levels of the new patient if treatment k were assigned to that patient.

One can rank treatments according to their values G_k. The treatment will be assigned according the following set of probabilities:

Conditions	G_a probability	G_b probability
$G_a > G_b$	0.40	0.60
$G_a = G_b$	0.50	0.50

$\forall \quad a \neq b \in \quad \{1,2\}$.

This ordering of probabilities means that treatments with small values of G_k have a higher probability of being chosen. The entire procedure is repeated when the next patient enters the trial.

Appendix 18 – Staging of Midgut Carcinoids by TNM criteria

(Rindi G et al, 2007)

TNM classification for endocrine tumors of lower jejunum and ileum

T-primary tumor
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor invades mucosa or submucosa and size ≤1 cm
- T2 Tumor invades muscularis propria or size >1 cm
- T3 Tumor invades subserosa
- T4 Tumor invades peritoneum/other organs

For any T add (m) for multiple tumors

N regional lymph nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M Distant metastasis
- MX Distant metastasis cannot be assessed
- M0 No distant metastases
- M1 Distant metastasis

Disease staging for endocrine tumors of lower jejunum and ileum

Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

TNM classification for endocrine tumors of the appendix

T-primary tumor
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor ≤1 cm invading submucosa and muscularis propria
- T2 Tumor ≤2 cm invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix
- T3 Tumor >2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix
- T4 Tumor invades peritoneum/other organs

For any T add (m) for multiple tumors

N regional lymph nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M Distant metastasis
- MX Distant metastasis cannot be assessed
- M0 No distant metastases
- M1 Distant metastasis

Disease staging for endocrine tumors of the appendix

Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

LIST OF PROTOCOL CHANGES

*Pages are referred to the new REDLINE version

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1, 17	FINAL version 1.0, November 14th, 2011	**FINAL version 2.0, August 28th, 2012 (Replaces version 1.0, November 14th, 2011)**	Protocol version updated
1	-	IND N° 77219	IND Number added
4	administered ~~radiation doses~~	administered radioactivity	**§Protocol footnote "f1"** The term 'radioactivity' is more appropriate in this context.
4, 10, 34	~~first treatment~~	randomization	**§Protocol footnote "f2"** Responses to treatment are to be recorded from the date of randomization, instead of from the date of first treatment. *Revision to response to treatment determination based on FDA Comment 3, FDA Memorandum dated May 21, 2012, and Sponsor's reply (Response Letter-2) dated May 22, 2012.*
5, 34	cumulative ~~dose~~ of 29.6 GBq (800 mCi)	total cumulative administered radioactivity of 29.6 GBq (800 mCi)	**§Protocol footnote "f1"** The term 'total administered radioactivity' is more appropriate in this context.
6, 42	1. Presence of inoperable (curative intent) at enrolment time, histologically proven, midgut carcinoid tumour. 2. Ki67 index ≤ 20%.	1. Presence of inoperable (curative intent) at enrolment time, histologically proven, midgut carcinoid tumour (to be centrally confirmed). 2. Ki67 index ≤ 20% (to be centrally confirmed)	**§Protocol footnote "f3"** Text added to Protocol to clarify that assessments of specific eligibility requirements are centrally confirmed.
	5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 (Appendix 2)	5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 (Appendix 2)	**§Protocol footnote "f3"** Text added to Protocol to clarify that

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	evidenced with CT scans/MRI obtained within 3 years from enrolment;	evidenced with CT scans/MRI obtained within 3 years from enrolment (to be centrally confirmed);	assessments of specific eligibility requirements are centrally confirmed.
7, 42	6. Confirmed presence of somatostatin receptors on all technically evaluable tumour lesions documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to enrolment in the study. 7. The tumour uptake observed using OctreoScan® must be ≥ normal liver uptake observed on planar imaging (Appendices 5 and 6).	6. Confirmed presence of somatostatin receptors on all technically evaluable tumour lesions documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to enrolment in the study (to be centrally confirmed). 7. The tumour uptake observed using OctreoScan® must be ≥ normal liver uptake observed on planar imaging (to be centrally confirmed). (Appendices 5 and 6).	**§Protocol footnote "f3"** Text added to Protocol to clarify that assessments of specific eligibility requirements are centrally confirmed.
	-	10. [Applicable only for France] All patients included in the trial must be affiliated with a social security regime or be a beneficiary of the same in order to be included in the study.	**§Protocol footnote "f4"** Additional inclusion criteria requested by the French Leading Ethic Committee. *Revision to response to French Leading Ethic Committee deficiency letter dated Mar 01, 2012*
7, 43	5. Pregnancy (see protocol Appendix 7).	5. Pregnancy (see protocol Appendix 7) or lactation.	**§Protocol footnote "f5"** Additional Exclusion Criteria – lactation. *Additional exclusion criteria based on FDA Comment 1.f., FDA Memorandum dated May 18, 2012, and Sponsor reply (Response Letter-1) dated May 22, 2012.*
9, 44	20.	20. Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency.	**§Protocol footnote "f4"** Additional exclusion criteria requested by the French Leading Ethic Committee. *Revision to response to French Leading Ethic Committee deficiency letter dated Mar 01, 2012*

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10	-	In addition, for the second, third, and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional safety assessment will be performed on the same day of treatment, or within one day before treatment.	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
12, 37	**Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm**	**Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm**	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.* **§Protocol footnotes "f10" and "f12"** -Recommendations, 1) to consider hospitalization of the patients following treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate because of possible occurrence of hormone or bioactive substance

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			2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012. *-Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 24, 2012.*
		Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in section 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the Protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.	**§Protocol footnote "f7"** Ensure that laboratory parameters meet required treatment criteria before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. *Statement added based on FDA Comment 5.e., FDA Memorandum dated May 18, 2012; Sponsor's reply (Response Letter-1) dated May 22, 2012.*
13, 38	[2]Tests included in the local laboratory assessments: - Haematology: WBC with differential, Platelets, Hb, MCV - Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb, fT4 .	[2]Tests included in the local laboratory assessments: - Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit - Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose.	**§Protocol footnote "f3"** Haematocrit assessment added in the local laboratory tests panel **§Protocol footnote "f9"** Clarify that Glyco HB is haemoglobin A1C. *Based on FDA Comment 6, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.* **§Protocol footnote "f8"**

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			Sponsor's reply (Response Letter-1) dated May 22, 2012.
	- During 177Lu-DOTA0-Tyr3-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4 weeks after each treatment. ~~Then every 12±1 weeks~~	- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4 weeks after each treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, additional laboratory tests will be performed on the same day or within the day before each treatment. Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of study drug must include at minimum: a. serum blood urea nitrogen and creatinine b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.	**§Protocol footnote "f6a".** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical old Letter, Comment 1.*
15, 40	**Table 2: Visit Schedule: Octreotide LAR Arm**	**Table 2: Visit Schedule: Octreotide LAR Arm**	**§Protocol footnote "f6b"** Additional safety assessment will be performed 4 weeks after first treatment with Octreotide LAR. *Revision to safety assessments based on:* *-FDA Comment 2, FDA Memorandum dated May 18, 2012 .* *-Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 24, 2012.*

§Protocol footnotes "f12"
Advise Investigator to maintain phone contact with patient for the first week after

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			-Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 24, 2012.
	-	Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in sections 4.2.1 and 4.2.2. Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.	**§Protocol footnote "f7"** Ensure laboratory parameters meet required treatment criteria before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. *Statement added based on FDA Comment 5.e., FDA Memorandum dated May 18, 2012;* *-Sponsor's reply (Response Letter-1) dated May 22, 2012.* **§Protocol footnotes "f12"** Advise Investigator to maintain phone contact with patient for the first week after the first treatment in both arms to verify patient status. Based on: *-FDA Comment 2, and 3, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.* *-Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 24, 2012.*
16, 41	[2]Tests included in the local laboratory assessments: - Haematology: WBC with differential, Platelets, Hb, MCV - Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb, fT4	[2]Tests included in the local laboratory assessments: - Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit - Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose	**§Protocol footnote "f3"** Haematocrit assessment added to the local laboratory tests panel **§Protocol footnote "f8".** Calcium and Glucose tests added to blood chemistry assessments.

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			§Protocol footnote "f9" Clarify that Glyco HB is haemoglobin A1C. *Based on FDA Comment 6, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*
22	-	Appendix 19 – Determination of LUTATHERA Administered Radioactivity	**§Protocol footnote "f3"** Appendix added to provide method for measurement of LUTATHERA Administered Radioactivity
23	Figure 2: Flebo Infusion Method (A) Showing Operations Details (B).	Figure 2: Flebo Infusion Method (A) Showing Operations Details (B, C, D).	List of Figures updated
24	GlycoHb Glycosylated Haemoglobin	GlycoHb Glycosylated Haemoglobin (haemoglobin A1C)	**§Protocol footnote "f9"** Clarify that Glyco HB is haemoglobin A1C. *Based on FDA Comment 6, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*
25	-	I.V. Intravenous	**§Protocol footnote "f3"** 'I.V.' added in the abbreviations list
30	The third patient, a 76 years old man suffering from liver ~~cirrhosis~~, developed hyperbilirubinemia after the second administration of 200 mCi and passed away 3 weeks from treatment.	The third patient, a 76 years old man suffering from liver fibrosis , developed hyperbilirubinemia after the second administration of 7.4 GBq (200 mCi) and passed away 3 weeks from treatment.	**§Protocol footnote "f3"** Typo correction ('fibrosis' instead of 'cirrhosis') **§Protocol footnote "f1"** Radioactivity is reported in GBq and in parentheses in mCi for clarity
	~~Acute Myeloid Leukemia (AML) occurred in two patients, both suspected to be treatment related. One of these patients, with a pancreatic gastrinoma, had previously received extensive~~	Acute leukaemia was reported for 2 of the 367 Dutch patients and it occurred in 1 French patient. It was diagnosed up to 7 years after the last ^{177}Lu-	**§Protocol footnote "f3"** This paragraph has been rephrased for clarity, and safety data have been

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	~~chemotherapy, fractionated radiation therapy, and a liver transplant prior to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octerotate. This patient was diagnosed with AML, 30 months after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The other patient, with a gastrinoma metastasized to the liver, and no prior therapy, developed MDS (as mentioned above), 33 months post-treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octerotate. Nine months later (42 months post-treatment) the patient developed AML and died soon thereafter.~~	DOTA^{0}-Tyr^{3}-Octreotate treatment with a cumulative administered activity of either 22.2 GBq (600 mCi; 1 patient) or 29.6 GBq (800 mCi, 2 patients). One patient received prior chemotherapy and one patient received external beam radiation for breast cancer 7 years before ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy.	corrected
31	~~dose~~	administered radioactivity	**§Protocol footnote "f1"** The term 'administered radioactivity' is more appropriate in this context.
	the cumulative (800 mCi-~~dose~~)	the cumulative 29.6 GBq (800 mCi) administered radioactivity,	**§Protocol footnote "f1"** Radioactivity is reported both in GBq and mCi for clarity
	consisting of ~~405~~ subjects with diagnosed GEPNETs,	consisting of 404 subjects with diagnosed GEPNETs,	**§Protocol footnote "f3"** Typo correction
	• Objective tumour response (complete response (CR) + partial response (PR) + minor response (MR is defined as a tumour diameter decrease of 25% to 50%, Kwekkeboom DJ et al., 2005) in the overall GEPNET FAS population was ~~59.3~~% (95% CI; ~~54.30-64.09~~%); in the subgroup of 157 Dutch carcinoid tumour patients the objective tumour response was 61.2% (95% CI; 53.05 - 68.81%);	Objective tumour response (complete response (CR) + partial response (PR) + minor response (MR is defined as a tumour diameter decrease of 25% to 50%, Kwekkeboom DJ et al., 2005) in the overall GEPNET FAS population was 59.4% (95% CI; 54.44-64.23%); in the subgroup of 157 Dutch carcinoid tumour patients the objective tumour response was 61.2% (95% CI; 53.05 - 68.81%);	
32	• Time to progression (TTP) from start of treatment in the overall GEPNET FAS population was 1164 days (38 months) with a 95% CI of ~~1014~~-1357 days (~~33.3-44.6~~	• Time to progression (TTP) from start of treatment in the overall GEPNET FAS population was 1164 days (38 months) with a	

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	months); • Median PFS from start of treatment in the overall GEPNET FAS population was 904 days (~~30~~ months) with a 95% CI of ~~813~~-994 days (~~26.7-32.7~~ months); • Median OS from start of treatment in the overall GEPNET FAS population was: ~~1501~~ days (49 months) with a 95% CI of 1375-1667 days (~~45.1-54.7~~ months).	95% CI of 994-1357 days (32.6-44.5 months); • Median PFS from start of treatment in the overall GEPNET FAS population was 904 days (29 months) with a 95% CI of 812-994 days (26.6-32.6 months); • Median OS from start of treatment in the overall GEPNET FAS population was: 1496 days (49 months) with a 95% CI of 1375-1667 days (45.1-54.7 months).	
33	~~radiation dose~~	administered radioactivity	**§Protocol footnote "f1"** The term 'administered radioactivity' is more appropriate in this context.
34	Baseline evaluations will be performed 2 weeks prior to their first treatment (Treatment Day 1).	Baseline evaluations will be performed 2 weeks prior to their first treatment (Treatment Day 1) (§ Section 6.5.2).	**§Protocol footnote "f3"** Added paragraphs cross-reference for clarity
	…which provide a safe radiation dose to the critical organs, the bone marrow and the kidneys	…which results in a safe radiation dose to the critical organs, the bone marrow and the kidneys	English text improved
35	~~dose~~	amount of radioactivity.	**§Protocol footnote "f1"** The term 'amount of radioactivity' is more appropriate in this context.
42	-	(§Section 6.1.4)	Added paragraph cross-reference for clarity
46	~~A~~ radioactivity ~~dose of~~ 7.4 GBq (±5%)	The amount of administered radioactivity	**§Protocol footnote "f1"** The term 'amount of administered radioactivity' is more appropriate in this context.
47, 50	cumulative ~~dose~~ of 29.6 GBq (800 mCi)	total cumulative amount of radioactivity of 29.6 GBq (800 mCi)	**§Protocol footnote "f1"** The term 'amount of radioactivity' is more appropriate in this context.

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50	-	The total amount of administered radioactivity is determined by measuring the radioactivity in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Infusion Solution (Lutathera) vial before and after administration (the procedure is provided in Appendix 19).	**§Protocol footnote "f18"** Text added in response to FDA Comment 4, Full Clinical Hold Letter..
51			**§Protocol footnote "f3"** Additional text to improve Protocol clarity of the infusion methods
51, 157	**Table 5: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm Administration Schedule.**	**Table 5: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm Administration Schedule.**	**§Protocol footnote "f3"** **Table 5** modified to improve Protocol clarity of the infusion methods
51, 52, 157	[1] ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be infused directly into the line. The line must be flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.	[1] When the two pump method is used, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is pumped directly into the infusion line. The infusion line must be flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. [2] When the Flebo infusion method is used, a sodium chloride 9 mg/ml (0.9%) solution for injection gravity flows directly into to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate solution, which is connected to the infusion line.	**§Protocol footnote "f3"** Footnote modified to improve Protocol clarity of the infusion methods
52	-	In the event of toxicity, the only change allowed to the treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a dose reduction and treatment postponement or discontinuation. Lutathera® overdose, has a very low probability of occurring since it will be supplied as a single dose "ready to use product" in order to avoid any manipulation outside the production facilities. In	**§Protocol footnote "f3"** Additional text to provide instructions for patient management in case of Lutathera® overdose, double administration, or deliberate treatment interruption

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		addition the infusion system methods (see Protocol Appendix 8) do not allow the concurrent use of two separate ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate solution vials. No doubling of the administered radioactivity is ever allowed either in absolute amount or by shortening the time intervals between treatments. Treatments (amount of radioactivity and time of administration) will be monitored during the study and any unallowed treatment modification will be considered a major protocol violation. • In the unlikely occurrence of Lutathera® double administration: - if not clinically contraindicated, hydration must be enhanced up to 48 h after Lutathera® administration in order to force diuresis - every week and up to the 10th week after treatment laboratory tests have to be performed (hematology: WBC with differential, Platelets, Hb and Haematocrit; blood chemistry: albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, serum creatinine, calcium and glucose). In addition, rigorous procedures are in place to minimise the risk of accidental overexposure and, in general, the correct study drug management and administration. Attention will be given also to respect the threshold of radiation emission from the patients before their dismissal from the hospitals according to the local legislation.	

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		• Deliberate treatment interruption In case of study interruption in single patients (based on either the patient's or the Investigator's decision), patients will undergo an End-of-study (EOS) visit with all exams scheduled for such visit, as scheduled after 76 weeks of study, unless early termination (See Protocol Section 6). If the interruption occurs because of laboratory abnormality, or any evidence of toxicity, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value redresses. Appropriate remedial measures should be taken and the response recorded (See Protocol Section 6.5.2). All patients will be followed in the long-term follow-up every 6 months up to 3 years after the End of study (See Protocol Section 6.5.2), regardless the early interruption or regular completion of the study.	
53	-	Crises due to excessive release of hormones or bioactive substances may occur following treatment, therefore, observation of patients by overnight hospitalization should be considered. Recommended treatment of patients with hormonal crises are: i.v. high dose somatostatin analogues, i.v. fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and	**§Protocol footnotes "f10"** Recommendations, 1) to consider hospitalization of the patients following treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate because of possible occurrence of hormone or bioactive substance induced crises, and 2) for treatment of patients with hormonal crises. *Added statements based on FDA Comment*

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		vomiting.	*3, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*
54	In the treatment arm with Sandostatin® LAR Depot, a dose adjustment scheme will be applied in case of Grade 3 or 4 toxicity, especially in cases of severe abdominal symptoms, and hypoglycaemia.	In the treatment arm with Sandostatin® LAR Depot, a dose adjustment scheme will be applied in case of Grade 3 or 4 toxicity, especially in cases of severe abdominal symptoms, and hypoglycaemia/hyperglycemia.	**§Protocol footnote "f3"** Hyperglycemia added as possible Sandostatin® LAR adverse reaction
57	Specimen of primary tumour or liver metastases.	Specimen of primary tumour or liver metastases or soft tissue metastases. *(repeated in the two first lines)*	**§Protocol footnote "f3"** Soft tissue metastases will be accepted as tumor site for centralized histological tumor assessment
58	-	Refer to Section 6 for further details on Visits Assessments. Ensure that the laboratory parameters meet the retreatment criteria outlined in section 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.	**§Protocol footnote "f7"** Ensure laboratory parameters meet required treatment criteria before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. *Statement added based on FDA Comment 5.e., FDA Memorandum dated May 18, 2012; Sponsor's reply (Response Letter-1) dated May 22, 2012*
59	The specific 12-week interval assessments for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments are ~~independly~~ shown in Table 7, without the treatment specific assessments that are performed 2 week before and 4 weeks after treatment.	The specific 12-week interval assessments for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments are independently shown in Table 7, without the treatment specific assessments that are performed 2 week before, on the day of treatment or the day before (only for the second, third, and fourth treatment) and 4 weeks after treatment.	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
	~~All patients are required to have central~~	~~All patients are required to have central~~	**~~§Protocol footnote "f3"~~**

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	histological confirmation of midgut carcinoid tumours in accordance with WHO classification and ENETS grading and staging guidelines (Rindi G et al., 2011), based on surgery/biopsy specimens of the primary tumour or liver metastases and assessed by immunohistochemical staining for CgA, synaptofysine and Ki67 (for the latter see Section 6.1.1.2).	histological confirmation of midgut carcinoid tumours in accordance with WHO classification and ENETS grading and staging guidelines (Rindi G et al., 2011), based on surgery/biopsy specimens of the primary tumour or liver metastases or soft tissue metastases and assessed by immunohistochemical staining for CgA, synaptofysine and Ki67 (for the latter see Section 6.1.1.2).	Soft tissue metastases is accepted as a tumor site for centralized histological tumor assessment.
	All patients are required to have central assessment of the Ki67 proliferation index based on surgery/biopsy specimens of the primary tumour or liver metastases and assessed by the microscopy and immunohistochemical staining.	All patients are required to have central assessment of the Ki67 proliferation index based on surgery/biopsy specimens of the primary tumour or liver metastases or soft tissue metastases and assessed by the microscopy and immunohistochemical staining.	**§Protocol footnote "f3"** Soft tissue metastases is accepted as tumor site for centralized histological tumor assessment
60	-	The inclusion would be centrally validated under the condition that target lesions are considered as positive on Octreoscan. It is not mandatory that all lesions will show at least grade 2 uptake.	**§Protocol footnote "f3"** Text added to improve Protocol clarity for assessment of Octreoscan uptake.
	-	If a patient has had an OctreoScan® performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan® performed after 3 months of Octreotide LAR treatments before entering the clinical study.	**§Protocol footnote "f3"** Text added to improve Protocol clarity for assessment of Octreoscan uptake.
61, 86	~~start of study treatment~~	randomization date *(repeated 4 times at page 85))*	**§Protocol footnote "f2"** Responses to treatment are to be recorded from the date of randomization, instead of from the date of first treatment. *Revision to response to treatment determination based on FDA Comment 3, FDA Memorandum dated May 21, 2012, and Sponsor's reply (Response Letter-2)*

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			dated May 22, 2012.
61, 87	12±1 week ~~after~~ the ~~first treatment~~ date	12±1 week <u>from</u> <u>the randomization</u> date	**§Protocol footnote "f2"** Responses to treatment are to be recorded from the date of randomization, instead of from the date of first treatment. *Revision to response to treatment determination based on FDA Comment 3, FDA Memorandum dated May 21, 2012, and Sponsor's reply (Response Letter-2) dated May 22, 2012.*
62	-	<u>An Independent Data Safety Monitoring Board will evaluate patient's safety throughout the study (§ Section 12.1 - *Independent Data Safety Monitoring Board*).</u>	**§Protocol footnote "f13"** Provide further details on the interim safety analysis plan. *Based on FDA request in Full Clinical hold letter, Comment-2.*
	-	<u>In addition, for the second, third, and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional laboratory assessment will be performed on the same day, or within one day before treatment.</u>	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
	• In the 60 mg Sandostatin® LAR Depot arm: throughout the study laboratory assessments will be performed every 12<u>+</u>1 weeks (see Visit Schedule in Table 2).	• In the 60 mg Sandostatin® LAR Depot arm: throughout the study laboratory assessments will be performed <u>4 weeks after the first treatment</u>, <u>and</u> every 12<u>+</u>1 <u>weeks from randomization</u> (see Visit Schedule in Table 2).	**§Protocol footnote "f6b"** Additional safety assessment will be performed 4 weeks after first treatment with Octreotide LAR. *Revision to safety assessments based on: FDA Comment 2, FDA Memorandum dated May 18, 2012* *Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response*

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			Letter-3) dated May 24, 2012.
64	**Table 8: Laboratory Assessments.**	**Table 8: Laboratory Assessments[1].**	**Protocol footnote "f3"** Haematocrit assessment added in the local laboratory tests panel **§Protocol footnote "f8".** Calcium and Glucose added to blood chemistry assessments. *Additional assessments added based on FDA Comment 5.b. and 5.d., FDA Memorandum dated May 18, 2012; Sponsor's reply (Response Letter-1) dated May 22, 2012.* **§Protocol footnote "f9".** Recommendation to clarify that Glyco HB is haemoglobin A1C. *Added clarification in all occurrences of the term glycoHB, based on FDA Comment 6, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*
	-	[1] Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must include at minimum: a. serum blood urea nitrogen and creatinine b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
66	~~A single ECG~~ will be taken supine, after 5 minutes rest, and not immediately after a meal	An ECG in triplicate (at least 5 minutes apart) will ~~be taken supine, after 5 minutes rest, and not~~ immediately after a meal.	**§Protocol footnote "f11"** ECG test will be performed in triplicate. *Based on FDA Comment 8, FDA*

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			Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.
	- Provide histological sample of the primary tumour or liver metastases or soft tissue metastases for central confirmation of diagnosis (Histology and Ki67)	- Provide histological sample of the primary tumour or liver metastases <u>or soft tissue metastases</u> for central confirmation of diagnosis (Histology and Ki67)	**§Protocol footnote "f3"** Soft tissue metastases is accepted as a tumor site for centralized histological tumor assessment
67	o haematology: WBC with differential count, PLTs, Hb, Mean Corpuscolar Volume (MCV)	o haematology: WBC with differential count, PLTs, Hb, Mean Corpuscolar Volume (MCV) <u>and Haematocrit</u> *(repeated at pages 68, 69, 70, 71, 72, 73, 74, 75)*	**§Protocol footnote "f3"** Haematocrit assessment added in the local laboratory tests panel
	o biochemistry: blood urea nitrogen (BUN), serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate Aminotransferase (AST/ASAT), Alanine Aminotransferase (ALT/ALAT), gamma-Glutamyl Transferase (γ-GT), sodium, potassium, Lactic Dehydrogenase (LDH), glycosylated haemoglobin (glycoHb), free Thyroxine (fT4)	o biochemistry: blood urea nitrogen (BUN), serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate Aminotransferase (AST/ASAT), Alanine Aminotransferase (ALT/ALAT), gamma-Glutamyl Transferase (γ-GT), sodium, potassium, Lactic Dehydrogenase (LDH), glycosylated haemoglobin (glycoHb, <u>haemoglobin A1C</u>), free Thyroxine (fT4), <u>calcium and glucose</u>. *(68, 69, 70, 71, 72, 73, 74, 75)*	**§Protocol footnote "f8".** Calcium and Glucose added to blood chemistry assessments. *Additional assessments added based on FDA Comment 5.b. and 5.d., FDA Memorandum dated May 18, 2012; Sponsor's reply (Response Letter-1) dated May 22, 2012.* **§Protocol footnote "f9".** Recommendation to clarify that Glyco HB is haemoglobin A1C. *Added clarification in all occurrences of the term glycoHB, based on FDA Comment 6, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*
	-	<u>Data for patients in the Dosimetry sub-study will be carefully examined for dose limiting radiation to bone marrow, kidneys, and other high-dose organs before administering each additional treatment of</u>	**§Protocol footnote "f19"** Text added in response to FDA Comment 5 in Full Clinical Hold Letter

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		^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.	
	- Perform laboratory tests (local assessment. NB: screening and baseline ~~lab~~ evaluations can be combined if sampling is within 3 weeks before the first treatment date):	- Perform laboratory tests (local assessment). NB: screening and baseline laboratory evaluations can be combined if sampling is within 3 weeks before the first treatment date (however laboratory assessments in the 177Lu-DOTA0-Tyr3-Octreotate arm should be done preferably within 2 weeks before treatment):	**§Protocol footnote "f3"** Text added to improve Protocol clarity of the laboratory tests schedule.
68	Safety assessments will be performed 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment (see section 6.5.2).	Safety assessments will be performed 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional safety assessment will be performed on the same day or within one day before each treatment (see section 6.5.2).	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment. *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
69	**Table 1: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm – Safety Assessment and Treatment Visit Schedule**	**Table 2: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm – Safety Assessment and Treatment Visit Schedule**	**§Protocol footnote "f7"** Ensure laboratory parameters meet required treatment criteria before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. *Statement added based on FDA Comment 5.e., FDA Memorandum dated May 18, 2012; Sponsor's reply (Response Letter-1) dated May 22, 2012.*
	-	Refer to Protocol Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in section 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the Protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.	
	-	Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.	**§Protocol footnotes "f12"** Advise Investigator to maintain phone contact with patient for the first week after the first treatment in both arms to verify patient status.

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			Based on: *.FDA Comment 2, and 3, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) date May 22, 2012.* *-Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 24, 2012.*
70	At all visits (in addition to exams at specific visits): At all visits (in addition to exams at specific visits):	At all visits (in addition to exams at specific visits):	**§Protocol footnotes "f3"** Redundancy deleted
70	-	Week 0 - Phone contact with the patient for the first week after the first treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate + 30 mg Octreotide LAR Depot to verify the general status of the patient.	**§Protocol footnotes "f12"** Advise Investigator to maintain phone contact with patient for the first week after the first treatment in both arms to verify patient status. *Based on:* *FDA Comment 2, and 3, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) date May 22, 2012.* *-Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 24, 2012.*
73	-	Week 0 - Phone contact with the patient for the first week after the first treatment with 60 mg Octreotide LAR Depot to verify the general status of the patient	
70, 72	- ECG (at the end of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)	- ECG (in triplicate, at the end of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)	**§Protocol footnote "f11"** ECG test will be performed in triplicate. *Based on FDA Comment 8, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*

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70	-	- At weeks 8 and 16 perform laboratory tests (local assessment) on the same day or within one day prior to administration of study drug. Safety assessments must include at minimum: o serum blood urea nitrogen and creatinine o serum total bilirubin, aspartate aminotransferase and alanine aminotransferase o hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
71	o collect sample for central evaluation of CgA (only week ~~23~~)	o collect sample for central evaluation of CgA (only week 22)	**§Protocol footnote "f3"** Typo correction
72	-	- Perform laboratory tests (local assessment) on the same day or within one day prior to administration of study drug. Safety assessments must include at minimum: - a. serum blood urea nitrogen and creatinine - b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase - c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count	**§Protocol footnote "f6a"** Additional safety assessment will be performed on the same day or within one day before treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the second, third, and fourth treatment *Revision to safety assessments based on FDA comment in Full Clinical Hold Letter, Comment 1.*
73	- Perform ECG	- Perform ECG (in triplicate) *(repeated on pages 74 and 75)*	**§Protocol footnote "f11"** ECG test will be performed in triplicate. *Based on FDA Comment 8, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) dated May 22, 2012.*
75	A Dosimetry, Pharmacokinetics and ECG	A Dosimetry, Pharmacokinetics and ECG substudy	**§Protocol footnote "f14"**

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	substudy will be performed in 20 patients at 2-3 selected ~~Sites performing~~ full body (planar) and 3D SPECT scans on the day of the first ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Blood and urine samples will be collected at different intervals after the first ^{177}Lu-DOTA^{0}-Tyr^{3}-administration.	will be performed in 20 patients at 2-3 selected sites. The substudy will be conducted, concurrent with the general study. Selected substudy sites must give high priority to early enrolment of patients into the substudy. Patients participating in the substudy will be patients who have been determined to be eligible for the general study and have been randomized into the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, and have signed an additional informed consent specific for the substudy. Aside from the specific tests conducted in the dosimetry study as described above, the patient treatment regimen and patient care management will be identical to that conducted in the general study. The patients will also be considered to be members of the general study group. As per specific request, the results of this substudy will be included in a preliminary Dosimetry Study Report that will be provided to the FDA as soon as the substudy is completed and the report written. This preliminary report will also be made available to the DSMB. The substudy patients will receieve full body (planar) and 3D SPECT scans on the day of the first ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Blood and urine samples will be collected at different intervals after the first ^{177}Lu-DOTA^{0}-Tyr^{3}-administration.	Provide further details on the substudy conduction. *Statement added based on FDA Comment 1, FDA Memorandum dated May 21, 2012, and Sponsor's reply (Response Letter-2) dated May 22, 2012; and Sponsor's Question-1 comment, reply to May 23, 2012 teleconference (Response Letter-3) dated May 23, 2012.*
76, 168	a COBRA-Packard auto-gamma ~~counting~~ system	a COBRA-Packard auto-gamma counter system	**§Protocol footnote "f3"**

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	(Packard, Meriden, Conn., USA)	(Packard, Meriden, Conn., USA) or similar system. *(repeated two times at page 166)*	Text added to improve Protocol to correctly identify auto-gamma counter equipment.
77	1. Well counter with multichannel analyzer or gamma counter to determine ^{177}Lu ~~activity~~ in blood and urine samples. 2. A dose calibrator to measure the ~~activity~~ in the reference source and the injected ~~activity~~.	1. Well counter with multichannel analyzer or gamma counter to determine ^{177}Lu radioactivity in blood and urine samples. 2. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.	**§Protocol footnote "f1"** The term "radioactivity" is more appropriate in this context. The "dose calibrator" device is also referred to as an "activimeter" in some regions.
	a. Determine the transmission factor $\Im$ ~~(= e$^{-\mu}$~~ e^{t}) For abdominal uptakes the attenuation correction is considerable and should be performed. The μe/ρ for the 208 keV window of ^{177}Lu may be determined by counting a point source during e.g. 5 minutes. This measurement must be repeated with several thicknesses of absorbing material with unit density. (In a narrow beam geometry the average tissue μ_e/ρ(208 keV) = 0.134 cm^2/g [2]).	a. Determine the transmission factor $\Im$ = exp(- $\mu_e \cdot t$) For abdominal uptakes the attenuation correction is considerable and should be performed. The μe/ρ for the 208 keV window of ^{177}Lu may be determined by counting a point source during e.g. 5 minutes. This measurement must be repeated with several thicknesses of absorbing material with unit density. (In a narrow beam geometry the average tissue μ_e/ρ(208 keV) = 0.134 cm^2/g = 0.0134 m^2/kg [2]).	**§Protocol footnote "f1"** Dosimetry formulas have been corrected
78	The calibration factor C (count rate per MBq ^{177}Lu) is measured by counting a known reference standard (usually 37-74 MBq ^{177}Lu, or 0.5-1% of	The calibration factor C (count rate per MBq ^{177}Lu) is measured by counting a known radioactivity reference standard (usually 37-74 MBq ^{177}Lu, or	**§Protocol footnote "f1"** The term "radiatioactivity" as been added to improve text clarity.

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	the injected activity; measured in the dose calibrator). Count this standard in air for 3 minutes	0.5-1% of the injected activity; measured in the dose calibrator). Count this standard in air for 3 minutes	
79-80	The total absorbed dose to red marrow will be extrapolated from the blood curve. Absorbed ~~doses~~ to target organs will be calculated by entering the ND values for all the source organs in the OLINDA/EXM software and adjusting the ~~doses~~ reported by the software for individual weight and organ masses for kidneys, liver, spleen (determined from CT), and red marrow.	The total absorbed radiation dose to red marrow will be extrapolated from the blood curve. Absorbed radiation dose to target organs will be calculated by entering the ND values for all the source organs in the OLINDA/EXM software and adjusting the radiation dose reported by the software for individual weight and organ masses for kidneys, liver, spleen (determined from CT), and red marrow.	**§Protocol footnote "f1"** The term "radiation dose" is more appropriate in this context.
80	1. . A general code for numerical and compartmental modeling is the SAAM II software (http://www.saam.com) (Cobelli C et al., 1998).	1. A general code for numerical and compartmental modeling is the SAAM II software (http://www.saam.com) (Cobelli C et al., 1998). Based on time-activity blood curve, the main pharmacokinetic parameters will be calculated, such as systemic exposure, clearance, volume of distribution, and terminal half-life.	**§Protocol footnote "f15"** Pharmacokinetic parameters will be calculated based on time-activity blood curves, and include systemic exposure, clearance, volume of distribution, and terminal half-life. *Statement added based on FDA Comment 10, FDA Memorandum dated May 18, 2012, and Sponsor's reply (Response Letter-1) date May 22, 2012.*
81	~~activity~~	amount of radioactivity	**§Protocol footnote "f1"** The term "amount of radioactivity" is more appropriate in this context.
85	~~The overall event rate in the trial will be monitored to assess the extent to which the trial is achieving the design assumptions. This could be undertaken by the Trial Management Group, blind to the treatment under which each event occurs. The determination of this overall event rate could trigger potential modfications to the trial design~~	-	**§Protocol footnote "f16"** Delete statement regarding monitoring the event rate in the trial for the purpose of potential modification to the trial design. *Paragraph deleted based on FDA Comment 7, FDA Memorandum dated May 21, 2012, and Sponsor's reply*

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	~~during the trial.~~		*(Response Letter-2) dated May 22, 2012.*
87	-	An Independent Data Safety Monitoring Board will evaluate patient safety throughout the study (§ Section 12.1 - Independent Data Safety Monitoring Board).	**§Protocol footnote "f13"** Describe in greater detail the interim safety analysis plan. *Based on request by FDA in Full Clinical hold letter, Comment-2.*
89	~~Not applicable. There are no interim analyses planned for this study.~~	Interim safety analyses will be conducted by an Independent Data Safety Monitoring Board (§ Section 12.1 - *Independent Data Safety Monitoring Board*). This Board will provide the Sponsor with a recommendation to continue the trial as planned, or to discontinue the trial, according to the Safety Analysis Plan. This Plan is described in detail in the Data Safety Monitoring Board (DSMB) Charter, provided as separate document. As described in the DSMB Safety Plan (Appendix 1, DSMB Charter) the DSMB will conduct 4 interim safety analyses that will be initiated at the time when 25%, 50%, 75% and 100% percent of the total ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments in the trial have been completed (that is out of 400 planned treatments), or where such treatments would have taken place had treatment not been withdrawn form subjects in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm. The DSMB will meet and assess up-to-date safety information within two weeks of a treatment exposure rate being achieved (i.e., the point when 25%, 50%, 75%, and 100% of treatments have occurred). Further patients may only be randomized two weeks after the treatment exposure rate has been reached and after a positive opinion from the DSMB.	**§Protocol footnote "f13"** Describe in greater detail the interim safety analysis plan. *Based on request by FDA in Full Clinical hold letter, Comment-2.*

Page*	Previous version *V 1.0, November 14th, 2011*	New version *Final V 2.0, August 28th, 2012*	Change reason
107	An Independent Data Monitoring ~~Committee (IDMC)~~ will evaluate safety throughout the study. The ~~IDMC~~ will be independent from the Sponsor, specific agents of the Sponsor, Investigators, and any other study oversight bodies. The ~~IDMC~~ will review ongoing examinations of safety data and promptly give recommendations to continue, continue with modification, or terminate the study. ~~The IDMC monitoring plan will be provided as a separate charter.~~	An Independent Data Safety Monitoring Board (DSMB) will evaluate safety throughout the study. The DSMB will be independent from the Sponsor, specific agents of the Sponsor, Investigators, and any other study oversight bodies. The DSMB will review ongoing examinations of safety data and promptly give recommendations to continue, continue with modification, or terminate the study. The DSMB Charter, and the DSMB Safety Plan (Appendix 1 of the DSMB Charter) are provided as separate documents.	**§Protocol footnote "f13"** Describe in greater detail the interim safety analysis plan. *Based on request by FDA in Full Clinical hold letter, Comment-2.*
124	**4.4 Evaluation of Best Overall Response**	**4.4 Evaluation of Best Overall Response [NB: see Protocol Section 6.3 for assessment methods and endpoints]**	**§Protocol footnote "f2"** Responses to treatment are recorded from date of randomization, instead of from date of first treatment. *Revision to response to treatment determination based on FDA Comment 3, FDA Memorandum dated May 21, 2012, and Sponsor's reply (Response Letter-2) date May 22, 2012.*
144	-	[**NB: 220 MBq is the recommended amount of administered radioactivity for this trial, according to Appendix 6, Part 2**].	**§Protocol footnote "f1"** Additional text to improve Protocol clarity on the OctreoScan® Planar Imaging Protocol.
160	**Figure 1: Flebo Infusion Method (A) Showing Operations Details (B).** ~~From US Patent *No.* US 7842023~~	**Figure 2: Flebo Infusion Method (A) Showing Operations Details (B, C, D)**	**§Protocol footnote "f3"** Figures added to improve Protocol clarity of Flebo infusion system method.
169	Appendix 11 – Dosimetry and Pharmacokinetics Study: Time Schedule for Biological Samples	Appendix 11 – Dosimetry and Pharmacokinetics Study: Time Schedule for Biological Samples	**§Protocol footnote "f3"** Typos on urine collection time points corrected

Page*	Previous version *V 1.0, November 14th, 2011*	New version *Final V 2.0, August 28th, 2012*	Change reason
		(two lines added in the urine collection table)	
172	-	Tables "Investigations"	**§Protocol footnote "f3"** National Cancer Institute Common Terminology Criteria for *Investigations Adverse Events* added.
176	~~The therapeutic benefit~~ of this medicine is due to the presence of the radioactivity.	We think that the potential activity of this medicine in treating your tumour is due to the presence of the radioactivity.	**§Protocol footnote "f20"** *Revision based on FDA Comment 10, stated in Full Clinical Hold Letter, Comment 10.*
	It is ~~known~~ that the health risks of this medicine are low because of its physical and radiopharmaceutical properties and its metabolic properties. ~~Nevertheless~~, the following rules ~~will ensure a high level of~~ safety.	It is estimated that the health risks of this medicine to your family members and the general public are low because of its physical and radiopharmaceutical properties and its metabolic properties. You must adhere to the following rules to maximize the safety of other persons.	
	-	Furthermore, after you receive treatment, empty your bladder (urinate) every hour on the day of treatment and for two more days after treatment. After expelling fluids, drink a glass of water. You can substitute juice or a sports drink as a means to replace expelled fluids. Follow any additional advice that your doctor provides on how much to drink.	**§Protocol footnote "f17"** Modification to appendix 15 regarding instructions to patients on frequency to urinate, and drink fluids. *Revision based on FDA Comment 5, stated in Sponsor's reply to teleconference comment (Response Letter-3) dated May 22, 2012.*
180	specific activity of 48 GBq/~~umol~~ at calibration time	specific activity of 48 GBq/µmol at calibration time	**§Protocol footnote "f3"** Typo correction
183	-	Figure: Lead container inserted in the plastic container.	**§Protocol footnote "f3"** Figure added to improve Protocol clarity.
184	~~The vials must not be opened. After disinfecting~~	~~The vials must not be opened. After disinfecting~~	**~~§Protocol footnote "f3"~~**

Page*	**Previous version** *V 1.0, November 14th, 2011*	**New version** *Final V 2.0, August 28th, 2012*	**Change reason**
	the stopper, the solution ~~should~~ be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.	the stopper, the vial must be connected to the needle of the infusion system (§Appendix 8: Example 1 (Two Pumps Method) or Example 2 (Flebo Infusion Method)). The 'Two Pumps Method' and the 'Flebo Infusion Method' are the recommended infusion systems for this trial. However, if a syringe infusion system is available at the centre this can be used, provided that the dose calibrator (activimeter) calibration is done for both the vial and the syringe. In addition, the radioactivity must be measured, before and after the infusion, in both the vial and the syringe. After disinfecting the stopper, the solution must be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.	Text added to improve Protocol clarity of infusion system methods.
	-	The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes.	**§Protocol footnote "f3"** Text added to improve Protocol clarity of Lutathera vial, visual inspection method.
187	G_a probability: 0.40 G_b probability: 0.60	G_a probability: 0.25 G_b probability: 0.75	**§Protocol footnote "f3"** The proposed change in the set of probabilities (if $G_a > G_b$ then the probability to assign next patient to treatment b is 0.75) maintains a higher control on the chance of treatment imbalance (Pocock SJ et al., 1975) while the unpredictability on the next assignment is kept. As the randomization is centralized: o No single investigator is aware of treatment assignments at other sites and consequently it is impossible for him to

Page*	**Previous version** *V 1.0, November 14th, 2011*	**New version** *Final V 2.0, August 28th, 2012*	**Change reason**
			determine for his next patient that treatment *k* which minimizes G_k. o If his site has fewer patients on one particular treatment arm he may guess that the other treatment arm will be chosen, but with three stratification factors contributing to $\{G_k\}$ and a probability to 0.25 to assign next patient to treatment arm that increase the imbalance he would be wrong in a high proportion of cases.
191	-	Appendix 19 – Determination of LUTATHERA Administered Radioactivity *(the entire appendix has been added)*	**§Protocol footnote "f18"** Appendix added to provide instructions on calculation of LUTATHERA Administered Radioactivity

September 11, 2013

NETTER- 1 Study: A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.
PROTOCOL N° AAA-III-01; EudraCT N° 2011-005049-11; IND N° 77219
SPONSOR: Advanced Accelerator Applications SA,

RE:Submission of Protocol Amendment Version 3.0, July 24th, 2013 (replaces version 2.0, August 28th, 2012)

MAIN ISSUES ADDRESSED IN PROTOCOL Version 3.0

- **FDA COMMENT:**

We strongly discourage you from using biased coin randomization. If biased coin randomization is used, then the primary analysis should be a re-randomization test. This would involve reproducing the randomization, accounting for subject stratification factors and time of randomization, a large number of times and conducting a permutation test on this basis

The Clinical Protocol, version 3.0 has been amended to address the Agency's request (see Section 5.6, Section 7, and Appendix 17)

- **FDA COMMENT:**

Because there are approximately 41 centers and 200 patients, you may consider dropping center as a stratification factor.

The Clinical Protocol, version 3.0 has been amended to address the Agency's request (see Section 5.6 and Appendix 17)

FDA COMMENT:
You have proposed three secondary endpoints and have not controlled for multiplicity. Since time to tumor progression (TTP) and PFS are correlated, it is highly unlikely that the results of TTP will be included in the product labeling. Include a method to control the family-wise type I error rate for the two other secondary endpoints.

The Clinical Protocol, version 3.0 has been amended to address the Agency's request (see Section 7.5 and 7.5.2).

FDA COMMENT:
Even though the analysis for overall survival (OS) may be underpowered, please provide a statistical analysis plan for OS including the difference to be detected, power, the number of deaths for the final OS analysis, and the estimated number of deaths for an interim OS analysis at the final PFS analysis.

The Clinical Protocol, version 3.0 has been amended to address the Agency's request (see Section 7.1).

FDA COMMENT:
Since the power calculation of a log-rank test is based on the number of events, please perform the final analysis based on the planned number of events. You propose that "The End of Study is defined as the moment that the last enrolled patient has completed 72 weeks of assessments (unless early termination) after the patient's first treatment in either arm of the study," which is not acceptable.

The Clinical Protocol, version 3.0 has been amended to address the Agency's request. The Final Analysis will occur at the moment the planned number of events (disease progression or death) has occurred (Sections amended: Section 3.2 End of Study; Section 7.5.1; and other sections have been amended to account for the change in the End of Study point).

FDA COMMENT:
All randomized patients should be included in the primary analysis, regardless of whether they received study medication, and no replacement should be done.

The Clinical Protocol, version 3.0 has been amended to address the Agency's request (see Section 4.5).

FDA COMMENT:
Specify whether the primary log-rank test is a stratified or un-stratified.

The Clinical Protocol, version 3.0 has been amended to address the Agency's request (see Sections 7.5.1, and 7.5.2)

ADDITIONAL ISSUES AND RESPONSES (Protocol changes at the request of European regulatory authorities)

The German Radioprotection Authority has requested that "metastatized primary tumour" be added to requirement for inclusion.

The Sponsor has agreed to this request and has made appropriate modifications to the Protocol to include metastatic disease in the inclusion criteria (see Section 3.3; Section 4.1.1; other sections of the Protocol have been amended to account for this change).

ADDITIONAL ISSUES AND RESPONSES (Protocol changes at the request Investigators)

- *The timing of the CT or MRI scans prior to enrollment is not clear.*

The Sponsor has amended the inclusion criterion (#5 Protocol) to explain more clearly the requirements for timing CT and MRI scans. Other sections of the Protocol have been amended to account for this change.

- *The requirements for the timing of the Octreotide® scan prior to enrollment are not clear.*

The Sponsor has amended the inclusion criterion #6 to clarify the correct timing of the Octreotide® scan – the scan must be obtain at least 12 weeks after the start of Somatostatin analog therapy.

- *What are the recommended medication to give patients who become nauseated during infusion with the amino acid solution infusion (with* ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate *treatment).*

The Sponsor has amended the Protocol to include use of medications to treat patients who become nauseated (and/or vomit) during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion (see Section 5.7.2).

ADDITIONAL ISSUES AND RESPONSES (Sponsor initiated changes)

The term "technically evaluable lesion" is confusing and not defined.

The Sponsor has amended the inclusion criterion (#6, Protocol) to explain more clearly which lesions must be somatostatin receptors positive. The term "technically evaluable lesion" has been deleted and replaced where appropriate with RECIST v1.1, defined terms; target lesion, non-target lesion, and measurable lesion.

FOOTNOTE LIST OF PROTOCOL CHANGES (Version, 02 Oct 2013)

*Page refers to Protocol V 3.1 REDLINE version

Page**	**Previous version** *V 3.0, July 24th, 2013*	**New version** *V 3.1, September 23rd, 2013*	**Change reason**
1, 15	FINAL version 3.0, July 24th, 2013 (Replaces version 2.0, August 28th, 2012)	**FINAL version 3.1, September 23rd, 2013 (Replaces version 3.0, July 24th, 2013)**	Protocol version updated
whole document	enrolment	enrollment	Typo correction
whole document	metastasized	metastasized	Typo correction
whole document	tumor	tumour	Typo correction
whole document	177Lu-DOTA0-Tyr3-Octreotate	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	Typo correction
34	A 20 patient Dosimetry, Pharmacokinetics, and ECG study will be performed in about 1-2 selected sites.	A 20 patient Dosimetry, Pharmacokinetics, and ECG study will be performed in about **5** selected sites.	Increased number of sites participating in the substudy
45, 75	There are a number of studies published which demonstrate that commercial and custom made amino acid solutions reduce the kidney retention of radiolabeled somatostatin analogs in humans. Researchers at the Erasmus MC have directly demonstrated the benefit of 2.5% lysine/arginine in 1L solution in blocking kidney retention of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreoate.	There are a number of studies published which demonstrate that commercial and custom made amino acid solutions reduce the kidney retention of **radiolabelled** somatostatin **analogues** in humans. Researchers at the Erasmus MC have directly demonstrated the benefit of 2.5% lysine/arginine in 1L solution in blocking kidney retention of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreo**t**ate.	Typos correction
76-77	The substudy patients will receive full body (planar) and 3D SPECT scans on the day of the first ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Blood and urine samples will be collected at different intervals after ^{177}Lu-DOTA^{0}-Tyr^{3}-administration. All patients included	The substudy patients will receive full body (planar) and 3D SPECT scans on the day of the ~~**first**~~ ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Preferably dosimetry should be performed at treatment cycle 1, but dosimetry at cycle 2 or cycle 3 are also acceptable**. In the**	Provide additional details on the dosimetry substudy procedures. Allow dosimetry cycle 2 or cycle 3, in addition to cycle 1. Make as optional dosimetry procedures at

Page**	Previous version *V 3.0, July 24th, 2013*	New version *V 3.1, September 23rd, 2013*	Change reason
	in the substudy will undergo a 24-hour continuous ECG recording via a 12-lead Holter machine. Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and 168 h (or within 156-168 h). The time point ranges indicated in brackets are to be considered if the specific timepoint is not feasible. 3D SPECT scans will be performed at 24 h and 48 h in the upper abdomen (comprising kidneys, liver and spleen) and, if deemed necessary based on the outcome of the planar imaging, also in different regions. Blood samples (whole blood) will be collected from each patient just before administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapeutic dose from the opposite arm of drug infusion and then at the following time-points:two time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 64 and 72 h (Day 4), 160 and 168 h (Day 8).	**event that dosimetry measurements are performed after cycle 2 or 3 only the dose estimates for the kidneys and the bone marrow can be used in the overall evaluation, as the tumours (and by that also liver) and spleen may be influenced by the prior therapy effect. In the same treatment cycle,** blood and urine samples will be collected at different intervals after ^{177}Lu-DOTA^{0}-Tyr^{3}-administration. All patients included in the substudy will undergo a 24-hour continuous ECG recording via a 12-lead Holter machine. Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h) and 72 h (or within 60-72 h). If one or more images are skipped or are not performed at the correct time, then an additional whole body scan will be scheduled at 168 h (or within 156-168 h). Patients that live in the vicinity of the clinic can be requested to come back for the last whole body scan at 168 h, in that case the whole body imaging at 48 h could be skipped. ~~Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and 168 h (or within 156-168 h).~~ The time point ranges indicated **above** in brackets are to be considered if the specific timepoint is not feasible. 3D SPECT scans will be performed at 24 h and 48 h in the upper	Day8. Correct typos

Page**	Previous version *V 3.0, July 24th, 2013*	New version *V 3.1, September 23rd, 2013*	Change reason
		abdomen (comprising kidneys, liver and spleen) and, if deemed necessary based on the outcome of the planar imaging, also in different regions. Blood samples (whole blood) will be collected from each patient just before administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapeutic dose from the opposite arm of drug infusion and then at the following time-points: two time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), **60** and 72 h (Day 4), ~~160 and 168 h (Day 8).~~ If one or more blood samplings are skipped or are not performed at the correct time, an additional blood sampling will be scheduled at 168 h (or within 156-168 h). Patients that live in the vicinity of the clinic can be requested to come back for the last blood sampling at 168 h.	
78	The uptake of peptides in liver, spleen and kidneys occurs almost immediately. Based on previous experience (Phase I/II Erasmus study) the proposed measurement points are at approximately 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and 168 h (or within 156-168 h) after administration.	The uptake of peptides in liver, spleen and kidneys occurs almost immediately. Based on previous experience (Phase I/II Erasmus study) the proposed measurement points are at approximately 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and **optionally** 168 h (or within 156-168 h) after administration **(see section 6.6).**	Make as optional dosimetry procedures at Day8.
80, 167, 168	Blood samples will be taken just before administration of the therapeutic dose and	Blood samples will be taken just before administration of the therapeutic dose and at	Make as optional dosimetry procedures at Day8.

Page**	**Previous version** *V 3.0, July 24th, 2013*	**New version** *V 3.1, September 23rd, 2013*	**Change reason**
	at the following time-points: 2 time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 64 and 72 h (Day 4) and 160 and 168 h (Day 8).	the following time-points: 2 time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), **60** and 72 h (Day 4) and **optionally 156** and 168 h (Day 8) **(see section 6.6).**	Correct typos
95	If the Investigator is not able to access the eCRF, a paper version of the SAE form is available on the study documentation at site and this form should be completed and sent by fax to Sponsor Pharmacovigilance Department in order to report the SAE. When the access problem is resolved, the investigator must report the event into the eCRF.	If the Investigator is not able to access the eCRF, a paper version of the SAE form is available on the study documentation ~~**at**~~ site and this form should be completed and sent by fax to **the** Sponsor Pharmacovigilance Department in order to report the SAE. When the access problem is resolved, the investigator must report the event into the eCRF.	Correct typos

Protocol No AAA-III-01, V4.0
TABLE OF CHANGES

*Page refers to Protocol V 4.0- REDLINE version

Page**	Previous version *V 3.0, July 24th, 2013*	New version *V 4.0, March 25, 2014*	Reason for change
Within the entire document	-	**Typos correction or minor changes**	**Improving the document clarity and correcting remaining typos**
1, 21	FINAL version 3.0, July 24th, 2013 (Replaces version 2.0, August 28th, 2012)	Protocol N° AAA-III-01, version 4.0, March 25, 2014 Replaces version 3.0, July 24, 2013 and version 3.1, September 23, 2013	Protocol version updated
2-21	-	HEAD OF CLINICAL DEVELOPMENT Claude Hariton, Ph.D., DSc Advanced Accelerator Applications SA Tel:+33 681 587 825 E-mail: claude.hariton@adacap.com	Update Sponsor contact information
4, 36	-	- To evaluate the Duration of Response (DoR) in the two study arms; - To evaluate the Time to Second Progression (PFS2) in the two study arms	Added two secondary exploratory objectives
4	Objective tumour response in both arms will be assessed every 12±1 weeks from the randomization date according to RECIST Criteria. The baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date.	Objective tumour response in both arms will be assessed every 12±1 weeks from the randomization date according to RECIST Criteria until progression centrally confirmed. The baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date. In order to provide a consistent CT/MRI scan	Clarify baseline CT scan time-point and the need to follow patients after week 72 (treatment and assessment), until 74 events are reached. Only centrally confirmed progressions will be considered

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		timepoint between the two arms of the study it may be necessary for the site to repeat the baseline CT scan immediately before randomization if the CT timepoint is greater than 4 weeks before randomization to provide more current lesion data. - Any progressive patient (confirmed by central review of CT scans) ceases treatment/assessment and proceeds to long-term follow-up. - Any non-progressive patient continues treatment/assessments until the PFS Primary End-Point is met (i.e. 74 evaluable and centrally confirmed disease progressions or death events). Once the Primary End-Point is reached, a. Patients who have received more than 76 weeks treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last patient randomized. b. Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last patient During the long-term follow-up assessment phase, toxicities suspected in relation with the study drug (including haematology, biochemistry, urine analyses), anti-tumour treatment administered	for the primary PFS analysis.

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		after progression/discontinuation, disease status based on local CT/MRI assessment, and OS data will be collected every 6 months (phone contact or visit at site). In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.	
5	**^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm** 30 mg Octreotide LAR treatment for symptom control will continue until Week 72, unless the patient progresses or dies;	**^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm** 30 mg Octreotide LAR treatment for symptoms control will continue until ~~the end of the study~~the PFS Primary End-Point, unless the patient progresses or dies. When the PFS endpoint has been reached, the treatment/assessment period becomes fixed and all patients receive 30 mg for 72 weeks before entering the long-term assessment follow-up phase.	Clarify that Octreotide LAR treatment will continue until the PFS Primary End-Point
5	**Octreotide LAR arm:** 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) ± 3 days until the End of the Study, unless the patient progresses or dies;	**Octreotide LAR arm:** 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) ± 3 days until the ~~end of the study~~ PFS Primary End-Point~~, unless the patient progresses or dies,~~ unless the patient progresses or dies (see below for Dose Modifying Toxicity (DMT)~~ below~~). When the PFS endpoint has been reached, the treatment/assessment period becomes fixed and all patients receive 60 mg for 72 weeks before entering the long-term assessment follow-up phase.	Clarify that Octreotide LAR treatment will continue until the PFS Primary End-Point
5	**Dose modifying toxicity** According to National Cancer Institute	**Dose modifying toxicity** ~~According to~~With reference to the grading system	Correct typos, provide more details on Dose Modifying

Page**	Previous version *V 3.0, July 24th, 2013*	New version *V 4.0, March 25, 2014*	Reason for change
	Common Terminology Criteria for Adverse Events Version 4.0 DMT is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity possibly related to study drug and regardless of its duration. **If the patients experiences DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy**, the subsequent treatments of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. After resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient goes off-study. If the DMT event does not reoccur, the next treatment is at full dose.	of the NCI (National Cancer Institute, ~~(~~Common Terminology Criteria for Adverse Events Version 4.0), DMT in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity possibly related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate ~~study drug~~ and regardless of its duration. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and regardless of its duration. The DMT principles will also be applied if renal – hepatic – hematological adverse events are observed which are unlikely related to the study drug, but to other possible or concomitant causes, and the full administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate would represent a safety risk for the patient. In the Sandostatin LAR arm a dose adjustment scheme will also be applied in case of NCI Grade 3 or 4 toxicity possibly related to study drug. **If the patient~~s~~ experiences DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy**, the subsequent treatments of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg Sandostatin LAR at monthly intervals. After	Toxicity rules

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		resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT reoccurs after treatment with the reduced dose~~,~~ or the DMT does not resolve within 16 weeks, the patient ~~goes off~~ stops further treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate but continues the study with monthly Sandostatin LAR 30 mg (if Sandostatin LAR is unlikely to be the causative agent of the observed toxicity). If the DMT event does not reoccur, the next treatment is administered at full dose.	
6	Projected 43 months total: 25 months recruitment (Last Patient In: Q2 2014) and 18 months treatment and assessments until the Last Patient Out (Q4 2015). Long-term toxicities suspected in relationship to the study drug (included haematology, biochemistry, urine analyses), PFS (based on local assessments), OS data will be collected every 6 months for 3 years after Week 76 or early termination for each patient (phone contact or visit at site).	Study Duration : ~~Projected 43 months total: 25 months recruitment (Last Patient In: Q2 2014) and 18 monthstreatment and assessments until the Last Patient Out (Q4 2015).~~ 1. Total number of randomized patients: 230 2. First Patient In: Q3 2012 3. Pre-defined accrual period: 18 months 4. Expected Last Patient In: Q3 2014 5. PFS primary analysis point occurs at 74 evaluable and centrally confirmed disease progressions or death events. 6. Long term follow-up: 5-years from the date of randomization of the last randomized patient. 7. End-of-Study (EOS): when 158 deaths are recorded or when 5 years from the date of randomization of the last randomized patient	Clarify that Octreotide LAR treatment will continue until the PFS Primary End-Point. Clarify that only centrally confirmed progressions will be considered for the primary PFS analysis. The end-of-study is now defined as the last pre-specified safety or efficacy data point collected during the conduct of the study, 158 death events (or when 5 years from the randomization of the last randomized patient have elapsed, whichever comes first), which is the endpoint for overall

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		have lapsed, whichever occurs first. 8. OS primary analysis point occurs at 158 deaths or 5 years from the date of randomization of the last randomized patient, whichever occurs first. The primary analysis is performed at 74 events (74 evaluable disease progressions centrally confirmed or death events). Patients who are randomized should continue to receive the assigned treatment until tumour progression or until the PFS Primary End-Point is reached. After the PFS Primary End-Point has been reached, the treatment/assessment period becomes fixed and all patients receive 60 mg (Octreotide LAR arm) or 30 mg (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) until week 72 and then proceed to the long-term follow-up assessment phase. ~~Long-term toxicities suspected in relationship to the study drug (included haematology, biochemistry, urine analyses), PFS (based on local assessments), OS data will be collected every 6 months for 3 years after Week 76 or early termination for each patient (phone contact or visit at site).~~ EOS is defined as the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.	survival assessment, and not the time of the primary analysis of PFS. **Procedures timing corrected within the entire document according to the new Primary End-Point analysis and EOS time-points**
7	Planned number of patients: 200 randomized patients (considering the	Planned number of patients: ~~200~~ 230 randomized patients (~~considering the~~	As requested by the Regulatory Agencies, the sample size of the

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	drop-out rate, 100 patients per treatment group will be randomly assigned to open-label treatment).	~~drop-out rate, 100~~ 115 will be randomly assigned to open-label treatment).	study has been adjusted in order to detect a statistically significant and clinically relevant difference in OS (80% power) between the two arms of the study.
8; 48	Exclusion criteria n 1 Serum creatinine >150 µmol/L or >1.7 mg/dL, or a measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) of <50 mL/min.	Exclusion criteria n 1 ~~Serum creatinine >150 µmol/L or >1.7 mg/dL, or a measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) of <50 mL/min.~~ Either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min calculated by the Cockroft Gault method, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) <50 mL/min (the measured creatinine clearance / GFR is required only as confirmatory exam).	Clarify that at baseline the measured creatinine clearance / GFR is required only as confirmatory exam.
10	Long-term follow-up after Week 76 or early termination Long-term toxicity to critical organs (bone marrow and kidney) suspected in relationship to the study drug (including haematology, biochemistry, urine analyses) will be monitored every 6 months for 3	Long-term follow-up after ~~Week 76~~End of Study treatment or early termination Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up assessment. Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point, then:	Clarify that treatment/assessment phase will continue until the PFS Primary End-Point, then will return to the fixed 76-week scheme. Clarify that only centrally confirmed progressions will be used for the primary PFS analysis.

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	years after Week 76 or early termination. PFS (based on local assessments) and OS data will be recorded every 6 months for 3 years after Week 76 or early termination. Phone contacts or site visits will be performed during the 3 years follow-up after end of the study.	a. Patients who have 76week or more treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last randomized. b. Remaining randomized patients continue in the fixed 76-week treatment/assessment phase unless progression occurs, then proceed to the long-term follow-up assessment phase for 5 years overall from the date of randomization of the last randomized patient. Sponsor will notify all the Centres and their Ethic Committees as soon as 74 evaluable disease progressions or death events (PFS Primary End-Point) have occurred. During the long-term follow-up assessment phase, toxicities suspected in relation with the study drug (including haematology, biochemistry, urine analyses), anti-tumour treatment administered after progression/discontinuation, disease status based on local CT/MRI assessment, and OS data will be collected every 6 months (phone contact or visit at site). In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site. ~~Long-term toxicity to critical organs (bone~~	Increase the follow-up period from 3 to 5 years

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		~~marrow and kidney) suspected in relationship to the study drug (including haematology, biochemistry, urine analyses) will be monitored every 6 months for 3 years after Week 76 or early termination.~~ ~~PFS (based on local assessments) and OS data will be recorded every 6 months for 3 years after Week 76 or early termination.~~ ~~Phone contacts or site visits will be performed during the 3 years follow-up after end of the study.~~	
10	End Of Study Definition The End of Study is defined as the moment that 75 disease progression or death events have occurred.	End Of Study Definition ~~The End of Study is defined as the moment that 75 disease progression or death events have occurred.~~ The End of Study (EOS) is defined as the moment when 158 deaths have occurred, or 5 years have elapsed since the date of randomization of the last randomized patient, whichever occurs first.	Modify the End Of Study definition as requested by the Regulatory Agencies. The end-of-study is now defined as the last pre-specified safety or efficacy data point collected during the conduct of the study, 158 death events (or when 5 years from the randomization of the last randomized patient have elapsed, whichever comes first), which is the endpoint for overall survival assessment, and not the time of the primary analysis of PFS.
10; 59	Dosage In total 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administered in four	Dosage In total 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administered in four equally divided doses. Each dose to be infused over 30 minutes.	Provide details on the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion duration

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	equally divided doses.		
11	Progressive disease as determined by RECIST Criteria;	Centrally confirmed ~~P~~progressive disease as determined by RECIST Criteria;	Clarify that only centrally confirmed progressions will be considered for the primary PFS analysis.
11	Efficacy Long-term toxicity to critical organs suspected to be study drug related will be monitored every 6 months for 3 years after Week 76 or early termination.	Efficacy Objective CT/MRI tumour assessment in both arms will be performed every 12±1 weeks from the randomization date ~~until End of Study~~ (central assessment). Every effort should be made to avoid differences between these timings for patients in the two arms. Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up assessment. Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point, then: a. Patients who have 76 weeks or more treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last patient randomized; b. Remaining randomized patients continue the fixed 76week treatment/assessment period unless progression occurs, then continue the	As requested by the Regulatory Agencies, the sample size of the study has been adjusted in order to detect a statistically significant and clinically relevant difference in OS (80% power) between the two arms of the study. Sponsor also agreed to increase the follow-up period from 3 to 5 years.

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		long-term follow-up assessment for 5 years overall from the date of randomization of the last patient randomized. Date of death will be recorded at any time during the treatment/assessment phase and the long term follow-up assessment phase, when known.	
11	Safety Safety assessments will be performed2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and every 12±1 weeks from the randomization date in both study arms. In addition, for the second, third, and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional safety assessment will be performed on the same day of treatment, or within one day before treatment. Long-term toxicity to critical organs suspected to be study drug related will be monitored every 6 months for 3 years after Week 76 or early termination.	Safety Safety assessments will be performed within 2 weeks before and 4±1 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and every 12±1 weeks from the ~~randomization~~ first treatment date in both study arms. In addition, for the second, third, and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional safety assessment will be performed on the same day of treatment, or within one day before treatment. Long-term toxicity to critical organs suspected to be ~~study drug~~ related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be monitored every 6 months ~~for 3 years~~ until the End of Study~~Week 76 or early termination~~.	Clarify timing for safety assessments
12	Sample size POWER Procedure Log-Rank Test for Two Survival Curves (SAS 9.2) based on the following assumptions: Median PFS for group 1 (Octreotide	Sample size POWER Procedure Log-Rank Test for Two Survival Curves (SAS 9.2) based on the following assumptions: – Median PFS for group 1 (Octreotide LAR): 14 months	As requested by the Regulatory Agencies, the sample size of the study has been adjusted in order to detect a statistically significant and clinically relevant difference in OS (80% power) between the

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	LAR): 14 months Median PFS for group 2 (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate): 30 months Nominal Power: 90% Alpha: 0.05 Accrual period: 0 months (patients enrolled over 14 month period but follow-up for each patients is fixed at 72 weeks) Follow-up period: 18 months (72 weeks) Based on the above median PFS assumptions, a sample size of 162 patients in total with an expected number of 75 events is obtained. Controlling for a drop-out rate of approximately 20% a total of 200 patients (100 patients per treatment group) will be randomized and treated. This sample size also provides the availability of sufficient safety data.	– Median PFS for group 2 (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate): 30 months – Nominal Power: 90% – Alpha: 0.05 ~~– Accrual period: 0 months (patients enrolled over 14 month period but follow-up for each patients is fixed at 72 weeks)~~ ~~– Follow-up period: 18 months (72 weeks)~~ – Pre-defined accrual period: 18 months – Follow-up period: 18 months Based on the above median PFS values, a sample size of ~~162~~ 124 patients with an expected number of ~~75~~74 events (disease progression centrally confirmed or death due to any cause) is ~~obtained~~ needed. ~~Controlling for a drop-out rate of approximately 20% a total of 200 patients (100 patients per treatment group) will be randomized and treated. This sample size also provides the availability of sufficient safety data.~~ However, the sample size of the study has also been adjusted in order to detect a statistically significant and clinical relevant difference in the overall survival (OS, secondary end-point, (80% power) between the two arms of the study, with the following assumptions: – Median OS for group 1 (Octreotide LAR): 32 months – Median OS for group 2 (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate): 50 months – Nominal power: 80%	two arms of the study.

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		− Alpha: 0.05 − Number of Patients: 230 − Pre-defined accrual period: 18 months − Study duration (treatment/assessment phase and long-term follow-up assessment): 60 months Accordingly, 230 patients will be randomized. The length of the overall survival assessment period includes a pre-defined 18-month accrual period, and a 5 years treatment and follow-up period. The 5-year period of treatment and follow-up is the predicted length of the study.	
13	Statistical analysis The primary efficacy variable of this study is PFS. The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method and the stratified log-rank test incorporating the randomization factors will be used to compare the PFS between the two treatment groups. The secondary efficacy variables are: Objective Response Rate (ORR), Time to Tumour Progression (TTP) and OS. Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups	Statistical analysis The primary efficacy variable of this study is PFS from the randomization date. The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method and the unstratified log-rank test ~~incorporating the randomization factors~~ will be used to compare the PFS between the two treatment groups. The secondary efficacy variables are: Objective Response Rate (ORR), Time to Tumour Progression (TTP) and OS. Duration of Response (DoR) and Time to Second Progression (PFS2) will be descriptively analyzed as secondary explorative end-points. Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in	Provide further details on the PFS calculation method. The protocol and statistical analysis plan have been amended accordingly in order to state that the primary analysis of PFS will be an unstratified log-rank test, as requested by the Regulatory Agencies. Include Duration of Response (DoR) and Time to Second Progression (PFS2) as secondary exploratory end-points.

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	will be compared by Fisher's exact test. OS and TTP will be similarly analyzed as the primary efficacy variable.	the two treatment groups will be compared by Fisher's exact test. OS and TTP will be similarly analyzed as the primary efficacy variable. OS will not be censored if a patient receives other anti-tumour treatments after study medication. Survival data will be analyzed at the time of the primary end-point (PFS) analysis, and at the moment when 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever is first.	
The revised Protocol flow-charts (tables I-II) are reported at the end of this document			
32	Everolimus (Afinitor® Tablets, Novartis Pharmaceuticals Corporation, an oral inhibitor of mammalian target of rapamycin (mTOR)) has been approved in the US for treatment of progressive neuroendocrine tumors of pancreatic origin, but not for any other GEPNET indication. Approval for the same indication in Europe is presumed to be pending.	Everolimus (Afinitor® Tablets, Novartis Pharmaceuticals Corporation, an oral inhibitor of mammalian target of rapamycin (mTOR)) has been approved in the US for treatment of progressive neuroendocrine ~~tumors~~tumours of pancreatic origin, but not for any other GEPNET indication. ~~Approval for the same indication in Europe is presumed to be pending.~~ Afinitor has also been approved in the EU for the treatment of progressive unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin.	Correct a typo and update the Protocol
37	If a patient experiences a Dose Modifying Toxicity (DMT) during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves	If a patient experiences a Dose Modifying Toxicity (DMT) during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks	Provide further details on Dose Modifying Toxicity procedures

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	within 16 weeks following the non-tolerated administration. After resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient goes off- .study If the DMT event does not re-occur, the next treatment is at full dose. Patients in the comparator arm will receive 60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) intramuscular (i.m.) injections every 4 weeks ± 3 days., for the overall 72 weeks of therapy, unless the patient progresses or dies. If the patient experiences toxicity with the increased dose, the dose will be adjusted to the previous well-tolerated dose, to be increased again with the next treatment to 60 mg.	following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg Sandostatin LAR at monthly intervals. After resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient ~~goes off~~ will no longer receive any ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate but continues the study with monthly Sandostatin LAR 30 mg (if Sandostatin LAR is unlikely to be the causative agent of the observed toxicity), and continues scheduled scans, until progression; after progression, the patient will continue the observation in the long term follow-up assessment phase. ~~is withdrawn from study~~ If the DMT event does not re-occur, the next treatment is at full dose. Patients in the comparator arm will receive 60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) intramuscular (i.m.) injections every 4 weeks ± 3 days. ~~for the overall 72 weeks of therapy, unless the patient progresses or dies.~~ If the patient experiences toxicity with the increased dose, the dose will be adjusted to the previous well-tolerated dose, to be increased again with the next treatment to 60 mg if the toxicity has resolved.	
38	Objective tumour assessment in both arms will be performed every 12±1 weeks from	Objective tumour assessment in both arms will be performed every 12±1 weeks from the	Clarify that treatment/assessment phase will continue until the PFS

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	the randomization date until Week 76, unless the patient progresses or dies. Patients that are RECIST progressive are treatment failures. Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up.	~~randomization~~ date until the analysis of PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then until Week 76, unless the patient progresses or dies. Patients that are RECIST progressive according to central reading assessment are treatment failures and proceed to the long-term follow-up phase. In case of discrepancies between Investigator and central assessor on the evaluation of the progression of disease, see Section 4.4.1. The primary analysis will be performed after 74 PFS events (74 evaluable and centrally confirmed disease progressions or death events) have occurred. Patients who are randomized should continue to receive either Octreotide 60 mg (Octreotide LAR arm) or Octreotide 30 mg (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) until progression (or until 74 evaluable and centrally confirmed disease progressions or death events). When the PFS Primary End-Point has been reached, the 76-week treatment period becomes fixed and all patients receive Octreotide 60 mg (Octreotide LAR arm) or Octreotide 30 mg (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) until week 72 before entering the long-term follow-up assessment phase after week 76. Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up assessment.	Primary End-Point, then it will return to the fixed 76-week schema.

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		Any non-progressive patient continues treatment/assessments until the PFS Primary End-Point has been reached, then: - Patients who have 76-weeks or more treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years from the date of randomization of the last randomized patient. - Remaining randomized patients continue in the fixed 76week treatment/assessment period unless progression occurs, then continue the long-term follow-up assessment for 5 years from the date of randomization of the last randomized patient.	
38	The End of Study is defined as the moment that 75 disease progression or death events have occurred. All patients enrolled at the End of Study point will continue treatments, and assessment unless early termination, or the patient progresses or dies. All surviving patients will continue to be monitored in the 3-year long term follow up.	The End of Study is defined as the moment that 158 deaths have occurred, or 5 years have elapsed from the date of randomization of the last randomized patient, whichever occurs first. ~~75 disease progression or death events have occurred.~~ ~~All patients enrolled at the End of Study point will continue treatments, and assessment unless early termination, or the patient progresses or dies.~~ ~~All surviving patients will continue to be monitored in the 3-year long term follow up.~~	Modify the End Of Study definition as requested by the Regulatory Agencies. The end-of-study is now defined as the last pre-specified safety or efficacy data point collected during the conduct of the study, 158 death events (or when 5 years from the randomization of the last randomized patient have elapsed, whichever comes first), which is the endpoint for overall survival assessment, and not the time of the primary analysis of PFS.

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49	Inclusion Criteria Subsequent Treatments Serum creatinine ≤150 µmol/L or 1.7 mg/dL, or a measured creatinine clearance (or measured GFR) of ≥50 mL/min. Should a 40% increase over *the* baseline serum creatinine value occur during the course of treatment**,** with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockroft's method, patients must also have a *measured creatinine clearance* (or *GFR*) performed, unless resolved within 16 weeks.	Inclusion Criteria Subsequent Treatments Both serum creatinine ≤150 µmol/L (≤1.7 mg/dL) and calculated creatinine clearance ≥50 mL/min, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) ≥50 mL/min (*the measured creatinine clearance / GFR is required only as confirmatory exam*). ~~Serum creatinine ≤150 µmol/L or 1.7 mg/dL, or a measured creatinine clearance (or measured GFR) of ≥50 mL/min. Should a 40% increase over *the* baseline serum creatinine value occur during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockroft's method, patients must also have a *measured creatinine clearance* (or *GFR*) performed, unless resolved within 16 weeks.~~	Clarify that the measured creatinine clearance / GFR is required only as confirmatory exam
50	All exclusion criteria for baseline apply to all subsequent treatments.	~~All exclusion criteria for baseline apply to all subsequent treatments.~~ Exclusion criteria for baseline # 1, 2, 3, 4, 13 apply to all subsequent treatments, when a relationship ~~can not~~cannot be excluded with either study drugs and the corresponding toxicity has not resolved. In relation to renal function: subjects are also excluded from further therapy in case of >40%	Provide further details on Exclusion Criteria Subsequent Treatments

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		increase of serum creatinine over the baseline and with a concomitant decrease of >40% in creatinine clearance as calculated according to the Cockroft Gault method, eventually confirmed by measured creatinine clearance (or GFR), if a relationship may not be excluded with either study drugs and the corresponding toxicity has not resolved. For patients in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, criteria for dose modifying toxicity should be verified, when applicable. When such exclusion criteria events occur, the patient will postpone any subsequent study treatment (any ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate or Sandostatin LAR) until resolution of the event (normalization or return to baseline values). Sandostatin LAR can be continued (in either arms, at monthly intervals) if its causative relation with the exclusion criteria can be reasonably excluded, after consultation with the Medical Monitor of the study. In any case, the patient remains in the study and continues observation with the scheduled tumour and clinical assessments. All other exclusion criteria for enrolment eligibility apply to all subsequent treatments	
50	-	A "screening failure" is a patient who consented to participate in the study but was not randomized.	Provide further clarifications on the definition of "screening failure"
50	A "withdrawal" is a patient who is enrolled	"Study termination" occurs when the patient is	Provide further clarifications on

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	into the study, but who prematurely terminated the treatment or follow-up period for any reason. The patient is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice It is also possible that the Sponsor or the Competent Authorities request termination of the study if there are concerns about conduct or safety. A patient will be withdrawn from the study if: • a Dose Modifying Toxicity (DMT) occurs (see Protocol Section 5.7.3) that has not resolved, or occurred at a reduced dose; • due to safety reasons, and in the Investigator opinion it is in the best interest of the patient. Such considerations will be made in the case of serious adverse events not representing a DMT, which are likely to be related to study drugs and are of relevant clinical severity (especially for events of grade 3 and 4 according to CTCAE Criteria	definitively discontinued from any study-related activity, upon completion of the 5-year study (and accrual period, if applicable), or because of premature termination for any reason. ~~A~~"Study withdrawal" ~~is a patient who is enrolled in the study but who prematurely terminated the treatment or follow-up period for any reason~~ occurs when the patient is withdrawn from the treatment/assessment phase of the study because of disease progression. These patients proceed immediately to the long term follow-up assessment phase. Investigators should make every effort to avoid patient's withdrawal before the central imaging centre has confirmed disease progression. - Any progressive patient (confirmed by central review of CT scans) ceases the treatment/assessment phase and proceeds to the long-term follow-up assessment phase. During long-term follow-up every effort must be made by the Investigator to collect additional information on further anti-tumour therapies and scan assessment outcomes (RECIST local evaluation) to evaluate the Time to Second Progression (PFS2) in the two study arms. - Any non-progressive patient continues treatment/assessments until the PFS Primary End-Point is reached, then:	the discontinuation Criteria for Individual Patients

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	version 4.0) • conditions have occurred that do not satisfy the inclusion / exclusion criteria for subsequent treatments after baseline (see Protocol Section 4.2.1 and 4.2.2); • the patient withdraws his/her consent ; • the patient is pregnant; • the patients has repeatedly and severely failed to comply with the dosing (less than 80% study drug assumption, or severe irregularity in the scheduling/timing of assumptions), evaluations, or other requirements of the study; • the patient has started treatment with one of the medications listed as disallowed (see Protocol section 5.5). The final decision to withdraw a patient who starts treatment with disallowed medication will be made by Investigator following consultation with the Sponsor, based on the nature of the medication - dose - duration – concomitance with	- Patients who have 76 weeks or more treatment/assessment stop treatment but continue the long-term follow-up assessment for 5 years from the randomization date of the last randomized patient; - Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last randomized patient. The informed consent form (ICF) signed at the time of the inclusion foresees the patient's participation in the Study until the end of the long term follow-up assessment phase. Patients should sign an addendum to the consent to participate in the long term follow-up assessment phase only in case they have withdrawn the initially signed consent. The patient is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. However, in this case, the patient should be requested to continue the observation in the long term follow-up phase of the study after signing the addendum ICF for the long term follow-up. It is also possible that the Sponsor or the	

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	assessment visits. The date, time, and reason for discontinuation must be documented in the e-CRF. All patients who prematurely withdraw from the study will be asked to have a CT/MRI evaluation of their disease at the time of exit, except in case of pregnancy. If a patient withdraws from the study for any reason, the Investigator must determine the primary reason for the withdrawal and record this information in the e-CRF. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show 'due diligence' by documenting in the source documents steps taken to contact the patient or his/her caregivers, dates of telephone calls, registered letters, etc.	Competent Authorities request termination of the study if there are concerns about conduct or safety. A Dose Modifying Toxicity (DMT - see Protocol Section 5.7.3), or any other safety issue, is neither a cause of "study termination", nor "withdrawal" from the treatment/assessment phase, by itself, but requires the temporary suspension or definitive interruption of either suspect study drugs. In any case, the patient will continue the scheduled visits and clinical/tumour assessments until tumour progression, if possible, even in case of study treatment suspension or interruption. In case of interruption of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment due to suspected toxicity, the administration of Sandostatin LAR 30 mg should be continued, if it is safe for the patient. A patient may have completed and may be withdrawn from the "treatment/assessment phase" of the study (but not from the long term follow-up phase), even if tumour progression has not occurred or has not been centrally confirmed, in the following cases: ~~A patient will be withdrawn from the study if:~~ • ~~a Dose Modifying Toxicity (DMT) occurs (see Protocol Section 5.7.3) that has not resolved, or occurred at a reduced dose;~~ • ~~in the Investigator opinion~~ it is in the best	

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		interest of the patient. Such considerations will be made in the case of ~~serious adverse events not representing a DMT, which are likely to be related to study drugs and are of relevant clinical severity (especially for events of grade 3 and 4 according to CTCAE Criteria version 4.0)~~ unethical continuation of the "treatment/assessment phase" (e.g., need of alternate systemic anti-tumour therapy because of safety or ineffectiveness of the assigned treatments – see also item #6), logistic / physical impossibility for the patient to follow the scheduled visits, or other documented reasons; • conditions have occurred that have compromised the regular continuation of the clinical and tumour assessments according to the protocol until disease progression ~~do not satisfy the inclusion / exclusion criteria for subsequent treatments after baseline~~ (see Protocol Section 4.2.1 and 4.2.2); • the patient withdraws his/her consent; in this case, the patient may enter the long term follow-up phase of the study only after signing an addendum to the main consent; • the patient is pregnant;	

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		• the patients has repeatedly and severely failed to comply with the protocol requirements or dosing (e.g. less than 80% study drug assumption, or severe irregularity in the scheduling/timing of assumptions of any study drug), evaluations, or other requirements of the study; • the patient has started ~~treatment with one of the medications~~ systemic anti-tumour therapy which is listed as disallowed (see Protocol section 5.5). The final decision to withdraw a patient who starts treatment with disallowed medication will be made by the Investigator following consultation with the Sponsor, based on the nature of the medication - dose - duration – concomitance with assessment visits. ~~The~~Before the patient's actual withdrawal, the case should be discussed with the Medical Monitor of the study. In case of a patient's premature withdrawal, an "early termination visit" should be performed and patient's data be collected in the CRF including date, time, and primary reason for discontinuation ~~must be documented in the e-CRF.~~ as well as the latest information available on the clinical condition and tumour progression. ~~All patients who prematurely withdraw from the study will be~~	

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		~~asked to have a~~ A CT/MRI ~~evaluation of their disease~~ scan should be obtained at the time of ~~exit~~ withdrawal, except in case of pregnancy. ~~If a patient withdraws from the study for any reason, the Investigator must determine the primary reason for the withdrawal and record this information in the e-CRF.~~ For patients who are lost to follow-up (i.e., those patients whose status is unknown because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show 'due diligence' by documenting in the source documents steps taken to contact the patient or his/her caregivers, dates of telephone calls, registered letters, etc. Documented information obtained on patient's clinical condition, in particular the survival status, will be used as follow-up documentation.	
52	-	***4.4.1 Discrepancies on the evaluation of the progressive status between Investigator and central assessor*** Central, blinded, real-time IRC (Independent Review Committee) assessment is implemented in this trial for an independent re-evaluation of progressive disease. In case of discrepancies between Investigator and central assessor on the evaluation of the progression of disease, the Investigator may request the assessment by a third evaluator for	Added a new paragraph to describe how to handle discrepancies in the evaluation of the progressive status between Investigator and central assessor

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		final adjudication. If the discrepancy persists: - Investigator assessment: non-PD; central assessment: PD. The "treatment/assessment" phase of the study is terminated and the patient should proceed to the long term follow-up assessment period. The investigator may request the continuation of treatment and assessments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate until the cumulative dose limit has been reached and/or Sandostatin LAR provided by the Sponsor according to randomization; 12-week local tumour assessments; safety assessments as in the treatment/assessment phase of the study) until progression has been documented by the Investigator, thereafter, the patient will proceed to the long term follow-up assessment phase. - Investigator assessment: PD; central assessment: non-PD. The "treatment/assessment" phase of the study should be continued as planned. However, the Investigator may decide to withdraw the patient from the "treatment/assessment phase" because of unethical continuation of the study in his/her opinion, and start the follow-up phase of the study. Such cases should be	

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		limited as much as possible and discussed with the local CRO representative before withdrawing the patient.	
53	**4.5 Dropouts and Replacements** For the purpose of this study, an "enrolled patient" is a patient who has signed the ICF and is then randomized to participate in a study arm after verification of all inclusion/exclusion criteria. A "screening failure" is a patient who has signed the ICF, but who does not meet all selection criteria and has not been randomized. A screening failure is not counted as an enrolled patient. However, a patient who has signed the ICF and has been randomized, but who is (later) found not to meet all selection criteria, is considered a "protocol violator". All randomized patients will be included in the primary analysis, regardless of whether they received study medication, and no replacement will be done. A subject can be re-screened when intercurrent conditions emerging after consent signature and impeding the planned randomization are resolved Such cases will have to be discussed and approved by the Sponsor. The site will be informed about	**4.5 Dropouts and Replacements** For the purpose of this study, an "enrolled patient" is a patient ~~who has signed the ICF and~~ is ~~then~~ randomized to participate in a study arm, after signature of the ICF and verification of all inclusion/exclusion criteria. A "screening failure" (see Section 4.3) is a patient who has signed the ICF, but who does not meet all selection criteria and has not been randomized. ~~A screening failure is not counted as an enrolled patient.~~ However, a patient who has signed the ICF and has been randomized, but who is (later) found not to meet all selection criteria, is considered a "protocol violator". All randomized patients will be included in the primary analysis, regardless of whether they received study medication, and no replacement will be done. A subject can be re-screened with a new study number when intercurrent conditions emerging after consent signature and impeding the planned randomization are resolved, or because of previously missed confirmation of the tumor progression after the central assessment. Such cases will have to be discussed and approved by	Provide clarifications on the procedures for Dropouts and Replacements

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	the procedures to be followed for re-screening.	the Sponsor. The site will be informed about the procedures to be followed for re-screening.	
54	The investigational drug product ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be provided by the Sponsor. The Sponsor will also provide/reimburse the amino acid solution for infusion as well as the Sandostatin® LAR Depot according to local regulations. Granisterin, Ondansetron, Tropisetron, Tropisetron, short-acting Sandostatin® or any other supportive care medication will not be provided by Sponsor.	The investigational drug product ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be provided by the Sponsor. The Sponsor will also provide/reimburse the amino acid solution for infusion as well as the Sandostatin® LAR Depot according to local regulations - for the whole duration of the treatment phase of the study (but not during the follow-up period). ~~Granisterin, Ondansetron, Tropisetron.~~ Anti-emetics, short-acting Sandostatin® or any other supportive care medication will not be provided by Sponsor.	Provide clarifications on Sandostatin® LAR administration.
55	30 mg Sandostatin® LAR Depot is administered the day after each administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, according to the schedule in Section 5.7.2. Once completed the four treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate patients will continue the 4-week interval administrations of 30 mg Sandostatin® LAR Depot until 72 weeks from enrolment (according to the schedule in Table 1) unless the patient progresses or dies. Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is	30 mg Sandostatin® LAR Depot is preferably administered the day after each administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, according to the schedule in Section 5.7.2 ~~.~~, and no earlier than 4 hours after completion of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Once completed the four treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, and also in case the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusions have been suspended, patients will continue the 4-week interval administrations of 30 mg Sandostatin® LAR Depot until the PFS Primary End-Point or until 72 weeks from ~~enrolment~~ randomization after the PFS end-point has been reached (according to the schedule in Table 1), unless the patient progresses	Provide clarifications on Sandostatin® LAR administration.

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<tr><td></td><td>available in a single-use kit containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½” 19 gauge needles, and two alcohol wipes.</td><td>or dies.

Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in a single-use kit containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½” 19 gauge needles, and two alcohol wipes. For prolonged storage, Sandostatin LAR® Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use.</td><td></td></tr>
<tr><td>56</td><td>-</td><td>Recommendations on the minimum infusion rate or maximum infusion time for treatment of nausea and vomiting

The suggested reduced rates calculated for each solution are:

<table><tr><th>Solution</th><th>Vol (L)</th><th>Time (h)</th><th>Rate (mL/h)</th></tr><tr><td>AminoSynII 10% - maximum infusion rate</td><td rowspan="3">2</td><td>4</td><td>500</td></tr><tr><td>AminoSynII 10% (5h)</td><td>5</td><td>400</td></tr><tr><td>AminoSynII 10% (6.25h) – minimum infusion rate*</td><td>6.25</td><td>320</td></tr><tr><td>Vamin 18 – maximum infusion rate</td><td rowspan="3">2</td><td>4</td><td>500</td></tr><tr><td>Vamin 18 (5h)</td><td>5</td><td>400</td></tr><tr><td>Vamin 18 (6.15h) – minimum infusion rate*</td><td>6.15</td><td>325</td></tr></table>* It is strongly advised not to reduce infusion rates below the stated minimum (e.g., 320 mL/h for Aminosyn II 10%, or 325 mL/h for Vamin 18).

Additional recommendations regarding</td><td>Provide additional recommendations on the minimum infusion rate or maximum infusion time and on the use of antiemetics for treatment of nausea and vomiting</td></tr>
</table>

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		the use of antiemetics Investigators are advised to use antiemetics which are commonly prescribed in their institutions for treatment of nausea induced by chemotherapeutic drugs. Among such antiemetics, the use of Aprepitant (Emend®) as a prophylactic treatment prior to the start of the infusion with the amino acids solution should be considered. Haloperidol (Haldol®) could also be considered as an adjunct treatment (either i.v. or oral) in case the advised antiemetic regimens are not successful and patients continue to vomit. Lorazepam (Ativan®) could also be considered as an adjunct treatment. There is some evidence that corticosteroids can induce down-regulation of sstr receptors, therefore their use should be avoided in the setting of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Nevertheless, in the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion.	
57	In the control arm patients will receive administrations of Sandostatin® LAR Depot 60 mg at 4-week intervals until Week 72 according to the schedule in Table 2 (i.e., two injections of Sandostatin® LAR 30 mg per treatment), unless the patient progresses or dies. Sandostatin® LAR Depot (Octreotide	In the control arm, patients will receive administrations of Sandostatin® LAR Depot 60 mg at 4-week intervals (+/- 3 days) until the PFS Primary End-Point, or until Week from randomization after the PFS end-point has been reached, according to the schedule in Table 2 (i.e., two injections of Sandostatin® LAR 30 mg per treatment), unless the patient progresses or dies-.	Provide clarifications on Sandostatin® LAR administration and storage condition.

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	Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.	Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. For prolonged storage, Sandostatin LAR® Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.	
58	-	The last administration of Sandostatin LAR before the start of the study treatment is allowed during the screening period, before randomization.	Provide clarifications on Sandostatin® LAR administration.
59	In addition to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients will receive 30 mg Sandostatin® LAR Depot, until Week 72 or early termination, unless the patient progresses or dies.	In addition to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients will receive 30 mg Sandostatin® LAR Depot until the PFS Primary End-Point, then until Week 72 from randomization after the PFS Primary End-Point, or early termination, unless the patient progresses or dies.	Provide clarifications on Sandostatin® LAR administration.
61	***5.7.3 Dose Modifying Toxicity*** In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm, dose modifying toxicity (DMT), according to National Cancer	***5.7.3 Dose Modifying Toxicity*** In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm, dose modifying toxicity (DMT), according to the grading system of the National Cancer	Provide clarifications on Dose Modifying Toxicity criteria.

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	Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE), is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity possibly related to study drug and regardless of its duration. Lymphocytopenia and liver enzyme toxicities (ALAT (ALT), ASAT (AST) and AP) will not be used to define a DMT. If a patient experiences a DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT recurs after treatment with the reduced dose, the patient goes off-study and will continue to be followed for the long-term follow-up up to 3 years after withdrawal. If the DMT event does not reoccur, the next treatment is at full dose.	Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE), is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity ~~possibly related to study drug and regardless of its duration~~, when any of the above is possibly related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and regardless of its duration. The DMT schema will also be applied if renal – hepatic – hematological adverse events are observed which are unlikely related to the study drug, but to other possible or concomitant causes, and the full administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate would represent a safety risk for the patient. Lymphocytopenia and liver enzyme toxicities (ALAT (ALT), ASAT (AST) and AP) will not be used to define a DMT. Nonetheless, a DMT schema may be applied if the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is thought to severely and clinically significantly worsen the lymphocyte count and liver function. If a patient experiences a DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg Sandostatin LAR at	

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		monthly intervals. However, Sandostatin LAR should not be administered within 6 weeks of the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, if the latter treatment is resumed. After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose, if this is felt to be safe for the patient, or the risk-benefit assessment is favourable. If the same DMT recurs after treatment with the reduced ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate dose, the patient will remain in the study and continue the scheduled clinical / tumour assessments until tumour progression, but no further ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment will be given. Sandostatin LAR will be continued at monthly intervals. If the DMT event does not reoccur, the next treatment is at full dose, if it is considered to be safe for the patient, or the risk-benefit assessment is favorable. If a patient experiences a DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg Sandostatin LAR at monthly intervals. However, Sandostatin LAR should not be administered within 6 weeks of the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, if the latter treatment is resumed.	

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		After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose, if this is felt to be safe for the patient, or the risk-benefit assessment is favourable. If the same DMT recurs after treatment with the reduced dose, the patient goes off-study and will continue to be followed for the long-term follow-up up to 3 years after withdrawal. If the DMT event does not reoccur, the next treatment is at full dose. If the same DMT recurs after treatment with the reduced ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate dose, the patient ~~goes off-study~~ will remain in the study and continue the scheduled clinical / tumour assessments until tumour progression, but no further^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment will be given.~~and will continue to be followed for the long-term follow-up up to 3 years after withdrawal.~~ If the same DMT recurs after treatment with the reduced dose, the patient Sandostatin LAR will be continued at monthly intervals. If the DMT event does not reoccur, the next treatment is at full dose if it is considered to be safe for the patient, or the risk-benefit assessment is favorable.	
62	-	• DMT in relation to Sandostatin LAR toxicity in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm In case of Grade 3 or 4 toxicity at any time during the study, especially in cases of severe abdominal	Provide clarifications on Dose Modifying Toxicity criteria.

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		symptoms, and hypoglycaemia/ hyperglycemia, which is possibly related to Sandostatin LAR, the subsequent Sandostatin LAR treatment dose will be reduced, or (temporarily) suspended. If the event has resolved and there are no foreseeable risks for the patient, the next treatment dose will be increased to the initial 30 mg dose of Sandostatin® LAR.	
62	• Deliberate treatment interruption In case of study interruption or early termination in single patients (based on either the patient's or the Investigator's decision), patients will undergo all exams scheduled for Week 76 visit (See Protocol Section 6). If the interruption occurs because of laboratory abnormality, or any evidence of toxicity, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value redresses. Appropriate remedial measures should be taken and the response recorded (See Protocol Section 6.5.2). All patients will be followed in the long-term follow-up every 6 months up to 3	• Deliberate treatment interruption ~~In case~~ The discontinuation of either study ~~interruption~~treatments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate or Sandostatin LAR) is not a reason for patient's withdrawal either from the clinical/tumor assessments until tumour progression, or for early study termination (reasons for the patient's withdrawal are discussed in Section 4.4 – Study discontinuation). However, in case of a patient's withdrawal from the clinical/tumour assessments or early study termination ~~in single patients~~ (based on either the patient's or the Investigator's decision), patients will undergo all exams scheduled for Week 76 visit (See Protocol Section 6). If the ~~interruption~~ treatment discontinuation occurs because of laboratory abnormality, or any evidence of toxicity, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed	Provide clarifications on deliberate treatment interruption criteria.

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	years after Week 76 or early termination (See Protocol Section 6.5.2), regardless the early interruption or regular completion of the study.	until sufficient information is obtained to determine the cause or the value regresses ~~redgresses~~. Appropriate remedial measures should be taken and the response recorded (See Protocol Section 6.5.2). ~~All patients will be followed in the long-term follow-up every 6 months up to 3 years after Week 76 or early termination (See Protocol Section 6.5.2), regardless the early interruption or regular completion of the study.~~	
63	60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) should be given as i.m. concurrent injections once every 4 weeks ± 3 days up to 72 weeks (two injections of Sandostatin® LAR 30 mg per treatment). Each of these injections should be administered in accordance with the product prescribing instructions for single-use kits, containing 5-ml vials of either 10 mg, 20 mg, or 30 mg strength.	60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) should be given as i.m. concurrent injections (two injections of Sandostatin® LAR 30 mg per treatment) once every 4 weeks ± 3 days until the PFS Primary End-Point, or until Week 72 from randomization after the PFS Primary End-Point has been reached, or until early termination. Each of these injections should be administered in accordance with the product prescribing instructions for single-use kits, containing 5-ml vials of either 10 mg, 20 mg, or 30 mg strength.	Provide clarifications on 60 mg Sandostatin® LAR Depot injection schedule.
64	***5.9.3 Dose Modifying Toxicity*** In the treatment arm with Sandostatin® LAR Depot, a dose adjustment scheme will be applied in case of Grade 3 or 4 toxicity, especially in cases of severe abdominal symptoms, and	***5.9.3 Dose Modifying Toxicity*** In the treatment arm with Sandostatin® LAR Depot, a dose adjustment scheme will be applied in case of Grade 3 or 4 toxicity, especially in cases of severe abdominal symptoms, and hypoglycaemia/ hyperglycemia possibly related to	Provide clarifications on Dose Modifying Toxicity for 60 mg Sandostatin® LAR Depot.

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	hypoglycaemia/hyperglycemia. If a patient experiences a DMT during Sandostatin® LAR Depot treatment, the subsequent treatment dose will be reduced to the previous well-tolerated dose and then at the next treatment, the dose will be increased again to 60 mg Sandostatin® LAR Depot.	Sandostatin® LAR Depot. The DMT schema will also be applied if such adverse events are observed which are unlikely related to the study drug, but to other possible or concomitant causes, and the full administration of Sandostatin® LAR Depot would represent a safety risk for the patient. If a patient experiences a DMT during Sandostatin® LAR Depot treatment, the subsequent treatment dose will be reduced to the previous well-tolerated dose (or even temporarily suspended) and then at the next treatment, the dose will be increased to the initial 60 mg dose of Sandostatin® LAR Depot, if this is felt to be safe for the patient, or the risk-benefit assessment is favorable. In any case (also in case of Sandostatin LAR treatment dose suspension), the patient remains in the study and continues the scheduled clinical / tumour assessments until tumor progression, unless the patient's withdrawal becomes inevitable (see Section 4.4 – Study discontinuation).	
65	Figure 2	Figure 2 modified	Clarify that in case of persisting toxicity related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, only ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is discontinued, while 30 mg Sandostatin® LAR Depot treatment continues.
67	-	It should be observed that a misalignment may occur between the tumour imaging exams	Provide clarifications on CT/MRI scans timing schedule.

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		(CT/MRI scans) which are scheduled from the date of randomization, and the other clinical and laboratory assessments which are scheduled from the first treatment date (W0).	
70	Table 7	Table 7 modified	Include extra visits at the centre after W72, until the PFS Primary End-Point is reached.
72	All enrolled patients in either arm have assessments conducted at 12-week intervals from the start of treatment up to 76 weeks (EOS, unless early termination). The 12-week interval assessments are in the treatment / assessment schedules shown in Figures 1 and 2. The specific 12-week interval assessments for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments are independently shown in Table 7, without the treatment specific assessments that are performed 2 week before, on the day of treatment or the day before (only for the second, third, and fourth treatment) and 4 weeks after treatment.	During the main portion of the study ("treatment/assessment" phase, until tumour progression), ~~All~~ all enrolled patients in either arm have assessments conducted at 12-week intervals from either the start of treatment (safety assessments) or the randomization date (tumour staging)~~up to 76 weeks (EOS, unless early termination)~~. The assessment are conducted until the PFS Primary End-Point, or up to 76 weeks from randomization (unless early termination) after the 74 PFS Primary End-Point has been reached. The 12-week interval assessments are included in the treatment / assessment schedules shown in Figures 1 and 2. The specific 12-week interval assessments for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments are independently shown in Table 7, without the treatment specific assessments that are performed 2 week before, on the day of treatment or the day before (only for the second, third, and fourth treatment), and 4 weeks after treatment. After tumour progression, the patient proceeds to the long term follow-up assessment phase and visits every 6 months until the last randomized subject has completed 5 years of study overall from date of randomization.	Include extra visits at the centre after W72, until the PFS Primary End-Point is reached

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72	-	Supportive information on the tumour origin may be obtained by specific immunohistochemistry analysis (e.g. determination of positive CDX2, negative TTF1, negative PP-ISL1 markers).	Provide further information on histology supportive information.
74	-	In order to provide a consistent CT scan timepoint between the two arms of the study, it may be necessary for the site to repeat the baseline CT scan immediately before randomization if this timepoint is greater than 4 weeks before randomization to provide more current lesion data. <….> All previous CT scans (prior to randomization) that permits to unequivocally confirm a progression based on RECIST 1.1 criteria, will be considered.	Provide clarifications on CT/MRI scans timing schedule and procedures.
74	All medications taken at the time of start of screening through Week 76 or early termination are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.	All medications taken at the start of screening ~~through~~ until the PFS Primary End-Point, then until Week 76 after randomization, or early termination, are to be recorded. This includes prescription and over-the-counter medications taken during this time frame. Further anti-tumour treatments after progression must be reported until the end of the long term follow up period.	Provide clarifications on concomitant medication data collection procedures.
75	-	Restaging is scheduled at intervals of 12±1 weeks starting from the date of randomization. In case of delays, the reason of the delay has to be documented and the CT/MRI assessment has to be	Provide clarifications on CT/MRI scans timing schedule and procedures.

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		done as soon as possible. When a CT/MRI assessment is > 6 weeks earlier or later than the original schedule, the next reassessments have to be discussed and adjusted with the Medical Monitor of the study in a way to progressively come back to the original schedule. Every effort should be done to avoid differences between these timings for patients in the two arms.	
75	Additional PFS data will be collected up to 3 years after Week 76 or early termination based on local assessments.	Sponsor will notify all the Centres and their Ethic Committees as soon as the 74 PFS Primary End-Points have occurred. Additional PFS data will be collected up to ~~3 years after Week 76 or early termination based on local assessments.~~ the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever is first. After progression and during the long-term follow-up every effort must be made by the Investigator to collect additional information on further anti-tumour therapies and scan assessments outcome (RECIST local evaluation) to evaluate the Time to Second Progression (PFS2) in the two study arms.	Provide clarifications on CT/MRI scans timing schedule and procedures.
76	-	The Duration of Response (DoR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. DoR will be reported descriptively for each group without comparison between	Include DoR and PFS2 as additional secondary exploratory end-points

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		groups. TTP is defined as the time (number of days) from randomization to objective tumour progression centrally assessed. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date). As additional secondary exploratory end-point (local RECIST assessment), the Time to Second Progression (PFS2) will be assessed in the two study arms. PFS2 is defined as the time from randomization to the time of disease progression or death due to any cause (on any treatment) following the first episode of disease progression.	
76	Survival data will be collected at the End of Study and for each patient up to 3 years after Week 76 or early termination.	Survival data will be collected at the ~~End of Study and for each patient up to 3 years after Week 76 or early termination.~~time of the analysis of the primary end-point (PFS), and updated 6-monthly thereafter until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.	Provide clarification on the OS analysis timing
77	-	If laboratory data are available from a date which is less than 2 weeks since the signature of the ICF, those data can be considered acceptable for the initial screening of the patient (as acknowledged in the ICF), if the repetition of the same exams is regarded as useless.	Provide clarifications on laboratory data schedule

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	Any clinically relevant change from baseline onwards, will be recorded on the Adverse Event page of the e-CRF.	Any clinically relevant change from baseline onwards, will be recorded on the Adverse Event page of the e-CRF, possibly with a single diagnosis encompassing all changes possibly supporting to the single diagnosis.	Clarify adverse events data collection procedures
79	During the Long-term Follow-up: In both study arms laboratory assessments will be performed every 6 months for 3 years after Week 76 or early termination. The Safety Assessment Schedule for the 3 year follow-up visits is shown in Table 9.	During the Long-term Follow-up: In both study arms laboratory assessments will be performed every 6 months ~~for 3 years after Week 76 or early termination~~ up to the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever is first. The Safety Assessment Schedule for the long-term follow-up visits is shown in Table 9.	Provide clarifications on long--term follow up duration
79	Table 9	Table 9 modified	Include extra visits due to the long-term follow up extension (from 3 to 5 years).
80	-	For the patients participating in the substudy, the 12-lead ECG data collected during the Holter ECG recording on Day 1 (ECG recorded at the end of the infusion) will be used, in order to avoid interfering with the signal acquired by the Holter machine. At other times, the ECG machine supplied by the Sponsor or the local site ECG machine may be used.	Provide additional information on ECG assessments for the patients participating in the substudy.
80	Significant findings that are present prior to baseline will be recorded in the Medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.	Significant findings that are present prior to baseline will be recorded in the medical history page, while changes during the study (including significant changes of the symptoms due to the underlying disease vs baseline, as reported in the	Provide clarifications on Physical Examination and Vital Signs data collection procedures

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		diary card) will be recorded on the Adverse Event page of the e-CRF.	
83	Importantly, if the scheduled 12-week assessment were to overlap with one of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment visits, then the 12-week assessment can not be performed at that time. However, it is critical that the 12-week assessment be conduct within the ±1-week window shown in Table 7. The 12-week assessment visit should be combined with the assessment visit that occurs two week before or four weeks after treatment if the 12-week safety and efficacy assessment would be within ± 1 week of its scheduled time, or the treatment schedule may be adjust ±1-week. See Table 7 and Table 10 for the listing of assessments that are required for pre- and post treatment, and at the 12-week intervals for safety and efficacy assessments.	~~Importantly, if the scheduled 12-week assessment were to overlap with one of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment visits, then the 12-week assessment can not be performed at that time. However, it is critical that the 12-week assessment be conduct within the ±1-week window shown in Table 7. The 12-week assessment visit should be combined with the assessment visit that occurs two week before or four weeks after treatment if the 12-week safety and efficacy assessment would be within ± 1 week of its scheduled time, or the treatment schedule may be adjust ±1-week. See Table 7 and Table 10 for the listing of assessments that are required for pre- and post treatment, and at the 12-week intervals for safety and efficacy assessments.~~ Exams to be done in relation to the ^{177}Lu-DOTA0-Tyr^{3}-Octreotate treatments (one the day of the infusion, within two weeks before the infusion, 4±1 weeks after infusion) can be combined with those required at 12-week intervals during the study, if less than 2 weeks apart.	Provide clarifications on the timing of the timing of the exams to be done in relation to the ^{177}Lu-DOTA0-Tyr^{3}-Octreotate treatments
91	-	The 24-hour continuous ECG recording via 12-lead Holter machine can be done at a treatment cycle different from the one chosen for the Dosimetry and PK analyses.	Clarify that the 24-hour continuous ECG recording via 12-lead Holter machine can be done at a treatment cycle different from the one chosen for the Dosimetry and PK analyses
92	The substudy patients will receieve full body (planar) and 3D SPECT scans on the day of the first ^{177}Lu-DOTA^{0}-Tyr^{3}-	• **Dosimetry assessments** The substudy patients will receive full body (planar) and 3D SPECT scans on the day of the	Provide clarifications on the dosimetry assessments

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	Octreotate administration. Blood and urine samples will be collected at different intervals after the first ^{177}Lu-DOTA^{0}-Tyr^{3}-administration. All patients included in the substudy will undergo a 24-hour continuous ECG recording via a 12-lead Holter machine. Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and 168 h (or within 156-168 h). The time point ranges indicated in brackets are to be considered if the specific timepoint is not feasible.	~~first~~ ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Preferably dosimetry should be performed at treatment cycle 1, but dosimetry at cycle 2 or cycle 3 is also acceptable. In the event that dosimetry measurements are performed after cycle 2 or 3, only the dose estimates for the kidneys and the bone marrow can be used in the overall evaluation, as the tumours (and by that also liver) and spleen may be influenced by the prior therapy effect. In the same treatment cycle, ~~B~~blood and urine samples will be collected at different intervals after ~~the first~~ ^{177}Lu-DOTA^{0}-Tyr^{3}-administration. All patients included in the substudy will undergo a 24-hour continuous ECG recording via a 12-lead Holter machine. Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h) and 72 h (or within 60-72 h). If one or more images are skipped or are not performed at the correct time, then an additional whole body scan will be scheduled at 168 h (or within 156-168 h). Patients that live in the vicinity of the clinic can be requested to come back for the last whole body scan at 168 h, in that case the whole body imaging at 48 h could be skipped. The time point ranges indicated above in brackets are to be considered if the specific timepoint is not feasible.	

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92		If one or more blood samplings are skipped or are not performed at the correct time, an additional blood sampling will be scheduled at 168 h (or within 156-168 h). Patients that live in the vicinity of the clinic can be requested to come back for the last blood sampling at 168 h.	Provide clarifications on the PK assessments (day 8 sampling: optional)
93	-	Samples will be obtained for the periods 0-1 h (immediately post start infusion to 1 h post start infusion), 1 h – 4 h, 4 h – 16 h, and 16 h – 48 h post start infusion.	Provide clarifications on the urine sampling for HPLC analyses
93	-	Sites participating in the substudy are strongly recommended to perform an additional 24-hour continuous ECG recording via 12-lead Holter machine at one of the subsequent study treatments. After enrollment in the study, subsequent 12-lead ECGs will be performed as clinically indicated (and interpreted locally, as per routine clinical practice, for safety at bedside). However, in the event a 12-lead ECG needs to be performed during the Holter ECG recording on Day 1, this should be performed using the ECG machine supplied by the Sponsor (rather than the site machine), in order to avoid interfering with the signal acquired by the Holter machine. At other times, the ECG machine supplied by the Sponsor or the local site ECG machine may be used. Often, cancer patients are likely to have cardiovascular disease that is not clinically manifest. The presence of cardiac disease might	Provide additional information on cardiac assessments for the patients participating in the substudy

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		be associated with greater prolongation of QTc interval after the administration of QT-prolonging drug. The typical symptoms of carcinoid syndrome include valvular heart disease in 30-40% of patient. Carcinoid heart disease is characterized by plaque-like fibrous endocardial thickening that classically involves the right side of the heart, occurring in 50-70% of patients with carcinoid syndrome. Hemodynamically significant heart disease is observed in about 5-10% of patients. It is therefore recommended that the following baseline conditions are NOT present before to include the patient in the substudy: • Prior history of torsades de pointe, or congenital long QT syndrome, • Conditions with screening ECG repolarization difficult to interpret, or showing significant abnormalities. This includes, but is not limited to: high degree AV block, pacemaker, atrial fibrillation or flutter, • QTcF internal > 480 msec on screening ECG, • Significant hypokalemia at screening (K+ <3.5 mMol/L), • Significant hypomagnesemia at screening (Mg++ <0.7 mMol/L), Of note, patients can be assessed after correction of these laboratory abnormalities and new laboratory tests performed a few days later to check the above exclusion criteria.	

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		In addition, cancer patients commonly receive medications known to cause QTc prolongation, such as antiemetics, antibiotics and antihistamines. The use of concomitants therapies can confound the results of the intensive QT study. The sequence and timing of treatments administered should therefore be carefully controlled and registered. Because of the multiple treatments received at Day 1, which may interfere with the evaluation of the ECG parameters, the sequence and timing of treatments administered at Day 1 must be carefully recorded in the patient clinical chart (the eCRF will be amended to collect these additional information). • All pre-medication will be administered during the time interval ranging from 90 to 60 min before the start of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion; the purpose of this requirement is to allow the recording of the baseline ECG intervals used in the primary ECG analysis and to capture the potential ECG effects of the pre-medication regimen. • If other treatments (other than pre-medications) are planned to be administered on Day 1, these should be administered at least 1h before the start of	

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		infusion, as best as practically possible. In general, best effort will be made to avoid introducing new treatment between 1h before, until 8h after the start of infusion unless clinically required.	
102	Based on the above median PFS assumptions, an estimate of 162 patients was determined according to the following conditions: • 81 patients per arm • ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: median PFS of 30 months • Octreotide LAR: median PFS of 14 months (PROMID study) • Significance level 5% two sided (or 2.5% one-sided), power 90% • Accrual period: 0 months (patient enrolment occurs over 14 months, but treatment is fixed at 72 weeks). • Follow-up period: 18 months (corresponding to the length of treatment period) An accrual period of 0 months results from the fact that the primary variable (PFS) will be investigated for all patients during the same study period (= follow-up period) of	Based on the above median PFS assumptions, an estimate of ~~162~~124 patients was determined according to the following conditions: • ~~81~~62 patients per arm • ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: median PFS of 30 months • Octreotide LAR: median PFS of 14 months (PROMID study) • Significance level 5% two sided (or 2.5% one-sided), power 90% • ~~Accrual period: 0 months (patient enrolment occurs over 14 months, but treatment is fixed at 72 weeks).~~ • Pre-defined accrual period: 18 months • Follow-up period: 18 months (corresponding to the length of treatment period) ~~An accrual period of 0 months results from the fact that the primary variable (PFS) will be investigated for all patients during the same study period (= follow-up period) of 18 months.~~	Based on the Regulatory Agencies recommendation to use event-based end-points for both PFS and OS, a 18-month accrual period, and a 5-year follow-up period have been defined. The accrual time applies to both PFS and OS evaluation. The PFS endpoint occurs a 74 events and the Overall Survival endpoint occurs at 158 events. Furthermore, the sample size of the study has been adjusted in order to detect a statistically significant and clinically relevant difference in OS (80% power) between the two arms of the study.

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	18 months. • Based on these conditions, a total number of 75 events are expected. <…> Therefore, controlling for a drop-out rate of approximately 20%, a total of 200 patients will be randomized and treated (100 patients in each treatment group). Power analysis for OS The median OS in the ^{177}Lu-DOTA-Tyr^{3}-Octreotate arm is expected to be in the range of 45 to 49 months. This estimate is based on the observed median OS of 47.3 months in the Erasmus MC phase I/II study subgroup analysis of 51 patients with midgut carcinoid tumors that had progressive disease within 12 months before entering the study. But, because this subgroup is small, the median OS has a large confidence interval (95% CI [27.8-75.3] months) making the robustness of the result difficult to assess. The median OS in the control arm (Octreotide LAR) is expected to be in the	• Based on these conditions, a total number of ~~75~~74 PFS events are expected. Therefore, the PFS primary analysis point occurs at the timepoint when 74 evaluable and centrally confirmed disease progressions or death events are reached. <….> Therefore, controlling for a drop-out rate of approximately 20%, a total of ~~200~~160 patients ~~will be randomized and treated~~ (~~100~~80 patients in each treatment group) should be required. The sample size has also been adjusted to detect a statistically significant and clinical relevant difference in OS (80% power) between the two arms of the study, based on the following assumptions: 1. Octreotide LAR median OS: 32 months 2. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate median OS: 50 months 3. Significance level: 5% two sided 4. Nominal power: 80% 5. Accrual time: 18 months 6. Long-term follow-up: 5 years Accordingly, 230 patients (115 patients in each treatment group) should be randomized. The median OS in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm is expected to be ~~in the range of 45 to 49 months~~ 50 months. ~~This estimate is based on~~	

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	range of 34 to 38 months. This range is derived from the results observed in the RADIANT-2 study. The median survival times were not estimated in this study, however, based on the assumption of exponential distribution, the median survival time for Placebo + Octreotide LAR arm was estimated to be about 36.4 months. Extrapolation of this median survival time must be performed with care since RADIANT-2 was not restricted to patients with midgut carcinoid tumors. Based on these estimates, differences of 7 to 15 months in median OS between ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and Octreotide LAR are expected to be observed in the current Study Protocol. For the final OS analysis, an accrual period of 0 months is considered (OS being investigated for all patients during the same study period of 76 weeks + 3 years). An interim analysis for OS will be performed at the time of the final PFS analysis. A drop-out rate of about 25% at the time of final OS analyses is considered. The assumptions for the final OS analysis are as below:	~~the observed~~ The median OS of 47.3 months, with a large confidence interval (95% CI [27.8 - 75.3], reported in the Erasmus MC Phase I/II study subgroup analysis of 51 patients with midgut carcinoid tumours has limited relevance for the purpose of this study, since the patients ~~that~~ had progressive disease within 12 months before entering the ~~study~~treatment schedule, and at a latest stage of disease. ~~But, because this subgroup is small, the median OS has a large confidence interval (95% CI [27.8- 75.3] months) making the robustness of the result difficult to assess.~~ However, most recent survival analysis in a similar population treated with PRRT has been reported. In 2012, Baum RP et al. reported an overall survival of 59 months from the first cycle of PRRT using ^{177}Lu-DOTATATE. This group also published in 2014 the outcome of a retrospective analysis assessing the efficacy of PRRT in 1,000 patients with metastatic and/or progressive NETs using ^{177}Lu (n=331), ^{90}Y (n=170) or both (n=499). The median OS for all patients was 52 months from the start of the treatment. With regard to the used radionuclide, the following OS were reported: 24 months with ^{90}Y, 55 months with ^{177}Lu, and 64 months with both. There is however no indication of the used peptide, albeit this group is known to use mainly DOTATOC and DOTATATE. Additionally, in 2013, Kunikowska J. et al	

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	• ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: median OS between 45 and 49 months • Octreotide LAR: median OS between 34 and 38 months • Significance level 0.05% two sided • Accrual period: 0 months • Follow-up period: 53.5 months (76 weeks + 3 years) • Total number of evaluable patients: 150 Based on these assumptions, a conservative estimate of powers for the OS interim analysis range from 0.0245% to 0.14% and for the final OS analysis from 12.5% to 40.2%. The number of death s estimated for the OS interim analysis range from 35 (16 and 19 in the test and control groups, respectively) to 36 (15 and 21 in the test and control groups, respectively); and for the final OS analysis they range from 89 (42 and 47 in the test and control groups, respectively) to 90 (40 and 50 in the test and control groups, respectively).	published their results from 358 patients treated with PRRT involving ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and ^{90}Y/^{177}Lu-DOTATATE collected from April 2004 to December 2010. They reported a median OS of 49.8 - 52.8 months in the group of patients treated with ^{90}Y/^{177}Lu-DOTATATE. Finally, in a study published in 2014, Paganelli G. et al. have reported the most recent overall survival data in 49 patients with advanced well-differentiated gastrointestinal NETs (79% midgut NETs) treated with ^{177}Lu-DOTATATE.The median OS was not reached at the time of publication, after a median follow-up of 38 months, ranging from 11 to 59 months. The median OS in the control arm (Octreotide LAR) is expected to be~~in the range of 34 to 38 months. This range is derived from the results observed in the RADIANT-2 study. The median survival times were not estimated in this study, however, based on the assumption of exponential distribution, the median survival time for Placebo + Octreotide LAR arm was estimated to be about 36.4 months. Extrapolation of this median survival time must be performed with care since RADIANT-2 was not restricted to patients with midgut carcinoid tumors. Based on these estimates, differences of 7 to 15 months in median OS between ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and Octreotide LAR are expected to be observed in~~	

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		~~the current Study Protocol.~~ 32 months, as per the updated results reported in the RADIANT-2 study. ~~For the final OS analysis, an accrual period of 0 months is considered (OS being investigated for all patients during the same study period of 76 weeks + 3 years). An interim analysis for OS will be performed at the time of the final PFS analysis.~~ ~~A drop-out rate of about 25% at the time of final OS analyses is considered.~~ ~~The assumptions for the final OS analysis are as below:~~ ~~^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: median OS between 45 and 49 months~~ ~~Octreotide LAR: median OS between 34 and 38 months~~ ~~Significance level 0.05% two sided~~ ~~Accrual period: 0 months~~ ~~Follow-up period: 53.5 months (76 weeks + 3 years)~~ ~~Total number of evaluable patients: 150~~ ~~Based on these assumptions, a conservative estimate of powers for the OS interim analysis range from 0.0245% to 0.14% and for the final OS analysis from 12.5% to 40.2%.~~ ~~The number of death s estimated for the OS interim analysis range from 35 (16 and 19 in the test and control groups, respectively) to 36 (15 and 21 in the test and control groups,~~	

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		~~respectively); and for the final OS analysis they range from 89 (42 and 47 in the test and control groups, respectively) to 90 (40 and 50 in the test and control groups, respectively).~~ The length of the overall survival assessment period includes a 18-month accrual period, and a 5-year follow-up period. The 5-year follow-up is the predicted length of the study; however, the actual end-of-study will be based on death events (158), or after 5 years from the randomization date of the last randomized patient, whichever occurs first. The analysis on OS will be conducted when 158 deaths have been recorded in the study or when 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first.	
105	The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method, and the stratified log-rank test incorporating the randomization factors will be used to compare the PFS between the two treatment groups. However, if the number of events in some strata is too low and doesn't allow for the use of the stratified test, the un-stratified test will be used instead. This evaluation will be performed by an independent statistician before the finalization of the Statistical Analysis Plan (SAP) (more details on this	The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method, and the unstratified log-rank test ~~incorporating the randomization factors~~ will be used to compare the PFS between the two treatment groups.~~However, if the number of events in some strata is too low and doesn't allow for the use of the stratified test, the un-stratified test will be used instead. This evaluation will be performed by an independent statistician before the finalization of the Statistical Analysis Plan (SAP) (more details on this process will be reported in the SAP).~~	State that the primary analysis of PFS will be an unstratified log-rank test, as requested by the Regulatory Agencies.

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	process will be reported in the SAP).	<….> Additional PFS data are collected after the Primary End-Point has been reached as an effect of the continuation of the study in the treatment/assessment phase for patients who have not experienced tumour progression, or during the long term follow-up phase in case of discrepancy in the evaluation of the progression of disease (see Section 4.4.1). This additional PFS data will be collected and analyzed descriptively.	
105	-	The Duration of Response (DoR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. DoR will be reported descriptively for each group without comparison between groups. Time to Second Progression (PFS2) will be based on RECIST local assessments. PFS2 (time to second disease progression) is defined as the time from randomization to the time of disease progression or death due to any cause (on any treatment) following the first episode of disease progression.	Include Duration of Response (DoR) and Time to Second Progression (PFS2) as secondary exploratory end-points.
108	-	Information on possible co-morbidities factors will be collected in the eCRF.	Clarify which data need to be collected for a proper QT analysis
127	-	Baum RP, Kulkarni HR. Theranostics: From molecular imaging using Ga-68 labeled tracers and PET/CT to personalized	Updated references list

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		radionuclide therapy - The Bad Berka Experience. Theranostics 2012, 2: 437-447. Baum RP, Kulkarni H, Zachert C, Kaemmerer D, Petrovitch A, Niepsch K, Hommann M, Horsch D. Peptide receptor radionuclide therapy for progressive and metastatic neuroendocrine tumors: Analysis of efficacy in 1,000 patients from a single center. Abstract N1, ENETS Annual Conference, March 5-7, 2014, Barcelona.	
130	-	Kunikowska J, Królicki L, Sowa-Staszczak A, Hubalewska-Dydejczyk A, Pawlak D, Mikolajczak R, Handkiewicz-Junak D, Szaluś N, Kamiński G, Cwikla J, Jakuciński M, Lukiewicz A, Kowalska A, Gut P. Polish experience in peptide receptor radionuclide therapy. Recent Results Cancer Res. 2013; 194:467-78.	Updated references list
131	-	Paganelli G, Sansovini M, Ambrosetti A, Severi S, Monti M, Scarpi E, Donati C, Ianniello A, Matteucci F, Amadori D. ^{117}Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. Eur J Nucl Med Mol Imaging 2014; available online 11 March 2014, DOI 10.1007/s00259-014-2735-5.	Updated references list

Table I

Previous Lutathera arm flow chart

Visit	Eligibility	Baseline	Treatments / Assessments										Assessments											Last Visit[6]	FOLLOW-UP[7]
Week		Week -3	0☎	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	76	6-month for 3 yrs
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																									
OctreoScan®	< 24 weeks																									
Histology and Ki67[1]	x																									
Diagnosis and Extent of Cancer	x																									
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																									
Demographic Data	x																									
Relevant Medical History		x																								
Prior Therapy for Carcinoid Tumour	x	x																								
Confirmation of Eligibility and Randomization		▼																								
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																								
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x												x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x	x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x					x					x			x			x			x			x		
Hematology[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x	x	x
Blood Chemistry[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x	x	x
Urinalysis[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x	x	x
Pregnacy test[2]		x			x			x			x															
Serum CgA[1]		x					x				x				x			x			x			x		
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy			----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	→	
Adverse Events[5]			----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	→
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x
Survival Information			----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	→

New lutathera arm flow chart and footnotes

Visit	Eligibility	Baseline	Study Treatment Phase																							Follow-Up Phase[7]
																							Further visits[6]		End of Study Treatment Phase Visit	
Week		Week -3	0☎	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																											
OctreoScan®	< 24 weeks																											
Histology and Ki67[1]	x																											
Diagnosis and Extent of Cancer	x																											
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																											
Demographic Data	x																											
Relevant Medical History		x																										
Prior Therapy for Carcinoid Tumour	x	x																										
Confirmation of Eligibility and Randomization		▼																										
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																										
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x														x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x	x	x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x	x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x					x					x			x			x			x			x	x		
Hematology[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x	x	x	x	x
Blood Chemistry[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x	x	x	x	x
Urinalysis[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x	x	x	x	x
Pregnacy test[2]		x			x			x			x																	
Serum CgA[1]		x					x				x				x			x			x			x	x			
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																												
Antitumor-therapies after progression																												
Adverse Events[5]																												
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x	x	x
Survival Information																												

Comment [PS1]:

<u>Week 12 – 36 – 48 – 60 – 72</u> (and every subsequent 12 weeks until the PFS Primary-End-Point (74 evaluable PFS events centrally confirmed) occurs)
- -Perform physical examination, record signs and symptoms currently present, and record vital signs and body weight
- -Determine Karnofsky performance score
- -Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- -Perform laboratory tests (local assessment)
- -Collect sample for central evaluation of CgA
- -Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

<u>Week 32 – 40 – 44 – 52 – 56 – 64 – 68</u> (and every subsequent 4 weeks until the PFS Primary-End-Point (74 evaluable PFS events centrally confirmed) occurs)
- -Document concomitant therapy
- -Document adverse events
- -Report survival information
- - Deliver patient diary for the collection of cancer-related symptoms and rescue medication
- -Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary
- -Treatment with 30 mg Octreotide LAR Depot

<u>Follow-up visits (every 6-months for 5 years)</u> after PFS Primary-End-Point (74 evaluable PFS events centrally confirmed) occurs
- -Perform laboratory tests (local assessment)
- -Document serious adverse events suspected to be related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
- -Report survival information
- -Collect information on tumour progression by CT/MRI (local assessment after the 74 evaluable PFS events are reached)

Table 1 Footnotes

TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, 4 administrations at 8±1-week intervals

TREATMENT: 30 mg Sandostatin® LAR Depot injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion

Last Sandostatin® LAR Depot injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)

[a] ~~Centrally~~ [f]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the PFS Primary-End-Point occurs; then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of ~~enrollment~~randomization and the most recent scan must not be older than 4 weeks from the date of ~~enrollment~~randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a ~~new~~ fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan has been obtained.

RECIST Disease Assessment during the ~~3 years~~long-term follow-up will be performed locally.

[c] Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose.
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter at baseline for female of childbearing potential and during 177Lu-DOTA0-Tyr3-Octreotate therapy within 7 days prior to each treatment; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urines the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits ~~At baseline it is preferable that laboratory tests will be performed within 2 weeks before treatment administration~~
- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4±1 weeks after each treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, additional laboratory tests will be performed on the same day or within the day before each treatment. Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of study drug must include at minimum:
  a. serum blood urea nitrogen and creatinine
  b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
  c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.
- If a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured

[d] During the study, symptoms will be recorded in the e-CRF according to patient diary notes

[e] Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[g] AEs/SAEs will be reported from signing the informed consent form onwards until ~~Week 76 or early termination~~the end of the treatment phase. During the long-term ~~3 year~~ follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[h] ~~Last Visit or Early Termination Visit for each patient (in case of Early Termination Visit, in addition to assessments described in the flow chart, disease status must be evaluated according to RECIST and CT/MRI images must be submitted for central evaluation)~~

[i] Any progressive patient ceases treatment/assessment and proceeds to the 5years long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:
a) Patients who have 76 weeks or more treatment/assessment stop treatment but continue 6-monthly assessments for overall 5-years from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[l] Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient whichever is first (phone contacts or visits at Site). Laboratory assessments (haematology, biochemistry, urinalysis), further anti-tumour treatments, SAEs suspected in relationship to the study drug, tumor progression ~~free survival~~ (local evaluation after the analysis of the PFS Primary End-Point) and ~~overall survival data~~death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

----▶ Information to be collected during the entire study

Table II
Previous control arm flow chart

Visit	Eligibility	Baseline	Treatments / Assessments																			Last Visit[5]	FOLLOW-UP[6]
Week		Week -3	0☎	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	6-month for 3 yrs
Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇		
Informed Consent	x																						
OctreoScan®	< 24 weeks																						
Histology and Ki67[1]	x																						
Diagnosis and Extent of Cancer	x																						
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																						
Demographic Data	x																						
Relevant Medical History		x																					
Prior Therapy for Carcinoid Tumour	x	x																					
Confirmation of Eligibility and Randomization		▼																					
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																					
ECG		x	x		x		x		x													x	
Physical Exam and Vital Signs		x				x			x			x			x			x			x	x	
Karnofsky Performance Status	x	x				x			x			x			x			x			x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x		
Hematology[2]	x	x		x		x			x			x			x			x			x	x	x
Blood Chemistry[2]	x	x		x		x			x			x			x			x			x	x	x
Urinalysis[2]	x	x		x		x			x			x			x			x			x	x	x
Pregnancy Test		x																					
Serum CgA[1]		x				x			x			x			x			x			x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy			----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	
Adverse Events			----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x
Survival Information	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----

New control arm flow chart and footnotes

Visit	Eligibility	Baseline	Study Treatment Phase																				Follow-Up Phase[7]
																					Further visits[6]		End of Study Treatment Phase Visit	
Week		Week -3	0☎	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇		
Informed Consent	x																								
OctreoScan®	< 24 weeks																								
Histology and Ki67[1]	x																								
Diagnosis and Extent of Cancer	x																								
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																								
Demographic Data	x																								
Relevant Medical History		x																							
Prior Therapy for Carcinoid Tumour	x	x																							
Confirmation of Eligibility and Randomization		▼																							
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																							
ECG		x	x		x		x		x			x			x			x			x		x		
Physical Exam and Vital Signs		x				x			x			x			x			x			x		x		
Karnofsky Performance Status	x	x				x			x			x			x			x			x		x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x		x		
Hematology[2]	x	x		x		x			x			x			x			x			x		x	x	x
Blood Chemistry[2]	x	x		x		x			x			x			x			x			x		x	x	x
Urinalysis[2]	x	x		x		x			x			x			x			x			x		x	x	x
Pregnancy Test		x																							
Serum CgA[1]		x				x			x			x			x			x			x		x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																									
Anti-tumour therapies after prgression																									
Adverse Events																									
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x	x	x
Survival Information																									

Comment [PS2]:

<u>At all visits (in addition to exams at specific visits) and</u> every 4 weeks until the PFS Primary-End-Point (74 evaluable PFS events centrally confirmed) occurs):
- -Document concomitant therapy
- -Document adverse events
- -Report survival information
- - Deliver patient diary for the collection of cancer-related symptoms and rescue medication
- -Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary
- -Treatment with 60 mg Octreotide LAR Depot

<u>Week 12 – 36 – 48 – 60 – 72</u> (and every subsequent 12 weeks until the PFS Primary-End-Point (74 evaluable PFS events centrally confirmed) occurs)
- -Perform physical examination, record signs and symptoms currently present, and record vital signs and body weight
- -Determine Karnofsky performance score
- -Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- -Perform laboratory tests (local assessment)
- -Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

<u>Follow-up visits (every 6-months for 5 years)</u> after PFS Primary-End-Point (74 evaluable PFS events centrally confirmed) occurs
- -Perform laboratory tests (local assessment)
- -Record information on tumour progression by CT/MRI (local assessment after the 74 evaluable PFS events are reached)
- -Collect information on anti-tumour treatment administered after progression/discontinuation

Table 2 Footnotes

TREATMENT: 60 mg 4-week interval Octreotide LAR Depot injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1] ~~Centrally~~ Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the analysis of the PFS Primary End-Point (74 evaluable and centrally confirmed progressions or death events), then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of ~~enrollment~~randomization and the most recent scan must not be older than 4 weeks from the date of ~~enrollment~~randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-~~4~~ weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a ~~new~~ fixed dose regimen of Octreotide LAR (20-30 mg/3-~~4~~ weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has ~~switch~~switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan has been obtained.

RECIST Disease Assessment during the ~~3 year~~long-term follow-up will be performed locally.

[2] Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein -(dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter only at baseline for female of childbearing potential; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urines the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits)

[3] During the study symptoms will be recorded in the e-CRF according patient diary notes

[4] Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5] AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

~~[5] Last Visit or Early Termination Visit for each patient (in case of Early Termination Visit, in addition to assessments described in the flow-chart, disease status must be evaluated according to RECIST and CT/MRI images must be submitted for central evaluation)~~

[6] Any progressive patient ceases treatment/assessment and proceeds to the long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:

a) Patients who have 76-weeks or more treatment/assessment stop treatment but continue assessments for overall 5-year from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[6] ~~Patient~~[7] Patient must be contacted every 6 months ~~up to 3~~until the moment 158 deaths have occurred, or 5 years ~~after~~from the ~~end~~date of ~~the study~~randomization of the last randomized patient, whichever is first (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), tumor progression ~~free survival~~ (local evaluation~~)~~ after the analysis of PFS Primary End-Point, further anti-tumour treatments and ~~overall survival data~~death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

------► Information to be collected during entire the study

NETTER-1 Protocol AAA-III-01

A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.

EXTRACT OF CHANGES from Previous Protocol version 4.0 (March 25, 2014) to New Protocol version 4.1 (June 5, 2014)

PROTOCOL SYNOPSIS

Study design	[……] **Dosimetry, PK, ECG substudy:** A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites to provide a more complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. To facilitate the patients recruitment in this substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. As soon as the Study Protocol Amendment 4.1 is approved by the substudy site IRB, the randomization protocol of the study is halted at the substudy sites until a cumulative 20 patients are enrolled in the substudy and all the patients included in the substudy sites will be treated in arm A (4 infusions of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate +30 mg Octreotide LAR). During this period, the sites not participating in the substudy continue to enroll patients using the randomization protocol of the main study. When the target for the substudy will be reached the randomization protocol (Study Protocol 4.0) will restart again in the substudy sites. In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary and secondary analysis of the main study groups. Patients participating in the substudy will be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the substudy. Aside from the specific tests conducted in the dosimetry study, as described in Section 6.6 and the separate substudy manual, the treatment regimen and patient care management remain identical to that implemented in the main study.
Planned number of patients	230 randomized patients (115 will be randomly assigned to open-label treatment). To facilitate the patients recruitment in the dosimetry, PK and ECG substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily

	activated (Study Protocol version 4.1) at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. This substudy is conducted in a subset of 20 patients. In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will not be considered in the primary and secondary analysis of the main study groups.
Sample size	[……] The data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary and secondary analysis of the main study groups.

3. STUDY DESIGN

3.1 Study Outline

[……]

Dosimetry, PK, ECG substudy

A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites to provide a more complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

To facilitate the patients recruitment in this substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies (Study Protocol 4.1, June 5, 2014). As soon as the Protocol Amendment 4.1 is approved by the substudy site IRB, the randomization protocol of the study is halted at the substudy sites until 20 patients are enrolled in the substudy and all the patients included in the substudy sites will be treated in arm A (4 infusions of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate +30 mg Octreotide LAR). During this period, the sites not participating in the substudy continue to enroll patients using to the randomization protocol of the main study.

In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary and secondary analysis of the main study groups.

Patients participating in the substudy will be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the substudy.

Aside from the specific tests conducted in the dosimetry study as described in Section 6.6 and the separate substudy manual, the treatment regimen and patient care management remain identical to that implemented in the main study.

3.3.1 Substudy Design Rationale

A 20 patient dosimetry, pharmacokinetics, and ECG substudy will be performed in ~~about 10~~ selected sites. ~~This is a substudy of the present phase III clinical trial, and will be performed on patients who have been randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm.~~

See §Section 6.6 for further details on sub-study procedures; in addition, a study manual of the substudy will be provided to participating sites.

3.3.1.3 Eligibility

~~Any patient enrolled in the present phase III study who has been randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm is eligible to participate in the Dosimetry, Pharmacokinetics and ECG substudy.~~

~~Voluntary informed consent has to be given by every patient in order to be screened for sub-study eligibility and prior to the initiation of any sub-study-related procedures.~~

Patients participating in the substudy will be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the dosimetry, pharmacokinetics and ECG substudy prior to the initiation of any substudy-related procedures.

6.6 Dosimetry, Pharmacokinetics and ECG

[……]

Before the approval of the Amended Protocol 4.1, ~~P~~patients participating in the substudy will be patients who have been determined to be eligible for the main study and have been randomized into the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, and have signed an additional informed consent specific for the substudy.

To facilitate the patients recruitment in this substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) has been temporarily activated at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. As soon as the Amended Protocol 4.1 is approved by the substudy site IEC/IRB, the randomization protocol of the study is halted at the substudy site until 20 patients are enrolled in the substudy.

7- STATISTICAL METHODS

7.1 Sample Size

[……]

To facilitate the patients recruitment in the dosimetry, PK and ECG substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated (Study Protocol Amendment 4.1) at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. This substudy is conducted in a subset of 20 patients. In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary and secondary analysis of the main study groups.

Remaining few Protocol typos have been corrected.

STUDY PROTOCOL

TITLE	A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.
STUDY	Phase III
PROTOCOL N°	AAA-III-01
EudraCT N°	2011-005049-11
IND N°	77219
Version/DATE	Protocol N° AAA-III-01, version 4.1, June 5, 2014 Replaces version 4.0, March 25, 2014
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GOOD CLINICAL PRACTICE AND CONFIDENTIALITY STATEMENT

This trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

PROTOCOL SYNOPSIS

Clinical Study Protocol Synopsis		
Version date	Protocol N° AAA-III-01, version 4.1, June 5, 2014 Replaces version 4.0, March 25, 2014	
Study number AAA-III-01	Clinical phase III	IND Number 77219
EudraCT number 2011-005049-11	Drug substance ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	
Title of the study	A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.	
Study centres	Centres in EU and USA (approximately 35 EU sites and 15 USA sites)	
Sponsor	Advanced Accelerator Applications SA	
Indication	Patients with inoperable, progressive, OctreoScan® positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours), who are treated with 20 mg or 30 mg Octreotide LAR every 3-4 weeks at a fixed dose for at least 12 weeks prior to randomization in the study.	
Objectives	**Primary objective:** • To compare Progression Free Survival (PFS) after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria), somatostatin receptor positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours). **Secondary objectives:** • To compare the Objective Response Rate (ORR) between the two study arms; • To compare the Overall Survival (OS) between the two study arms; • To compare the Time to Tumour Progression (TTP) between the two study arms; • To evaluate the safety and tolerability of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; • To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire; **Exploratory objectives:** • To explore the correlation of toxicity outcomes and administered radioactivity corrected for body weight and body surface area; • To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-	

	Hydroxyindoleacetic acid (5-HIAA) in the urine; • To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients; • To explore the correlation of clinical efficacy outcomes with OctreoScan® tumour uptake score; • To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP): • To evaluate the Duration of Response (DoR) in the two study arms; • To evaluate the Time to Second Progression (PFS2) in the two study arms
Study design	A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study. In this study, treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) will be compared to treatment with high dose (60 mg) Octreotide LAR in patients with metastasized or locally advanced, inoperable, somatostatin receptor positive, histologically proven midgut carcinoid tumours; these patients should be progressive under Octreotide LAR. In case patients in either arm experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections are allowed. Objective tumour response in both arms will be assessed every 12±1 weeks from the randomization date according to RECIST Criteria until progression centrally confirmed. The baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date. In order to provide a consistent CT/MRI scan timepoint between the two arms of the study it may be necessary for the site to repeat the baseline CT/MRI scan immediately before randomization if the CT/MRI timepoint is greater than 4 weeks before randomization to provide more current lesion data. - Any progressive patient (confirmed by central review of CT/MRI scans) ceases treatment/assessment and proceeds to long-term follow-up. - Any non-progressive patient continues treatment/assessments until the PFS Primary End-Point is met (i.e. 74 evaluable and centrally confirmed disease progressions or death events). Once the Primary End-Point is reached, a. Patients who have received more than 76 weeks treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last patient randomized. b. Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last patient During the long-term follow-up assessment phase, toxicities suspected in relation with the study drug (including haematology, biochemistry, urine analyses), anti-tumour treatment administered after progression/discontinuation, disease status based on local CT/MRI assessment, and OS data will be collected every 6 months (phone contact or visit at site). In case of phone contacts, medical reports/CT-

	MRI images must be provided by the patient to the Investigational Site. Patients will be evaluated for safety and tolerability in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm as indicated in Table 1 and Table 2, respectively. **Dosimetry, PK, ECG substudy:** A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites to provide a more complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. To facilitate the patients recruitment in this substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. As soon as the Study Protocol Amendment 4.1 is approved by the substudy site IRB, the randomization protocol of the study is halted at the substudy sites until a cumulative 20 patients are enrolled in the substudy and all the patients included in the substudy sites will be treated in arm A (4 infusions of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate +30 mg Octreotide LAR). During this period, the sites not participating in the substudy continue to enroll patients using the randomization protocol of the main study. When the target for the substudy will be reached the randomization protocol (Study Protocol 4.0) will restart again in the substudy sites. In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary and secondary analysis of the main study groups. Patients participating in the substudy will be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the substudy. Aside from the specific tests conducted in the dosimetry study, as described in Section 6.6 and the separate substudy manual, the treatment regimen and patient care management remain identical to that implemented in the main study.
Treatment	**^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm:** • 30 mg Octreotide LAR treatment for symptoms control will continue until the PFS Primary End-Point, unless the patient progresses or dies. When the PFS Primary End-Point has been reached, the treatment/assessment period becomes fixed and all patients receive 30 mg for 72 weeks and then proceed to the long-term follow-up assessment phase. • Treatment will consist of a total cumulative administered radioactivity of 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; • Four administrations of 7.4 GBq (200 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate;

	• Concomitant amino acids will be given with each administration for kidney protection; • ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be administered at 8±1-week intervals, which can be extended up to 16 weeks to accommodate resolving acute toxicity (see Dose Modifying Toxicity (DMT) below); • In case patients experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections are allowed. **Octreotide LAR arm:** • 60 mg Octreotide LAR treatment every 4 weeks (i.m. injections) ± 3 days until the PFS Primary End-Point, unless the patient progresses or dies (see below for Dose Modifying Toxicity (DMT)). After the PFS Primary End-Point has been reached, the treatment/assessment period becomes fixed and all patients receive 60 mg for 72 weeks and then proceed to the long-term follow-up assessment phase. • In case patients experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, s.c. Octreotide rescue injections are allowed.
Dose modifying toxicity	With reference to the grading system of the NCI (National Cancer Institute, Common Terminology Criteria for Adverse Events Version 4.0), DMT in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity possibly related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and regardless of its duration. The DMT principles will also be applied if renal – hepatic – hematological adverse events are observed which are unlikely related to the study drug, but to other possible or concomitant causes, and the full administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate would represent a safety risk for the patient. In the Sandostatin® LAR arm a dose adjustment scheme will also be applied in case of NCI Grade 3 or 4 toxicity possibly related to study drug. 1. **If the patient experiences DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy**, the subsequent treatments of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg Sandostatin® LAR at monthly intervals. After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT reoccurs after treatment with the reduced dose, or the DMT does not resolve within 16 weeks, the patient stops further treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate but continues the study with monthly Sandostatin® LAR 30 mg (if Sandostatin® LAR is unlikely to be the

	causative agent of the observed toxicity). If the DMT event does not reoccur, the next treatment is administered at full dose. 2. **If the patient experiences DMT with the increased dose Octreotide LAR**, the dose will be adjusted to the previous well-tolerated dose, to be increased again with the next treatment to 60 mg.
Study duration	1. Total number of randomized patients: 230 2. First Patient In: Q3 2012 3. Pre-defined accrual period: 18 months 4. Expected Last Patient In: Q4 2014 5. PFS primary analysis point occurs at 74 evaluable and centrally confirmed disease progressions or death events. 6. Long term follow-up: 5-years from the date of randomization of the last randomized patient. 7. End-of-Study (EOS): when 158 deaths are recorded or when 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first. 8. OS primary analysis point occurs at 158 deaths or 5 years from the date of randomization of the last randomized patient, whichever occurs first. 9. The primary analysis is performed at 74 events (74 evaluable disease progressions centrally confirmed or death events). Patients who are randomized should continue to receive the assigned treatment until tumour progression or until the PFS Primary End-Point is reached. After the PFS Primary End-Point has been reached, the treatment/assessment period becomes fixed and all patients receive 60 mg (Octreotide LAR arm) or 30 mg (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) until week 72 and then proceed to the long-term follow-up assessment phase. 10. EOS is defined as the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.
Planned number of patients	230 randomized patients (115 will be randomly assigned to open-label treatment). To facilitate the patients recruitment in the dosimetry, PK and ECG substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated (Study Protocol version 4.1) at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. This substudy is conducted in a subset of 20 patients. In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will not be considered in the primary and secondary analysis of the main study groups.

Inclusion criteria	1. Presence of metastasized or locally advanced, inoperable (curative intent) at enrollment time, histologically proven, midgut carcinoid tumour (to be centrally confirmed). 2. Ki67 index ≤ 20% (to be centrally confirmed). 3. Patients on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study. 4. Patients ≥18 years of age. 5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 (§Appendix 2) while receiving an uninterrupted fixed dose of Octreotide LAR (20-30 mg/3-4 weeks). Disease progression must be centrally confirmed. In order to make the assessment, two CT (or MRI) scans are required. The oldest scan must not be older than 3 years from the date of randomization. The most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained. 6. Confirmed presence of somatostatin receptors on all target lesions (for target/non-target/measurable lesions definition see §Appendix 2, Section 1 and 2, RECIST Criteria, Version 1.1) documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to randomization in the study (to be centrally confirmed). The OctreoScan® should be one that was performed while the patient was on a fixed dose of Octreotide LAR. If a patient has had an OctreoScan® performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan® performed after 3 months of Octreotide LAR treatments before entering the clinical study to prove that the index lesions or new lesions still meet the criteria for inclusion. It is acceptable to have patients temporarily switched to Octreotide s.c. (up to six weeks) in order to obtain an OctreoScan®, provided they return to the same fixed dose of Octreotide LAR prior to the scan. 7. The tumour uptake observed in each target lesion (for target/non-target/measurable lesions definition see §Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1) using OctreoScan® must be ≥ normal liver uptake observed on planar imaging (to be centrally confirmed) (§Appendices 5 and 6). 8. Karnofsky Performance Score (KPS) ≥60.

	9. Presence of at least 1 measurable site of disease. 10. [Applicable only for France] All patients included in the trial must be affiliated with a social security regime or be a beneficiary of the same in order to be included in the study.
Exclusion criteria	1. Either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min calculated by the Cockroft Gault method, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) <50 mL/min (the measured creatinine clearance / GFR is required only as confirmatory exam). 2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x10^9/L (2000/mm^3); platelets <75x10^9/L (75x10^3/mm^3). 3. Total bilirubin >3 x ULN. 4. Serum albumin ≤3.0 g/dL unless prothrombin time is within the normal range. 5. Pregnancy (see §Appendix 7) or lactation. 6. For female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel) as defined in §Appendix 7. 7. Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to randomization in the study. 8. Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study. 9. Any surgery, radioembolization, chemoembolization, chemotherapy and radiofrequency ablation within 12 weeks prior to randomization in the study. 10. Interferons, Everolimus (mTOR-inhibitors) or other systemic therapies within 4 weeks prior to randomization in the study. 11. Known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks, prior to enrollment in the study. Patients with a history of brain metastases must have a head CT with contrast to document stable disease prior to randomization in the study. 12. Uncontrolled congestive heart failure (NYHA II, III, IV). 13. Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN. 14. Any patient receiving treatment with short-acting Octreotide, which

	cannot be interrupted for 24 h before and 24 h after the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, unless the tumour uptake on target lesions observed by OctreoScan® imaging during continued Octreotide LAR treatment is at least as high as normal liver uptake observed by planar imaging (§Appendices 5 and 6). 15. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study. 16. Prior external beam radiation therapy to more than 25% of the bone marrow. 17. Current spontaneous urinary incontinence. 18. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years. 19. Patients who have not provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities. 20. Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency. If such a patient can be imaged with MRI, then the patient would not be excluded. 21. Patients who have participated in any therapeutic clinical study/received any investigational agent within the last 30 days are excluded from participation in this trial.
Long-term follow-up after end of study treatment or early termination	Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up assessment. Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point, then: a. Patients who have 76week or more treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last randomized. b. Remaining randomized patients continue in the fixed 76-week treatment/assessment phase unless progression occurs, then proceed to the long-term follow-up assessment phase for 5 years overall from the date of randomization of the last randomized patient. Sponsor will notify all the Centres and their Ethic Committees as soon as 74 evaluable disease progressions or death events (PFS Primary End-Point) have occurred. During the long-term follow-up assessment phase, toxicities suspected in relation with the study drug (including haematology, biochemistry, urine analyses), anti-

	tumour treatment administered after progression/discontinuation, disease status based on local CT/MRI assessment, and OS data will be collected every 6 months (phone contact or visit at site). In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.
End of Study	The End of Study (EOS) is defined as the moment when 158 deaths have occurred, or 5 years have elapsed since the date of randomization of the last randomized patient, whichever occurs first.
Treatment	
Form/dosing route	A ready-to-use radioactive liquid solution for intravenous infusion.
Investigational drug	[Lutetium-177]-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl)acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic(2-7)disulfide. Abbreviated: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
Dosage	In total 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administered in four equally divided doses. Each dose to be infused over 30 minutes.
Duration of treatment	Four administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (each treatment 7.4 GBq (200 mCi) at 8±1-week intervals, which can be extended to 16 weeks for resolving acute toxicity. Patients are scheduled to continue to receive study treatment until any of the following occurs: 1. Unacceptable toxicity; 2. Centrally confirmed progressive disease as determined by RECIST Criteria; 3. Inability or unwillingness of the patient to comply with study procedures; 4. Patient withdrawing consent to participate.
Assessments (see accompanying Visit Schedules)	
Efficacy	Objective CT/MRI tumour assessment in both arms will be performed every 12±1 weeks from the randomization date (central assessment). Every effort should be made to avoid differences between these timings for patients in the two arms. Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up assessment. Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point, then: a. Patients who have 76 weeks or more treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last patient randomized; b. Remaining randomized patients continue the fixed 76week treatment/assessment period unless progression occurs, then continue the

	long-term follow-up assessment for 5 years overall from the date of randomization of the last patient randomized. Date of death will be recorded at any time during the treatment/assessment phase and the long term follow-up assessment phase, when known.
Safety	Safety assessments will be performed within 2 weeks before and 4±1 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and every 12±1 weeks from the first treatment date in both study arms. In addition, for the second, third, and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional safety assessment will be performed on the same day of treatment, or within one day before treatment. Long-term toxicity to critical organs suspected to be related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be monitored every 6 months until the End of Study.
Statistical methods	
Sample size	POWER Procedure Log-Rank Test for Two Survival Curves (SAS 9.2) based on the following assumptions: • Median PFS for group 1 (Octreotide LAR): 14 months • Median PFS for group 2 (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate): 30 months • Nominal Power: 90% • Alpha: 0.05 • Pre-defined accrual period: 18 months • Follow-up period: 18 months Based on the above median PFS values, a sample size of 124 patients with an expected number of 74 events (disease progression centrally confirmed or death due to any cause) is needed. However, the sample size of the study has also been adjusted in order to detect a statistically significant and clinical relevant difference in the overall survival (OS, secondary end-point, (80% power) between the two arms of the study, with the following assumptions: • Median OS for group 1 (Octreotide LAR): 32 months • Median OS for group 2 (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate): 50 months • Nominal power: 80% • Alpha: 0.05 • Number of Patients: 230 • Pre-defined accrual period: 18 months • Study duration (treatment/assessment phase and long-term follow-up assessment): 60 months Accordingly, 230 patients will be randomized. The length of the overall survival assessment period includes a pre-defined 18-month accrual period, and a 5 years treatment and follow-up period. The 5-year period of treatment and follow-up is the predicted length of the study.The data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary

	and secondary analysis of the main study groups.
Stratification before randomization	1. OctreoScan® tumour uptake score (Grade 2, 3 and 4); the highest Octreoscan® score measured among all the target lesions (for target/non-target/measurable lesions definition see §Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1) will be used for stratification purpose (see §Appendix 5). 2. The length of time that patients have been on the most recent constant dose of Octreotide prior to randomization (≤6 and >6 months).
Statistical Analysis	The primary efficacy variable of this study is PFS measured from the randomization date. The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method and the unstratified log-rank test will be used to compare the PFS between the two treatment groups. The secondary efficacy variables are: Objective Response Rate (ORR), Time to Tumour Progression (TTP) and OS. Duration of Response (DoR) and Time to Second Progression (PFS2) will be descriptively analyzed as secondary exploratory end-points. Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups will be compared by Fisher's exact test. OS and TTP will be similarly analyzed as the primary efficacy variable. OS will not be censored if a patient receives other anti-tumour treatments after study medication. Survival data will be analyzed at the time of the Primary End-Point (PFS) analysis, and at the moment when 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first. Survival curves will be compared by the log-rank test. The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of PFS, TTP, and OS at any time point (i.e.: S1=S2), against the two sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2). The comparison of ORR by Fisher's exact test investigates the null hypothesis that the two treatment group proportions are equal (i.e.: p1=p2) against the two sided alternative hypothesis that the two treatment group proportions are not equal (i.e.: p1≠p2).

Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm

Visit	Eligibility	Baseline	Study Treatment Phase																								Follow-Up Phase[7]
																									Further visits[6]		End of Study Treatment Phase Visit	
Week		Week -3	0☎	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																											
OctreoScan®	< 24 weeks																											
Histology and Ki67[1]	x																											
Diagnosis and Extent of Cancer	x																											
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																											
Demographic Data	x																											
Relevant Medical History		x																										
Prior Therapy for Carcinoid Tumour	x	x																										
Confirmation of Eligibility and Randomization		▼																										
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																										
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x														x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x		x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x			
Quality of Life (EORTC GI-NET21; EORTC C30)		x					x					x			x			x			x			x			
Hematology[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	x
Blood Chemistry[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	x
Urinalysis[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	x
Pregnacy test[2]		x			x			x			x																	
Serum CgA[1]		x					x				x				x			x			x			x				
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																												
Antitumor-therapies after progression																												
Adverse Events[5]																												
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x	x	x
Survival Information																												

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Sections 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the Protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

Table 1 Footnotes

↓ TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; 4 administrations at 8±1-week intervals

↓ TREATMENT: 30 mg Sandostatin® LAR Depot injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion

Last Sandostatin® LAR Depot injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)

[1]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the PFS Primary-End-Point occurs; then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.

RECIST Disease Assessment during the long-term follow-up will be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose.
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter at baseline for female of childbearing potential and during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy within 7 days prior to each treatment; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits
- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4±1 weeks after each treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, additional laboratory tests will be performed on the same day or within the day before each treatment. Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of study drug must include at minimum:
  a. serum blood urea nitrogen and creatinine
  b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
  c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.
- If a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured

[3]During the study, symptoms will be recorded in the e-CRF according to patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]Any progressive patient ceases treatment/assessment and proceeds to the 5years long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:

a) Patients who have 76 weeks or more treatment/assessment stop treatment but continue 6-monthly assessments for overall 5-years from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[7]Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient whichever occurs first (phone contacts or visits at Site). Laboratory assessments (haematology, biochemistry, urinalysis), further anti-tumour treatments, SAEs suspected in relationship to the study drug, tumour progression (local evaluation after the analysis of the PFS Primary End-Point) and death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

– – – ▶ Information to be collected during the entire study

Table 2: Visit Schedule: Octreotide LAR Arm

Visit	Eligibility	Baseline	Study Treatment Phase																			Further visits[6]		End of Study Treatment Phase Visit	Follow-Up Phase[7]
Week		Week -3	0☎	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇		
Informed Consent	x																								
OctreoScan®	< 24 weeks																								
Histology and Ki67[1]	x																								
Diagnosis and Extent of Cancer	x																								
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																								
Demographic Data	x																								
Relevant Medical History		x																							
Prior Therapy for Carcinoid Tumour	x	x																							
Confirmation of Eligibility and Randomization		▼																							
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																							
ECG		x	x		x		x		x			x			x			x			x		x		
Physical Exam and Vital Signs		x				x			x			x			x			x			x		x	x	
Karnofsky Performance Status	x	x				x			x			x			x			x			x		x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x		x		
Hematology[2]	x	x		x		x			x			x			x			x			x		x	x	x
Blood Chemistry[2]	x	x		x		x			x			x			x			x			x		x	x	x
Urinalysis[2]	x	x		x		x			x			x			x			x			x		x	x	x
Pregnancy Test		x																							
Serum CgA[1]		x				x			x			x			x			x			x		x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																									
Anti-tumour therapies after prgression																									
Adverse Events																									
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x	x	x
Survival Information																									

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Sections 4.2.1 and 4.2.2.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

Table 2 Footnotes

⬇TREATMENT: 60 mg 4-week interval Octreotide LAR Depot injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the analysis of the PFS Primary End-Point (74 evaluable and centrally confirmed progressions or death events), then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained. RECIST Disease Assessment during the long-term follow-up will be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter only at baseline for female of childbearing potential; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits)

[3]During the study symptoms will be recorded in the e-CRF according patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]Any progressive patient ceases treatment/assessment and proceeds to the long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:

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[7]Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), tumour progression (local evaluation after the analysis of PFS Primary End-Point, further anti-tumour treatments and death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

- - - - -▶ Information to be collected during entire the study

INVESTIGATOR APPROVAL SIGNATURE PAGE - Protocol N°AAA III-01
Version 4.1, June 5, 2014, Replaces version 4.0, March 25, 2014

1. I have carefully read this protocol entitled "**A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours**", and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Ethics Committee and that all administrative requirements of the governing body of the institution will be complied with fully.
3. I confirm that I will conduct the study in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and FDA requirements as specified in Title 21, Code of Federal Regulations, Part 50, 54, 56, 312 and the provisions of the Helsinki Declaration (§Appendix 1); copies of these documents have been given to me by the Sponsor.
4. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines, and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents.
5. Informed written consent will be obtained from all participating patients in accordance with institutional and ICH Guidelines for Good Clinical Practice.
6. I will enrol patients who meet the protocol criteria for entry and who can be followed up in accordance with this protocol.
7. I understand that my signature on each completed Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
8. I understand that the information presented in this study protocol is confidential and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration/European Medicines Agency, European Competent Authorities and Ethic Committees.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

_____

Affiliation

SPONSOR APPROVAL SIGNATURE PAGE

Advanced Accelerator Applications SA, Head of Research & Development

Maurizio Franco Mariani	Maurizio Franco Mariani	12 JUNE 2014
Name	Signature	Date

Advanced Accelerator Applications SA, Head of Clinical Development

Claude Hariton		10 JUNE 2014
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Paola Santoro	Paola Santoro	11 JUNE 2014
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Designated CRO Authorized Representative

PIERGIORGIO GALLETTI		09 June 2014
Name		Date

Signature

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5-HIAA	5-Hydroxyindoleacetic Acid
^{90}Y	Yttrium-90
^{111}In	Indium-111
^{177}Lu	Lutetium-177
AAA	Advanced Accelerator Applications
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AP	Alkaline Phosphatase
ALAT/ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
ASAT/AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CgA	Chromogranin-A
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Dose Modifying Toxicity
DoR	Duration of Response
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DSMB	Data Safety Monitoring Board
DTPA	Diethylene Triamine Pentaacetic Acid
EC	Ethics Committee
ECG	Electrocardiogram
E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumour Society
EORTC	European Organization for Research and Treatment of Cancer
Erasmus MC	Erasmus Medical Centre, Rotterdam, NL
FAS	Full Analysis Set
FDA	Food and Drug Administration
fT4	Free Thyroxine
FSH	Follicle Stimulating Hormone
γ-GT	Gamma-Glutamyl Transferase
GBq	Giga Becquerel (Bq = unit of radioactivity)
GCP	Good Clinical Practice
GHS	Global Health Status
GEP	Gastro-Entero-Pancreatic
GFR	Glomerular Filtration rate
GlycoHb	Glycosylated Haemoglobin (haemoglobin A1C)
GMP	Good Manufacturing Practice
Gy	Gray (unit of radiation exposure; equal to 100 rad)
H	Hours
Hb	Haemoglobin
HPF	High-Power Field (microscopic exam)
ICF	Informed Consent Form
ICH	International Conference of Harmonisation

ID	Identification (Number)
IDMC	Independent Data Monitoring Committee
I.M.	Intramuscular
IMPD	Investigational Medicinal Product Dossier
IRC	Independent Review Committee
IRB	Institutional Review Board
I.V.	Intravenous
IWRS	Interactive Web-Based Response System
KPS	Karnofsky Performance Score
LAR	Long Acting Release
LDH	Lactic Dehydrogenase
LPF	Low-Power Field (microscopic exam)
MBq	Mega Becquerel (Bq = unit of radioactivity)
MCi	MilliCurie (unit of radioactivity; 1 mCi = 37 MBq)
MCV	Mean Corpuscular Volume (red blood cells)
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Millimole
MRI	Magnetic Resonance Imaging
MST	Median Survival Time
NaCl	Sodium Chloride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (USA)
NET	Neuroendocrine Tumour
NIH	National Institute of Health (USA)
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDEC	Poorly Differentiated Endocrine Carcinoma
PFS	Progression Free Survival
PFS2	Progression Free Survival (Second Progression)
PLT	Platelets
PPS	Per Protocol Set
PK	Pharmacokinetics
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
QoL	Quality of Life
QC	Quality Control
QP	Qualified Person
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RSE	Radiation Stability Enhancer
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAF	Safety Set (SAF)
S.C.	Subcutaneous
SD	Stable Disease
SNM	Society of Nuclear Medicine
SOP	Standard Operating Procedures
Sstr2	Somatostatin Receptor Subtype 2
SWOG	South West Oncology Group

ULN	Upper Limit of Normal (according to local laboratory normal values)
VIPoma	VIP Producing Tumour
VIP	Vasoactive Intestinal Peptide
WBC	White Blood Cells
WDEC	Well-differentiated Endocrine Carcinoma
WDET	Well-differentiated Endocrine Tumour
WHO	World Health Organization
WMA	World Medical Association

1- INTRODUCTION

1.1 Background

Gastro-entero-pancreatic neuroendocrine tumours (GEPNETs) are rare neoplasms that arise from neuroendocrine cells throughout the body. Most are more indolent than other epithelial malignancies; however, they can be aggressive and resistant to therapy (Yao J et al., 2008b). Symptomatic GEPNETs are often metastasized at diagnosis (Chamberlain RS et al., 2000; Öberg K, 2004, 2010). Neuroendocrine tumour hepatic metastases may lead to liver dysfunction but are often associated with a long deteriorating disease course, in many cases with debilitating clinical symptoms, either due to hormonal overproduction or to large tumour burden.

The typical symptoms of carcinoid syndrome include flushing (80%), diarrhoea (70%), abdominal pain (40%), valvular heart disease (30–40%), telangiectasia (25%), wheezing (15%) and pellagra-like skin lesions (5%). Carcinoid heart disease is characterized by plaque-like fibrous endocardial thickening that classically involves the right side of the heart, occurring in 50-70% of patients with carcinoid syndrome. Haemodynamically significant heart disease is observed in about 5-10% of patients (Caplin ME et al, 1998; Kulke MH and Mayer RJ, 1999, Öberg K, 2004).

In this protocol, a midgut carcinoid tumour is defined as a neuroendocrine tumour arising in the midgut (i.e. distal duodenum, jejunum, ileum, caecum and appendix, ascending and transverse colon, first two thirds). Sixty six percent of carcinoid tumours arise in the midgut; the small bowel being the most common site, followed by the appendix (Clark et al., 2009).

The primary treatment for carcinoid tumours is surgery with curative intent. However, only a minority of the patients with GEPNETs can be cured by surgery (Öberg K, 2000). In inoperable disease, external beam radiation therapy or chemotherapy are not particularly effective (Cheng PNM et al., 1999; Bukowski RM et al., 1994; Andreyev HJN et al., 1995; Neijt JP et al., 1995; Ritzel U et al., 1995; Ansell SM et al., 2001; Kouvaraki MA et al., 2004; Sun W et al., 2005; Ducreux MP et al., 2006; Bajetta E et al., 2007). Consequently, there are few if any approved treatment options with significant efficacy for patients with advanced disease. Well-differentiated carcinoid tumours express somatostatin receptors, specifically subtype 2 (sstr2), in high abundance. Somatostatin derivatives, such as Octreotide, are used to treat symptoms of hormonal overproduction, and to a lesser extent these have a cytostatic effect (Öberg K, 2000, 2002; Rinke A et al., 2009), apart from stabilization.

1.2 Peptide Receptor Radionuclide Therapy

Tumour-targeted peptide receptor radionuclide therapy (PRRT) is under clinical evaluation since 1992 for GEPNETs expressing somatostatin receptors. Initial results have been obtained with ^{111}In-DTPA^{0}-Octreotide, but more promising results were obtained from Novartis and/or Investigator sponsored phase I/II studies with ^{90}Y-DOTA^{0}-Tyr^{3}-Octreotide and, in particular, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (De Jong M et al., 2002; Valkema R et al., 2002, 2006; Waldherr C et al., 2001; Paganelli G et al., 2001; Bodei L et al., 2008, 2009, 2010, 2011; Kwekkeboom DJ et al., 2003, 2005, 2008; Forrer F et al., 2007, 2009; Menda Y et al., 2010) .

DOTA^{0}-Tyr^{3}-Octreotide (Octreotide) and DOTA^{0}-Tyr^{3}-Octreotate (Octreotate) consist of a somatostatin peptide analogue, coupled with a metal-ion complexing moiety (DOTA). They can be labelled with the beta-emitters Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu). By targeting somatostatin receptor positive

tumours (as imaged by OctreoScan®, Mallinckrodt/Covidien), a tumouricidal radiation dose is delivered. ^{90}Y is a high-energy beta-emitter with a maximum tissue penetration of 12 mm and a physical half-life of 64.1 hours (h). ^{177}Lu is a medium-energy beta-emitter with a maximum tissue penetration of 2 mm and a physical half-life of 6.7 days. It also emits medium and low-energy gamma radiation, which can be used for imaging and dosimetry. Octreotate and Octreotide bind with high-affinity to somatostatin receptors (especially sstr2) and retain both their binding properties and physiological function when complexed with ^{90}Y or ^{177}Lu (Reubi JC et al., 2000).

Studies in patients on biodistribution, excretion, and organ and tumour dosimetry have been performed using ^{111}In-DTPA-Pentetreotide (OctreoScan®, Covidien), ^{86}Y-DOTA^{0}-Tyr^{3}-Octreotide, and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Cremonesi M et al., 1999; Krenning E et al., 1992; Kwekkeboom DJ et al., 1999, 2001; Rosch F et al., 1999; Barone R et al., 2005; Wehrmann C et al., 2007; Bodei L et al., 2008; Forrer F et al., 2009; Sandström M et al., 2009; Garkavaij M et al., 2010; Claringbold PG et al., 2011; Bodei L et al., 2011). Comparisons between ^{86}Y-DOTA^{0}-Tyr^{3}-Octreotide and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on the one hand, and OctreoScan® on the other, showed that the uptake in physiological target organs (liver, spleen and kidneys) is not significantly different, whereas uptake in sstr2 expressing NETs is about 2 times higher for ^{86}Y-DOTA^{0}-Tyr^{3}-Octreotide (Barone R et al., 2008) and 3 to 4 times higher for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Kwekkeboom DJ et al., 2001) when compared to OctreoScan® tumour uptake. This advantage is slightly offset by a higher radiation dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the bone marrow (Forrer F et al., 2009).

There is a rapid urinary clearance of radiolabelled Octreotide and Octreotate from the circulation, which gives these radiopharmaceuticals a major advantage over radiolabelled antibodies which provide another way for cell targeted delivery of radiation. Antibodies have long plasma half-lives (several days), that result in high levels of whole-body irradiation. However, because of the absorbed radiation dose to the kidneys, therapy with radiolabelled (ß-particle emission) somatostatin analogues is not recommended in patients whose creatinine clearance is less than 50 mL/min. A mean decrease in creatinine clearance by 30%, as observed in some patients treated with ^{90}Y-DOTA^{0}-Tyr^{3}-Octreotide, could leave these patients in need of dialysis (Cybulla M et al., 2001).

Concomitant administration of amino acids reduces renal radioactivity uptake without altering tumour uptake (Kwekkeboom DJ et al., 2001). This phenomenon of protection ("blocking" renal tubular uptake of proteins, or peptides, by amino acid infusion) is similar to that demonstrated in humans using OctreoScan® or endogenous proteins (Hammond PJ et al., 1993; Rolleman EJ et al., 2003). Cationic amino acids appear to be responsible for the effect since physiological solutions containing only lysine and arginine are able to provide protection equivalent to more complex formulations.

1.3 Risk-Benefit Assessment

1.3.1 Treatment Options

GEPNETs constitute a life-threatening disease, and functioning GEPNETs are associated with debilitating clinical symptoms.

- Streptozocin (Zanosar®, Sicor Pharmaceuticals / Pfizer, a chemotherapeutic drug) was approved in the US for treating progressive metastatic pancreatic islet cell cancer in 1982. To the best of our knowledge, Streptozocin is only registered in France for treatment of insulinoma and metastasized carcinoid tumour, and therefore not widely available in EU Member States.

- Sunitinib (Sutent®, Pfizer, a multi-targeted receptor tyrosine kinase (RTK) inhibitor) has been approved in the US for treatment of renal cell carcinoma and gastrointestinal stromal tumour, but not for any GEPNET indication. In the EU, it was approved in November 2010 for treatment of adults with unresectable or metastatic, progressive well-differentiated pancreatic neuroendocrine tumours.
- Everolimus (Afinitor® Tablets, Novartis Pharmaceuticals Corporation, an oral inhibitor of mammalian target of rapamycin (mTOR)) has been approved in the US for treatment of progressive neuroendocrine tumours of pancreatic origin, but not for any other GEPNET indication. Afinitor has also been approved in the EU for the treatment of progressive unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin.

1.3.2 Efficacy of Sandostatin® LAR

Except for Sandostatin® LAR Depot, medications registered for the treatment of GEPNETs are restricted to those of pancreatic origin (see §Section 1.3.1). Therefore these agents are only beneficial to a small subset of GEPNET patients. In the case of Sandostatin® LAR Depot, the drug is registered in EU countries (but not in the US) "to treat neuroendocrine tumours located in the gut" (§Appendix 4). The drug has been shown to provide a modest increase in progression free survival in patients with progressive, mid-gut carcinoid tumours (Rinke A et al., 2009). Sandostatin® LAR and Octreotide acetate (daily s.c.) are registered for transient relief of the debilitating symptoms associated with carcinoid syndrome or caused by other types of functioning GEPNETs (§Appendix 4).

1.3.3 ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Phase I/II Study Data

615 subjects were treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with concomitant amino acid infusion in an Investigator sponsored Phase I/II study at the Erasmus Medical Center (Erasmus MC) between January 2000 and March 2007. As a result of the unmet medical need, the patients population enrolled was heterogeneous including various somatostatin receptor positive tumour types; the majority consisted of GEPNETs, including carcinoid tumours and pancreatic isle cell tumours, but patients with melanoma, thyroid tumours and non-small cell lung carcinomas, among others, were also included. The standard treatment for the enrolled patients was 4 administration of 7.4 Gbq (200 mCi) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Follow-up monitoring for all enrolled patients continued beyond treatment until a patient was lost to follow-up, patient death or for a maximum of 10 years, whichever occurred first. Long-term follow-up has been performed for 367 Dutch patients. Nearly all the 248 patients from outside the Netherlands were lost to follow-up within 1 year post treatment.

The Erasmus MC phase I/II study has been conducted according to the ethical principles of GCP, however, it was an Investigator Initiated trial. A retrospective, independent verification of the source data, and a statistical analysis of the study results have been conducted by a contract CRO to support the initiation of the present phase III study.

1.3.3.1 Safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

All enrolled 615 subjects were included in the Safety analyses of the independent data review, which consisted of all subjects who entered the trial and received at least one dose of trial medication.

Acute adverse effects occurring within 24 h after the administration of the radiopharmaceutical were nausea (25% of administrations), vomiting (10%) and abdominal discomfort or pain (10%).

13% of the subjects experienced one or more severe events suspected to be related to the study drug.

Six patients were hospitalized within 2 days of the administration because of hormone-related crises (de Keizer B et al, 2008). All recovered after supportive care.

Three patients presented with serious liver toxicity, two of them had diffuse liver metastases, one had liver fibrosis. In one patient liver functions deteriorated in the weeks following the first administration. The patient died of hepatic failure after 6 weeks. Because this patient experienced a similar deterioration due to rapid tumour growth after previous courses of chemotherapy, the liver failure after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment was considered more likely tumour growth–related rather than radiation induced. A second patient, who had multiple liver metastases, had temporary increases in serum ALAT (ALT), ASAT (AST), and bilirubin concentrations. This condition resolved without causative treatment and resumed treatment at half dose, uneventfully. The third patient, a 76 years old man suffering from liver fibrosis, developed hyperbilirubinemia after the second administration of 7.4 GBq (200 mCi) and passed away 3 weeks from treatment. In general, liver parameters in the whole population did not show a clear trend towards worsening under treatment.

There were two cases of renal insufficiency with suspected relationship with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. This relative benign profile was confirmed both by serum/urine analyses performed during the study. The evaluation of the dosimetry data collected on all treated patients indicated that there was no correlation between creatinine clearance loss per year and the administered activity.

Haematological toxicity was experienced by 12.8% of the whole population.

Myelodysplastic Syndrome (MDS) suspected to be related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate occurred in five patients. MDS was diagnosed 1 to 3 years after treatment.

Acute leukaemia was reported for 2 of the 367 Dutch patients and it occurred in 1 French patient. It was diagnosed up to 7 years after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment with a cumulative administered activity of either 22.2 GBq (600 mCi; 1 patient) or 29.6 GBq (800 mCi, 2 patients). One patient received prior chemotherapy and one patient received external beam radiation for breast cancer 7 years before ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy.

A sub-analysis of the hematological data has been conducted on the 367 Dutch patients for whom a longer follow-up was available, leading to the following results:

- Leucopoenia CTC grade 3-4 occurred in 4.1% of patients (26.7% of them already had a CTC grade 1 toxicity at baseline and 33.3% of the subjects received prior Chemotherapy or Radionuclide therapy or Radiotherapy). The nadir was experienced during treatments 1-2 by 28.3% of cases, during treatments 3-4 by 52.2% of cases and during follow-up for the rest (especially between months 3 and 6);

- Anaemia CTC grade 3-4 occurred in 4.9% of patients (66.7% of them already had a CTC grade 1 toxicity at baseline, 11.1% had a CTC grade 2-3 toxicity at baseline, 44.4% received prior Chemotherapy or Radionuclide therapy or Radiotherapy and 11.1% experienced Hb toxicity after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate re-treatments exceeding the cumulative 29.6 GBq (800 mCi) administered radioactivity). The nadir was experienced during treatments 1-2 in 15.2% of cases, during treatments 3-4 in 41.3% of cases and during follow-up for the rest (especially between months 3 and 6);

- Thrombocytopenia CTC grade 3-4 occurred in 7.3% of patients (7.4 % of them already had a CTC grade 1 toxicity at baseline, 40.7% received prior Chemotherapy or Radionuclide therapy or Radiotherapy and 7.4% experienced the PLT toxicity after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate re-treatments exceeding the 29.6 GBq (800 mCi) administered radioactivity). The nadir was experienced during treatments 1-2 in 15.2% of cases, during treatments 3-4 in 56.5% of cases and during follow-up for the rest (especially between months 12 and 24).

- Pancytopenia was observed in 8.2% of cases. As general rule, an event was classified as Pancytopenia when a reduction in the number of red and white blood cells, as well as platelets, occurred concomitantly; at least one out of these three parameters (Haemoglobin, White Blood Cells and Platelets) was CTC Grade 3-4, while the other two parameters were CTC Grade ≥1. In 80% of the pancytopenia cases, at least one of the three parameters was already CTC Grade ≥1 at baseline, 6.7% of the patients experienced pancytopenia after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate re-treatments exceeding the cumulative 29.6 GBq (800 mCi) administered radioactivity, and 27.7% of the subjects had received Chemotherapy or Radionuclide therapy or Radiotherapy prior to enrollment in the Study.

The haematological toxicity nadir was observed in the 74.5% of cases during treatment, the rest during the follow-up period. Although classified as suspected to be treatment related, it can't be excluded that the decrease in the laboratory parameters observed during the follow-up period may at least partially be due to a concomitant deterioration of patients condition or disease progression.

1.3.3.2 Efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

Efficacy end-points of the phase I/II Erasmus MC data have been independently evaluated on the Full Analysis Set (FAS), consisting of 404 subjects with diagnosed GEPNETs, who had an OctreoScan® tumour uptake score ≥ Grade 2 and at least one valid primary efficacy variable on active treatment, showing the following results according to modified SWOG Criteria (note standard SWOG Criteria does not include minor responses):

- Objective tumour response (complete response (CR) + partial response (PR) + minor response (MR is defined as a tumour diameter decrease of 25% to 50%, Kwekkeboom DJ et al., 2005) in the overall GEPNET FAS population was 59.4% (95% CI; 54.44-64.23%); in the subgroup of 157 Dutch carcinoid tumour patients the objective tumour response was 61.2% (95% CI; 53.05 - 68.81%);
- Time to progression (TTP) from start of treatment in the overall GEPNET FAS population was 1164 days (38 months) with a 95% CI of 994-1357 days (32.6-44.5 months);
- Median PFS from start of treatment in the overall GEPNET FAS population was 904 days (29 months) with a 95% CI of 812-994 days (26.6-32.6 months);
- Median OS from start of treatment in the overall GEPNET FAS population was: 1496 days (49 months) with a 95% CI of 1375-1667 days (45.1-54.7 months).

Special attention was paid to patients with the same diagnosis as proposed for this phase III trial. A subset of 51 subjects with the diagnosis carcinoid midgut with progressive disease at study entry was independently re-assessed.

Median PFS of these subjects was:

- 1375 days (45 months) 95% CI 678-1732 days (22-57 months) according to RECIST Criteria, Version 1.1.
- 1174 days (39 months) 95% CI 560-1732 days (18-57 months) according to SWOG Criteria.

Global Health Status (GHS) Quality of Life (QoL), Karnofsky Performance Score (KPS) and clinical symptoms before and after therapy have also been analyzed, as important end-points of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy. QoL, KPS, and clinical symptoms improved and there was no significant decrease in QoL in patients, who had no symptoms before therapy. In patients who had suboptimal scores for GHS/QoL or symptoms before therapy, a clinically significant improvement was demonstrated (Teunissen JJ et al., 2004).

These results are in agreement with a recent publication of the Erasmus MC group (Khan S et al., 2011) on the phase I/II data, on a sample of 265 out of 282 Dutch patients with metastatic inoperable GEPNETs or bronchial NET, who completed the QoL questionnaire (EORTC QLQ-C30).

These results indicate that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy not only reduces tumours and prolongs overall survival but also improves the patients' self-assessed QoL.

2- STUDY OBJECTIVES

2.1 Primary Objective

- To compare Progression Free Survival (PFS) after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria Version 1.1, Eisenhauer EA et al., 2009; §Appendix 2), somatostatin receptor positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours).

2.2 Secondary Objectives

Secondary objectives:

- To compare the Objective Response Rate (ORR) between the two study arms;
- To compare the Overall Survival (OS) between the two study arms;
- To compare the Time to Tumour Progression (TTP) between the two study arms;
- To evaluate the safety and tolerability of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate;
- To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire (§Appendix 3);

Exploratory objectives

- To explore the correlation of toxicity outcomes and administered radioactivity corrected for body weight and body surface area;
- To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;
- To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients;
- To explore the correlation of clinical efficacy outcomes with OctreoScan® tumour uptake score;
- To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP);
- To evaluate the Duration of Response (DoR) in the two study arms;
- To evaluate the Time to Second Progression (PFS2) in the two study arms.

3- STUDY DESIGN

3.1 Study Outline

This is a multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

Key criteria for enrollment in the study are; i) metastasized or locally advanced, histologically proven midgut carcinoid tumours; ii) target lesions are somatostatin receptor positive based on OctreoScan® scintigraphy within 24 weeks prior to randomization in the study while the patient was on a fixed dose of Sandostatin® LAR (except for the temporary interruption of Sandostatin® LAR use for the purpose of obtaining an OctreoScan®); iii) the patient is at a fixed dose of 20 mg or 30 mg Octreotide at 3-4 weeks intervals for least 12 weeks prior to randomization in the study; and iv) has progressive disease centrally confirmed by RECIST Criteria; for the purpose of determining disease status the oldest CT/MRI scan must not be older than 3 years and the most recent scan must not be older than 4 weeks from the projected randomization date.

Patients who have signed the informed consent form (ICF) and are eligible for study participation according to the inclusion and exclusion criteria will be randomly assigned to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm or the Octreotide LAR arm in an equal ratio (1:1). Baseline evaluations should be completed within 4 weeks prior to their first treatment (Treatment Day 1) (§Section 6.5.2). Patients will be evaluated for the safety, tolerability, and renal excretion pharmacokinetics (the latter only in a subset of 20 patients in pre-identified centres) in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm in Table 1 and Table 2, respectively.

Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a total cumulative administered radioactivity of 29.6 GBq (800 mCi), which results in a safe radiation dose to the critical organs, the bone marrow and the kidneys (Bodei L et al., 2010, 2011; Kwekkeboom DJ et al., 2008). Concomitant amino acids will be given with each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration for kidney protection. Also, in addition to the treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, the patients will receive supportive care with cold Octreotide (§Section 5.2.1.1).

If a patient experiences a Dose Modifying Toxicity (DMT) during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg Sandostatin® LAR at monthly intervals. After resolution of a DMT, a patient may receive his/her subsequent planned treatment(s) at 50% of the standard treatment dose. If the same DMT reoccurs after treatment with the reduced dose or the DMT does not resolve within 16 weeks, the patient will no longer receive any ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate but continues the study with monthly Sandostatin® LAR 30 mg (if Sandostatin® LAR is unlikely to be the causative agent of the observed toxicity), and continues scheduled scans, until progression; after progression, the patient will continue the observation in the long term follow-up assessment phase. If the DMT event does not reoccur, the next treatment is at full dose.

Patients in the comparator arm will receive 60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) intramuscular (i.m.) injections every 4 weeks ± 3 days. If the patient experiences toxicity with the increased dose, the dose will be adjusted to the previous well-tolerated dose, to be increased again with the next treatment to 60 mg if the toxicity has resolved.

Objective tumour assessment in both arms will be performed every 12±1 weeks from the randomization date until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then until Week 76, unless the patient progresses or dies. Patients that are RECIST progressive according to central reading assessment are treatment failures and proceed to the long-term follow-up phase.

In case of discrepancies between Investigator and central assessor on the evaluation of the progression of disease, see §Section 4.4.1.

The primary analysis will be performed after 74 PFS events (74 evaluable and centrally confirmed disease progressions or death events) have occurred. Patients who are randomized should continue to receive either Octreotide 60 mg (Octreotide LAR arm) or Octreotide 30 mg (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) until progression (or until 74 evaluable and centrally confirmed disease progressions or death events). When the PFS Primary End-Point has been reached, the 76-week treatment period becomes fixed and all patients receive Octreotide 60 mg (Octreotide LAR arm) or Octreotide 30 mg (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) until week 72 before entering the long-term follow-up assessment phase after week 76. Any progressive patient ceases treatment/assessment and proceeds to long-term follow-up assessment.

Any non-progressive patient continues treatment/assessments until the PFS Primary End-Point has been reached, then:

- Patients who have 76-weeks or more treatment/assessment stop treatment but continue the long-term follow-up assessments for 5 years from the date of randomization of the last randomized patient.
- Remaining randomized patients continue in the fixed 76week treatment/assessment period unless progression occurs, then continue the long-term follow-up assessment for 5 years from the date of randomization of the last randomized patient.

If patients in either arm experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, Octreotide s.c. rescue injections are allowed.

Details on the timing of the administration of study medication and assessments are provided in the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm in Table 1 and Table 2, respectively.

Dosimetry, PK, ECG substudy

A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites to provide a more complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

To facilitate the patients recruitment in this substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies (Study Protocol 4.1, June 5, 2014). As soon as the Protocol Amendment 4.1 is approved by the substudy site IRB, the randomization protocol of the study is halted at the substudy sites until 20 patients are enrolled in the substudy and all the patients included in the substudy sites will be treated in arm A (4 infusions of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate +30 mg Octreotide LAR). During this period, the sites not participating in the substudy continue to enroll patients using to the randomization protocol of the main study.

In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed

descriptively only and they will not be considered in the primary and secondary analysis of the main study groups.

Patients participating in the substudy will be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the substudy.

Aside from the specific tests conducted in the dosimetry study as described in Section 6.6 and the separate substudy manual, the treatment regimen and patient care management remain identical to that implemented in the main study.

3.2 End of Study

The End of Study is defined as the moment that 158 deaths have occurred, or 5 years have elapsed from the date of randomization of the last randomized patient, whichever occurs first.

3.3 Study Design Rationale

This study is the first controlled comparative study with a radiolabelled versus non-radioactive somatostatin analogue. In this study, safety and efficacy of treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate versus Octreotide LAR will be investigated in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

The chosen regimen for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm with a cumulative amount of radioactivity of 29.6 GBq (800 mCi), divided into 4 administrations, is identical to the regimen used in the Erasmus MC Phase I/II study. In this study, kidney dosimetry was scheduled after the third treatment in all the enrolled patients. The dosimetry evaluation was conducted on 408 out of 615 patients who had quantifiable kidney uptake. The follow-up results of kidney function parameters confirmed that the fourth treatment could be safely administered, even in the instance of some patient exceeding the 23 Gy kidney threshold. In patients for whom kidney dosimetry could not be performed, a fixed amount of radioactivity of 29.6 GBq (800 mCi) was administered without any deleterious effect on kidney function in any patient. This is consistent with the previous publication of Kwekkeboom DJ et al. (2008).

Patients in the comparator arm will receive 60 mg Octreotide LAR. The dose is supported by the report that 30% of carcinoid tumour patients receive >30 mg (Anthony LB et al., 2004). In current clinical practice, it is likely that even a higher percentage of patients receive >30 mg of Octreotide LAR (Joseph S et al., 2010). 4-Week interval injections of 60 mg Octreotide LAR is a higher dose than the 4-week interval injections with 20 mg or 30 mg, which is presently the registered dose for relief of symptoms associated with functional GEPNETs, such as midgut carcinoid tumour (Sandostatin® LAR Depot prescribing information; see §Appendix 4 for adverse events). With this type of treatment, the majority of symptomatic patients show an improvement in QoL, and most patients obtain temporary stable disease based on CT scans, although tumour regression rarely occurs (Faiss S et al., 2003; Rinke A et al., 2009; Ludlam W et al., 2011; Anthony L et al., 2011). Furthermore the patients in the present study must have confirmed metastatic progressive disease carcinoid tumours and also receiving 20-30 mg Octreotide LAR (or somatostatin analogue equivalent) to be eligible for enrollment. Therefore, if Sandostatin® LAR Depot is to be administered as an anti-tumour drug to patients that have already failed treatment (confirmed PFS at 20-30 mg Octreotide LAR), then a higher dose is required. Consequently, a 60 mg, 4-week interval dose is proposed for the control (best standard of care) arm of the present phase III study.

3.3.1 Substudy Design Rationale

A 20 patient Dosimetry, Pharmacokinetics, and ECG study will be performed in about 10 selected sites. This is a substudy of the present phase III clinical trial.

See §Section 6.6 for further details on sub-study procedures; in addition, a study manual of the substudy will be provided to participating sites.

3.3.1.1 Primary Objective:

- Calculate whole body and organ radiation dosimetry of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to determine the dose to critical organs (e.g., kidney and bone marrow) and correlate with findings of the Erasmus MC Phase I/II Clinical study.

3.3.1.2 Secondary Objectives:

- Define the pharmacokinetic profile (ADME) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate;
- Correlate safety, dosimetry, and pharmacokinetic data obtain in this study with the Erasmus MC phase I/II Clinical study to confirm previous findings;
- Evaluate cardiac safety: determine the acute electrophysiological changes during treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (through 24-hour continuous ECG recording via 12-lead Holter monitoring).

3.3.1.3 Eligibility

Patients participating in the substudy will be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the dosimetry, pharmacokinetics and ECG substudy prior to the initiation of any substudy-related procedures.

Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm

Visit	Eligibility	Baseline	Study Treatment Phase																							Follow-Up Phase[7]
																								Further visits[6]		End of Study Treatment Phase Visit	Every 6 months
Week		Week -3	0☎	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																											
OctreoScan®	< 24 weeks																											
Histology and Ki67[1]	x																											
Diagnosis and Extent of Cancer	x																											
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																											
Demographic Data	x																											
Relevant Medical History		x																										
Prior Therapy for Carcinoid Tumour	x	x																										
Confirmation of Eligibility and Randomization		▼																										
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																										
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x														x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x		x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x			
Quality of Life (EORTC GI-NET21; EORTC C30)		x					x					x			x			x			x			x			
Hematology[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	
Blood Chemistry[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	
Urinalysis[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	
Pregnacy test[2]		x			x			x			x																	
Serum CgA[1]		x					x				x				x			x			x			x				
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																												
Antitumor-therapies after progression																												
Adverse Events[5]																												
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x	x	
Survival Information																												

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Section 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the Protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

Table 1 Footnotes

↓ TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; 4 administrations at 8±1-week intervals

↓ TREATMENT: 30 mg Sandostatin® LAR Depot injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion

Last Sandostatin® LAR Depot injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)

[1]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the PFS Primary-End-Point occurs; then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.

RECIST Disease Assessment during the long-term follow-up will be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose.
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter at baseline for female of childbearing potential and during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy within 7 days prior to each treatment; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits
- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4±1 weeks after each treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, additional laboratory tests will be performed on the same day or within the day before each treatment. Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of study drug must include at minimum:
  a. serum blood urea nitrogen and creatinine
  b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
  c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.
- If a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured

[3]During the study, symptoms will be recorded in the e-CRF according to patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]Any progressive patient ceases treatment/assessment and proceeds to the 5years long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:

a) Patients who have 76 weeks or more treatment/assessment stop treatment but continue 6-monthly assessments for overall 5-years from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[7]Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first (phone contacts or visits at Site). Laboratory assessments (haematology, biochemistry, urinalysis), further anti-tumour treatments, SAEs suspected in relationship to the study drug, tumour progression (local evaluation after the analysis of the PFS Primary End-Point) and death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

– – – ▶ Information to be collected during the entire study

Table 2: Visit Schedule: Octreotide LAR Arm

Visit	Eligibility	Baseline	Study Treatment Phase																			Further visits[6]		End of Study Treatment Phase Visit	Follow-Up Phase[7]
Week		Week -3	0☎	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇		
Informed Consent	x																								
OctreoScan®	< 24 weeks																								
Histology and Ki67[1]	x																								
Diagnosis and Extent of Cancer	x																								
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																								
Demographic Data	x																								
Relevant Medical History		x																							
Prior Therapy for Carcinoid Tumour	x	x																							
Confirmation of Eligibility and Randomization		▼																							
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																							
ECG		x	x		x		x		x			x			x			x			x		x		
Physical Exam and Vital Signs		x				x			x			x			x			x			x		x	x	
Karnofsky Performance Status	x	x				x			x			x			x			x			x		x		
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x		x		
Hematology[2]	x	x		x		x			x			x			x			x			x		x	x	x
Blood Chemistry[2]	x	x		x		x			x			x			x			x			x		x	x	x
Urinalysis[2]	x	x		x		x			x			x			x			x			x		x	x	x
Pregnancy Test		x																							
Serum CgA[1]		x				x			x			x			x			x			x		x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																									
Anti-tumour therapies after prgression																									
Adverse Events																									
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x	x	x
Survival Information																									

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Sections 4.2.1 and 4.2.2.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

Table 2 Footnotes

⬇TREATMENT: 60 mg 4-week interval Octreotide LAR Depot injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the analysis of the PFS Primary End-Point (74 evaluable and centrally confirmed progressions or death events), then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained. RECIST Disease Assessment during the long-term follow-up will be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter only at baseline for female of childbearing potential; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits)

[3]During the study symptoms will be recorded in the e-CRF according patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]Any progressive patient ceases treatment/assessment and proceeds to the long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:
a) Patients who have 76-weeks or more treatment/assessment stop treatment but continue assessments for overall 5-year from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[7]Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first (phone contacts or visits at Site). Laboratory assessments (haematology, biochemistry, urinalysis), tumour progression (local evaluation after the analysis of PFS Primary End-Point, further anti-tumour treatments and death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

- - - - -► Information to be collected during entire the study

4- SELECTION OF STUDY POPULATION

4.1 Inclusion and Exclusion Criteria at Baseline

A total of 230 patients (115 patients per treatment arm) will be randomly assigned to open-label treatment.

In order to assure a balanced study design, randomization will be stratified by OctreoScan® highest tumour uptake score (Grade 2, 3 and 4), and length of time that patients have been on the most recent constant dose of Octreotide prior to randomization (≤6 and >6 months).

4.1.1 Inclusion Criteria at Baseline

1. Presence of metastasized or locally advanced, inoperable (curative intent) at randomization time, histologically proven, midgut carcinoid tumour (to be centrally confirmed).
2. Ki67 index ≤ 20% (to be centrally confirmed).
3. Patients on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study.
4. Patients ≥18 years of age.
5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 (§Appendix 2) while receiving an uninterrupted fixed dose of Octreotide LAR (20-30 mg/3-4 weeks). Disease progression must be centrally confirmed. In order to make the assessment, two CT (or MRI) scans are required. The oldest scan must not be older than 3 years from the date of randomization. The most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.
6. Confirmed presence of somatostatin receptors on all target lesions (for target/non-target/measurable lesions definition see §Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1) documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to randomization in the study (to be centrally confirmed) (§Section 6.1.4). The OctreoScan® should be one that was performed while the patient was on a fixed dose of Sandostatin® LAR. If a patient has had an OctreoScan® performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan® performed after 3 months of Octreotide LAR treatments before entering the clinical study to prove that the index lesions or new lesions still meet the criteria for inclusion. It is acceptable to have patients temporarily switched from Sandostatin® LAR to Sandostatin® s.c. (up to six weeks) in order to obtain an OctreoScan®, provided they return to the same fixed dose of Sandostatin® LAR prior to the scan.
7. The tumour uptake observed in each target lesion (for target/non-target/measurable lesions definition see §Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1) using OctreoScan®

should be ≥ normal liver uptake observed on planar imaging (to be centrally confirmed) (§Appendices 5 and 6, and §Section 6.1.4).

8. Karnofsky Performance Score (KPS) ≥60
9. Presence of at least 1 measurable site of disease.
10. [Applicable only for France] All patients included in the trial must be affiliated with a social security regime or be a beneficiary of the same in order to be included in the study.

4.1.2 Exclusion Criteria at Baseline

1. Either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min calculated by the Cockroft Gault method, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) <50 mL/min (the measured creatinine clearance / GFR is required only as confirmatory exam).
2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <$2x10^9$/L ($2000/mm^3$); platelets <$75x10^9$/L ($75x10^3/mm^3$).
3. Total bilirubin >3 x ULN.
4. Serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
5. Pregnancy (see §Appendix 7) or lactation.
6. For female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel) as defined in §Appendix 7.
7. Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to randomization in the study.
8. Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study.
9. Any surgery, radioembolization, chemoembolization, chemotherapy and radiofrequency ablation within 12 weeks prior to randomization in the study.
10. Interferons, Everolimus (mTOR-inhibitors) or other systemic therapies within 4 weeks prior to randomization in the study.
11. Known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks, prior to randomization in the study. Patients with a history of brain metastases must have a head CT with contrast to document stable disease prior to enrollment in the study.
12. Uncontrolled congestive heart failure (NYHA II, III, IV).
13. Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN.
14. Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, unless the tumour uptake observed on target

and non-target but measurable lesions by OctreoScan® imaging during continued Octreotide LAR treatment is at least as high as normal liver uptake observed by planar imaging (Appendices 5 and 6).

15. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study.
16. Prior external beam radiation therapy to more than 25% of the bone marrow.
17. Current spontaneous urinary incontinence.
18. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
19. Patients who have not provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities.
20. Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency. If such patients can be imaged without the use of CT contrast material (i.e., can tolerate MRI scans), such patients would not be excluded.
21. Patients who have participated in any therapeutic clinical study/received any investigational agent within the last 30 days are excluded from participation in this trial.

4.2 Inclusion and Exclusion Criteria Subsequent Treatments

4.2.1 Inclusion Criteria Subsequent Treatments

1. Both serum creatinine ≤150 μmol/L (≤1.7 mg/dL) and calculated creatinine clearance ≥50 mL/min, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) ≥50 mL/min (*the measured creatinine clearance / GFR is required only as confirmatory exam*).
2. Hb concentration ≥5.0 mmol/L (≥8.0 g/dL); WBC ≥$2x10^9$/L ($2000/mm^3$); platelets ≥$75x10^9$/L ($75x10^3/mm^3$).
3. Total bilirubin ≤3 x ULN.
4. Serum albumin >3.0 g/dL, or serum albumin ≤3.0 g/dL, but normal prothrombin time.
5. KPS ≥60.

4.2.2 Exclusion Criteria Subsequent Treatments

Exclusion criteria for baseline # 1, 2, 3, 4, 13 apply to all subsequent treatments, when a relationship can not be excluded with either study drugs and the corresponding toxicity has not resolved.

In relation to renal function: subjects are also excluded from further therapy in case of >40% increase of serum creatinine over the baseline and with a concomitant decrease of >40% in creatinine clearance as calculated according to the Cockroft Gault method, eventually confirmed by measured creatinine clearance (or GFR), if a relationship may not be excluded with either study drugs and the corresponding toxicity has not resolved. For patients in the ^{177}Lu-DOTA^0-Tyr^3-Octreotate arm, criteria for dose modifying toxicity should be verified, when applicable.

When such exclusion criteria events occur, the patient will postpone any subsequent study treatment (any ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate or Sandostatin® LAR) until resolution of the event (normalization or return to baseline values). Sandostatin® LAR can be continued (in either arms, at monthly intervals) if its causative relation with the exclusion criteria can be reasonably excluded, after consultation with the Medical Monitor of the study. In any case, the patient remains in the study and continues observation with the scheduled tumour and clinical assessments.

All other exclusion criteria for enrollment eligibility apply to all subsequent treatments.

4.3 Screening Failures

A "screening failure" is a patient who consented to participate in the study but was not randomized.

For patients not considered eligible after the screening period, the reason for not being eligible must be documented. No additional assessments are needed.

4.4 Discontinuation Criteria for Individual Patients

"Study termination" occurs when the patient is definitively discontinued from any study-related activity, upon completion of the 5-year study (and accrual period, if applicable), or because of premature termination for any reason.

"Study withdrawal" occurs when the patient is withdrawn from the treatment/assessment phase of the study because of disease progression or other reasons. These patients proceed immediately to the long term follow-up assessment phase.

Investigators should make every effort to avoid patient's withdrawal before the central imaging centre has confirmed disease progression.

- Any progressive patient (confirmed by central review of CT/MRI scans) ceases the treatment/assessment phase and proceeds to the long-term follow-up assessment phase. During long-term follow-up every effort must be made by the Investigator to collect additional information on further anti-tumour therapies and scan assessment outcomes (RECIST local evaluation) to evaluate the Time to Second Progression (PFS2) in the two study arms.

- Any non-progressive patient continues treatment/assessments until the PFS Primary End-Point is reached, then:

  - Patients who have 76 weeks or more treatment/assessment stop treatment but continue the long-term follow-up assessment for 5 years from the randomization date of the last randomized patient;
  - Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue the long-term follow-up assessments for 5 years overall from the date of randomization of the last randomized patient.

The informed consent form (ICF) signed at the time of the inclusion foresees the patient's participation in the Study until the end of the long term follow-up assessment phase. Patients should sign an addendum to the consent to participate in the long term follow-up assessment phase only in case they have withdrawn the initially signed consent.

The patient is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. However, in this case, the patient should be requested to continue the observation in the long term follow-up phase of the study after signing the addendum ICF for the long term follow-up.

It is also possible that the Sponsor or the Competent Authorities request termination of the study if there are concerns about conduct or safety. A Dose Modifying Toxicity (DMT - see §Section 5.7.3), or any other safety issue, is neither a cause of "study termination", nor "withdrawal" from the treatment/assessment phase, by itself, but requires the temporary suspension or definitive interruption of either suspect study drugs. In any case, the patient will continue the scheduled visits and clinical/tumour assessments until tumour progression, if possible, even in case of study treatment suspension or interruption. In case of interruption of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment due to suspected toxicity, the administration of Sandostatin® LAR 30 mg should be continued, if it is safe for the patient. A patient may have completed and may be withdrawn from the "treatment/assessment phase" of the study (but not from the long term follow-up phase), even if tumour progression has not occurred or has not been centrally confirmed, in the following cases:

1. in the Investigator opinion it is in the best interest of the patient. Such considerations will be made in the case of unethical continuation of the "treatment/assessment phase" (e.g., need of alternate systemic anti-tumour therapy because of safety or ineffectiveness of the assigned treatments – see also item #6), logistic / physical impossibility for the patient to follow the scheduled visits, or other documented reasons ;
2. conditions have occurred that have compromised the regular continuation of the clinical and tumour assessments according to the protocol until disease progression;
3. the patient withdraws his/her consent; in this case, the patient may enter the long term follow-up phase of the study only after signing an addendum to the main consent;
4. the patient is pregnant;
5. the patients has repeatedly and severely failed to comply with the protocol requirements or dosing (e.g. less than 80% study drug assumption, or severe irregularity in the scheduling/timing of assumptions of any study drug), evaluations, or other requirements of the study;
6. the patient has started systemic anti-tumour therapy which is listed as disallowed (see §Section 5.5). The final decision to withdraw a patient who starts treatment with disallowed medication will be made by the Investigator following consultation with the Sponsor, based on the nature of the medication - dose - duration – concomitance with assessment visits.

Before the patient's actual withdrawal, the case should be discussed with the Medical Monitor of the study.

In case of a patient's premature withdrawal, an "early termination visit" should be performed and patient's data be collected in the CRF including date, time, and primary reason for discontinuation, as well as the latest information available on the clinical condition and tumour progression. A CT/MRI scan should be obtained at the time of withdrawal, except in case of pregnancy.

For patients who are lost to follow-up (i.e., those patients whose status is unknown because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show 'due diligence' by documenting in the source documents steps taken to contact the patient or his/her

caregivers, dates of telephone calls, registered letters, etc. Documented information obtained on patient's clinical condition, in particular the survival status, will be used as follow-up documentation.

4.4.1 Discrepancies on the evaluation of the progressive status between Investigator and central assessor

Central, blinded, real-time IRC (Independent Review Committee) assessment is implemented in this trial for an independent re-evaluation of progressive disease.

In case of discrepancies between Investigator and central assessor on the evaluation of the progression of disease, the Investigator may request the assessment by a third evaluator for final adjudication.

If the discrepancy persists:

1. Investigator assessment: non-PD; central assessment: PD. The "treatment/assessment" phase of the study is terminated and the patient should proceed to the long term follow-up assessment period. The investigator may request the continuation of treatment and assessments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate until the cumulative dose limit has been reached and/or Sandostatin® LAR provided by the Sponsor according to randomization; 12-week local tumour assessments; safety assessments as in the treatment/assessment phase of the study) until progression has been documented by the Investigator, thereafter, the patient will proceed to the long term follow-up assessment phase.
2. Investigator assessment: PD; central assessment: non-PD. The "treatment/assessment" phase of the study should be continued as planned. However, the Investigator may decide to withdraw the patient from the "treatment/assessment phase" because of unethical continuation of the study in his/her opinion, and start the follow-up phase of the study. Such cases should be limited as much as possible and discussed with the local CRO representative before withdrawing the patient.

4.5 Dropouts and Replacements

For the purpose of this study, an "enrolled patient" is a patient who is randomized to participate in a study arm, after signing the ICF and verification of all inclusion/exclusion criteria.

A "screening failure" (see §Section 4.3) is a patient who has signed the ICF, but who does not meet all selection criteria and has not been randomized. However, a patient who has signed the ICF and has been randomized, but who is (later) found not to meet all selection criteria, is considered a "protocol violator".

All randomized patients will be included in the primary analysis, regardless of whether they received study medication, and no replacement will be done.

A subject can be re-screened with a new study number when intercurrent conditions emerging after consent signature and impeding the planned randomization are resolved, or because of previously missed confirmation of the tumour progression by central assessment. Such cases will have to be discussed and approved by the Sponsor. The site will be informed about the procedures to be followed for re-screening.

4.6 Prohibition and Restrictions

The patient must be willing to adhere to the prohibitions and restrictions during the course of the study as stated in the ICF and in the Patient Information Sheet.

5- STUDY MEDICATION AND TREATMENT

5.1 Description of Study Medication

The investigational drug product ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be provided by the Sponsor. The Sponsor will also provide/reimburse the amino acid solution for infusion as well as the Sandostatin® LAR Depot according to local regulations for the entire duration of the treatment/assessment phase of the study (but not during the long term follow-up assessment phase).

Anti-emetics, short-acting Sandostatin® or any other supportive care medication will not be provided by Sponsor.

5.1.1. Investigational Drug Product: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radiopharmaceutical solution for infusion supplied as a ready-to-use product. No manipulation of the product in needed at the clinical site. The only Quality Control (QC) tests that must be performed at the clinical site are; 1) confirm correct product certificate; 2) determine total radioactivity; 3) confirm visual appearance. Since ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is manufactured in centralized GMP facilities, the majority of required QC tests are performed before product shipment. A batch release certificate of the product will be sent to the investigational centres. This batch release certificate is provided by the Qualified Person (QP) of the manufacturing site to ensure that the product is suitable for administration and that it meets the specifications indicated in the Investigational Medicinal Product Dossier (IMPD).

The product is manufactured and supplied to the clinical sites in monodose vials. One vial, for one administration, contains 7.4 GBq (200 mCi) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at calibration time (the time of infusion) in a formulation solution of 22 to 25 mL. The variability of the volume depends on the time between the calibration date and the production date. The product will be shipped and calibrated for use at 24h or 48h after production in a centralized GMP facility. The calibration time of a dose depends on the distance from the manufacturing facility to the clinical sites. The amount of administered radioactivity, 7.4 GBq (±10%), is specified at the time of infusion.

Chemical-physical properties of each dose are listed in Table 3 below.

Table 3: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Infusion Solution Composition.

Component	Composition (one vial)	Function
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	7.4 GBq / 200 mCi	Active Pharmaceutical Ingredient
X-DOTA^{0}-Tyr^{3}-Octreotate	10 µg/mL	Total peptide content
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	4.57 µg/mL*	Active Pharmaceutical Ingredient
DOTA^{0}-Tyr^{3}-Octreotate	5.92 µg/mL*	Active Pharmaceutical Ingredient Precursor
Volume	From 22-25 mL	
Specific Activity (GBq/Total peptide)	53 GBq/µmol (at EOP)*	
Radioconcentration	370 MBq/mL (at EOP)	
Other Constituents/Excipients Acetic Acid	mg/mL 0.48*	 pH adjuster

Sodium Acetate	0.66*	pH adjuster
Gentisic Acid	0.63*	Radiation Stability Enhancer
Ascorbic Acid	2.80	Radiation Stability Enhancer
DTPA	0.05	Masking Agent
NaCl	6.85	Blood isotonic solution
Water for Injection	-	Solvent

*Values calculated assuming ^{177}Lu specific activity of 740 GBq/mg at labelling time and a mean synthesis yield of 80% and radiochemical purity ≥97%.

Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a total cumulative amount of radioactivity of 29.6 GBq (800 mCi) with the dosing equally divided among 4 administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at 8±1-weeks intervals.

Additional information on the study drug preparation, radioprotection notes and recommendations for treated patients are provided in Appendices 14, 15 and 16.

5.1.1.1 Concomitant Treatment: 30 mg Sandostatin® LAR Depot

30 mg Sandostatin® LAR Depot is preferably administered the day after each administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, according to the schedule in §Section 5.7.2, and no earlier than 4 hours after completion of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Once completed, the four treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, and also in case the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusions have been suspended, patients will continue the 4-week interval administrations of 30 mg Sandostatin® LAR Depot until the PFS Primary End-Point or until 72 weeks from randomization after the PFS End-Point has been reached (according to the schedule in Table 1), unless the patient progresses or dies.

Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in a single-use kit containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. For prolonged storage, Sandostatin® LAR Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

5.1.1.2 Concomitant Infusion with Amino Acid Solution

There are a number of studies published which demonstrate that commercial and custom made amino acid solutions reduce the kidney retention of radiolabelled somatostatin analogues in humans. Researchers at the Erasmus MC have directly demonstrated the benefit of 2.5% lysine/arginine in 1L solution in blocking kidney retention of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The 2.5% lysine and arginine solution is somewhat better tolerated, with vomiting occurring more often in patients co-infused with commercial amino acid solutions, but in both cases the side effects are usually mild and transient.

A number of groups have used commercial amino acid solutions instead of the custom lysine/arginine formulation developed at the Erasmus MC. Based on the published reports, solutions which contain a total amount of lysine and arginine of up to 24 g each in 1 to 2L would be expected to be the most effective in blocking renal uptake. Nevertheless, amino acid solution containing smaller amount of lysine and arginine (such as found in AminoSyn II 7% and Vamin 14) are also reported to be effective. Solutions containing greater than 24g lysine and 24 g arginine may pose a risk of inducing elevated serum potassium levels. The specifications of the recommended formulation of an amino acid solution for co-infusion therapy are listed in Table 4.

Table 4: Specifications of the Recommended Amino Acid Solution for Co-Infusion.

Component	Specification	Function
Lysine	≥18 g, ≤24g	Renal protection
Arginine	≥18g, ≤24g	Renal protection
Saline or other suitable diluent	<2L ± 25%	Osmolarity (<1100 mOsmol approximately), solvent
All other amino acids	No Specification	Inert nutrients

Some examples of commercial solutions that would meet or exceed these specifications (with grams lysine and arginine, and total infusion volume noted) are listed below, in order of preference:

- Aminosyn II 15% (23.6 g lysine, 22.9 g arginine, in 1.5L)
- Aminosyn II 10% (21.0 g lysine, 20.4 g arginine, in 2L)
- VAMIN-18 (18 g lysine, 22.6 g arginine in 2L)
- CLINISOL 15% (18g lysine, 18g arginine, in 1.6L)

In the present study patients randomized in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm will receive a concomitant commercially available, locally approved parenteral amino acid infusion, which supplies ≥36 g of lysine + arginine in ≤2 L (<1100 mOsm/L approximately). Eligible solutions must have the highest amount of lysine and arginine (of up to 24 g each) among the commercially available products in order to ensure adequate renal protection.

In the case of Clinisol 15% and Aminosyn II 15% the administration volume must be adjusted to around 2L by dilution with sterile water in order to reduce the osmolarity to specifications (see §Appendix 8).

Recommendations on the minimum infusion rate or maximum infusion time for treatment of nausea and vomiting

The suggested reduced rates calculated for each solution are:

Solution	Vol (L)	Time (h)	Rate (mL/h)
AminoSynII 10% - **maximum infusion rate**	2	4	**500**
AminoSynII 10% (5h)		5	400
AminoSynII 10% (6.25h) – **minimum infusion rate***		6.25	**320**
Vamin 18 – **maximum infusion rate**	2	4	**500**
Vamin 18 (5h)		5	400
Vamin 18 (6.15h) – **minimum infusion rate***		6.15	**325**

* It is strongly advised not to reduce infusion rates below the stated minimum (e.g., 320 mL/h for Aminosyn II 10%, or 325 mL/h for Vamin 18).

Additional recommendations regarding the use of antiemetics

Investigators are advised to use antiemetics which are commonly prescribed in their institutions for treatment of nausea induced by chemotherapeutic drugs. Among such antiemetics, the use of Aprepitant (Emend®) as a prophylactic treatment prior to the start of the infusion with the amino acids solution should be considered. Haloperidol (Haldol®) could also be considered as an adjunct treatment (either i.v. or oral) in case the advised antiemetic regimens are not successful and patients continue to vomit. Lorazepam (Ativan®) could also be considered as an adjunct treatment.

There is some evidence that corticosteroids can induce down-regulation of sstr receptors, therefore their use should be avoided in the setting of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Nevertheless, in the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion.

5.1.2 Comparative Drug: 60 mg Sandostatin® LAR Depot

In the control arm, patients will receive administrations of Sandostatin® LAR Depot 60 mg at 4-week intervals (+/- 3 days) until the PFS Primary End-Point, or until Week 72 from randomization after the PFS end-point has been reached, according to the schedule in Table 2 (i.e., two injections of Sandostatin® LAR 30 mg per treatment), unless the patient progresses or dies.

Sandostatin® LAR Depot (Octreotide Acetate for injectable suspension, Novartis; Octreotide LAR) is a pharmaceutical that is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength for intramuscular injection, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. For prolonged storage, Sandostatin® LAR Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

5.1.3 Rescue Medication: Short-acting Sandostatin®

Subcutaneous, short-acting Sandostatin® (Octreotide Acetate solution, Novartis; Octreotide short-acting) injections may be indicated for control of symptoms (i.e. diarrhoea and flushing) in patients in both study arms, in accordance with the manufacturer's prescribing information. Short-acting Sandostatin® for symptom control is administered by the patient (at home) at their discretion. Patients will be asked to record rescue medication administrations on a paper diary.

5.2 Packaging and Labelling

All medications used in this study, except the investigational drug product, are commercially available.

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be prepared, packaged, labelled, and released under the responsibility of Advanced Accelerated Application´s Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations. Instructions for shipment, storage and handling of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Solution of Infusion are provided in §Appendix 16.

5.3 Handling of Study Medication

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and Sandostatin® LAR Depot must be administered at the investigational site. Short-acting Octreotide is self-administered by the patient.

The study medication must be stored, handled and administered only by qualified/authorized personnel and must be prepared in accordance with pharmaceutical quality requirements, and radiation safety regulations for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Drug inventory and accountability records for the study medication and rescue medication, as well as drug returns by the patient, will be kept by the Investigator/Pharmacist, and must be documented throughout the study. Returned supplies should not be distributed again, not even to the same patient. The Investigator will not supply investigative study medication to any person, except the patients in this study.

The Octreotide LAR and aminoacids not used must be stored at site and made available till the monitoring visits, to allow the CRA to monitor the drug accountability.

The used/unused medications, except for^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, which will be locally discarded, will be returned to the proper local depot for destruction at the study completion or upon expiration, according to IPM/Sponsor decision and approval.

On ongoing basis the Investigator/Pharmacist agrees to conduct a study medication supply inventory and to record the results of this inventory on the study Medication Accountability Record. It must be possible to reconcile delivery records with those of used and unused medication. Any discrepancies must be accounted for and explained. Appropriate forms of deliveries and returns must be signed and dated by the responsible person at the clinical site and maintained as records.

Used and unused study medication and packaging provided by Sponsor must be returned at the study completion or upon expiration, except for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, which will be locally discarded according to all disposal requirements for radioactive materials. The return or disposal of all study medication will be documented appropriately.

5.4 Medication Prior to the Study

Patients must be on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study.

5.5 Medication During the Study

The patient may not receive any other systemic therapy for the treatment of GEPNET (chemotherapeutic, biologic, or any investigational agent) other than ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and/or short-acting Octreotide and/or Sandostatin® LAR Depot during the study period. Localized therapy such as surgery or external beam irradiation may be performed on additional site(s), provided that it does not affect treatment response assessment. The last administration of Sandostatin® LAR before the start of the study treatment is allowed during the screening period, before randomization.

5.6 Stratification and Randomization

For all patients who have signed the ICF, a screening number will be assigned in chronological order starting with the lowest number available on site. Patients will be identified by a unique patient identification number (Patient ID No.) composed of the centre number (four digits) and the screening number (three digits).

After the screening period, eligible patients will be randomly assigned in an equal ratio (1:1) to one of the two study groups for treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (plus best supportive care 30 mg Sandostatin® LAR Depot) or high dose (60 mg) Sandostatin® LAR Depot. The e-CRF will assign a unique randomization number to the patient, which will be used to link the patient to a treatment arm. Randomization will be stratified according to OctreoScan® tumour uptake score (Grade 2, 3 and 4; the highest Octreoscan® score measured among all the target lesions will be used for stratification purpose), length of time that patients have been on the most recent constant dose of Octreotide prior to randomization (≤6 and >6 months), according to a stratified permuted block scheme (§Appendix 17).

The details of the procedure to obtain the patient randomization number will be described in the Investigator's Manual.

5.7 Administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

5.7.1 Patient Preparation

There is no need for the patients to fast before treatment.

5.7.2 Administration Schedule

Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a cumulative amount of radioactivity of 29.6 GBq (800 mCi) with the dosing divided among 4 administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at 8±1-week intervals or up to 16 weeks to accommodate resolving acute toxicity (see §Section 5.7.3). Each dose is infused over 30 minutes.

In addition to treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients will receive 30 mg Sandostatin® LAR Depot until the PFS Primary End-Point, then until Week 72 from randomization after the PFS Primary End-Point, or early termination, unless the patient progresses or dies.

Before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment:

1. Unless clinically impossible, Sandostatin® LAR must not be administered within 6 weeks of the next treatment of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. While not treated with Sandostatin® LAR, the patient must be treated with an equivalent dosing of short acting Octreotide s.c. "Clinically impossible" means that the actual clinical condition of the patient would contraindicate the suspension of treatment because of an otherwise untreatable carcinoid syndrome. After enrollment, Sandostatin® LAR injections should be planned in order to allow for suitable washout time before first ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment. If the time interval between treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (§Section 5.7.3), is prolonged for any reason, Sandostatin® LAR administration continues every 4 weeks, however it should not be administered within 6 weeks of the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment.
2. Short-acting Octreotide is not allowed during the 24 h before the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date, unless the actual patient clinical conditions would contraindicate the treatment

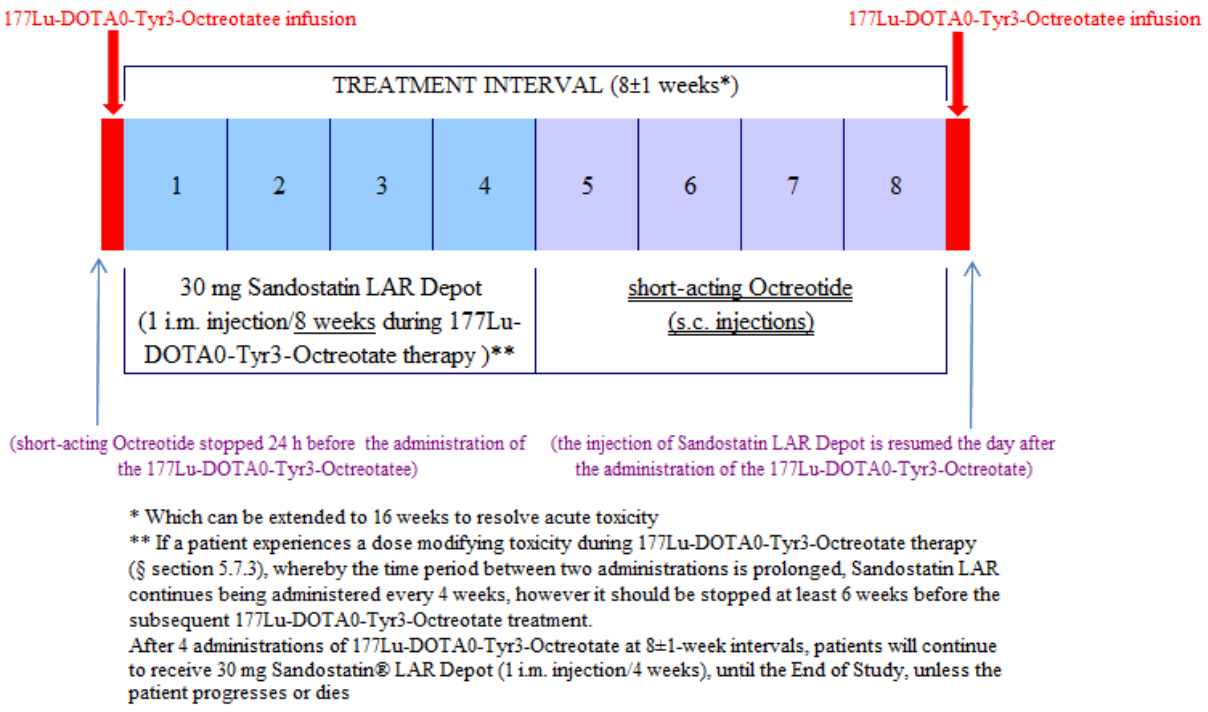
suspension due to otherwise untreatable carcinoid syndrome symptoms. Short-acting Octreotide can only be continued if the tumour uptake on the OctreoScan® during continued somatostatin analogue medication is ≥ liver uptake (Exclusion Criterion 14 (§Sections 4.1.2 and 4.2.2) and §Appendix 5).

3. Treatment with 30 mg Sandostatin® LAR Depot can be resumed after the administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Specifically, the recommended period before resuming Sandostatin® LAR Depot (or short acting Octreotide s.c.) is one day, however the minimum interval to receive Sandostatin® LAR Depot (or short acting Octreotide s.c.) after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is 4 hours, unless contraindicated as noted above.

The total amount of administered radioactivity is determined by measuring the radioactivity in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Infusion Solution (Lutathera) vial before and after administration (the procedure is provided in §Appendix 19).

The scheme for supportive treatment with 30 mg Sandostatin® LAR Depot is presented in Figure 1.

Figure 1: Concomitant Supportive Treatment with 30 mg Sandostatin® LAR Depot in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm.



* Which can be extended to 16 weeks to resolve acute toxicity
** If a patient experiences a dose modifying toxicity during 177Lu-DOTA0-Tyr3-Octreotate therapy (§ section 5.7.3), whereby the time period between two administrations is prolonged, Sandostatin LAR continues being administered every 4 weeks, however it should be stopped at least 6 weeks before the subsequent 177Lu-DOTA0-Tyr3-Octreotate treatment.
After 4 administrations of 177Lu-DOTA0-Tyr3-Octreotate at 8±1-week intervals, patients will continue to receive 30 mg Sandostatin® LAR Depot (1 i.m. injection/4 weeks), until the End of Study, unless the patient progresses or dies

On the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, and before the infusion with amino acids is started, an intravenous bolus of anti-emetic is given (suggested options: Granisetron (3 mg), or Ondansetron (8 mg), or Tropisetron (5 mg)). Prednisone must be avoided as preventive anti-emetic treatment because of potential somatostatin receptor down-regulation.

In case nausea or vomiting occurs despite this medication, patients can be treated with other anti-emetic drugs at the discretion of the physician.

The amino acid solution and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (22-25 mL) are administered in parallel by peripheral vein infusion in one arm at a constant infusion rate through pumps or any other infusion system. The infusion with amino acids starts 30 minutes before the start of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion, and continues for a total of 4 h. During amino acid infusion patient is allowed to void.

Infusion rates are listed in Table 5 and see §Appendix 8 for the infusion system scheme.

Table 5: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm Administration Schedule.

Preparation	Starting Time (h)	Infusion Rate* (ml/h)	Duration (h)
Granisetron 3 mg (or alternative)	0	Bolus	-
Amino Acids: 2 L solution	0	500	4
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate[1]	0.5	50	0.5
Saline solution – (two pumps method, §Appendix 8)[1]	1.0	50	up to 0.5
Saline solution – (Flebo infusion method, §Appendix 8)[2]	0.5	50	up to 1.0

[1] When the two pump method is used, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is pumped directly into the infusion line. The infusion line must be rapidly flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. [2] When the Flebo infusion method is used, a sodium chloride 9 mg/ml (0.9%) solution for injection gravity flows directly into to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate solution, which is connected to the infusion line.

*The rate of 500ml/h is suggested but may be reduced at the discretion of the physician.

5.7.3 Dose Modifying Toxicity

In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm, dose modifying toxicity (DMT), according to the grading system of the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE), is defined as a Grade 2 toxicity for blood platelet count, any Grade 3 or 4 haematological toxicity other than lymphocytopenia, a 40% increase over the baseline in serum creatinine value with a concomitant decrease of over 40% in creatinine clearance, or any other Grade 3 or 4 toxicity, when any of the above is possibly related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and regardless of its duration. The DMT schema will also be applied if renal – hepatic – hematological adverse events are observed which are unlikely related to the study drug, but to other possible or concomitant causes, and the full administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate would represent a safety risk for the patient. Lymphocytopenia and liver enzyme toxicities (ALAT (ALT), ASAT (AST) and AP) will not be used to define a DMT. Nonetheless, a DMT schema may be applied if the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is thought to severely and clinically significantly worsen the lymphocyte count and liver function.

If a patient experiences a DMT during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy, subsequent treatments with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permissible, provided the DMT resolves within 16 weeks following the non-tolerated administration. In any case, the patient will continue the administration of 30 mg

Sandostatin® LAR at monthly intervals. However, Sandostatin® LAR should not be administered within 6 weeks of the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, if the latter treatment is resumed.

After resolution of a DMT, a patient may receive subsequent planned treatment(s) at 50% of the standard treatment dose, if this is felt to be safe for the patient, or the risk-benefit assessment is favourable. If the same DMT recurs after treatment with the reduced ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate dose, the patient will remain in the study and continue the scheduled clinical / tumour assessments until tumour progression, but no further^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment will be given. Sandostatin® LAR will be continued at monthly intervals. If the DMT event does not reoccur, the next treatment is at full dose, if it is considered to be safe for the patient, or the risk-benefit assessment is favorable.

The scheme for dose modification after toxicity in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm is schematically presented in Figure 2.

In the event of toxicity, the only change allowed to the treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a dose reduction and treatment postponement or discontinuation. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate overdose, has a very low probability of occurring since it will be supplied as a single dose "ready to use product" in order to avoid any manipulation outside the production facilities. In addition, the infusion system methods (see §Appendix 8) do not allow the concurrent use of two separate ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate solution vials. No doubling of the administered radioactivity is ever allowed either in absolute amount or by shortening the time intervals between treatments. Treatments (amount of radioactivity and time of administration) will be monitored during the study and any unallowed treatment modification will be considered a major protocol violation.

- In the unlikely occurrence of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate double administration:

- if not clinically contraindicated, hydration must be enhanced up to 48 h after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration in order to force diuresis

- every week and up to the 10th week after treatment, laboratory tests have to be performed (hematology: WBC with differential, Platelets, Hb and Haematocrit; blood chemistry: albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, serum creatinine, calcium and glucose).

In addition, rigorous procedures are in place to minimise the risk of accidental overexposure and, in general, the correct study drug management and administration.

Attention will be given also to respect the threshold of radiation emission from the patients before their dismissal from the hospitals according to the local legislation.

- DMT in relation to Sandostatin® LAR toxicity in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm

In case of Grade 3 or 4 toxicity at any time during the study, especially in cases of severe abdominal symptoms, and hypoglycaemia/ hyperglycemia, which is possibly related to Sandostatin® LAR, the subsequent Sandostatin® LAR treatment dose will be reduced, or (temporarily) suspended. If the event has resolved and there are no foreseeable risks for the patient, the next treatment dose will be increased to the initial 30 mg dose of Sandostatin® LAR.

- Deliberate treatment interruption

The discontinuation of either study treatments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate or Sandostatin® LAR) is not a reason for patient's withdrawal either from the clinical/tumour assessments until tumour progression, or for early study termination (reasons for the patient's withdrawal are discussed in §Section 4.4 – Study discontinuation). However, in case of a patient's withdrawal from the clinical/tumour

assessments or early study termination (based on either the patient's or the Investigator's decision), patients will undergo all exams scheduled for Week 76 visit (See §Section 6).

If the treatment discontinuation occurs because of laboratory abnormality, or any evidence of toxicity, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value regresses. Appropriate remedial measures should be taken and the response recorded (See §Section 6.5.2).

5.7.4 Patient Release and Radioprotection Precautions

Following administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, patients should remain at the clinical site for an additional 4 to 5 hours in an area with suitable radiation shielding to protect others from unnecessary exposure (see §Appendix 14). At the time of release, patients are given written instructions (§Appendix 15) which outline the precautions the patient must take to minimize radiation exposure to people around them.

Crises due to excessive release of hormones or bioactive substances may occur following treatment, therefore, observation of patients by overnight hospitalization should be considered. Recommended treatments of patients with hormonal crises are: i.v. high dose somatostatin analogues, i.v. fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and vomiting.

5.8 Administration of 30 mg Sandostatin® LAR Depot in ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Arm

30 mg Sandostatin® LAR Depot (Octreotide LAR) should be given as an i.m. injection in accordance with the product prescribing instructions for a single-use kit, containing a 5-ml vial of 10 mg, 20 mg, or 30 mg strength. See for further details on the administration schedule §Section 5.7.2 and Figure 1.

5.9 Administration of 60 mg Sandostatin® LAR Depot in Comparator Arm

5.9.1 Patient Preparation

There are no specific requirements.

5.9.2 Administration Schedule

60 mg Sandostatin® LAR Depot (Octreotide Acetate, Novartis; Octreotide LAR) should be given as i.m. concurrent injections (two injections of Sandostatin® LAR 30 mg per treatment) once every 4 weeks ± 3 days until the PFS Primary End-Point, or until Week 72 from randomization after the PFS Primary End-Point has been reached,, or until early termination. Each of these injections should be administered in accordance with the product prescribing instructions for single-use kits, containing 5-ml vials of either 10 mg, 20 mg, or 30 mg strength.

5.9.3 Dose Modifying Toxicity

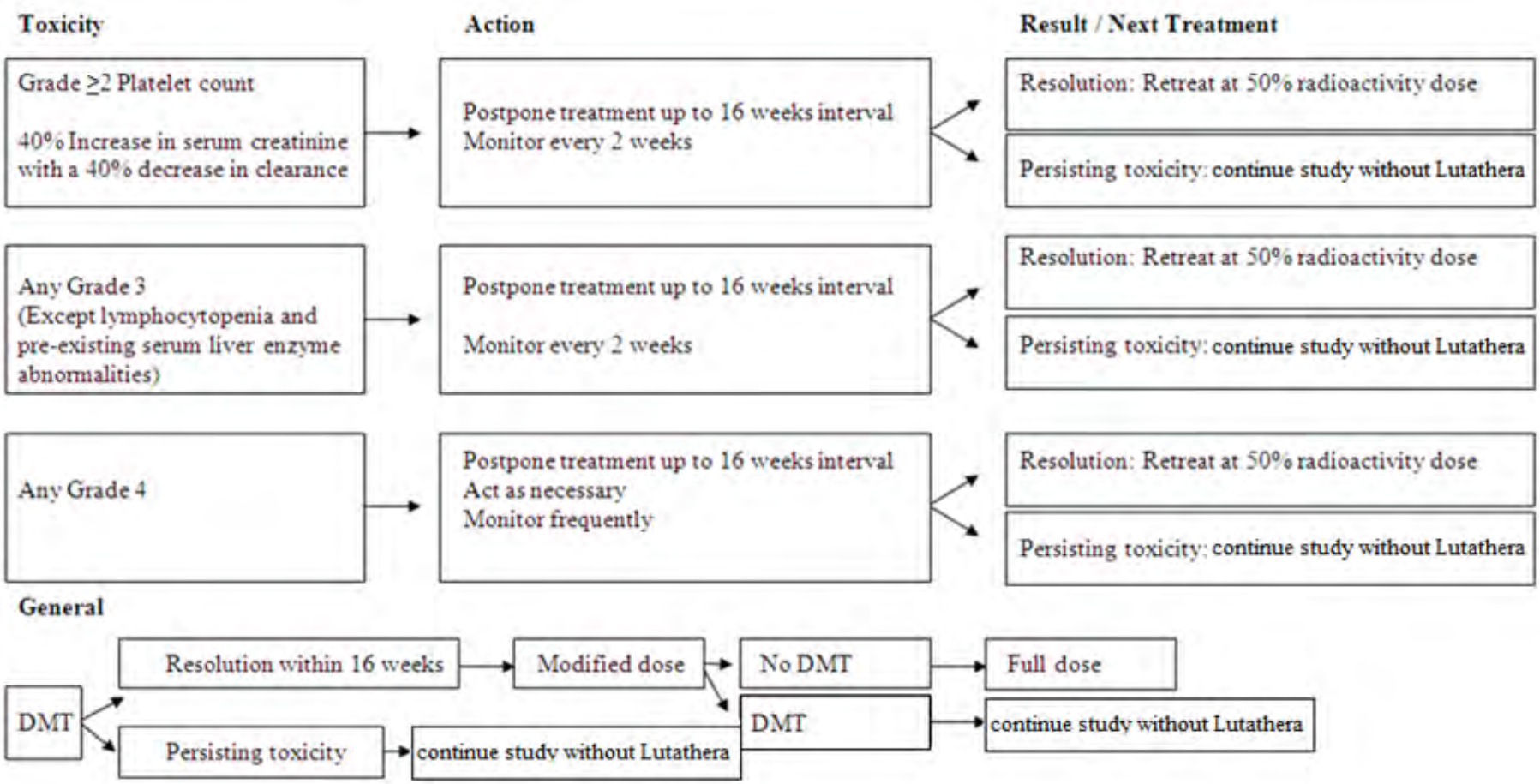
In the treatment arm with Sandostatin® LAR Depot, a dose adjustment scheme will be applied in case of Grade 3 or 4 toxicity, especially in cases of severe abdominal symptoms, and hypoglycaemia/ hyperglycemia possibly related to Sandostatin® LAR Depot. The DMT schema will also be applied if such adverse events are observed which are unlikely related to the study drug, but to other possible or

concomitant causes, and the full administration of Sandostatin® LAR Depot would represent a safety risk for the patient.

If a patient experiences a DMT during Sandostatin® LAR Depot treatment, the subsequent treatment dose will be reduced to the previous well-tolerated dose (or even temporarily suspended) and then at the next treatment, the dose will be increased to the initial 60 mg dose of Sandostatin® LAR Depot, if this is felt to be safe for the patient, or the risk-benefit assessment is favorable.

In any case (also in case of Sandostatin® LAR treatment dose suspension), the patient remains in the study and continues the scheduled clinical / tumour assessments until tumour progression, unless the patient's withdrawal becomes inevitable (see §Section 4.4 – Study discontinuation).

Figure 2: Dose Modifying Schemes for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm.



6- ASSESSMENTS

Patients will be evaluated for safety and tolerability in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm as indicated in Table 1 and Table 2, respectively (variations of ±1 week in the visits schedule are allowed).

It should be observed that a misalignment may occur between the tumour imaging exams (CT/MRI scans) which are scheduled from the date of randomization, and the other clinical and laboratory assessments which are scheduled from the first treatment date (W0).

The assessments listed in Table 6 will be performed centrally. Procedures for centralized evaluations will be detailed in the Laboratory Manuals provided to each participating site.

Table 6: Centrally Performed Assessments.

Assessment	Material to be Delivered	Time-point	Section
Proven midgut carcinoid tumour diagnosis. *Centralized diagnosis confirmation is requested before randomization.*	Specimen of primary tumour or liver metastases or soft tissue metastases	Screening	6.1.1.1
Immunohistochemical staining for CgA, synaptophysine and Ki67. *Centralized confirmation of Ki67 index ≤ 20% is requested before randomization. The central laboratory will also evaluate CgA and synaptophysine.*	Specimen of primary tumour or liver metastases or soft tissue metastases	Screening	6.1.1.2
OctreoScan® tumour uptake in documented target lesions*. *Centralized confirmation of tumour uptake at least as high as normal liver uptake observed on planar imaging (Appendices 5 and 6) is requested before randomization.* *for target/non-target/measurable lesions definition see §Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1	(Existing) OctreoScans® *The OctreoScans® obtained within 24 weeks of* randomization *will be accepted for inclusion only if the patient has not received other treatments for the indication in that time frame.* *The OctreoScan® should be one that was performed while the patient was on a fixed dose of Sandostatin® LAR (it is acceptable to have patients temporarily switched to Sandostatin® s.c. (up to six weeks) in order to obtain an OctreoScan®, provided they return to the same fixed dose of Sandostatin® LAR prior to the scan). If a patient has had an OctreoScan® performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan® performed after 3 months of Octreotide LAR treatments before entering the clinical study to prove that the index lesions or new lesions still meet the criteria for inclusion.*	Screening	6.1.4
Progression of disease according to RECIST Criteria. *Centralized confirmation of tumour progression according to RECIST is*	(Existing) CT/MRI scans. It is recommended that for each patient identical acquisition and reconstruction protocols be used when comparing	Screening	6.1.5

requested before randomization.	these two periods and subsequent time points within the study. *For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a new fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.*		
Objective tumour response according to RECIST Criteria. *Tumour response according to RECIST is re-evaluated centrally during the study.*	CT/MRI scans. It is recommended that for each patient identical acquisition and reconstruction protocols be used at all time-points.	Every 12 weeks	6.3.1
Serum CgA.	Blood sample	Every 12 weeks	6.5.2.2

Table 7: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm –Efficacy and Safety Assessments Visit Schedule

		Minimum Assessments								Last Visit or Early Termination
	Screening	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit n	Visit 7+n
Week		**-3**	**12**	**24**	**36**	**48**	**60**	**72**	*****	**76+n**
Procedure										
Informed Consent		X								
OctreoScan®	< 24 wks									
Histology and Ki67										
CT/MRI		< 4 wks								
Demographic Data	X									
Relevant Medical History		X								
Prior Carcinoid Tumour Therapy	X	X								
Randomization (Eligibility)		X								
Octreotide LAR 30 mg			X	X	XXX	XXX	XXX	XXX	XXX	
Diary Delivery (symptoms and rescue medication)	X		X	X	X	X	X	X	X	
Relevant Medical History		X								
Cancer Related Symptoms		X								
Diagnosis and Extent of Cancer	X									
Cardiac Ejection Fraction		X								
ECG		X								X
Physical Exam		X	X	X	X	X	X	X	X	X
Karnofsky Performance	X	X	X	X	X	X	X	X	X	
Quality of Life		X	X	X	X	X	X	X	X	
Haematology	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Rescue Therapy (report in diary)	< 12 wks	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Disease Assessment RECIST (CT/MRI)	< 12 wks		X	X	X	X	X	X	X	**
Survival Data		X	X	X	X	X	X	X	X	X

Refer to §Section 6 for further details on Visits Assessments. Ensure that the laboratory parameters meet the retreatment criteria outlined in §Section 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

*Extra visits at the centre foreseen every 12 weeks only until the PFS Primary End-Point.

**In case of Early Termination Visit, in addition to assessments described in the flow-chart, disease status must be evaluated according to RECIST and CT/MRI images must be submitted for central evaluation

During the main portion of the study ("treatment/assessment" phase, until tumour progression), all enrolled patients in either arm have assessments conducted at 12-week intervals from either the start of treatment (safety assessments) or the randomization date (tumour staging). The assessment are conducted until the PFS Primary End-Point, or up to 76 weeks from randomization (unless early termination) after the 74 PFS Primary End-Point has been reached. The 12-week interval assessments are included in the treatment / assessment schedules shown in Figures 1 and 2. The specific 12-week interval assessments for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments are independently shown in Table 7, without the treatment specific assessments that are performed 2 week before, on the day of treatment or the day before (only for the second, third, and fourth treatment), and 4 weeks after treatment.

After tumour progression, the patient proceeds to the long term follow-up assessment phase and visits every 6 months until the last randomized subject has completed 5 years of study overall from date of randomization.

6.1 Demographics and Baseline Characteristics

Each patient's date of birth, gender, ethnicity, weight, height and relevant baseline characteristics will be recorded in the e-CRF.

6.1.1 Diagnosis and Extent of Cancer

The patient's disease history, including primary diagnosis, date of diagnosis, as well as disease status at study entry, will be collected. This includes the date of first diagnosis of midgut carcinoid tumour and the date of the first presence of metastases with specification of the metastatic site(s). For the determination of the stage of disease, TNM criteria will be used (Rindi G et al, 2007; §Appendix 18). Staging to be reported is that which was recorded at the time of first diagnosis, also in operated subjects.

6.1.1.1 Histology

All patients are required to have central histological confirmation of midgut carcinoid tumours [in this protocol, a midgut carcinoid tumour is defined as a neuroendocrine tumour arising in the midgut (i.e. distal duodenum, jejunum, ileum, caecum and appendix, ascending and transverse colon (first two thirds)] in accordance with WHO classification and ENETS grading and staging guidelines (Rindi G et al., 2011), based on single surgery/biopsy specimens (with specification of the biopsied site indicated in the requisition form, without attaching any diagnostic sheet) of the primary tumour or liver metastases or soft tissue metastases and assessed by immunohistochemical staining for CgA, synaptofysine and Ki67 (for the latter see §Section 6.1.1.2). A historical biopsy taken at the time of original diagnosis or at any time previous to enrollment or a newly-acquired biopsy taken for the purpose of inclusion in this study will be accepted. Supportive information on the tumour origin may be obtained by specific immunohistochemistry analysis (e.g. determination of positive CDX2, negative TTF1, negative PP-ISL1 markers). The primary tumour may or may not be surgically resected. A progressive, locally advanced, inoperable (usually mesenteric, and curative intent) non metastatic tumour may qualify for enrollment. It would be preferable that samples were fixated in formalin and embedded in paraffin within two days of resection. If this fixation procedure has been undertaken, immuno-reaction will remain in the paraffin blocks at an adequate level for analysis.

It is not required to repeat the biopsy at study entry if a previous tumour sample is available for central review (samples embedded in paraffin, should be stable for up to 30 years, provided that the samples have been fixated appropriately in formalin prior to paraffin embedding).

For operating details and quality certificates see the Laboratory Assessment Manual.

6.1.1.2 Ki67

All patients are required to have central assessment of the Ki67 proliferation index based on surgery/biopsy specimens of the primary tumour or liver metastases or soft tissue metastases and assessed by microscopy and immunohistochemical staining.

Ki67 must be ≤20% for a patient to be eligible.

For operating details see the Laboratory Assessment Manual.

6.1.2 Cancer Related Symptoms

Each patient will be provided with a diary to record symptoms experienced and rescue medication (short-acting Octreotide s.c. injections) taken during the study.

6.1.3 Prior Antineoplastic Medications / Radiotherapy / Surgery

Information pertaining to any chemotherapy, hormonal therapy, immunotherapy, radiation, or surgery the patient has previously received will be documented.

6.1.4 OctreoScan® Tumour Uptake in Documented Lesions and Tumour Uptake Score

All patients are required to have OctreoScan® scintigraphy performed within 24 weeks prior to randomization in the study, according to ENETS Consensus Guidelines (Kwekkeboom DJ et al., 2009) (§Appendix 6).

Individual tumour uptake and extent (as per §Appendix 5) will be determined on existing scans and/or scans that are retrieved from the investigational site through central, IRC (Independent Review Committee) assessment; confirmation of OctreoScan® tumour uptake in documented target lesions and the OctreoScan® tumour uptake score will be documented.

The inclusion would be centrally validated under the condition that target lesions are considered as positive on OctreoScan® (greater than grade 2 uptake) (for target/non-target/measurable lesions definition see §Appendix 2, RECIST Criteria, Version 1.1).

Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability according to RECIST 1.1 (in any case, blastic bone lesions are not measurable). Therefore, if the bone lesion has the characteristic as above, and OctreoScan® is positive, the patient may be enrolled.

OctreoScan® images obtained within 24 weeks of randomization will be accepted for inclusion only if the patient has not received other treatments for the indication in that time frame.

If the primary tumour has been resected, tumour evaluations including OctreoScan® will be performed on metastases. The OctreoScan® should be one that was performed while the patient was on a fixed dose of Octreotide LAR (it is acceptable to have patients temporarily switched to Sandostatin® s.c. (up to six weeks) in order to obtain an OctreoScan®, provided they return to the same fixed dose of Octreotide LAR prior to the scan). If a patient had an OctreoScan® performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan® performed after 3 months of Octreotide LAR treatments before entering the clinical study to prove that the index lesions or new lesions still meet the criteria for inclusion.

Operating details and quality certificates are specified in the OctreoScan® Assessment Manual.

6.1.5 Progressive Disease According to RECIST Criteria

All patients are required to have progressive disease at the time of inclusion according to RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009; §Appendix 2) confirmed by central laboratory. For the purpose of determining disease progression the oldest CT/MRI scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a new fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.

In order to provide a consistent CT/MRI scan timepoint between the two arms of the study, it may be necessary for the site to repeat the baseline CT/MRI scan immediately before randomization if this timepoint is greater than 4 weeks before randomization to provide more current lesion data.

For CT imaging at entry, a triphasic and contrast enhanced study should be performed with a slice distance of 5 mm or less, and continuous slices (§Appendix 9).

Progressive disease assessment will be based on existing CT/MRI scans and/or scans that are retrieved from the investigational site. Central, blinded, real-time IRC (Independent Review Committee) assessment will be employed for an independent re-evaluation of progressive disease. Information will be collected pertaining to measurable, evaluable, or non-evaluable disease at baseline. All previous CT/MRI scans (prior to randomization) that permit to unequivocal confirmation of progression based on RECIST 1.1 criteria, will be considered.

It is recommended that identical acquisition and reconstruction protocols be used for each patient at all time-points.

Patients with progressive disease will be accepted for inclusion only if the patient has been on a fixed dose of 20 mg or 30 mg Octreotide (Sandostatin® LAR Depot) at 3-4 weeks intervals for 12 weeks prior to randomization in the study (except as noted above when a patient temporarily switches, up to six weeks) to daily injection Octreotide for the purpose of obtaining an OctreoScan®).

Operating details and quality certificates are specified in the CT/MRI Assessment Manual.

6.2 Prior/Concomitant Medications

All medications taken at the start of screening until the PFS Primary End-Point, then until Week 76 after randomization, or early termination, are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.

Further anti-tumour treatments after progression must be reported until the end of the long term follow up period.

6.3 Efficacy Assessment

6.3.1 Progression Free Survival

The primary efficacy end-point is PFS as measured by objective tumour response, which is determined by RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009; §Appendix 2).

Triphasic CT imaging is the preferred modality over MRI for determining objective tumour response (§Appendix 9).

The tumour diameters of indicator lesions used for response assessment should be measured in the closest position to that used for the baseline CT or MRI assessment. Restaging is scheduled at intervals of 12±1 weeks starting from the date of randomization. In case of delays, the reason of the delay has to be documented and the CT/MRI assessment has to be done as soon as possible. When a CT/MRI assessment is > 6 weeks earlier or later than the original schedule, the next reassessments have to be discussed and adjusted with the Medical Monitor of the study in a way to progressively come back to the original schedule.

Every effort should be done to avoid differences between these timings for patients in the two arms.

It is recommended that for each patient identical acquisition and reconstruction protocols be used at all time-points. Central, blinded, real-time IRC (Independent Review Committee) assessment will be conducted for determining progressive disease. Changes from randomization date will be assessed every 12±1 week until the PFS Primary End-Point, then until Week 76 after randomization, unless the patient progresses or dies.

Sponsor will notify all the Centres and their Ethic Committees as soon as the 74 PFS Primary End-Points have occurred.

Additional PFS data will be collected up to the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

After progression and during the long-term follow-up every effort must be made by the Investigator to collect additional information on further anti-tumour therapies and scan assessments outcome (RECIST local evaluation) to evaluate the Time to Second Progression (PFS2) in the two study arms.

Operating details and quality certificates are specified in the CT/MRI Assessment Manual.

6.3.2 Objective Response Rate (ORR), Time To Progression (TTP), Duration of Response (DoR), Time to Second Progression (PFS2)

Objective Response Rate (ORR) will be calculated as the proportion of patients with tumour size reduction of a predefined amount (the sum of partial responses (PR) plus complete responses (CR)) and for a minimum time period. Response duration will be calculated from the time of initial response until documented tumour progression.

The Duration of Response (DoR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. DoR will be reported descriptively for each group without comparison between groups.

TTP is defined as the time (number of days) from randomization to objective tumour progression centrally assessed. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date).

As additional secondary exploratory end-point (local RECIST assessment), the Time to Second Progression (PFS2) will be assessed in the two study arms. PFS2 is defined as the time from randomization to the time of disease progression or death due to any cause (on any treatment) following the first episode of disease progression.

6.3.3 Overall Survival

Overall Survival (OS) will be calculated from the randomization date until the day of death due to any cause; OS will not be censored if a patient receives other anti-tumour treatments after study medication.

Survival data will be collected at the time of the analysis of the primary end-point (PFS), and updated 6-monthly thereafter until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

6.4 Quality of Life

The impact of treatment on health related QoL will be assessed using the EORTC QLQ-G.I.NET21 questionnaire (§Appendix 3), which will be filled in by the patient prior to know CT scan/MRI result. Changes from baseline will be assessed every 12±1 week from the first treatment date until the PFS Primary End-Point, then until Week 72 after randomization, unless the patient progresses or dies. The EORTC QLQ-G.I.NET21 questionnaire is a module for carcinoid/neuroendocrine tumours. This module comprises questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

Outcomes for both study arms will be collected and evaluated in relation to objective tumour response, KPS, and other parameters of clinical relevance.

Forms in Country-specific languages will be provided by the Sponsor.

6.5 Safety and Tolerability

6.5.1 Adverse Events

All adverse events (AEs), whether or not spontaneously reported by the patient, will be recorded starting from the signing of the ICF until the last study-related visit. Definitions and reporting procedures are outlined in §Section 8. An Independent Data Safety Monitoring Board will evaluate patient's safety throughout the study (§Section 12.1 - *Independent Data Safety Monitoring Board*).

6.5.2 Laboratory Assessments

The laboratory assessments require that blood samples for haematology and blood chemistry, and a urine sample for urinalysis are taken, as listed in Table 8. Laboratory assessments will be performed at the investigational site, except for the evaluation of serum CgA.

At Screening: all patients will have screening laboratory assessments including haematology, blood chemistry and urinalysis (see Table 8): this assessment can be combined with baseline evaluation if sampling is within 3 weeks (preferably 2 weeks in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm) before the first treatment date.

If laboratory data are available from a date which is less than 2 weeks since the signature of the ICF, those data can be considered acceptable for the initial screening of the patient (as acknowledged in the ICF), if the repetition of the same exams is regarded as useless.

During the Study:

- In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: within 2 weeks before and 4±1 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment. In addition, for the second, third, and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional laboratory assessment will be performed on the same day, or within one day before treatment. Blood tests performed 4 weeks after any treatment cannot serve as baseline values for the next treatment. A wash-out period is required between treatments. Patients are not eligible for their next treatment until a minimum of 7 weeks has passed since the last administration of study drug (maximum 16 weeks). Throughout the study, laboratory assessments will be performed every 12±1 weeks since the first treatment date (W0) (see Visit Schedule in Table 1).
- In the 60 mg Sandostatin® LAR Depot arm: throughout the study laboratory assessments will be performed 4 weeks after the first treatment, and every 12±1 weeks since the first treatment date (W0) (see Visit Schedule in Table 2).

In the event of a significant laboratory abnormality, or if clinical or laboratory evidence of toxicity occurs, the Investigator will collect additional specimens for repeat or additional analyses, at intervals appropriate to the abnormality. The patient will be closely followed until sufficient information is obtained to determine the cause or the value regresses. Appropriate remedial measures should be taken and the response recorded.

All safety laboratory results must be evaluated by the Investigator before administration of study medication.

Any clinically relevant change from baseline onwards, will be recorded on the Adverse Event page of the e-CRF, possibly with a single diagnosis encompassing all changes possibly supporting to the single diagnosis.

Table 8: Laboratory Assessments[1].

Haematology	**Blood Chemistry**	**Urinalysis[4]**
• WBC with differential[2] • Platelets[2] • Hb[2] • MCV • Haematocrit	• BUN • Serum creatinine[3] • Creatinine Clearance[3] • Uric acid • Albumin • Total bilirubin[3] • AP • AST/ASAT • ALT/ALAT • Gamma-GT • Sodium • Potassium • LDH • CgA (centralized assessment) • GlycoHb (haemoglobin A1C) • fT4 • Calcium • Fasting blood Glucose	• RBC/hpf • WBC/hpf • Casts/lpf • Protein (dipstick test is accepted to assess protein) • 5-HIAA (on 24h urine collection)[5] • Pregnancy test, *if applicable* (urine pregnancy test is accepted)

[1] Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must include at minimum:

a. serum blood urea nitrogen and creatinine
b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.

[2]Patients must meet the criteria for Hb, WBC, and platelets, as defined in the inclusion criteria, at baseline and before each subsequent treatment. If the patient cannot be retreated due to haematological abnormalities, the evaluation must be repeated at least once weekly until re-treatment.

[3]Patients must meet the criteria for serum creatinine and total bilirubin as defined in the inclusion criteria at baseline and before every re-treatment. As entry criterion, patients must not have either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min calculated by the Cockroft Gault method, eventually confirmed by measured creatinine clearance (or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based) <50 mL/min (the measured creatinine clearance / GFR through two 24-h urine collections is required only as confirmatory exam). During the course of the study, if in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured in these collections. If the measured urinary creatinine clearance is ≤40% treatment can continue.

[4]Total urinary protein and other urinary measurements should be repeated at follow-up visits every 12±1 weeks.

The Cockcroft-Gault formula allows this estimation based on the occurrence of creatininemia, and correlating patient muscular mass (and so the consequent creatinine production) to weight, gender and age:

*Est. Creatinine Clearance = [[140 - age (yr)]*weight (kg)]/[72*serum Cr(**mg/dL**)]*
(multiply by 0.85 for women)
or
*Est. Creatinine Clearance = [[140-age(yr)]*weight (kg)]/[48816* serum Cr(**mmol/L**)]*
(multiply by 0.85 for women)

[5]5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site). 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and every 12 weeks only until the PFS Primary End-Point and at 6-months follow-up visits

During the Long-term Follow-up: In both study arms laboratory assessments will be performed every 6 months up to the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first. The Safety Assessment Schedule for the long-term follow-up visits is shown in Table 9.

Table 9: Long-Term Follow-Up Visits Safety Assessments Schedule

	Assessments										
Months	Last Visit Or Early Termination	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Procedure											
Haematology	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Disease Assessment RECIST (CT/MRI) – Local assessment	*	X	X	X	X	X	X	X	X	X	X
Survival Data	X	X	X	X	X	X	X	X	X	X	X

*In case of Early Termination Visit, in addition to assessments described in the flow-chart, disease status must be evaluated according to RECIST and CT/MRI images must be submitted for central evaluation

6.5.3 Pregnancy Test

Women and men should not procreate until six months after the end of their last treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Due to the CT scans foreseen during the study (every 12±1 weeks), women should not procreate during the study.

A pregnancy test (either on urine or blood) must be performed at baseline and within 7 days prior to each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment for every female patient of childbearing potential (§Section 8.9 and §Appendix 7).

6.5.4 Cardiac Ejection Fraction

Patients with uncontrolled congestive heart failure (NYHA II, III, IV) are not eligible according to exclusion criterion Nº 12. Patients with history of congestive heart failure who do not violate the above exclusion criteria will undergo an evaluation of their cardiac ejection fraction prior to baseline, preferably via gated equilibrium radionuclide ventriculography. The results from an earlier study (not exceeding 30 days) may substitute the evaluation at the discretion of the Investigator, if no clinical worsening is noted. It is recommended that the patient's measured cardiac ejection fraction is $\geq$ 40% before randomization.

6.5.5 ECG

ECGs will be recorded at baseline, immediately after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment procedure (following the completion of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion) and at the end of study to measure the different ECG intervals (RR, PR, QRS, and a more extended QT evaluation according to ICH E14, and heart rate (HR)). ECGs will be taken also in the 60 mg Sandostatin® LAR

Depot arm at same time points (before the Sandostatin® LAR injection), according to Table 2 schedule. Standard 12-lead ECG is the preferred option, but if not possible, a 3-lead ECG is acceptable.

An ECG in triplicate (at least 5 minutes apart) will be taken supine, after 5 minutes rest, and not immediately after a meal. The parameters will be measured as a mean value of minimally 3 beats; the mean of each parameter has to be used for eCRF completion.

For the patients participating in the substudy, the 12-lead ECG data collected during the Holter ECG recording on Day 1 (ECG recorded at the end of the infusion) will be used, in order to avoid interfering with the signal acquired by the Holter machine. At other times, the ECG machine supplied by the Sponsor or the local site ECG machine may be used.

The Investigator/local cardiologist will note in the source documents (and in the e-CRF) whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs results and the different ECG intervals measurements, calculating by the mean value of 3 measurements for each parameter. Relevant abnormalities at baseline will be recorded in the medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

6.5.6 Physical Examination and Vital Signs

Physical examinations will be performed by the Investigator, or qualified designee. All body systems will be examined and any relevant findings will be documented in the source documents and CRF. Physical examinations should include heart rate, blood pressure and weight measurement (height will only be measured at baseline). Blood pressure and pulse rate will be performed after the patient rests for 5 minute. For each patient, all blood pressure recordings shall be made using the same type of instrument (i.e., manual BP recording vs. automatic digital vital signs monitor) on the same arm.

Significant findings that are present prior to baseline will be recorded in the medical history page, while changes during the study (including significant changes of the symptoms due to the underlying disease vs baseline, as reported in the diary card) will be recorded on the Adverse Event page of the e-CRF.

6.5.7 Karnofsky Performance Score

KPS forms must be completed by a medical professional at each treatment and follow-up visit, and before any current clinical information is given to the patient (§Appendix 13).

6.5.8 Study Visits and Assessments

<u>Eligibility visit</u>

Prior to any study activities, patient will be asked to read and sign an ICF that has been approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and which complies with regulatory requirements. Once the ICF has been signed the patient enters the eligibility screening period.

The following patient data will be assessed for both treatment arms:

- Confirm that the patient has signed ICF and obtain patient demographic data
- Determine body weight (for calculation of creatinine clearance)
- Provide OctreoScan® image for central evaluation (positive OctreoScan® image should have been documented within 24 weeks prior to randomization in the study)

- Provide histological sample of the primary tumour or liver metastases or soft tissue metastases for central confirmation of diagnosis (Histology and Ki67)
- Report cancer lesions, TNM staging at diagnosis (local assessment), and submit CT/MRI documentation for a central confirmation of progressive disease and evaluation of extent of disease. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a new fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.
- Document prior therapy for carcinoid tumour
- Assess Karnofsky performance score
- Deliver patient diary to record cancer-related symptoms experienced from eligibility to week 1
- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, PLTs, Hb, Mean Corpuscolar Volume (MCV) and Haematocrit
    - biochemistry: blood urea nitrogen (BUN), serum creatinine and creatinine clearance measured by Cockroft-Gault formula, uric acid, albumin, total bilirubin, Alkaline Phosphatase (AP), Aspartate Aminotransferase (AST/ASAT), Alanine Aminotransferase (ALT/ALAT), gamma-Glutamyl Transferase (γ-GT), sodium, potassium, Lactic Dehydrogenase (LDH), glycosylated haemoglobin (glycoHb, haemoglobin A1C), free Thyroxine (fT4), calcium and glucose.
    - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Unless the actual clinical condition of the patient after enrollment would contraindicate treatment suspension because of an otherwise untreatable carcinoid syndrome symptoms, Sandostatin® LAR injections should be carefully planned to allow for an adequate wash out period: particularly, if the patient is randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, Sandostatin® LAR should be stopped at least 6 weeks before the first and the subsequent ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments (during this period short-acting Octreotide s.c. injections are allowed).

Data for patients in the Dosimetry sub-study will be carefully examined for dose limiting radiation to bone marrow, kidneys, and other high-dose organs before administering each additional treatment of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (for the Sub-Study protocol, see specific paragraphs in §Section 6.6).

Baseline visit

The baseline visit should occur as close as possible to the randomization date to confirm patient eligibility (based on all inclusion and exclusion criteria, including those evaluated centrally). Baseline checks will enable randomization and the release of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the study subjects in this arm.

The following patient data will be assessed for both treatment arms:

- Document relevant past medical history, and current medical conditions not related to the diagnosis of carcinoid tumour
- Document other therapies for concomitant diseases
- Assess ejection fraction in subjects with history of congestive heart failure
- Perform ECG
- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate), body weight, height
- Assess Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
    - Perform laboratory tests (local assessment). NB: screening and baseline laboratory evaluations can be combined if sampling is within 3 weeks before the first treatment date (however laboratory assessments in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm should be done preferably within 2 weeks before treatment):
    - o haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
    - o biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (or measured through two 24-h urine collections, if indicated), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb (haemoglobin A1C), fT4, sodium, potassium, calcium and glucose
    - o Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (unless already done at eligibility visit). 5-HIAA must be done on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
    - o urinary pregnancy test (women of childbearing potential), preferably within 7 days prior to treatment for patients randomized in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm
- Collect sample for central evaluation of CgA

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm

Visits during treatment / exams to be performed during the treatment period, per treatment arm.

Safety assessments will be performed within 2 weeks before and 4±1 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, an additional safety assessment will be performed on the same day or within one day before each treatment (see §Section 6.5.2).

The ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment / assessment schedule shown in Table 1 is idealized in the sense that all ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments occur at defined 8-week interval (±1 week). In the event that the intervals are greater than the defined 8-week interval (±1 week), the investigator will need to ensure that the correct safety assessments before and after each treatment have been conducted (safety assessments must be performed within 2 weeks before and 4 weeks after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, see §Section 6.5.2 for further details).

Exams to be done in relation to the ^{177}Lu-DOTA0-Tyr^{3}-Octreotate treatments (one the day of the infusion, within two weeks before the infusion, 4±1 weeks after infusion) can be combined with those required at 12-week intervals during the study, if less than 2 weeks apart.

Table 10: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm – Safety Assessment and Treatment Visit Schedule

	Treatment 1 Visits			Treatment 2 Visits			Treatment 3 Visits			Treatment 4 Visits		
	Baseline Visit	Visit T1B	Visit T1C	Visit T2A	Visit T2B	Visit T2C	Visit T3A	Visit T3B	Visit T3C	Visit T4A	Visit T4B	Visit T4C
Week	**- 3**	**0**	**4**	**6**	**8**	**12**	**14**	**16**	**20**	**22**	**24**	**28**
Procedure												
^{177}Lu-DOTA^{0}-Ty^{3}-Octreotate Treatment		X			X			X			X	
ECG	X	X			X			X			X	
Physical Exam	X			X			X			X		
Karnofsky Performance	X			X			X			X		
Quality of Life	X											
Haematology	X		X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X	X	X	X	X	X	X	X
Pregnancy Test*	X			X			X			X		
Concomitant Rescue Therapy	X		X	X			X			X		
Adverse Events	X		X	X		X	X		X	X		X
Creatinine Clearance	X											

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Section 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the Protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

*Preferably within 7 days prior to each administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

At all visits (in addition to exams at specific visits):

- Document concomitant therapy
- Document adverse events
- Deliver patient diary for the collection of cancer-related symptoms and rescue medication (except at weeks6, 14, 22)
- Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary (except at weeks 6, 14, 22)
- Report survival information

At 12-week intervals since randomization:

- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

Week 0

- Phone contact with the patient for the first week after the first treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate + 30 mg Octreotide LAR Depot to verify the general status of the patient.

Week 0 – 8 – 16

- Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate + 30 mg Octreotide LAR Depot
- ECG (in triplicate, at the end of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)
- At weeks 8 and 16 perform laboratory tests (local assessment) on the same day or within one day prior to administration of study drug. Safety assessments must include at minimum:
    - serum blood urea nitrogen and creatinine
    - serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
    - hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count
- urinary pregnancy test (women of childbearing potential), preferably within 7 days prior to treatment for patients randomized in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm

Week 4 – 20 - 28

- (only week 28) Treatment with 30 mg Octreotide LAR Depot
- Determine body weight (for calculation of creatinine clearance)
- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV and haematocrit
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections when indicated (see §Sections 4.2.1 and 4.2.2), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb (haemoglobin A1C), fT4, calcium and fasting blood glucose

- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein)

Week 6 – 14 – 22

- Perform physical examination and record vital signs (systolic, diastolic blood pressure; pulse rate), body weight
- Determine Karnofsky performance score
- Perform laboratory tests (local assessment; within 2 weeks of the treatment date):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections when indicated (see §Sections 4.2.1 and 4.2.2), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb (haemoglobin A1C), fT4, calcium and glucose
  - urinary pregnancy test: only in women of childbearing potential (preferably within 7 days prior to each administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate)
  - collect sample for central evaluation of CgA (only week 22)

Week 12 – 36 – 48 – 60 – 72 (and every subsequent 12 weeks until the PFS Primary End-Point):

- (except week 12) Treatment with 30 mg Octreotide LAR Depot
- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Determine Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula (creatinine clearance measured through two 24-h urine collections when indicated (see §Sections 4.2.1 and 4.2.2), uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb (haemoglobin A1C), fT4, sodium, potassium, calcium and fasting blood glucose
  - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Collect sample for central evaluation of CgA

Week 24

- Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate + 30 mg Octreotide LAR Depot
- ECG (in triplicate, at the end of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)

- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- urinary pregnancy test (women of childbearing potential), preferably within 7 days prior to treatment for patients randomized in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm
- Perform laboratory tests (local assessment) on the same day or within one day prior to administration of study drug. Safety assessments must include at minimum:
    - a. serum blood urea nitrogen and creatinine
    - b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
    - c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count
    - d. urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)

Week 32 – 40 – 44 – 52 – 56 – 64 – 68 (and every subsequent 4 weeks until the PFS Primary End-Point):

- Document concomitant therapy
- Document adverse events
- Report survival information
- Deliver patient diary for the collection of cancer-related symptoms and rescue medication
- Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary

Treatment with 30 mg Octreotide LAR Depot

End of study treatment (or early termination)

Perform final physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight

- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb (haemoglobin A1C), fT4, calcium and fasting blood glucose
    - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (unless not done at visit 72). 5-HIAA must be done on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Record cancer-related symptoms and rescue medication (through data reported in the patient's diary)
- Perform ECG

- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation

Follow-up visits (every 6 months) after the End of study treatment phase, until 158 deaths occur, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb (haemoglobin A1C), fT4, calcium and fasting blood glucose
  - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Document serious adverse events suspected to be related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
- Report survival information
- Collect information on tumour progression by CT/MRI (local assessment after the 74 evaluable and centrally confirmed disease progressions or death events are reached)
- Collect information on anti-tumour treatment administered after progression/discontinuation

The Safety Assessment Schedule for the follow-up visits is shown in Table 9.

Octreotide LAR arm

At all visits (in addition to exams at specific visits) and every 4 weeks until the End of the study treatment phase:

Document concomitant therapy

- Document adverse events
- Report survival information
- Deliver patient diary for the collection of cancer-related symptoms and rescue medication
- Document cancer-related symptoms (last 4 weeks) and rescue medication through data reported in the patient's diary
- Treatment with 60 mg Octreotide LAR Depot

At 12-week intervals since randomization:

- Disease assessment according to RECIST and submission of CT/MRI images for central evaluation (see §Section 6.3.1 for details)

Week 0

- Phone contact with the patient for the first week after the first treatment with 60 mg Octreotide LAR Depot to verify the general status of the patient

Week 0 – 8 – 16

- Perform ECG (in triplicate)

Week 4

- Perform laboratory test (local assessment);
    - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb (haemoglobin A1C), fT4, sodium, potassium, calcium and fasting blood glucose
    - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein)

Week 12 – 36 – 48 – 60 – 72 (and every subsequent 12 weeks until the PFS Primary End-Point)

- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Determine Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb (haemoglobin A1C), fT4, sodium, potassium, calcium and fasting blood glucose
    - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Collect sample for central evaluation of CgA

Week 24

- Perform ECG (in triplicate)
- Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight
- Determine Karnofsky performance score
- Administer Quality of Life questionnaires (EORTC GI-NET21; EORTC C30)
- Perform laboratory tests (local assessment):
    - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
    - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, LDH, glycoHb (haemoglobin A1C), fT4, sodium, potassium, calcium and fasting blood glucose

- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)

- Collect sample for central evaluation of CgA

End of study treatment (or early termination)

Perform physical examination, record signs and symptoms currently present, and record vital signs (systolic, diastolic blood pressure; pulse rate) and body weight

- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault formula, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb (haemoglobin A1C), fT4, calcium and fasting blood glucose
  - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (unless not done at visit 72). HIAA must be done on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Record cancer-related symptoms and rescue medication (through data reported in the patient's diary)
- Perform ECG (in triplicate)

Follow-up visits (every 6 months) after the End of study treatment phase, until 158 deaths occur, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

- Perform laboratory tests (local assessment):
  - haematology: WBC with differential count, platelets, haemoglobin, MCV and Haematocrit
  - biochemistry: BUN, serum creatinine and creatinine clearance calculated by Cockroft-Gault, uric acid, albumin, total bilirubin, AP, AST/ASAT, ALT/ALAT, γ-GT, sodium, potassium, LDH, glycoHb (haemoglobin A1C), fT4, calcium and fasting blood glucose
  - Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), 5-HIAA (on 24h urine collection; in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site)
- Record survival information
- Record information on tumour progression by CT/MRI (local assessment after the 74 evaluable and centrally confirmed disease progressions or death events are reached)
- Collect information on anti-tumour treatment administered after progression/discontinuation

The Safety Assessment Schedule for the follow-up visits is shown in Table 9.

6.6 Dosimetry, Pharmacokinetics and ECG

A Dosimetry, Pharmacokinetics and ECG substudy will be performed in 20 patients in about 10 selected sites. The substudy will be conducted, concurrent with the general study. Selected substudy sites must give high priority to early enrollment of patients into the substudy.

Before the approval of the Amended Protocol 4.1, patients participating in the substudy will be patients who have been determined to be eligible for the main study and have been randomized into the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, and have signed an additional informed consent specific for the substudy.

To facilitate the patients recruitment in this substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) has been temporarily activated at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. As soon as the Amended Protocol 4.1 is approved by the substudy site IEC/IRB, the randomization protocol of the study is halted at the substudy site until 20 patients are enrolled in the substudy.

Aside from the specific tests conducted in the dosimetry study as described above, the patient treatment regimen and patient care management will be identical to that conducted in the general study. The patients will also be considered to be members of the general study group.

As per specific request, the results of this substudy will be included in a preliminary Dosimetry Study Report that will be provided to the FDA as soon as the substudy is completed and the report written. This preliminary report will also be made available to the DSMB.

The 24-hour continuous ECG recording via 12-lead Holter machine can be done at a treatment cycle different from the one chosen for the Dosimetry and PK analyses.

- **Dosimetry assessments**

The substudy patients will receive full body (planar) and 3D SPECT scans on the day of the^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration. Preferably dosimetry should be performed at treatment cycle 1, but dosimetry at cycle 2 or cycle 3 is also acceptable. In the event that dosimetry measurements are performed after cycle 2 or 3, only the dose estimates for the kidneys and the bone marrow can be used in the overall evaluation, as the tumours (and by that also liver) and spleen may be influenced by the prior therapy effect. In the same treatment cycle, blood and urine samples will be collected at different intervals after ^{177}Lu-DOTA^{0}-Tyr^{3}-administration. All patients included in the substudy will undergo a 24-hour continuous ECG recording via a 12-lead Holter machine.

Serial full body planar images will be obtained at 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h) and 72 h (or within 60-72 h). If one or more images are skipped or are not performed at the correct time, then an additional whole body scan will be scheduled at 168 h (or within 156-168 h). Patients that live in the vicinity of the clinic can be requested to come back for the last whole body scan at 168 h, in that case the whole body imaging at 48 h could be skipped.

The time point ranges indicated above in brackets are to be considered if the specific timepoint is not feasible. 3D SPECT scans will be performed at 24 h and 48 h in the upper abdomen (comprising kidneys, liver and spleen) and, if deemed necessary, based on the outcome of the planar imaging, also in different regions.

- **PK assessments**

Blood samples (whole blood) will be collected from each patient just before administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapeutic dose from the opposite arm of drug infusion and then at the following time-points: two time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 60 and 72 h (Day 4. If one or more blood samplings are skipped or are not performed at the correct time, an additional blood sampling will be scheduled at 168 h (or within 156-168 h). Patients that live in the vicinity of the clinic can be requested to come back for the last blood sampling at 168 h.

A urine sample will be collected within 24 h prior to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration, preferable just prior to the infusion of study drug (0 h sample) to achieve bladder emptying before study drug administration. Quantitative urine collections will be obtained for the periods 0-1 h (immediately post start infusion to 1 h post start infusion), 1 h – 4 h, 4 h – 16 h, and 16 h – 48 h post start infusion (§Appendix 10). The rate and extent of elimination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be determined by analyzing the actual and cumulative percent injected dose (radioactivity) in the sequential, quantitative urine collections.

Radioactivity in blood and urine will be measured at the investigational site, with a COBRA-Packard auto-gamma counter system (Packard, Meriden, Conn., USA) or similar system.

- **HPLC assessments**

Additional urine samples will be collected and further analyzed at a central laboratory by HPLC according to validated procedures in order to examine the chemical status of the radionuclide in urine. Samples will be obtained for the periods 0-1 h (immediately post start infusion to 1 h post start infusion), 1 h – 4 h, 4 h – 16 h, and 16 h – 48 h post start infusion

- **Cardiac assessments**

A 24-hour continuous ECG recording via 12-lead Holter machine will be performed on the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Data recording will start two hours prior to the start of the amino acid infusion, will continue during the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and will continue after completion of the treatment procedure for a total of 24 hours.

Sites participating in the substudy are strongly recommended to perform an additional 24-hour continuous ECG recording via 12-lead Holter machine at one of the subsequent study treatments.

After enrollment in the study, subsequent 12-lead ECGs will be performed as clinically indicated (and interpreted locally, as per routine clinical practice, for safety at bedside). However, in the event a 12-lead ECG needs to be performed during the Holter ECG recording on Day 1, this should be performed using the ECG machine supplied by the Sponsor (rather than the site machine), in order to avoid interfering with the signal acquired by the Holter machine. At other times, the ECG machine supplied by the Sponsor or the local site ECG machine may be used.

Often, cancer patients are likely to have cardiovascular disease that is not clinically manifest. The presence of cardiac disease might be associated with greater prolongation of QTc interval after the administration of QT-prolonging drug**.**

The typical symptoms of carcinoid syndrome include valvular heart disease in 30-40% of patient. Carcinoid heart disease is characterized by plaque-like fibrous endocardial thickening that classically involves the right side of the heart, occurring in 50-70% of patients with carcinoid syndrome. Hemodynamically significant heart disease is observed in about 5-10% of patients. It is therefore

recommended that the following baseline conditions are NOT present before to include the patient in the substudy:

- Prior history of torsades de pointe, or congenital long QT syndrome,
- Conditions with screening ECG repolarization difficult to interpret, or showing significant abnormalities. This includes, but is not limited to: high degree AV block, pacemaker, atrial fibrillation or flutter,
- QTcF interval > 480 msec on screening ECG,
- Significant hypokalemia at screening (K+ <3.5 mMol/L),
- Significant hypomagnesemia at screening (Mg++ <0.7 mMol/L),

Of note, patients can be assessed after correction of these laboratory abnormalities and new laboratory tests performed a few days later to check the above exclusion criteria.

In addition, cancer patients commonly receive medications known to cause QTc prolongation, such as antiemetics, antibiotics and antihistamines. The use of concomitants therapies can confound the results of the intensive QT study. The sequence and timing of treatments administered should therefore be carefully controlled and registered.

Because of the multiple treatments received at Day 1, which may interfere with the evaluation of the ECG parameters, the sequence and timing of treatments administered at Day 1 must be carefully recorded in the patient clinical chart (the eCRF will be amended to collect these additional information).

- All pre-medication will be administered during the time interval ranging from 90 to 60 min before the start of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion; the purpose of this requirement is to allow the recording of the baseline ECG intervals used in the primary ECG analysis and to capture the potential ECG effects of the pre-medication regimen.

- If other treatments (other than pre-medications) are planned to be administered on Day 1, these should be administered at least 1h before the start of infusion, as best as practically possible. In general, best effort will be made to avoid introducing new treatment between 1h before, until 8h after the start of infusion unless clinically required.

Data obtained will be analyzed to determine whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Relevant abnormalities at baseline will be recorded in the medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

Data from continuous recording over the 24-hour period will be analyzed to evaluate the effects of the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate electrocardiographic parameters and their relationship with drug plasma concentrations.

Descriptive statistics (N, mean, median, minimum, maximum, 95% confidence interval for the mean, etc.) of the observed values as well as for the changes from baseline value will be created. Frequency tabulations with values within, below or above the normal ranges will be made.

ECG parameters will include heart rate (HR), RR interval, PR interval, QRS width and QT interval.

QT intervals will be corrected for heart rate. ECG results will be evaluated by means of descriptive statistics (mean, median, 95% confidence interval for mean, etc.) and frequency tabulations.

Graphical presentations might be created to facilitate the interpretation.

6.6.1 Dosimetry of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

An extensive dosimetry analysis will be performed in 20 patients enrolled at selected clinical sites. The substudy will require planar and 3-D SPECT imaging, and will also include urine collection and blood sampling.

According to the MIRD scheme, the radiation dose to a target organ is the sum of the self-dose from this organ and the cross doses from all other target organs. In order to calculate the radiation dose to the various target organs the amount of radioactivity present in the source organs must be measured. The radioactivity uptake in each organ is determined at various time points. This uptake defines the kinetics of the radiopharmaceutical. By integrating the kinetic curve, the number of interactions from each source organ per injected activity dose is obtained, and this is the so-called residence time.

DATA ACQUISITION

Equipment

1. A gamma-camera with medium energy collimator. Energy window setting at 208 keV (20%).

2. Well counter with multichannel analyzer or gamma counter to determine ^{177}Lu radioactivity in blood and urine samples.

3. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.

Timing of measurements

The uptake of peptides in liver, spleen and kidneys occurs almost immediately. Based on previous experience (Phase I/II Erasmus study) the proposed measurement points are at approximately 1 h, 4 h (or within 4-6 h), 24 h (or within 16-24 h), 48 h (or within 40-48 h), 72 h (or within 60-72 h) and optionally 168 h (or within 156-168 h) after administration (see §Section 6.6).

Performing the measurements

1. Conjugate view counting

Quantification of the ^{177}Lu radioactivity will be performed by using 180° opposed planar images (typically Anterior and Posterior views) in combination with transmission data through the subject and a system calibration factor (Siegel, 1999).

a. Determine the transmission factor $\Im = \exp(-\mu_e \cdot t)$

For abdominal uptakes the attenuation correction is considerable and should be performed. The $\mu e/\rho$ for the 208 keV window of ^{177}Lu may be determined by counting a point source during e.g. 5 minutes. This measurement must be repeated with several thicknesses of absorbing material with unit density. (In a narrow beam geometry the average tissue μ_e/ρ(208 keV) = 0.134 cm^2/g = 0.0134 m^2/kg

[2]). The patient thickness (t) at the Region Of Interest (ROI) in the abdomen is determined on a CT scan or measured with a ruler.

b. Determine the system calibration factor C

The calibration factor C (count rate per MBq ^{177}Lu) is measured by counting a known radioactivity reference standard (usually 37-74 MBq ^{177}Lu, or 0.5-1% of the injected activity; measured in the dose calibrator). Count this standard in air for 3 minutes.

c. Acquire anterior and posterior planar views

Patient measurements are performed with a medium energy collimator and the 208 keV peak is used. The posterior and anterior views can be made as static planar images for a fixed time.

d. Determine the anterior IA and posterior IP count rates

Regions of interest (ROI) are drawn around the liver, kidneys and spleen both in the anterior and posterior views. Subtraction of the background can be performed by drawing a background ROI adjacent to the source ROI. Normalize the background count rate IADJ to the same area in the source ROIs IA and IP. The background correction factor F is determined by: $F \cong 1 - \frac{I_{ADJ}}{I_A}\left(1 - \frac{t_j}{t}\right)$, with t_j the source thickness. When ROI shows large overlap by other source organs, like e.g. in the right kidney ROI with overlapping liver, ROIs should be drawn over both the non-overlapped regions of each organ to estimate the background.

e. Determine the absolute activity A

The absolute activity in each source region is calculated by the following equation: $A = F\sqrt{\frac{I_A I_P}{\Im}} \times \frac{f}{C}$. The source region attenuation factor *f* can usually be approximated by unity for smaller organs. For larger source thickness t_j, f is defined by: $f = \frac{\mu_j t_j / 2}{\sinh(\mu_j t_j / 2)}$. As for example the calculation for the liver is very time consuming and the fact that for some patients a CT may not be available, a hollow liver phantom filled with the same activity as in the reference standard ^{177}Lu in a container filled with water can be used to calculate f. For the kidneys infusion bottles of 150 cc were used.

In alternative to the calibration based method described above, another method based on relative calibration is proposed for the quantification of the ^{177}Lu radioactivity (Cremonesi, 2007). The conjugate-view technique will be applied to anterior and posterior images after background, scatter, attenuation, and physical decay corrections. Counts in whole-body images will be normalized at the first image, scanning the patient with 100% of the injected activity (Cremonesi 2006) subtracted by the percent of injected activity eliminated in the urine before the first image acquisition.

2. Blood and urine sample counting (see §Appendix 10 and 11)

a. Urine sample counting

The majority of the infused ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is excreted via the kidneys into the urine. Urine will be collected at the following time intervals:

0-1 h, 1-4 h, 4-16 h, 16-48 h post ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration.

Samples of the urine collected are counted in the well- or gamma counter and compared to the count rate from a reference of the injected dose. The total radioactivity excreted at each time point as percentage of the injected dose can be calculated and used for determination of the total body distribution of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, as well as urinary bladder residence time.

b. Blood sample counting

Blood samples will be taken just before administration of the therapeutic dose and at the following time-points: 2 time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 60 and 72 h (Day 4) and optionally at 156 168 h (Day 8) (see §Section 6.6).

The blood samples will be counted in the well- or gamma counter and compared to the count rate from a representative percentage of the injected activity inside the same counter.

3. Data analysis and radiation dosimetry calculations

The number of decays (NDs) per unit injected activity —mathematically equivalent to the quantity of residence time (Stabin MG et al., 2005)—will be calculated from multiexponential fits to the time–activity curves for spleen, kidneys, liver, testes, and remainder of body.

The time–activity curve for blood will be evaluated with rescaling for the individual blood mass based on patient sex, weight, and height. The ND in the red marrow (ND_{RM}) will be derived from the blood-based method (Cremonesi M et al., 2006, Forrer F et al., 2009): $ND_{RM} = ND_{blood} \cdot m_{RM} / m_{blood}$, where m_{RM} and m_{blood} are the individual red marrow and blood masses, and ND_{blood} is the ND in the blood. The red marrow mass will be derived assuming a fixed ratio of red marrow to blood mass (male, 1120/5000; female, 1300/3500). The total absorbed radiation dose to red marrow will be extrapolated from the blood curve. Absorbed radiation dose to target organs will be calculated by entering the ND values for all the source organs in the OLINDA/EXM software and adjusting the radiation dose reported by the software for individual weight and organ masses for kidneys, liver, spleen (determined from CT), and red marrow.

Whenever possible and for comparison purposes only, the patient specific red marrow mass will be also derived based the individual volume of the lumbar vertebrae L2, L3, L4 (V_{L2-L4}) estimated from CT images Ferrer L et al., 2010), according to the equation: $m_{RM} = 6.7\% V_{L2-L4}$.

The dose to the red marrow will be then rescaled with the red marrow mass determined from the L2-L4 methods and compared with the previous one derived by proportionality with the blood volume.

Some more details on pharmacokinetic and radiation dosimetry calculations are given below.

a. Pharmacokinetic profile

1. Determine the time-activity curves in the source organs by either numerical fitting of exponential curves to the data or by compartmental modeling to all organ uptake, blood and excretion data. A general code for numerical and compartmental modeling is the SAAM II software (http://www.saam.com) (Cobelli C et al., 1998). Based on time-activity blood curve, the main pharmacokinetic parameters will be calculated, such as systemic exposure, clearance, volume of distribution, and terminal half-life.

2. Integrate the time-activity curve in each source region to determine the cumulated activity $\tilde{A}$ [in MBq.h]. For a typical result of step 1: a bi-exponential curve $A_{organ} = A_1 e^{-\lambda 1 t} + A_2 e^{-\lambda 1 t}$ the cumulated activity is:

$$\tilde{A}_{organ} = \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}$$, with λ_p the physical decay constant of ^{177}Lu.

3. The quotient of $\tilde{A}$ and the injected activity IA yields the residence time $\tau = \tilde{A}/IA$ [in h].
   i. The bi-exponential clearance pattern is assumed to apply.
   ii. If step 1 was not successful, numerical integration by the trapezoid method can be used. Linear extrapolation to t = 0 can be performed by assuming A(0) = A(4).

4. Determine the fraction of administered activity that is excreted by the urinal pathway. Perform a numerical fit of a bi-exponential curve with a curve-fitting program like SAAM II to the urinary data to determine the fractions and elimination rates in the subsequent clearance stages.

$$A_{Urine}(t) = A_0 - A_1 e^{-\lambda_1 t} - A_2 e^{-\lambda_2 t}$$

The cumulated activity in the total body $\tilde{A}_{TB}$ and residence time τ_{TB} is derived from the urine excretion curve by:

$$\tilde{A}_{TB} = \frac{A_0 - A_1 - A_2}{\lambda_p} + \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}, \quad \tau_{TB} = \frac{\tilde{A}_{TB}}{IA}$$

The cumulated activity in the total body is needed for the calculation of the cumulated activity in the remainder of the body (source contribution to the bone marrow dose) and the clearance stages are needed for the calculation of the bladder residence time. The residence time for the remainder

of the body is calculated by subtraction of the sum of the residence times in all known source organs from the total body residence time:

$$\tau_{remainder} = \tau_{TB} - \sum_{source.organ.i} \tau_i$$

b. Radiation dosimetry calculation

Data for ^{177}Lu are available in the OLINDA/EXM (Stabin MG et al., 2005) software package. Alternatively, the S-factors can be also taken from the Radiation Dose Assessment Resource (RADAR) site (http://www.doseinfo-radar.com/RADARphan.html). By using these S-factors and the residence times for the source organs, the radiation dose to all target organs can be calculated.

4. Result reporting and documentation

a. Therapy administration and camera settings

1. Record the date, time and amount of radioactivity of ^{177}Lu-DOTA^0-Tyr^3-Octreotate administered.
2. Express the radioactivity uptake in the organs as a percentage of the activity administered and in relation to the time after administration.
3. Record patient body thickness at each ROI and source to skin distance, when the conjugate view method fails.

b. Pharmacokinetics

1. Blood curve
   i. Indicate date, time, activity and volume of each blood sample.
   ii. Record the results of the exponential curve fitting to the blood data.

2. Urinary clearance pattern
   i. Indicate date, time, activity and volume of each urine sample as well as the total collected urine volume at each time interval.
   ii. Record the results of the exponential curve fitting to the urine data.
   iii. Total body residence time derived from urinary excretion curve.

3. Radioactivity uptake in organs
   i. Indicate date, time and count rate in ROI over organs, background and reference source.

ii. Record the results for the conjugate view quantification as percentage of the injected activity at each time point.

iii. Record the results of the exponential curve fitting to the organ uptake.

c. Dosimetry results

Prepare dosimetry table output showing the organ doses per injected activity for the reference phantom.

7- STATISTICAL METHODS

The statistical analysis will be performed in accordance with the principles stated in the Consensus-Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonisation (ICH). The data of the study will be analyzed when the database is discrepancy free and hard locked.

7.1 Sample Size

Currently, there is only one published clinical trial that provides source data on ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate's effect on a treated patient population with midgut carcinoid tumours. In the Erasmus MC phase I/II study ("A phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with somatostatin receptor positive tumours") an objective tumour response rate of 23% (CR + PR according to SWOG Criteria at 3 to 4 months after the last treatment) was determined in patients treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. This is based on an analysis in 188 patients with carcinoid tumours (Kwekkeboom DJ et al., 2008).

Recently a retrospective, independent verification of the Erasmus MC phase I/II study source data and a statistical analysis of the study results have been conducted by a contract CRO to support the initiation of the present phase III study. Within this study, an analysis of a subgroup of 51 patients with midgut carcinoid tumours that had progressive disease within 12 months before entering the study (notably similar to the population in the present phase III Study), a median PFS of 45 months with a 95% CI of 22-57 months was observed. However, because this subgroup size is small, the median PFS has a large confidence interval (95% CI of 22-57 months).

Additionally, when considering the second arm (Octreotide LAR) of the present phase III study, there are only two sets of relevant data for patients with midgut carcinoid tumours treated with Octreotide LAR available in literature: the PROMID study (Rinke A et al., 2009), which recently reported a median PFS of 14 months, and the RADIANT-2 study (Pavel M et al., data presented at the 8th Annual ENETS Conference, 9–11 March 2011, Lisbon, Portugal) reported a median PFS of 11 months. In the PROMID study, patients with midgut carcinoid tumours were enrolled in a double blinded randomized two armed trial. Patients in the control arm received a placebo, and patients in the treatment arm received 30 mg Octreotide LAR (Rinke A et al., 2009). In the RADIANT-2 study, patients with carcinoid tumours (diverse sites) were randomized for treatment in two comparator arms (Yao J et al., 2008). In one arm, patients received 30 mg Octreotide LAR alone, and in the other arm patients received Octreotide LAR plus Everolimus (Afinitor®). For the purpose of calculating sample size for the present phase III study, the results of the PROMID study were deemed to be the most applicable. This study was performed using a similar patient group (progressive midgut carcinoid tumours at enrollment) whereas the RADIANT-2 study was not restricted to midgut carcinoid tumours. The PROMID study however, was conducted as a fully double-blinded clinical trial, and it would be expected that such a study would not be significantly impacted by high patient dropout rates; rather the likely decision point for a patient to participate in such a study would be before enrollment – thus low impact on the trial for either dropout or intent to treat issues.

The median PFS of 45 months for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the subgroup of 51 patients with midgut carcinoid tumours that had progressive disease within 12 months before entering the Erasmus MC phase I/II study is associated with a high degree of uncertainty based on the wide 95% CI for the median PFS of 22-57 months. Furthermore, as the Erasmus MC Phase I/II study has been conducted by a single center with specially trained investigators of high expertise, it can be assumed that survival times might

be higher than might be observed in an average study site. This has to be considered in the present multi-national, multi-center study.

Therefore, the assumption that the median PFS for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm could be 45 months might be too optimistic with regards to the expected composition of study centers. In order to account for that, a median PFS of 30 months is chosen (which is obtained by calculating the mean of the median PFS of 45 months for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm for the subgroup of 51 patients mentioned above and of the median of 14 months for the Octreotide LAR, i.e. (45 months +14 months)/2 ≈30 months). This would still constitute a clinical relevant improvement in PFS compared to the control group (Octreotide LAR).

Based on the above median PFS assumptions, an estimate of 124 patients was determined according to the following conditions:

- 62 patients per arm
- ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: median PFS of 30 months
- Octreotide LAR: median PFS of 14 months (PROMID study)
- Significance level 5% two sided (or 2.5% one-sided), power 90%
- Pre-defined accrual period: 18 months
- Follow-up period: 18 months (corresponding to the length of treatment period)
- Based on these conditions, a total number of 74 PFS events are expected. Therefore, the PFS primary analysis point occurs at the timepoint when 74 evaluable and centrally confirmed disease progressions or death events are reached.

As stated above, there are limitations in the data currently available to confirm the accuracy of the sample size calculations, based on the primary end-point assumptions. The present phase III study is different from the source data studies. With respect to the PROMID and RADIANT-2 studies, both studies were double-blinded. In the PROMID study the control arm was a true placebo. With respect to the Erasmus MC phase I/II trial, patients enrolled in the study were assured to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment.

In order to ensure an adequately sized clinical trial it is necessary to have a realistic estimate for dropout rates. In the PROMID study the dropout rate was predicted to be 10% before the start of the study. At the interim analysis (Rinke A et al., 2009), 9 patients (21%) out of 42 patients in the Octreotide LAR treatment arm had withdrawn from the study. Four of the dropouts were because of withdrawal of consent, and five were because of adverse events. This contrasts with the dropout of only 3 patients in the placebo arm (2 – withdrawn consent, 1 – switched treatment). Since the patients were unaware of what treatment they received, one can expect the dropout rate of the Octreotide LAR arm to be a lower limit for the present phase III study, because there will be additional dropouts due to patient 'treatment awareness'. In addition, the treatment arm of the current phase III trial will have a much longer time span of follow-up and time to progression, meaning that virtually all of the ^{177}Lu- DOTA^{0}-Tyr^{3}-Octreotate treated patients will need to complete at least a full year follow-up, because very few will have progression during this period. Consequently, dropout rates (and intent to treat penalties) could also be expected to be high in this arm. For these reasons the study is planned to account for approximately 20% dropouts.

Therefore, controlling for a drop-out rate of approximately 20%, a total of 160 patients (80 patients in each treatment group) should be required.

The sample size has also been adjusted to detect a statistically significant and clinical relevant difference in OS (80% power) between the two arms of the study, based on the following assumptions:

- Octreotide LAR median OS: 32 months
- ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate median OS: 50 months
- Significance level: 5% two sided
- Nominal power: 80%
- Accrual time: 18 months
- Long-term follow-up: 5 years

Accordingly, 230 patients (115 patients in each treatment group) should be randomized.

The median OS in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm is expected to be 50 months. The median OS of 47.3 months, with a large confidence interval (95% CI [27.8 - 75.3], reported in the Erasmus MC Phase I/II study subgroup analysis of 51 patients with midgut carcinoid tumours has limited relevance for the purpose of this study, since the patients had progressive disease within 12 months before entering the treatment schedule, and at a latest stage of disease. However, most recent survival analysis in a similar population treated with PRRT has been reported. In 2012, Baum RP et al. reported an overall survival of 59 months from the first cycle of PRRT using ^{177}Lu-DOTATATE. This group also published in 2014 the outcome of a retrospective analysis assessing the efficacy of PRRT in 1,000 patients with metastatic and/or progressive NETs using ^{177}Lu (n=331), ^{90}Y (n=170) or both (n=499). The median OS for all patients was 52 months from the start of the treatment. With regard to the used radionuclide, the following OS were reported: 24 months with ^{90}Y, 55 months with ^{177}Lu, and 64 months with both. There is however no indication of the used peptide, albeit this group is known to use mainly DOTATOC and DOTATATE.

Additionally, in 2013, Kunikowska J. et al published their results from 358 patients treated with PRRT involving ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and ^{90}Y/^{177}Lu-DOTATATE collected from April 2004 to December 2010. They reported a median OS of 49.8 - 52.8 months in the group of patients treated with ^{90}Y/^{177}Lu-DOTATATE.

Finally, in a study published in 2014, Paganelli G. et al. have reported the most recent overall survival data in 49 patients with advanced well-differentiated gastrointestinal NETs (79% midgut NETs) treated with ^{177}Lu-DOTATATE.The median OS was not reached at the time of publication, after a median follow-up of 38 months, ranging from 11 to 59 months.

The median OS in the control arm (Octreotide LAR) is expected to be 32 months, as per the updated results reported in the RADIANT-2 study.

The length of the overall survival assessment period includes a 18-month accrual period, and a 5-year follow-up period. The 5-year follow-up is the predicted length of the study; however, the actual end-of-study will be based on death events (158), or after 5 years from the randomization date of the last randomized patient, whichever occurs first. The analysis on OS will be conducted when 158 deaths have been recorded in the study or when 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first.

To facilitate the patients recruitment in the dosimetry, PK and ECG substudy, a non-randomized cohort (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only) is temporarily activated (Study Protocol Amendment 4.1) at all sites participating in the substudy in order to accelerate the collection of the relevant information required by the Agencies. This substudy is conducted in a subset of 20 patients. In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the substudy according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate cohort) will be analyzed descriptively only and they will not be considered in the primary and secondary analysis of the main study groups.

7.2 Populations in the Analysis

Before the database is locked and statistical analysis of study is initiated, all problematic cases where evaluability remains unclear will be *scrutinized* by a Data Review Committee. The data review committee will consist of the biostatistician assigned to the study, and the study manager of the CRO responsible for the execution of the study along with the responsible persons within the Sponsor. Other persons may be invited.

For analysis of study results, the following patient populations have been defined:

Full Analysis Set (FAS): consists of all patients randomized. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

Safety Set (SAF): consists of all randomized patients, who received at least one dose of study drug. Patients will be analyzed according to treatment received.

Per Protocol Set (PPS): consists of all randomized patients, who had no major protocol violations. The PPS will be identified prior to database lock. Major protocol deviations refer to deviations that critically impact efficacy analysis materially, such as not following important inclusion/exclusion criteria (e.g. incorrect diagnoses), taking wrong study medication, etc.

The FAS will be used for all analyses of efficacy, demographics and baseline characteristics. The PPS will be used for the per-protocol analyses of primary objective and key secondary variables. The safety set will be used for all safety analyses.

7.3 Demographics and Other Patient Characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for the FAS and the PPS. The summary of demographics will also be provided for the safety set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. All background and demographic data will be listed in detail.

7.4 Previous and Concomitant Medication

Previous and concomitant medications will be coded using World Health Organization (WHO) dictionary. Type and incidence of previous and concomitant medications will be tabulated (generic terms).

7.5 Analysis of Efficacy

All inferential statistics will be interpreted at the 5% 2-sided level, with the exception of OS where the significance level is adjusted to 0.0085% to account for an interim analysis at the time of the final PFS analysis. The primary objective will be tested confirmatorily. A method to control the family-wise type I error rate for the ORR and OS end-points is reported in §Section 7.5.2. All other efficacy variables will only be evaluated exploratorily, i.e. all reported p-values for all other efficacy variables will only be interpreted in an exploratory sense.

7.5.1 Primary Objective

The primary efficacy variable of this study is Progression Free Survival (PFS). PFS is defined as the time from randomization to documented centrally assessed progression according to RECIST Criteria or death due to any cause, as evaluated by the Independent Review Committee, i.e. the time from randomization until the date of last evaluable tumour assessment or date of death. If a patient has no centrally assessed progression and has not died, the patient will be regarded as censored in the context of a time to event analysis at the date of last evaluable tumour assessment.The median point estimate and 95% Confidence Interval (CI) for the PFS will be provided using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the PFS between the two treatment groups. The primary efficacy analysis will be conducted for the FAS. In addition, the primary efficacy variable will be analyzed for the PPS.

The final primary analysis on the PFS will be performed when the planned number of 74 PFS events (centrally assessed progression or death) is observed.

Additional PFS data are collected after the Primary End-Point has been reached as an effect of the continuation of the study in the treatment/assessment phase for patients who have not experienced tumour progression, or during the long term follow-up phase in case of discrepancy in the evaluation of the progression of disease (see §Section 4.4.1). This additional PFS data will be collected and analyzed descriptively.

7.5.2 Secondary Objectives

The secondary efficacy variables are: Objective Response Rate (ORR), Time to Tumour Progression (TTP), and Overall Survival (OS). These key secondary efficacy variables will be reported using the FAS and PPS. Duration of Response (DoR) and Time to Second Progression (PFS2) will be also descriptively analyzed as secondary exploratory end-points.

ORR is defined in §Section 6.3.2. Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups will be compared by Fisher's exact test.

TTP is defined as the time (number of days) from randomization to objective tumour progression centrally assessed. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date).

The Duration of Response (DoR) is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. DoR will be reported descriptively for each group without comparison between groups.

Time to Second Progression (PFS2) will be based on RECIST local assessments. PFS2 (time to second disease progression) is defined as the time from randomization to the time of disease progression or death due to any cause (on any treatment) following the first episode of disease progression.

OS is defined as the time from the date of randomization to the date of death due to any cause or the date of last contact (censored observation) at the date of data cut-off. An interim analysis for OS will be performed at the time of the final PFS analysis. The final analysis for OS will be performed when 158 deaths have been recorded in the study (based on 6-monthly collection of information) or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

OS and TTP will be similarly analyzed as the primary efficacy variable.

Survival curves will be compared by the unstratified log rank test. The null hypothesis will be investigated that the survival experience in the two groups is the same, i.e., there is no difference between the treatment groups in the probability of PFS, TTP, and OS at any time point (i.e.: $S_1=S_2$), against the two sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: $S_1 \neq S_2$).

The comparison of response rates by Fisher's exact test investigates the null hypothesis that the two treatment group proportions are equal (i.e.: $p_1=p_2$) against the two sided alternative hypothesis that the two treatment group proportions are not equal (i.e.: $p_1 \neq p_2$).

A gate-keeping testing procedure will be used to adjust the multiple testing for the primary variable and the family of secondary variables ORR and OS, (i.e., the family for the secondary variables will be tested only if the hypothesis for the primary variable (PFS) is rejected at the 5% significance level).

The hypotheses for ORR and OS will be tested using a fixed sequence procedure approach to control for the family-wise error. No adjustment will be applied to TTP since this variable is not considered for regulatory purposes.

ORR will be tested first at the 5% significance level at the time of the final PFS analysis. If the ORR hypothesis is rejected, then the OS hypotheses will be tested; otherwise no formal OS testing will be performed and the procedure stops.

OS analyses will be adjusted using O'Brien-Fleming spending function strategy with a 0.0085% significance level at the interim analysis (PFS final analysis).

The gate-keeping and fixed sequence testing procedures strongly control the family-wise type I error rate at 5%.

The following correlation analyses will be performed:

- the correlation of toxicity outcomes with body weight and body surface area;
- the correlation of clinical efficacy outcomes (ORR, PFS, OS, TTP) with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;
- the correlation of clinical efficacy outcomes (ORR, PFS, OS, TTP) with OctreoScan® tumour uptake score;
- the correlation of clinical outcome (ORR, PFS, OS, TTP) with serum levels of Alkaline Phosphatase (AP);

- Outcomes for both treatment groups will be evaluated in relation to objective tumour response, KPS, and other parameters of clinical relevance.

For this purpose the correlation coefficient according to Pearson and the correlation coefficient according to Spearman are calculated depending on the respective type of the respective variable.

Statistical analysis will be coordinated by the responsible CRO biostatistician. A detailed Statistical Analysis Plan (SAP) providing more details on the analysis and presentation of the results will be finalized before the database is locked. Any deviations from the SAP will be justified in the Study Report.

Health related QoL will be assessed using the EORTC QLQ-G.I.NET21 questionnaire (§Appendix 3), which will be filled in by the patient. Changes from baseline will be assessed every 12±1 weeks from the randomization date until Week 72 (and every subsequent 12 weeks until the PFS Primary End-Point, unless patient's progression or death. The impact of treatment on health related QoL will be assessed by comparison of the changes from baseline by means of Wilcoxon's rank sum test on an alpha-level of 5%.

7.6 Safety

The statistical analysis of safety data will be mainly descriptive in nature.

7.6.1 Adverse Events

An Independent Data Safety Monitoring Board will evaluate patient safety throughout the study (§Section 12.1 - Independent Data Safety Monitoring Board).

All original AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ classes and preferred terms will be used in the analyses.

Type and incidence of AEs, as well as severity and relatedness to the study medication will be recorded and notified appropriately. Special attention will be given to those patients who prematurely discontinue the study or the study medication due to an AE, or who experience a severe AE or an SAE. The investigator and the monitor will ensure that information on serious adverse events immediately notified with a SAE form are consistent with information on the same event contained in the e-CRF and in the source documents.

The number and percentage of patients with at least one AE will be determined, overall and separately for both treatment groups. The rate of patients with at least one AE is compared between the two treatment groups using Fisher's exact test on an α-level of 5%.

These analyses will be performed additionally for AEs leading to premature discontinuation and for serious adverse events.

Summary statistics will also be provided according to the intensity and the causality assessment (i.e. relationship to study medication). Frequencies and percentages will be provided for all categories. Percentages are based on the number of AE episodes, i.e. the number of AE forms filled in, and not on the number of symptoms, as one AE might be coded with more than one code.

A summary of adverse events will be given according to the primary system organ class (SOC) and preferred term (PT). Frequencies and percentages will be given overall and by treatment group in separate columns for SOC followed by those for PT in alphabetical order. All AE symptoms are taken into account for calculations.

Based on the preferred term, additionally an overview will be given for the most frequent AEs according to the intensity and the causality assessment to the study medication. Frequencies of symptoms will be presented in descending order and will be determined for each PT together with the associated frequencies of categories. The number and percentage of patients with an AE of the respective PT will be given as well.

7.6.2 Laboratory Tests

Descriptive statistics including shift tables will be generated for all laboratory tests performed (haematology, blood chemistry, and urinalysis), i.e. the actual values and the changes from pre-treatment by cross-tabulations (with classes for below, within, and above normal range).

Abnormal laboratory test results will be tabulated.

7.6.3 Vital Signs and ECG

The normal ranges for the vital signs are as follows:

- Pulse rate: 40 – 100 bpm
- Systolic blood pressure (SBP): 100 – 150 mmHg
- Diastolic blood pressure (DBP): 45 – 90 mmHg

Descriptive statistics (N, mean, median, minimum, maximum, 95% confidence interval for the mean, etc.) of the observed values as well as for the changes from baseline value will be created. Frequency tabulations with values within, below or above the normal ranges will be made.

ECG parameters will include heart rate (HR), RR interval, PR interval, QRS width and QT interval.

QT intervals will be corrected for heart rate. Information on possible co-morbidities factors will be collected in the eCRF. ECG results will also be evaluated by means of descriptive statistics (mean, median, 95% confidence interval for the mean, etc.) and frequency tabulations.

Graphical presentations might be created to facilitate the interpretation.

7.6.4 Physical Examination

Physical examination results will be tabulated; abnormalities will be listed.

7.6.5 Karnofsky Performance Score

Descriptive statistics for KPS of the observed values as well as for the changes from baseline will be created.

7.7 Dosimetry

Descriptive statistics for the dosimetry parameters will be created (for further details please refer to §Section 6.6.1).

7.8 Pharmacokinetics

A separate PK analysis plan and a separate report will be created for the PK data.

7.9 Interim Analysis

Interim safety analyses will be conducted by an Independent Data Safety Monitoring Board (§Section 12.1 - *Independent Data Safety Monitoring Board*). This Board will provide the Sponsor with a recommendation to continue the trial as planned, or to discontinue the trial, according to the Safety Analysis Plan. This Plan is described in detail in the Data Safety Monitoring Board (DSMB) Charter, provided as separate document.

As described in the DSMB Safety Plan (DSMB Charter Appendix 1) the DSMB will conduct 4 interim safety analyses that will be initiated at the time when 25%, 50%, 75% and 100% percent of the total ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments in the trial have been completed (that is out of 400 planned treatments), or where such treatments would have taken place had treatment not been withdrawn from subjects in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm. The DSMB will meet and assess up-to-date safety information within two weeks of a treatment exposure rate being achieved (i.e., the point when 25%, 50%, 75%, and 100% of treatments have occurred). Further patients may only be randomized two weeks after the treatment exposure rate has been reached and after a positive opinion from the DSMB.

An interim analysis for OS will be performed at the time of the final PFS analysis.

7.10 Other Analysis

Study termination reasons will be tabulated.

Protocol deviations will be tabulated.

7.11 Handling of Missing Data, Outliers, Visit Window and Other Information

Details on visit windows, analysis phases and how to deal with missing data will be specified in the Statistical Analysis Plan.

8- ADVERSE EVENTS AND OTHER SAFETY ASPECTS

8.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a patient and which does not necessarily have a causal relationship with the study medication. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a study medication, whether or not causally related to the study medication. Symptoms of the underlying diseases are not considered AEs, except a significant change as assessed by the Investigator.

AEs will be reported from the time the ICF is signed onwards until the PFS Primary End-Point occurs, or until Week 76 post randomization if the PFS Primary End-Point has been reached, or until early termination. If the information of an untoward medical occurrence is collected before starting the intake of study medication, this information will be listed as a pre-treatment AE during statistical analysis.

During the long-term follow-up of the patient, the Investigator must report only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the Sponsor Safety Officer.

8.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;

  Note: “life-threatening” refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly or birth defect;
- Requires in-patient hospitalisation or leads to prolongation of hospitalisation, with the exception of elective pre-planned hospitalisations.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for severe allergic reactions that do not result in hospitalisation.

If a patient becomes pregnant during treatment, this should be reported as if it were an SAE to the Sponsor Safety Officer.

The Investigator must report all SAEs by sending a completed SAE Reporting Form to the Safety Officer designee within 24 h of becoming aware of the event.

8.3 Criteria for Causal Relationship to the Clinical Study Medication

The investigator should indicate the probable cause of the specific SAE in the appropriate section(s) of the SAE Reporting Form:

Possible Causes of the Serious Adverse Event	
Check off all that apply	**Specify**
Pre-existing / underlying disease ❑	
Study treatment ❑	
Other treatment ❑	
Protocol-related procedure ❑	
Other (e.g., accident, new / intercurrent illness) ❑	

8.4 Criteria for Defining the Severity of an Adverse Event

National Cancer Institute Common Terminology for Adverse Events (CTCAE), Version 4.0(DSMB CharterAppendix 12) will be used for determining the severity of adverse events.

8.5 Investigator Reporting Requirements

Throughout the study, the study staff will question the patient in a non-directive way as to the occurrence of AEs. The patient will also be instructed upon signing the ICF to contact the Investigator to report any study medication or non-study medication-related adverse or unusual event that occurs during participation to the study.

The study staff will record all these events in the patient's medical records and e-CRF, whether observed by the Investigator, the investigational staff, or spontaneously reported by the patient.

The Investigator will provide a complete description of the event in standard medical terminology, the date of onset and termination, the date when the Investigator became aware of the event, severity, relationship to the study medication, action taken regarding the study medication, any treatment given, the outcome, and whether or not the event is considered an SAE. If known, the Investigator should report the underlying illness or disorder rather than the individual signs and symptoms.

8.6 Reporting of Serious Adverse Events

In the case of an SAE, the Investigator must immediately (within 24 h of awareness or at the earliest possible time point) complete the SAE section of the e-CRF, reporting all information that is required by

the Regulatory Authorities and contact the delegated Safety Officer designee, if needed. The name and contact details of the delegated Safety Officer designee will be available in the Investigator File (and will be updated when needed).

If the Investigator is not able to access the eCRF, a paper version of the SAE form is available on the study documentation site and this form should be completed and sent by fax to the Sponsor Pharmacovigilance Department in order to report the SAE. When the access problem is resolved, the investigator must promptly report the event into the eCRF.

The minimum information required for immediate reporting is the event description, the Subject ID, the study medication concerned, and the identifiable reporter (Investigator or designee). Even if not all the facts are known, an initial report should be made. The Investigator must provide follow-up information as soon as possible. If requested by the delegated Safety Officer designee, documents relevant to the diagnosis, treatment, and course of the event must be submitted (e.g. technical investigation reports, histology findings, hospital discharge documents). All documents must be blinded with respect to the patient's name.

When the Investigator determines that no additional information is likely to be available, a final report should be provided.

The Sponsor or delegated CRO will assume responsibility for appropriate reporting of AEs to the competent authorities and Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB) according to local laws and regulations.

SAEs will be recorded once the patient has provided written consent to participate in the study. The collection of SAE information will continue to be reported by the Investigator for each patient until 5 years after the end of the treatment phase only if the SAE is related to the product.

Deaths due to progression of the underlying midgut carcinoid tumours are considered SAEs and must be reported to the sponsor as detailed above. Nonetheless, the deaths occurring in the wake of a documented progression of the underlying cancer shall not be reported to the competent authorities and Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB).

8.7 Adverse Events of Special Interest

In addition to the Serious Adverse Events defined above, a set of potential risks deserve special attention even if they do not fulfill any of the seriousness criteria. These non-serious adverse events of special interest (AESI) occurring in patients enrolled in the investigational arm (^{177}Lu -DOTA0-Tyr^{3}-Octreotate) should equally be reported to the clinical trial pharmacovigilance department for safety analysis so long as they occur any time after enrollment including long term follow-up. The following types of pathology have been observed during ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate treatment and AESIs related to these categories should be reported to pharmacovigilance when they occur.

- **Hematotoxicity**: The main critical organ of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate treatment is the marrow. Significant hematotoxicity, defined as Grade 2 or higher thrombocytopenia, or Grade 3 or 4 of any other hematotoxicity (anaemia, leuko-/neutropenia) are considered dose-modifying toxicities in the study and should be reported as AESIs when not strictly fulfilling the criteria of serious adverse events. Haematological toxicities to be considered AESIs should not be limited to

the CTCAE-defined Grades specified above but should be expanded to include hematotoxicities regardless of severity if accompanied by clinical consequences, i.e., infections in the presence of leuko-/neutro-/lymphopenia, hemorrhages / purpuric lesions under thrombocytopenia that is not explained by another coagulation disorder, dyspnea / fatigue in the presence of anaemia not otherwise explained by the underlying carcinoid syndrome or other co-morbidity).

- **Secondary haematological malignancies**: such as MDS and acute myeloid leukemia, should be reported in every case, either as SAEs or AESIs. Given their delayed latency of onset, their period of detection and follow-up should be as long as possible, i.e., at least covering 5 years counted from the end of the 48-weeks of the scheduled follow-up.
- **Nephrotoxicity**: Since ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate is cleared through the kidneys and reabsorbed by the kidneys, the kidneys have always been considered the ‘‘critical organs’’. An infusion of amino acid is used for kidneys protection by inhibition of tubular reabsorption of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate. Pursuant to these risk minimization efforts and in addition to the criteria of dose-modifying toxicities and criteria of inclusion (at baseline and before subsequent treatments) pertinent to renal function measurements, renal and urinary tract toxicities should be considered AESIs. Investigators are encouraged to report, e.g., renal failure (ranging from significantly reduced measured or estimated creatinine clearance to clinically overt renal failure other than that of obvious non-IMP-induced origin), suspected radiation nephropathy of any type, such as radiation-induced thrombotic microangiopathy (manifested with, e.g., proteinuria, hypertension, edema, anaemia, decrease serum haptoglobin), or general symptoms and signs of acute radiation toxicity (e.g., increased frequency and urgency of urination, nocturia, dysuria, bladder spasm, bladder obstruction, genitourinary ulceration or necrosis).
- **Cardiovascular events**: In line with the objectives of planned safety pharmacology studies, the potential effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on blood pressure, heart rate, electrocardiogram changes justify reporting as AESIs all significant departures of these parameters from the pre-treatment baseline if they occur within reasonable propinquity of ^{177}Lu -DOTA^{0}-Tyr^{3}-Octreotate administration in the judgment of the Investigator. Likewise, clinically manifest and/or consequences of hypo-/hypertension, arrhythmias, cardiac conduction disturbances, and other cardiac pathologies evidenced by objective findings / changes on electrocardiogram or echocardiography should also be considered for AESIs reporting.

8.8 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterised. An assessment should be made at the last study-related visit for each patient. Certain long-term AEs cannot be followed until resolution within the settings of this protocol. In these cases follow-up will be the responsibility of the treating physician.

Since it is unpredictable how long such a follow-up might take, data from this follow-up generated after the patient’s last study-related visit will be recorded by the Investigator. Full details regarding this follow-up will be described in the Clinical Study Report, if necessary.

If during AE follow-up the case has progressed to the level of “SAE”, or if a new SAE is observed whose relationship to the study medication could not be ruled out, the situation must be reported immediately by

the Investigator becoming aware of the information (considering that the "date of SAE onset" is the date of the first manifestations of that AE).

8.9 Procedure in Case of Pregnancy

Prior to clinical study enrollment, women of childbearing potential (see §Appendix 7 for definition) must be advised of the importance of avoiding pregnancy until six months after the end of the last treatment and the potential risk factors for an unintentional pregnancy. Due to the CT scans foreseen during the study (every 12±1 weeks), woman should not procreate during the study. The patient must sign an ICF documenting this discussion. During the clinical study, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual period).

If a patient or Investigator suspects that the patient may be pregnant prior to study medication administration, the study medication must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the patient must not receive study medication and must not be enrolled in the clinical study. If pregnancy is suspected while the patient is receiving study medication, the study medication must immediately be withheld if it can be done safely until the result of pregnancy testing is known. If pregnancy is confirmed, the Investigator must immediately terminate the patient from the study but follow the patient to determine the outcome. The study medication must be permanently discontinued if this can be done safely. If study medication is to be discontinued, it should be done in an appropriate manner and the patient must be withdrawn from the clinical study.

The Investigator must report any pregnancy associated with investigational product exposure including conceptions occurring until 6 months after the last study medication administration. The report should be carried out within 24 hours of pregnancy confirmation by sending a completed Pregnancy Reporting Form to the Safety Officer.

Appropriate pregnancy follow-up procedures should be considered if indicated. The Investigator must report follow-ups within 24 hours of the receipt of any new information on the course of the pregnancy, including perinatal and neonatal outcome, by sending a completed Pregnancy Reporting Form to the Safety Officer.

When the outcome of the pregnancy, delivery, and newborn fulfill the criteria of SAEs [e.g., spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried foetus)], the Investigator should respond in accordance with the reporting procedure for SAEs described in §Section 8.6. Additional information regarding the outcome of pregnancy (which is categorised as an SAE) is mentioned below.

Death of a newborn within 1 month after birth should be reported as an SAE regardless of its relationship with the study medication.

If an infant dies more than 1 month after birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as reasonably related by the Investigator.

In case of a delivery of a living newborn, the newborn's condition is evaluated at birth. The miscarried foetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

Every case of pregnancy requires expedited reporting by the Sponsor to the competent authorities and Independent Ethics Committee(s)/ Institutional Review Board(s) (IEC/IRB).

8.10 New Safety Information Affecting the Conduct of the Study

When new information, including "Dear Doctor Letters" but not limited to that, necessary for conducting the clinical study properly will lead to a protocol amendment, the Sponsor should inform all Investigators involved in the clinical study, the head of the study site, ethics committees, and Regulatory Authorities of such information, and when needed, should amend the patient information.

8.11 Institutional Policies

Where there are institutional policies regarding: 1) patient instructions; 2) roles of personnel in the conduct or recording of information/data; or 3) the recording of data; those policies, exceeding the requirement stated in this protocol, supercede the instructions in this protocol.

9- TERMINATION OF THE STUDY

Early termination of the study can occur in the following cases:

- When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the Investigator and applicable authorities.
- The Sponsor reserves the right to discontinue the study at any time for failure to meet expected enrollment goals.

Termination of a study site:

- If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor of the discontinuation and the reason for it.

10- OPERATIONAL, ETHICAL, AND ADMINISTRATIVE CONSIDERATIONS

10.1 Data Quality Control

10.1.1 Data Collection, Review, and Clarification

10.1.1.1 Data collection

The study will be monitored by the Sponsor or a designee according to the current SOP for the monitoring of studies.

Shortly before the study starts, the Study Monitor will meet with the Investigator and Investigational Staff involved reviewing the procedures regarding study conduct and recording of data in the e-CRF. During the study, the Investigator will permit the Study Monitor to verify coherence of recorded data in the e-CRF and the progress of the study at the centre as frequently as necessary. The Investigator will make the electronic data screens available, provide missing or corrected data, and sign the e-CRFs. Key data transcribed into the e-CRF will be reviewed against the source documents. Personal information will be treated as strictly confidential and will not be made publicly available. Any inconsistency between the source data and the data recorded in the e-CRF will be corrected.

Clinical data will be captured via Electronic Data Capture (EDC) using the HyperSuite-Hypernet XMR® system, in an electronic CRF (e-CRF). The Investigator site staff will enter and edit the data via a secure network, with secure access features (user ID, password). The study paper questionnaire EORTC QLQ-G.I.NET21 will be completed directly by the patient at the investigator's site. The Investigator will provide to insert into a specific form of the e-CRF the questionnaire's answers for each patient.

The Sponsor will ensure that appropriate Quality Control (QC) steps are included in the different clinical processes to adequately protect the study patients and the quality of the study data.

An independent Quality Assurance (QA) department, Regulatory Authorities and/or IECs/IRBs may review this study. This implies that auditors/inspectors have the right to inspect the study centre(s) at any time during and/or after completion of the study and have access to source documents, including the patient's file. By participating in this study, the Investigator(s) agree(s) to this requirement.

For any data transfer, measures will be undertaken to protect patient data handed over against disclosure to unauthorised third parties and patient confidentiality will be maintained at all times.

10.1.1.2 Data Review

All data relating to the study must be recorded in the e-CRFs provided by the Sponsor or designated CRO. These e-CRFs should always reflect the latest observations on the patient's participation in the study. Therefore, e-CRFs are to be completed as soon as possible after (or during) the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the study determinations are completed by the same individual who made the initial ones at baseline. The Investigator must verify that all data entries in the e-CRFs are accurate and correct. At the end of each visit he must approve the data using an electronic signature. This approval is used to confirm the accuracy of the data recorded. The electronic case report form must be kept current to reflect patient status at each phase during the course of the trial.

The monitor will review the e-CRFs and evaluate them for completeness and consistency. The e-CRF will be compared with the source documents to ensure that there are no discrepancies between critical data.

All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the e-CRFs. Once clinical e-CRF data have been submitted, corrections of the data fields will be audit trailed, meaning that the reason for change, as well as the name of the person performing the change will be logged together with the date and time. Roles and rights of the site personnel responsible for entering the date into the e-CRF will be determined in advance.

10.1.1.3 Data Clarification

If corrections to an e-CRF are needed, the responsible monitor or data manager will raise a query in the electronic data capture application. The appropriate investigational staff will answer queries sent to the Investigator. This will be audit-trailed by the e-CRF application.

10.1.2 Study Documents

10.1.2.1. Source Documents

Source data must be available at the study centre to document the existence of the study patients and substantiate the integrity of the study data collected. They must include the original documents relating to the study, as well as the medical treatment and medical history documentation of the patient.

The source medical records should at least include the following information for each patient:

- Patient identification (name, date of birth, gender);
- Documentation of eligibility criteria, i.e. medical and medication history, physical examination, and confirmation of diagnosis, including pathology assessment report;
- Participation in study (including study number);
- Study discussed, signed and dated ICF;
- Dates of all visits;
- Pathology, laboratory and Specialist's (e.g., ECG, dosimetry, pharmacokinetics) reports;
- Images/scans (e.g., OctreoScan® and CT/MRI) and reports;
- Patient QoL questionnaires;
- Documentation that protocol-specific procedures were performed;
- Randomization number (if applicable), study medication start and end dates;
- Dispensation and return of study medication;
- Record of all AEs and other safety parameters;
- Record of all previous and concomitant therapies;
- Date of study completion or reason for early discontinuation (if applicable).

The following documents are considered as source documents as well: patient diaries, nurse records, and worksheets.

The author of an entry in the source documents must be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the e-CRF are consistent with the original source data.

10.1.3 Clinical Study Monitoring

The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that patients' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and ICH GCP, and that the data reported by the Investigator or designee are accurate, complete, and verifiable with the source documents. The Sponsor or delegated CRO is responsible for assigning (a) Clinical Study Monitor(s), who will monitor the study in accordance with the monitoring guidelines. A copy of their Monitoring Log will be obtained at the study close-out visits.

10.1.4 Direct Access to Source Data/Documents

The Investigator and the study centre must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IEC(s)/IRB(s) and/or relevant Regulatory Authorities. They must provide all study-related records, as well as source documents to these instances when they are requested to. The confidentiality of the patient's identity shall be well protected and consistent with local and national regulations when the source documents are patient to direct access.

10.1.5 Data Management

Data management activities will be coordinated by the CRO under supervision of the Sponsor.

Final review of the clinical data will be executed by Data-Management staff. The Data manager will generate queries for the clarification of unclear / missing / inconsistent data. The errors found will be assessed by the Data Manager of the study and Investigators will be involved in resolving them. All changes to the database will be automatically recorded in an audit trail file. All changes will be requested from the Investigator through the EDC system. If a change is necessary once the Investigator has no further access to the database, a query will be sent to the Investigator for confirmation of the change. The Investigator's signature is required to show he/she agrees with the change that was made. The process of data-entry and data-cleaning for all patients starts when the study is still in the phase of 'treatment / follow-up' and should be completed soon after the completion of the study. After all corrections to the data are made, the database will be "locked" and no data can be changed without adequate documentation.

Copies of the electronic CRF together with all data changes made will be supplied to the Investigator at the end of the trial. The Investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract. When the trial is concluded, a copy of all data-sets will be provided to the Sponsor on electronic support.

All study-specific processes and definitions will be described in the Data Management Plan. Coding of AEs and Medical History terms will be performed using MedDRA; previous and concomitant medication will be coded using WHO codes.

10.2 Ethics and Protection of Patient Confidentiality

10.2.1 Ethical Conduct of Clinical Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki (§Appendix 1), GCP, ICH guidelines, and the applicable laws and regulations.

ICH-GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting study activities that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of the patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the study data are credible.

The Investigator and all study staff will conduct the study in compliance with the IEC/IRB approved version of this protocol. The protocol, ICF, any information provided to the patient, recruitment advertisements, and any amendments to these items will have IEC/IRB approval prior to their use in the study. Voluntary informed consent will be given by every patient in order to be screened for study eligibility and prior to the initiation of any study-related procedures. The informed consent process must meet all applicable local laws. The rights, safety, and well-being of the patient are the most important consideration and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities.

10.2.2 Authorities

The protocol, name, and study centre of the Investigators, the votes of the IEC(s)/IRB(s), as well as other locally required documents will be submitted to the Health Authorities of the participating countries, according to local requirements for review and approval before the beginning of the study. The Health Authorities will be informed about the end of the study. Individual patient medical information obtained as a result of this study is considered.

10.2.3 Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such information may only be given to a third party after approval of the patient, to the patient's general practitioner or to other appropriate medical personnel responsible for the patient's well-being.

The Sponsor, its board members, and its personnel shall not disclose any confidential information on patients obtained during the performance of their duties in the study without justifiable reasons.

All individuals and organisations involved in conducting the study and/or processing the study data, must pay very careful attention to protect the patients' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a patient (e.g. name or address). These details shall be processed in accordance with the applicable local and regional laws.

10.2.4 Patient Information/Written Informed Consent

According to ICH GCP (CPMP/ICH135/95) the patient must give consent to participate in the study, only after being fully informed by the Investigator of the nature, significance, and implications of the study, as well as to the associated risks involved. Such meetings must be carried out on an individual basis, and adapted to the educational background and previous knowledge of the patient. Participation to this meeting will be documented in the patient's file.

The patient will be instructed by the Investigator that the consent for study participation can be withdrawn at any time, without justifying a reason, and that no disadvantageous consequences will follow regarding further medical treatment. The Investigator shall ask for the reason of premature termination without violating the patient's rights (ICH GCP Definition 4.3.4).

Furthermore, the patient must be informed about insurance coverage and the corresponding patient obligations (see Patient Information). **The ICF must be personally dated and signed in duplicate by both the Investigator and the patient.** The patient receives 1 of the 2 original documents of the patient information and consent form **signed and dated** by both Investigator and the patient.

The other original of the signed ICF will be retained by the Investigator in the Investigator's File, who will confirm the patient's consent in the e-CRF. The patient will only be included in the study after written consent is given.

Furthermore, it is recommended that the Investigator inform the patient's general practitioner of his/her participation in the study, provided that the patient has a general practitioner and the patient agrees to disclose this information.

10.2.5 Patient Cards

After signing an ICF for participation in the study, each patient is given a patient card, which indicates the contact details of the Investigator (e.g. stamp with telephone number), the patient's Subject ID, as well as the medication number. The patient shall carry this card with him/her during participation in the study so that the Investigator may be contacted in case of emergency.

10.3 Administration

10.3.1 Arrangement for Use of Information and Publication of Clinical Study Data

All information regarding the investigational product under study in the outlined protocol and Sponsor's operations, such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by the Sponsor and not previously published, are considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes including publications and presentations without the Sponsor's written consent.

It is understood by the Investigator that the information developed during the conduct of this study is considered confidential and will be used by the Sponsor for the development of the specified investigational medication. This information may be disclosed as deemed necessary by the Sponsor to other Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this study and to ensure complete and thorough analysis, the Investigator is obligated to provide the Sponsor with complete test results and all data developed in this study, and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

Any publication or public presentation of the results of this study must be according to the Sponsor's standards. The first publication is multicentre and coordinated by the Sponsor. The Investigator agrees that before he/she publishes any results of this study, he/she shall send the draft manuscripts and copies of the information to be presented to the Sponsor at least 30 working days before submission to a publisher or presentation. The Sponsor reserves the right to review these materials before submission for publication or presentation. This is not intended to restrict or hinder publication or presentation but instead to allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator(s).

10.3.2 Documents and Records Related to the Clinical Study

The Investigator must retain e-CRFs and source documents of all enrolled patients (i.e. all patients who gave consent to be screened for the study), study medication disposition, and other documents required by regulation, in his/her possession or in an accessible area for at least 15 years after the completion of this study, or at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, if required by the applicable regulatory requirements. The Sponsor will notify the Investigator when the records no longer need to be kept.

The Investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the Investigator relocate or dispose any study documents before obtaining the Sponsor's written approval.

If it becomes necessary for the Sponsor or the appropriate Regulatory Authority to review any documentation relating to this study, the Investigator must permit, with the approval of the patient, access to such reports.

Any difficulty in archiving and storage of clinical study documents must be discussed with the study monitor prior to the initiation of the study.

The data and information collected during this study will be reported in Study Report(s) by the Sponsor. In accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for study reports, a coordinating Investigator will review and sign the Study Report(s) for this study. The signing coordinating Investigator will be selected by the Sponsor from the Investigators who participate in this study, based on the level of participation, the significant level of clinical research, and adherence to the clinical study protocol.

10.3.3 Protocol Amendment and/or Revision

Any changes to the study, which arise after approval of the protocol, must be documented as protocol amendments and/or revisions. Depending on the nature of the amendment and/or revision, either IEC/IRB approval or notification is required. The changes will become effective only after the approval of the Sponsor, the Competent Authority, and the IEC/IRB (if applicable).

10.3.4 Qualification of the Investigators

The Investigator(s) should be qualified by education, language, training, and experience to assume responsibility for the proper conduct of the study. He/she should meet all qualifications specified by the applicable regulatory requirements and should provide evidence of such qualifications through an up-to-date curriculum vitae (Principal as well as all other Investigators) and/or other relevant documentation requested.

The Investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, the current Investigator's Brochure, the product information, and other information sources provided by the Sponsor.

The Investigator should be aware of, and should comply with, ICH-GCP and the applicable regulatory requirements.

The Investigator should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

10.4 Finance and Insurance

The disclosed financial interest of the Investigator must be reported prior to enrollment of the first patient into the study, following study centre completion, and 1 year following study completion. The Investigator should promptly update this information if any relevant changes occur during this period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of his/her participation to the study. For any Investigator(s) leaving the site prior to study completion, an Investigator Financial Disclosure Form should be obtained at the end of his/her participation.

10.4.1 Insurance of Patients and Others

The Sponsor has covered this study by means of insurance according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number, and the sum insured are provided in the Investigator's File.

10.4.2 Investigator Indemnity

The Sponsor shall be liable towards the patients in accordance with the provisions of the Clinical Study Law. Notwithstanding the foregoing; the Sponsor does not, however, agree to indemnify, defend, or hold the Investigator harmless against liability, damage, loss, cost or expense (including reasonable attorney's fees and expenses), including liabilities arising out of or in connection with claims of any nature by third parties, including, without limitation, in respect of bodily injury or death, arising out of or in connection with the negligence, wrongful acts or omissions or willful misconduct of the Investigator, the Institution, or its affiliates.

Including but not limited to:

- The making of unauthorised representations and warranties concerning the study medication or the study;
- The failure to obtain a signed ICF;
- Non-compliance with applicable rules or regulations;
- Failure to conduct the study in accordance with this protocol.

A condition of this indemnity obligation is that, whenever the Investigator has information from which it may be reasonably concluded that an incident of bodily injury, sickness, disease, or death has occurred, the Investigator must immediately notice the Sponsor of all pertinent data surrounding any such incident, and, in the event a claim is made or a suit is brought, the Investigator will assist the Sponsor and cooperate in gathering information with respect to the time, place, and circumstances, and in obtaining the names and addresses of the injured parties and available witnesses.

The Investigator shall not, except at his/her own cost, voluntarily make any payment or incur any expense in connection with any such claim or suit without the prior written consent of the Sponsor.

11- QUALITY ASSURANCE

The Sponsor or delegated CRO is implementing and maintaining QA and QC systems with written SOPs to ensure that studies are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or designee may arrange to inspect or audit the study at any or all study centres. The auditor is independent from the clinical monitoring and project management team at the Sponsor's site. The audit may include on-site review of regulatory documents, e-CRFs and source documents. The auditors will have direct access to these documents.

12- CLINICAL STUDY ORGANISATION

12.1 Independent Data Safety Monitoring Board

An Independent Data Safety Monitoring Board (DSMB) will evaluate safety throughout the study. The DSMB will be independent from the Sponsor, specific agents of the Sponsor, Investigators, and any other study oversight bodies. They will advise the Sponsor, Investigators and investigational sites regarding the continuing safety of study patients and the patients yet to be recruited to the study as well as maintaining validity and scientific merit of the study, The DSMB will review ongoing examinations of safety data and promptly give recommendations to continue, continue with modification, or terminate the study. The DSMB Charter, and the DSMB Safety Plan (Appendix 1 of the DSMB Charter) are provided as separate documents.

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14- APPENDICES

Appendix 1 – Helsinki Declaration

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations

involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must

immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented

by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix 2 – RECIST Criteria, Version 1.1 (Eisenhauer EA et al., 2009)

The complete criteria are included in the published RECIST document (Eisenhauer EA et al., 2009), also available at http://www.eortc.be). A summary is provided below.

1 Measureability of Tumour at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see §Appendix 9 on imaging guidance).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

Non-measurable are all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before first treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions

can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See §Appendix 9 for more details.

CT, MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. As is described in §Appendix 9, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in §Appendix 9.

***Ultrasound*:**

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in §Appendix 9). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy:

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers:

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, Histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2 Tumour Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In trials where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Figure 3 of §Appendix 9.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement (see also the example in Figure 4 in §Appendix 9). All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

2.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions. Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm. Lesions that split or coalesce on treatment. As noted in §Appendix 9, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.4 Evaluation of Best Overall Response [NB: see Protocol §Section 6.3 for assessment methods and endpoints]

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see §Section 2.6 below). Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

2.5 Frequency of Tumour Re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently.

For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory measurement/duration of response

2.6.1 Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies (see the paper by Bogaerts et al. in this Special Issue10). However, in all other circumstances, i.e. in randomized studies (phase II or III) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different trials and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Overview of renewed RECIST Criteria, Version 1.1.

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ≥15 mm short axis for target ≥10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]
		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Appendix 3 – EORTC Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:			Not at all	A little	Quite a bit	Very much
31.	Did you have hot flushes?		1	2	3	4
32.	Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33.	Did you have night sweats?		1	2	3	4
34.	Did you have abdominal discomfort?		1	2	3	4
35.	Did you have a bloated feeling in your abdomen?		1	2	3	4
36.	Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37.	Have you had acid indigestion or heartburn?		1	2	3	4
38.	Have you had difficulties with eating?		1	2	3	4
39.	Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40.	Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41.	Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42.	Were you concerned about disruption of home life?		1	2	3	4
43.	Have you worried about your health in the future?		1	2	3	4
44.	How distressing has your illness or treatment been to those close to you?		1	2	3	4
45.	Has weight loss been a problem for you?		1	2	3	4
46.	Has weight gain been a problem for you?		1	2	3	4
47.	Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48.	Have you had aches or pains in your muscles or bones?		1	2	3	4
49.	Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:						
50.	Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51.	Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

Appendix 4 – Sandostatin® LAR Depot (Patient Information Leaflet, Novartis Pharmaceuticals UK Ltd)

SANDOSTATIN® LAR® 10, 20 and 30 mg powder and solvent for suspension for injection

(octreotide)

Note: Doctors and other health professionals involved in the administration of Sandostatin LAR please consult the Summary of Product Characteristics (SmPC) and the administration instructions following Section 6 of this leaflet.

Patient Information Leaflet

This medicine will be referred to as Sandostatin LAR in this leaflet.

What you need to know about Sandostatin LAR

Your doctor has decided that you need this medicine to help treat your condition.
Please read this leaflet carefully before you start to have your medicine. It contains important information. Keep the leaflet in a safe place because you may want to read it again.
If you have any other questions, or if there is something you don't understand, please ask your doctor or nurse.
This medicine has been prescribed for you. Never give it to someone else. It may not be the right medicine for them even if their symptoms seem to be the same as yours.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Sandostatin LAR is and what it's used for

Sandostatin LAR is a long-acting injection, often called a 'depot' injection because the active ingredient is released into the body slowly. This means that you don't have to have an injection every day. Sandostatin LAR contains the active ingredient octreotide (as the acetate). Octreotide is a synthetic form of the natural hormone, somatostatin. It helps stop the release of some hormones, including growth hormone, in the body.

Sandostatin LAR can be used for three conditions.

1. <u>To treat acromegaly</u>

Acromegaly is a condition where the body produces too much growth hormone. The level of growth hormone controls the growth of tissues, organs and bones. Too much hormone means the size of bones and tissues, especially in the hands and feet, is larger than normal. The symptoms of acromegaly include headache, excessive perspiration, numb hands and feet, tiredness, and joint pain. In most cases, the overproduction of growth hormone is caused by an enlargement in the pituitary gland (a pituitary adenoma).

Sandostatin LAR is used to treat people with acromegaly;

- when daily treatment with Sandostatin injection given subcutaneously (under the skin) has been proved to be satisfactory; (Switching to Sandostatin LAR means that the injections will be much less frequent.)
- when other types of treatment for acromegaly (surgery or radiotherapy) are not suitable or haven't worked;
- after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective;
- before surgery on the pituitary gland.

2. <u>To relieve stomach or bowel symptoms associated with certain tumours known as 'gastroenteropancreatic' tumours (rare tumours of the stomach, bowels or pancreas)</u>

Overproduction of specific hormones and other related natural substances can be caused by some rare conditions of the stomach, bowels or pancreas. This upsets the natural hormonal balance of the body, and results in a variety of symptoms, such as flushing, diarrhoea, low blood pressure, rash, and weight loss. Treatment with Sandostatin LAR helps to control these symptoms. It is generally given to people who have already responded well to treatment with daily Sandostatin injections.

3. <u>To treat neuroendocrine tumours located in the gut (e.g. appendix, small intestine or colon)</u>

Neuroendocrine tumours are rare tumours which can be found in different parts of the body. Sandostatin LAR is also used to control the growth of these tumours, when they are located in the gut.

2. Things to consider before you are given Sandostatin LAR

Some people MUST NOT be given Sandostatin LAR. Talk to your doctor if:

- You think you may be allergic to octreotide or to any of the other ingredients of Sandostatin LAR. (These are listed at the end of the leaflet).
- You are breastfeeding.

You should also ask yourself these questions before having Sandostatin LAR:

- Are you pregnant ?
- Do you have diabetes?
- Do you have thyroid problems, or have you had a disease which may have affected your thyroid?
- Do you have any problems with your liver, or have you had a disease which may have affected your liver?
- Have you ever suffered from gallstones or other stomach problems?
- Do you have a history of Vitamin B12 deficiency?

If the answer to any of these questions is YES, tell your doctor or nurse because Sandostatin LAR might not be the right medicine for you.

Are you taking other medicines?

Sandostatin interacts with a large number of other medicines. Tell your doctor or nurse if you are taking any of the following:
Insulin, or other drugs for diabetes
Ciclosporin
Cimetidine
Bromocriptine

Medicines to control blood pressure (beta-blockers or calcium channel blockers) or agents to control fluid and electrolyte balance (diuretics)
Medicines metabolised by the liver for example carbamazepine, digoxin and warfarin and terfenadine.
Always tell your doctor or pharmacist about all the medicines you are taking. *This means medicines you have bought yourself as well as medicines on prescription from your doctor.*

Will there be any problems with driving or using machinery?
No problems have been reported.

Other special warnings

- Your doctor may want to give you a check up from time to time while you are being treated with Sandostatin LAR.
- Growth hormone secreting pituitary tumours may sometimes expand and cause problems. Tell your doctor if you experience any problems with your eyes or sight.
- Tell your doctor if your stomach or bowel problems get worse.
- There is very little experience of using Sandostatin LAR in children.
- Sandostatin LAR should only be used during pregnancy if clearly needed. Tell your doctor if you are pregnant or want to become pregnant.
- Women of child bearing potential must use an effective contraceptive method during treatment with Sandostatin LAR.

3. Taking Sandostatin LAR

Your doctor will work out the correct dose for you.

If you receive Sandostatin LAR for the treatment of acromegaly, or for the relief of symptoms of gastropancreatic tumours, the starting dose is usually 20 mg Sandostatin LAR, which is given at 4-week intervals. After about the first 3 months of treatment with Sandostatin LAR, your doctor will probably want to reassess your treatment. This may involve measuring the levels of growth hormone or other hormones in your blood. Depending on these results, and on how you are feeling, the dose of Sandostatin LAR may need to be changed. The dose given in each injection can be reduced to 10 mg or, if the treatment is not fully effective, it can be increased to 30 mg. After the most suitable dose for you has been found, your doctor will probably want to reassess your treatment about every 6 months.

Sandostatin LAR must be injected into the gluteal muscles in your buttocks. For repeat injections the doctor or nurse will use the left and right buttocks alternately.

If you have had no problems with Sandostatin injected subcutaneously, you can immediately be changed over to Sandostatin LAR. If you haven't had Sandostatin before, the doctor will give you a test dose to see how you react, before switching to Sandostatin LAR, if appropriate.

Depending on why you are having Sandostatin LAR, you may need to continue having subcutaneous Sandostatin for about two weeks after your first injection of Sandostatin LAR until it becomes fully effective. You might also occasionally need to use subcutaneous Sandostation as well when your symptoms are troublesome.

When Sandostatin LAR is being used prior to surgery on the pituitary gland, you must have the last dose at least 3 to 4 weeks before the surgery.

If you receive Sandostatin LAR for the treatment of neuroendocrine tumours located in the gut, the usual dose is 30mg at 4-week intervals. Your doctor will decide how long you should be treated with Sandostatin LAR.

Ask your doctor or pharmacist if you are unsure about how much medicine you are being given or how often you are being given it.

What if you forget a dose?
If you forget to go for your appointment for your injection, you should contact your doctor as soon as possible to arrange another appointment.

What if you have had too much? (Overdose)
If you think you have been given the wrong dose talk to the nurse or doctor.

4. Possible side effects

Most people who are prescribed Sandostatin LAR benefit from taking it, but a few can be upset by it. If you are receiving this medicine on a long term basis then you will go to hospital from time to time to have regular check-ups.

Some side effects can be serious
Tell your doctor immediately if you notice that:
- Your face becomes flushed or swollen or you develop spots or a rash
- Your chest feels tight, you become short of breath or wheezy
- You feel faint, possibly as a result of a fall in blood pressure.

These might be the result of an allergic reaction.

If you develop any of the following see your doctor immediately:
- Prolonged/troublesome bloating of the stomach with pain
- Nausea/vomiting associated with drowsiness
- Feeling restless or giddy
- Yellowing of skin or the whites of your eyes
- Acute pancreatitis (sudden, severe pains in the lower stomach). This may happen within the first few hours or days of treatment and resolves itself upon drug withdrawal.

These other side effects have been reported in clinical trials:

Up to 1 in 10 people have experienced:
- Local pain at the site of the injection
- Stomach ache, nausea, wind, diarrhoea or constipation
- Headache
- Changes in blood sugar levels (Hyperglycaemia)
- Gallstones.

Up to 1 in 100 people have experienced:
- Slow heart beat
- Hair loss
- Itching
- Rash
- Shortness of breath

- Dizziness
- Loss of appetite
- Changes in blood sugar levels (Hypoglycaemia)
- Impaired glucose tolerance
- Stomach discomfort after a meal
- Vomiting
- Bloated stomach
- Loose faeces (stools)
- Discolouration of faeces
- Fat in your faeces (pale and fatty loose stools)
- Inflammation of the gallbladder
- Biliary sludge
- Yellow skin and eyes
- Abnormal liver function test results
- Changes in activity of the thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight, tiredness, feeling cold or sweating too much, anxiety or swelling at the front of the neck.

Up to 1 in 1,000 people have experienced:
- Dehydration
- Fast heart beat.

Patients taking Sandostatin have reported experiencing the following additional side effects:
- Anaphylaxis (a type of allergic reaction which causes difficulty in breathing or dizziness), allergy/hypersensitivity reactions
- Itchy rash
- Inflammation of the pancreas
- Liver inflammation (hepatitis); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine
- Irregular heart beat
- Liver dysfunction.

If any of the symptoms become troublesome, or if you notice anything else not mentioned here, please go and see your doctor. He/she may want to give you a different medicine.

5. How to store Sandostatin LAR

Keep all medicines out of the reach and sight of children.

Sandostatin LAR should be stored in the fridge (between 2°C and 8°C). Keep in the original packaging to protect it from light. Sandostatin LAR can be kept below 25°C on the day of injection, but it must be kept in the outer carton to protect it from light. The suspension must only be prepared immediately before injection.

Do not use Sandostatin LAR after the expiry date which is printed on the outside of the pack.

6. Further information

Sandostatin LAR contains the active ingredient octreotide (as octreotide acetate) in a powder (microspheres) for suspension for injection. The powder also contains the inactive ingredients poly(DL-lactide-co-glycolide) and mannitol. The powder is white to off-white in colour.

Before it can be used, the powder must be suspended in a special liquid (vehicle), which is provided in a pre-filled syringe. This liquid consists of sodium carboxymethylcellulose, mannitol and sterile water. The liquid is clear and colourless.

Once the powder has been mixed with the liquid to be used for suspending the powder, Sandostatin LAR suspension contains less than 1mmol (23mg) of sodium per dose i.e. essentially sodium free.

Sandostatin LAR is supplied in a kit which contains

- one 5 ml glass vial containing either 10, 20, or 30 mg octreotide powder (as the acetate),
- one syringe containing 2.5 mL of the liquid to be used for suspending the powder,
- two needles [40 mm (1.5 inch), 19 gauge].

The product licence holder is Novartis Pharmaceuticals UK Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, England.

Manufacturer responsible for batch release Novartis Pharmaceuticals UK Ltd, Wimblehurst Road, Horsham, West Sussex RH12 5AB, England.

This leaflet was revised in July 2011.

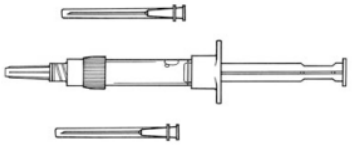
If you would like any more information, or would like the leaflet in a different format, please contact Medical Information at Novartis Pharmaceuticals UK Ltd, telephone number 01276 698370.
SANDOSTATIN is a registered trade mark

For the Medical and Pharmaceutical Professions

Instructions for intramuscular injection of Sandostatin LAR:

FOR DEEP INTRAGLUTEAL INJECTION ONLY
Content:

One vial containing
Sandostatin LAR

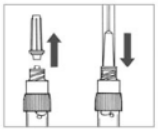


One prefilled syringe containing vehicle solution
+ two needles

Follow the instructions below carefully to ensure complete saturation of the powder and its uniform suspension before i.m. injection.

Sandostatin LAR suspension must only be prepared **immediately** before administration. Sandostatin LAR should only be administered by a trained health professional.

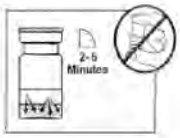
Allow the Sandostatin LAR vial and the vehicle syringe to reach room temperature.
Remove the cap from vial containing Sandostatin LAR. Ensure that the powder is settled at the bottom of the vial by lightly tapping the vial.



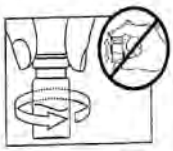
Remove the cap from the vehicle syringe.
Attach one of the supplied needles to the vehicle syringe.

Disinfect the rubber stopper of the vial with an alcohol swab.
Insert the needle through the centre of the rubber stopper of the Sandostatin LAR vial.

Without disturbing the Sandostatin LAR powder, gently inject all the vehicle into the vial by running the vehicle down the inside wall of the vial. **Do not inject the vehicle directly into the powder.** Withdraw the needle from the vial.

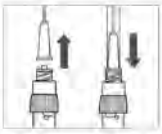


Do not disturb the vial until the vehicle has totally wetted the Sandostatin LAR powder (at least 2-5 minutes). **Without inverting the vial** check the powder on the walls and bottom of the vial. If dry spots exist, allow undisturbed wetting to continue. At this stage, prepare the patient for injection.



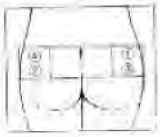
Once complete wetting has occurred, the vial should be moderately swirled for about 30 to 60 seconds until a uniform milky suspension is achieved. **Do not vigorously shake the vial** as this may cause the suspension to flocculate, making it unusable.

Immediately re-insert the needle through the rubber stopper and then, with the bevel down and the vial tipped at approximately 45 degree angle, slowly draw the contents of the vial into the syringe. **Do not invert the vial** when filling the syringe as this may affect the amount withdrawn.
It is normal for a small amount of suspension to remain on the walls and bottom of the vial. This is a calculated overfill.



Immediately change the needle (supplied).

Administration must occur immediately after the suspension has been prepared. Gently invert the syringe as needed to maintain a uniform suspension. Eliminate air from syringe.



Disinfect the injection site with an alcohol swab.
Insert needle into right or left gluteus and draw back to ensure that no blood vessel has been penetrated. Inject slowly i.m. by deep intragluteal injection with steady pressure. If the needle blocks, attach a new needle of the same diameter [1.1 mm, 19 gauge].

Sandostatin LAR must be given only by deep intragluteal injection, never i.v. If a blood vessel has been penetrated, attach a new needle and select another injection site.

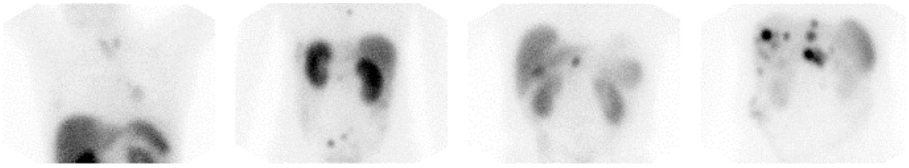
Appendix 5 – OctreoScan® Tumour Uptake and Extent of Tumour Burden Scales

The Tumour Uptake and the Extent of Tumour Burden scores are based solely on the planar images obtained at 24 hours after administration of OctreoScan® according to the Tumour Scoring methods described below. Planar image acquisition is to be performed according to the technical protocol specified in §Appendix 6 - Part 1.

Tumour Scoring

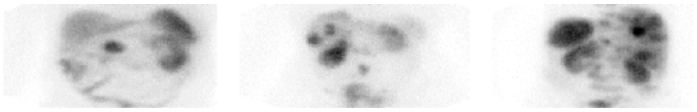
The intensity of Tumour Uptake and the Extent of Tumour Burden is to be scored according to simple scaling systems.

The Tumour Uptake score is determined by comparing the uptake of OctreoScan® (24 hour planar scintigrams) in the selected tumour to the uptake observed in the liver according to the following examples:



Tumour Uptake:	1) < Liver	2) ≈ Liver	3) > Liver	4) Very intense
Grade OctreoScan®:	(Excluded)			(>>Kidneys, spleen)

The Extent of Tumour Burden score is determined by assessing the number of OctreoScan® positive tumours and is scored according to following examples and descriptions:



Tumour Burden score OctreoScan®:	Limited	Moderate	Extensive

Limited: Up to 5 sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen).

Moderate: Multiple metastatic lesions in up to 2 parts of the body, neither qualifying for limited nor for extensive.

Extensive: Many tumour sites in ≥ 2 parts of the body, usually a combination of extensive liver and lymph node involvement or diffuse skeletal metastases; diffuse liver metastases with limited abdominal involvement does not qualify.

Appendix 6 - Part 1 - OctreoScan® Planar Imaging Protocol (ENETS Guidelines)

ENETS Guidelines

Neuroendocrinology 2009;90:184–189
DOI: 10.1159/000225946

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Somatostatin Receptor Imaging with ^{111}In-Pentetreotide

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Introduction

The purpose of this guideline is to assist nuclear medicine practitioners in performing, interpreting, and reporting the results of somatostatin receptor scintigraphy with ^{111}In-pentetreotide. It is not this guideline's aim to give recommendations on the use of PET tracers for somatostatin receptor imaging (SRI). The reason for this is that valid comparisons between state of the art SRI with ^{111}In-pentetreotide and these newer PET imaging methods are lacking, and that these newer methods have not been fully validated. Besides, because of the local production of PET radiopharmaceuticals and the diversity of peptide analogs that are applied, each with a different affinity profile and therefore potentially a different biodistribution and a different tumor detection sensitivity, it is virtually impossible to make guidelines for the application of these PET radiopharmaceuticals. The general recommendations on patient preparation and image interpretation, however, do apply. This guideline is adapted from the procedure guideline for somatostatin receptor scintigraphy with ^{111}In-pentetreotide, published by the Society of Nuclear Medicine [1]. ^{99m}Tc-Depreotide (Neotect®) is another commercially available somatostatin analog that has been approved specifically for the detection of lung cancer in patients with pulmonary nodules [2]. Because of the relatively high abdominal background and the impossibility of performing delayed imaging due to the short half-life of the tracer, it is less suited for the detection of abdominal neuroendocrine tumors [3]. Somatostatin is a regulatory peptide widely distributed in the human body, in particular in the central and peripheral nervous system, in the endocrine glands, in the immune system as well as in the gastrointestinal tract. In all these tissues, somatostatin action is mediated through membrane-bound receptors, of which five have been cloned (sst1–sst5) [4].They all belong to the family of G-protein-coupled receptors. Only sst2, sst5 and, to some extent, sst3 have a high affinity for the commercially available synthetic octapeptide octreotide [5].Somatostatin receptors are expressed in several normal human tissues, including brain, pituitary, gastrointestinal tract, pancreas, thyroid, spleen, kidney, immune cells, vessels and peripheral nervous system [6–9]. Somatostatin receptors have been identified in vitro in a large number of human neoplasias. A high incidence and density of somatostatin receptors are found in particular in neuroendocrine tumors, such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer and small cell lung carcinoma [10].Tumors of the nervous system including meningioma, neuroblastoma and medulloblastoma also very often express a high density of somatostatin receptors. But also tumors not known to classically originate from endocrine or neural cells, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma and gastric cancer can express somatostatin receptors. In the majority of these tumors, the sst2 receptor subtype is predominantly expressed, although low amounts of other somatostatin

receptor subtypes may be concomitantly present [11].It should also be emphasized that selected non-tumoral lesions may express somatostatin receptors. For instance, active granulomas in sarcoidosis express somatostatin receptors on epithelioid cells [12] and inflamed joints in active rheumatoid arthritis express somatostatin receptors, preferentially located in the proliferating synovial vessels [13].The expression of somatostatin receptor is therefore not specific for tumoral pathologies.

Imaging Results in Neuroendocrine and Other Tumors

Imaging results in tumors and other diseases are listed and subdivided according to reported sensitivity of SRI in table 1.

Normal Scintigraphic Findings and Artifacts

Normal scintigraphic features include visualization of the thyroid, spleen, liver, and kidneys, and the pituitary in some of the patients. Also, the urinary bladder and bowel are usually visualized to variable degrees. The visualization of the pituitary, thyroid, and spleen is due to receptor binding. Uptake in the kidneys is for the most part due to re-absorption of the radiolabeled peptide in the renal tubular cells after glomerular filtration. There is predominant renal clearance of the somatostatin analog, although hepatobiliary clearance into the bowel also occurs, necessitating the use of laxatives in order to facilitate the interpretation of abdominal images. False-positive results of SRI have been reported. In virtually all cases the term 'false-positive' is a misnomer because somatostatin receptor-positive lesions that are not related to the pathology for which the investigation is performed, are present. Many of these have been reviewed by Gibril et al. [46].The most common of these are listed in table 2 (which is not exhaustive). Diminished uptake in the spleen due to ongoing treatment with (unlabeled) octreotide may occur, which may be accompanied by a lower liver uptake. In case of hepatic metastases, this phenomenon may be misinterpreted as a better uptake in liver metastases. during octreotide treatment, the uptake of [^{111} In-DTPA^{0}]-octreotide in somatostatin receptor-positive tumors is also diminished. This may lead to a lower detection rate of somatostatin receptor-positive lesions, although there are also literature reports of improved tumor-to-background ratio after pretreatment with nonradioactive octreotide. A number of causes for a potential false-negative study interpretation are given in table 3.

Table 1. Sensitivity of SRI using pentetreotide

High sensitivity

- Pituitary tumors [14]
- GEPNETs
  - Gastrinomas [15, 16]
  - Nonfunctioning endocrine pancreatic tumors [17, 18]
  - Functioning endocrine pancreatic tumors except insulinomas [17, 18]
  - Carcinoids [19–22]
- Paragangliomas [23–25]
- Small cell lung cancer [26–29]
- Meningiomas [30, 31]
- Sarcoidosis and other granulomatous diseases [12, 32]
- Graves' disease and Graves' ophthalmopathy [33, 34]

Intermediate sensitivity

- Insulinomas [17, 35]
- Medullary thyroid carcinoma [36–38]
- Differentiated thyroid carcinoma (including Hurthle cell carcinoma) [39–41]
- Breast cancer [42]
- Lymphoma (NHL, HL) [43, 44]
- Pheochromocytoma [45]
- Astrocytoma [31]

High sensitivity = Detection rate >75%; intermediate sensitivity = detection rate 40–75%. Sensitivity is either patient- or lesion-based. GEPNET = Gastroenteropancreatic neuroendocrine tumor; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma

Common Indications

- Detection and localization of a variety of neuroendocrine and other tumors and their metastases
- Staging patients with neuroendocrine tumors
- Follow-up of patients with known disease to evaluate potential recurrence
- Selection of patients with metastatic tumors for peptide receptor radionuclide therapy and prediction of the effect of peptide receptor radionuclide therapy

Procedure

Patient Preparation

- When appropriate and clinically feasible, therapy with short-acting somatostatin analogs should be discontinued for 24 h before ^{111}In-pentetreotide administration. Such therapy can be resumed the day after injection of the radiopharmaceutical. Long-acting preparations should preferably be stopped 5–6 weeks before the study, and patients should be switched to short-acting formulations up to 1 day before the study. In follow-up studies, it may be more convenient to plan the injection of the radiopharmaceutical just before a new administration of the long-acting formulation is due. The reader should be aware that in such a condition, tumor and spleen uptake may be diminished due to receptor occupancy
- To reduce radiation exposure, patients should be well hydrated before and for at least 1 day after injection
- Laxatives are advised, especially when the abdomen is the area of interest. A mild oral laxative may be administered in the evening before injection and in the evening after injection. The need for bowel preparation should be assessed on an individual basis and laxatives should not be used in patients with active diarrhoea
- There is no need for fasting prior to the investigation
- The feasibility of the investigation in patients on hemodialysis (with imaging after dialysis) should be discussed with local nephrologists and radiation protection experts

Precautions

- In patients suspected of having insulinoma, an intravenous infusion of glucose should be available because of the potential for inducing severe hypoglycemia
- ^{111}In-pentetreotide should not be injected into intravenous lines for or together with solutions for total parenteral nutrition
- The usual precautions and considerations for nuclear medicine investigations in pregnant or breastfeeding women apply

Information Pertinent to Performing the Procedure

- A relevant history of the type of suspected or known primary tumor, its hormonal activity, the results of other imaging studies (CT or MRI), laboratory results (tumor markers), history of recent surgery, chemotherapy, radiation therapy, and octreotide therapy should be obtained

Table 2. Pitfalls and causes of potential misinterpretation of positive results

Radiation pneumonitis
Accessory spleen
Focal collection of stools
Surgical scar tissue
Gallbladder uptake
Nodular goiter
Ventral hernia
Bacterial pneumonia
Respiratory infections
Common cold (nasal uptake)

Cerebrovascular accident
Concomitant granulomatous disease
Diffuse breast uptake
Adrenal uptake
Urine contamination
Concomitant second primary tumor

Table 3. Causes of potential misinterpretation of negative results

Presence of unlabeled somatostatin, either because of octreotide therapy or resulting from production of somatostatin by the tumor itself, may lower tumor detectability.
Different somatostatin receptor subtypes have different affinities for the radioligand; variable tumor differentiation and receptor expression also influence tumor detectability. This may be important especially in patients with insulinomas and medullary thyroid carcinomas.
Liver metastases of neuroendocrine tumors may appear iso-intense because of a similar degree of tracer accumulation by the normal liver. Correlation with anatomic imaging and/or SPECT imaging may be helpful

Radiopharmaceutical

- ^{111}In-pentetreotide is a [^{111}In-DTPA^{0}] conjugate of octreotide, a somatostatin analog (OctreoScan®). The recommended administered radioactivity is 185–222 MBq (5–6 mCi) in adults and 5 MBq/kg (0.14 mCi/kg) in children. [**NB: 220 MBq is the recommended amount of administered radioactivity for this trial, according to Appendix 6, Part 2**]. The amount of pentetreotide injected is 10–20 μg; this dose is not expected to have a clinically significant pharmacologic effect. ^{111}In-pentetreotide is cleared rapidly from the blood. Excretion is almost entirely through the kidneys (50% of the injected dose is recovered in the urine by 6 h, 85% within 24 h). Hepatobiliary excretion is only about 2% of the administered dose
- The effective dose equivalent is 0.054 mSv/MBq. For a full patient dose of 222 MBq this is 12 mSv
- Before the administration of ^{111}In-pentetreotide, the labeling yield of the radiopharmaceutical should be tested according to the manufacturer's instructions
- The radiopharmaceutical should be used within 6 h of preparation
- ^{111}In-pentetreotide should be inspected visually before administration. Preparations containing particulate matter or color should not be administered

Image Acquisition

- Patients should void before imaging
- Images are acquired at 4 and 24 h or 24 and 48 h after injection. The 48-hour images may be needed when there is significant bowel activity at 24 h, which may potentially obscure lesions. Four-hour images may be obtained to enable evaluation before appearance of activity in the gut, but since the tumor-to-background ratio is lower at 4 h than at 24 and 48 h, some lesions may be missed at 4 h
- Planar images are acquired using a large-field-of-view gamma camera fitted with a medium-energy collimator. Symmetrical 20% energy windows are centered over both photopeaks of ^{111}In (173 and 247 keV) and the data from both windows are added. Planar localized images of the head, chest, abdomen, pelvis, and, if needed, the extremities can be acquired for 10–15 min/image. For whole-body images using a dual-head camera, acquisition should be for a minimum of 30 min (head to upper femurs) and longer for the entire body (e.g., a speed of up to 3 cm/min has been suggested) in a single pass. Since cervical lymph node metastases may be missed on the whole-body images, additional planar localized images of the head and neck, including lateral views, are suggested
- SPECT imaging of the appropriate regions, as indicated based on the clinical history, should be performed preferably with a multi-detector gamma camera. Early and delayed SPECT (i.e. 4 and 24 h after injection) may be helpful in distinguishing bowel activity from pathological lesions. If only one SPECT acquisition is obtained, acquisition at 24 h is preferred because of a higher target-to-

background ratio. Although imaging systems may vary, an example of potentially useful acquisition parameters for a multi-detector system are the following: 3° angular sampling, 128x128 matrix, 360° rotation, 20–30 s/stop

Interpretation Criteria

- When possible, images should be evaluated in conjunction or fused with relevant anatomic images e.g., CT or MRI)
- The optimal time interval to localize tumors is 24 h after injection or later. At 4 h the background activity may be high. Nevertheless, early images may be important for comparison and evaluation of abdominal activity imaged at 24 h
- Knowledge of normal tissue accumulation of ^{111}In-pentetreotide is important for study interpretation. This radiotracer is seen in the pituitary, thyroid, liver, spleen, kidneys, bladder, and occasionally the gallbladder. Intestinal activity is usually not present at 4 h, but may be present at 24 h; images at 48 h may be necessary to clarify abdominal activity

Reporting

- In addition to the general information to be provided in each nuclear medicine report, it is suggested that the report contain the following information
- *Indication:* Results of laboratory tests (e.g., neuroendocrine tumor markers if applicable) or results of other imaging studies as well as other relevant history (known tumor and its type, recent radiation therapy, and chemotherapy)
- *Relevant medications:* For example, octreotide therapy and, when stopped, chemotherapy and/or laxatives, if given
- *Procedure description:* Timing of imaging relative to radiopharmaceutical administration; areas imaged; whether SPECT was performed and, if so, its timing and body areas included
- *Study limitations:* The referring physician may be reminded that some tumors may lack somatostatin receptors or the appropriate receptor subtypes and, therefore, may not be detected. The differential diagnosis should consider the many potential causes for a false-positive study, as listed in table 2

List of Participants

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

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Appendix 6 – Part 2 – OctreoScan® Summary of Product Characteristics

QUALITATIVE AND QUANTITATIVE COMPOSITION

OctreoScan® is supplied as two vials which cannot be used separately.

1 vial 4920/A with 1.1 ml solution contains at activity reference time: (^{111}In) Indium(III)chloride 122 MBq

1 vial 4920/B contains:
Pentetreotide 10 µg

After reconstitution and labelling the solution contains ^{111}In-pentetreotide.

Physical characteristics of ^{111}In:

^{111}In is cyclotron produced and decays with a half-life of 2.83 days to stable cadmium.
Emission characteristics:
γ-rays 172 keV (90 % abundance)
γ-rays 247 keV (94 % abundance)
X-rays 23-26 keV

Radionuclidic purity: ^{111}In ≥ 99%, other γ-emitting nuclides ≤ 0.1%.
^{114m}In: max. 500 Bq per 1 MBq of ^{111}In at activity reference time/date.

Half-life of ^{114m}In: 49.51 days.

PHARMACEUTICAL FORM

Vial A: Radiopharmaceutical precursor.
Vial B: Powder for solution for injection.
Vial A is a glass vial shielded with lead, containing a clear and colourless solution.
Vial B is a glass vial with grey rubber stopper and an aluminium crimp cap with orange flip off. It contains a white lyophilised powder.

CLINICAL PARTICULARS

Therapeutic indications

^{111}In pentetreotide specifically binds to receptors for somatostatin.
OctreoScan® is indicated for use as adjunct in the diagnosis and management of receptor bearing gastro-entero-pancreatic neuroendocrine (GEP) tumours and carcinoid tumours, by aiding in their localisation. Tumours which do not bear receptors will not be visualised.

In a number of patients suffering from GEP or carcinoid tumours the receptor density is insufficient to allow visualisation with OctreoScan®. Notably in approximately 50% of patients suffering from insulinoma the tumour can not be visualised.

Posology and method of administration

The dose for planar scintigraphy is 110 MBq in one single intravenous injection. Careful administration is necessary to avoid paravasal deposition of activity. For single photon emission tomography the dose depends on the available equipment. In general, an activity dose of 110 to 220 MBq in one single intravenous injection should be sufficient. No special dosage regimen for elderly patients is required.

There is limited experience on administrations in paediatric patients, but the activity to be administered in a child should be a fraction of the adult activity calculated from the bodyweight according to the following table (Paediatric Task Group, European Association of Nuclear Medicine).

3 kg = 0.1	4 kg = 0.14	6 kg = 0.19	8 kg = 0.23	10 kg = 0.27
12 kg = 0.32	14 kg = 0.36	16 kg = 0.40	18 kg = 0.44	20 kg = 0.46
22 kg = 0.50	24 kg = 0.53	26 kg = 0.56	28 kg = 0.58	30 kg = 0.62
32 kg = 0.65	34 kg = 0.68	36 kg = 0.71	38 kg = 0.73	40 kg = 0.76
42 kg = 0.78	44 kg = 0.80	46 kg = 0.82	48 kg = 0.85	50 kg = 0.88
52-54 kg = 0.90	56-58 kg = 0.92	60-62 kg = 0.96	64-66 kg = 0.98	68 kg = 0.99

Scintigraphy takes place approx. 24 hours after administration. When activity in the abdomen is observed at 24 hours which cannot be interpreted with certainty as uptake in tumour or activity in bowel contents, scintigraphy should be repeated at 48 hours. In some cases, scintigraphy after 4 hours gives acceptable results. Physiologic uptake occurs in spleen, liver, kidneys and bladder. Thyroid, pituitary and intestines are visible in most patients.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
No specific contraindications have been identified.
For use during pregnancy and lactation see below.

Special warnings and special precautions for use

Because of the potential hazard of the ionizing radiation ^{111}In-pentetreotide should not be used in children under 18 years of age, unless the value of the expected clinical information is considered to outweigh the possible damage from radiation.

Administration of a laxative is necessary in patients not suffering from diarrhoea, to differentiate stationary activity accumulations in lesions in, or adjacent to, the intestinal tract from moving accumulations in the bowel contents.

In patients with significant renal failure administration of ^{111}In-pentetreotide is not advisable because the reduced or absent function of the principal route of excretion will lead to delivery of an increased radiation dose (E.D.E. 1.9E-01 mSv/MBq). Administration should be considered only when the possible damage from radiation is outweighed by the potential diagnostic information. Interpretable scintigrams may be obtained after haemodialysis during which the high background activity can at least partially be removed. Prior to dialysis images are non-diagnostic because of activity in the circulation. After dialysis a higher than usual uptake in liver, spleen and intestinal tract, and a higher than usual activity in circulation, were observed.

^{111}In-pentetreotide not bound to receptors, and non-peptide bound ^{111}In, are rapidly eliminated through the kidneys. To enhance the process of excretion, in order to reduce background noise and to reduce the radiation dose to kidneys and bladder, a liberal fluid intake (at least 2 litres) is required for 2 or 3 days following administration.

In diabetic patients, receiving high doses of insulin, the administration of pentetreotide may cause paradoxical hypoglycaemia via a temporary inhibition of glucagon secretion.

Regarding patients on octreotide therapy it is recommended to withdraw this therapy temporarily to avoid a possible blockade of somatostatin receptors. This recommendation is given on empirical grounds, the absolute need for such measure has not been demonstrated. In some patients the withdrawal of therapy might be not tolerated and may cause rebound effects. This is notably the case in insulinoma patients, where the danger of sudden hypoglycaemia must be considered, and in patients suffering from the carcinoid syndrome.

If the clinician responsible for the patients therapeutic management considers withdrawal of octreotide therapy tolerable a three days withdrawal period is recommended.

Positive scintigraphy with ^{111}In-pentetreotide reflects the presence of an increased density of tissue somatostatin receptors rather than a malignant disease. Furthermore positive uptake is not specific for GEP- and carcinoid-tumours. Positive scintigraphic results require evaluation of the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. An increase in somatostatin receptor density can also occur in the following pathological conditions: tumours arising from tissue embryologically derived from the neural crest, (paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas), tumours of the pituitary gland, endocrine neoplasms of the lungs (small-cell carcinoma), meningiomas, mamma-carcinomas, lympho-proliferative disease (Hodgkin's disease, non-Hodgkin lymphomas), and the possibility of uptake in areas of lymphocyte concentrations (subacute inflammations) must be considered.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Therefore, radiation protection precautions in accordance with national regulations must be taken.

Interaction with other medicinal products and other forms of interaction

No drug interactions have been reported to date.

Pregnancy and lactation

There is no experience with the use of OctreoScan® in pregnant women. When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation have to be considered.

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. The administration of the maximal diagnostic activity of 220 MBq to the patient results in an absorbed dose to the uterus of 8.6 mGy. In this dose range lethal effects and the induction of malformations, growth retardations and functional disorders are not to be expected; however the risk for the induction of cancer and hereditary defects may be increased. Therefore, OctreoScan® should not be used during pregnancy unless clearly necessary.

It is not known whether ^{111}In pentetreotide is excreted into the breast milk. Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If administration during lactation is considered necessary, breast feeding has to be discontinued and the expressed milk has to be discarded.

Effects on the ability to drive and use machines

^{111}In-pentetreotide does not affect the ability to drive or to use machines.

Undesirable effects

Adverse effects attributable to the administration of OctreoScan® are uncommon (>1/1000, <1/100). Specific effects have not been observed.

The symptoms reported are suggestive of vasovagal reactions or of anaphylactoid drug effects.

The withdrawal of octreotide therapy as a preparatory step to scintigraphy might provoke severe adverse effects, generally of the nature of a return of the symptoms seen before this therapy was started.

Exposure to ionising radiation can lead to cancer or development of hereditary defects. As most diagnostic nuclear medicine investigations involve levels of radiation less than 20 mSv (effective dose), these adverse events can be expected with a low probability. However, with this product when performing SPECT this level might be exceeded. The EDE in a 70 kg individual with normal renal function is maximally 26 mSv. The higher dose may be justified under some clinical circumstances.

This product contains no excipients that have a recognised action or effect, or knowledge of which is important for safe and effective use of the product.

Overdose

The pharmaceutical form (monodose injection) makes inadvertent overdosing improbable. The renal elimination of ^{111}In-pentetreotide, not bound to receptors, and of non-peptide bound ^{111}In can be enhanced by administration of fluids.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals for tumour detection.
ATC: V09I B 01.

OctreoScan® attaches to somatostatin receptors in tissues where, as consequence of disease, the cell-surfaces contain these receptors in a more than physiologic density. In individual patients, where the disease did not lead to an increased receptor density, scintigraphy will not be successful.

In carcinoid and GEP-tumours the prevalence of increased receptor density in the tumour-tissue in general is rather high.

Only limited studies of pharmacodynamic effects have been performed. The in vitro biological activity is approximately 30% of the biological activity of natural somatostatin. The in vivo biological activity, measured in rats, is less than that of equal amounts of octreotide. Intravenous administration of 20 µg of pentetreotide resulted in some patients in a measurable but very limited decrease of serum gastrin and serum glucagon levels of less than 24 hours duration.

Pharmacokinetic properties

Approximately 80% (resp. 90%) of intravenously administered radiolabelled pentetreotide is eliminated through the urinary system in 24 (resp. 48) hours. ^{111}In-pentetreotide is taken up by the following organs:

liver (approx. 2% at 24 hours) and spleen (approx. 2.5% at 24 hours). Uptake in thyroid and pituitary occurs but not reproducibly. The uptake in kidneys is partly a reflection of ongoing elimination through the urine and partly due to delayed excretion by the kidney. The elimination via the gallbladder and subsequently the faeces is approx. 2% of the administered activity dose in patients with normal intestinal function.

Up to 6 hours post-administration radioactivity in urine is predominantly intact ^{111}In-pentetreotide. Thereafter, increasing amounts of non-peptide-bound activity are excreted.

Preclinical safety data

Preclinical safety testing did not yield remarkable findings. No testing has been done on carcinogenic potential nor of the influence of pentetreotide on fertility or on embryotoxicity.

Radiation dosimetry

The following radiation dosimetry are calculated according to the MIRD system. The data are given in ICRP publication 80 in 1999.

"According to the biokinetic model described in ICRP 80 intravenously injected 111In-pentreotide is assumed to be immediately taken up in liver, spleen, kidneys and thyroid, while the rest is assumed to be homogeneously distributed in the remainder of the body. The experimentally found retention data is best described by mono- or bi-exponential functions. The biokinetic data come from patients with carcinoid tumours and endocrine tumours in the GI-tract. Uptake in tumour tissue present in any given organ may therefore be included in the published organ uptake values. The main route of excretion is via the kidneys and less than 2 % is excreted in faeces. An observed excretion of 85 % via urine after 24 h fits well with the model. The small excretion via the GI tract is not included in the model, since its contribution to the absorbed dose in normal circumstances is negligible."

Organ(s)	F_s	$T_{1/2}$	a	$\bar{A}_s/A_0$
Liver	0.06	2 h	0.40	2.59 h
		2.5 d	0.30	
		70 d	0.30	
Spleen	0.05	2.5 d	1.00	2.30 h
Kidney	0.06	2.5 d	1.00	2.76 h
Thyroid	0.001	2.5 d	1.00	2.76 min
Other organs and tissues	0.829	3 h	0.90	6.90 h
		2.5 d		
Bladder	1.00			
Adults and 15 years				1.63 h
10 years				1.40 h
5 years and 1 year				54.3 min

F_s	fractional distribution to organ or tissue
$T_{1/2}$	biological half-time for uptake or elimination
a	fraction of F_s taken up or eliminated with the corresponding half-time. A minus sign indicates uptake.
$\bar{A}_s/A_0$	cumulated activity in organ or tissue per unit of administered activity

Absorbed dose per unit activity administered (mGy/MBq)					
Organ	**Adult**	**15 Years**	**10 Years**	**5 Years**	**1 Year**
Adrenals	5.8E-02	7.5E-02	1.2E-01	1.7E-01	3.0E-01
Bladder	2.0E-01	2.5E-01	3.1E-01	4.6E-01	8.2E-01
Bone surfaces	2.7E-02	3.4E-02	5.0E-02	7.6E-02	1.5E-01
Brain	9.6E-03	1.2E-02	2.0E-02	3.3E-02	5.8E-02
Breast	1.2E-02	1.5E-02	2.3E-02	3.7E-02	6.8E-02
Gall bladder	5.2E-02	6.3E-02	9.2E-02	1.4E-01	2.2E-01
GI- tract					
Stomach	4.3E-02	5.0E-02	7.8E-02	1.1E-01	1.8E-01
SI	2.9E-02	3.8E-02	5.9E-02	9.1E-02	1.6E-01
Colon	2.9E-02	3.6E-02	5.5E-02	8.9E-02	1.5E-02
(ULI	3.0E-02	3.7E-02	5.8E-02	9.4E-02	1.6E-01)
(LLI	2.7E-02	3.4E-02	5.0E-02	7.6E-02	1.3E-01)
Heart	2.5E-02	3.2E-02	4.9E-02	7.1E-02	1.3E-01
Kidneys	4.1E-01	4.9E-01	6.7E-01	9.6E-01	1.6E+00
Liver	1.0E-01	1.3E-01	2.0E-01	2.7E-01	4.8E-01
Lungs	2.3E-02	3.0E-02	4.4E-02	6.8E-02	1.2E-01
Muscles	2.0E-02	2.6E-02	3.8E-02	5.7E-02	1.1E-01
Oesophagus	1.4E-02	1.9E-02	2.8E-02	4.4E-02	7.8E-02
Ovaries	2.7E-02	3.5E-02	5.1E-02	8.1E-02	1.4E-01
Pancreas	7.2E-02	8.8E-02	1.3E-01	2.0E-01	3.2E-01
Red marrow	2.2E-02	2.7E-02	3.9E-02	5.3E-02	8.7E-02
Skin	1.1E-02	1.3E-02	2.1E-02	3.3E-02	6.2E-02
Spleen	5.7E-01	7.9E-01	1.2E+00	1.8E+00	3.1E+00
Testes	1.7E-02	2.3E-02	3.5E-02	5.5E-02	1.0E-01
Thymus	1.4E-02	1.9E-02	2.8E-02	4.4E-02	7.8E-02
Thyroid	7.6E-02	1.2E-01	1.8E-01	3.7E-01	6.9E-01
Uterus	3.9E-02	4.9E-02	7.1E-02	1.1E-01	1.9E-01
Remaining organs	2.3E-02	2.8E-02	4.2E-02	6.3E-02	1.1E-01
Effective dose per unit administered (mSv/MBq)	**5.4E-02**	**7.1E-02**	**1.0E-01**	**1.6E-01**	**2.8E-01**

For an administered maximal recommended activity of 220 MBq the effective dose is 12 mSv (in an adult of 70 kg).

PHARMACEUTICAL PARTICULARS

List of excipients

Vial 4920/A
Hydrochloric acid
water for injections
Ferric Chloride Hexahydrate

Vial 4920/B
Sodium citrate dihydrate
citric acid monohydrate
inositol
gentisic acid
After reconstitution and labelling the pH of the aqueous solution is 3.8-4.3. The ready to use solution does not contain a preservative agent.

Incompatibilities

Major incompatibilities: not known. After reconstitution and labelling OctreoScan® may be diluted with 0.9% sodium chloride solution. Do not mix the injectate with any other solution in order to avoid possible incompatibilities.

Shelf life

Vial A and by consequence vial B of OctreoScan® expire 24 hours after the activity reference time/date of the ^{111}In. Activity reference time/date and expiry time/date are both stated on the label on the shielding

(sealed container) and appear in the documents that accompany each shipment. After reconstitution and labelling the solution must be used within 6 hours.

Special precautions for storage

The vials A and B are to be stored below 25 °C. Storage should take place in accordance with national regulations for radioactive materials. Store the ready to use solution below 25°C during the prescribed shelf life.

Nature and contents of container

Both 10 ml vials comply with the requirements for glass Type I, Ph.Eur. The vial containing pentetreotide is closed with a butyl rubber stopper. The vial containing 111In-indium chloride is closed with a teflon-coated butylrubber stopper. Both vials are sealed with an aluminium crimp cap. OctreoScan® is supplied as one pack containing two vials that cannot be used separately, one of which has a lead shielding. Both vials are packed in a closed, folded tin. Enclosed in the tin is a Sterican Luer Lock 0.90 x 70 mm / 20 G x 2 4/5 needle to be used for the labeling procedure.

Instructions for use/handling

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides.
This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

Instructions for labelling

1 Add the contents of vial A (^{111}In-chloride) to vial B (lyophilised pentetreotide) to obtain the product Indium (^{111}In) pentetreotide; only the Sterican (0.90 x 70) needle supplied with the shipped patient dose should be used to remove the indium chloride from its vial
2 Observe an incubation period of 30 minutes following the reconstitution
3 The preparation may be diluted with 2-3 ml of 0.9% sodium chloride solution if a larger volume is desired for easier handling in the syringe
4 The solution must be clear and colourless, this can be checked behind a lead wall containing a lead glass window. If the solution does not comply it should be discarded.
5 Use a tiny sample of this (diluted or not) volume for the quality control, which is described in the following paragraph
6 The solution is ready for use.

N.B.: FOR THE RECONSTITUTION DO NOT USE ANY OTHER ^{111}IN-CHLORIDE SOLUTION THAN THE ONE SUPPLIED IN THE SAME CONTAINER THAT HOLDS THE LYOPHILISED PENTETREOTIDE

Instructions for quality control

Analysis of ^{111}In-bound peptides versus ^{111}In-bound non-peptide compounds may be done on silicagel impregnated glass fiber strips (ITLC SG by GELMAN, cat.nr.61885). Prepare a thoroughly dried strip, approx. 10 cm long and 2.5 cm wide by marking a starting line at 2 cm, with additional marks at 6 and 9 cm. Apply 5 to 10 µl of the reconstituted and labelled solution to the starting line and develop in freshly prepared sodium citrate solution 0.1M, adjusted with HCl to pH 5. In approximately 2-3 min the front will have reached the 9 cm mark. Cut the strip at the 6 cm mark and measure the activity of both halves. Non-peptide bound ^{111}In moves with the front. Requirement: The lower end of the chromatogram should contain ≥ 98% of the applied activity.

Instructions for waste disposal

Unused ^{111}In activity or unused OctreoScan® should be allowed to decay until the activity has dropped to such a low level that, according to local
regulations, it is no longer considered radioactive. Then it may be disposed of as harmless waste. Unused vials with lyophilized pentetreotide may be disposed of as harmless waste.

Waste must be disposed of according to national regulations for radioactive material.

Appendix 7 – Precautions for Pregnancy

Men and women should not procreate until six months after the date of their last treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Due to the CT scans foreseen during the study (every 12±1 weeks), woman should not procreate until the end of the study.

It is noteworthy that β-HCG may be secreted by a small percentage of NETs, such that, in addition to being a pregnancy marker it also is a tumour marker. Consequently, NET female patients with positive β-HCG at baseline can be eligible to enter the study and receive treatment if pregnancy can be excluded by lack of expected doubling of β-HCG. Normally in pregnant subjects β-HCG doubles every 2 days during the first 4 weeks of pregnancy and every 3 ½ days by weeks 6 to 7.

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral ovariectomy) or is not postmenopausal (defined as amenorrhoea >24 consecutive months, and for women on hormone replacement therapy, only with a documented plasma follicle-stimulating hormone level >35 mIU/mL). Even women who are using oral, implanted or injected contraceptive hormones, an IUD, or barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, are practicing abstinence or where the partner is sterile (e.g. vasectomy) should be considered to be of childbearing potential. Postmenopausal women who have fertilised eggs implanted are also considered to be of childbearing potential.

Acceptable methods of contraception may include total abstinence at the discretion of the Investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensures compliance. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 6 months after investigational drug discontinuation.

All women of childbearing potential must use a double-barrier method of birth control or practice continuous abstinence from heterosexual contact throughout the study and for six months after the end of the last treatment.

Appendix 8 – ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Administration and Amino Acid Co-Infusion Scheme; Examples of Infusion Methods

Granisetron 3 mg (or suitable alternative) is injected intravenously. The amino acid solution and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (22-25 mL) are administered in parallel by peripheral vein infusion in one arm at a constant infusion rate. The infusion with amino acids starts 30 minutes before the start of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion, and runs for a total of 4 h. The infusion is performed through pumps or any other infusion system. Table 11 shows the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration with amino acid co-infusion scheme.

Table 11: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate[1] Administration and Amino Acid Co-Infusion Schemes.

Preparation	**Starting Time (h)**	**Infusion Rate* (ml/h)**	**Duration (h)**
Granisetron 3 mg (or alternative)	0	Bolus	-
Amino Acids: 2 L solution	0	500	4
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate[1, 2]	0.5	50	0.5
Saline solution – (two pump method)[1]	1.0	50	0.5
Saline solution – (Flebo infusion method)[2]	0.5	50	1.0

[1] When the two pump method is used, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is pumped directly into the infusion line. The infusion line must be flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. [2] When the Flebo infusion method is used, a sodium chloride 9 mg/ml (0.9%) solution for injection, gravity flows directly into to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate solution, which is connected to the infusion line.

*This recommended rate of infusion may be reduced at the discretion of the physician.

Examples of Infusion Methods

Example 1: Two Pumps Method

Two infusion pumps (pump 1 and pump 2) infuse the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and amino acids solution. A standard infusion set is connected to each pump and allows the infusion of the two pharmaceuticals products (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and amino acid solution) independently one each other.

The infusion set consists of:

1- a pre-filled, sterile container (glass bottle) of physiological solution that permit the fluid to flow one drop at a time, making it easy to see the flow rate (and also reducing air bubbles);

2- a long sterile tube with a clamp to regulate or stop the flow;

3- connectors to allow "piggybacking" of another infusion set onto the same line. This second line is connected to the amino acids solution bottle (pump 1) and to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate vial (pump 2).

By means of a 3 way cock another sterile tube guarantees the connection of the tube coming from the physiological solution bottle and the tube coming from the second bottle (amino acid solution in the case of the pump 1 or ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in the case of pump 2) to the device (the infusion pump) that allows precise control over the flow rate and total amount of products delivered. The confluence of the two fluids that flows into the l vein infusion tube is allowed by another cock.

A scheme of the pumps infusion method is shown in Figure 1.

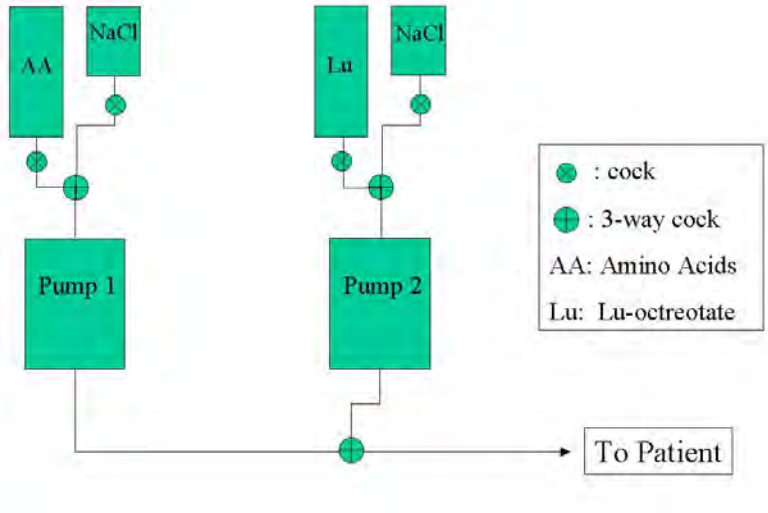


Figure 1: Two Pumps Infusion Method.

Example 2: Flebo Infusion Method

The Flebo infusion method is schematically presented in Figure 2. It consists of a container for a vial of radiopharmaceutical made of polymethyl methacrylate with a cavity capable of containing the vial of radiopharmaceutical, and of a lid screwed onto the receptacle for closing the container, said lid presenting a central through-hole. A set, in combination with this container with the vial of radiopharmaceutical, consisting of a bottle of saline solution and two infusion catheters, enhances the radioprotection during the infusion of a radiopharmaceutical in an infusion operation.

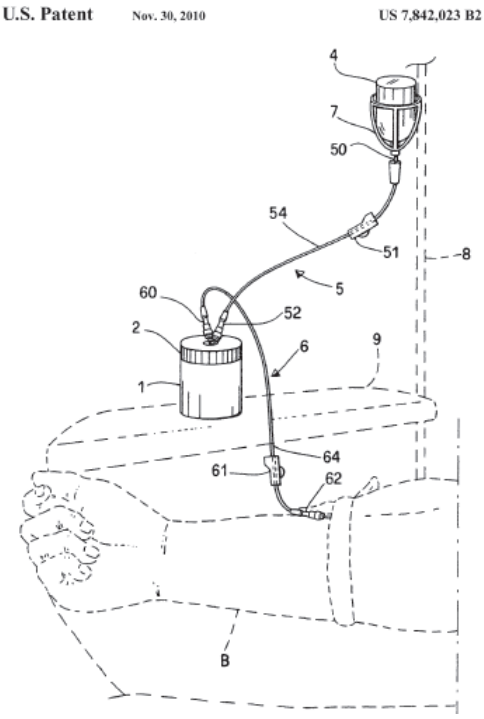
In an infusion operation, saline bottle **4** is conventionally suspended in a cradle **7** attached to a stand **8**, equipped with a support shelf **9**. The first infusion catheter is inserted with the first needle **50** in the cap of bottle **4**, while the second needle **52** is inserted, via flared portion and central through-hole of lid **2**, into the cap of radiopharmaceutical vial **3** in such a way as not to be immersed in the pharmaceutical.

The second infusion catheter **6** also has its first needle **60** inserted via flared portion and through-hole of lid **2**, into the cap of the vial of radiopharmaceutical, whereas the second needle **62** is inserted in the brachial vein B of a patient. The first needle **60** is long enough to touch the bottom of the vial of radiopharmaceutical, where it must be held in place for the complete extraction of the radiopharmaceutical, as shown in Figure 2B.

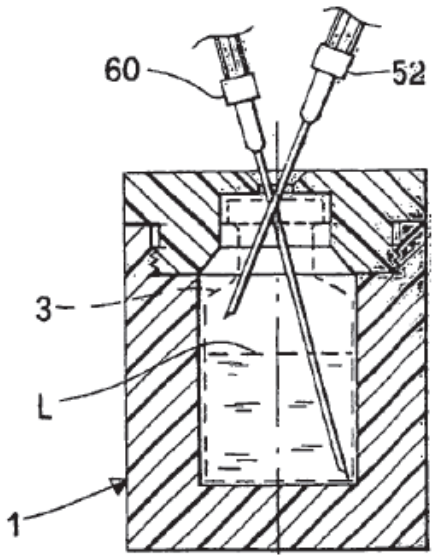
The provision of flow via the bottle of saline solution **4**, the first infusion catheter **5**, vial **3** in container **1-2**, and the second infusion catheter **6** allows the radiopharmaceutical to be delivered by gravity. The saline solution is fed from bottle **4** into radiopharmaceutical vial **3** with flow regulation by means of flow-regulator **51**. The influx of saline brings about an increase in pressure in radiopharmaceutical vial **3** which

has its entire contents aspirated by the second infusion catheter **6**, the flow rate of which is regulated by flow-regulator **61** (See US Patent 7842023) .

A.



B.



C.

D.

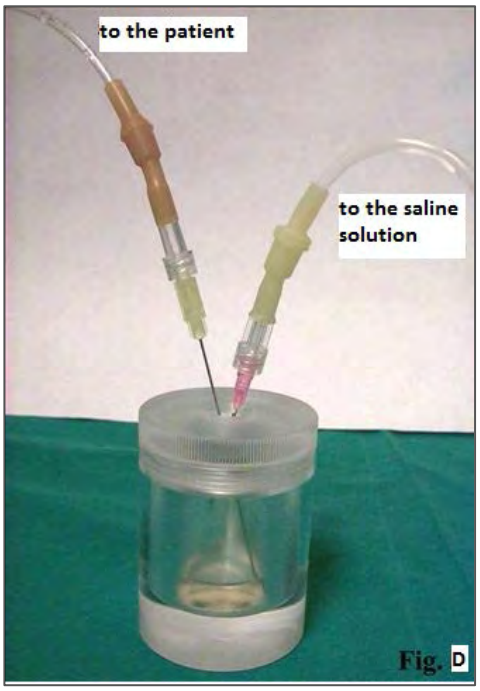


Figure 2: Flebo Infusion Method (A) Showing Operations Details (B, C, D)

Appendix 9 – CT and MRI Imaging Protocols

The imaging protocols are performed according to Revised RECIST Criteria, Version 1.1 (Eisenhauer EA et. al., 2009, see Protocol §Appendix 2).

CT is the preferred imaging modality for assessing RECIST Criteria. The use of MRI should be limited to additional investigation uses only (such as liver studies). In the event that MRI is used for RECIST Criteria analysis, it must be used throughout the relevant study period, using the same acquisition protocol including that used at inclusion and baseline.

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

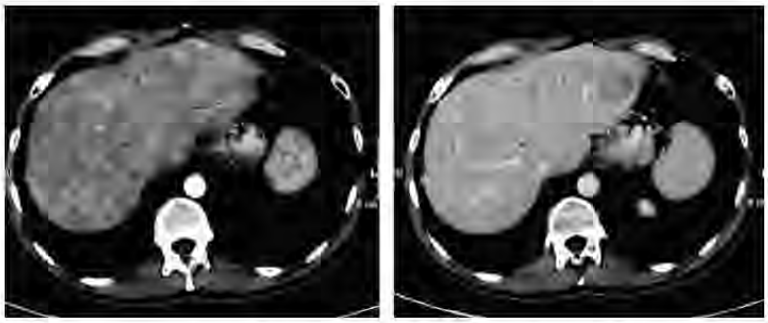


Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

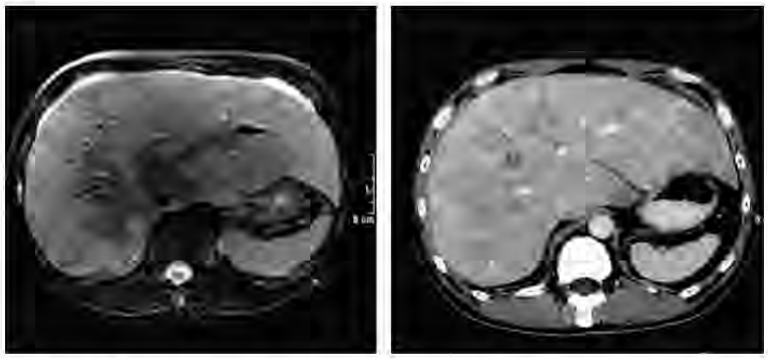


Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials.*

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

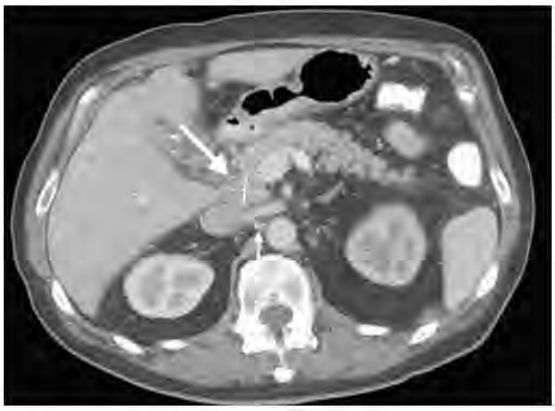


Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

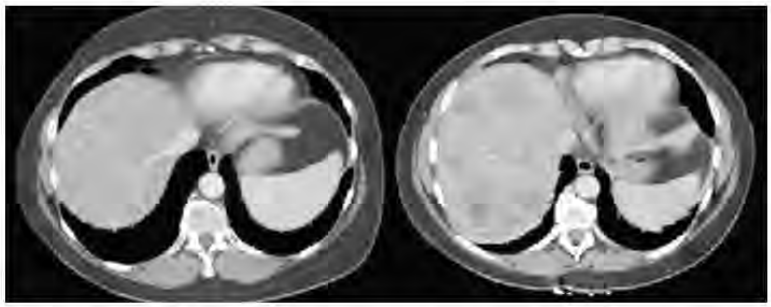


Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

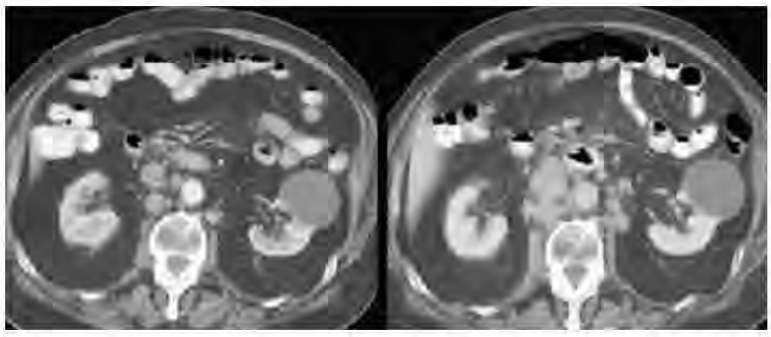


Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(*continued on next page*)

continued

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

Appendix 10 – Dosimetry and Pharmacokinetics Study: Manual for Procurement, Storage and Handling of Blood and Urine Samples

Blood samples (1 mL) will be collected in heparinized tubes just before administration of the therapeutic dose and then at the following time intervals:

two time-points during the infusion (one in the middle of infusion and one just before the end of infusion), then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, then twice a day on Day 2, Day 3, Day 4 and Day 8, e.g. 16 and 24 h (Day 2), 40 and 48 h (Day 3), 60 and 72 h (Day 4) and optionally 156 and 168 h (Day 8) (see Protocol §Section 6.6).

The blood samples will be counted with a COBRA-Packard auto-gamma counter system (Packard, Meriden, Conn., USA) or similar system.

A urine sample will be collected within 24 h prior to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration, preferable just prior to the infusion of study drug (0 h sample) to achieve bladder emptying before study drug administration. Quantitative urine collections will be obtained for the periods 0-1 h (immediately post start infusion to 1 h post start infusion), 1 h – 4 h, 4 h – 16 h, and 16 h – 48 h post start infusion.

Quantitative urine collection samples will be weighed and 1 mL of each of them will be counted with a COBRA-Packard auto-gamma counter system (Packard, Meriden, Conn., USA) or similar system.
Moreover, a 10 mL aliquot will be withdrawn from each urine collection sample. Urine samples will be processed and further analyzed by HPLC according to validated procedures in order to examine the chemical status of the radionuclide in urine.

The collection of biological samples (blood and urine) will be recorded in the time-schedule template shown in §Appendix 11.

Appendix 11 – Dosimetry and Pharmacokinetics Study: Time Schedule for Biological Samples

Patient ID: _____

weight: _____kg; height:_____cm; Haematocrit:_____%

Date of injection_____ time: _____

Administered activity (background corrected) _____GBq

BLOOD SAMPLES - 1 ml/sample			**URINE COLLECTION - COMPLETE**		
n.	**Time**	**date**	**n.**	**Time interval**	**date**
1	Before treatment	Day 1	1	Before treatment	Day 1
2	Half infusion	Day 1	2	Up to 1 h p.i. (before image n.1)	Day 1
3	End of infusion	Day 1	3	From 1h p.i. (after image n.1) → 4 h	Day 1
4	20 min p.i.	Day 1	4	4 h p.i. → 16 h p.i.	Day 1
5	40 min p.i.	Day 1	5	16 h p.i. → 48 h p.i. (before image n.4)	Day 2-3
6	1 h p.i.	Day 1			
7	2 h p.i.	Day 1			
8	4 h p.i.	Day 1			
9	8 h p.i.	Day 1			
10	16 h p.i.	Day 2			
11	24 h p.i.	Day 2			
12	40 h p.i.	Day 3			
13	48 h p.i.	Day 3			
14	60 h p.i.	Day 4			
15	72 h p.i.	Day 4			
16	156 h p.i.*	Day 8			
17	168 h p.i.*	Day 8			

URINE COLLECTION: Please ask the patient to void their bladder BEFORE the acquisition of each scintigraphic image, especially within the first 24 h post injection, when the activity elimination rate is high.

***optional (see Protocol §Section 6.6)**

Appendix 12 – National Cancer Institute Common Terminology Criteria for Adverse Events

This is an extract of the whole document. For the complete CTCAE guide, version 4.0, please refer to the following website: *http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf*

Blood and lymphatic system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.					
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node.					
Spleen disorder	Incidental findings (e.g., Howell-Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the spleen.					
Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death

Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach.					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents.					
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).					

Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Lipase increased	>ULN- 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <800 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increase	-	>4000/mm3 – 20,000/mm3 10e9 /L	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, Bulk, or odor, steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-

Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; Limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - < 10% from baseline	10 - <20% from baseline	<=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to < 10% from baseline; Intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube Feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Metabolism and nutrition disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

Appendix 13 – Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 14 – Radioprotection Precautions for Patients Treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

- **Technical Data**

The principle characteristics of lutetium-177 (^{177}Lu) are specified in Table 1 (from *Les principales caractéristiques du 177 lutetium (^{177}Lu)* and *Guide Pratique Radionucléides & Radioprotection*, D. Delacroix, J.P. Guerre, P. Leblanc, EDP Sciences, 2004).

Table 1: Emissions of ^{177}Lu

$^{177}_{71}$Lu — *Période :* 6,71 jours — *Activité massique :* 4,07.10^{15} Bq.g^{-1} — *Groupe de risque :* 4

Lutétium - 177

Principales émissions

	Gamma / X		Beta (Emax)		Electrons		Alpha	
	E (keV)	%	E (keV)	%	E (keV)	%	E (keV)	%
E1	55	5	208	11	6	9		
E2	113	6	384	9	48	5		
E3	208	11	497	79	110	9		
% omis		5		< 1		4		

Seuils d'exemption

Quantité en Bq	1.10^{7}
Concentration en Bq.g^{-1}	1.10^{3}

Transport (Bq)

A1	3.10^{13}
A2	7.10^{11}

^{177}Lu is generally produced using enriched ^{176}Lu placed in a reactor, following a reaction of the type [^{176}Lu n,γ ^{177}Lu]. This reaction results the production of a small amount of ^{177}Lu meta-stable (^{177m}Lu) which varies according to sources between 10^{-5} and 4×10^{-4} per MBq of ^{177}Lu produced. The characteristics of this radionuclide are given in Table 2.

Table 2: Emissions of ^{177m}Lu

Période : 160,4 jours — *Activité massique :* 1,69.10^{14} Bq.g^{-1} — *Groupe de risque :* 3* — *Descendant :* Embr. = 0,215 ; T = 6,71 jours — $^{177m}_{71}$Lu/$^{177}_{71}$Lu

Lutétium - 177m / Lutétium - 177

Principales émissions

	Gamma / X		Beta (Emax)		Electrons		Alpha	
	E (keV)	%	E (keV)	%	E (keV)	%	E (keV)	%
E1	328	18	152	79	5	60		
E2	379	28	384	2	45	51		
E3	419	20	497	17	95	41		
% omis		450		12		60		

Seuils d'exemption

Quantité en Bq	-
Concentration en Bq.g^{-1}	-

Transport (Bq)

A1	-
A2	-

- **Recommendations**

Based on radiation exposure calculations employing whole body clearance data (Wehrmann C et al, 2007) and exposure rates at one meter at 24 h (7.5 ± 3.6 µSv/h, Dpt. of Nucl. Med. Erasmus MC Rotterdam), patients may be treated on an outpatient basis for an administration of 7.4 GBq of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. As a precaution, it is recommended that patients be kept in radiation isolation for a period of 4 – 5 hours following administration, and be allowed to urinate during that time, and before release. This precaution is deemed prudent because this is the method of elimination (approximately 50% by urination within the first 6 hours; Kwekkeboom et al, 2001). At the time of release, the patient is given written instructions which summarize the precautions to take, in order to keep the exposure to others below regulatory limits.

Appendix 15 – Recommended Precautions for Patients Treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera)

In accordance with the medical staff, you have agreed to receive a treatment using a radioactive medicine. We think that the potential activity of this medicine in treating your tumor is due to the radioactivity of this medicine; it is also for this reason that it is necessary to follow certain precautions in order to limit the exposure of the people around you and to avoid contaminating them with radioactivity.

Because of knowledge and experience in the field, it is estimated that the health risks to your family members and the general public are low because of the physical and radiopharmaceutical properties and the metabolism of the radiopharmaceutical. You must adhere to the following rules to maximize the safety of other persons. They are the result of many years of experience in the use of radioactivity in medicine, and they include recommendations by international organizations.

1- General rule

You must avoid close contact with people who live with you, and should try to keep a distance of at least one meter for 7-days after you receive Lutathera.

2- Use of toilets

Toilets must be used in a seated position, even for men. It is absolutely necessary to use toilet paper each time. It is equally important to wash your hands to avoid contaminating the door handles. It is strongly recommended to move your bowels every day and use a laxative if you need help. Furthermore, empty your bladder (urinate) every hour or so on the day you received treatment and for day after. Follow your doctor's advice on how much fluid to drink. Furthermore, after you receive treatment, empty your bladder (urinate) every hour on the day of treatment and for two more days after treatment. After expelling fluids, drink a glass of water. You can substitute juice or a sports drink as a means to replace expelled fluids. Follow any additional advice that your doctor provides on how much to drink.

3- Contact with children (less than 10 years old)

Because of the high sensitivity of children to radioactivity, it is strongly advised to limit contact to them to less than 15 minutes for each day while keeping a distance of at least 1-2 meters. It is strongly recommended that there be no contact with children who are less than 10 years old for 7-days after the administration of Lutathera.

4- The spouse and people in the family circle

It is strongly advised to sleep in separate beds at a distance of at least 1 meter. Embraces and sexual activity are not advised for eight days after the administration of Lutathera.

5- Seniors

Older people are less sensitive to radioactivity (between 3 and 10 times less than a middle-aged person). Therefore, the previous recommendations can be followed with a little more flexibility in the presence of the elderly.

6- Contact with pregnant women

Contact with pregnant women should follow the same restrictions recommended for children less than 10 years old.

7- Breastfeeding

Breastfeeding should be stopped because it is not compatible with a treatment using a radioactive product.

8- Pregnancy

Pregnancy must be excluded before the start of treatment. Any woman who has missed a period must be assumed to be pregnant until proven otherwise and alternative therapies which do not involve ionizing radiation must be then considered.

There is a potential risk that ionizing radiation by Lutathera could cause toxic effects on female and male gonads. Due to the nature of the compound, women of child-bearing potential, as well as males, must abstain from procreation (using effective contraceptive measures) during and up to 6 months after treatment with Lutathera.

9- People who need extra assistance

People who are confined to the bed or have reduced mobility will preferably receive assistance by a care provider. It is recommended that when providing assistance in the bathroom, the care provider wear disposable gloves for 2-3 days after administration. In the case of the use of special medical equipment such as catheters, colostomy bags bedpan, water nozzle, or anything that could be contaminated by your body fluids they must be emptied immediately in the toilet and then cleaned. If anyone helps you clean up vomit, blood, urine, or stool they should wear plastic gloves; the gloves should then be put in the specified trash plastic bag.

10- Dishes and bathroom accessories

For the first two days after your treatment wipes and/or toilet paper must be flushed down the toilet. Always wash your hands well after using the toilet.

It is strongly recommended to shower every day for at least the first 7 days after your treatment.

Try to flush any tissues or any other items that contain anything from your body, such as blood, urine and faeces down the toilet (at least for two days after the therapy). Items that cannot be flushed, such as menstrual pads and bandages, must be placed in specified plastic trash bags.

Wash your underwear, pyjamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of others in your household. Wash your items two or three times; use a standard washing machine; you do not need to use bleach and do not need extra rinses.

11- Trash recommendations

Keep the specified plastic trash bags separate from other trash; keep the bags away from children and animals.

A member of the Study Staff will tell you how and when to get rid of the specified plastic trash bag; you may be asked to bring the bag back to your treatment facility, or, after 70 days, the bag may be removed as other trash bags.

12- Professional activities

Lutathera could affect your ability to drive and to use machines, as dizziness has been reported as a common side effect.

If there is a risk of frequent contact and being in close vicinity to the public and/or with children, the activity must be temporarily suspended.

13- Use of public transportation

For short trips (less than 30 minutes), the precautions are minimum. If you ride with someone else, confirm she is not pregnant, and maintain a distance of >1 meter (use the back seat on opposite side of the driver). If you are able to do so, it is best to drive yourself.

14- Public activities

Avoid assisting in shows or public meetings which could expose third-parties for more than 30 minutes in the first week after your treatment.

Ask Your Doctor or a member of the Study Staff when:

- It will be safe to eat out, go shopping and attend events such as religious services, parties and movies;
- You will be able to return to work and to care for or teach others;
- It would be safe to donate blood;
- Special or longer distance travel is possible (Note: For up to 3 months or more following radioactive treatment you may set off radiation detectors at: national borders, airports, bus and train stations, tunnels, bridges, trash collection sites and even your place of employment); a member of your Study Staff will issue you a letter or card describing the therapy and the phone number of a person knowledgeable about your treatment (usually at the treating facility) in case local law enforcement agents need to check on this information; you should keep the letter or card containing the information with you whenever you are travelling for at least 3 months.

15- Hospitalization

In the case that an unplanned hospitalization occurs, it is important to notify your doctor.

There is a possibility that due to an excessive release of hormones following the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate your doctor may request that you stay in hospital overnight for observation and treatment if necessary, normally consists of intravenous fluids, corticosteroids and the correction of any chemical imbalance in the blood.

16- Domesticated animals

The lifespan of domesticated animals is much less than that of humans. Therefore, the effect of the radioactivity is less. It is not necessary to take any particular precautions. But do not sleep with pets (ask your doctor for how long) since your secretions may be carried away by the pet.

17- Emergency Care

You will get an information card or letter at the time of your treatment that will show the date, type and amount of radioactivity that you were treated with; carry this card with you at all times for at least 3 months following your treatment.

If you are in a traffic accident or any other medical emergency and require medical assistance during the first week after your treatment, you should show this card to the medical providers to let them know about the date and dose of your radioactive treatment.

18- Important information for patients on risks of radiation

Radiation exposure to others should always be As Low As Reasonably Achievable, a goal often abbreviated as ALARA. If you follow the above advice, the radiation from you to others is likely to be less than what they receive from radiation in nature over a year's time.

Please phone us if:

- you have any questions, and particularly if
- any of the above instructions cannot be followed and/or if
- you see anything that may have accidentally or unavoidably increased exposure of others to radiation.

19- Recommended Precautions after Lutathera treatments

		mCi (MBq) administered			
		200 (7400)	200 (7400)	200 (7400)	200 (7400)
		Precaution Days			
Night-time restrictions					
	Sleep in a separate (1 meter separation) bed from adults for days shown	8	8	8	8
	Sleep in a separate bedroom from pregnant partners, infants, or children for days shown	15	15	15	15
Day-time restrictions					
	You may return to work after days shown	8	8	8	8
	Maximize your distance (1 meter) from children and pregnant women for days shown.	8	8	8	8
	Avoid extended time in public places for days shown	8	8	8	8

Appendix 16 – Instructions for Shipment, Storage and Handling of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) Solution for Infusion

NAME OF THE MEDICINAL PRODUCT

Lutathera 7400 MBq, radiopharmaceutical solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lutathera is supplied as a ready for use radiopharmaceutical solution for infusion.

A vial contains 7400 MBq of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with a specific activity greater than 53 GBq/umol and with a radioconcentration of 370 MBq/mL at end of production.

PHARMACEUTICAL FORM

Sterile Solution for infusion.

Clear, colorless or slightly yellow solution.

PHARMACEUTICAL COMPONENTS

List of excipients

Acetic Acid

Sodium Acetate

Gentisic Acid

Ascorbic Acid

DTPA

NaCl

Water for Injection

Shelf life

72 hours after end of production.

Special precautions for storage

Store below 25°C.

Store in the original package for radioprotection purposes.

The product must be stored according to national regulations concerning radioactive products.

Nature and contents of container

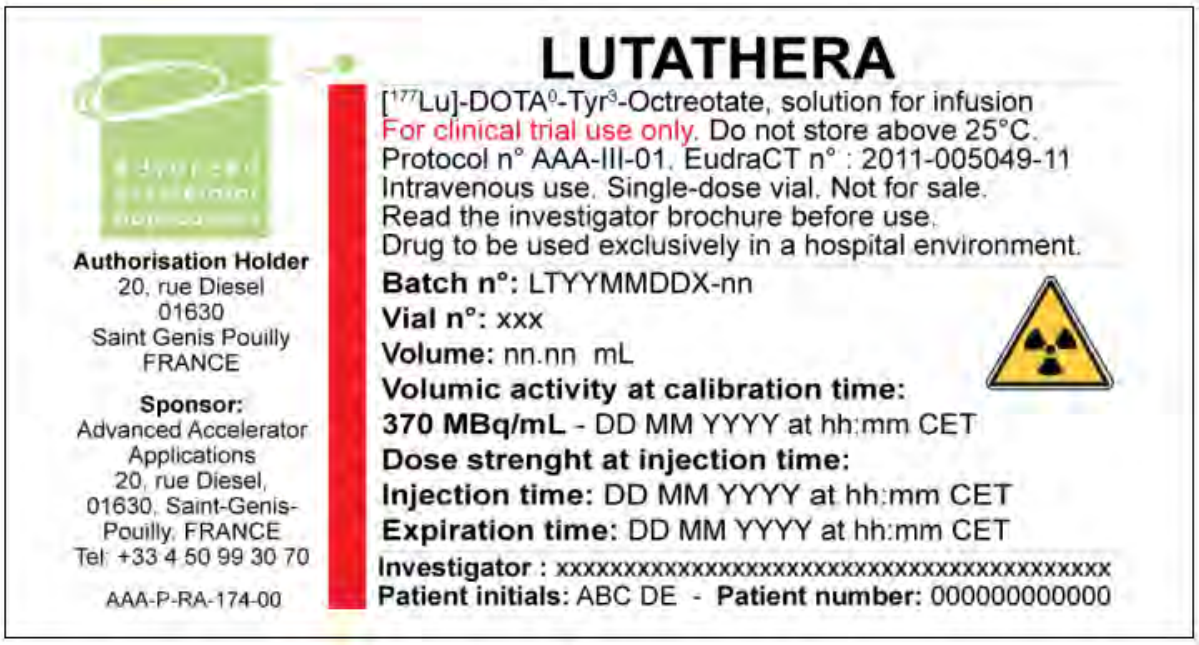
A 30 mL vial, colourless Type I glass, closed by a rubber stopper and sealed by an aluminum cap. One vial contains 22 to 25 mL of solution. The vial is inserted into a lead shielded container protected by a plastic sealed container closed in a Type A package (according to the Accord Dangereuses Route agreement or ADR).

Type A container

Plastic container

Lead container inserted in the plastic container.

The Type A container, the sealed Plastic container, the Lead container inset in the plastic container, and the 30 ml vial are all labeled with the product information. The labels are compliant with the annex 13 of Current GMP regulations. An example of the label is shown below.



Special precautions for disposal and other handling

The administration of radiopharmaceuticals creates risks for other people from external radiation or contamination from spills of urine, vomit, etc. Radiation protection precautions must be taken according to national regulations.

Radioactive waste disposal must be according to relevant national and international regulations.

The disposal of any unused product must be according to local requirements as well as applicable national requirements.

INSTRUCTIONS FOR THE USE OF Lutathera (7400 MBq)

Lutathera is delivered in monodose vials.

The integrity of the Lutathera package must be inspected before use and the product vial total radioactivity measured using a dose calibrator (or activimeter). The residual radioactivity in the vial should be determined after the product is administered.

The activimeter or dose calibrator must be periodically calibrated by means of a standard source of Lu-177. If this procedure is not in place at the clinical site, Advanced Accelerator Applications will provide a calibration protocol and will ship a source of Lu-177 to perform the calibration.

Lutathera does not need to be manipulated before administration because it is delivered as a ready to use monodose vial.

The vials must not be opened. After disinfecting the stopper, the vial must be connected to the needle of the infusion system (§Appendix 8: Example 1 (Two Pumps Method) or Example 2 (Flebo Infusion Method)).

The 'Two Pumps Method' and the 'Flebo Infusion Method' are the recommended infusion systems for this trial. However, if a syringe infusion system is available at the centre this can be used, provided that the dose calibrator (activimeter) calibration is done for both the vial and the syringe. In addition, the radioactivity must be measured, before and after the infusion, in both the vial and the syringe. After disinfecting the stopper, the solution must be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle. The filled syringe in then connected to the infusion system.

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes.

Disposal of radioactive waste must be according to relevant national and international regulations.

A product batch release certificate will be sent to each center receiving the product. The manufacturing site's Qualified Person provides a product batch release certificate to the clinical site to guarantee that the product is suitable for injection and that it meets the specifications indicated in the Investigation Medicinal Product Dossier (IMPD). The product is not to be used before the site has received the release certificate. The product is not to be used if the site is notified that the product batch has not been released for use, or if the product batch has been recalled because of fabrication defects.

Lutathera must not be used after the expiry date which is stated on the label of the outer package.

Product receipt, tracking and administration data will be recorded using a informatics system provided by the CRO. In the event that the product is not administered for any reason, AAA will be notified, and a disposal verification record will be provided.

Quality Control of Lutathera

Minimum Quality Control is needed at the site, before the administration of Lutathera. The site will confirm that the product received has the correct release certificate. The results will be recorded. Additionally, the site's measurement of total radioactivity and product administration data (start and stop time, and residual radioactivity not administered) will also be recorded.

Lutathera storage requirements

Lutathera must be stored at a temperature below 25°C (77° F) but not lower than 3 °C (37.4 °F), in its original package for radioprotection purposes, according to national regulations concerning radioactive products.

Shelf life: 72 hours after end of production.

The disposal of any unused product or waste material must be according to local and national requirements.

Further information

The clinical site must request the required Lutathera dose for each patient at least 10 days before the scheduled treatment. A product order must be placed with AAA through the informatics system provided to each Investigator by the CRO. The administration date of the product for each patient should not be confirmed until the clinical site has received both an order confirmation and a production dose confirmation from AAA. The scheduled date of treatment must be accepted by AAA so that the Manufacturer's Production Planning matches patient treatment schedules.

Appendix 17 – Randomization Procedure of Patients after Enrollment.

Patient randomization will be performed according to a centralized stratified permuted block randomization scheme with a balanced ratio (1:1) between the two treatment arms, stratifying for the following factors; 1) OctreoScan® tumour uptake score (Grade 2, 3 and 4) (the highest Octreoscan® score measured among all the target lesions will be used for stratification purpose, see §Appendix 5); and 2) length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤6 and > 6 months).

Appendix 18 – Staging of Midgut Carcinoids by TNM criteria (Rindi G et al, 2007)

TNM classification for endocrine tumors of lower jejunum and ileum

T-primary tumor
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor invades mucosa or submucosa and size ≤1 cm
- T2 Tumor invades muscularis propria or size >1 cm
- T3 Tumor invades subserosa
- T4 Tumor invades peritoneum/other organs

For any T add (m) for multiple tumors

N regional lymph nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M Distant metastasis
- MX Distant metastasis cannot be assessed
- M0 No distant metastases
- M1 Distant metastasis

Disease staging for endocrine tumors of lower jejunum and ileum

Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

TNM classification for endocrine tumors of the appendix

T-primary tumor
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor ≤1 cm invading submucosa and muscularis propria
- T2 Tumor ≤2 cm invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix
- T3 Tumor >2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix
- T4 Tumor invades peritoneum/other organs

For any T add (m) for multiple tumors

N regional lymph nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M Distant metastasis
- MX Distant metastasis cannot be assessed
- M0 No distant metastases
- M1 Distant metastasis

Disease staging for endocrine tumors of the appendix

Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

TNM classification for endocrine tumors of colon and rectum

[the anatomical sites to be considered for the purpose of enrollment in this trial are only: caecum, ascending and transverse colon (first two thirds)]

T-primary tumor
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor invades mucosa or submucosa
  - T1a size <1 cm
  - T1b size 1–2 cm
- T2 Tumor invades muscularis propria or size >2 cm
- T3 Tumor invades subserosa/pericolic/perirectal fat
- T4 Tumor directly invades other organs/structures and/or perforates visceral peritoneum

For any T add (m) for multiple tumors

N-regional lymph nodes
- NX Regional lymph node status cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M-distant metastases (subspecification as in small bowel)
- MX Distant metastasis cannot be assessed
- M0 No distant metastases
- M1[a] Distant metastasis

[a] M1 specific sites defined according to Sobin LH and Wittekind Ch

Disease staging for endocrine tumors of colon and rectum

Stage

Disease stages	T-primary tumor	N-regional nodes	M-distant metastasis
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

Appendix 19 – Determination of LUTATHERA Administered Radioactivity

The total amount of radioactivity administered to the patient is determined by measuring the radioactivity present in the LUTATHERA (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, Infusion Solution) Vial before and after administration. The procedure is as follows:

A. Measurement of LUTATHERA Vial radioactivity *before* LUTATHERA **administration:**

1) remove the LUTATHERA Vial from the original package;
2) place the LUTATHERA Vial in the dose calibrator (activimeter) chamber;
3) select the Lu-177 setting on the dose calibrator;
4) press the "measure" button (or equivalent function button);
5) record the measured radioactivity, and the time of measurement in the appropriate electronic Case Report Form (eCRF);
6) remove the LUTATHERA Vial from the dose calibrator chamber;
7) return the LUTATHERA Vial to its original package or prepare the Vial for patient administration.

B. Measurement of LUTATHERA vial radioactivity *after* LUTATHERA **administration:**

1) remove needles and tubing attached to the LUTATHERA Vial (NB: The investigator must confirm that there is no significant residual radioactivity remaining in delivery needles and tubing after administration (< 0.1% of original Total Radioactivity in LUTATHERA Vial);
2) if the dose calibrator is in a different location, place the LUTATHERA Vial in the original package so that the material can be moved safely – otherwise go to step 4;
3) remove the LUTATHERA Vial from the original package;
4) place the LUTATHERA Vial in the dose calibrator chamber;
5) select the Lu-177 setting on the dose calibrator;
6) press the "measure" button (or equivalent function button);
7) record the measured radioactivity, and the time of measurement in the appropriate eCRF;
8) remove the LUTATHERA Vial from the dose calibrator chamber and dispose according to national and local regulations for disposal of radioactive waste;

C. Calculation of Total Administered and Residual Radioactivity:

1) Total Administered Radioactivity
   = (amount of radioactivity in LUTATHERA Vial before administration minus amount of radioactivity in LUTATHERA Vial after administration) times vial geometry correction factor
   $$= (A.5 - B.7)\ x\ Correction\ Factor;$$
2) Residual Radioactivity = amount of radioactivity remaining in LUTATHERA Vial after administration times vial geometry correction factor
   $$= B.7\ x\ Correction\ Factor;$$
3) record Total Administered Radioactivity and Residual Radioactivity in the appropriate sections of the patient's eCRF.

Statistical Analysis Plan

Study AAA-III-01

Version 1.0

15-JAN-2015

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Table of contents

List of Abbreviations

Abbreviations	Description of abbreviations
5-HIAA	5-Hydroxyindoleacetic Acid
^{90}Y	Yttrium-90
^{177}Lu	Lutetium-177
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALAT/ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASAT/AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CgA	Chromogranin-A
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contract / Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of Response
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
Erasmus MC	Erasmus Medical Center, Rotterdam, NL
FAS	Full Analysis Set
FDA	Food and Drug Administration
GlycoHb	Glycosylated Haemoglobin (haemoglobin A1C)
Hb	Haemoglobin
hpf	High-Power Field (microscopic exam)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRC	Independent Review Committee

I.V.	Intravenous
KPS	Karnofsky Performance Score
LAR	Long Acting Release
LDH	Lactic Dehydrogenase
LLN	Lower Limit of Normal (according to local laboratory normal values)
lpf	Low-Power Field (microscopic exam)
LVEF	Left Ventricular Ejection Fraction
MCV	Mean Corpuscular Volume (red blood cells)
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute (USA)
NET	Neuroendocrine Tumour
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDF	Adobe® Portable Document Format
PFS	Progression Free Survival
PFS2	Progression Free Survival (Second Progression)
PLT	Platelets
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
PT	Preferred Term
PV	Protocol Violator
QoL	Quality of Life
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
s.c.	Subcutaneous
SOC	System Organ Class
SOP	Standard Operating Procedure
SWOG	South West Oncology Group
TTP	Time to Tumour Progression

ULN	Upper Limit of Normal (according to local laboratory normal values)
WBC	White Blood Cells
WHO-DRL	World Health Organization – Drug Reference List
WI	Working instruction

1 Overview and investigational plan

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy and methodology to be used to conduct the analysis of the data generated in the NETTER-1 clinical trial. The purpose of the SAP is to ensure the appropriate analysis of the study data by using pre-specified statistical approaches to the analysis prior to the database lock.

This SAP is a detailed technical extension of the clinical Study Protocol and follows the principles of the International Conference on Harmonization (ICH) guidelines E3, E6 and E9 and the relevant Working Instructions (WIs) and Standard Operating Procedures (SOPs).

This SAP is based on the current version of the NETTER-1 clinical study protocol, version 4.1, dated June 5, 2014.

1.1 Study design and randomization

This is a multicenter, multinational, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

In this study, treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) is compared to a treatment with high dose (60 mg) of Octreotide LAR. In case patients in either arm experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, short-acting Octreotide s.c. rescue injections are allowed.

Objective tumour response in both arms is assessed every 12±1 weeks from the randomization date according to RECIST Criteria until progression is centrally confirmed. The baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date. In order to provide a consistent CT/MRI scan time-point between the two arms of the study it may be necessary for the site to repeat the baseline CT/MRI scan immediately before randomization if the CT/MRI time-point is greater than 4 weeks before randomization to provide more recent and protocol-compliant lesion data.

Two hundred thirty patents patients (115 patients per treatment group) are to be recruited and randomized from approximately 35 EU sites and 15 USA sites, and randomly assigned to open-label treatment (see study protocol Appendix 17).

Patient randomization is performed according to a centralized stratified permuted block randomization scheme with a balanced ratio (1:1) between the two treatment arms, stratifying for the following factors:

1) somatostatin receptor scintigraphy (OctreoScan®) tumour uptake score (Grade 2, 3 and 4): the highest Octreoscan® score measured among all the target lesions (for target / non-target / measurable lesions definition, see study protocol Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1) will be used for stratification purpose (see study protocol Appendix 5);

   and

2) length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤6 and > 6 months).

Study main features:

1. Total number of randomized patients: 230
2. First patient randomized: Q3 2012
3. Pre-defined accrual period: 18 months
4. Expected last patient in: Q4 2014
5. PFS primary analysis occurs at 74 evaluable and centrally confirmed disease progressions or death events
6. Long term follow-up: 5 years from date of randomization of the last randomized patient
7. End-of-study (EOS): when 158 deaths are recorded or when 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first.
8. OS primary analysis point occurs at 158 deaths or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

Dosimetry, PK, ECG substudy:

A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites to provide a complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. To prevent biasing the results obtained from patients randomized in the main study, the patients enrolled in the substudy according to the Study Protocol version 4.1 (enrolled without randomization) will not be considered in the primary analysis of the main study groups. The statistical analysis of this substudy is described in a separate statistical analysis plan (SAP).

1.2 Objectives

1.2.1 Primary objective

The primary objective of the study is to compare Progression Free Survival (PFS) after treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, well-differentiated midgut neuroendocrine tumours.

1.2.2 Secondary objectives

- To compare the Objective Response Rate (ORR) between the two study arms;
- To compare the Overall Survival (OS) between the two study arms;
- To compare the Time to Tumour Progression (TTP) between the two study arms;

- To evaluate the safety and tolerability of ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate;
- To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire (Appendix 3 of the study protocol).

1.2.3 Exploratory objectives:

- To explore the correlation of toxicity outcomes and administered radioactivity corrected for body weight and body surface area;
- To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;
- To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients (this objective will not be investigated in this Statistical Analysis Plan but in a separate SAP for the substudy analysis);
- To explore the correlation of clinical efficacy outcomes with OctreoScan® tumour uptake score;
- To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP);
- To evaluate the Duration of Response (DoR) in the two study arms;
- To evaluate the Time to Second Progression (PFS2) in the two study arms.

1.3 Determination of sample size

A Phase I/II clinical trial conducted at the Erasmus MC ("A phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate in patients with somatostatin receptor positive tumours") provided supportive information on the efficacy of treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate in patients with midgut carcinoid tumours. In this study, an objective tumour response rate of 23% (CR + PR according to SWOG Criteria), at 3 to 4 months after the last treatment, was determined in patients treated with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate, based on an analysis in 188 patients with carcinoid tumours (Kwekkeboom DJ et al., 2008).

A retrospective, independent verification of the Erasmus MC Phase I/II study source data and a statistical analysis of the study results have been conducted to support the initiation of the Phase III study. Within this assessment, a median PFS of 45 months with a 95% CI of 22-57 months was observed in a subgroup of 51 patients with midgut carcinoid tumours and with progressive disease within 12 months before entering the study (notably similar to the population in the present phase III Study). However, due to the small size of this subgroup, the median PFS has a large confidence interval (95% CI of 22-57 months).

With respect to the second arm (Octreotide LAR) of the Phase III study, there are only two relevant data sets for patients with midgut carcinoid tumours treated with Octreotide LAR available in literature: the PROMID study (Rinke A et al., 2009), with a median PFS of 14 months, and the RADIANT-2 study (Pavel M et al., data presented at the 8th Annual ENETS Conference, 9–11 March 2011, Lisbon, Portugal) with a median PFS of 11 months. In the PROMID study, patients with midgut carcinoid tumours were enrolled in a double blinded randomized two-arm trial. Patients in the control arm received a placebo, and patients in the treatment arm received 30 mg Octreotide LAR (Rinke A et al., 2009). In the RADIANT-2 study, patients with carcinoid tumours (diverse sites) were randomized for treatment in two comparator arms (Yao J et al., 2008). In one arm, patients received 30 mg Octreotide LAR alone, and in the other arm patients received Octreotide LAR plus Everolimus (Afinitor®).

For the purpose of calculating sample size in the NETTER-1 Phase III study, the results of the PROMID study were deemed to be the most applicable. This study was performed using a similar group of patients (progressive midgut carcinoid tumours at enrolment) whereas the RADIANT-2 study was not restricted to midgut carcinoid tumours. The PROMID study however, was conducted as a fully double-blind clinical trial, and it would be expected that such a study would not be significantly impacted by high patient dropout rates; rather the likely decision point for a patient to participate in such a study would be before enrolment – thus low impact on the trial for either dropout or intent to treat issues.

The subgroup of progressive midgut carcinoid patients, treated with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate in the Erasmus MC Phase I/II trial, were determined to have a median PFS of 45 months. This PFS estimate has substantial uncertainty because of the wide 95% CI of 22-57 months, and because of the relatively small number of evaluated patients. Therefore, a median PFS of 45 months for the ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate arm was considered to be optimistic. Consequently, a median PFS of 30 months (obtained by calculating the mean of the median PFS of the ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate arm and the median of 14 months for the Octreotide LAR arm, i.e. (45 months +14 months)/2 $\approx$ 30 months) was used to determine the sample size of this study. This more conservative value still represents a highly relevant clinical improvement in PFS compared to the control group (Octreotide LAR).

The number of patients to be randomized into the study was determined using the following criteria:

- ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate arm: median PFS of 30 months
- Octreotide LAR: median PFS of 14 months (PROMID study)
- Significance level 5% two sided (or 2.5% one-sided), power 90%
- Pre-defined accrual period: 18 months
- Follow-up period: 18 months (corresponding to the length of treatment period)

Based on these criteria, the study would need to randomize 124 patients (62 per arm), and would observe 74 PFS events during the course of the study. Therefore, the PFS primary analysis point

occurs when there are 74 evaluable and centrally confirmed disease progressions or death events in the study.

With respect to the Erasmus MC Phase I/II trial, all patients enrolled in the study received ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate treatment.

In order to ensure an adequately sized clinical trial, it is also necessary to have a realistic estimate for dropout rates. In the PROMID study, the dropout rate was predicted to be 10% before the start of the study. At the interim analysis (Rinke A et al., 2009), 9 patients (21%) out of 42 patients in the Octreotide LAR treatment arm had withdrawn from the study. Four of the dropouts were due to consent withdrawal, and five were due to adverse events. This contrasts with the dropout of only 3 patients in the placebo arm (2 withdrawn consents, and 1 switched treatment). Since the patients were unaware of what treatment they received, one can expect the dropout rate of the Octreotide LAR arm to be a lower limit for the present Phase III study, because there will likely be additional dropouts due to patient 'treatment awareness'. In addition, the treatment arm of the current Phase III trial will have a much longer time span of follow-up and time to progression, meaning that virtually all of the ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate treated patients will need to complete at least a full year follow-up, because very few are expected to progress during this period. Consequently, dropout rates (and intent to treat penalties) could also be expected to be high in this arm. For these reasons, a 20% dropout is anticipated.

Therefore, a total of 160 patients (80 patients in each treatment group) are necessary to control for an estimated 20% drop-out rate.

In addition, the sample size was also adjusted to allow detection of a statistically significant and clinically relevant difference in OS (80% power) between the two arms of the study. The determination of sample size for OS is based on the following assumptions:

- Octreotide LAR median OS: 32 months
- ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate median OS: 50 months
- Significance level: 5% two-sided
- Nominal power: 80%
- Pre-defined accrual period: 18 months
- Long-term follow-up: 5 years

Accordingly, 230 patients (115 patients in each treatment group) are to be randomized.

The median OS in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm is expected to be 50 months. The median OS reported in the Erasmus MC Phase I/II study was 47.3 months (95% CI [27.8 - 75.3]), for the subgroup of 51 patients with progressive midgut carcinoid tumours. More recent survival analyses in a similar population treated with PRRT have been reported. In 2012, Baum RP et al. reported an overall survival of 59 months from the first cycle of PRRT using ^{177}Lu-DOTATATE. Baum et al. (2014) also published the outcome of a retrospective analysis assessing the efficacy of PRRT in

1,000 patients with metastatic and/or progressive NETs using ^{177}Lu (n=331), ^{90}Y (n=170) or both (n=499). The median OS for all patients was 52 months from the start of the treatment. With regard to the used radionuclide, the following OS were reported: 24 months with ^{90}Y, 55 months with ^{177}Lu, and 64 months with both. There is however no indication of the used peptide, albeit this investigators group is known to use mainly DOTATOC and DOTATATE.

Additionally, Kunikowska J. et al (2013) published their results from 358 patients treated with PRRT with ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and ^{90}Y/^{177}Lu-DOTATATE collected from April 2004 to December 2010. They reported a median OS of 49.8 - 52.8 months in the group of patients treated with ^{90}Y/^{177}Lu-DOTATATE.

Finally, Paganelli G. et al. (2014), reported the most recent overall survival data from a study with 49 patients with advanced well-differentiated gastrointestinal NETs (79% midgut NETs) treated with ^{177}Lu-DOTATATE. The median OS was not reached at the time of publication, after a median follow-up of 38 months, ranging from 11 to 59 months.

Therefore, a median overall survival of 50 months is expected.

The median OS in the control arm (Octreotide LAR) is expected to be 32 months, as per the updated results reported in the RADIANT-2 study.

In the NETTER-1 study design, the length of the overall survival assessment period includes an 18-month accrual period, and a 5-year follow-up period. The 5-year follow-up is the predicted length of the study; however, the actual end-of-study will be based on death events (158), or after 5 years from the randomization date of the last randomized patient, whichever occurs first. The analysis of OS will be conducted at that time (158 deaths or 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first).

1.4 Modifications from the statistical section of the protocol

Not applicable.

2 Statistical and analytical procedure

The statistical analysis will be performed in accordance with the principles stated in the Consensus-Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonisation (ICH). The data will be analysed when the database is discrepancy free and locked.

2.1 Analysis populations

Before the database is locked and the statistical analysis is initiated, all problematic cases where evaluability remains unclear will be scrutinized by a Data Review Committee. The Data Review Committee will consist of the biostatistician assigned to the study, the study manager of the CRO responsible for the execution of the study, and one or more designated person from the Sponsor.

For the analysis of the study results, the following patient populations have been defined:

2.1.1 Efficacy populations

2.1.1.1 Full Analysis Set (FAS)

The Full Analysis Set consists of all patients randomized. Following the intent-to-treat principle, patients will be analysed according to the treatment they were assigned at randomization.

2.1.1.2 Per Protocol Set (PPS)

The Per Protocol Set (PPS) consists of all randomized patients, who had no major protocol violations. The PPS will be identified prior to database lock. Major protocol deviations refer to deviations that critically impact efficacy analysis materially, such as not following important inclusion/exclusion criteria (e.g. incorrect diagnosis), taking wrong study medication, etc…

A final independent assessment will enable confirmation of eligibility in the per-protocol analysis of the primary endpoint. Should a case not be selected for the PPS analysis, the reasons will be fully documented, and the non-selected case will nevertheless be included in the clinical study report. The reasons for non-eligibility include images of inadequate quality which casts doubt on the outcome of the readings, questionable decisions in selecting target lesions, or other reasons which impact the relevance of the information assessment within the frame of the clinical trial protocol.

2.1.2 Safety Set (SAF)

The Safety Set (SAF) consists of all randomized patients, who received at least one dose of study drug. Patients will be analysed according to treatment received.

The FAS will be used for all analyses of efficacy, demographics and baseline characteristics. The PPS will be used for the per-protocol analyses of primary objective and key secondary variables. The safety set will be used for all safety analyses.

2.2 Analysis variables and their statistical analysis

In general, for descriptive analyses of continuous data, number of non-missing values (N), number of missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum will be presented. Categorical data will be presented in frequency tables, i.e. as frequencies and percentages. Inferential statistics will be only performed for the primary variable and selected key secondary variables (i.e. ORR and OS).

2.2.1 Demographic and baseline characteristics

Demographic data determined at screening or baseline visit like age [years], gender (female, male), ethnicity (Caucasian/White, Black or African American, Asian, Hispanic, Other), height [cm], weight [kg], body mass index (BMI) [kg/m²] will be analysed.

Additionally, baseline characteristics of the underlying disease conditions such as primary tumour site, site of metastases, prior cancer surgery (in case of resections: site of resection, in case of ablation: type of ablation, i.e. cryotherapy or radio frequency), OctreoScan® Tumour Uptake, extent of overall tumour burden (at baseline), TNM criteria, disease stage, objective tumour response (sum

of diameters for target lesions, Overall tumour response) at screening and Karnofsky performance status (KPS) at screening will be investigated.

Demographic and other baseline patient data (including disease characteristics) will be summarized descriptively by treatment group for the FAS and the PPS. The summary of demographics will also be provided for the Safety Set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum will be presented. All background and demographic data will be listed in detail.

2.2.2 Efficacy variables and their statistical analysis

All inferential statistics will be interpreted at the 5% 2-sided level, with the exception of OS where the significance level is adjusted to 0.0085% to account for an interim analysis at the time of the final PFS analysis. The primary objective will be tested with a confirmatory intent. A method to control the family-wise type I error rate for the ORR and OS end-points is reported in Section 7.5.2 of the Study Protocol and in Section 2.2.2.2.3 of this SAP. All other efficacy variables will only be evaluated with an exploratory intent, i.e. all reported p-values for all other efficacy variables will only be interpreted in an exploratory sense.

2.2.2.1 Primary efficacy variable

The primary efficacy variable of this study is Progression Free Survival (PFS). PFS is defined as the time from randomization to documented centrally assessed disease progression, as evaluated by the Independent Review Committee (IRC), and death due to any cause. If a patient has no centrally assessed progression and has not died at the time of the primary end-point analysis, the patient will be regarded as censored in the context of a time to event analysis at the date of last evaluable tumour assessment.

Disease progression is determined by objective tumour response status using RECIST Criteria, Version 1.1. Objective tumour response and progression status are determined by comparing follow-up and baseline tumour measurements in all patients based on scans done every 12±1 weeks after randomization until the PFS Primary End-Point for the overall study is reached (74 PFS events). At that time patients who have been on study less than 76 weeks continue the same assessment schedule until Week 76 unless the patient progresses or dies.

If a patient is switched to another anti-tumour treatment prior to a confirmed progression event, the patient will discontinue study treatment, but will continue to be followed for overall survival. Information regarding the alternative anti-tumour treatment is to be documented in the CRF.

The following rules will be used to determine the event / censoring date as well as the status of event or censoring at the time of the analysis of the primary end-point PFS:

Situation	Date of Progression or Censoring	Outcome
No baseline tumour assessments	Date of randomization	Censored
Progression documented between scheduled assessment visits	Date of radiological assessment showing progression, if centrally confirmed	Event (Progressed)
No progression	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for undocumented progression and no additional scans are collected	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for toxicity or other reason with no additional scans	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for toxicity, but with continued scanning and subsequently documented progression	Date of radiological assessment (date of the scan) showing progression, if centrally confirmed	Event (Progressed)
New anti-cancer treatment started	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Death before first progression assessment	Date of death	Event (Death)
Death between adequate assessment visits	Date of death	Event (Death)
Death or progression after more than one missed assessment visit during the treatment phase*	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored

(*) In this trial, one missed assessment visit is defined as an assessment visit not occurring within 2 times the length between two assessment visits (i.e. 168 days following the last visit).

Sensitivity analyses for PFS will also be conducted,

- Assigning the event time to the next scheduled imaging time rather than the actual time, to correct for any difference in timing of scans,

- Ignoring new anti-cancer treatments started before progressive disease, instead of censoring the PFS at the time of starting any such treatments,

- Evaluating the impact of the presence and number of distant metastases,

- Evaluating the impact of the extent of tumour burden (centrally assessed),

- Evaluating the impact of the Karnofsky Performance status,

- Evaluating the impact of Ki67 value (centrally assessed),

- Evaluating the impact of ssr scintigraphy (uptake) grading (centrally assessed),

- Evaluating the impact of treatment compliance.

Acceptable treatment compliance is defined as follows:

- In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: a full cycle of 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (in 4 administrations of 200 mCi) or at least 80% of the dose has been administered. 30 mg Octreotide LAR is administered every 4 weeks as concomitant treatment for symptoms control. In case of dose reduction due to toxicity, at least 75% of the cumulative dose should have been administered. There should be no rule of compliance because of missed administrations of Octreotide LAR.

- In the 60 mg Octreotide LAR arm: one i.m. injection of 60 mg Octreotide LAR every 4 weeks or at least 80% of the scheduled dose has been administered till progression with a minimum of three doses.

A radiological assessment is considered as an adequate assessment if the RECIST response (as per IRC) is CR, PR, SD or PD. A response of NE or missing will not be considered as an adequate assessment.

As indicated in the Table above, the date of progression should be assigned based on the documented time of progression and not, for example, based on scheduled time of evaluation.

The final primary analysis on the PFS will be performed when the planned number of 74 evaluable and centrally confirmed PFS events or deaths is observed. Further details on the centralized imaging assessment process and evaluable cases are presented in the Imaging Charter (Appendix III).

The median point estimate and 95% Confidence Interval (CI) for the PFS will be calculated using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the PFS between the two treatment groups. The size of effect will be quantified by plotting the estimates of the survivor functions for PFS, estimating the hazard ratio, the median time-to-event and other percentiles (e.g. upper quartile, lower quartile), and the percentage of patients event-free at particular time-points (e.g. percentage of patients event-free at 1-year), based on semi-parametric procedures. Censoring patterns will be described appropriately (e.g. time-to-censoring).

The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of PFS at any time point (i.e.: S1=S2), against the two-sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2).

The primary efficacy analysis will be conducted for the FAS. In addition, the primary efficacy variable will be analysed for the PPS.

Additional PFS data are collected after the Primary End-Point has been reached as an effect of the continuation of the study in the treatment/assessment phase for patients who have not experienced tumour progression, or during the long term follow-up phase in case of discrepancy in the evaluation of the progression of disease (see Study Protocol Section 4.4.1). This additional PFS data will be collected and analysed descriptively. These additional PFS data will be collected up to the

moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

For sensitivity analysis, Cox's proportional hazards model will be used to assess the impact of covariates on the estimated hazard ratio. The model will first be fitted with a binary indicator for randomized treatment and all covariates that may potentially influence PFS. A step-down procedure will be used to eliminate covariates (other than treatment) that do not reach a significance level of 0.05. Multicollinearity will be explored, and the hypothesis of proportional hazards tested. These analyses are exploratory in nature and will serve to support the primary efficacy analysis.

2.2.2.2 Secondary efficacy variables and their statistical analysis

The secondary efficacy variables are:

- Objective Response Rate (ORR),
- Overall Survival (OS) and
- Time to Tumour Progression (TTP)

These key secondary efficacy variables will be reported using the FAS and PPS.

Duration of Response (DoR) and Time to Second Progression (PFS2) will also be analysed descriptively as secondary exploratory end-points. Both local and central assessment will be considered in these analyses.

2.2.2.2.1 Objective response rate (ORR)

Objective Response Rate (ORR) will be calculated as the proportion of patients with tumour size reduction of a predefined amount (the sum of partial responses (PR) plus complete responses (CR)) at the time of the statistical analysis. Response duration will be calculated from the time of initial response until documented tumour progression.

Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups will be compared by Fisher's exact test.

The comparison of ORR by Fisher's exact test investigates the null hypothesis that the two treatment group proportions are equal (i.e.: p1=p2) against the two-sided alternative hypothesis that the two treatment group proportions are not equal (i.e.: $p1 \neq p2$).

2.2.2.2.2 Overall survival (OS)

Overall Survival (OS) is defined as the time (number of days) from the date of randomization to the date of death due to any cause, or to the date of last contact (censored observation) at the date of data cut-off, and during the entire study period (i.e. the treatment phase + follow-up). OS will not be censored if a patient receives other anti-tumour treatments after the NETTER-1 study medication.

Survival data will be collected at the time of the analysis of the primary end-point (PFS), and updated 6-monthly thereafter until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

An interim analysis for OS will be performed at the time of the PFS analysis.

The median point estimate and 95% Confidence Interval (CI) for the OS will be provided using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the OS between the two treatment groups.

The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of OS at any time point (i.e.: S1=S2), against the two-sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2).

Sensitivity analyses will also be conducted, including:

- Impact of subsequent antitumor treatments after progression,
- Impact of the presence and number of distant metastases,
- Impact of the extent of tumour burden (centrally assessed),
- Impact of treatment compliance.

Patients who have withdrawn from the study, or who have progressed, may receive subsequent non-study PRRT (e.g. compassionate use programs or local radiopharmacy products). The impact of this treatment on OS will also be assessed.

2.2.2.2.3 Hierarchical Testing Procedure for PFS, ORR and OS

A gate-keeping testing procedure will be used to adjust the multiple testing for the primary variable and the family of secondary variables ORR and OS, (i.e. the family for the secondary variables will be tested only if the null hypothesis for the primary variable (PFS) is rejected at the 5% significance level).

The hypotheses for ORR and OS will be tested using a fixed sequence procedure approach to control for the family-wise error. No adjustment will be applied to TTP since this variable is not considered for regulatory purposes.

ORR will be tested first at the 5% significance level at the time of the final PFS analysis. If the ORR null hypothesis is rejected, then the OS hypotheses will be tested; otherwise no formal OS testing will be performed and the procedure stops.

OS analyses will be adjusted using O'Brien-Fleming spending function strategy with a 0.0085% significance level at the interim analysis (PFS final analysis).

The gate-keeping and fixed sequence testing procedures strongly control the family-wise type I error rate at 5%.

2.2.2.2.4 Time to tumour progression (TTP)

Time to tumour progression (TTP) is defined as the time (number of days) from randomization to objective tumour progression centrally assessed. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date).

TTP will be similarly analysed as the primary efficacy variable.

The median point estimate and 95% Confidence Interval (CI) for the TTP will be provided using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the TTP between the two treatment groups.

The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of TTP at any time point (i.e.: S1=S2), against the two-sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: $S1 \neq S2$).

2.2.2.2.5 Duration of Response (DoR)

Duration of Response is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. DoR will be analysed descriptively for each treatment group without comparison between groups.

2.2.2.2.6 Time to Second Progression (PFS2)

As additional secondary exploratory end-point (local RECIST assessment), the Time to Second Progression (PFS2) will be assessed in the two study arms. PFS2 is defined as the time from randomization to the time of disease progression or death due to any cause (on any treatment) following the first episode of disease progression.
After progression and during the long-term follow-up additional information on further anti-tumour therapies and scan assessments outcome (RECIST local evaluation) will be collected to be able to evaluate the Time to Second Progression (PFS2) in the two study arms.

PFS2 will be analysed descriptively for each treatment group without comparison between groups.

2.2.2.2.7 Correlation analyses

The following correlation analyses will be performed to assess prognostic value:

- the correlation of clinical efficacy outcomes (PFS, OS, TTP) with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;
- the correlation of clinical efficacy outcomes (PFS, OS, TTP) with OctreoScan® tumour uptake score;
- the correlation of clinical outcome (PFS, OS, TTP) with serum levels of alkaline phosphatase (AP);

- Impact on PFS, OS and TPP for both treatment groups will be correlated to objective tumour response, KPS, and other parameters of clinical relevance.

In addition, the relationship of toxicity outcomes with body weight and body surface area will be determined.

For this purpose, the correlation coefficient according to Pearson and the correlation coefficient according to Spearman are calculated depending on the respective type of the respective variable.

2.2.3 Additional efficacy variables and their statistical analysis

Within the scope of the overall tumour evaluation the following variables will be investigated:

- TNM criteria (T-Primary tumour lesions, N-Regional lymph nodes involvement and M-Distant metastasis),
- Disease stage (for endocrine tumours of lower jejunum and ileum) and
- Objective tumour response (Sum of diameters for target lesions, Response of target lesions, Response of non-target lesions, Overall tumour response).

For the parameter “Sum of diameters for target lesions”, descriptive statistics (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) of the observed values as well as for the changes from baseline value (i.e. pre-post differences) will be presented.

For all other variables, frequency tables presenting frequencies and percentages will be created by visit, overall and by treatment group.

The follow-up time and percentage of dropouts will be compared between the randomized treatment groups. Follow-up times are defined as the time between randomization and the latest recorded assessment (or death) date known for a patient. Follow-up times will be compared between the randomized treatment groups using an unstratified log-rank test, with the censoring indicator inverted (i.e. censored observations considered complete observations, and vice versa). The percentage of dropouts will be compared between the randomized treatment groups using a chi-squared test. These analyses will be used to interpret and/or support the primary efficacy analysis.

2.2.4 Multiplicity issues

A gate-keeping testing procedure will be used to adjust the multiple testing for the primary variable (PFS) and the family of secondary variables ORR and OS as described in section 2.2.2.2.3. The gate-keeping and fixed sequence testing procedure strongly control the family-wise type I error rate at 5%.

All other efficacy variables will only be evaluated with an exploratory intent, i.e. all reported p-values for all other efficacy variables will only be interpreted in an exploratory sense.

2.2.5 Safety variables and their statistical analysis

2.2.5.1 Adverse events

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject, which does not necessarily have a causal relationship with the study medication.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a study medication, whether or not causally related to the study medication. Symptoms of the underlying diseases are not considered AEs, except a significant change as assessed by the Investigator occurred.

All AEs, whether or not spontaneously reported by the patient, will be reported from the time the ICF is signed onwards until the PFS Primary End-Point is reached, then until Week 76 post randomization after the PFS Primary End-Point has been reached (i.e. 74 evaluable and centrally confirmed disease progressions), or until early termination.

An AE is defined as treatment-emergent, if its onset occurred after the first administration / intake of study medication or if an existing event worsened during the treatment phase relative to the pre-treatment state.

An AE is defined as baseline AE if its onset occurred after the date of Informed Consent and prior to the first administration / intake of study medication, i.e. if the information of an untoward medical occurrence is collected before starting the intake of study medication, this information will be listed as a pre-treatment AE (also called baseline AE) during statistical analysis. Baseline AEs are considered not to be treatment-emergent.

If date of onset is missing for an AE, it will be considered treatment-emergent unless there is information to suggest otherwise (for example, date of recovery is before date of first administration / intake of study medication).

Separate analyses will be performed for baseline AEs and treatment-emergent AEs.

Criteria for Defining the Severity of an Adverse Event: National Cancer Institute Common Terminology for Adverse Events (CTCAE), Version 4.0 will be used for determining the severity of adverse events.

During the long-term follow-up of the patient, the Investigator must report only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the Sponsor Safety Officer.

In general, adverse events will be attributed to the last treatment administered prior to the onset of the adverse event.

2.2.5.2 Serious adverse events

Definition of Serious Adverse Events:

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
  Note: "life-threatening" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly or birth defect;
- Requires in-patient hospitalisation or leads to prolongation of hospitalisation, with the exception of elective pre-planned hospitalisations.

2.2.5.3 Adverse events of special interest (AESI)

In addition to the Serious Adverse Events defined above, a set of potential risks deserve special attention even if they do not fulfil any of the seriousness criteria. These non-serious adverse events of special interest (AESI) occurring in patients enrolled in the investigational arm (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate) should equally be reported to the clinical trial pharmacovigilance department for safety analysis so long as they occur any time after enrolment including long term follow-up and will additionally be investigated within the scope of the safety analysis. The following types of pathology have been observed during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and AESIs related to these categories will be investigated:

- Haematotoxicity
- Secondary haematological malignancies such as MDS and acute myeloid leukaemia
- Nephrotoxicity
- Cardiovascular events

For further details please refer to section 8.7 of the study protocol.

2.2.5.4 Analysis of adverse events

All original AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ classes and preferred terms will be used in the analyses.

Type and incidence of AEs, as well as severity and relatedness to the study medication will be recorded and notified appropriately. Special attention will be given to those patients who prematurely discontinue the study or the study medication due to an AE, or who experience a severe AE, an SAE or an AESI. The investigator and the monitor will ensure that information on serious adverse events immediately notified with a SAE form are consistent with information on the same event contained in the e-CRF and in the source documents.

An Adverse Event (AE) is defined as *treatment-emergent AE*, if its onset occurred after the first use of randomized study medication or if an existing event worsened during the treatment phase relative to the pre-treatment state.

An AE will be defined as *baseline AE* if its onset occurred after the date of Informed Consent and prior to the first use of randomized study medication. Baseline AEs are considered not to be treatment-emergent.

In case of incomplete or missing data for the onset of an AE the following rules have to be applied:
- If the AE start day is missing, and if the AE month is equal to or greater than the month in which treatment was first administered, then the AE will be considered treatment-emergent.
- If the AE start day and month are missing and the AE year is equal to or greater than the year in which treatment was first administered, then the AE will be considered treatment-emergent.
- If the AE day, month, and year are missing, then the AE will be considered treatment-emergent.

In general, separate analyses will be performed for baseline AEs and treatment-emergent AEs.

For listings, the duration of each adverse event will be calculated as the difference between the onset date and the end date (in days), with the following formula:

AE duration = [AE stop date – AE start date + 1].

The number and percentage of patients with at least one AE will be determined, overall and separately for both treatment groups. The rate of patients with at least one AE will be compared between the two treatment groups using Fisher's exact test on an α-level of 5%.
These analyses will be performed for treatment-emergent AEs and additionally for treatment-emergent AEs leading to premature discontinuation, and for serious adverse events.

Summary statistics will also be provided according to the intensity and the causality assessment (i.e. relationship to study medication). Frequencies and percentages will be provided for all categories. Percentages are based on the number of AE episodes, i.e. the number of AE forms filled in, and not on the number of symptoms, as one AE might be coded with more than one code.

A summary of adverse events will be given according to the primary system organ class (SOC) and preferred term (PT). Frequencies and percentages will be given overall and by treatment group in separate columns for SOC followed by those for PT in alphabetical order. All AE symptoms are taken into account for calculations.

In addition, based on the preferred term, an overview will be presented for the most frequent AEs according to the intensity and the causality assessment (i.e. relationship) to the study medication. Frequencies of symptoms will be presented in descending order and will be determined for each PT together with the associated frequencies of categories. The number and percentage of patients with an AE of the respective PT will be given as well.

2.2.5.5 Laboratory safety variables

Laboratory assessments are performed at the investigational site, except serum CgA (CgA is evaluated by central laboratory).

The following laboratory parameters will be investigated and analysed:

(1) Haematology: White blood cells (WBC) with differential (i.e. Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils), Platelets, Haemoglobin (Hb), Haematocrit, MCV

(2) Blood chemistry: Blood urea nitrogen (BUN), Serum creatinine, Uric acid, Albumin, Total bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, CgA (centralized assessment), Haemoglobin A1C (GlycoHb), fT4, Calcium, Fasting blood glucose, Creatinine clearance (calculated by the Cockroft-Gault formula)

(3) Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (by dipstick test), 5-HIAA (on 24h urine collection), Pregnancy test (if applicable)

If there is more than one laboratory value available for one visit, for example in order to confirm laboratory values obtained at a scheduled visit, the first valid measurement will be used for analysis.

Laboratory values outside normal ranges will be listed and flagged. The following flags will be used:

'+': 'Higher than reference value'
'-': 'Lower than reference value'

The respective parameter and the flagged value will be presented patient-wise by visit together with the reference values.
Descriptive statistics including shift tables will be generated for all laboratory tests performed (haematology, blood chemistry, and urinalysis), i.e. descriptive summary statistics will be presented for all laboratory parameters by visit, overall and by treatment group, and within treatment groups overall and by gender. Mean, standard deviation, minimum, median, maximum, 16%- and 84%-percentiles and 68%-range will be determined. Summary statistics for the pre-post differences (value at visit after baseline – baseline value) and the percentage of differences [(value at visit after baseline – baseline value) / baseline value x 100] will be presented analogously. Abnormal laboratory test results will be tabulated, i.e. baseline laboratory values for each parameter and values for each parameter at all respective visits after baseline at which a safety lab was performed will be categorized whether they are within the respective normal range or outside. Abnormal values will be classified according to CTCAE classification version 4.0 [1]. Frequencies and percentages will be provided.

Shift analyses will be performed for each parameter separately for all treatment groups, i.e. the numbers and percentages for all combinations of categories will be calculated comparing baseline and end of study categories. Frequencies and percentages will be given by treatment group based on the respective total number.

The changes at any visit versus baseline (i.e. pre-post differences) and percent variations at any visit vs baseline (i.e. the percentage of changes versus baseline) of selected parameters (serum creatinine, creatinine clearance, total bilirubin, serum albumin, ALT, AP, Hb, WBC, neutrophils, lymphocytes, platelets) will be analysed and compared in the two study arms using the two-sided Wilcoxon Rank

[1] serum creatinine will be assessed under the Adverse Event term "Creatinine increased", not as "Acute kidney injury"

Sum test on an alpha-level of 0.05. For the investigation of possible trends of the changes from baseline and of the percent variations, a graphical presentation of boxplots will be given for these variables for both treatment arms at any visit.

Analogously, the following changes at any visit versus baseline (i.e. pre-post differences) and percent variations at any visit vs baseline will be analysed for

- creatinine and creatinine clearance in subjects with risk factors for renal function in the medical history
- total bilirubin, ALT, AP, and serum albumin in subjects with risk factors for liver function in the medical history
- Haemoglobin, WBC, neutrophils, lymphocytes, platelets in subjects with risk factors for haematological function in the medical history

For this purpose, the two-sided Wilcoxon Rank Sum test will be applied on an alpha-level of 0.05. For the investigation of possible trends of the changes from baseline and of the percent variations, a graphical presentation of boxplots will be given for these variables for both treatment arms at any visit.

Risk factors for renal function are:

- essential hypertension
- diabetes mellitus
- renal insufficiency (acute, chronic)
- proteinuria, haematuria
- history of urinary tract infections
- glomerulonephritis
- renal cysts
- kidney stones
- renal tumour (primary, secondary)
- ischemic cardiovascular disease
- hypercholesterolemia
- obesity (BMI > 30 kg/m^2)
- smoking
- previous treatments with platinum-based chemotherapy

Risk factors for liver function are:

- alcohol abuse
- chronic hepatitis
- obesity
- biliary obstruction / stones
- cystic fibrosis
- liver tumour (primary, secondary)
- metastasis from carcinoid
- previous chemotherapy

Risk factors for haematological function are:

- history of chronic anaemia, leukopenia, thrombocytopenia
- previous chemo- or radiotherapy
- haematological malignancy

- chronic autoimmune disease
- chronic inflammatory disease
- alcohol abuse.

2.2.5.6 Physical examination and vital signs

Physical examinations are performed by the Investigator, or qualified designee. All body systems will be examined and any relevant findings will be documented in the source documents and CRF. Physical examinations include heart rate, blood pressure and weight measurement (height will only be measured at baseline). Blood pressure and pulse rate will be performed after the patient rests for 5 minute. For each patient, all blood pressure recordings shall be made using the same type of instrument (i.e., manual BP recording vs. automatic digital vital signs monitor) on the same arm.

Significant findings that are present prior to baseline will be recorded in the medical history page, while changes during the study (including significant changes of the symptoms due to the underlying disease vs baseline, as reported in the diary card) will be recorded on the Adverse Event page of the e-CRF.

Physical examination results will be tabulated, i.e. frequencies and percentages will be presented and all abnormalities will be listed.

The normal ranges for the vital signs are as follows:

- Pulse rate: 40 – 100 bpm
- Systolic blood pressure (SBP): 100 – 150 mmHg
- Diastolic blood pressure (DBP): 45 – 90 mmHg

Descriptive statistics (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed values as well as for the changes from baseline value (i.e. pre-post differences) will be presented by visit, overall and by treatment group, and within treatment groups overall and by gender. Frequency tabulations with values within, below or above the normal ranges will be presented.

2.2.5.7 Electrocardiogram (ECG)

ECGs are recorded at baseline, immediately after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment procedure (following the completion of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion) and at the End of Study. ECGs will be taken also in the 60 mg Sandostatin® LAR Depot arm at the same time points, according to the schedule presented in Table 2 schedule. Standard 12-lead ECG is the preferred option, but if not possible, a 3-lead ECG is acceptable.

An ECG in triplicate (at least 5 minutes apart) is recorded with the patient supine, after 5 minutes rest, and not immediately after a meal. The parameters will be measured as a mean value of minimally 3 beats; the mean of each parameter has to be used for eCRF completion.

The Investigator/local cardiologist will note in the source documents (and in the e-CRF) whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs results and the

different ECG intervals measurements, calculating by the mean value of 3 measurements for each parameter. Relevant abnormalities at baseline will be recorded in the medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

The following ECG parameters will be investigated and analysed:

- Heart rate [beats/min]
- RR interval [msec]
- PR interval [msec]
- QRS width [msec]
- QT interval [msec]: QT intervals will be corrected for heart rate (more extended QT evaluation according to ICH E14)
- Interpretation of the ECG with the following categories: normal / abnormal, not clinically relevant / abnormal, clinically relevant

Descriptive statistics (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed values of heart rate (HR), RR interval, PR interval, QRS width and QT interval will be presented by visit, overall and by treatment group, and within treatment groups overall and by gender. QT intervals will be corrected for heart rate.

The changes of these ECG parameters from baseline value (i.e. pre-post differences) will be analysed descriptively analogous to the analysis of the observed values.
Frequency tabulations for the ECG interpretation (Normal / Abnormal, not clinically relevant / Abnormal, clinically relevant) will be presented.

2.2.5.8 Karnofsky performance score (KPS)

KPS forms must be completed by a medical professional at each treatment and follow-up visit, and before any current clinical information is given to the patient (cf. Study Protocol Appendix 13).

Descriptive statistics for KPS (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed values as well as for the changes from baseline will be presented overall and by treatment group.

2.2.5.9 Other safety variables

Pregnancy test: A pregnancy test (either on urine or blood) must be performed at baseline and within 7 days prior to each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment for every female patient of childbearing potential (cf. Section 8.9 and Appendix 7 of the study protocol).

Frequencies and percentages will be calculated for the “Female reproductive status” and the “Result of ß-HCG pregnancy test”.

Left ventricular ejection fraction/Cardiac ejection fraction: Patients with uncontrolled congestive heart failure (NYHA II, III, IV) are not eligible according to exclusion criterion 12. Patients with history of congestive heart failure who do not violate the exclusion criterion 12 will undergo an evaluation of their cardiac ejection fraction prior to baseline, preferably via gated equilibrium radionuclide ventriculography. The results from an earlier study (not exceeding 30 days) may substitute the evaluation at the discretion of the Investigator, if no clinical worsening is

noted. It is recommended that the patient's measured cardiac ejection fraction is ≥40% before randomization.

Descriptive statistics for LVEF (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed LVEF values will be presented overall and by treatment group.

Patient diary: Each patient is provided with a diary to record cancer related symptoms experienced and rescue medication (short-acting Octreotide s.c. injections) taken through the study.

Descriptive statistics for continuous variables of the patient diary (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) will be presented overall and by treatment group. For categorical variables of the patient diary, frequencies and percentages will be calculated overall and by treatment group.

2.2.6 Diseases and Medication

The following variables will be analysed:

- Previous and concomitant medications classified by ATC classes,
- Medical history and concomitant diseases classified by MedDRA preferred term (PT) and system organ class (SOC).

All medications taken at the start of screening until the PFS Primary End-Point is reached, then until Week 76 post randomization after the PFS Primary End-Point has been reached (i.e. 74 evaluable and centrally confirmed disease progressions), or early termination, are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.

Further anti-tumour treatments after progression must be reported until the end of the long term follow up period.

A medication counts as concomitant if it is still given after the first administration / intake of the study medication. If the application of a medication has stopped prior to the first exposure to the study medication, it counts as being previous. Medications will be analysed divided by previous and concomitant medication.

Previous and concomitant diseases will be defined analogously.

Previous and concomitant diseases will be summarized according to MedDRA coding.
The number of diseases and the number and percentage of patients with diseases will be determined overall and by treatment group. Indications with the same code count as often as they appear.

According to the MedDRA coding system, summary statistics will be calculated for disease classes, i.e. by MedDRA SOC and PT. The number and percentage of patients with at least one disease within the respective disease class will be presented by treatment group and also the number of diseases. Separate tables will be provided for previous and concomitant diseases.

Previous and concomitant medications will be analysed in the same way. Based on the ATC-coding summary statistics will be calculated for ATC-code levels. The number and percentage of patients with at least one medication within the respective ATC class will be presented by treatment group

and also the number of medications. ATC-level 1 and ATC-level 2 will be taken into account. The same summary statistics will be provided based on the substances.

2.2.7 Study termination

Premature study termination as documented in the "End of treatment period" section of the eCRF, and also the reason for premature study termination will be investigated. Additionally, the patient status up until the last visit of the treatment phase (alive, dead, unknown) and in case of death, the cause of death (disease progression, other) will be investigated.

All patients who terminate the study prematurely will be listed according to their treatment group including the reason for termination. The number and percentage of patients with premature study termination will be determined overall and by treatment group. Study termination reasons will be tabulated, i.e. frequencies and percentages for single reasons for premature study termination will be presented.

Additionally, the patient status until the last visit (alive, dead, unknown) and in case of death, the cause of death (disease progression, other) will be tabulated, i.e. frequencies and percentages will be calculated for these variables. Protocol deviations and compliance with the visit schedule will be tabulated.

2.2.8 Analyses of pharmacokinetic variables

Please refer to the sub-study analysis for pharmacokinetic variables.

2.2.9 Quality-of-life variables

The impact of treatment on health related QoL will be assessed using the EORTC QLQ-C30 and the EORTC QLQ-G.I.NET21 questionnaire (cf. Study Protocol Appendix 3). Both questionnaires will be completed by the patient. EORTC QLQ questionnaires variables will be handled according to the EORTC QLQ Scoring Manual recommendations. Changes from baseline will be assessed every 12±1 week from the first treatment date until the PFS Primary End-Point, then until Week 72 after randomization, unless the patient progresses or dies. The EORTC QLQ-G.I.NET21 questionnaire is a module for carcinoid/neuroendocrine tumours. This module comprises questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

Calculation of the scores for both questionnaires:

(a) EORTC QLQ-C30 includes 30 items. The following 9 scales and 6 single items are defined (where FS = Functional scale and SS = Symptom scale):

- Global health status / QoL (items 29 and 30)
- Physical functioning (FS) (items 1, 2, 3, 4 and 5)
- Role functioning (FS) (items 6 and 7)
- Emotional functioning (FS) (items 21, 22, 23 and 24)
- Cognitive functioning (FS) (items 20 and 25)
- Social functioning (FS) (items 26 and 27)
- Fatigue (SS) (items 10, 12 and 18)

- Nausea and vomiting (SS) (items 14 and 15)
- Pain (SS) (items 9 and 19)
- Dyspnoea (item 8)
- Insomnia (item 11)
- Appetite loss (item 13)
- Constipation (item 16)
- Diarrhoea (item 17)
- Financial difficulties (item 28)

For all scales the Raw Score (RS) is defined as the mean of the respective items:

$$RS = (\text{item } i_1 + \text{item } i_2 + \ldots + \text{item } i_n) / n$$

For a single item, RS is identical to the score of the item itself.

Then for the functional scales (FS) the score is calculated by the formula:

$$\text{Score} = \{1 - (RS - 1) / \text{range}\} \times 100$$

For the symptom scales (SS), the single items and Global health status /QoL the score is calculated by the formula:

$$\text{Score} = \{(RS - 1) / \text{range}\} \times 100,$$

The "range" value is the difference between the maximum possible value of RS and the minimum possible value for RS. The range = 3 for all scales and single items except for "Global health status /QoL". For "Global health status /QoL" the range is 6.

The formulas for the scores are linear transformations of 0-100.

(b) EORTC QLQ-GI.NET21 includes 21 items. The following 5 scales and 4 single items are defined:

- Endocrine scale (items 31, 32 and 33)
- G.I. scale (items 34, 35, 36, 37 and 38)
- Treatment scale (items 39, 40 and 46)
- Social function scale (items 42, 44 and 49)
- Disease related worries scale (items 41, 43 and 47)
- Single item 1: Muscle/bone pain symptom (item 48)
- Single item 2: Sexual function (item 51)
- Single item 3: Information/communication function (item 50)
- Single item 4: Body image (item 45)

For all scales the Raw Score (RS) is defined as the mean of the respective items:

$$RS = (\text{item } i_1 + \text{item } i_2 + \ldots + \text{item } i_n) / n$$

For a single item, RS is identical to the score of the item itself.

For the scales and the single items the score is calculated by the formula:

$$\text{Score} = \{(RS - 1) / \text{range}\} \times 100$$

Where "range" is the difference between the maximum possible value of RS and the minimum possible value for RS. The range = 3 for all scales and single items.

The formulas for the scores are linear transformations to 0-100.

Missing items in scores will be imputed by the following method:
If at least half of the items from the scale have been answered then use all the items that were completed and apply the standard equation for calculating the Raw Score (RS).

The impact of treatment on health related QoL will be assessed by comparison of the changes of the different scales and single items from baseline (i.e. pre-post differences) by means of Wilcoxon's rank sum test on an alpha-level of 5%.

2.3 Data handling conventions

2.3.1 Replacement of data

2.3.1.1 Missing values

Unless otherwise stated during the blind review, missing values will not be replaced for the main calculation of the primary variable and secondary parameters (including key secondary parameters [OS, TTP and ORR]).

If relevant (e.g. the number of missing values is found to be substantial during the blind review), an investigation will be performed to determine how sensitive the results are to the method of handling missing values, at least for the primary variable and key secondary parameters. No replacements will be applied to any descriptive analysis or listings.

2.3.1.2 Outliers

Unless otherwise stated during the blind review, all outliers will not be eliminated nor replaced in the main analysis of primary variable and secondary parameters (including key secondary parameters [OS, TTP and ORR]).

If relevant (e.g. substantial number of blind review statistically and medically justified outliers), a sensitivity analysis eliminating outliers might be conducted, at least for the primary variables and key secondary parameters.

2.3.2 Transformation of data

Age will be calculated as follows:

(a) If the date of birth is completely known:

$$\text{age} = (\text{date of informed consent} - \text{date of birth}) / 365.25$$

(b) If only the year of birth is known:
age = (year of informed consent – year of birth).

The formula for BMI is: weight in kg / (height in m)^2

All laboratory values will be presented in SI units. If a parameter is given with the conventional unit the respective conversion factor will be used to transform the values to SI units.

2.3.3 Windows for time points

For the definition of time windows for visits please refer to the study protocol, Tables 1, 2, 7 and 10. Variations of ± 1 week in the visits schedule are allowed.

2.3.4 Unscheduled visits

Data of unscheduled visits will only be listed.

3 Interim analysis

Interim safety analyses will be conducted by an Independent Data Safety Monitoring Board (See Section 12.1 of the study protocol - Independent Data Safety Monitoring Board). This Board is regularly providing the Sponsor with recommendations to either continue the trial as planned, or to discontinue the trial, according to the Safety Analysis Plan. This Plan is described in detail in the Data Safety Monitoring Board (DSMB) Charter, provided as separate document.

An interim analysis for OS will be performed at the time of the final PFS analysis (see sections 2.2.2.2.2 and 2.2.2.2.3 for further details).

4 General appearance of output

The study-specific project code and/ or study code will be noted in the first line of every table, listing or graph. The date and name of the SAS-program creating the report will be indicated on the bottom left of the output. Numbering of pages is performed separately for each table.

The titles of the report will be clear and understandable to reflect the contents of the report. The type of analysis should be given, the analysis variable as well as the analysis set used. If important details are required to understand the output, these should be included in the document. All descriptions start with an uppercase and thereafter only lowercase characters.

The total number of patients within a report will be the number of patients within the collective the analysis is based on, so if there are missing values, their frequency will also be presented.

The number of decimal places displayed in a number will be the same as present in the original data value. Minimum and maximums will have as many decimal places as the original data values. Means, medians, and all other percentiles will have one more decimal place, and the standard deviation will have two more decimal places than the data values they are derived from. Percentage values will be printed with one decimal place. All p-values will be presented with four decimal places. If a rounded value of ‘p = 0.0000’ occurs, it will be indicated as ‘p < 0.0001’.

The reports will be presented using Times-Roman as the standard font, and the standard text size will be 12. The standard page orientation will be landscape, and the paper size will be Letter, with 1 inch margins. Headers and footers will also be 1 inch, but may be adjusted to accommodate additional information.

5 Software documentation

Statistical analyses performed by Pierrel Research Europe will be carried out using SAS®, release 9.3 (SAS/STAT 12.1, SAS Institute Inc., Cary, NC, USA) on a Microsoft® Windows® Server 2008 R2 or subsequent platform.

6 Coding systems

Domain	Coding System	Reporting Terms
Previous and concomitant diseases	MedDRA version 16.0	SOC = MedDRA SOC Preferred term = MedDRA Preferred term
Previous and concomitant medication	WHO Drug Dictionary (Version SEP/2012)	ATC Code Medication Group = ATC Level 4 term Drug Number
Adverse Events	MedDRA version 16.0	SOC = MedDRA SOC Preferred term = MedDRA Preferred term

Coding of previous and concomitant diseases, adverse events (AEs) and previous and concomitant medication will be performed by Pierrel Research Europe GmbH.

7 List of appendices

Appendix number	Title
Appendix I	Overview of statistical analyses
Appendix II	Overview of individual data listings
Appendix III	NETTER-1 Imaging Charter
Appendix IV	Pharmacokinetics and dosimetry data analysis
Appendix V	ECG data analysis

8 References

1 Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooija PP, Feelders RA, van Aken MO, Krenning EP: Treatment with the radiolabeled somatostatin analog [177 lu-dota0,tyr3]octreotate: Toxicity, efficacy, and survival. J Clin Oncol 2008; 26:2124-2130.

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7 Paganelli G, Sansovini M, Ambrosetti A, Severi S, Monti M, Scarpi E, Donati C, Ianniello A, Matteucci F, Amadori D. 117Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. Eur J Nucl Med Mol Imaging 2014; available online 11 March 2014, DOI 10.1007/s00259-014-2735-5.

8 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 'E9: Statistical Principles for Clinical Trials', (ICH E9)

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11 FDA Guidance for Industry, Standards for clinical trial imaging endpoints. Food and Drug Administration, August, 2011.

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9 Signature Page

I have carefully read this statistical analysis plan and agree to the described methods and proceedings.

Advanced Accelerator Applications SA, Snr Clinical Study Manager

Paola Santoro		15 Jan 2015
Name	Signature	Date

Advanced Accelerator Applications SA, Head of Clinical Development

Claude Hariton		15 JAN 2015
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Erich Geschwentner		16-JAN-2015
Name	Signature	Date

Appendix I: Overview of statistical analyses

Table / Figure No.	Report	Analyses sets	Output file (*.PDF)
14.1 Demographic data			
14.1.1 Study centers and patients			
14.1.1.1	No. of patients screened, treated, completed and withdrawn by center	Total	patnum_center
14.1.1.2	Incidences and reasons for premature study termination at End of Treatment Period (Eligibility, Treatment period completion, Survival)	Total / SAF / FAS	Termination
14.1.1.3	Frequencies of minor and major deviations from the Study Protocol	FAS	Deviation
14.1.1.4	Minor and major deviations from the Study Protocol – Patient numbers	FAS	deviation_patnr
14.1.1.5	Number of patients by analysis populations	SAF	patnum_pop
14.1.1.6	Listing of patients and their populations	Total	Pop
14.1.1.7	First/last patient in study, first/last patient out of study	Total	firstin_lastout
14.1.1.8	Compliance with the visit schedule	FAS	visit_compliance
14.1.2 Demographics and other baseline characteristics			
14.1.2.1	Demographic data - Continuous variables	SAF, FAS, PPS	demo1
14.1.2.2	Demographic data - Discrete / categorical variables	SAF, FAS, PPS	demo2
14.1.2.3	Diagnosis at screening visit	FAS, PPS	Diagnosis
14.1.2.4	Prior cancer surgery	FAS, PPS	prior_cancer_surgery
14.1.2.5	Previous treatment with Octreotide LAR at fixed dose / Other previous treatments of cancer	FAS, PPS	previous_cancer_treatment
14.1.2.6	Centralized diagnosis confirmation including Octreoscan Tumour Uptake score and Octreoscan Tumour Burden score at baseline (data source: IRC central lab database)	FAS, PPS	octreoscan_tumor_uptake
14.1.2.7	Overall tumor evaluation at screening visit	FAS, PPS	overall_tumor_evaluation1
14.1.2.8a	Overall tumor evaluation at screening visit: Summary statistics for sum of diameters for target lesions at screening by treatment group (data source: eCRF local assessment)	FAS, PPS	overall_tumor_evaluation2
14.1.2.8b	Overall tumor evaluation at screening visit: Summary statistics for sum of diameters for target lesions at screening by treatment group (data source: IRC central lab database)	FAS, PPS	overall_tumor_evaluation2
14.1.2.9	Karnofsky Performance Score (KPS) at screening and baseline (frequency table)	FAS, PPS	karnofsky_base1
14.1.2.10	Summary statistics for Karnofsky Performance Score (KPS) at screening and baseline	FAS, PPS	karnofsky_base2
14.1.2.11	Summary statistics for left ventricular ejection fraction (LVEF)	FAS, PPS	LVEF
14.1.2.12	Medical history by System Organ Class (SOC) and Preferred Term (PT)	FAS, PPS	medical_history
14.1.2.13	Concomitant diseases by System Organ Class (SOC) and Preferred Term (PT)	FAS, PPS	concom_diseases
14.1.2.14	Previous and concomitant medications by ATC-Code	FAS, PPS	medication_atc
14.1.2.15	Previous and concomitant medications by substances	FAS, PPS	medication_substance
14.1.3 Measurement of treatment compliance			
14.1.3.1	Treatment compliance / Dose reductions	SAF, FAS, PPS	compliance
14.2 Efficacy and other non-safety data analyses			
14.2.1 Analysis of primary efficacy variable			

14.2.1.1a	Primary efficacy analysis variable: Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: eCRF local assessment)	FAS, PPS	PFS_primary_criterion
14.2.1.1b	Primary efficacy analysis variable: Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database)	FAS, PPS	PFS_primary_criterion
14.2.1.2	Primary efficacy analysis variable: Progression Free Survival (PFS) - Original SAS-output of analysis according to Kaplan Meier method	FAS, PPS	PFS_primary_criterion
Figure 14.2.1.1	Primary efficacy analysis variable: Progression Free Survival (PFS) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. PFS; data source: IRC central lab database)	FAS, PPS	PFS_primary_criterion
14.2.1.3	Case final review outcome (data source: Prof Sundin assessment)	FAS, PPS	PFS_final_review_outcome
14.2.1.4	Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database; assigning the event time to the next scheduled imaging time rather than the actual time)	FAS	PFS_sensitivity_analysis1
14.2.1.5	Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database; ignoring new anti-cancer treatments started before progressive disease)	FAS	PFS_sensitivity_analysis2
14.2.1.6	Progression Free Survival (PFS) - Summary of analysis according to Cox's proportional hazards model (data source: IRC central lab database; covariates: see Section 2.2.2)	FAS	PFS_cox_regression
14.2.2 Analyses of secondary efficacy variables			
14.2.2.1a	Secondary efficacy variable: Objective response rates (ORR) and 95% CIs for both treatment groups (data source: eCRF local assessment)	FAS, PPS	ORR_second_criterion
14.2.2.1b	Secondary efficacy variable: Objective response rates (ORR) and 95% CIs for both treatment groups (data source: IRC central lab database)	FAS, PPS	ORR_second_criterion
14.2.2.2a	Secondary efficacy variable: Comparison of objective response rates (ORR) between both treatment groups (Fisher's exact test) (data source: eCRF local assessment)	FAS, PPS	ORR_second_criterion
14.2.2.2b	Secondary efficacy variable: Comparison of objective response rates (ORR) between both treatment groups (Fisher's exact test) (data source: IRC central lab database)	FAS, PPS	ORR_second_criterion
14.2.2.3	Secondary efficacy variable: Overall Survival (OS) - Summary of analysis according to Kaplan Meier method	FAS, PPS	OS_second_criterion
14.2.2.4	Secondary efficacy variable: Overall Survival (OS) - Original SAS-output of analysis according to Kaplan Meier method	FAS, PPS	OS_second_criterion
Figure 14.2.2.1	Secondary efficacy variable: Overall Survival (OS) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. OS)	FAS, PPS	OS_second_criterion

14.2.2.5a	Secondary efficacy variable: Time to Tumour Progression (TTP) - Summary of analysis according to Kaplan Meier method (data source: eCRF local assessment)	FAS, PPS	TTP_second_criterion
14.2.2.5b	Secondary efficacy variable: Time to Tumour Progression (TTP) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database)	FAS, PPS	TTP_second_criterion
14.2.2.6a	Secondary efficacy variable: Time to Tumour Progression (TTP) - Original SAS-output of analysis according to Kaplan Meier method (data source: eCRF local assessment)	FAS, PPS	TTP_second_criterion
14.2.2.6b	Secondary efficacy variable: Time to Tumour Progression (TTP) - Original SAS-output of analysis according to Kaplan Meier method (data source: IRC central lab database)	FAS, PPS	TTP_second_criterion
Figure 14.2.2.2a	Secondary efficacy variable: Time to Tumour Progression (TTP) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. TTP) (data source: eCRF local assessment)	FAS, PPS	TTP_second_criterion
Figure 14.2.2.2b	Secondary efficacy variable: Time to Tumour Progression (TTP) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. TTP) (data source: IRC central lab database)	FAS, PPS	TTP_second_criterion
14.2.2.7a	Secondary exploratory efficacy variable: Duration of Response (DoR) - Descriptive summary statistics (data source: eCRF local assessment)	FAS, PPS	DoR_second_criterion
14.2.2.7b	Secondary exploratory efficacy variable: Duration of Response (DoR) - Descriptive summary statistics (data source: IRC central lab database)	FAS, PPS	DoR_second_criterion
14.2.2.8	Secondary exploratory efficacy variable: Time to Second Progression (PFS2) – Descriptive summary statistics	FAS, PPS	PFS2_second_criterion
14.2.3 Correlation analyses			
14.2.3.1	Correlation of toxicity outcomes with body weight	FAS, PPS	Corr_tox_body_weight
14.2.3.2	Correlation of toxicity outcomes with body surface area	FAS, PPS	Corr_tox_body_surface
14.2.3.3	Correlation of clinical efficacy outcomes (PFS, OS, TTP) with the levels of the biomarker Chromogranin-A (CgA) in the serum (data source: Interlab central lab database for CgA and IRC central lab database for efficacy outcomes)	FAS, PPS	Corr_efficacy_CgA
14.2.3.4	Correlation of clinical efficacy outcomes (PFS, OS, TTP) with the levels of the biomarker 5-Hydroxyindoleacetic acid (5-HIAA) in the urine (data source for efficacy outcomes: IRC central lab database)	FAS, PPS	Corr_efficacy_5HIAA
14.2.3.5	Correlation of clinical efficacy outcomes (ORR, PFS, OS, TTP) with OctreoScan® tumour uptake score (data source: IRC central lab database)	FAS, PPS	Corr_efficacy_OctreoScan
14.2.3.6	Correlation of clinical efficacy outcome (PFS, OS, TTP) with serum levels of Alkaline Phosphatase (AP) (data source for efficacy outcome: IRC central lab database)	FAS, PPS	Corr_efficacy_AP
14.2.4 Analyses of additional efficacy variables			
14.2.4.1	Overall tumour evaluation: TNM criteria (T-Primary tumour lesions, N-Regional lymph nodes involvement and M-Distant metastasis) (frequency tables by treatment group and by visit)	FAS, PPS	overall_tumor_evaluation3

14.2.4.2	Overall tumour evaluation: Disease stage (for endocrine tumours of lower jejunum and ileum) (frequency tables by treatment group and by visit) (data source: Interlab central lab database)	FAS, PPS	overall_tumor_evaluation3
14.2.4.3a	Overall tumour evaluation: Objective tumour response (Response of target lesions, Response of non-target lesions, Overall tumour response) (frequency tables by treatment group and by visit) (data source: eCRF local assessment)	FAS, PPS	overall_tumor_evaluation3
14.2.4.3b	Overall tumour evaluation: Objective tumour response (Response of target lesions, Response of non-target lesions, Overall tumour response) (frequency tables by treatment group and by visit) (data source: IRC central lab database)	FAS, PPS	overall_tumor_evaluation3
14.2.4.4a	Overall tumour evaluation: Summary statistics for sum of diameters for target lesions by treatment group and by visit (data source: eCRF local assessment)	FAS, PPS	overall_tumor_evaluation4
14.2.4.4b	Overall tumour evaluation: Summary statistics for sum of diameters for target lesions by treatment group and by visit (data source: IRC central lab database)	FAS, PPS	overall_tumor_evaluation4
14.2.5 Analyses of health-related quality of life variables			
14.2.5.1	Health related QoL as assessed using the EORTC QLQ-30 and QLQ G.I.NET21 questionnaire: Summary statistics for all questions, domains and overall score as well as for their changes from baseline (by visit)	FAS, PPS	EORTC_summary
14.2.5.2	EORTC QLQ-30 and QLQ-G.I.NET21 questionnaire: Investigation of impact of treatment on health related QoL as assessed by comparison of the changes from baseline between both treatment groups (using Wilcoxon's rank sum test)	FAS, PPS	EORTC_test
14.3 Safety analyses			
14.3.1 Display of adverse events			
14.3.1.1	Number and percentage of patients with at least one • AE • Baseline AE • Treatment-emergent AE (TEAE) • TEAE leading to premature study termination • Serious TEAE (SAE) Comparison for each of these rates between both treatment groups using Fisher's exact test	SAF	ae_number
14.3.1.2	Summary of adverse events by severity and causality assessment (causal relationship) to study medication for: • Any AE • Any TEAE • Any TEAE related to study medication (ADR) • Any SAE • Any SAE related to study medication (SADR) • Any AE of special interest (AESI) • Any AESI related to study treatment • Any fatal AE	SAF	ae_summary
14.3.1.3	Incidence of treatment-emergent AEs by System Organ Class (SOC) and Preferred Term (PT)	SAF	ae_socpt
14.3.1.4	Incidence of treatment-emergent AEs by SOC, PT, and worst maximal severity	SAF	ae_differint

14.3.1.5	Incidence of treatment-emergent AEs by SOC, PT, and worst causality / relationship to study medication	SAF	ae_differcaus
14.3.1.6	Most frequent treatment-emergent AEs by PT	SAF	ae_pthitlist.
14.3.1.7	Listing of all adverse events	SAF	ae_list
14.3.1.8	Incidence of treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT)	SAF	sae_socpt
14.3.1.9	Listing of all serious adverse events	SAF	sae_list
14.3.2 Analyses of laboratory data (haematology, clinical chemistry and urinalysis)			
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14.3.2.2	Summary statistics for pre-post differences of laboratory parameters by visit	SAF	lab_summary
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14.3.3.2	Summary statistics for physical examination at all respective visits (frequency tables)	SAF	physical_examination
14.3.3.3	Summary statistics for ECG parameters by treatment group and by visit	SAF	ecg1
14.3.3.4	Summary statistics for ECG interpretation by treatment group and by visit	SAF	ecg2
14.3.3.5	Summary statistics for pregnancy test (frequency table)	SAF	pregnancy_test.
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14.3.3.9	Substudy: Summary statistics for dosimetry assessment safety outcome (data source: IEO central lab database)	SAF (substudy)	substudy_dosimetry
14.3.3.10	Substudy: Summary statistics for PK assessment (data source: IEO central lab database)	SAF (substudy)	substudy_PK_assessment
14.3.3.11	Substudy: Summary statistics for HPLC assessment (data source: IEO central lab database)	SAF (substudy)	substudy_HPLC_assessment
14.3.3.12	Substudy: Summary statistics for 24h cardiac assessment (data source: iCardiac central lab database)	SAF (substudy)	substudy_cardiac_assessment
14.3.3.13	Substudy: Summary statistics for local assessment of blood sample radioactivity	SAF (substudy)	substudy_blood_radioactivity
14.3.3.14	Substudy: Summary statistics for local assessment of urine sample radioactivity	SAF (substudy)	substudy_urine_radioactivity
14.3.4 Analyses of patient diary data			
14.3.4.1	Summary statistics for all variables of patient's diary	SAF	patient_diary_analysis

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Table No.	Report	Analyses sets	Output file (*.PDF)
16.2 Patient data listings			
16.2.1 Discontinued patients			
16.2.1.1	End of treatment period (study termination page for main part of study)	Total	termination1
16.2.1.2	End of long term follow-up period (study termination page for follow-up period of study)	Total	termination2
16.2.1.3	Anti-tumour therapies post discontinuation	Total	anti_tumor_therapies
16.2.2 Protocol deviations			
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16.2.3 Patients excluded from populations			
16.2.3.1	Patients excluded from populations	Total	Population
16.2.4 Demographic and baseline data			
16.2.4.1	Informed consent data	Total	informed_consent
16.2.4.2	Demographic data	Total	Demographics
16.2.4.3	Inclusion and exclusion criteria	Total	incl_exclusion
16.2.4.4	Randomization data	Total	Randomization
16.2.4.5	Diagnosis and prior cancer surgery data	Total	Diagnosis
16.2.4.6	Specimens and images for central eligibility assessment	Total	Specimens
16.2.4.7	Previous treatment with Octreotide LAR at fixed dose / Other previous treatments of disease	Total	previous_treatment
16.2.4.8	Centralized diagnosis confirmation (data source: Interlab central lab database)	Total	diagnosis_confirmation
16.2.4.9	Left ventricular ejection fraction (LVEF)	Total	LVEF
16.2.4.10	Medical history	Total	medical_history
16.2.4.11	Previous and concomitant medications	Total	concom_medication
16.2.5 Study medication data			
16.2.5.1	Study drug administration	Total	study_drug_administration
16.2.5.2	Individual compliance and dose reduction data	Total	compliance
16.2.6 Individual efficacy data			
16.2.6.1a	Identification of target lesions, non target lesions, new lesions (data source: eCRF local assessment)	Total	target_lesions1
16.2.6.1b	Identification of target lesions, non target lesions, new lesions (data source: IRC central lab database)	Total	target_lesions1
16.2.6.2a	Evaluation of target lesions (data source: eCRF local assessment)	Total	target_lesions2a
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16.2.6.3b	Evaluation of non target lesions and new lesions (data source: IRC central lab database)	Total	target_lesions2b
16.2.6.4	Overall tumor evaluation (according to TNM criteria)	Total	tumor_evaluation
16.2.7 Adverse event listings			
16.2.7.1	Adverse events	Total	ae_list
16.2.7.2	Serious adverse events	Total	sae_list
16.2.7.3	eSAE reports	Total	eSAE
16.2.8 Laboratory measurements			

Table No.	Report	Analyses sets	Output file (*.PDF)
16.2.8.1	Laboratory values of blood tests	Total	lab_values_blood_tests
16.2.8.2	Laboratory values of additional blood tests	Total	lab_values_add_blood_tests
16.2.8.3	Laboratory values of urinalysis	Total	lab_values_urinalysis
16.2.8.4	Laboratory values of additional urinalysis	Total	lab_values_add_urinalysis
16.2.8.5	Creatinine clearance	Total	creatinine_clearance
16.2.8.6	Substudy: dosimetry assessment safety outcome (data source: IEO central lab database)	Total (substudy)	substudy_dosimetry
16.2.8.7	Substudy: PK assessment (data source: IEO central lab database)	Total (substudy)	substudy_PK_assessment
16.2.8.8	Substudy: HPLC assessment (data source: IEO central lab database)	Total (substudy)	substudy_HPLC_assessment
16.2.8.9	Substudy: Local assessment of blood sample radioactivity	Total (substudy)	substudy_blood_radioactivity
16.2.8.10	Substudy: Local assessment of urine sample radioactivity	Total (substudy)	substudy_urine_radioactivity
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16.2.9.3	Electrocardiogram (ECG)	Total	ECG
16.2.9.4	Substudy: 24h cardiac assessment (data source: iCardiac central lab database)	Total (substudy)	substudy_cardiac_assessment
16.2.9.5	Karnofsky performance status	Total	Karnofsky
16.2.9.6	Pregnancy test	Total	pregnancy_test.
16.2.9.7	ePregnancy report	Total	ePregnancy
16.2.10 Patient questionnaires and patient diaries			
16.2.10.1	EORTC QLQ-30 and QLQ-G.I.Net21 Questionnaire	Total	EORTC
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16.2.11.2	Visit information data of main study	Total	visit_information1
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Appendix III: NETTER-1 Imaging Charter

INFORMATION PROVIDED AS PART OF
NETTER-1 STUDY PROTOCOL
AAA-III-01

IMAGING CHARTER

Version 1.0

28 November 2014

A multicentre, stratified, open, randomized, comparator-controlled, parallel-group Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours

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1 LIST OF ABBREVIATIONS

^{177}Lu	Lutetium-177
CRO	Contract Research Organization
CT	Computerized Tomography
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DTPA	Diethylene Triamine Pentaacetic Acid
e-CRF	Electronic Case Report Form
ENETS	European Neuroendocrine Tumour Society
FAS	Full Analysis Set
FOV	Field of View
GBq	Giga Becquerel (Bq = unit of radioactivity)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Gy	Gray (unit of radiation exposure; equal to 100 rad)
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Reading Center
I.V.	Intravenous
LAR	Long Acting Release
MBq	Mega Becquerel (Bq = unit of radioactivity)
mCi	MilliCurie (unit of radioactivity; 1 mCi = 37 MBq)
MRI	Magnetic Resonance Imaging
NANETS	North American Neuroendocrine Tumor Society
PFS	Progression Free Survival
PPS	Per Protocol Set
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumours
SOP	Standard Operating Procedures
Sstr2	Somatostatin Receptor Subtype 2
TIV	Trial Initiation Visit

2 TRIAL DESIGN AND THE ROLE OF IMAGING IN THE TRIAL

2.1 NETTER-1 trial design

The NETTER-1 clinical trial is a Phase III multicentric, stratified, open, randomized, controlled, parallel-group study, comparing ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with Octreotide LAR (Sandostatin® LAR Depot) in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

^{177}Lu is a medium-energy, beta-emitter with a maximum tissue penetration of 2 mm and a physical half-life of 6.7 days. It also emits medium and low-energy gamma radiation, which allow imaging and dosimetry. Octreotate binds with high-affinity to somatostatin receptors (especially sstr2) and retains its binding properties and physiological function when complexed with ^{177}Lu through an N-terminal DOTA-linked chelator.

The main criteria for enrolment in the study are: i) metastasized or locally advanced, histologically proven midgut carcinoid tumours; ii) target lesions which are somatostatin receptor positive based on scintigraphy with OctreoScan® within 24 weeks prior to randomization in the study while the patient was on a fixed dose of Sandostatin® LAR (except for the temporary interruption of Sandostatin LAR use for the purpose of obtaining an OctreoScan®); iii) the patient is at a fixed dose of 20 mg or 30 mg Octreotide at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study; and iv) has progressive disease according to RECIST 1.1.

Patient randomization is performed according to a centralized stratified permuted block randomization scheme with a balanced ratio (1:1) between the two treatment arms, stratifying for the following factors; 1) somatostatin receptor scintigraphy tumor uptake score centrally assessed (Grade 2, 3 and 4) (the highest score measured among all the target lesions will be used for stratification purpose); and 2) length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization ($\leq$ 6 and > 6 months).

Treatment with a cumulative dose of 29.6 GBq of ^{177}Lu-DOTATATE (7.4 GBq x 4 at 8±1-week intervals) plus supportive care with 30 mg Octreotide LAR is compared to 60 mg Octreotide LAR (injections at 4-week intervals).

The primary objective is to compare Progression Free Survival (PFS) between the two arms. During the treatment phase, objective tumor assessment is performed every 12 weeks from the date of randomization until progression. Tumor progressions and objective tumor response during the study treatment phase are assessed by an independent Image Reading Center (IRC) according to RECIST 1.1.

The main secondary objectives are to compare Objective Response Rate, Overall Survival (OS), and Time to Tumour Progression between the two arms, and to assess safety, tolerability and health related quality of life.

2.2 NETTER-1 trial imaging centralized assessments

In clinical trial practice, the analysis of imaging data represents an important component in regards to determining patient trial eligibility, assessing drug safety, and identifying treatment efficacy endpoints. Because of non-standardized methodologies, the measurements derived from imaging data are

vulnerable to site-to-site variability. Therefore centralized assessment is preferred over a site-base process. This approach also provides for verifiable and uniform reader training, as well as ongoing management of reader performance, ensuring that the assessment process is uniformly accurate, and that bias and scan-to-scan variability are minimized (Douglas PS et al, 2009; Ford R et al, 2009; Tang PA et al, 2010).

In the NETTER-1 trial, the Sponsor has contracted an Independent Image Reading Center (IRC), Keosys, Saint Herblain, France, to conduct the following image analyses and centralized confirmation procedures:

a) verify that at the time of inclusion, all patients have progressive disease according to RECIST, Version 1.1, (Section 6.1.5 of the NETTER-1 Study Protocol) confirmed by the IRC;

b) select and verify that all patients target lesions, documented by CT/MRI (Section 6.1.4 of the NETTER-1 Study Protocol), have somatostatin receptor positivity on planar somatostatin receptor scintigraphy with OctreoScan® (performed within 24 weeks prior to randomization in the study). The tumor uptake observed in each target lesion using planar scintigraphy must be greater than or equal to the uptake of normal liver;

c) verify the extensive dosimetric analysis performed in the subset of 20 patients enrolled at selected clinical sites and treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The substudy will require planar and 3-D SPECT imaging centrally assessed (Substudy Central Lab, IEO: European Institute of Oncology, Milan, Italy), and will also include urine collection and blood sampling. Details of the procedures are included in the NETTER-1 Study Protocol (Section 6.6) and the substudy Manual;

d) verify that each disease progression event is according to RECIST (Section 6.3.1 of the NETTER-1 Study Protocol);

2.3 Charter objectives

This Imaging Charter summarizes all of the processes related to the analysis of imaging data to verify study endpoint events. The primary focus is to describe the imaging standards implemented in the clinical trial, and the technical, organizational, operational aspects in the exchange and processing of images. The aims are to ensure that; 1) all imaging data are obtained in a manner that complies with the study protocol; 2) the quality of imaging data is maintained within and among clinical sites, and 3) there is a verifiable record of the imaging process in order to minimize variability, improve data quality and enhance the accuracy of assessing drug treatment effects.

This Charter is based on the following reference documents:

- FDA Guidance on clinical evidence of effectiveness for human drugs and biological products (1998)
- FDA Guidance on clinical trial endpoints for the approval of cancer drugs and biologics (2007)
- FDA Draft Guidance on clinical trial imaging endpoints (2011)

2.4 Image Acquisition Standards

All the imaging examinations performed for the purpose of this clinical trial are generated by the site radiologists according to locally assessed procedures and evaluated by using RECIST 1.1. The examinations are sent for central real-time assessment to the IRC, as soon as obtained (Refer to IRC Core Imaging Manual and IRC Operating Manual).

Before each site activation, individual training to the site staff is provided by the ICR as e-training on the specific to the Imagys platform (Refer to Images Acquisition Guideline) and by the appointed Contract Research Organization (CRO) during the Trial Initiation Visit (TIV) focusing on the overall process of centralized assessments in the context of the clinical trial, the procedures for images/data transfer and timelines (Refer to Pierrel Monitoring Plan).

In addition, training on the centralized procedure of image evaluation is performed at the Investigators Meeting planned at the beginning of the trial.

The purpose of the IRC Images Acquisition Guideline is to detail the imaging acquisition process, the qualification and quality control requirements for the production of optimal images with the aim of maintaining technical consistency within and among clinical sites, and optimizing the imaging acquisition modality.

Sites are checked as to the capability to produce adequate standard quality examinations and the availability of computer/internet connection intended to be used to upload the images into the IRC web platform. In this regard, each site undergoes a two-step qualification related to: i) the site's ability to use the Imagys' platform (network and computer configuration for effective upload of images), and ii) the user's ability to use the platform (based on the acquisition and validation of test CT/MRI and scintigraphy images) (Section 2.4.1.8). Sites unable to satisfy the quality pre-requirements will not be eligible to participate in the NETTER-1 trial.

2.4.1 Equipment Standardization and Operation

Response in patients with metastatic carcinoid tumors is most often defined on the basis of regression in the size of metastatic lesions. According to RECIST 1.1 criteria (Eisenhauer EA et al, 2009), triphasic, contrast-enhanced CT is regarded as the primary imaging modality to assess lesions size in oncological clinical trials and constitutes the primary imaging method of choice during the present study on neuroendocrine tumors.

The use of MRI is acceptable when CT is not advisable (e.g. in case of renal insufficiency, or allergy to iodinated i.v. contrast agents), or for additional investigational uses (such as liver studies when results of CT are inconclusive or equivocal). However, MRI sequences (T1- and T2-weighted; unenhanced, gadolinium-enhanced) have become increasingly more attractive also as a primary imaging technique. Therefore, other factors such as availability of up-to-date instrumentation, technical and clinical expertise, cost, and patient tolerance can also be taken into consideration for the choice of primary imaging modality and clinical site selection. When tumor staging shows the presence of soft tissue metastases, an already available MRI examination is deemed as acceptable for abdominal and pelvis examinations, instead of requiring the repetition of CT. For chest imaging, CT is more appropriate because of its better spatial resolution as compared to MRI to detect small lung metastases.

The diagnostic examination used to determine progression during enrolment screening (by comparison with the previous examination of the same modality - CT or MRI) is used as the baseline imaging study. Otherwise, if too long time (as a rule, more than 4 weeks) has passed from the time of the diagnostic examination and the randomization, staging should be repeated before randomization, preferably by using CT.

Nevertheless, the imaging modality chosen for subsequent RECIST analysis, either CT or MRI, needs to be consistently used throughout the study treatment period and applying the same acquisition protocol as used at baseline. Substitution of one imaging modality for another is acceptable in the exceptional circumstance of unavailability of the same instrumentation. Any such substitution must be justified and documented. Then, the baseline method should be recovered as soon as possible for the continuation of the study.

The standard requirement is to perform an i.v. contrast-enhanced CT and to obtain an appropriate field-of-view (FOV) covering clinically relevant anatomical areas. This should include the thorax, abdomen and pelvis. At the very least, the abdomen and pelvis should be examined. When possible, the neck must also be included when the thorax is examined. The slice thickness should never exceed 5 mm and should be contiguous throughout all the defined FOVs. It is recommended that for each patient identical acquisition and reconstruction protocols be used at all time-points.

Additional details are reported in the IRC Core Imaging Manual and the IRC Images Acquisition Guideline.

- **CT scanners**

During the entire study, scanner quality control is recommended and should always be performed as instructed by the manufacturer. The radiologist should always optimize the examination protocol to comply with the ALARA principle for radiation exposure, i.e. "As Low As Reasonably Achievable" (Refer to NETTER-1 study Protocol, Appendix 15 – Section 18), however, without compromising the image quality.

Reconstruction settings must be as recommended by the manufacturer, not exceeding 5mm slice thickness and contiguous throughout the entire FOVs.

- **MRI scanners**

MRI scanner quality control is recommended during the entire study and should be performed on a regular basis according to manufacturer instructions. Multislice imaging is the default mode of MRI images acquisition. Reconstruction settings must be as recommended by the manufacturer, and not greater than 5mm slice thickness and contiguous throughout the entire FOVs.

- **Somatostatin receptor scintigraphy with OctreoScan™**

The scintigraphic acquisitions must be performed as recommended by the European Neuroendocrine Tumour Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS) Consensus Guidelines (Kwekkeboom DJ et al, 2009; Vinik AI et al, 2010; Boudreaux JP et al., 2010).
Considering the large number of centers involved in the study and the associated variability, it is of the

utmost importance that each center does its best to comply with these protocols in order to achieve optimal image quality, according to the instructions provided by the IRC before site activation.

2.4.1.1 Vendor-specific equipment/platforms (e.g. scanners, software)

Throughout the entire study, DICOM images transmission between the investigational center and the IRC will be performed through the IRC web platform, unless digital images are made available through hardware support. Image print-outs on paper or films are allowed only in exceptional situations.

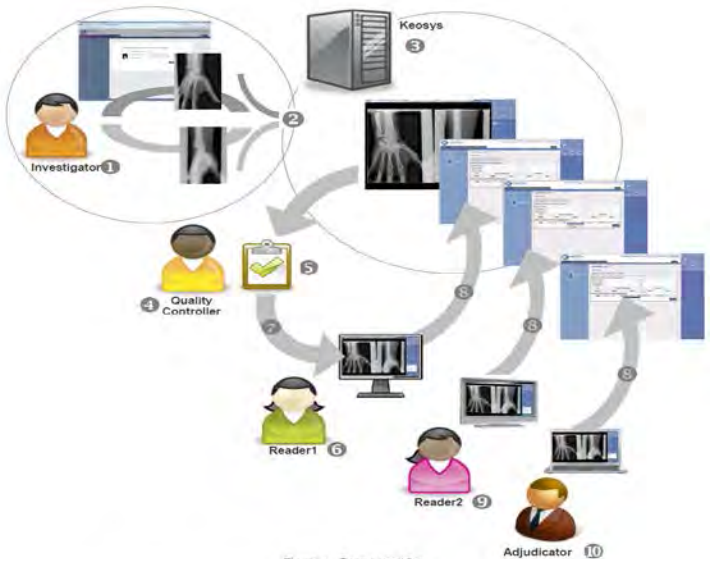
The technological / electronic infrastructure and programs used by the IRC for the upload, reading and storing of images, including all upgraded versions are validated by the IRC. In case of system changes the changed components are validated. A differentiation is made between 'patch', 'minor' and 'major' changes. All minor and major system changes will include appropriate user training. The validation reports are signed by the test manager and the quality manager. Additional information on data storage and back-up is provided in Section 2.4.1.10.

The IRC is audited at the start and during the project by the Sponsor or the appointed CRO.

The processes for image reading and data assessment, which are performed by third parties under the responsibility of the IRC, are described in specifications provided by the IRC. The process for the definition of acceptable/unacceptable images by the IRC is described in the IRC Core Imaging Manual.

The IRC provides the technological platform for the physical management of images, and an organized system for the Quality Control (QC) and the evaluation of the images uploaded for analysis (images used for the screening and selection of the patients; images used for the follow-up evaluation of the tumor progression; images submitted for adjudication in case of discrepancies between primary assessors). Corresponding processes are described in the Quality Controller User Guide and in the Core Imaging Manual, and in Section 2.4.1.9 and 2.5.1 of this Charter.

The entire process is illustrated in Figure 1.
Figure 1: Image acquisition and evaluation workflow



The investigator ① uploads, through a web browser, the patient examination images ② on the IRC server ③. The Quality Controller ④ validates the image data and determines if ⑤ the reading process is to proceed. The readers ⑥ ⑨ visualizes patient image data ⑦ from the IRC server, provided quality control is positive. Each reader completes a reading form ⑧ which is stored on the IRC server. The adjudicator ⑩ complete the adjudication form when readings are done.

Details on the specific steps in the evaluation of images are presented in Section 2.5.2.4.

Technical characteristics of the IRC system

The IRC platform can be used without the need for specialized software, and only basic components (Java and Active X) are required. It is compliant with any web browser and with Java compatible operating systems (Windows, MacOS, Linux).

Access to the documentation is limited to IRC appointed personnel, in order to ensure that images and data are retained in their original form. All users (i.e. local and central readers, adjudicator, QC person, supervisor, administrator) have an individual log-in to the web-platform. The system provides Login credentials which are automatically sent by email upon account creation. At first connection, users must update their password (password lifetime is 90 days). As a standard, the password must have special length and characters and expires every 90 days (criteria are provided for the password renewal). The different user groups have different screens. Only the administrator (the one who creates and manages user accounts) has an overview of the whole platform.

The IRC platform permits visualization and comparison of 3D imaging scan data in different modalities (including CT or MRI scans) for the central readers. The display of modalities can be made independently from each other or in fusion mode. Adjustment tools are available (a color map choice for the functional modality, a color bar to adjust the boundaries of the functional modality and an adjustment button for the blending between the two modalities).

The following measurements from 3D scans are determined: simple volumes: parallelepiped, sphere. Automatic 3D contouring by thresholding or region growing, ratio with reference zone, manual correction of segmentation, volumes naming.

The platform can also manage planar scans with different features (zoom, drag & drop, vertical and horizontal axial symmetry, reverse mode), LUT controls for the image corrections (grey and color scales). The following measurements are determined from planar scan: distances, open and closed angles, segments, surfaces, ROI/VOI with statistical calculation (mean, min., max., total) including SUV for PET, display of the maximum focal tracer accumulation with cursor.

<u>Characteristics of visualization system</u>

Central unit:

Processor : Intel i5-680

Memory : 4 Go 1333MHz DDR3 ECC

HDD : 300 Go SATA II 10k

Diagnostic display:

Diagonal display : 30''

Resolution : 4MP : 2560x1600@60Hz

Contrast : 1000 : 1

Luminosity : 350 cd/m²

Dimensions [H x W x D] : 18.4in x 27.1in x 11.9in

Dimensions [H x W x D]:

Diagonal display : 19''

Resolution : 1280x1024@60Hz

Dimensions [H x W x D] : 55,9cm x 39,2cm x 24,73cm

No planning is made by the IRC for evaluations by external readers on possible systematic errors in computer-generated analyses. The IRC has obtained FDA 510k Pre-Market notification for the imaging workstation, and is certified according to ISO 13485 for medical devices. The IRC undergoes regular inspections by the national Regulatory Authorities (in France: LNE/GMED).

2.4.1.2 Equipment technical settings to be used at each site

Imaging equipment in use at the investigational centers should have been approved by local Regulatory Authorities. The IRC will discuss the required technical settings for image acquisition with the site at the study initiation, based on the protocol requirements and the IRC Images Acquisition Guideline. Sites' specifications are collected by the IRC during the site qualification process.

Minimal requirements for a successful upload check:

- Any operating system running the Java Runtime Environment (JRE) (Windows, MacOS, Linux)
- JRE 1.5 or later
- A Java compatible web browser such as Internet Explorer (IE8 or above), Firefox, Safari or Google Chrome
- Adobe Flash 9.0 or later
- The user must have the rights to download and execute Java Applet / ActiveX from the Gateway Server
- Internet access
- Enough free space on the computer to upload data
- Direct access to DICOM or imaging files to upload.

The de-identification of DICOM files is automated and performed in accordance with NEMA DICOM standards Part 15 guidelines (ftp://medical.nema.org/medical/dicom/final/sup1542_ft.pdf). This process consists of three steps:

- Overwrite all references to the patient by number inclusion,
- Overwrite the patient birthdate
- Overwrite all unique identifiers

The DICOM file is then compressed and encrypted, and the file is uploaded via secured web transfer process as a de-identified DICOM file.

2.4.1.3 The role of site imaging technicians in equipment operation, including identification of faulty or unacceptable images and the need to repeat imaging

The Investigator(s) are qualified by education, language, training, and experience to assume responsibility for the proper conduct of the study. He/she must meet all qualifications specified by the applicable regulatory requirements and provide evidence of such qualifications through an up-to-date curriculum vitae (Principal as well as all other Investigators) and/or other relevant documentation requested. The Principal Investigator of each site maintains a list of appropriately qualified persons to whom the Investigator has delegated significant study related duties. The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that the trial is properly conducted in adherence to the current protocol and ICH GCP (Refer to CRO Monitoring Manual).

In order to ensure that each site has the operational (technical and methodological) capability to provide quality images according to protocol requirements, a site qualification step is mandatory before the site activation (Refer to IRC Core Imaging Manual).

An e-training specific to the IRC web platform use is also mandatory before each site activation (Section 2.4.1.8).

2.4.1.4 Patient preparation, positioning, and comfort measures

Image acquisition procedures at each site follow local, standard practice. The procedures must also conform with the instructions provided by the specific equipment manufacturer.

The somatostatin receptor scintigraphy planar imaging protocol to be followed is the one suggested by the ENETS Guidelines, and reported in Appendix 6 of the Study Protocol. This includes discontinuation of somatostatin analogs, hydration, use of laxatives, need for fasting, voiding before imaging, among others.

2.4.1.5 The date and time for imaging and alternatives

Image scan timing for restaging is described in the NETTER-1 Study Protocol and is scheduled over 12 ± 1 weeks intervals, starting from the date of randomization. In case of different scheduling, a protocol deviation can be identified. Correction measures are needed in order to come back to the original schedule, as described in the study protocol (Section 6.3.1 of Study Protocol version 4.0).

Analysis and Interpretation of Image Information is also provided in Section 2.10 of this Charter.

Investigators are requested to upload images as soon as these are available, by using the IRC platform and after having de-identified the images (Section 2.4.1.2). An email alert is sent to the person in charge of the Quality Control at the Central Reading Center when a set of images are uploaded for central review. The IRC performs the images QC and analysis, and communicates the final results to the site by email within 5 working days.

Information on the time from images upload to QC analysis and to evaluation by independent readers is reported in a Status Report listing various information:

- Examination date locally
- Upload date
- Information on tumor response, as evaluated locally (information available only to the QC person, not to the independent readers)
- Date of QC approval
- QC state (validated)
- Date of evaluation by the independent reader
- Name of the independent reader
- Date of adjudication (if any required)
- Name of adjudicator
- Information on tumor response, as evaluated centrally
- Discrepancy between Local and Central response (information available only to the QC person, not to the independent readers)

2.4.1.6 Handling of off-protocol imaging examinations

Imaging examinations are used for patients inclusion according to the trial inclusion criteria #5 and #6 (Refer to NETTER-1 Study Protocol), while the primary efficacy variable of the study, Progression Free Survival (PFS), is based on in-protocol images scheduled every 12±1 weeks from randomization (Refer to NETTER-1 Study Protocol, Section 6.31 for further details).

Patients in a clinical trial lasting many months are likely to undergo imaging examinations in addition to the ones intended to assess the response to therapy or to detect disease progression (off-protocol images). All the in/off-protocol images requested by the Study for (re)staging purpose are assessed by the IRC (blinded, real-time assessment). Whether such patient assessment will be used or not for the end-point analysis, and how this is managed statistically, is a matter of ad-hoc evaluations, depending on the severity of the deviation observed.

In case the patients will undergo imaging examinations outside the investigational center before or after the first progression is assessed, the Investigator will make any effort to collect the images to be submitted to the IRC during the treatment phase or to be locally assessed at the investigational center during the long term follow-up.

If the DICOM files of the examinations obtained outside the investigational center are not available, at least the corresponding diagnostic sheets will be requested for filing as supportive documentation.

2.4.1.7 Imaging risks

In this trial, patients will be exposed to radiation, both during (re)staging imaging procedures and treatment with the radioactive drug ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radioactive treatment. ^{177}Lu emits β^-, and medium and low-energy gamma radiation, which can be used for treatment, imaging and dosimetry. As described in the

Appendix 15 of the NETTER-1 Study Protocol, the physical and radiopharmaceutical properties and the metabolism of this radiopharmaceutical compound is associated to a low health risks to patients, patient's family members, patient's care givers and the general public. However, it is necessary to follow certain precautions in order to limit the exposure to radiation and maximize the safety of the patients and other persons, as indicated in the Protocol.

According to ICH GCP (CPMP/ICH135/95) the patient must give the consent to participate in the study, only after being fully informed by the Investigator of the nature, significance, and implications of the study, as well as to the associated risks involved. Such meetings must be carried out on an individual basis, and adapted to the educational background and previous knowledge of the patient. For the patients enrolled in the NETTER-1 trial, attendance to this meeting is documented in the patient's file. The extent of the risks related to exposure to radiation and administration of contrast agents is described in the Informed Consent Form (ICF) which is dated and signed by both the Investigator and the patient. (Refer to last version of the Main Study ICF).

Occasionally, imaging detects incidental findings that are important for further investigations. Some of these findings may represent false positive findings of disease and expose patients to additional examinations that would otherwise not have been performed. Some of these findings may also provide the first important signals of a clinically important condition.

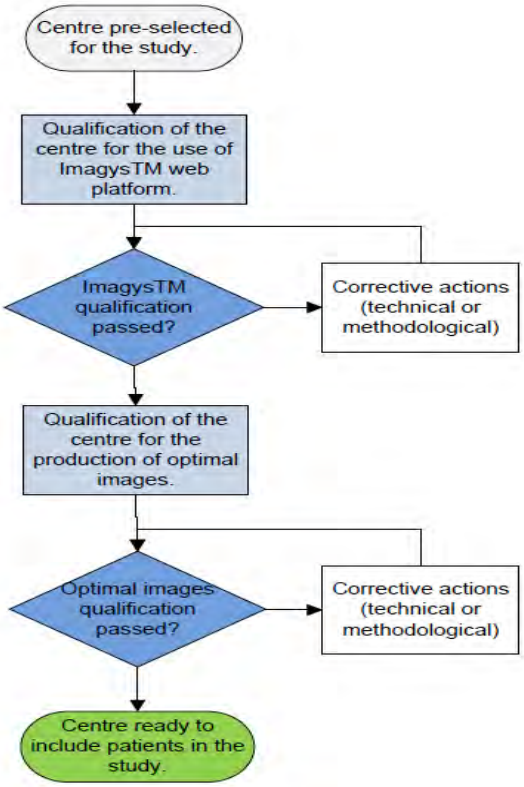
All incidental image findings that may have clinical consequences are reported by the Investigator as adverse events in the study electronic Case Report Form (eCRF), and will be managed accordingly (especially in terms of patient information, diagnostic or therapeutic actions, reporting to Health Authorities).

2.4.1.8 Site qualification process

Each site is requested to undergo a site qualification process by transferring test CT/MRI and scintigraphy examinations to the IRC before site activation. The IRC verifies the site capability to generate adequate standard quality examinations and the characteristics of the site computer/internet connection intended to upload the images onto the IRC web platform (Refer to IRC Web Upload Qualification User's Guideline and IRC Images Acquisition Guideline).

A graphical overview of the process is illustrated in the Figure 2.

Figure 2: Qualification process



During the site qualification process, each site will have to upload to the IRC web platform sample data to be generated in the same way they will be provided during the entire study.

The sample data for CT/MRI and somatostatin receptor scintigraphy must be examinations that are already available at the center (no new examinations are to be performed) and should be uploaded to the IRC web platform where the patient data will be automatically anonymized by the system. The examinations that are uploaded for the qualification step and during the entire study have to be in the standard DICOM format. Additional information about DICOM requirements are provided in the IRC Viewer DICOM Conformance Statement.

Sample examinations required during this qualification step are to control that all the quality and technical requirements described in the IRC Images Acquisition Guideline are fully respected by the site. Sites are invited to read this guideline carefully prior to upload any qualification data, in order to minimize possible corrective actions.

Before site activation, each site has to upload three sets of CT examinations (arterial and venous phases) of patients scanned for metastatic carcinoid tumours.

If a center plans to perform MRI during the study, then it is mandatory to upload MRI examinations during the imaging qualification step.

The same process occurs with scintigraphy test images.

At reception of these examinations, the IRC contacts the site by email or phone within 5 working days in order to confirm the success of the qualification or to provide a dedicated support if inadequacies are detected during the review.

A certificate is sent to each site to confirm the successful outcome of the qualification process, while sites unable to satisfy the quality pre-requirements are not eligible for participation in the NETTER-1 trial.

2.4.1.9 Acquisition quality control monitoring process

Each time a new examination has been uploaded by the investigational center onto the IRC web-platform, it undergoes the IRC quality review (QC). The QC person is informed about uploaded images via email alert. After the initial QC check, the QC person informs the central reader via email and phone. In case the QC person is not provided with a reply within the specified delay, he will send the request to another central reader.

Quality checks include both automatic and manual checks on technical criteria and will characterize the images as appropriate or inappropriate for central reading by labeling the quality level of images as optimal - suboptimal - poor.

Possible deviations to be encountered and recorded include the following (among others):

- no de-identification;
- change in the imaging modality, compared to the baseline scan (*e.g. from CT to MRI, or vice-versa*);
- unavailability of sufficient anatomical regions within FOV (at least 2 FOVs are needed);
- poor quality.

In such instances, the QC prevents images to be passed forward for the evaluation by the independent reviewer.

In case of non-validated data, the images are rejected by the IRC and the reason is available on the platform (Section 2.5.1 for further details). The center is informed either directly, or via the clinical monitor or project manager and requested to perform corrective actions or send additional information.

2.4.1.10 Data storage, transfer, and site display

The original images are stored at the investigational sites, in the Institution's server. The IT functionality, back-up, and security, in particular under the perspective of data protection is the responsibility of the Institution.

The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that the study is properly conducted in adherence to the current protocol and ICH GCP, and that the data reported by the Investigator or designee are accurate, complete, and verifiable with the source documents. The Sponsor or delegated CRO is responsible for assigning (a) Clinical Study Monitor(s),

who monitor the study in accordance with the monitoring guidelines.

The Investigator and the study center must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the Ethics Committee / Institutional Review Board [IEC(s)/IRB(s)] and/or relevant Regulatory Authorities. They must provide all study-related records they are requested to generate and provide, as well as images and supporting documentation / diagnoses source documents. The confidentiality of the patient's identity shall be well protected and consistent with local and national regulations when the source documents are subject to direct access.

Images uploaded for central assessment are kept at the IRC facilities during the study conduct and for long-term archival. Two servers are available at the IRC facility. All data are saved in real-time on both servers. In case of a failure or abnormal termination of the main server, the second server will automatically switch to take over the part of the main server, and the administrator will be informed via email.

A daily back-up process is foreseen, which is followed by a back-up every 5 days, every 5 weeks and every 5 months.

Access to the server room of the IRC is restricted to persons specified in the SOP. All changes done in the server room are documented (who, when, what) on a log outside the server room. Servers are plugged to a redundant uninterruptable power supply (UPS) which also sent emails to the technical team in case of power outage.

Information on the technical characteristics of the IRC system is provided in Section 2.4.1.1.

2.4.2 Imaging Drug Standardization

If not contraindicated, appropriate contrast agents are used for either CT or MRI. Because the contrast medium administration may vary due to variability of for example local imaging protocols, each site will be using commercial contrast agents as available locally, and following the manufacturer's instructions. However, in case of allergy to iodinated contrast agents used for CT, or renal insufficiency, the examination is performed without contrast-enhancement or an MRI will instead be performed.

Guidelines on performing, interpreting, and reporting the results of somatostatin receptor scintigraphy with Octreoscan are available in Appendix 6 to the study protocol, including patient preparation, precautions and drugs to be used (e.g. hydration, use of laxatives).

A secondary explorative objective of the NETTER-1 trial is to evaluate $DOTA^0$-Tyr^3-Octreotate dosimetry in a subset of 20 patients. The substudy will require planar and 3-D SPECT imaging centrally assessed (IRC: European Institute of Oncology, Milan, Italy), and will also include urine collection and blood sampling. Details of the procedures are included in the NETTER-1 Study Protocol (Section 6.6 of the Protocol) and the NETTER-1 Dosimetry Substudy Manual.

^{177}Lu-$DOTA^0$-Tyr^3-Octreotate will be provided by the Sponsor, and it will be used at the same dose as used in the subjects enrolled in the main study.

^{177}Lu-$DOTA^0$-Tyr^3-Octreotate is a radiopharmaceutical solution for infusion supplied as a ready-to-use product. The Quality Control tests that must be performed at the clinical site are to; 1) confirm correct product certificate; 2) determine total radioactivity; 3) confirm visual appearance. Since ^{177}Lu-

DOTA^0-Tyr^3-Octreotate is manufactured in centralized GMP facilities, the majority of required QC tests are performed before product shipment. A batch release certificate of the product will be sent to the investigational centers. This batch release certificate is provided by the Qualified Person (QP) of the manufacturing site to ensure that the product is suitable for administration and that it meets its specifications.

The product is manufactured and supplied to the clinical sites in monodose vials. One vial, for one administration, contains 7.4 GBq (200 mCi of ^{177}Lu-DOTA^0-Tyr^3-Octreotate at calibration time (the time of infusion) in a formulation solution of 22 to 25 mL. The variability of the volume depends on the time between the calibration date and the production date. The product will be shipped and calibrated for use at 24h or 48h after production in a centralized GMP facility. The calibration time of a dose depends on the distance from the manufacturing facility to the clinical sites. The amount of administered radioactivity, 7.4 GBq (±10%), is specified at the time of infusion.

2.5 Clinical Trial Standards for Image Interpretation

2.5.1 Image Transfer, Receipt Documentation, and Initial Quality Assessment

As a rule, during the entire study, image transmission between the investigational center and the IRC will be performed through the IRC web platform, unless digital images are not available or the electronic platform is not working, in which case print-outs on film or paper may exceptionally be forwarded to the IRC for the central evaluation (Refer to Paper Scans Transmission procedures, IRC Web Upload Qualification User's Guideline and IRC Images Acquisition Guideline).

Sites unable to satisfy the quality pre-requirements will not be eligible to participate in the NETTER-1 trial (Section 2.4.1.8).

The imaging quality control (QC) is divided into two steps:

1) Automated quality control by IRC web platform.
2) Expert quality control performed centrally by a qualified IRC Quality Controller.

During this data-transmission process, several quality controls will be automatically performed as detailed in the Table 1 below.

Table 1: Web platform automated systematic acceptance controls

Controls	**Acceptance criteria**
Continuity of the modality	The modality of the visit uploaded does correspond with the previous modality used for the previous visit. Unvalidated case: MRI received for visit 6 whereas CT scan were used for visit 5
Centre identification	The center identification will be checked and compared to the CRO database
Patient identification	The patient identification will be checked and compared to the CRO database
Patient birth date	The patient birth date 8included in the DICOM data) will be checked and compared to CRO database.
Images compatibility with Imagys reader	The images uploaded by the investigational center must be compatible with Keosys Imagys software (DICOM format)
Scan redundancy	The uploaded scan should not already exist on the platform

In addition to the automated quality controls described above, expert quality assessments will be performed centrally at the IRC (Table 2). As soon as a new patient visit has been successfully uploaded by the investigational center through IRC web platform, and the automated controls passed, the IRC quality controller is informed by an automatic email alert that a new visit (set of scans) is ready for evaluation. The outcome of this quality control can be either "validated" or "corrective action needed". If the visit is "validated", the process continues with the centralized analysis.

Table 2: IRC quality controller assessments

Control	Optimal quality	Sub-optimal quality	Poor quality
Apparatus model and capabilities	Multi-slice CT		Other
Slice thickness	≤ 5 mm		> 5 mm
Contrast media injected CT	YES		NO
Contiguous slices	YES	Overlapping slices	NO
Acquisition settings	According to manufacturer, taking into account patient obesity if required		Other
Reconstruction method and filters	According to the manufacturer		Other
Exam phase	Arterial and venous phase	One single venous phase	Native scan
Scan FOV	3 FOV: thoracic, abdominal and pelvic.	2 FOV (cervical FOV is not included).	1 FOV (cervical FOV is not included)
Artefacts	None	Cervical metallic artefacts, prosthetic artefacts, thoracic iodine contrast media artefacts	Any artefact that precludes the accurate analyses of 2 FOV or more

If the quality controller identifies an un-validated visit, the quality controller informs the site about the reasons why the examination was rejected and the information is traced in the platform audit trail. If at least the outcome of one control for the set of provided examinations is "poor quality", it will lead to an un-validated visit (Refer to IRC Core Imaging Manual).

The minimal requirements in order to obtain an optimal somatostatin receptor scintigraphy with OctreoScan™ image are reported in Table 3.

Table 3: Minimal requirements for somatostatin receptor scintigraphy with OctreoScan™

Control	Optimal quality	Sub-optimal quality	Poor quality
Date of Octreoscan	24 weeks prior to the patient enrolment in the study		More than 24 weeks prior to the patient enrolment in the study
Time points	2 or more time points. For example, 4h and 24h after injection or 24h and 48h		Less than 2 time points
Scan FOV	As clinically indicated most often, the 3 FOV are available: thoracic, abdominal, and pelvic. Additional cervical FOV if indicated.	2 FOV (abdominal and pelvic)	1 FOV (cervical FOV is not included)
Collimator energy	Medium energy		Low of high energy collimator
Global quality	Quality is optimal for evaluation of the exam	Quality is sufficient for evaluation of the exam	Any major artifact, image contrast alteration or major digestive activity that preclude the accurate analyses of 2 FOV or more

The quality controller will also check that the uploaded set of images does not contain visible patient identification data. In case patient identifying data is present on the reviewed exam, the quality controller will automatically ask for a corrective action.
Furthermore, the quality controller will also verify (for CT/MRI scans) that all the series were acquired at the same date (in order to avoid that several visits are mixed). If this is not the case, the quality controller will automatically ask for a corrective action.

Data on single images uploaded are made available to the CRO by means of patient/visit listings (NETTER-1 Project Status.xls) (see also Section 2.5.2.4).

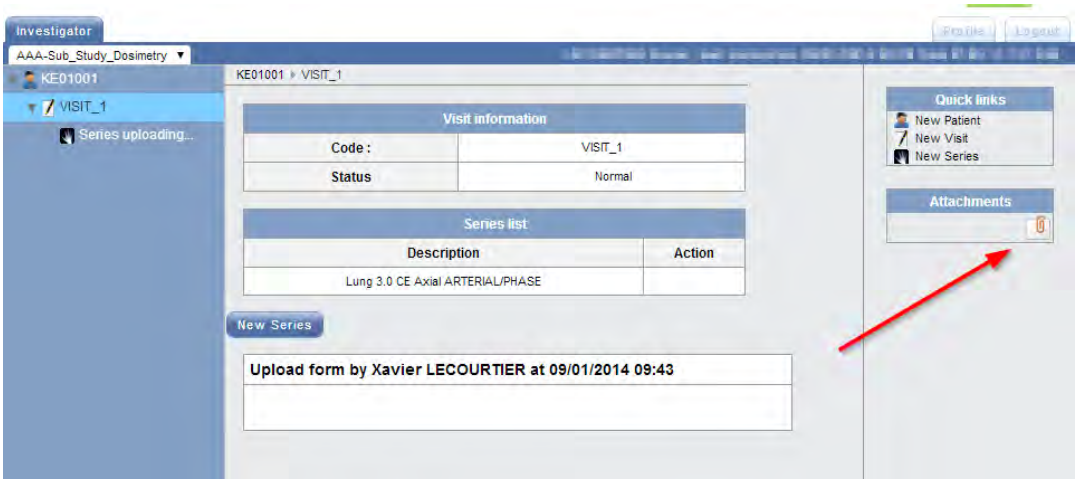
Image transfer for the dosimetry substudy

The evaluations made in the dosimetry substudy, in a subset of 20 study patients treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, are based on the reading and interpretation of WB planar and SPECT images (in addition to other non-imaging data) which are uploaded by the Investigator into the IRC platform and read by the Substudy Central Lab (IEO, Milan - Italy). In this regard, the IRC platform is used only for the image transfer. No quality control is performed on these images by the IRC. Images are uploaded by the investigator into the specific CRF of the Platform by selecting the appropriate modalities, as displayed in Figure 3 and 4, in the same way as conducted for the images uploaded in the main study.

The platform also allows the attachment of other files (Word, pdf, and Excel formats) which contain non-imaging data (e.g. calibration data; radiation detected in blood and urine) as needed for the dosimetry analysis.

Figure 3: Selection of the CRF section for the upload of substudy images

Figure 4: Screenshot for the upload of substudy images



The Substudy Central Lab finally downloads images for central analysis, after being alerted by the Investigational site or the CRO. Substudy images are QC checked by the Substudy Central Lab. Specific accounts are created by the IRC for the upload / download of the Substudy images. The process of Substudy data management and analysis is described in the Substudy Manual (Refer to NETTER-1 Substudy Manual).

Dosimetry data are elaborated at the Substudy Central Lab and outcomes on irradiation to specific critical organs (in particular, bone marrow and kidneys) released as soon as available. A final report with all patients data on radiation accumulation at all target organs and tumor lesions will be provided for inclusion in the clinical study database.

2.5.2 Image Display and Interpretation

2.5.2.1 Selection of images for interpretation, display sequence, and randomization

The selection and evaluation of the images previously uploaded by the Investigator are made independently by the central reader(s), and the evaluation is performed according to RECIST 1.1 criteria. The selection of the target lesions must be made with reference to the receptor positive tumors on somatostatin receptor scintigraphy with Octreoscan™. There is no pre-selection of images made by either the QC person, or the readers (either first reader, or adjudicator). There is no use of any supportive clinical information in the read. Information on local assessment (PD, SD, PR or CR) is given to the IRC QC person only, without detailed information on which lesions have been identified as target by the investigational site. Data on specific lesions are reported in the clinical eCRF of the main study, but central readers do not have access to the eCRF.

During the data review, readers complete a specific reading form attached to the image data in the electronic system. These data are kept on file by the IRC. In case of the need for adjudication, an email alert is automatically triggered to call an appointed adjudicator.

If the discrepancy is in relation to the screening process, the adjudicator performs a blinded analysis of the two contrasting assessments (local and central readers). If local assessment claiming tumor progression during eligibility screening is confirmed the adjudicator, the adjudicator's analysis replaces

the assessment of the first central reader and the patient is included in the study, otherwise, the adjudicator confirms the invalid PD status of the patient (see Figure 5).

If the discrepancy is in relation to follow-up data, the adjudicator will review the images independently of the previous assessments, but using targets defined during previous analyses. If local assessment shows same response as the adjudicator's, the adjudicator's analysis replaces the assessment of the first central reader. If a different response vs the local assessment is confirmed by the adjudicator (as also assessed by the first central reader), the adjudicator is also considered the reference over the first central reader (see Figure 6).The Investigator receives only the result of the adjudication, by email. The database is updated with the results of both the central reader's and the adjudicator's review.

The IRC is responsible of the quality control on the raw imaging database.

2.5.2.2 Number of readers and their background qualifications

The Quality Controller is familiar with Web browsing, medical imaging and quality control. Careful attention is assigned to the Quality Controller to warrant that the same radiologist reads successive examinations of the same patient.

Readers and adjudicators are familiar with Web browsing and medical imaging. They have expertise in Nuclear Medicine, scintigraphy evaluation and CT/MRI RECIST assessments in line with protocol requirements. A limited number of readers (up to 4) and of adjudicators (up to 2) is made available by the IRC for central reading.

2.5.2.3 Reader training and qualification

IRC performs annual interviews with their employees about their knowledge, experience and qualifications. The results are rated and documented, and serve as basis for an employee specific training according to their actual position (as per IRC internal SOP named "personal interview procedure").

During the course of hardware and software validation, all involved personnel are trained and this training is documented. The IRC, either directly or through third parties, is further responsible for the selection and training of the central readers, who have to be approved by the Sponsor. Central readers are initially trained by the Medical Director on the specific protocol, on RECIST 1.1, on the use of the Keosys platform, on the study specific eCRF, and undergo documented periodic training. IRC performs inter-readers and intra-reader assessments of variability, which are made available to the Sponsor or the appointed CRO.

2.5.2.4 Timing of image evaluation and the evaluation process

The IRC performs the image analysis and communicates the final results to the investigator site within 5 working days. Prompt interpretation of images is important for determining trial eligibility and to identify and document study events (tumor progression).

The read process is illustrated in the following Figures (Figure 5: Screening of the patient; Figure 6: Follow-up evaluation; Figure 7: Octreoscan™ adjudication process).

Figure 5: Screening evaluation process

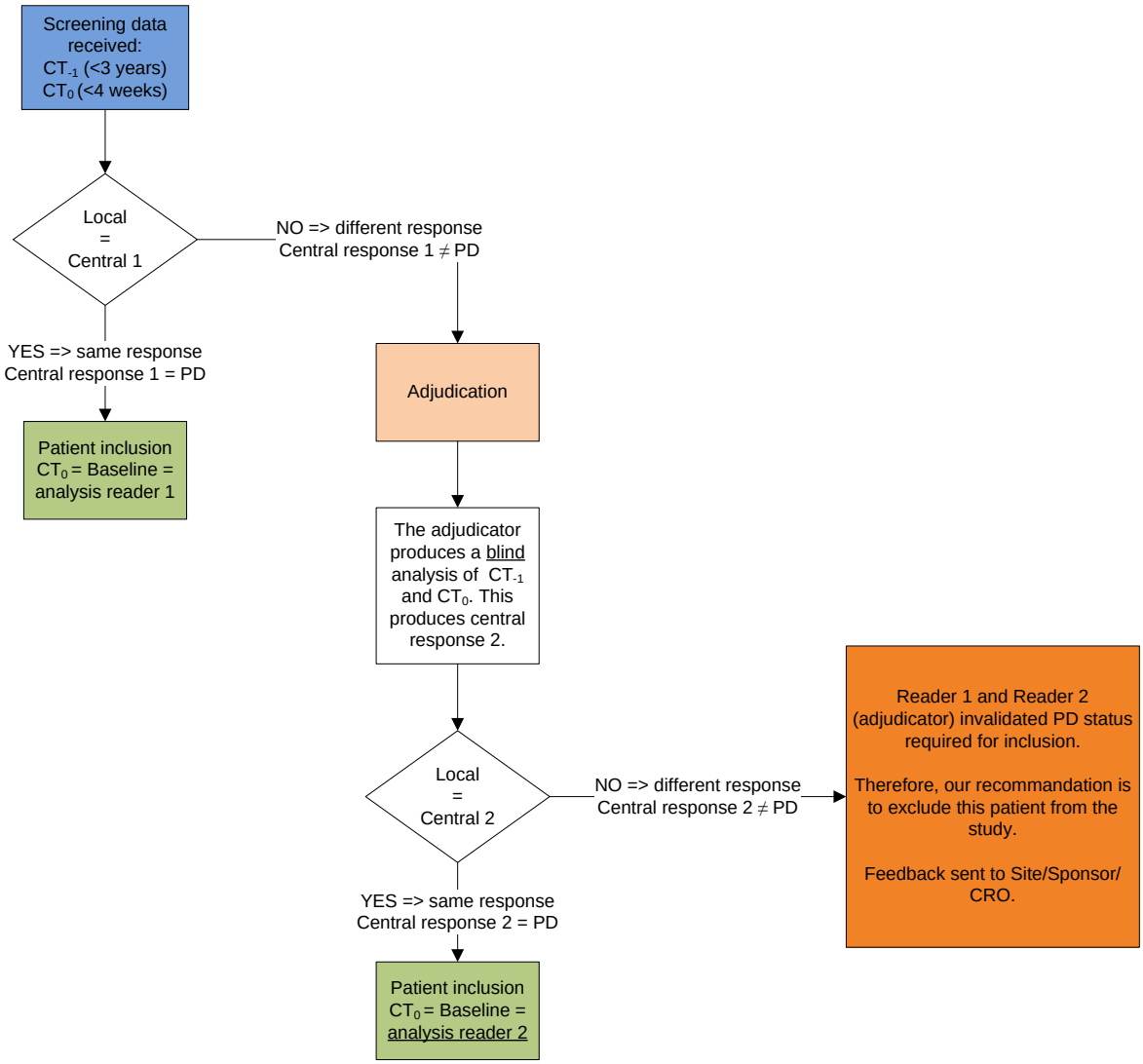


Figure 6: Follow-up evaluation process

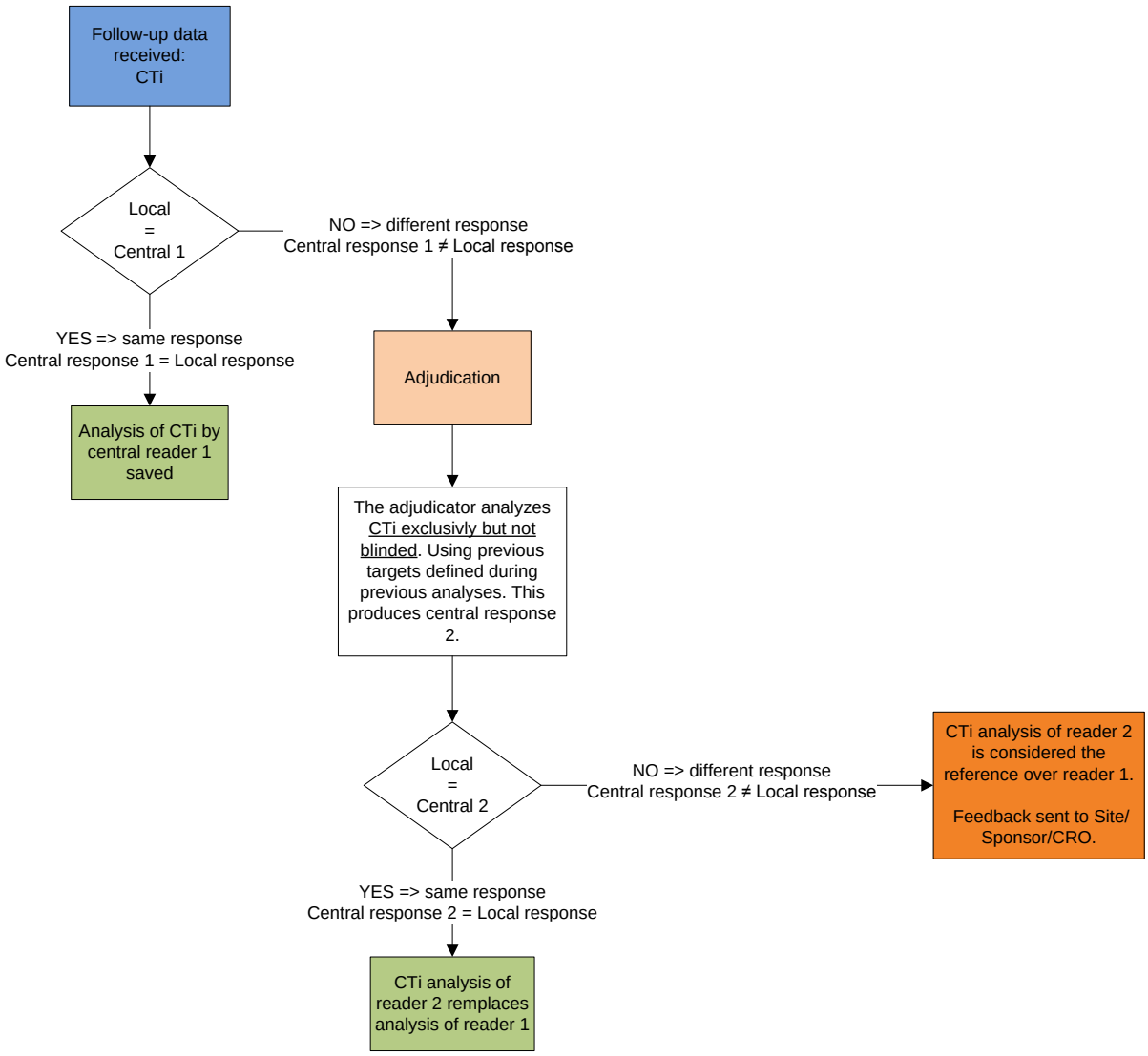
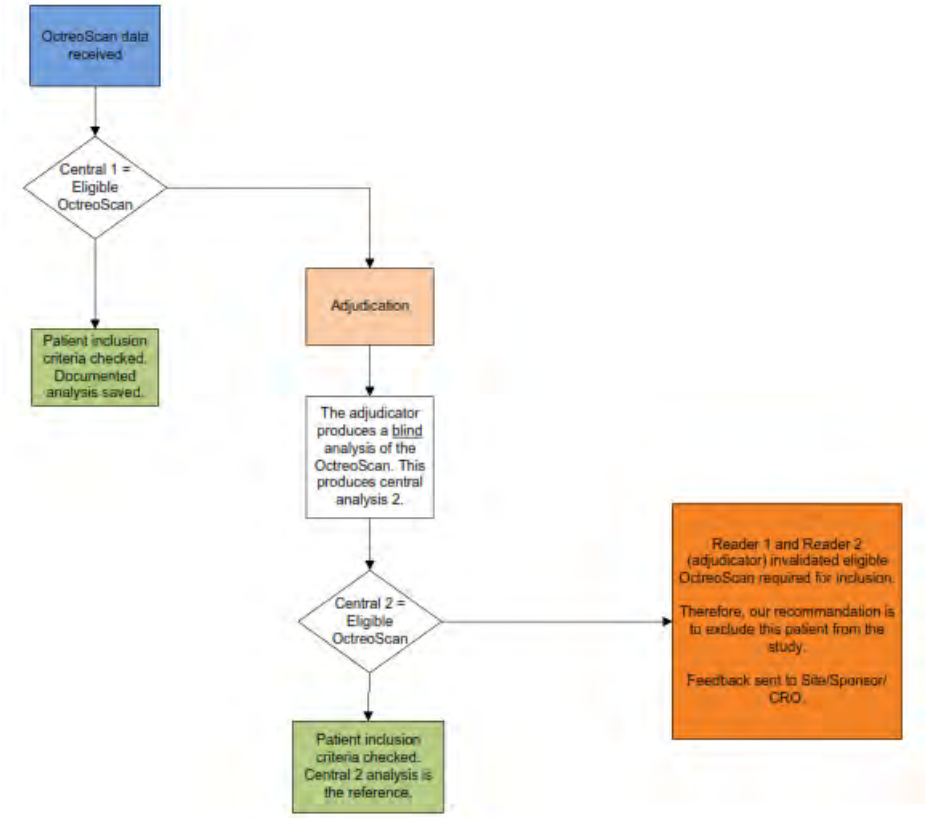


Figure 7: Octreoscan™ adjudication process



The central reading process of the CT/MRI scans is based on the independent evaluation of the central readers.

The independent central readers do not have access to the local evaluation; they receive automatic notifications when the scans need to be evaluated. As soon as the central reading is available, the central lab web platform, Imagys, automatically compares it with the local assessment (Progressive Disease). In case of discrepancies between Investigator and IRC on the evaluation of the real-time progression of disease, a third IRC evaluator ("the Adjudicator") will perform a final assessment for final adjudication (Refer to NETTER-1 Study Protocol, Section 4.4.1, and Core Image Manual Amendment, Section 5.3). The IRC Adjudicator then evaluates the scan and provide a final assessment (the Adjudicator does not have access to the local evaluation, only to the first central assessment).

If the discrepancy persists:

- Investigator assessment: non-PD; central assessment: PD. The "treatment/assessment" phase of the study is terminated and the patient should proceed to the long term follow-up assessment period. The investigator may request the continuation of treatment and assessments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate until the cumulative dose limit has been reached and/or Sandostatin LAR provided by the Sponsor according to randomization; 12-week local tumor assessments; safety assessments as in the treatment/assessment phase of the study) until progression has been documented by the Investigator, thereafter, the patient will proceed to the long term follow-up assessment phase.
- Investigator assessment: PD; central assessment: non-PD. The "treatment/assessment" phase of

the study should be continued as planned. However, the Investigator may decide to withdraw the patient from the "treatment/assessment phase" because of unethical continuation of the study in his/her opinion, and start the follow-up phase of the study. Such cases should be limited as much as possible and discussed with the local CRO representative before withdrawing the patient.

In case of adjudication due to disagreement between the IRC and the site assessment, the discrepancy is documented, and, for the Primary End-Point analysis, only the adjudication IRC assessment is considered.

The final central response (eventually as the result of the adjudication process) is communicated to the Investigator by email, and the Investigator is requested to report this outcome into the eCRF.
Additional information on the process of image reading is reported in Section 2.5.2.1.

2.5.2.5 Imaging case report forms

Images are uploaded by the Investigators into the IRC platform by opening the screen for the selection of the required protocol, and by attaching the DICOM folders and providing additional information including:

- patient code ID
- visit information
- the local (as assessed at the investigational site) assessment (CR - PR - SD - PD), without specifications on the target lesion selected (information available to the IRC QC person only)

Figures 8, 9 and 10 provide screenshots of the main CRF page of the IRC Platform, the process of file selection, the upload of the local RECIST assessment, respectively.

Additional description of the CRF functionalities is reported in the Quality Controller User's Guide and in the Investigator User's Guide.

Specific training was provided to Investigators on the use of the CRF for the image upload.

Figure 8: IRC Platform – main CRF page

Figure 9: IRC Platform – files selection

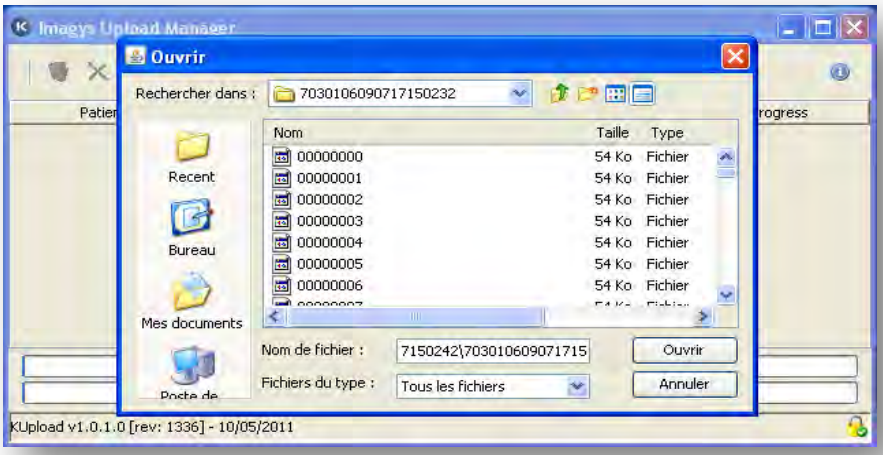


Figure 10: IRC Platform – local RECIST information

2.5.2.6 Imaging data lock process

The final IRC assessment will be transmitted to the investigator who will report the result in the clinical database via the eCRF which will be subsequently locked according to study procedures.

2.5.2.7 Quality control of the image display and interpretation process

Information on the technical equipment and the reader interpretation process is provided in Section 2.4.1.1 and 2.5.2.4.

The process of image interpretation is controlled by way of reader performance metrics (inter-, intra-reader variability), as reported in Section 2.5.2.3.

2.6 Imaging Data Transfer Process to the Sponsor

The final central review determination (CR, PR, SD or PD), as the result of the adjudication process, is communicated to the Investigator by email within 5 days of the images upload. The Investigator is requested to report this outcome into the main eCRF of the study , which becomes immediately part of the clinical data-base.

The original information on tumor progression as assessed by the IRC is also transferred to the clinical database at the end of the study. These data will represent the data-set for the statistical analysis of the tumor response-related study end-points (IRC images assessment).

Supportive data are collected separately as described in Section 2.9.

2.7 Archiving of Images

Case report forms and assessment tabulations represent source data and are retained by the IRC for potential inspection and auditing.

Images are retained by the IRC within its platform during the study and until images and all information on tumor response is transferred to the CRO. The CRO will transfer to Sponsor a copy of all images at the end of the study, after closure of the database.

Back-up storage is guaranteed. Archiving is performed in a manner conducive to a clear audit trail, including date and time recording. The IRC is responsible for the long-term archiving within its platform of images and supporting data provided by the Investigators. Copy of images and supporting data are returned to the Sponsor (via CRO) at the end of the study.

2.8 Monitoring Plans

The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that patients human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and ICH GCP, and that the data reported by the Investigator or designee are accurate, complete, and verifiable with the source documents. The Sponsor or delegated CRO is responsible for assigning (a) Clinical Study Monitor(s), who will monitor the study in accordance with the monitoring guidelines.
The Sponsor or delegated CRO implements and maintains QA and QC systems and written SOPs for clinical trial monitoring.

The Sponsor will arrange to inspect or audit the study at the IRC, clinical sites, and CRO facilities during the conduct of the NETTER-1 trial. The auditor is independent from the clinical monitoring and project management team at the Sponsor's site.

The Sponsor may delegate the CRO for specific inspection / auditing activities at the IRC.

2.9 Data Transfer and Archiving

Copies (identical to the originals) of all data pertaining to the process and the outcomes of the central imaging assessments must be returned to the Sponsor at the end of the study. Such data include (but it is not limited to):

- images received at, and managed by, Keosys for central assessments (CT/MRI, planar whole body scintigraphy and SPECT images for patients in the substudy),
- supporting documentation pertaining the single subjects (*as detailed below*).

The delegated CRO will operate on behalf of the Sponsor in this process.

Images and supporting documentation are returned to the Sponsor with data collected "by patient", at the patient's completion of the main treatment phase of the study.

Images and supporting documentation must be provided on suitable electronic support (HD, DVD). Images will be provided within folders containing the same original DICOM files as uploaded by the Investigator.

Images and supporting documentation must not contain patient identification notations (neither the patient's name, nor initials, nor birth date), but identification information on the type of scan, site/patient ID code and the visit number of reference (the date of the examination may either be reported in the file name, or be reported separately in a log with all details for each patient).

Therefore, image files must be named using the following format:

- sitecode#_patient#_Week#

For example: "BE01001_Incl_-1" or "BE01001_Incl_Octreoscan", or "BE01001_W000"
Each folder will contain sub-folders with the DICOM files (file extension .dcm).

A log with details for each patient and additional comments as needed ("supporting documentation"), should be attached to the files that are sent to the CRO.

The supporting documentation pertaining to the single subjects includes

- read outcome information;
- dates of visit by visit assessments;
- central readers identification;
- the specific reading form completed by readers, which is attached to the image data in the electronic system;
- quality-control checks upon critical software functions and notes on deviations;
- comments.

Shipments to the CRO will be made in batches including completed cases (subjects), at shipment intervals no longer than two months from the date of any patient's study ending.

General documentation on the platform and the process will also be provided, including:

- description of the platform/system characteristics, validation, reading process within the central lab;
- deviations detected in the general process either within the IRC procedures, or as sites' deviations (*NB: single patients' deviations are to be reported in the patients' supporting documentation*);
- information on central readers / adjudicators (CVs, training records, inter-readers and intra-reader assessments of variability);
- outcomes of the sites' qualification process.

The IRC is advised to keep its "original" images for archival purposes and as documentation for possible audits. The appointed CRO will cross-check data provided by Keosys with data available in

the clinical study data-base for consistency (e.g. read outcome information). The CRO will in turn provide AAA with all images / files received from Keosys, in due time.

2.10 Analysis and Interpretation of Image Information

If a patient does not have centrally assessed disease progression and is living, the patient will be regarded as censored in the context of a time to event analysis at the date of last evaluable tumor assessment. The final primary analysis of PFS will be performed when the planned number of 74 PFS events (centrally assessed progressions or deaths) is observed.

Additional PFS data are collected after the Primary End-Point has been reached during the treatment/assessment phase, or during the long term follow-up phase in case of a discrepancy in the evaluation of the progression of disease (Refer to NETTER-1 Study Protocol, Section 4.4.1). This additional PFS data will be collected and analyzed descriptively.

When a case is complete (i.e. after disease progression is centrally confirmed), the locked file (including all information available at the central reading center) is returned to the CRO (Section 2.9). A final review is then conducted by an independent radiologist and nuclear medicine specialist, member of a well-recognized nuclear medicine organization. This radiologist is blinded to the patient treatment arm. The objective of the review is to confirm that all steps of the collection, quality control, and assessment process have been conducted according to the study protocol and the Imaging Charter.

As discussed in the SAP, the primary efficacy analysis will be based on the full analysis data set of all randomized patients. A per protocol analysis will also be performed on the evaluable patients data set. Evaluability will be determined by Pr. Anders Sundin, MD, PhD, Professor and Senior Consultant at the Department of Radiology, Uppsala University Hospital, Sweden.

The following information (blind on the treatment arm and anonymised) will be provided to support his final assessment:

- All images generated during the study, including somatostatin receptors scintigraphy used to assess the lesions, images available before inclusion to confirm eligibility and data on cases which have been rejected or disputed by the IRC,
- Reports on all discrepancies (target lesions or outcome) between the local and central readers,
- Protocol violations for each case (including violation of inclusion / exclusion criteria),
- Previous anti-tumor treatments and procedures, incl. local ablation, microwave, embolization, as well as any prior surgical toraco-abdomino-pelvic procedures,
- Clinical anamnesis, including number and localization of metastases and co-morbidities at baseline,
- Previous radiology reports,
- Data on all parameters at inclusion, including date of first diagnosis, TNM and Ki67 levels.

No information on hematology or renal function (unless part of the inclusion/exclusion criteria), biochemistry / chemical markers (unless part of the inclusion/exclusion criteria), safety and adverse events, or clinical status at the time of case finalisation, will be provided.

This final assessment enables confirmation of eligibility in the per-protocol analysis of the primary end-point. Should a case not be selected for the statistical analysis, the reasons will be fully documented, and the non-selected case will nevertheless be included in the clinical study report.

The reasons for non-eligibility include images of inadequate quality which casts doubt on the outcome of the readings, questionable decisions in selecting target lesions, or other reasons which impact the relevance of the information assessment within the frame of the clinical trial protocol.

The confirmation of eligibility will be formally notified by Prof Sundin to the CRO statistician through the *Case Assessment Form* (see Appendix). All cases will be analysed (ITT), but only those "confirmed" in the overall assessment process will be part of the "per protocol" analysis.

3 REFERENCES

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Douglas PS et al., Echocardiographic imaging in clinical trials: American Society of Echocardiography standards for echocardiography core laboratories. J Am Soc Echocardiogr, 2009, 22: 755-765.

Eisenhauer EA et al., New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), Eur J Cancer, 2009, 45: 228-247.

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Ford R et al., Lessons learned from independent central review, Eur J Cancer, 2009, 45(2): 268-274.

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Keosys (IRC) Imaging Qualification

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Kwekkeboom DJ et al., ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with ^{111}In-Pentetreotide, Neuroendocrinol, 2009, 90: 184–189.

NETTER-1 Protocol NETTER-1 Informed Consent Form

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NETTER-1 Substudy Manual

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Tang PA et al., Influence of an independent review committee on assessment of response rate and progression-free survival in Phase III clinical trials, Ann Oncol, 2010, 21(1): 19-26.

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4 APPENDIX

Case Assessment Form

NETTER-1 Phase III Study
Progression case review

This final blind assessment enables confirmation of eligibility of the PD case for inclusion in the "per protocol" analysis of the primary end-point, according to the Imaging Charter*

Patient N°: |_|_|_|_|_|_|_|_| - Age: |_|_| years

Section to be filled in by the CRO:

- Are the local and the central evaluations in agreement on the PD assessment? ☐ Yes ☐ No
- Date of the PD assessed by the IRC: |_|_| / |_|_| / |_|_|_|_|
- Date of the PD assessed by the Site: |_|_| / |_|_| / |_|_|_|_|
- Comments entered in the eCRF by the Investigator, if any (in case of disagreement with the IRC):

_____
_____
_____
_____
_____

Section to be filled in by the independent reviewer:

- The independent reviewer confirms that all steps of the collection, quality control, and assessment process for this patient have been conducted according to the study protocol and the Imaging Charter? ☐ Yes ☐ No
- If No, please explain:

_____
_____
_____

- Is the independent reviewer in agreement with the IRC (presence and date of the progression)? ☐ Yes ☐ No
- If No, please explain:

_____
_____
_____
_____

FINAL ASSESSMENT:

The independent reviewer confirms that this case can be included in the Per Protocol analysis

☐ Yes ☐ No

Reviewer name: Anders Sundin, MD, PhD Reviewer signature and date: _____

*The following information (anonymised) are provided by the CRO to support this final assessment: All images generated during the study: all images (including somatostatin receptors scintigraphy) used to assess the lesions, images available before inclusion, and data on cases which have been rejected or disputed by the IRC; Reports on all discrepancies (target lesions or outcome) between the local and central readers; Protocol violations for each case (including violation of inclusion / exclusion criteria); Previous anti-tumor treatments and procedures, incl. local ablation, microwave, embolization as well as any prior surgical toraco-abdomino-pelvic procedure; Clinical anamnesis, incl. localization/number of metastases and co-morbidities at baseline; Previous radiology reports; Data on all parameters at inclusion, including date of first diagnosis, TNM and Ki67 levels.

Appendix IV: Pharmacokinetics and dosimetry data analysis

Statistical Analysis Plan

Study AAA-III-01

APPENDIX IV

DOSIMETRY AND PHARMACOKINETICS DATA ANALYSIS

Version 1.0

18-DEC-2014

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Table of contents

List of Abbreviations

Abbreviations	Description of abbreviations
^{177}Lu	Lutetium-177
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
BED	Biologically Effective Dose
CI	Confidence Interval
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
ECG	Electrocardiogram
FWHM	Full Width at Half Maximum
GBq	Giga Becquerel (Bq = unit of radioactivity)
Gy	Gray (unit of radiation exposure; equal to 100 rad)
HPLC	High-Performance Liquid Chromatography
HR	Heart Rate
ICH	International Conference on Harmonization
IEO	European Institute of Oncology
i.v.	Intravenous
LAR	Long Acting Release
mCi	MilliCurie (unit of radioactivity; 1 mCi = 37 MBq)
ND	Number of Decays
PK	Pharmacokinetics
PRRT	Peptide Receptor Radionuclide Therapy
RP	Reverse Phase (HPLC)
RT	Retention Time
SAP	Statistical Analysis Plan
SPECT	Single-Photon Emission Computerized Tomography
WB	Whole Body

1 Sub-study plan

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and methodology to be used to conduct the analysis of data generated in the sub-study of the NETTER-1 clinical trial.

The purpose of this Appendix to the SAP is to ensure the appropriate analysis of the sub-study data by using pre-specified statistical approaches prior to the database lock. It is based on the current version of the NETTER-1 clinical study protocol, version 4.0 dated March 25, 2014 and version 4.1, dated June 5, 2014. The two protocol versions do not differ for the procedures related to sub-study.

This Appendix to the SAP is a detailed technical extension of the clinical Study Protocol and follows the principles of the International Conference on Harmonization (ICH) Guidelines E3, E6 and E9 and the relevant Working Instructions and Standard Operating Procedures.

In this Appendix to the SAP, a description of dosimetry and pharmacokinetic data pertaining to the sub-study portion of the NETTER-1 trial is provided. These represent exploratory objectives of the NETTER-1 study.

A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites with the objective to provide a more complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. In addition, the pharmacokinetics of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and its metabolites will be investigated. Also the acute cardiac effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be assessed by way of a 24-hour Holter electrocardiogram (ECG) monitoring. Reference is made to Section 6.6 of the study protocol. Data will be collected according to the NETTER-1 sub-study Manual (Version 4.1 dated June 16, 2014).

According to protocol version 4.0, sub-study data are collected from patients who have been randomized to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, in addition to 30 mg Sandostatin LAR. In spite of all the efforts to increase the rate of patient enrolment in the substudy, the recruitment was not fulfilling expectations for an on-time completion. To further facilitate the enrolment, subsequent protocol Amendment 4.1 has allowed non-randomization for the patients newly enrolled in the substudy.
Dosimetry data (based on planar whole body (WB) and 3D single-photon emission computerized tomography (SPECT) scintigraphy, and blood / urine radioactivity levels) are analyzed at the Nuclear Medicine Dept of the European Institute of Oncology (IEO) (Milan- Italy) under the coordination of Dr. Marta Cremonesi. Dosimetry outcome data will be made available by IEO in MS Excel (.xls) files for data transfer into the clinical database within a SAS sub-study (dosimetry) dataset.

In addition to the dosimetry data assessed by IEO as per protocol, additional dosimetry data will be available from German centers not participating to the dosimetry substudy, but having performed similar analyses as requested by the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz - BfS). Those data will be part of the clinical dataset and will be analyzed separately.

Pharmacokinetic (PK) profiles from urines samples are assessed by the Radiopharmacy Dept of IEO (Milan – Italy) under the coordination of Dr. Marco Chinol and Dr. Stefano Papi. Urine samples will be analyzed for the determination of the rate and extent of elimination of ^{177}Lu-

$DOTA^0$-Tyr^3-Octreotate (the radiochemical status of the parent radionuclide and of its metabolites) by gamma-detector RP-HPLC. PK data will be made available by IEO in MS Excel (.xls) files for data transfer into the clinical database within a SAS sub-study (pharmacokinetics) dataset.

Electrocardiographic data are analyzed by iCardiac Technologies Inc (Rochester, NY - USA) for the determination of ECG parameters, including the QT/QTc interval. ECG data will be made available by iCardiac in .xls files for data transfer into the clinical database within a SAS sub-study (electrocardiographic) dataset. A specific SAP for ECG data has been prepared by iCardiac and included as Annex V to the NETTER-1 SAP.

1.1 Determination of sample size

20 patients will be enrolled in the sub-study.
No specific statistics-based calculation of the sample size was made.

2 Statistical and analytical procedure

2.1 Analysis variables

2.1.1 Demographic and baseline characteristics

Data from the specific eCRF pages will be used.

Dosimetry study
- date of birth, gender, body height and body weight

Pharmacokinetic study and metabolites characterization
- date of birth, gender

2.1.2 Variables on study

The following variables will be calculated.

Dosimetry study

Variables obtained from WB planar and SPECT images, as well as from blood/urine radioactivity, will be collected for the dosimetry analysis and reported in a separate document ("NETTER-1 Dosimetry Results Template") including data for each subject. This data will be used for the determination of the absorbed doses to target organs and tumor lesions, and for the biokinetics.

The analysis of data and radiation dosimetry calculations are performed at IEO.

The number of decays (ND) per unit injected activity, mathematically equivalent to the quantity of residence time (Stabin MG et al., 2005), will be calculated from multiexponential fits to the time–activity curves for spleen, kidneys, liver, testes, and remainder of body.

The time-activity curve for blood will be evaluated with rescaling for the individual blood mass based on patient gender, weight, and height. The ND in the red marrow (ND_{RM}) will be derived from the blood-based method (Cremonesi M et al., 2006; Forrer F et al., 2009): $ND_{RM} = ND_{blood} \times m_{RM} / m_{blood}$, where m_{RM} and m_{blood} are the individual red marrow and blood masses, and ND_{blood} is the ND in the blood. The red marrow mass will be derived assuming a fixed ratio of red marrow to

blood mass. The total absorbed dose to red marrow will be extrapolated from the blood curve. Absorbed doses to target organs will be calculated by entering the ND values for all the source organs in the OLINDA/EXM software and adjusting the doses reported by the software for individual weight and organ masses for kidneys, liver, spleen (determined from CT), and red marrow.

Whenever possible and for comparison purposes only, the patient specific red marrow mass will also be derived based on the individual volume of the lumbar vertebrae L2, L3, L4 (V_{L2-L4}) estimated from CT images (Ferrer L et al., 2010), according to the equation: $m_{RM} = 6.7\% V_{L2-L4}$. The dose to the red marrow will then be rescaled with the red marrow mass determined from the L2-L4 methods and compared with the previous one derived by proportionality with the blood volume.

Pharmacokinetic profiles

The Pharmacokinetic profiles will be assessed with the following procedure:

1. Determine the time-activity curves in the source organs by either numerical fitting of exponential curves to the data or by compartmental modeling to all organ uptake, blood and excretion data. A general code for numerical and compartmental modeling (the SAAM II software - http://www.saam.com) will be used (Cobelli C et al., 1998).

   The bi-exponential clearance pattern is assumed to be applied.

2. The time-activity curve in each source region will be integrated to determine the cumulated activity Ã [in MBq.h].

   A typical result of step 1 is a bi-exponential curve $A_{organ} = A_1 e^{-\lambda 1 t} + A_2 e^{-\lambda 1 t}$. The corresponding cumulated activity is:

   $$\tilde{A}_{organ} = \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}$$, with λ_p the physical decay constant of ^{177}Lu.

   If step 1 will not be successful, the cumulated activity will be calculated by applying the trapezoid method for numerical integration. Linear extrapolation to t = 0 will be performed by assuming A(0) = A(4).

3. The quotient of Ã and the injected activity IA will be calculated to yield the number of decays ND = Ã/IA (or residence time τ).

4. The fraction of administered activity that is excreted through the urinal pathway will be determined. A numerical fit (bi-exponential curve) to the urinary data will be performed to determine the fractions and elimination rates in the subsequent clearance stages:

   $$A_{Urine}(t) = A_0 - A_1 e^{-\lambda_1 t} - A_2 e^{-\lambda_2 t}$$

   A curve-fitting program, like SAAM II, will be used. The clearance stages are needed for the calculation of the bladder residence time.

5. The cumulated activity in the total body will be used to calculate the cumulated activity in the remainder of the body (source contribution to the bone marrow and other organs dose), by subtraction of the sum of the NDs in all known source organs from the total body NB:

$$\tau_{remainder} = \tau_{TB} - \sum_{source.organ.i} \tau_i$$

Radiation dosimetry calculation

Data for ^{177}Lu are available in the OLINDA/EXM (Stabin MG et al., 2005) software package. Alternatively, the S-factors can be also taken from the Radiation Dose Assessment Resource (RADAR) site (http://www.doseinfo-radar.com/RADARphan.html). By using these S-factors and the residence times for the source organs, the radiation dose to all target organs will be calculated.

For each target organ, the total dose /activity will be assessed as the sum of beta and photon radiation. For each tumour lesion, the total dose /activity will be assessed as the product of (number of disintegrations) x (dose factor for ND = 1 h).

The following parameters will be analyzed and reported in the dosimetry dataset of the study:

- Absorbed radiation dose to single organs (kidneys, liver, spleen, bone marrow, testes, bladder walls, total body, other organs) and tumour lesions per unit activity (Gy/GBq)
- Cumulative absorbed radiation dose to single organs (kidneys, liver, spleen, bone marrow, testes, bladder walls, total body, other organs) and tumour lesions, in four cycles, for a total activity of 29.6 GBq (cumulative dose calculated under the hypothesis that the biokinetics is maintained for all cycles) (Gy)
- Decay constants λ (a_1 ; a_2 ; a_3)
- Effective half-life ($T½_{eff}$), to be calculated as ln2 / λ (*ln = natural logarithm*)
- Number of Decays (ND; also referred to as “time integrated activity” or “equivalent residence time”) per unit activity (h)
- Cumulative kidney Biologically Effective Dose (BED) (Gy), to be calculated as BED x 4 (*4 cycles*)

The corresponding dosimetry data listings are shown in Appendix 8.1.

For each patient, additional information will be collected:

- information on whether the cumulative bone marrow radiation dose has exceeded 3.7 Gy,
- information on whether the cumulative kidney radiation dose has exceeded 38 Gy of BED,
- information on the cycle number when dosimetry analysis was performed
  (it is anticipated that, in the event that dosimetry calculations are performed in relation to the 2nd or 3rd cycle of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, only the dose estimates for the kidney and the bone marrow can be used in the overall evaluation, as the tumour lesions, liver and spleen can be influenced by the prior therapy effect),
- presence of risk factors for kidney toxicity (e.g.: diabetes, essential arterial hypertension, hypercholesterolemia, obesity, smoking, familiar history of kidney disease).

Pharmacokinetic study and metabolites characterization in urines

Rate and extent of elimination of ^{177}Lu-DOTA^0-Tyr^3-Octreotate in urines will be determined as % of the administered dose, over partial time-periods (0-1 hr; 1-4 hrs; 4-16 hrs; 16-48 hrs) and as cumulative elimination.

The following parameters will be calculated for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and other metabolites identified in each patient:

- Proportion of each compound in each sample (% of the peak area out of the total area).
- Retention Time (RT - min).
- Full Width at Half Maximum (FWHM) of the principal peak, as an indicator of changes in the chemical state.
- Chromatogram resolution of each peak.
- Concentration (MBq/mL), i.e. quantitative determination of each compound, calculated in relation to the radioactivity detected.

2.2 Analysis populations

All subjects with consistent data will be analysed. Subjects with insufficient availability of data will be discarded from the analysis. However, data from all enrolled subjects will be included in the substudy report as well as the reasons for eventual removal from the analysis.

Dosimetry study

For the dosimetry analysis, the following data should be available as minimum, in order to consider the case as valid:

- Site/Patient identification (Site #; Patient screening #)
- data from at least 5 time points from the WB planar images
- bladder emptying before the first image

Pharmacokinetic study and metabolites characterization

For the pharmacokinetic analysis, the following data should be available as minimum, in order to consider the case as valid:

- Site/Patient identification (Site #; Patient screening #)
- Date and time of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration
- Unavailability of all samples requested

2.3 Data analysis

Results will be presented as listings containing all data available for each single parameter and as analytical outcomes.

Each variable will be analyzed descriptively and reported as follows: for descriptive analyses of continuous variables and of changes from baseline of these continuous variables, number of non-missing values (N), number of missing values, mean, 95% CI for the mean (where appropriate), standard deviation, minimum, lower quartile, median, upper quartile and maximum will be presented. Categorical variables will be presented in frequency tables, i.e. as frequencies and percentages.

The correlation between changes in serum creatinine / creatinine clearance (calculated by the Cockroft-Gault formula) assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative kidney Biological Effective Dose (BED) up to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated.

The correlation between changes in serum creatinine / creatinine clearance (calculated by the Cockroft-Gault formula) assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative absorbed doses for kidneys up to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated.

The correlation between changes in total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (AP), serum albumin assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative absorbed doses for liver up to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated. This analysis will be conducted separately for (1) patients with normal livers and (2) patients with liver metastases.

The correlation between changes in Hb, WBCs, neutrophils, lymphocytes, platelets assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative absorbed doses for bone marrow to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated.

Results obtained from the radiation dosimetry calculations will be kept at the site (with indication of the precise archiving location) and made available upon request of the Sponsor, its delegates (e.g. the appointed CRO), or Regulatory Authorities.

2.4 Data handling conventions

2.4.1 Missing values

No replacements will be made in case of missing data for either the dosimetry, or the pharmacokinetic, or the ECG study.

2.4.2 Transformation of data

The following derived parameters will be calculated according to the following criteria / formulas:

Dosimetry study
The methods for data analysis are described in the NETTER-1 sub-study Manual. For the definition of the time-activity curves (radiation pharmacokinetic profile), appropriate numerical and compartment modelling will be applied using the SAAM II software (Cobelli C et al, 1998). Radiation dosimetry calculation will be made with the OLINDA/EXM software (Stabin MG et al, 2005).

Pharmacokinetic study and metabolites characterization
Concentration (MBq/mL) will be calculated using the following formula (derived from the calibration curve): $C = (Area - 1524) / 40161$

3 General appearance of output

Data will be presented as tables, figures, listings.
Every table, listing or graph contains the study-specific project code (Study AAA-III-01) in the first line.

For each analysis, the analysis variable will be reported. If important details are necessary to understand the output, these should be given as well.
The total number of patients within each report reflects the number of patients within the collective the analysis is based on, so if missing values occur, their frequency is also presented.

The number of decimals presented refers to the original values. Minimum and maximum have as many decimals as the original values, the mean and the median and all other percentiles have one additional decimal, and the standard deviation has two additional decimals.
Percentage values will be printed with one decimal.
No p-values are expected.

The Output will be presented using Times New Roman as the standard type of font and text size 10. The page setup is landscape and the paper size is A4 with a margin of 2.5 cm all around.

4 Software documentation

Data analyses are performed using the following specific softwares:

Dosimetry study
For the radiation pharmacokinetic profile: SAAM II® software (Cobelli C et al, 1998).
For the radiation dosimetry calculation: OLINDA/EXM® software (Stabin MG et al, 2005).

Pharmacokinetic study
Perkin Elmer TotalChrom Workstation-v6®.

5 Coding systems utilized

No internationally recognized coding systems are applicable to either the dosimetry or the pharmacokinetic analysis.

6 References

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Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med. 2005; 46:1023-7.

7 Signature Page

I have carefully read this statistical analysis plan and agree with the described methods and processing.

Marta Cremonesi
Nuclear Medicine Division
Istituto Europeo di Oncologia, Milano, Italy

Signature: Marta Cremonesi Date: 19.12.14

Marco Chinol
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Claude Hariton
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Jack Erion
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Signature: Date: 22, dec, 2014

Paola Santoro
Study Manager
Advanced Accelerator Applications SA
Saint Genis Pouilly, France

Signature: Paola Santoro Date: 22 December 2014

8 Appendices

8.1 Dosimetry outcomes data

		1 cycle x 7.4 GBq	n cycles x 7.4 GBq
Absorbed dose to	**absorbed doses per unit activity**	**absorbed doses in the cycle**	**cumulative absorbed doses in n cycles (*)**
TARGET ORGANS	**(Gy/GBq)**	**(Gy)**	**(Gy)**
Kidneys	**0.00**	**0.00**	**0.00**
Liver	**0.00**	**0.00**	**0.00**
Red Marrow	**0.00**	**0.00**	**0.00**
Spleen	**0.00**	**0.00**	**0.00**
testes	**0.00**	**0.00**	**0.00**
Bladder Wall	**0.00**	**0.00**	**0.00**
Total Body	**0.00**	**0.00**	**0.00**
Other organs	**0.00**	**0.00**	**0.00**
TUMORS			
Lesion 1	**0.00**	**0.00**	**0.00**
Lesion 2	**0.00**	**0.00**	**0.00**
Lesion 3	**0.00**	**0.00**	**0.00**
Lesion 4	**0.00**	**0.00**	**0.00**
Lesion 5	**0.00**	**0.00**	**0.00**
Lesion 6	**0.00**	**0.00**	**0.00**
Lesion 7	**0.00**	**0.00**	**0.00**
Lesion 8	**0.00**	**0.00**	**0.00**
Lesion 9	**0.00**	**0.00**	**0.00**
Lesion 10	**0.00**	**0.00**	**0.00**

(*) cumulative dose = absorbed doses in the cycle multiplied by the number of Lutathera cycles performed

	Number of decays per unit activity (ND) (h)
Red Marrow	**0.00**
Kidneys	**0.00**
Liver	**0.00**
Spleen	**0.00**
Testes	**0.00**
Remainder Body	**0.00**
Bladder Wall	**0.00**
Total Body	
Lesion 1	**0.00**
Lesion 2	**0.00**
Lesion 3	**0.00**
Lesion 4	**0.00**
Lesion 5	**0.00**
Lesion 6	**0.00**
Lesion 7	**0.00**
Lesion 8	**0.00**
Lesion 9	**0.00**
Lesion 10	**0.00**

	decay constants			T½ eff		
	a1 (h-1)	a2 (h-1)	a3 (h-1)	λ1	λ 2	λ 3
blood	0	0.0	0.00	Ln2/a1	Ln2/a2	Ln2/a3
red marrow						
kidney - left	0	0.0		Ln2/a1	Ln2/a2	
kidney - right	0	0.0		Ln2/a1	Ln2/a2	
kidneys	0	0.0		Ln2/a1	Ln2/a2	
liver	0	0.0		Ln2/a1	Ln2/a2	
spleen	0	0.0		Ln2/a1	Ln2/a2	
testes	0	0.0		Ln2/a1	Ln2/a2	
Remainder Body	0	0.0		Ln2/a1	Ln2/a2	
bladder (cumul.)	0	0.0		Ln2/a1	Ln2/a2	
OLINDA input:	0.000					
Lesion 1	0.0	0.00		Ln2/a1	Ln2/a2	
Lesion 2	0.0	0.00		Ln2/a1	Ln2/a2	
Lesion 3	0.0	0.00		Ln2/a1	Ln2/a2	
Lesion 4						
Lesion 5						
Lesion 6						
Lesion 7						
Lesion 8						
Lesion 9						
Lesion 10						

Cumulative Kidney Biologically Effective Dose (BED)

	Lu dose	**$T_{1/2\ eff}$**	**Lu-177**	**dose**	**BED pz sp**	**BED std**
	GBq	h	Gy/GBq	Gy	Gy	Gy
cy 1	0.0	00.0	**0.00**	**0.0**	**0.0**	0
cy 2	0.0	00.0	**0.00**	**0.0**	**0.0**	0
cy 3	0.0	00.0	**0.00**	**0.0**	**0.0**	0
cy 4	0.0	00.0	**0.00**	**0.0**	**0.0**	0
tot	**00.0**			**0**	**0**	**0**

Appendix V: ECG data analysis

A multicenter, stratified, open, randomized, comparator-controlled, parallel-group, Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.

(Protocol: AAA-III-01)

Analysis of ECGs from Continuous Recordings
Cardiac Substudy Statistical Analysis Plan (CS SAP)

Version: Final 1.0

Author: Meijian Zhou, PhD

Date: January 14, 2015

Review Page for Cardiac Substudy Statistical Analysis Plan (CS SAP)

Approval of CS SAP– Final Version

Distribution list of reviewers for this document prior to final sign-off.

Functional Zone Name	Reviewer's Name	Signature/Date
iCardiac-Cardiovascular Safety	Borje Darpo, MD, PhD	Jan 15, 2015
iCardiac Statistics	Meijian Zhou, PhD	15 Jan 2015
iCardiac Operations Protocol Lead	Brian Smith	15 Jan 2015

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

AIC	Akaike information criterion
bpm	Beats per minute
CI	Confidence Interval
C_{max}	Maximum plasma concentration
Δ	Change-from-baseline
ECG	Electrocardiographic
FDA	Food and Drug Administration
HR	Heart rate
ms	Millisecond
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PR	Time from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex (onset of ventricular depolarization)
QRS	Duration of the QRS complex in the ECG
QT	ECG interval between Q and T waves
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAD	Single ascending dose
SAP	Statistical analysis plan
SD	Standard Deviation
SE	Standard Error

2 AMENDMENTS FROM PREVIOUS VERSION(S)

None

3 INTRODUCTION

This cardiac substudy statistical analysis plan (CS SAP) will be used to evaluate the cardiac substudy data of the study protocol AAA-III-01, A multicenter, stratified, open, randomized, comparator-controlled, parallel-group, Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours (the NETTER-1 Study). It was developed after review of the protocol AAA-III-01 (Protocol version 4.0, dated March 25, 2014, and Protocol version 4.1, dated June 5, 2014), and finalized prior to database lock/data analysis. This document defines the populations to be analyzed and provides full details of the statistical analyses, data displays, and algorithms to be used for data derivations to aid in the production of the statistical output and the statistical section of the Clinical Study Report in regard to ECG and QTc Analysis. Relevant subject characteristics as well as the electrocardiographic parameters that will be evaluated are described along with the specific statistical methods.

4 STUDY DESIGN

This is a multicenter, stratified, open, randomized, comparator-controlled, parallel-group, Phase III study. In this study, treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) will be compared to treatment with high dose (60 mg) Octreotide LAR in patients with metastatized or locally advanced, inoperable, somatostatin receptor positive, histologically proven midgut carcinoid tumours; these patients should be progressive under Octreotide LAR. Objective tumour response in both arms is assessed every 12±1 weeks from the randomization date according to RECIST Criteria.

Patients will be evaluated for safety and tolerability in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm.

A 20-patient Dosimetry, Pharmacokinetics, and ECG study has been performed in about 10 selected sites. This substudy of the Phase III clinical trial NETTER-1 is conducted in patients who have been determined to be eligible for the main study and have signed the specific informed consent, and who have been randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm as per Protocol Amendment 4.0, or who have not been randomized but directly assigned to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, specifically for the purpose of this substudy, as per Protocol Amendment 4.1.

Regarding the cardiac portion of the substudy, a 24-hour continuous ECG recording via 12-lead Holter machine is performed on the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Data recording starts two hours prior to the start of the amino acid infusion, continue during the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and after completion of the treatment procedure for a total of 24 hours.

5 ECG OBJECTIVES AND ENDPOINTS

5.1 Objectives

This plan addresses the secondary objective of the substudy to evaluate cardiac safety: determine the acute electrophysiological changes during treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (through 24-hour continuous ECG recording via 12-lead Holter monitoring). Accordingly, this objective is further divided into the following sub-objectives:

Primary:

- To evaluate the effect of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on cardiac repolarization as measured by the QTcF interval in the enrolled patients.

Secondary:

- To evaluate the effect of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on other ECG parameters.

5.2 ECG Endpoints

Primary:

- The primary endpoint is change-from-baseline QTcF.

Secondary:

- Change-from-baseline heart rate, PR, QRS, QT, QTcB, and RR;
- Categorical outliers defined as QTcF > 450, > 480, and > 500 ms at any time point and change-from-baseline QTcF > 30 and > 60 ms;
- Categorical analyses for change-from-baseline HR > 25% decrease and HR < 50 bpm, change-from-baseline HR > 25% and HR > 100 bpm, change-from-baseline PR > 25% increase and PR > 200 ms, and change-from-baseline QRS > 25% increase and QRS > 120 ms;
- Frequency of T-wave morphology changes and U-wave presence;
- Relationship between ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plasma concentration and ΔQTcF.

6 STATISTICAL METHODS

6.1 General Methodology

All statistical analysis of the study will be performed using the statistical software SAS for Windows Version 9.3 (SAS Institute, Inc., Cary, NC). Data collected from all patients enrolled in the substudy will be presented in data listings. Both absolute values and change from baseline for each subject will be given where applicable. All continuous data

will be listed with the same precision as will be presented in the database. Data listings will be sorted by subject ID, and time point. Missing values will be represented by an empty cell and no imputation will be made.

Continuous data will be summarized in tables using missing data count, mean, median, range, standard deviation (SD), standard error (SE), and 90% 2-sided confidence interval (CI; based on a t-distribution if not otherwise stated) by time points. All continuous data will be rounded to the nearest tenth. Categorical data (including the missing data category) will be summarized by timepoint using counts and percentages. Percentages will be rounded up or down to next integer percentage. Population counts for the substudy will be used as the denominator in the calculation of percentages unless otherwise specified.

If QTc prolongation is observed which is deemed to be related to plasma levels of the drug (or its metabolites), other contributing factors will be explored. Such factors will include: hypokalemia, hypomagnesemia, presence of heart disease and concomitant medication with drugs known to interfere with ECG parameters.

6.2 Analysis Sets

Safety Set: consists of all patients enrolled in the substudy, who received at least one dose of study drug.

QTc Analysis Set: contains all patients in the safety set who had measurements at baseline as well as on-treatment data with at least1 postdose time point with a QTcF value.

Pharmacokinetic (PK) Analysis Set: consists of all patients enrolled in the substudy, who received the study drug and have at least one valid PK concentration measurement for study drug.

PK/QTc Analysis Set: contain all patients in both the QTc analysis and the PK analysis sets with at least one pair of postdose PK and QTc data from the same timepoint.

6.3 Baseline

The predose timepoint will be used as the baseline for postdose timepoints for all ECG variables.

6.4 ECG parameters

6.4.1 QT Correction Formulae

The QT and preceding RR value for each beat will be used for heart rate correction.

Replicate ECGs (up to 10) will be extracted from the continuous digital 12-lead ECG recording at predose, middle of infusion, end of infusion, then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, and 24h. The median value from each extracted

replicate will be calculated, and then the mean of all available medians from a nominal time point will be used as the patient reportable value at that time point.

QTcF:

QT corrected according to Fridericia's formula is defined as $QTcF = QT/RR^{1/3}$.

QTcB:

QT corrected according to Bazett's formula is defined as $QTcB = QT/RR^{1/2}$.

6.4.2 Central Tendency Analysis

The primary analysis will be based on a linear mixed effect model with the change from baseline QTcF as the dependent variable, time (categorical) as factor, and baseline QTcF as covariate. Subject will be included in the model as random effect for the intercept. An unstructured covariance matrix will be specified for the repeated measures at post-dose timepoints within subject. If the model with unstructured covariance matrix fails to converge, other covariance matrix such as compound symmetry can be considered. The least-squares (LS) means and their two-sided 90 % CIs will be calculated from the model and graphically displayed.

For heart rate, PR, QRS, QT, QTcB, and RR interval similar figures will be presented based on descriptive statistics. All parameters mentioned above will further be summarized in tables using mean, SE, and 90% CI by timepoint.

6.4.3 Categorical Analysis

The analysis results for categorical outliers, T-wave morphology and U-wave presence will be summarized in frequency tables with counts and percentages for both number of subjects and number of timepoints. A subject or timepoint will be determined as an outlier subject/timepoint if the following criteria (which are assessed separately) are met for the ECG intervals:

- QTcF

Treatment value of > 500 ms when not present at baseline (new onset)
Treatment value of > 480 and ≤ 500 ms when not present at baseline (new onset)
Treatment value of > 450 and ≤ 480 ms when not present at baseline (new onset)
Change in QTc from baseline of > 30 and ≤ 60 ms
Change in QTc from baseline > 60 ms

- PR

Change of PR from baseline of more than 25% increase leading to PR > 200 ms

- QRS

Change of QRS from baseline of more than 25% increase leading to QRS > 120 ms

- HR

HR changes reflecting a more than 25% decrease from baseline to a HR < 50 bpm
HR changes reflecting a more than 25% increase from baseline to a HR > 100 bpm

For T-wave morphology and U-wave presence, the analysis will be focused on change from baseline, i.e. treatment-emergent changes.

All outliers will be summarized on the basis of incidence rates. If a subject experiences more than one episode of a particular outlier event, the subject will be counted only once for that event.

6.4.4 Concentration-QTc Analysis

The relationship between plasma concentration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and primary endpoint ΔQTcF will be quantified using a linear mixed effects modeling approach. The following 3 linear models will be considered:

1. Model 1 will be a linear model with an intercept
2. Model 2 will be a linear model with mean intercept fixed to 0 (with variability)
3. Model 3 will be a linear model with no intercept.

Time matched concentration will be included in the model as covariate and subject as a random effect for both intercept and slope, when applicable.

The model that best fits the data best will be used for predicting population average Δ QTcF and its corresponding upper 95% one-sided CI bound at the geometric mean maximum plasma concentrations or other concentrations of interest.

In addition to the above analysis, alternate dependent variables such as QTcF to derive the ΔQTcF endpoint may be considered.

The plot of the observed median-decile ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentrations and associated mean ΔQTcF (90% CI) together with the mean (90% CI) predicted ΔQTcF is used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Additional exploratory analyses (via graphical displays and/or model fitting) may include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

6.5 Sample Size

Assuming a 1-sided 0.05 significance level and a standard deviation of 20 ms for ΔQTcF, a total of 20 evaluable subjects who complete the substudy will be sufficient to achieve 80% power to exclude a prolongation of 20 ms or longer of the upper 1-sided 95% CI of the mean ΔQTcF for up to 9 post-dose timepoints, assuming that the prolongation is 3 ms for all post-dose timepoints.

7 TABLES, LISTINGS, AND FIGURES

7.1 Tables

Tables will be presented in section 14.3 of the report. The numbering therefore starts with 14.3.

7.1.1 ECG parameters

Number	Title	Comments
14.3-1.1	Baseline values with descriptive statistics	Number of subjects, mean, SD, SE, min, max, median and 90% CI for each ECG parameters will be given.
14.3-1.2	Absolute values across time points for QTcF	Based on descriptive statistics
14.3-1.3	Change-from-baseline across time points for QTcF	Mean, SE and 90% CI from the linear mixed effects model will be given.
14.3-1.4	Absolute values across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-1.5	Change-from-baseline across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-1.6	QTcF outliers per absolute category (> 450 ms; > 480 ms and > 500 ms)	
14.3-1.7	QTcF outliers per change-from-baseline category (> 30 ms; > 60 ms)	
14.3-1.8	Categorical analyses for heart rate, PR, and QRS	
14.3-1.9	T-wave morphology and U-wave presence: treatment emergent changes	
14.3-1.10	Exposure-response analysis of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate associated ΔQTcF	Fixed effect estimates and corresponding p-values will be given.
14.3-1.11	Predicted ΔQTcF interval at geometric mean peak ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentration	

7.2 Figures

7.2.1 ECG parameters

Number	Title	Comments
14.3-2.2	Absolute values across time points for QTcF	Based on descriptive statistics
14.3-2.3	Change-from-baseline across time points for QTcF	Based on linear mixed effects model
14.3-2.4	Absolute values across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-2.5	Change-from-baseline across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-2.9	The relationship between ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentrations and ΔQTcF with 90% confidence interval.	Scatter plot of ΔQTc vs. concentration and regression line with CI.

7.3 Listings

7.3.1 ECG parameters

Number	Title	Comments
14.3-3.1	QT parameters – absolute values and change-from-baseline	Including QTcF, QTcB and QT
14.3-3.2	Other ECG parameters – absolute values and change-from-baseline	Including heart rate, PR, QRS and RR
14.3-3.3	T-wave morphology and U-wave presence listings	
14.3-3.4	ΔQTcF and time-matched plasma concentration for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for each subject	Data for concentration-QTc analysis

STATISTICAL ANALYSIS PLAN (SAP)
LIST OF CHANGES VERS 2.0 VS VERS 1.0

**Page refers to SAP V 2.0 REDLINE version*

Page*	**Previous version** *Vers 1.0, Jan 15, 2015*	**New version** *Vers 2.0, July 31, 2015*	**Reason for change**
Within the entire document	NA	NA	Page number format changed
1	Version 1.0 15-JAN-2015	Version 2.0 31-JUL-2015	Version 1.0 modified to Version 2.0, date updated
1	Pierrel Research Europe GmbH Email: office.europe@pierrel-research.com	THERAMetrics	CRO name changed: CRO internal reorganisation
15	In this trial, one missed assessment visit is defined as an assessment visit not occurring within 2 times the length between two assessment visits (i.e. 168 days following the last visit).	In this trial, more than one missed assessment visit is defined as an assessment visit not occurring within 2.5 times the length between two assessment visits (i.e. 210 days following the last visit).	Footnote clarified to better fit with the last criteria of the table
15	Sensitivity analyses for PFS will also be conducted,	Sensitivity and/or exploratory analyses for PFS will also be conducted, including (but not limited to),	Clarifications of the sensitivity analysis after discussions with regulatory agencies and external experts
	- Ignoring new anti-cancer treatments started before progressive disease, instead of censoring the PFS at the time of starting	- Ignoring new anti-cancer treatments started before progressive disease, instead of censoring the PFS prior to start of any such	

Page*	Previous version *Vers 1.0, Jan 15, 2015*	New version *Vers 2.0, July 31, 2015*	Reason for change
	any such treatments,	treatments, - Ignoring non-critical missed assessment visits during the treatment phase, instead of censoring the PFS prior to those missed visits,	
15,16	- Evaluating the impact of the extent of tumour burden (centrally assessed)	- Evaluating the impact of the extent of tumour burden/ tumour mass (centrally assessed), - Evaluating the impact of functioning VS. non-functioning tumour status,	
16	- Evaluating the impact of Ki67 value (centrally assessed),	- Evaluating the impact of Ki67 value / NET grading (centrally assessed),	
	- Evaluating the impact of treatment compliance	- Evaluating the impact of treatment compliance including the impact of additional potential concomitant administration of somatostatin analogues.	
17	Both local and central assessment will be considered in these analyses.	Both local and central assessment will be considered in exploratory analyses.	To anticipate any potential sensitivity analysis related to secondary parameters
	-	Such as for PFS, sensitivity and/or exploratory analyses can also be conducted to assess the impact of other parameters of clinical relevance on ORR.	
18	Sensitivity analyses will also be conducted, including:	Sensitivity analyses will also be conducted, including (but not limited to):	Clarifications of the sensitivity analysis after discussions with regulatory agencies

Page*	Previous version *Vers 1.0, Jan 15, 2015*	New version *Vers 2.0, July 31, 2015*	Reason for change
	- Impact of the extent of tumour burden (centrally assessed),	- Impact of the extent of tumour burden / tumour mass (centrally assessed),	and external experts
33	Pierrel Research Europe	THERAMetrics	CRO name changed: CRO internal reorganisation
	Pierrel Research Europe GmbH	THERAMetrics	
35	11 FDA Guidance for Industry, Standards for clinical trial imaging endpoints. Food and Drug Administration, August, 2011.	11 FDA Guidance for Industry, Clinical trial imaging endpoint process standards. Food and Drug Administration, Draft Rev 1, March 2015.	Updated reference
36	**Designated CRO Authorized Representative, Pierrel Research, Medical Director** Piergiorgio Galletti _____ _____ Name Signature Date	-	CRO name changed: CRO internal reorganisation
	Designated CRO Authorized Representative, Pierrel Research Europe, Snr Biostatistician	**Designated CRO Authorized Representative, Therametrics Europe, Snr Biostatistician**	

Statistical Analysis Plan

Study AAA-III-01

Version 2.0

31-JUL-2015

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Table of contents

List of Abbreviations

Abbreviations	Description of abbreviations
5-HIAA	5-Hydroxyindoleacetic Acid
^{90}Y	Yttrium-90
^{177}Lu	Lutetium-177
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALAT/ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASAT/AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CgA	Chromogranin-A
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contract / Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of Response
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
Erasmus MC	Erasmus Medical Center, Rotterdam, NL
FAS	Full Analysis Set
FDA	Food and Drug Administration
GlycoHb	Glycosylated Haemoglobin (haemoglobin A1C)
Hb	Haemoglobin
hpf	High-Power Field (microscopic exam)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRC	Independent Review Committee

I.V.	Intravenous
KPS	Karnofsky Performance Score
LAR	Long Acting Release
LDH	Lactic Dehydrogenase
LLN	Lower Limit of Normal (according to local laboratory normal values)
lpf	Low-Power Field (microscopic exam)
LVEF	Left Ventricular Ejection Fraction
MCV	Mean Corpuscular Volume (red blood cells)
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute (USA)
NET	Neuroendocrine Tumour
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDF	Adobe® Portable Document Format
PFS	Progression Free Survival
PFS2	Progression Free Survival (Second Progression)
PLT	Platelets
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PRRT	Peptide Receptor Radionuclide Therapy
PT	Preferred Term
PV	Protocol Violator
QoL	Quality of Life
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
s.c.	Subcutaneous
SOC	System Organ Class
SOP	Standard Operating Procedure
SWOG	South West Oncology Group
TTP	Time to Tumour Progression

ULN	Upper Limit of Normal (according to local laboratory normal values)
WBC	White Blood Cells
WHO-DRL	World Health Organization – Drug Reference List
WI	Working instruction

1 Overview and investigational plan

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy and methodology to be used to conduct the analysis of the data generated in the NETTER-1 clinical trial. The purpose of the SAP is to ensure the appropriate analysis of the study data by using pre-specified statistical approaches to the analysis prior to the database lock.

This SAP is a detailed technical extension of the clinical Study Protocol and follows the principles of the International Conference on Harmonization (ICH) guidelines E3, E6 and E9 and the relevant Working Instructions (WIs) and Standard Operating Procedures (SOPs).

This SAP is based on the current version of the NETTER-1 clinical study protocol, version 4.1, dated June 5, 2014.

1.1 Study design and randomization

This is a multicenter, multinational, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

In this study, treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) is compared to a treatment with high dose (60 mg) of Octreotide LAR. In case patients in either arm experience clinical symptoms (i.e. diarrhoea and flushing) associated with their carcinoid tumours, short-acting Octreotide s.c. rescue injections are allowed.

Objective tumour response in both arms is assessed every 12±1 weeks from the randomization date according to RECIST Criteria until progression is centrally confirmed. The baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date. In order to provide a consistent CT/MRI scan time-point between the two arms of the study it may be necessary for the site to repeat the baseline CT/MRI scan immediately before randomization if the CT/MRI time-point is greater than 4 weeks before randomization to provide more recent and protocol-compliant lesion data.

Two hundred thirty patents patients (115 patients per treatment group) are to be recruited and randomized from approximately 35 EU sites and 15 USA sites, and randomly assigned to open-label treatment (see study protocol Appendix 17).

Patient randomization is performed according to a centralized stratified permuted block randomization scheme with a balanced ratio (1:1) between the two treatment arms, stratifying for the following factors:

1) somatostatin receptor scintigraphy (OctreoScan®) tumour uptake score (Grade 2, 3 and 4): the highest Octreoscan® score measured among all the target lesions (for target / non-target / measurable lesions definition, see study protocol Appendix 2, Sections 1 and 2, RECIST Criteria, Version 1.1) will be used for stratification purpose (see study protocol Appendix 5);

   and

2) length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤6 and > 6 months).

Study main features:

1. Total number of randomized patients: 230
2. First patient randomized: Q3 2012
3. Pre-defined accrual period: 18 months
4. Expected last patient in: Q4 2014
5. PFS primary analysis occurs at 74 evaluable and centrally confirmed disease progressions or death events
6. Long term follow-up: 5 years from date of randomization of the last randomized patient
7. End-of-study (EOS): when 158 deaths are recorded or when 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first.
8. OS primary analysis point occurs at 158 deaths or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

Dosimetry, PK, ECG substudy:

A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites to provide a complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. To prevent biasing the results obtained from patients randomized in the main study, the patients enrolled in the substudy according to the Study Protocol version 4.1 (enrolled without randomization) will not be considered in the primary analysis of the main study groups. The statistical analysis of this substudy is described in a separate statistical analysis plan (SAP).

1.2 Objectives

1.2.1 Primary objective

The primary objective of the study is to compare Progression Free Survival (PFS) after treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, well-differentiated midgut neuroendocrine tumours.

1.2.2 Secondary objectives

- To compare the Objective Response Rate (ORR) between the two study arms;
- To compare the Overall Survival (OS) between the two study arms;
- To compare the Time to Tumour Progression (TTP) between the two study arms;

- To evaluate the safety and tolerability of ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate;

- To evaluate the health related quality of life (QoL) as measured by the EORTC QLQ-G.I.NET21 questionnaire (Appendix 3 of the study protocol).

1.2.3 Exploratory objectives:

- To explore the correlation of toxicity outcomes and administered radioactivity corrected for body weight and body surface area;

- To explore the correlation of clinical efficacy outcomes with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;

- To evaluate dosimetry, pharmacokinetics (PK) and ECG in a subset of 20 patients (this objective will not be investigated in this Statistical Analysis Plan but in a separate SAP for the substudy analysis);

- To explore the correlation of clinical efficacy outcomes with OctreoScan® tumour uptake score;

- To explore the correlation of clinical outcomes with serum levels of Alkaline Phosphatase (AP);

- To evaluate the Duration of Response (DoR) in the two study arms;

- To evaluate the Time to Second Progression (PFS2) in the two study arms.

1.3 Determination of sample size

A Phase I/II clinical trial conducted at the Erasmus MC ("A phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate in patients with somatostatin receptor positive tumours") provided supportive information on the efficacy of treatment with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate in patients with midgut carcinoid tumours. In this study, an objective tumour response rate of 23% (CR + PR according to SWOG Criteria), at 3 to 4 months after the last treatment, was determined in patients treated with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate, based on an analysis in 188 patients with carcinoid tumours (Kwekkeboom DJ et al., 2008).

A retrospective, independent verification of the Erasmus MC Phase I/II study source data and a statistical analysis of the study results have been conducted to support the initiation of the Phase III study. Within this assessment, a median PFS of 45 months with a 95% CI of 22-57 months was observed in a subgroup of 51 patients with midgut carcinoid tumours and with progressive disease within 12 months before entering the study (notably similar to the population in the present phase III Study). However, due to the small size of this subgroup, the median PFS has a large confidence interval (95% CI of 22-57 months).

With respect to the second arm (Octreotide LAR) of the Phase III study, there are only two relevant data sets for patients with midgut carcinoid tumours treated with Octreotide LAR available in literature: the PROMID study (Rinke A et al., 2009), with a median PFS of 14 months, and the RADIANT-2 study (Pavel M et al., data presented at the 8th Annual ENETS Conference, 9–11 March 2011, Lisbon, Portugal) with a median PFS of 11 months. In the PROMID study, patients with midgut carcinoid tumours were enrolled in a double blinded randomized two-arm trial. Patients in the control arm received a placebo, and patients in the treatment arm received 30 mg Octreotide LAR (Rinke A et al., 2009). In the RADIANT-2 study, patients with carcinoid tumours (diverse sites) were randomized for treatment in two comparator arms (Yao J et al., 2008). In one arm, patients received 30 mg Octreotide LAR alone, and in the other arm patients received Octreotide LAR plus Everolimus (Afinitor®).

For the purpose of calculating sample size in the NETTER-1 Phase III study, the results of the PROMID study were deemed to be the most applicable. This study was performed using a similar group of patients (progressive midgut carcinoid tumours at enrolment) whereas the RADIANT-2 study was not restricted to midgut carcinoid tumours. The PROMID study however, was conducted as a fully double-blind clinical trial, and it would be expected that such a study would not be significantly impacted by high patient dropout rates; rather the likely decision point for a patient to participate in such a study would be before enrolment – thus low impact on the trial for either dropout or intent to treat issues.

The subgroup of progressive midgut carcinoid patients, treated with ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate in the Erasmus MC Phase I/II trial, were determined to have a median PFS of 45 months. This PFS estimate has substantial uncertainty because of the wide 95% CI of 22-57 months, and because of the relatively small number of evaluated patients. Therefore, a median PFS of 45 months for the ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate arm was considered to be optimistic. Consequently, a median PFS of 30 months (obtained by calculating the mean of the median PFS of the ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate arm and the median of 14 months for the Octreotide LAR arm, i.e. (45 months +14 months)/2 $\approx$ 30 months) was used to determine the sample size of this study. This more conservative value still represents a highly relevant clinical improvement in PFS compared to the control group (Octreotide LAR).

The number of patients to be randomized into the study was determined using the following criteria:

- ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate arm: median PFS of 30 months
- Octreotide LAR: median PFS of 14 months (PROMID study)
- Significance level 5% two sided (or 2.5% one-sided), power 90%
- Pre-defined accrual period: 18 months
- Follow-up period: 18 months (corresponding to the length of treatment period)

Based on these criteria, the study would need to randomize 124 patients (62 per arm), and would observe 74 PFS events during the course of the study. Therefore, the PFS primary analysis point

occurs when there are 74 evaluable and centrally confirmed disease progressions or death events in the study.

With respect to the Erasmus MC Phase I/II trial, all patients enrolled in the study received ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate treatment.

In order to ensure an adequately sized clinical trial, it is also necessary to have a realistic estimate for dropout rates. In the PROMID study, the dropout rate was predicted to be 10% before the start of the study. At the interim analysis (Rinke A et al., 2009), 9 patients (21%) out of 42 patients in the Octreotide LAR treatment arm had withdrawn from the study. Four of the dropouts were due to consent withdrawal, and five were due to adverse events. This contrasts with the dropout of only 3 patients in the placebo arm (2 withdrawn consents, and 1 switched treatment). Since the patients were unaware of what treatment they received, one can expect the dropout rate of the Octreotide LAR arm to be a lower limit for the present Phase III study, because there will likely be additional dropouts due to patient 'treatment awareness'. In addition, the treatment arm of the current Phase III trial will have a much longer time span of follow-up and time to progression, meaning that virtually all of the ^{177}Lu-DOTA^{0}-Try^{3}-Octreotate treated patients will need to complete at least a full year follow-up, because very few are expected to progress during this period. Consequently, dropout rates (and intent to treat penalties) could also be expected to be high in this arm. For these reasons, a 20% dropout is anticipated.

Therefore, a total of 160 patients (80 patients in each treatment group) are necessary to control for an estimated 20% drop-out rate.

In addition, the sample size was also adjusted to allow detection of a statistically significant and clinically relevant difference in OS (80% power) between the two arms of the study. The determination of sample size for OS is based on the following assumptions:

- Octreotide LAR median OS: 32 months
- ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate median OS: 50 months
- Significance level: 5% two-sided
- Nominal power: 80%
- Pre-defined accrual period: 18 months
- Long-term follow-up: 5 years

Accordingly, 230 patients (115 patients in each treatment group) are to be randomized.

The median OS in the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm is expected to be 50 months. The median OS reported in the Erasmus MC Phase I/II study was 47.3 months (95% CI [27.8 - 75.3]), for the subgroup of 51 patients with progressive midgut carcinoid tumours. More recent survival analyses in a similar population treated with PRRT have been reported. In 2012, Baum RP et al. reported an overall survival of 59 months from the first cycle of PRRT using ^{177}Lu-DOTATATE. Baum et al. (2014) also published the outcome of a retrospective analysis assessing the efficacy of PRRT in

1,000 patients with metastatic and/or progressive NETs using ^{177}Lu (n=331), ^{90}Y (n=170) or both (n=499). The median OS for all patients was 52 months from the start of the treatment. With regard to the used radionuclide, the following OS were reported: 24 months with ^{90}Y, 55 months with ^{177}Lu, and 64 months with both. There is however no indication of the used peptide, albeit this investigators group is known to use mainly DOTATOC and DOTATATE.

Additionally, Kunikowska J. et al (2013) published their results from 358 patients treated with PRRT with ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and ^{90}Y/^{177}Lu-DOTATATE collected from April 2004 to December 2010. They reported a median OS of 49.8 - 52.8 months in the group of patients treated with ^{90}Y/^{177}Lu-DOTATATE.

Finally, Paganelli G. et al. (2014), reported the most recent overall survival data from a study with 49 patients with advanced well-differentiated gastrointestinal NETs (79% midgut NETs) treated with ^{177}Lu-DOTATATE. The median OS was not reached at the time of publication, after a median follow-up of 38 months, ranging from 11 to 59 months.

Therefore, a median overall survival of 50 months is expected.

The median OS in the control arm (Octreotide LAR) is expected to be 32 months, as per the updated results reported in the RADIANT-2 study.

In the NETTER-1 study design, the length of the overall survival assessment period includes an 18-month accrual period, and a 5-year follow-up period. The 5-year follow-up is the predicted length of the study; however, the actual end-of-study will be based on death events (158), or after 5 years from the randomization date of the last randomized patient, whichever occurs first. The analysis of OS will be conducted at that time (158 deaths or 5 years from the date of randomization of the last randomized patient have lapsed, whichever occurs first).

1.4 Modifications from the statistical section of the protocol

Not applicable.

2 Statistical and analytical procedure

The statistical analysis will be performed in accordance with the principles stated in the Consensus-Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonisation (ICH). The data will be analysed when the database is discrepancy free and locked.

2.1 Analysis populations

Before the database is locked and the statistical analysis is initiated, all problematic cases where evaluability remains unclear will be scrutinized by a Data Review Committee. The Data Review Committee will consist of the biostatistician assigned to the study, the study manager of the CRO responsible for the execution of the study, and one or more designated person from the Sponsor.

For the analysis of the study results, the following patient populations have been defined:

2.1.1 Efficacy populations

2.1.1.1 Full Analysis Set (FAS)

The Full Analysis Set consists of all patients randomized. Following the intent-to-treat principle, patients will be analysed according to the treatment they were assigned at randomization.

2.1.1.2 Per Protocol Set (PPS)

The Per Protocol Set (PPS) consists of all randomized patients, who had no major protocol violations. The PPS will be identified prior to database lock. Major protocol deviations refer to deviations that critically impact efficacy analysis materially, such as not following important inclusion/exclusion criteria (e.g. incorrect diagnosis), taking wrong study medication, etc…

A final independent assessment will enable confirmation of eligibility in the per-protocol analysis of the primary endpoint. Should a case not be selected for the PPS analysis, the reasons will be fully documented, and the non-selected case will nevertheless be included in the clinical study report. The reasons for non-eligibility include images of inadequate quality which casts doubt on the outcome of the readings, questionable decisions in selecting target lesions, or other reasons which impact the relevance of the information assessment within the frame of the clinical trial protocol.

2.1.2 Safety Set (SAF)

The Safety Set (SAF) consists of all randomized patients, who received at least one dose of study drug. Patients will be analysed according to treatment received.

The FAS will be used for all analyses of efficacy, demographics and baseline characteristics. The PPS will be used for the per-protocol analyses of primary objective and key secondary variables. The safety set will be used for all safety analyses.

2.2 Analysis variables and their statistical analysis

In general, for descriptive analyses of continuous data, number of non-missing values (N), number of missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum will be presented. Categorical data will be presented in frequency tables, i.e. as frequencies and percentages. Inferential statistics will be only performed for the primary variable and selected key secondary variables (i.e. ORR and OS).

2.2.1 Demographic and baseline characteristics

Demographic data determined at screening or baseline visit like age [years], gender (female, male), ethnicity (Caucasian/White, Black or African American, Asian, Hispanic, Other), height [cm], weight [kg], body mass index (BMI) [kg/m²] will be analysed.

Additionally, baseline characteristics of the underlying disease conditions such as primary tumour site, site of metastases, prior cancer surgery (in case of resections: site of resection, in case of ablation: type of ablation, i.e. cryotherapy or radio frequency), OctreoScan® Tumour Uptake, extent of overall tumour burden (at baseline), TNM criteria, disease stage, objective tumour response (sum

of diameters for target lesions, Overall tumour response) at screening and Karnofsky performance status (KPS) at screening will be investigated.

Demographic and other baseline patient data (including disease characteristics) will be summarized descriptively by treatment group for the FAS and the PPS. The summary of demographics will also be provided for the Safety Set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum will be presented. All background and demographic data will be listed in detail.

2.2.2 Efficacy variables and their statistical analysis

All inferential statistics will be interpreted at the 5% 2-sided level, with the exception of OS where the significance level is adjusted to 0.0085% to account for an interim analysis at the time of the final PFS analysis. The primary objective will be tested with a confirmatory intent. A method to control the family-wise type I error rate for the ORR and OS end-points is reported in Section 7.5.2 of the Study Protocol and in Section 2.2.2.2.3 of this SAP. All other efficacy variables will only be evaluated with an exploratory intent, i.e. all reported p-values for all other efficacy variables will only be interpreted in an exploratory sense.

2.2.2.1 Primary efficacy variable

The primary efficacy variable of this study is Progression Free Survival (PFS). PFS is defined as the time from randomization to documented centrally assessed disease progression, as evaluated by the Independent Review Committee (IRC), and death due to any cause. If a patient has no centrally assessed progression and has not died at the time of the primary end-point analysis, the patient will be regarded as censored in the context of a time to event analysis at the date of last evaluable tumour assessment.

Disease progression is determined by objective tumour response status using RECIST Criteria, Version 1.1. Objective tumour response and progression status are determined by comparing follow-up and baseline tumour measurements in all patients based on scans done every 12±1 weeks after randomization until the PFS Primary End-Point for the overall study is reached (74 PFS events). At that time patients who have been on study less than 76 weeks continue the same assessment schedule until Week 76 unless the patient progresses or dies.

If a patient is switched to another anti-tumour treatment prior to a confirmed progression event, the patient will discontinue study treatment, but will continue to be followed for overall survival. Information regarding the alternative anti-tumour treatment is to be documented in the CRF.

The following rules will be used to determine the event / censoring date as well as the status of event or censoring at the time of the analysis of the primary end-point PFS:

Situation	Date of Progression or Censoring	Outcome
No baseline tumour assessments	Date of randomization	Censored
Progression documented between scheduled assessment visits	Date of radiological assessment showing progression, if centrally confirmed	Event (Progressed)
No progression	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for undocumented progression and no additional scans are collected	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for toxicity or other reason with no additional scans	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for toxicity, but with continued scanning and subsequently documented progression	Date of radiological assessment (date of the scan) showing progression, if centrally confirmed	Event (Progressed)
New anti-cancer treatment started	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Death before first progression assessment	Date of death	Event (Death)
Death between adequate assessment visits	Date of death	Event (Death)
Death or progression after more than one missed assessment visit during the treatment phase*	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored

(*) In this trial, more than one missed assessment visit is defined as an assessment visit not occurring within 2.5 times the length between two assessment visits (i.e. 210 days following the last visit).

Sensitivity and/or exploratory analyses for PFS will also be conducted, including (but not limited to),

- Assigning the event time to the next scheduled imaging time rather than the actual time, to correct for any difference in timing of scans,

- Ignoring new anti-cancer treatments started before progressive disease, instead of censoring the PFS prior to start of any such treatments,

- Ignoring non-critical missed assessment visits during the treatment phase, instead of censoring the PFS prior to those missed visits,

- Evaluating the impact of the presence and number of distant metastases,

- Evaluating the impact of the extent of tumour burden / tumour mass (centrally assessed),

- Evaluating the impact of functioning VS. non-functioning tumour status,
- Evaluating the impact of the Karnofsky Performance status,
- Evaluating the impact of Ki67 value / NET grading (centrally assessed),
- Evaluating the impact of ssr scintigraphy (uptake) grading (centrally assessed),
- Evaluating the impact of treatment compliance including the impact of additional potential concomitant administration of somatostatin analogues.

Acceptable treatment compliance is defined as follows:

- In the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm: a full cycle of 29.6 GBq (800 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (in 4 administrations of 200 mCi) or at least 80% of the dose has been administered. 30 mg Octreotide LAR is administered every 4 weeks as concomitant treatment for symptoms control. In case of dose reduction due to toxicity, at least 75% of the cumulative dose should have been administered. There should be no rule of compliance because of missed administrations of Octreotide LAR.
- In the 60 mg Octreotide LAR arm: one i.m. injection of 60 mg Octreotide LAR every 4 weeks or at least 80% of the scheduled dose has been administered till progression with a minimum of three doses.

A radiological assessment is considered as an adequate assessment if the RECIST response (as per IRC) is CR, PR, SD or PD. A response of NE or missing will not be considered as an adequate assessment.

As indicated in the Table above, the date of progression should be assigned based on the documented time of progression and not, for example, based on scheduled time of evaluation.

The final primary analysis on the PFS will be performed when the planned number of 74 evaluable and centrally confirmed PFS events or deaths is observed. Further details on the centralized imaging assessment process and evaluable cases are presented in the Imaging Charter (Appendix III).

The median point estimate and 95% Confidence Interval (CI) for the PFS will be calculated using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the PFS between the two treatment groups. The size of effect will be quantified by plotting the estimates of the survivor functions for PFS, estimating the hazard ratio, the median time-to-event and other percentiles (e.g. upper quartile, lower quartile), and the percentage of patients event-free at particular time-points (e.g. percentage of patients event-free at 1-year), based on semi-parametric procedures. Censoring patterns will be described appropriately (e.g. time-to-censoring).

The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of PFS at any time point (i.e.: S1=S2), against the two-sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2).

The primary efficacy analysis will be conducted for the FAS. In addition, the primary efficacy variable will be analysed for the PPS.

Additional PFS data are collected after the Primary End-Point has been reached as an effect of the continuation of the study in the treatment/assessment phase for patients who have not experienced tumour progression, or during the long term follow-up phase in case of discrepancy in the evaluation of the progression of disease (see Study Protocol Section 4.4.1). This additional PFS data will be collected and analysed descriptively. These additional PFS data will be collected up to the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.

For sensitivity analysis, Cox's proportional hazards model will be used to assess the impact of covariates on the estimated hazard ratio. The model will first be fitted with a binary indicator for randomized treatment and all covariates that may potentially influence PFS. A step-down procedure will be used to eliminate covariates (other than treatment) that do not reach a significance level of 0.05. Multicollinearity will be explored, and the hypothesis of proportional hazards tested. These analyses are exploratory in nature and will serve to support the primary efficacy analysis.

2.2.2.2 Secondary efficacy variables and their statistical analysis

The secondary efficacy variables are:

- Objective Response Rate (ORR),
- Overall Survival (OS) and
- Time to Tumour Progression (TTP)

These key secondary efficacy variables will be reported using the FAS and PPS.

Duration of Response (DoR) and Time to Second Progression (PFS2) will also be analysed descriptively as secondary exploratory end-points.

Both local and central assessment will be considered in exploratory analyses.

2.2.2.2.1 Objective response rate (ORR)

Objective Response Rate (ORR) will be calculated as the proportion of patients with tumour size reduction of a predefined amount (the sum of partial responses (PR) plus complete responses (CR)) at the time of the statistical analysis. Response duration will be calculated from the time of initial response until documented tumour progression.

Response rates and 95% CIs will be calculated for the ORR by treatment group. Frequencies in the two treatment groups will be compared by Fisher's exact test.

The comparison of ORR by Fisher's exact test investigates the null hypothesis that the two treatment group proportions are equal (i.e.: $p1=p2$) against the two-sided alternative hypothesis that the two treatment group proportions are not equal (i.e.: $p1 \neq p2$).

Such as for PFS, sensitivity and/or exploratory analyses can also be conducted to assess the impact of other parameters of clinical relevance on ORR.

2.2.2.2.2 Overall survival (OS)

Overall Survival (OS) is defined as the time (number of days) from the date of randomization to the date of death due to any cause, or to the date of last contact (censored observation) at the date of data cut-off, and during the entire study period (i.e. the treatment phase + follow-up). OS will not be censored if a patient receives other anti-tumour treatments after the NETTER-1 study medication.

Survival data will be collected at the time of the analysis of the primary end-point (PFS), and updated 6-monthly thereafter until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first.
An interim analysis for OS will be performed at the time of the PFS analysis.

The median point estimate and 95% Confidence Interval (CI) for the OS will be provided using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the OS between the two treatment groups.

The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of OS at any time point (i.e.: S1=S2), against the two-sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2).

Sensitivity analyses will also be conducted, including (but not limited to):

- Impact of subsequent antitumor treatments after progression,
- Impact of the presence and number of distant metastases,
- Impact of the extent of tumour burden / tumour mass (centrally assessed),
- Impact of treatment compliance.

Patients who have withdrawn from the study, or who have progressed, may receive subsequent non-study PRRT (compassionate use programs or local radiopharmacy products). The impact of this treatment on OS will also be assessed.

2.2.2.2.3 Hierarchical Testing Procedure for PFS, ORR and OS

A gate-keeping testing procedure will be used to adjust the multiple testing for the primary variable and the family of secondary variables ORR and OS, (i.e. the family for the secondary variables will be tested only if the null hypothesis for the primary variable (PFS) is rejected at the 5% significance level).

The hypotheses for ORR and OS will be tested using a fixed sequence procedure approach to control for the family-wise error. No adjustment will be applied to TTP since this variable is not considered for regulatory purposes.

ORR will be tested first at the 5% significance level at the time of the final PFS analysis. If the ORR null hypothesis is rejected, then the OS hypotheses will be tested; otherwise no formal OS testing will be performed and the procedure stops.

OS analyses will be adjusted using O'Brien-Fleming spending function strategy with a 0.0085% significance level at the interim analysis (PFS final analysis).

The gate-keeping and fixed sequence testing procedures strongly control the family-wise type I error rate at 5%.

2.2.2.2.4 Time to tumour progression (TTP)

Time to tumour progression (TTP) is defined as the time (number of days) from randomization to objective tumour progression centrally assessed. It includes patients who drop out due to toxicity, but omits patients who die without measured progression (censored to last follow-up date or death date).

TTP will be similarly analysed as the primary efficacy variable.

The median point estimate and 95% Confidence Interval (CI) for the TTP will be provided using the Kaplan-Meier method, and the unstratified log-rank test will be used to compare the TTP between the two treatment groups.

The null hypothesis will be investigated, that the survival experience in the two groups is the same, i.e. there is no difference between the treatment groups in the probability of TTP at any time point (i.e.: S1=S2), against the two-sided alternative hypothesis that the survival experience in the two treatment groups is different (i.e.: S1≠S2).

2.2.2.2.5 Duration of Response (DoR)

Duration of Response is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST. DoR will be analysed descriptively for each treatment group without comparison between groups.

2.2.2.2.6 Time to Second Progression (PFS2)

As additional secondary exploratory end-point (local RECIST assessment), the Time to Second Progression (PFS2) will be assessed in the two study arms. PFS2 is defined as the time from randomization to the time of disease progression or death due to any cause (on any treatment) following the first episode of disease progression.
After progression and during the long-term follow-up additional information on further anti-tumour therapies and scan assessments outcome (RECIST local evaluation) will be collected to be able to evaluate the Time to Second Progression (PFS2) in the two study arms.

PFS2 will be analysed descriptively for each treatment group without comparison between groups.

2.2.2.2.7 Correlation analyses

The following correlation analyses will be performed to assess prognostic value:

- the correlation of clinical efficacy outcomes (PFS, OS, TTP) with the levels of the biomarkers Chromogranin-A (CgA) in the serum and 5-Hydroxyindoleacetic acid (5-HIAA) in the urine;

- the correlation of clinical efficacy outcomes (PFS, OS, TTP) with OctreoScan® tumour uptake score;

- the correlation of clinical outcome (PFS, OS, TTP) with serum levels of alkaline phosphatase (AP);

- Impact on PFS, OS and TPP for both treatment groups will be correlated to objective tumour response, KPS, and other parameters of clinical relevance.

In addition, the relationship of toxicity outcomes with body weight and body surface area will be determined.

For this purpose, the correlation coefficient according to Pearson and the correlation coefficient according to Spearman are calculated depending on the respective type of the respective variable.

2.2.3 Additional efficacy variables and their statistical analysis

Within the scope of the overall tumour evaluation the following variables will be investigated:

- TNM criteria (T-Primary tumour lesions, N-Regional lymph nodes involvement and M-Distant metastasis),

- Disease stage (for endocrine tumours of lower jejunum and ileum) and

- Objective tumour response (Sum of diameters for target lesions, Response of target lesions, Response of non-target lesions, Overall tumour response).

For the parameter “Sum of diameters for target lesions”, descriptive statistics (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) of the observed values as well as for the changes from baseline value (i.e. pre-post differences) will be presented.

For all other variables, frequency tables presenting frequencies and percentages will be created by visit, overall and by treatment group.

The follow-up time and percentage of dropouts will be compared between the randomized treatment groups. Follow-up times are defined as the time between randomization and the latest recorded assessment (or death) date known for a patient. Follow-up times will be compared between the randomized treatment groups using an unstratified log-rank test, with the censoring indicator inverted (i.e. censored observations considered complete observations, and vice versa). The percentage of dropouts will be compared between the randomized treatment groups using a chi-squared test. These analyses will be used to interpret and/or support the primary efficacy analysis.

2.2.4 Multiplicity issues

A gate-keeping testing procedure will be used to adjust the multiple testing for the primary variable (PFS) and the family of secondary variables ORR and OS as described in section 2.2.2.2.3. The gate-keeping and fixed sequence testing procedure strongly control the family-wise type I error rate at 5%.

All other efficacy variables will only be evaluated with an exploratory intent, i.e. all reported p-values for all other efficacy variables will only be interpreted in an exploratory sense.

2.2.5 Safety variables and their statistical analysis

2.2.5.1 Adverse events

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject, which does not necessarily have a causal relationship with the study medication.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a study medication, whether or not causally related to the study medication. Symptoms of the underlying diseases are not considered AEs, except a significant change as assessed by the Investigator occurred.

All AEs, whether or not spontaneously reported by the patient, will be reported from the time the ICF is signed onwards until the PFS Primary End-Point is reached, then until Week 76 post randomization after the PFS Primary End-Point has been reached (i.e. 74 evaluable and centrally confirmed disease progressions), or until early termination.

An AE is defined as treatment-emergent, if its onset occurred after the first administration / intake of study medication or if an existing event worsened during the treatment phase relative to the pre-treatment state.

An AE is defined as baseline AE if its onset occurred after the date of Informed Consent and prior to the first administration / intake of study medication, i.e. if the information of an untoward medical occurrence is collected before starting the intake of study medication, this information will be listed as a pre-treatment AE (also called baseline AE) during statistical analysis. Baseline AEs are considered not to be treatment-emergent.

If date of onset is missing for an AE, it will be considered treatment-emergent unless there is information to suggest otherwise (for example, date of recovery is before date of first administration / intake of study medication).

Separate analyses will be performed for baseline AEs and treatment-emergent AEs.

Criteria for Defining the Severity of an Adverse Event: National Cancer Institute Common Terminology for Adverse Events (CTCAE), Version 4.0 will be used for determining the severity of adverse events.

During the long-term follow-up of the patient, the Investigator must report only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the Sponsor Safety Officer.

In general, adverse events will be attributed to the last treatment administered prior to the onset of the adverse event.

2.2.5.2 Serious adverse events

Definition of Serious Adverse Events:

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
  Note: "life-threatening" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly or birth defect;
- Requires in-patient hospitalisation or leads to prolongation of hospitalisation, with the exception of elective pre-planned hospitalisations.

2.2.5.3 Adverse events of special interest (AESI)

In addition to the Serious Adverse Events defined above, a set of potential risks deserve special attention even if they do not fulfil any of the seriousness criteria. These non-serious adverse events of special interest (AESI) occurring in patients enrolled in the investigational arm (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate) should equally be reported to the clinical trial pharmacovigilance department for safety analysis so long as they occur any time after enrolment including long term follow-up and will additionally be investigated within the scope of the safety analysis. The following types of pathology have been observed during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment and AESIs related to these categories will be investigated:

- Haematotoxicity
- Secondary haematological malignancies such as MDS and acute myeloid leukaemia
- Nephrotoxicity
- Cardiovascular events

For further details please refer to section 8.7 of the study protocol.

2.2.5.4 Analysis of adverse events

All original AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ classes and preferred terms will be used in the analyses.

Type and incidence of AEs, as well as severity and relatedness to the study medication will be recorded and notified appropriately. Special attention will be given to those patients who prematurely discontinue the study or the study medication due to an AE, or who experience a severe AE, an SAE or an AESI. The investigator and the monitor will ensure that information on serious adverse events immediately notified with a SAE form are consistent with information on the same event contained in the e-CRF and in the source documents.

An Adverse Event (AE) is defined as *treatment-emergent AE*, if its onset occurred after the first use of randomized study medication or if an existing event worsened during the treatment phase relative to the pre-treatment state.

An AE will be defined as *baseline AE* if its onset occurred after the date of Informed Consent and prior to the first use of randomized study medication. Baseline AEs are considered not to be treatment-emergent.

In case of incomplete or missing data for the onset of an AE the following rules have to be applied:
- If the AE start day is missing, and if the AE month is equal to or greater than the month in which treatment was first administered, then the AE will be considered treatment-emergent.
- If the AE start day and month are missing and the AE year is equal to or greater than the year in which treatment was first administered, then the AE will be considered treatment-emergent.
- If the AE day, month, and year are missing, then the AE will be considered treatment-emergent.

In general, separate analyses will be performed for baseline AEs and treatment-emergent AEs.

For listings, the duration of each adverse event will be calculated as the difference between the onset date and the end date (in days), with the following formula:

AE duration = [AE stop date – AE start date + 1].

The number and percentage of patients with at least one AE will be determined, overall and separately for both treatment groups. The rate of patients with at least one AE will be compared between the two treatment groups using Fisher's exact test on an α-level of 5%.
These analyses will be performed for treatment-emergent AEs and additionally for treatment-emergent AEs leading to premature discontinuation, and for serious adverse events.

Summary statistics will also be provided according to the intensity and the causality assessment (i.e. relationship to study medication). Frequencies and percentages will be provided for all categories. Percentages are based on the number of AE episodes, i.e. the number of AE forms filled in, and not on the number of symptoms, as one AE might be coded with more than one code.

A summary of adverse events will be given according to the primary system organ class (SOC) and preferred term (PT). Frequencies and percentages will be given overall and by treatment group in separate columns for SOC followed by those for PT in alphabetical order. All AE symptoms are taken into account for calculations.

In addition, based on the preferred term, an overview will be presented for the most frequent AEs according to the intensity and the causality assessment (i.e. relationship) to the study medication. Frequencies of symptoms will be presented in descending order and will be determined for each PT together with the associated frequencies of categories. The number and percentage of patients with an AE of the respective PT will be given as well.

2.2.5.5 Laboratory safety variables

Laboratory assessments are performed at the investigational site, except serum CgA (CgA is evaluated by central laboratory).

The following laboratory parameters will be investigated and analysed:

(1) Haematology: White blood cells (WBC) with differential (i.e. Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils), Platelets, Haemoglobin (Hb), Haematocrit, MCV

(2) Blood chemistry: Blood urea nitrogen (BUN), Serum creatinine, Uric acid, Albumin, Total bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, CgA (centralized assessment), Haemoglobin A1C (GlycoHb), fT4, Calcium, Fasting blood glucose, Creatinine clearance (calculated by the Cockroft-Gault formula)

(3) Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (by dipstick test), 5-HIAA (on 24h urine collection), Pregnancy test (if applicable)

If there is more than one laboratory value available for one visit, for example in order to confirm laboratory values obtained at a scheduled visit, the first valid measurement will be used for analysis.

Laboratory values outside normal ranges will be listed and flagged. The following flags will be used:

‘+’: ‘Higher than reference value’
‘-’: ‘Lower than reference value’

The respective parameter and the flagged value will be presented patient-wise by visit together with the reference values.
Descriptive statistics including shift tables will be generated for all laboratory tests performed (haematology, blood chemistry, and urinalysis), i.e. descriptive summary statistics will be presented for all laboratory parameters by visit, overall and by treatment group, and within treatment groups overall and by gender. Mean, standard deviation, minimum, median, maximum, 16%- and 84%-percentiles and 68%-range will be determined. Summary statistics for the pre-post differences (value at visit after baseline – baseline value) and the percentage of differences [(value at visit after baseline – baseline value) / baseline value x 100] will be presented analogously. Abnormal laboratory test results will be tabulated, i.e. baseline laboratory values for each parameter and values for each parameter at all respective visits after baseline at which a safety lab was performed will be categorized whether they are within the respective normal range or outside. Abnormal values will be classified according to CTCAE classification version 4.0 [1]. Frequencies and percentages will be provided.

[1] serum creatinine will be assessed under the Adverse Event term “Creatinine increased”, not as “Acute kidney injury”

Shift analyses will be performed for each parameter separately for all treatment groups, i.e. the numbers and percentages for all combinations of categories will be calculated comparing baseline and end of study categories. Frequencies and percentages will be given by treatment group based on the respective total number.

The changes at any visit versus baseline (i.e. pre-post differences) and percent variations at any visit vs baseline (i.e. the percentage of changes versus baseline) of selected parameters (serum creatinine, creatinine clearance, total bilirubin, serum albumin, ALT, AP, Hb, WBC, neutrophils, lymphocytes, platelets) will be analysed and compared in the two study arms using the two-sided Wilcoxon Rank Sum test on an alpha-level of 0.05. For the investigation of possible trends of the changes from baseline and of the percent variations, a graphical presentation of boxplots will be given for these variables for both treatment arms at any visit.

Analogously, the following changes at any visit versus baseline (i.e. pre-post differences) and percent variations at any visit vs baseline will be analysed for

- creatinine and creatinine clearance in subjects with risk factors for renal function in the medical history
- total bilirubin, ALT, AP, and serum albumin in subjects with risk factors for liver function in the medical history
- Haemoglobin, WBC, neutrophils, lymphocytes, platelets in subjects with risk factors for haematological function in the medical history

For this purpose, the two-sided Wilcoxon Rank Sum test will be applied on an alpha-level of 0.05. For the investigation of possible trends of the changes from baseline and of the percent variations, a graphical presentation of boxplots will be given for these variables for both treatment arms at any visit.

Risk factors for renal function are:

- essential hypertension
- diabetes mellitus
- renal insufficiency (acute, chronic)
- proteinuria, haematuria
- history of urinary tract infections
- glomerulonephritis
- renal cysts
- kidney stones
- renal tumour (primary, secondary)
- ischemic cardiovascular disease
- hypercholesterolemia
- obesity (BMI > 30 kg/m^2)
- smoking
- previous treatments with platinum-based chemotherapy

Risk factors for liver function are:

- alcohol abuse
- chronic hepatitis
- obesity
- biliary obstruction / stones

- cystic fibrosis
- liver tumour (primary, secondary)
- metastasis from carcinoid
- previous chemotherapy

Risk factors for haematological function are:
- history of chronic anaemia, leukopenia, thrombocytopenia
- previous chemo- or radiotherapy
- haematological malignancy
- chronic autoimmune disease
- chronic inflammatory disease
- alcohol abuse.

2.2.5.6 Physical examination and vital signs

Physical examinations are performed by the Investigator, or qualified designee. All body systems will be examined and any relevant findings will be documented in the source documents and CRF. Physical examinations include heart rate, blood pressure and weight measurement (height will only be measured at baseline). Blood pressure and pulse rate will be performed after the patient rests for 5 minute. For each patient, all blood pressure recordings shall be made using the same type of instrument (i.e., manual BP recording vs. automatic digital vital signs monitor) on the same arm.

Significant findings that are present prior to baseline will be recorded in the medical history page, while changes during the study (including significant changes of the symptoms due to the underlying disease vs baseline, as reported in the diary card) will be recorded on the Adverse Event page of the e-CRF.

Physical examination results will be tabulated, i.e. frequencies and percentages will be presented and all abnormalities will be listed.

The normal ranges for the vital signs are as follows:

- Pulse rate: 40 – 100 bpm
- Systolic blood pressure (SBP): 100 – 150 mmHg
- Diastolic blood pressure (DBP): 45 – 90 mmHg

Descriptive statistics (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed values as well as for the changes from baseline value (i.e. pre-post differences) will be presented by visit, overall and by treatment group, and within treatment groups overall and by gender. Frequency tabulations with values within, below or above the normal ranges will be presented.

2.2.5.7 Electrocardiogram (ECG)

ECGs are recorded at baseline, immediately after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment procedure (following the completion of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion) and at the End of Study. ECGs will be taken also in the 60 mg Sandostatin® LAR Depot arm at the same time

points, according to the schedule presented in Table 2 schedule. Standard 12-lead ECG is the preferred option, but if not possible, a 3-lead ECG is acceptable.

An ECG in triplicate (at least 5 minutes apart) is recorded with the patient supine, after 5 minutes rest, and not immediately after a meal. The parameters will be measured as a mean value of minimally 3 beats; the mean of each parameter has to be used for eCRF completion.

The Investigator/local cardiologist will note in the source documents (and in the e-CRF) whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs results and the different ECG intervals measurements, calculating by the mean value of 3 measurements for each parameter. Relevant abnormalities at baseline will be recorded in the medical history page, while changes during the study will be recorded on the Adverse Event page of the e-CRF.

The following ECG parameters will be investigated and analysed:

- Heart rate [beats/min]
- RR interval [msec]
- PR interval [msec]
- QRS width [msec]
- QT interval [msec]: QT intervals will be corrected for heart rate (more extended QT evaluation according to ICH E14)
- Interpretation of the ECG with the following categories: normal / abnormal, not clinically relevant / abnormal, clinically relevant

Descriptive statistics (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed values of heart rate (HR), RR interval, PR interval, QRS width and QT interval will be presented by visit, overall and by treatment group, and within treatment groups overall and by gender. QT intervals will be corrected for heart rate.

The changes of these ECG parameters from baseline value (i.e. pre-post differences) will be analysed descriptively analogous to the analysis of the observed values.
Frequency tabulations for the ECG interpretation (Normal / Abnormal, not clinically relevant / Abnormal, clinically relevant) will be presented.

2.2.5.8 Karnofsky performance score (KPS)

KPS forms must be completed by a medical professional at each treatment and follow-up visit, and before any current clinical information is given to the patient (cf. Study Protocol Appendix 13).

Descriptive statistics for KPS (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed values as well as for the changes from baseline will be presented overall and by treatment group.

2.2.5.9 Other safety variables

Pregnancy test: A pregnancy test (either on urine or blood) must be performed at baseline and within 7 days prior to each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment for every female patient of childbearing potential (cf. Section 8.9 and Appendix 7 of the study protocol).

Frequencies and percentages will be calculated for the "Female reproductive status" and the "Result of ß-HCG pregnancy test".

Left ventricular ejection fraction/Cardiac ejection fraction: Patients with uncontrolled congestive heart failure (NYHA II, III, IV) are not eligible according to exclusion criterion 12. Patients with history of congestive heart failure who do not violate the exclusion criterion 12 will undergo an evaluation of their cardiac ejection fraction prior to baseline, preferably via gated equilibrium radionuclide ventriculography. The results from an earlier study (not exceeding 30 days) may substitute the evaluation at the discretion of the Investigator, if no clinical worsening is noted. It is recommended that the patient's measured cardiac ejection fraction is ≥40% before randomization.

Descriptive statistics for LVEF (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) of the observed LVEF values will be presented overall and by treatment group.

Patient diary: Each patient is provided with a diary to record cancer related symptoms experienced and rescue medication (short-acting Octreotide s.c. injections) taken through the study.

Descriptive statistics for continuous variables of the patient diary (N, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile and 95% confidence interval for the mean) will be presented overall and by treatment group. For categorical variables of the patient diary, frequencies and percentages will be calculated overall and by treatment group.

2.2.6 Diseases and Medication

The following variables will be analysed:

- Previous and concomitant medications classified by ATC classes,
- Medical history and concomitant diseases classified by MedDRA preferred term (PT) and system organ class (SOC).

All medications taken at the start of screening until the PFS Primary End-Point is reached, then until Week 76 post randomization after the PFS Primary End-Point has been reached (i.e. 74 evaluable and centrally confirmed disease progressions), or early termination, are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.

Further anti-tumour treatments after progression must be reported until the end of the long term follow up period.

A medication counts as concomitant if it is still given after the first administration / intake of the study medication. If the application of a medication has stopped prior to the first exposure to the study medication, it counts as being previous. Medications will be analysed divided by previous and concomitant medication.

Previous and concomitant diseases will be defined analogously.

Previous and concomitant diseases will be summarized according to MedDRA coding.

The number of diseases and the number and percentage of patients with diseases will be determined overall and by treatment group. Indications with the same code count as often as they appear.

According to the MedDRA coding system, summary statistics will be calculated for disease classes, i.e. by MedDRA SOC and PT. The number and percentage of patients with at least one disease within the respective disease class will be presented by treatment group and also the number of diseases. Separate tables will be provided for previous and concomitant diseases.

Previous and concomitant medications will be analysed in the same way. Based on the ATC-coding summary statistics will be calculated for ATC-code levels. The number and percentage of patients with at least one medication within the respective ATC class will be presented by treatment group and also the number of medications. ATC-level 1 and ATC-level 2 will be taken into account. The same summary statistics will be provided based on the substances.

2.2.7 Study termination

Premature study termination as documented in the "End of treatment period" section of the eCRF, and also the reason for premature study termination will be investigated. Additionally, the patient status up until the last visit of the treatment phase (alive, dead, unknown) and in case of death, the cause of death (disease progression, other) will be investigated.

All patients who terminate the study prematurely will be listed according to their treatment group including the reason for termination. The number and percentage of patients with premature study termination will be determined overall and by treatment group. Study termination reasons will be tabulated, i.e. frequencies and percentages for single reasons for premature study termination will be presented.

Additionally, the patient status until the last visit (alive, dead, unknown) and in case of death, the cause of death (disease progression, other) will be tabulated, i.e. frequencies and percentages will be calculated for these variables. Protocol deviations and compliance with the visit schedule will be tabulated.

2.2.8 Analyses of pharmacokinetic variables

Please refer to the sub-study analysis for pharmacokinetic variables.

2.2.9 Quality-of-life variables

The impact of treatment on health related QoL will be assessed using the EORTC QLQ-C30 and the EORTC QLQ-G.I.NET21 questionnaire (cf. Study Protocol Appendix 3). Both questionnaires will be completed by the patient. EORTC QLQ questionnaires variables will be handled according to the EORTC QLQ Scoring Manual recommendations. Changes from baseline will be assessed every 12±1 week from the first treatment date until the PFS Primary End-Point, then until Week 72 after randomization, unless the patient progresses or dies. The EORTC QLQ-G.I.NET21 questionnaire is a module for carcinoid/neuroendocrine tumours. This module comprises questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

<u>Calculation of the scores for both questionnaires:</u>

(a) EORTC QLQ-C30 includes 30 items. The following 9 scales and 6 single items are defined (where FS = Functional scale and SS = Symptom scale):

- Global health status / QoL (items 29 and 30)
- Physical functioning (FS) (items 1, 2, 3, 4 and 5)
- Role functioning (FS) (items 6 and 7)
- Emotional functioning (FS) (items 21, 22, 23 and 24)
- Cognitive functioning (FS) (items 20 and 25)
- Social functioning (FS) (items 26 and 27)
- Fatigue (SS) (items 10, 12 and 18)
- Nausea and vomiting (SS) (items 14 and 15)
- Pain (SS) (items 9 and 19)
- Dyspnoea (item 8)
- Insomnia (item 11)
- Appetite loss (item 13)
- Constipation (item 16)
- Diarrhoea (item 17)
- Financial difficulties (item 28)

For all scales the Raw Score (RS) is defined as the mean of the respective items:

$$RS = (\text{item } i_1 + \text{item } i_2 + \ldots + \text{item } i_n) / n$$

For a single item, RS is identical to the score of the item itself.

Then for the functional scales (FS) the score is calculated by the formula:

$$\text{Score} = \{1 - (RS - 1) / \text{range}\} \times 100$$

For the symptom scales (SS), the single items and Global health status /QoL the score is calculated by the formula:

$$\text{Score} = \{(RS - 1) / \text{range}\} \times 100,$$

The “range” value is the difference between the maximum possible value of RS and the minimum possible value for RS. The range = 3 for all scales and single items except for “Global health status /QoL”. For “Global health status /QoL” the range is 6.

The formulas for the scores are linear transformations of 0-100.

(b) EORTC QLQ-GI.NET21 includes 21 items. The following 5 scales and 4 single items are defined:

- Endocrine scale (items 31, 32 and 33)
- G.I. scale (items 34, 35, 36, 37 and 38)
- Treatment scale (items 39, 40 and 46)
- Social function scale (items 42, 44 and 49)

- Disease related worries scale (items 41, 43 and 47)
- Single item 1: Muscle/bone pain symptom (item 48)
- Single item 2: Sexual function (item 51)
- Single item 3: Information/communication function (item 50)
- Single item 4: Body image (item 45)

For all scales the Raw Score (RS) is defined as the mean of the respective items:

$$RS = (\text{item } i_1 + \text{item } i_2 + \ldots + \text{item } i_n) / n$$

For a single item, RS is identical to the score of the item itself.

For the scales and the single items the score is calculated by the formula:

$$\text{Score} = \{(RS - 1) / \text{range}\} \times 100$$

Where "range" is the difference between the maximum possible value of RS and the minimum possible value for RS. The range = 3 for all scales and single items.

The formulas for the scores are linear transformations to 0-100.

Missing items in scores will be imputed by the following method:
If at least half of the items from the scale have been answered then use all the items that were completed and apply the standard equation for calculating the Raw Score (RS).

The impact of treatment on health related QoL will be assessed by comparison of the changes of the different scales and single items from baseline (i.e. pre-post differences) by means of Wilcoxon's rank sum test on an alpha-level of 5%.

2.3 Data handling conventions

2.3.1 Replacement of data

2.3.1.1 Missing values

Unless otherwise stated during the blind review, missing values will not be replaced for the main calculation of the primary variable and secondary parameters (including key secondary parameters [OS, TTP and ORR]).

If relevant (e.g. the number of missing values is found to be substantial during the blind review), an investigation will be performed to determine how sensitive the results are to the method of handling missing values, at least for the primary variable and key secondary parameters. No replacements will be applied to any descriptive analysis or listings.

2.3.1.2 Outliers

Unless otherwise stated during the blind review, all outliers will not be eliminated nor replaced in the main analysis of primary variable and secondary parameters (including key secondary parameters [OS, TTP and ORR]).

If relevant (e.g. substantial number of blind review statistically and medically justified outliers), a sensitivity analysis eliminating outliers might be conducted, at least for the primary variables and key secondary parameters.

2.3.2 Transformation of data

Age will be calculated as follows:

(a) If the date of birth is completely known:
age = (date of informed consent – date of birth) / 365.25

(b) If only the year of birth is known:
age = (year of informed consent – year of birth).

The formula for BMI is: weight in kg / (height in m)^2

All laboratory values will be presented in SI units. If a parameter is given with the conventional unit the respective conversion factor will be used to transform the values to SI units.

2.3.3 Windows for time points

For the definition of time windows for visits please refer to the study protocol, Tables 1, 2, 7 and 10. Variations of ± 1 week in the visits schedule are allowed.

2.3.4 Unscheduled visits

Data of unscheduled visits will only be listed.

3 Interim analysis

Interim safety analyses will be conducted by an Independent Data Safety Monitoring Board (See Section 12.1 of the study protocol - Independent Data Safety Monitoring Board). This Board is regularly providing the Sponsor with recommendations to either continue the trial as planned, or to discontinue the trial, according to the Safety Analysis Plan. This Plan is described in detail in the Data Safety Monitoring Board (DSMB) Charter, provided as separate document.

An interim analysis for OS will be performed at the time of the final PFS analysis (see sections 2.2.2.2.2 and 2.2.2.2.3 for further details).

4 General appearance of output

The study-specific project code and/ or study code will be noted in the first line of every table, listing or graph. The date and name of the SAS-program creating the report will be indicated on the bottom left of the output. Numbering of pages is performed separately for each table.

The titles of the report will be clear and understandable to reflect the contents of the report. The type of analysis should be given, the analysis variable as well as the analysis set used. If important

details are required to understand the output, these should be included in the document. All descriptions start with an uppercase and thereafter only lowercase characters.

The total number of patients within a report will be the number of patients within the collective the analysis is based on, so if there are missing values, their frequency will also be presented.

The number of decimal places displayed in a number will be the same as present in the original data value. Minimum and maximums will have as many decimal places as the original data values. Means, medians, and all other percentiles will have one more decimal place, and the standard deviation will have two more decimal places than the data values they are derived from. Percentage values will be printed with one decimal place. All p-values will be presented with four decimal places. If a rounded value of 'p = 0.0000' occurs, it will be indicated as 'p < 0.0001'.

The reports will be presented using Times-Roman as the standard font, and the standard text size will be 12. The standard page orientation will be landscape, and the paper size will be Letter, with 1 inch margins. Headers and footers will also be 1 inch, but may be adjusted to accommodate additional information.

5 Software documentation

Statistical analyses performed by THERAMetrics will be carried out using SAS®, release 9.3 (SAS/STAT 12.1, SAS Institute Inc., Cary, NC, USA) on a Microsoft® Windows® Server 2008 R2 or subsequent platform.

6 Coding systems

Domain	Coding System	Reporting Terms
Previous and concomitant diseases	MedDRA version 16.0	SOC = MedDRA SOC Preferred term = MedDRA Preferred term
Previous and concomitant medication	WHO Drug Dictionary (Version SEP/2012)	ATC Code Medication Group = ATC Level 4 term Drug Number
Adverse Events	MedDRA version 16.0	SOC = MedDRA SOC Preferred term = MedDRA Preferred term

Coding of previous and concomitant diseases, adverse events (AEs) and previous and concomitant medication will be performed by THERAMetrics.

7 List of appendices

Appendix number	Title
Appendix I	Overview of statistical analyses
Appendix II	Overview of individual data listings
Appendix III	NETTER-1 Imaging Charter
Appendix IV	Pharmacokinetics and dosimetry data analysis
Appendix V	ECG data analysis

8 References

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9 Signature Page

I have carefully read this statistical analysis plan and agree to the described methods and proceedings.

Advanced Accelerator Applications SA, Snr Clinical Study Manager

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Name	Signature	Date

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Appendix I: Overview of statistical analyses

Table / Figure No.	Report	Analyses sets	Output file (*.PDF)
14.1 Demographic data			
14.1.1 Study centers and patients			
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14.1.1.2	Incidences and reasons for premature study termination at End of Treatment Period (Eligibility, Treatment period completion, Survival)	Total / SAF / FAS	Termination
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14.1.1.5	Number of patients by analysis populations	SAF	patnum_pop
14.1.1.6	Listing of patients and their populations	Total	Pop
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14.1.1.8	Compliance with the visit schedule	FAS	visit_compliance
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14.1.2.2	Demographic data - Discrete / categorical variables	SAF, FAS, PPS	demo2
14.1.2.3	Diagnosis at screening visit	FAS, PPS	Diagnosis
14.1.2.4	Prior cancer surgery	FAS, PPS	prior_cancer_surgery
14.1.2.5	Previous treatment with Octreotide LAR at fixed dose / Other previous treatments of cancer	FAS, PPS	previous_cancer_treatment
14.1.2.6	Centralized diagnosis confirmation including Octreoscan Tumour Uptake score and Octreoscan Tumour Burden score at baseline (data source: IRC central lab database)	FAS, PPS	octreoscan_tumor_uptake
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14.1.2.8a	Overall tumor evaluation at screening visit: Summary statistics for sum of diameters for target lesions at screening by treatment group (data source: eCRF local assessment)	FAS, PPS	overall_tumor_evaluation2
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14.1.2.10	Summary statistics for Karnofsky Performance Score (KPS) at screening and baseline	FAS, PPS	karnofsky_base2
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14.1.2.13	Concomitant diseases by System Organ Class (SOC) and Preferred Term (PT)	FAS, PPS	concom_diseases
14.1.2.14	Previous and concomitant medications by ATC-Code	FAS, PPS	medication_atc
14.1.2.15	Previous and concomitant medications by substances	FAS, PPS	medication_substance
14.1.3 Measurement of treatment compliance			
14.1.3.1	Treatment compliance / Dose reductions	SAF, FAS, PPS	compliance
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14.2.1 Analysis of primary efficacy variable			

14.2.1.1a	Primary efficacy analysis variable: Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: eCRF local assessment)	FAS, PPS	PFS_primary_criterion
14.2.1.1b	Primary efficacy analysis variable: Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database)	FAS, PPS	PFS_primary_criterion
14.2.1.2	Primary efficacy analysis variable: Progression Free Survival (PFS) - Original SAS-output of analysis according to Kaplan Meier method	FAS, PPS	PFS_primary_criterion
Figure 14.2.1.1	Primary efficacy analysis variable: Progression Free Survival (PFS) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. PFS; data source: IRC central lab database)	FAS, PPS	PFS_primary_criterion
14.2.1.3	Case final review outcome (data source: Prof Sundin assessment)	FAS, PPS	PFS_final_review_outcome
14.2.1.4	Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database; assigning the event time to the next scheduled imaging time rather than the actual time)	FAS	PFS_sensitivity_analysis1
14.2.1.5	Progression Free Survival (PFS) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database; ignoring new anti-cancer treatments started before progressive disease)	FAS	PFS_sensitivity_analysis2
14.2.1.6	Progression Free Survival (PFS) - Summary of analysis according to Cox's proportional hazards model (data source: IRC central lab database; covariates: see Section 2.2.2)	FAS	PFS_cox_regression
14.2.2 Analyses of secondary efficacy variables			
14.2.2.1a	Secondary efficacy variable: Objective response rates (ORR) and 95% CIs for both treatment groups (data source: eCRF local assessment)	FAS, PPS	ORR_second_criterion
14.2.2.1b	Secondary efficacy variable: Objective response rates (ORR) and 95% CIs for both treatment groups (data source: IRC central lab database)	FAS, PPS	ORR_second_criterion
14.2.2.2a	Secondary efficacy variable: Comparison of objective response rates (ORR) between both treatment groups (Fisher's exact test) (data source: eCRF local assessment)	FAS, PPS	ORR_second_criterion
14.2.2.2b	Secondary efficacy variable: Comparison of objective response rates (ORR) between both treatment groups (Fisher's exact test) (data source: IRC central lab database)	FAS, PPS	ORR_second_criterion
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14.2.2.4	Secondary efficacy variable: Overall Survival (OS) - Original SAS-output of analysis according to Kaplan Meier method	FAS, PPS	OS_second_criterion
Figure 14.2.2.1	Secondary efficacy variable: Overall Survival (OS) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. OS)	FAS, PPS	OS_second_criterion

14.2.2.5a	Secondary efficacy variable: Time to Tumour Progression (TTP) - Summary of analysis according to Kaplan Meier method (data source: eCRF local assessment)	FAS, PPS	TTP_second_criterion
14.2.2.5b	Secondary efficacy variable: Time to Tumour Progression (TTP) - Summary of analysis according to Kaplan Meier method (data source: IRC central lab database)	FAS, PPS	TTP_second_criterion
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14.2.2.6b	Secondary efficacy variable: Time to Tumour Progression (TTP) - Original SAS-output of analysis according to Kaplan Meier method (data source: IRC central lab database)	FAS, PPS	TTP_second_criterion
Figure 14.2.2.2a	Secondary efficacy variable: Time to Tumour Progression (TTP) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. TTP) (data source: eCRF local assessment)	FAS, PPS	TTP_second_criterion
Figure 14.2.2.2b	Secondary efficacy variable: Time to Tumour Progression (TTP) - Graphical representation of Kaplan Meier plot (plot of survival density function vs. TTP) (data source: IRC central lab database)	FAS, PPS	TTP_second_criterion
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14.2.3.4	Correlation of clinical efficacy outcomes (PFS, OS, TTP) with the levels of the biomarker 5-Hydroxyindoleacetic acid (5-HIAA) in the urine (data source for efficacy outcomes: IRC central lab database)	FAS, PPS	Corr_efficacy_5HIAA
14.2.3.5	Correlation of clinical efficacy outcomes (ORR, PFS, OS, TTP) with OctreoScan® tumour uptake score (data source: IRC central lab database)	FAS, PPS	Corr_efficacy_OctreoScan
14.2.3.6	Correlation of clinical efficacy outcome (PFS, OS, TTP) with serum levels of Alkaline Phosphatase (AP) (data source for efficacy outcome: IRC central lab database)	FAS, PPS	Corr_efficacy_AP
14.2.4 Analyses of additional efficacy variables			
14.2.4.1	Overall tumour evaluation: TNM criteria (T-Primary tumour lesions, N-Regional lymph nodes involvement and M-Distant metastasis) (frequency tables by treatment group and by visit)	FAS, PPS	overall_tumor_evaluation3

14.2.4.2	Overall tumour evaluation: Disease stage (for endocrine tumours of lower jejunum and ileum) (frequency tables by treatment group and by visit) (data source: Interlab central lab database)	FAS, PPS	overall_tumor_evaluation3
14.2.4.3a	Overall tumour evaluation: Objective tumour response (Response of target lesions, Response of non-target lesions, Overall tumour response) (frequency tables by treatment group and by visit) (data source: eCRF local assessment)	FAS, PPS	overall_tumor_evaluation3
14.2.4.3b	Overall tumour evaluation: Objective tumour response (Response of target lesions, Response of non-target lesions, Overall tumour response) (frequency tables by treatment group and by visit) (data source: IRC central lab database)	FAS, PPS	overall_tumor_evaluation3
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14.2.4.4b	Overall tumour evaluation: Summary statistics for sum of diameters for target lesions by treatment group and by visit (data source: IRC central lab database)	FAS, PPS	overall_tumor_evaluation4
14.2.5 Analyses of health-related quality of life variables			
14.2.5.1	Health related QoL as assessed using the EORTC QLQ-30 and QLQ G.I.NET21 questionnaire: Summary statistics for all questions, domains and overall score as well as for their changes from baseline (by visit)	FAS, PPS	EORTC_summary
14.2.5.2	EORTC QLQ-30 and QLQ-G.I.NET21 questionnaire: Investigation of impact of treatment on health related QoL as assessed by comparison of the changes from baseline between both treatment groups (using Wilcoxon's rank sum test)	FAS, PPS	EORTC_test
14.3 Safety analyses			
14.3.1 Display of adverse events			
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14.3.1.2	Summary of adverse events by severity and causality assessment (causal relationship) to study medication for: • Any AE • Any TEAE • Any TEAE related to study medication (ADR) • Any SAE • Any SAE related to study medication (SADR) • Any AE of special interest (AESI) • Any AESI related to study treatment • Any fatal AE	SAF	ae_summary
14.3.1.3	Incidence of treatment-emergent AEs by System Organ Class (SOC) and Preferred Term (PT)	SAF	ae_socpt
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14.3.1.6	Most frequent treatment-emergent AEs by PT	SAF	ae_pthitlist.
14.3.1.7	Listing of all adverse events	SAF	ae_list
14.3.1.8	Incidence of treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT)	SAF	sae_socpt
14.3.1.9	Listing of all serious adverse events	SAF	sae_list
14.3.2 Analyses of laboratory data (haematology, clinical chemistry and urinalysis)			
14.3.2.1	Summary statistics for laboratory parameters by visit	SAF	lab_summary
14.3.2.2	Summary statistics for pre-post differences of laboratory parameters by visit	SAF	lab_summary
14.3.2.3	Frequencies of patients with abnormal laboratory values by visit	SAF	lab_abnorm1
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14.3.2.5	Listing of all clinically relevant abnormal laboratory values	SAF	lab_abnorm2
14.3.2.6	Shift analyses: Post-baseline laboratory values (at all resp. visits) vs. baseline laboratory values with respect to normal ranges	SAF	lab_shift
14.3.2.7	Summary statistics for CgA central assessment (data source: Interlab central lab database)	SAF	CgA_assessment
14.3.3 Analyses of other safety variables			
14.3.3.1	Summary statistics for the observed vital sign parameters and for their changes from baseline (pre-post differences) by visit	SAF	vital_signs
14.3.3.2	Summary statistics for physical examination at all respective visits (frequency tables)	SAF	physical_examination
14.3.3.3	Summary statistics for ECG parameters by treatment group and by visit	SAF	ecg1
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14.3.3.5	Summary statistics for pregnancy test (frequency table)	SAF	pregnancy_test.
14.3.3.6	Frequency table for Karnofsky Performance Score (KPS) at all visits	SAF	karnofsky_1
14.3.3.7	Summary statistics for Karnofsky Performance Score (KPS) at all visits and pre-post differences to baseline	SAF	karnofsky_2
14.3.3.8	Shift tables for Karnofsky Performance Score (KPS) at all post-baseline visits versus baseline	SAF	karnofsky_3
14.3.3.9	Substudy: Summary statistics for dosimetry assessment safety outcome (data source: IEO central lab database)	SAF (substudy)	substudy_dosimetry
14.3.3.10	Substudy: Summary statistics for PK assessment (data source: IEO central lab database)	SAF (substudy)	substudy_PK_assessment
14.3.3.11	Substudy: Summary statistics for HPLC assessment (data source: IEO central lab database)	SAF (substudy)	substudy_HPLC_assessment
14.3.3.12	Substudy: Summary statistics for 24h cardiac assessment (data source: iCardiac central lab database)	SAF (substudy)	substudy_cardiac_assessment
14.3.3.13	Substudy: Summary statistics for local assessment of blood sample radioactivity	SAF (substudy)	substudy_blood_radioactivity
14.3.3.14	Substudy: Summary statistics for local assessment of urine sample radioactivity	SAF (substudy)	substudy_urine_radioactivity
14.3.4 Analyses of patient diary data			
14.3.4.1	Summary statistics for all variables of patient's diary	SAF	patient_diary_analysis

Appendix II: Overview of individual data listings

Table No.	Report	Analyses sets	Output file (*.PDF)
16.2 Patient data listings			
16.2.1 Discontinued patients			
16.2.1.1	End of treatment period (study termination page for main part of study)	Total	termination1
16.2.1.2	End of long term follow-up period (study termination page for follow-up period of study)	Total	termination2
16.2.1.3	Anti-tumour therapies post discontinuation	Total	anti_tumor_therapies
16.2.2 Protocol deviations			
16.2.2.1	Protocol deviations by type	Total	Population
16.2.3 Patients excluded from populations			
16.2.3.1	Patients excluded from populations	Total	Population
16.2.4 Demographic and baseline data			
16.2.4.1	Informed consent data	Total	informed_consent
16.2.4.2	Demographic data	Total	Demographics
16.2.4.3	Inclusion and exclusion criteria	Total	incl_exclusion
16.2.4.4	Randomization data	Total	Randomization
16.2.4.5	Diagnosis and prior cancer surgery data	Total	Diagnosis
16.2.4.6	Specimens and images for central eligibility assessment	Total	Specimens
16.2.4.7	Previous treatment with Octreotide LAR at fixed dose / Other previous treatments of disease	Total	previous_treatment
16.2.4.8	Centralized diagnosis confirmation (data source: Interlab central lab database)	Total	diagnosis_confirmation
16.2.4.9	Left ventricular ejection fraction (LVEF)	Total	LVEF
16.2.4.10	Medical history	Total	medical_history
16.2.4.11	Previous and concomitant medications	Total	concom_medication
16.2.5 Study medication data			
16.2.5.1	Study drug administration	Total	study_drug_administration
16.2.5.2	Individual compliance and dose reduction data	Total	compliance
16.2.6 Individual efficacy data			
16.2.6.1a	Identification of target lesions, non target lesions, new lesions (data source: eCRF local assessment)	Total	target_lesions1
16.2.6.1b	Identification of target lesions, non target lesions, new lesions (data source: IRC central lab database)	Total	target_lesions1
16.2.6.2a	Evaluation of target lesions (data source: eCRF local assessment)	Total	target_lesions2a
16.2.6.2b	Evaluation of target lesions (data source: IRC central lab database)	Total	target_lesions2a
16.2.6.3a	Evaluation of non target lesions and new lesions (data source: eCRF local assessment)	Total	target_lesions2b
16.2.6.3b	Evaluation of non target lesions and new lesions (data source: IRC central lab database)	Total	target_lesions2b
16.2.6.4	Overall tumor evaluation (according to TNM criteria)	Total	tumor_evaluation
16.2.7 Adverse event listings			
16.2.7.1	Adverse events	Total	ae_list
16.2.7.2	Serious adverse events	Total	sae_list
16.2.7.3	eSAE reports	Total	eSAE
16.2.8 Laboratory measurements			

Table No.	Report	Analyses sets	Output file (*.PDF)
16.2.8.1	Laboratory values of blood tests	Total	lab_values_blood_tests
16.2.8.2	Laboratory values of additional blood tests	Total	lab_values_add_blood_tests
16.2.8.3	Laboratory values of urinalysis	Total	lab_values_urinalysis
16.2.8.4	Laboratory values of additional urinalysis	Total	lab_values_add_urinalysis
16.2.8.5	Creatinine clearance	Total	creatinine_clearance
16.2.8.6	Substudy: dosimetry assessment safety outcome (data source: IEO central lab database)	Total (substudy)	substudy_dosimetry
16.2.8.7	Substudy: PK assessment (data source: IEO central lab database)	Total (substudy)	substudy_PK_assessment
16.2.8.8	Substudy: HPLC assessment (data source: IEO central lab database)	Total (substudy)	substudy_HPLC_assessment
16.2.8.9	Substudy: Local assessment of blood sample radioactivity	Total (substudy)	substudy_blood_radioactivity
16.2.8.10	Substudy: Local assessment of urine sample radioactivity	Total (substudy)	substudy_urine_radioactivity
16.2.8.11	CgA central assessment (data source: Interlab central lab database)	Total	CgA
16.2.9 Vital signs, physical examinations, ECG and other safety data listings			
16.2.9.1	Vital signs	Total	vital_signs
16.2.9.2	Physical examination	Total	physical_examination
16.2.9.3	Electrocardiogram (ECG)	Total	ECG
16.2.9.4	Substudy: 24h cardiac assessment (data source: iCardiac central lab database)	Total (substudy)	substudy_cardiac_assessment
16.2.9.5	Karnofsky performance status	Total	Karnofsky
16.2.9.6	Pregnancy test	Total	pregnancy_test.
16.2.9.7	ePregnancy report	Total	ePregnancy
16.2.10 Patient questionnaires and patient diaries			
16.2.10.1	EORTC QLQ-30 and QLQ-G.I.Net21 Questionnaire	Total	EORTC
16.2.10.2	Patient's diary	Total	patient_diary
16.2.11 Other individual patient data			
16.2.11.1	Patient registration data	Total	patient_registration
16.2.11.2	Visit information data of main study	Total	visit_information1
16.2.11.3	Visit information data of long term follow-up period	Total	visit_information2
16.2.11.4	Skip visit data	Total	skip_visit
16.2.11.5	Investigator's signature data	Total	Inv_signature

Appendix III: NETTER-1 Imaging Charter

INFORMATION PROVIDED AS PART OF NETTER-1 STUDY PROTOCOL AAA-III-01

IMAGING CHARTER

Version 2.0

29 June 2015

A multicentre, stratified, open, randomized, comparator-controlled, parallel-group Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours

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TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

^{177}Lu	Lutetium-177
CRO	Contract Research Organization
CT	Computerized Tomography
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
DTPA	Diethylene Triamine Pentaacetic Acid
e-CRF	Electronic Case Report Form
ENETS	European Neuroendocrine Tumour Society
FAS	Full Analysis Set
FOV	Field of View
GBq	Giga Becquerel (Bq = unit of radioactivity)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Gy	Gray (unit of radiation exposure; equal to 100 rad)
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Reading Center
I.V.	Intravenous
LAR	Long Acting Release
MBq	Mega Becquerel (Bq = unit of radioactivity)
mCi	MilliCurie (unit of radioactivity; 1 mCi = 37 MBq)
MRI	Magnetic Resonance Imaging
NANETS	North American Neuroendocrine Tumor Society
PFS	Progression Free Survival
PPS	Per Protocol Set
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumours
SOP	Standard Operating Procedures
Sstr2	Somatostatin Receptor Subtype 2
TIV	Trial Initiation Visit

2 Summary of Changes

This section is used to document the revision history of the Imaging Charter.

Charter Section	Revision Date	Version	Description of Additions/Changes
3.3	29-Jun-2015	2.0	Reference to the FDA Draft Guidance on clinical trial imaging endpoint process standards (March 2015) instead of the Draft Guidance issued in 2011.
3.10	29-Jun-2015	2.0	Case Assessment Spreadsheet replaces the Case Assessment Form.
4	29-Jun-2015	2.0	Reference to the most recent FDA Draft Guidance on clinical trial imaging endpoint process standards (March 2015) instead of the Draft Guidance issued in 2011.

Note: Non-substantive and orthographic changes (e.g., formatting, correction of typographical errors) are not mentioned in this Section.

3 TRIAL DESIGN AND THE ROLE OF IMAGING IN THE TRIAL

3.1 NETTER-1 trial design

The NETTER-1 clinical trial is a Phase III multicentric, stratified, open, randomized, controlled, parallel-group study, comparing ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with Octreotide LAR (Sandostatin® LAR Depot) in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours.

^{177}Lu is a medium-energy, beta-emitter with a maximum tissue penetration of 2 mm and a physical half-life of 6.7 days. It also emits medium and low-energy gamma radiation, which allow imaging and dosimetry. Octreotate binds with high-affinity to somatostatin receptors (especially sstr2) and retains its binding properties and physiological function when complexed with ^{177}Lu through an N-terminal DOTA-linked chelator.

The main criteria for enrolment in the study are: i) metastasized or locally advanced, histologically proven midgut carcinoid tumours; ii) target lesions which are somatostatin receptor positive based on scintigraphy with OctreoScan® within 24 weeks prior to randomization in the study while the patient was on a fixed dose of Sandostatin® LAR (except for the temporary interruption of Sandostatin LAR use for the purpose of obtaining an OctreoScan®); iii) the patient is at a fixed dose of 20 mg or 30 mg Octreotide at 3-4 weeks intervals for at least 12 weeks prior to randomization in the study; and iv) has progressive disease according to RECIST 1.1.

Patient randomization is performed according to a centralized stratified permuted block randomization scheme with a balanced ratio (1:1) between the two treatment arms, stratifying for the following factors; 1) somatostatin receptor scintigraphy tumor uptake score centrally assessed (Grade 2, 3 and 4) (the highest score measured among all the target lesions will be used for stratification purpose); and 2) length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤ 6 and > 6 months).

Treatment with a cumulative dose of 29.6 GBq of ^{177}Lu-DOTATATE (7.4 GBq x 4 at 8±1-week intervals) plus supportive care with 30 mg Octreotide LAR is compared to 60 mg Octreotide LAR (injections at 4-week intervals).

The primary objective is to compare Progression Free Survival (PFS) between the two arms. During the treatment phase, objective tumor assessment is performed every 12 weeks from the date of randomization until progression. Tumor progressions and objective tumor response during the study treatment phase are assessed by an independent Image Reading Center (IRC) according to RECIST 1.1.

The main secondary objectives are to compare Objective Response Rate, Overall Survival (OS), and Time to Tumour Progression between the two arms, and to assess safety, tolerability and health related quality of life.

3.2 NETTER-1 trial imaging centralized assessments

In clinical trial practice, the analysis of imaging data represents an important component in regards to determining patient trial eligibility, assessing drug safety, and identifying treatment efficacy endpoints.

Because of non-standardized methodologies, the measurements derived from imaging data are vulnerable to site-to-site variability. Therefore centralized assessment is preferred over a site-base process. This approach also provides for verifiable and uniform reader training, as well as ongoing management of reader performance, ensuring that the assessment process is uniformly accurate, and that bias and scan-to-scan variability are minimized (Douglas PS et al, 2009; Ford R et al, 2009; Tang PA et al, 2010).

In the NETTER-1 trial, the Sponsor has contracted an Independent Image Reading Center (IRC), Keosys, Saint Herblain, France, to conduct the following image analyses and centralized confirmation procedures:

a) verify that at the time of inclusion, all patients have progressive disease according to RECIST, Version 1.1, (Section 6.1.5 of the NETTER-1 Study Protocol) confirmed by the IRC;

b) select and verify that all patients target lesions, documented by CT/MRI (Section 6.1.4 of the NETTER-1 Study Protocol), have somatostatin receptor positivity on planar somatostatin receptor scintigraphy with OctreoScan® (performed within 24 weeks prior to randomization in the study). The tumor uptake observed in each target lesion using planar scintigraphy must be greater than or equal to the uptake of normal liver;

c) verify the extensive dosimetric analysis performed in the subset of 20 patients enrolled at selected clinical sites and treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The substudy will require planar and 3-D SPECT imaging centrally assessed (Substudy Central Lab, IEO: European Institute of Oncology, Milan, Italy), and will also include urine collection and blood sampling. Details of the procedures are included in the NETTER-1 Study Protocol (Section 6.6) and the substudy Manual;

d) verify that each disease progression event is according to RECIST (Section 6.3.1 of the NETTER-1 Study Protocol);

3.3 Charter objectives

This Imaging Charter summarizes all of the processes related to the analysis of imaging data to verify study endpoint events. The primary focus is to describe the imaging standards implemented in the clinical trial, and the technical, organizational, operational aspects in the exchange and processing of images. The aims are to ensure that; 1) all imaging data are obtained in a manner that complies with the study protocol; 2) the quality of imaging data is maintained within and among clinical sites, and 3) there is a verifiable record of the imaging process in order to minimize variability, improve data quality and enhance the accuracy of assessing drug treatment effects.

This Charter is based on the following reference documents:

- FDA Guidance on clinical evidence of effectiveness for human drugs and biological products (1998)
- FDA Guidance on clinical trial endpoints for the approval of cancer drugs and biologics (2007)
- FDA Draft Guidance on clinical trial imaging endpoint process standards (March 2015)

3.4 Image Acquisition Standards

All the imaging examinations performed for the purpose of this clinical trial are generated by the site radiologists according to locally assessed procedures and evaluated by using RECIST 1.1. The examinations are sent for central real-time assessment to the IRC, as soon as obtained (Refer to IRC Core Imaging Manual and IRC Operating Manual).

Before each site activation, individual training to the site staff is provided by the ICR as e-training on the specific to the Imagys platform (Refer to Images Acquisition Guideline) and by the appointed Contract Research Organization (CRO) during the Trial Initiation Visit (TIV) focusing on the overall process of centralized assessments in the context of the clinical trial, the procedures for images/data transfer and timelines (Refer to Pierrel Monitoring Plan).

In addition, training on the centralized procedure of image evaluation is performed at the Investigators Meeting planned at the beginning of the trial.

The purpose of the IRC Images Acquisition Guideline is to detail the imaging acquisition process, the qualification and quality control requirements for the production of optimal images with the aim of maintaining technical consistency within and among clinical sites, and optimizing the imaging acquisition modality.

Sites are checked as to the capability to produce adequate standard quality examinations and the availability of computer/internet connection intended to be used to upload the images into the IRC web platform. In this regard, each site undergoes a two-step qualification related to: i) the site's ability to use the Imagys' platform (network and computer configuration for effective upload of images), and ii) the user's ability to use the platform (based on the acquisition and validation of test CT/MRI and scintigraphy images) (Section 3.4.1.8). Sites unable to satisfy the quality pre-requirements will not be eligible to participate in the NETTER-1 trial.

3.4.1 Equipment Standardization and Operation

Response in patients with metastatic carcinoid tumors is most often defined on the basis of regression in the size of metastatic lesions. According to RECIST 1.1 criteria (Eisenhauer EA et al, 2009), triphasic, contrast-enhanced CT is regarded as the primary imaging modality to assess lesions size in oncological clinical trials and constitutes the primary imaging method of choice during the present study on neuroendocrine tumors.

The use of MRI is acceptable when CT is not advisable (e.g. in case of renal insufficiency, or allergy to iodinated i.v. contrast agents), or for additional investigational uses (such as liver studies when results of CT are inconclusive or equivocal). However, MRI sequences (T1- and T2-weighted; unenhanced, gadolinium-enhanced) have become increasingly more attractive also as a primary imaging technique. Therefore, other factors such as availability of up-to-date instrumentation, technical and clinical expertise, cost, and patient tolerance can also be taken into consideration for the choice of primary imaging modality and clinical site selection. When tumor staging shows the presence of soft tissue metastases, an already available MRI examination is deemed as acceptable for abdominal and pelvis

examinations, instead of requiring the repetition of CT. For chest imaging, CT is more appropriate because of its better spatial resolution as compared to MRI to detect small lung metastases.

The diagnostic examination used to determine progression during enrolment screening (by comparison with the previous examination of the same modality - CT or MRI) is used as the baseline imaging study. Otherwise, if too long time (as a rule, more than 4 weeks) has passed from the time of the diagnostic examination and the randomization, staging should be repeated before randomization, preferably by using CT.

Nevertheless, the imaging modality chosen for subsequent RECIST analysis, either CT or MRI, needs to be consistently used throughout the study treatment period and applying the same acquisition protocol as used at baseline. Substitution of one imaging modality for another is acceptable in the exceptional circumstance of unavailability of the same instrumentation. Any such substitution must be justified and documented. Then, the baseline method should be recovered as soon as possible for the continuation of the study.

The standard requirement is to perform an i.v. contrast-enhanced CT and to obtain an appropriate field-of-view (FOV) covering clinically relevant anatomical areas. This should include the thorax, abdomen and pelvis. At the very least, the abdomen and pelvis should be examined. When possible, the neck must also be included when the thorax is examined. The slice thickness should never exceed 5 mm and should be contiguous throughout all the defined FOVs. It is recommended that for each patient identical acquisition and reconstruction protocols be used at all time-points.

Additional details are reported in the IRC Core Imaging Manual and the IRC Images Acquisition Guideline.

- **CT scanners**

During the entire study, scanner quality control is recommended and should always be performed as instructed by the manufacturer. The radiologist should always optimize the examination protocol to comply with the ALARA principle for radiation exposure, i.e. "As Low As Reasonably Achievable" (Refer to NETTER-1 study Protocol, Appendix 15 – Section 18), however, without compromising the image quality.

Reconstruction settings must be as recommended by the manufacturer, not exceeding 5mm slice thickness and contiguous throughout the entire FOVs.

- **MRI scanners**

MRI scanner quality control is recommended during the entire study and should be performed on a regular basis according to manufacturer instructions. Multislice imaging is the default mode of MRI images acquisition. Reconstruction settings must be as recommended by the manufacturer, and not greater than 5mm slice thickness and contiguous throughout the entire FOVs.

- **Somatostatin receptor scintigraphy with OctreoScan™**

The scintigraphic acquisitions must be performed as recommended by the European Neuroendocrine Tumour Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS)

Consensus Guidelines (Kwekkeboom DJ et al, 2009; Vinik AI et al, 2010; Boudreaux JP et al., 2010). Considering the large number of centers involved in the study and the associated variability, it is of the utmost importance that each center does its best to comply with these protocols in order to achieve optimal image quality, according to the instructions provided by the IRC before site activation.

3.4.1.1 Vendor-specific equipment/platforms (e.g. scanners, software)

Throughout the entire study, DICOM images transmission between the investigational center and the IRC will be performed through the IRC web platform, unless digital images are made available through hardware support. Image print-outs on paper or films are allowed only in exceptional situations.

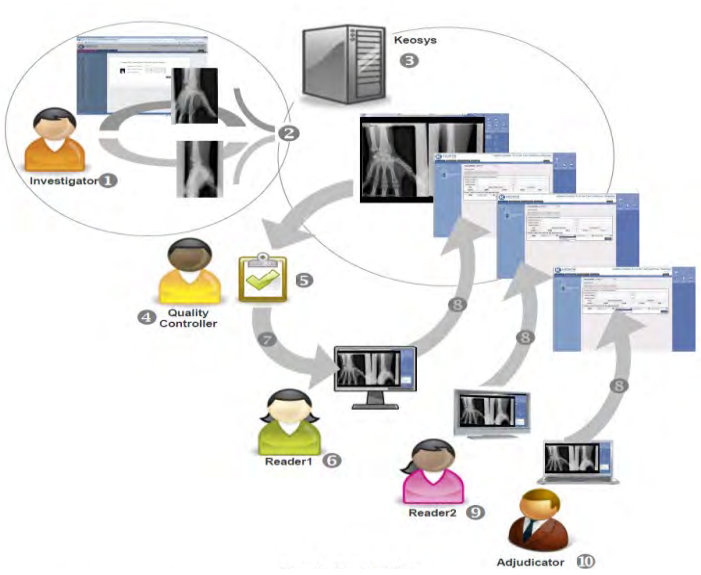
The technological / electronic infrastructure and programs used by the IRC for the upload, reading and storing of images, including all upgraded versions are validated by the IRC. In case of system changes the changed components are validated. A differentiation is made between 'patch', 'minor' and 'major' changes. All minor and major system changes will include appropriate user training. The validation reports are signed by the test manager and the quality manager. Additional information on data storage and back-up is provided in Section 2.4.1.10.

The IRC is audited at the start and during the project by the Sponsor or the appointed CRO.

The processes for image reading and data assessment, which are performed by third parties under the responsibility of the IRC, are described in specifications provided by the IRC. The process for the definition of acceptable/unacceptable images by the IRC is described in the IRC Core Imaging Manual.

The IRC provides the technological platform for the physical management of images, and an organized system for the Quality Control (QC) and the evaluation of the images uploaded for analysis (images used for the screening and selection of the patients; images used for the follow-up evaluation of the tumor progression; images submitted for adjudication in case of discrepancies between primary assessors). Corresponding processes are described in the Quality Controller User Guide and in the Core Imaging Manual, and in Section 2.4.1.9 and 2.5.1 of this Charter.

The entire process is illustrated in Figure 1.
Figure 1: Image acquisition and evaluation workflow



The investigator ① uploads, through a web browser, the patient examination images ② on the IRC server ③. The Quality Controller ④ validates the image data and determines if ⑤ the reading process is to proceed. The readers ⑥ ⑨ visualizes patient image data ⑦ from the IRC server, provided quality control is positive. Each reader completes a reading form ⑧ which is stored on the IRC server. The adjudicator ⑩ complete the adjudication form when readings are done.

Details on the specific steps in the evaluation of images are presented in Section 2.5.2.4.

Technical characteristics of the IRC system

The IRC platform can be used without the need for specialized software, and only basic components (Java and Active X) are required. It is compliant with any web browser and with Java compatible operating systems (Windows, MacOS, Linux).

Access to the documentation is limited to IRC appointed personnel, in order to ensure that images and data are retained in their original form. All users (i.e. local and central readers, adjudicator, QC person, supervisor, administrator) have an individual log-in to the web-platform. The system provides Login credentials which are automatically sent by email upon account creation. At first connection, users must update their password (password lifetime is 90 days). As a standard, the password must have special length and characters and expires every 90 days (criteria are provided for the password renewal). The different user groups have different screens. Only the administrator (the one who creates and manages user accounts) has an overview of the whole platform.

The IRC platform permits visualization and comparison of 3D imaging scan data in different modalities (including CT or MRI scans) for the central readers. The display of modalities can be made independently from each other or in fusion mode. Adjustment tools are available (a color map choice for the functional modality, a color bar to adjust the boundaries of the functional modality and an adjustment button for the blending between the two modalities).

The following measurements from 3D scans are determined: simple volumes: parallelepiped, sphere. Automatic 3D contouring by thresholding or region growing, ratio with reference zone, manual correction of segmentation, volumes naming.

The platform can also manage planar scans with different features (zoom, drag & drop, vertical and horizontal axial symmetry, reverse mode), LUT controls for the image corrections (grey and color scales). The following measurements are determined from planar scan: distances, open and closed angles, segments, surfaces, ROI/VOI with statistical calculation (mean, min., max., total) including SUV for PET, display of the maximum focal tracer accumulation with cursor.

Characteristics of visualization system

Central unit:
- Processor : Intel i5-680
- Memory : 4 Go 1333MHz DDR3 ECC
- HDD : 300 Go SATA II 10k

Diagnostic display:
- Diagonal display : 30''
- Resolution : 4MP : 2560x1600@60Hz
- Contrast : 1000 : 1
- Luminosity : 350 cd/m²
- Dimensions [H x W x D] : 18.4in x 27.1in x 11.9in

Dimensions [H x W x D]:
- Diagonal display : 19''
- Resolution : 1280x1024@60Hz
- Dimensions [H x W x D] : 55,9cm x 39,2cm x 24,73cm

No planning is made by the IRC for evaluations by external readers on possible systematic errors in computer-generated analyses. The IRC has obtained FDA 510k Pre-Market notification for the imaging workstation, and is certified according to ISO 13485 for medical devices. The IRC undergoes regular inspections by the national Regulatory Authorities (in France: LNE/GMED).

3.4.1.2 Equipment technical settings to be used at each site

Imaging equipment in use at the investigational centers should have been approved by local Regulatory Authorities. The IRC will discuss the required technical settings for image acquisition with the site at the study initiation, based on the protocol requirements and the IRC Images Acquisition Guideline. Sites' specifications are collected by the IRC during the site qualification process.

Minimal requirements for a successful upload check:

- Any operating system running the Java Runtime Environment (JRE) (Windows, MacOS, Linux)
- JRE 1.5 or later
- A Java compatible web browser such as Internet Explorer (IE8 or above), Firefox, Safari or Google Chrome

- Adobe Flash 9.0 or later
- The user must have the rights to download and execute Java Applet / ActiveX from the Gateway Server
- Internet access
- Enough free space on the computer to upload data
- Direct access to DICOM or imaging files to upload.

The de-identification of DICOM files is automated and performed in accordance with NEMA DICOM standards Part 15 guidelines (ftp://medical.nema.org/medical/dicom/final/sup1542_ft.pdf). This process consists of three steps:

- Overwrite all references to the patient by number inclusion,
- Overwrite the patient birthdate
- Overwrite all unique identifiers

The DICOM file is then compressed and encrypted, and the file is uploaded via secured web transfer process as a de-identified DICOM file.

3.4.1.3 The role of site imaging technicians in equipment operation, including identification of faulty or unacceptable images and the need to repeat imaging

The Investigator(s) are qualified by education, language, training, and experience to assume responsibility for the proper conduct of the study. He/she must meet all qualifications specified by the applicable regulatory requirements and provide evidence of such qualifications through an up-to-date curriculum vitae (Principal as well as all other Investigators) and/or other relevant documentation requested. The Principal Investigator of each site maintains a list of appropriately qualified persons to whom the Investigator has delegated significant study related duties. The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that the trial is properly conducted in adherence to the current protocol and ICH GCP (Refer to CRO Monitoring Manual).

In order to ensure that each site has the operational (technical and methodological) capability to provide quality images according to protocol requirements, a site qualification step is mandatory before the site activation (Refer to IRC Core Imaging Manual).

An e-training specific to the IRC web platform use is also mandatory before each site activation (Section 3.4.1.8).

3.4.1.4 Patient preparation, positioning, and comfort measures

Image acquisition procedures at each site follow local, standard practice. The procedures must also conform with the instructions provided by the specific equipment manufacturer.

The somatostatin receptor scintigraphy planar imaging protocol to be followed is the one suggested by the ENETS Guidelines, and reported in Appendix 6 of the Study Protocol. This includes discontinuation of somatostatin analogs, hydration, use of laxatives, need for fasting, voiding before imaging, among others.

3.4.1.5 The date and time for imaging and alternatives

Image scan timing for restaging is described in the NETTER-1 Study Protocol and is scheduled over 12 ± 1 weeks intervals, starting from the date of randomization. In case of different scheduling, a protocol deviation can be identified. Correction measures are needed in order to come back to the original schedule, as described in the study protocol (Section 6.3.1 of Study Protocol version 4.0).

Analysis and Interpretation of Image Information is also provided in Section 2.10 of this Charter.

Investigators are requested to upload images as soon as these are available, by using the IRC platform and after having de-identified the images (Section 2.4.1.2). An email alert is sent to the person in charge of the Quality Control at the Central Reading Center when a set of images are uploaded for central review. The IRC performs the images QC and analysis, and communicates the final results to the site by email within 5 working days.

Information on the time from images upload to QC analysis and to evaluation by independent readers is reported in a Status Report listing various information:

- Examination date locally
- Upload date
- Information on tumor response, as evaluated locally (information available only to the QC person, not to the independent readers)
- Date of QC approval
- QC state (validated)
- Date of evaluation by the independent reader
- Name of the independent reader
- Date of adjudication (if any required)
- Name of adjudicator
- Information on tumor response, as evaluated centrally
- Discrepancy between Local and Central response (information available only to the QC person, not to the independent readers)

3.4.1.6 Handling of off-protocol imaging examinations

Imaging examinations are used for patients inclusion according to the trial inclusion criteria #5 and #6 (Refer to NETTER-1 Study Protocol), while the primary efficacy variable of the study, Progression Free Survival (PFS), is based on in-protocol images scheduled every 12±1 weeks from randomization (Refer to NETTER-1 Study Protocol, Section 6.31 for further details).

Patients in a clinical trial lasting many months are likely to undergo imaging examinations in addition to the ones intended to assess the response to therapy or to detect disease progression (off-protocol images). All the in/off-protocol images requested by the Study for (re)staging purpose are assessed by the IRC (blinded, real-time assessment). Whether such patient assessment will be used or not for the end-point analysis, and how this is managed statistically, is a matter of ad-hoc evaluations, depending on the severity of the deviation observed.

In case the patients will undergo imaging examinations outside the investigational center before or after the first progression is assessed, the Investigator will make any effort to collect the images to be submitted to the IRC during the treatment phase or to be locally assessed at the investigational center during the long term follow-up.

If the DICOM files of the examinations obtained outside the investigational center are not available, at least the corresponding diagnostic sheets will be requested for filing as supportive documentation.

3.4.1.7 Imaging risks

In this trial, patients will be exposed to radiation, both during (re)staging imaging procedures and treatment with the radioactive drug ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radioactive treatment. ^{177}Lu emits β^-, and medium and low-energy gamma radiation, which can be used for treatment, imaging and dosimetry. As described in the Appendix 15 of the NETTER-1 Study Protocol, the physical and radiopharmaceutical properties and the metabolism of this radiopharmaceutical compound is associated to a low health risks to patients, patient's family members, patient's care givers and the general public. However, it is necessary to follow certain precautions in order to limit the exposure to radiation and maximize the safety of the patients and other persons, as indicated in the Protocol.

According to ICH GCP (CPMP/ICH135/95) the patient must give the consent to participate in the study, only after being fully informed by the Investigator of the nature, significance, and implications of the study, as well as to the associated risks involved. Such meetings must be carried out on an individual basis, and adapted to the educational background and previous knowledge of the patient. For the patients enrolled in the NETTER-1 trial, attendance to this meeting is documented in the patient's file. The extent of the risks related to exposure to radiation and administration of contrast agents is described in the Informed Consent Form (ICF) which is dated and signed by both the Investigator and the patient. (Refer to last version of the Main Study ICF).

Occasionally, imaging detects incidental findings that are important for further investigations. Some of these findings may represent false positive findings of disease and expose patients to additional examinations that would otherwise not have been performed. Some of these findings may also provide the first important signals of a clinically important condition.

All incidental image findings that may have clinical consequences are reported by the Investigator as adverse events in the study electronic Case Report Form (eCRF), and will be managed accordingly (especially in terms of patient information, diagnostic or therapeutic actions, reporting to Health Authorities).

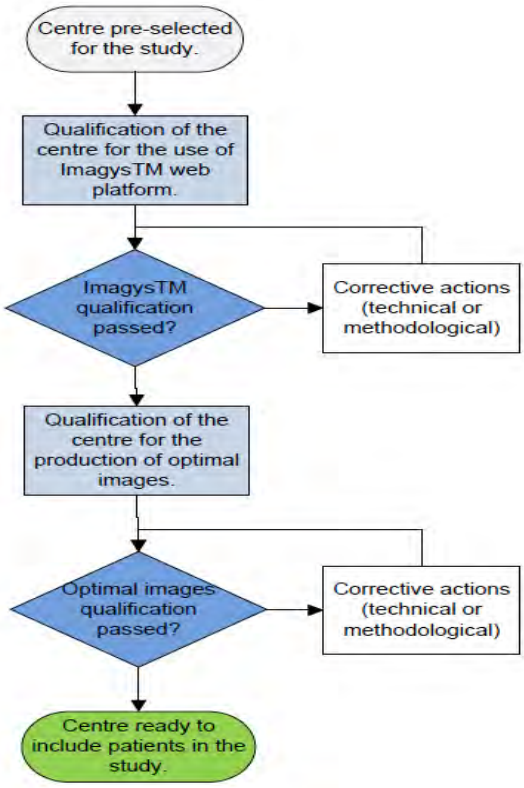
3.4.1.8 Site qualification process

Each site is requested to undergo a site qualification process by transferring test CT/MRI and scintigraphy examinations to the IRC before site activation. The IRC verifies the site capability to generate adequate standard quality examinations and the characteristics of the site computer/internet connection intended to upload the images onto the IRC web platform (Refer to IRC Web Upload

Qualification User's Guideline and IRC Images Acquisition Guideline).

A graphical overview of the process is illustrated in the Figure 2.

Figure 2: Qualification process



During the site qualification process, each site will have to upload to the IRC web platform sample data to be generated in the same way they will be provided during the entire study.

The sample data for CT/MRI and somatostatin receptor scintigraphy must be examinations that are already available at the center (no new examinations are to be performed) and should be uploaded to the IRC web platform where the patient data will be automatically anonymized by the system. The examinations that are uploaded for the qualification step and during the entire study have to be in the standard DICOM format. Additional information about DICOM requirements are provided in the IRC Viewer DICOM Conformance Statement.

Sample examinations required during this qualification step are to control that all the quality and technical requirements described in the IRC Images Acquisition Guideline are fully respected by the site. Sites are invited to read this guideline carefully prior to upload any qualification data, in order to minimize possible corrective actions.

Before site activation, each site has to upload three sets of CT examinations (arterial and venous phases) of patients scanned for metastatic carcinoid tumours.

If a center plans to perform MRI during the study, then it is mandatory to upload MRI examinations during the imaging qualification step.

The same process occurs with scintigraphy test images.

At reception of these examinations, the IRC contacts the site by email or phone within 5 working days in order to confirm the success of the qualification or to provide a dedicated support if inadequacies are detected during the review.

A certificate is sent to each site to confirm the successful outcome of the qualification process, while sites unable to satisfy the quality pre-requirements are not eligible for participation in the NETTER-1 trial.

3.4.1.9 Acquisition quality control monitoring process

Each time a new examination has been uploaded by the investigational center onto the IRC web-platform, it undergoes the IRC quality review (QC). The QC person is informed about uploaded images via email alert. After the initial QC check, the QC person informs the central reader via email and phone. In case the QC person is not provided with a reply within the specified delay, he will send the request to another central reader.

Quality checks include both automatic and manual checks on technical criteria and will characterize the images as appropriate or inappropriate for central reading by labeling the quality level of images as optimal - suboptimal - poor.

Possible deviations to be encountered and recorded include the following (among others):

- no de-identification;
- change in the imaging modality, compared to the baseline scan (*e.g. from CT to MRI, or vice-versa*);
- unavailability of sufficient anatomical regions within FOV (at least 2 FOVs are needed);
- poor quality.

In such instances, the QC prevents images to be passed forward for the evaluation by the independent reviewer.

In case of non-validated data, the images are rejected by the IRC and the reason is available on the platform (Section 3.5.1 for further details). The center is informed either directly, or via the clinical monitor or project manager and requested to perform corrective actions or send additional information.

3.4.1.10 Data storage, transfer, and site display

The original images are stored at the investigational sites, in the Institution's server. The IT functionality, back-up, and security, in particular under the perspective of data protection is the responsibility of the Institution.

The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that the study is properly conducted in adherence to the current protocol and ICH GCP, and that the data reported by the Investigator or designee are accurate, complete, and verifiable with the source

documents. The Sponsor or delegated CRO is responsible for assigning (a) Clinical Study Monitor(s), who monitor the study in accordance with the monitoring guidelines.

The Investigator and the study center must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the Ethics Committee / Institutional Review Board [IEC(s)/IRB(s)] and/or relevant Regulatory Authorities. They must provide all study-related records they are requested to generate and provide, as well as images and supporting documentation / diagnoses source documents. The confidentiality of the patient's identity shall be well protected and consistent with local and national regulations when the source documents are subject to direct access.

Images uploaded for central assessment are kept at the IRC facilities during the study conduct and for long-term archival. Two servers are available at the IRC facility. All data are saved in real-time on both servers. In case of a failure or abnormal termination of the main server, the second server will automatically switch to take over the part of the main server, and the administrator will be informed via email.

A daily back-up process is foreseen, which is followed by a back-up every 5 days, every 5 weeks and every 5 months.

Access to the server room of the IRC is restricted to persons specified in the SOP. All changes done in the server room are documented (who, when, what) on a log outside the server room. Servers are plugged to a redundant uninterruptable power supply (UPS) which also sent emails to the technical team in case of power outage.

Information on the technical characteristics of the IRC system is provided in Section 2.4.1.1.

3.4.2 Imaging Drug Standardization

If not contraindicated, appropriate contrast agents are used for either CT or MRI. Because the contrast medium administration may vary due to variability of for example local imaging protocols, each site will be using commercial contrast agents as available locally, and following the manufacturer's instructions. However, in case of allergy to iodinated contrast agents used for CT, or renal insufficiency, the examination is performed without contrast-enhancement or an MRI will instead be performed.

Guidelines on performing, interpreting, and reporting the results of somatostatin receptor scintigraphy with Octreoscan are available in Appendix 6 to the study protocol, including patient preparation, precautions and drugs to be used (e.g. hydration, use of laxatives).

A secondary explorative objective of the NETTER-1 trial is to evaluate $DOTA^0$-Tyr^3-Octreotate dosimetry in a subset of 20 patients. The substudy will require planar and 3-D SPECT imaging centrally assessed (IRC: European Institute of Oncology, Milan, Italy), and will also include urine collection and blood sampling. Details of the procedures are included in the NETTER-1 Study Protocol (Section 6.6 of the Protocol) and the NETTER-1 Dosimetry Substudy Manual.

^{177}Lu-$DOTA^0$-Tyr^3-Octreotate will be provided by the Sponsor, and it will be used at the same dose as used in the subjects enrolled in the main study.

^{177}Lu-$DOTA^0$-Tyr^3-Octreotate is a radiopharmaceutical solution for infusion supplied as a ready-to-use product. The Quality Control tests that must be performed at the clinical site are to; 1) confirm

correct product certificate; 2) determine total radioactivity; 3) confirm visual appearance. Since ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is manufactured in centralized GMP facilities, the majority of required QC tests are performed before product shipment. A batch release certificate of the product will be sent to the investigational centers. This batch release certificate is provided by the Qualified Person (QP) of the manufacturing site to ensure that the product is suitable for administration and that it meets its specifications.

The product is manufactured and supplied to the clinical sites in monodose vials. One vial, for one administration, contains 7.4 GBq (200 mCi of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at calibration time (the time of infusion) in a formulation solution of 22 to 25 mL. The variability of the volume depends on the time between the calibration date and the production date. The product will be shipped and calibrated for use at 24h or 48h after production in a centralized GMP facility. The calibration time of a dose depends on the distance from the manufacturing facility to the clinical sites. The amount of administered radioactivity, 7.4 GBq (±10%), is specified at the time of infusion.

3.5 Clinical Trial Standards for Image Interpretation

3.5.1 Image Transfer, Receipt Documentation, and Initial Quality Assessment

As a rule, during the entire study, image transmission between the investigational center and the IRC will be performed through the IRC web platform, unless digital images are not available or the electronic platform is not working, in which case print-outs on film or paper may exceptionally be forwarded to the IRC for the central evaluation (Refer to Paper Scans Transmission procedures, IRC Web Upload Qualification User's Guideline and IRC Images Acquisition Guideline).

Sites unable to satisfy the quality pre-requirements will not be eligible to participate in the NETTER-1 trial (Section 3.4.1.8).

The imaging quality control (QC) is divided into two steps:

1) Automated quality control by IRC web platform.
2) Expert quality control performed centrally by a qualified IRC Quality Controller.

During this data-transmission process, several quality controls will be automatically performed as detailed in the Table 1 below.

Table 1: Web platform automated systematic acceptance controls

Controls	**Acceptance criteria**
Continuity of the modality	The modality of the visit uploaded does correspond with the previous modality used for the previous visit. Unvalidated case: MRI received for visit 6 whereas CT scan were used for visit 5
Centre identification	The center identification will be checked and compared to the CRO database
Patient identification	The patient identification will be checked and compared to the CRO database
Patient birth date	The patient birth date 8included in the DICOM data) will be checked and compared to CRO database.
Images compatibility with Imagys reader	The images uploaded by the investigational center must be compatible with Keosys Imagys software (DICOM format)
Scan redundancy	The uploaded scan should not already exist on the platform

In addition to the automated quality controls described above, expert quality assessments will be performed centrally at the IRC (Table 2). As soon as a new patient visit has been successfully uploaded by the investigational center through IRC web platform, and the automated controls passed, the IRC quality controller is informed by an automatic email alert that a new visit (set of scans) is ready for evaluation. The outcome of this quality control can be either "validated" or "corrective action needed". If the visit is "validated", the process continues with the centralized analysis.

Table 2: IRC quality controller assessments

Control	Optimal quality	Sub-optimal quality	Poor quality
Apparatus model and capabilities	Multi-slice CT		Other
Slice thickness	≤ 5 mm		> 5 mm
Contrast media injected CT	YES		NO
Contiguous slices	YES		NO
Acquisition settings	According to manufacturer, taking into account patient obesity if required		Other
Reconstruction method and filters	According to the manufacturer		Other
Exam phase	Arterial and venous phase	One single venous phase	Native scan
Scan FOV	3 FOV: thoracic, abdominal and pelvic.	2 FOV (cervical FOV is not included).	1 FOV (cervical FOV is not included)
Artefacts	None	Cervical metallic artefacts, prosthetic artefacts, thoracic iodine contrast media artefacts	Any artefact that precludes the accurate analyses of 2 FOV or more

If the quality controller identifies an un-validated visit, the quality controller informs the site about the reasons why the examination was rejected and the information is traced in the platform audit trail. If at least the outcome of one control for the set of provided examinations is "poor quality", it will lead to an un-validated visit (Refer to IRC Core Imaging Manual).

The minimal requirements in order to obtain an optimal somatostatin receptor scintigraphy with OctreoScan™ image are reported in Table 3.

Table 3: Minimal requirements for somatostatin receptor scintigraphy with OctreoScan™

Control	Optimal quality	Sub-optimal quality	Poor quality
Date of Octreoscan	24 weeks prior to the patient enrolment in the study		More than 24 weeks prior to the patient enrolment in the study
Time points	2 or more time points. For example, 4h and 24h after injection or 24h and 48h		Less than 2 time points
Scan FOV	As clinically indicated most often, the 3 FOV are available: thoracic, abdominal, and pelvic. Additional cervical FOV if indicated.	2 FOV (abdominal and pelvic)	1 FOV (cervical FOV is not included)
Collimator energy	Medium energy		Low of high energy collimator
Global quality	Quality is optimal for evaluation of the exam	Quality is sufficient for evaluation of the	Any major artifact, image contrast alteration or major digestive activity

		exam	that preclude the accurate analyses of 2 FOV or more

The quality controller will also check that the uploaded set of images does not contain visible patient identification data. In case patient identifying data is present on the reviewed exam, the quality controller will automatically ask for a corrective action.
Furthermore, the quality controller will also verify (for CT/MRI scans) that all the series were acquired at the same date (in order to avoid that several visits are mixed). If this is not the case, the quality controller will automatically ask for a corrective action.

Data on single images uploaded are made available to the CRO by means of patient/visit listings (NETTER-1 Project Status.xls) (see also Section 2.5.2.4).

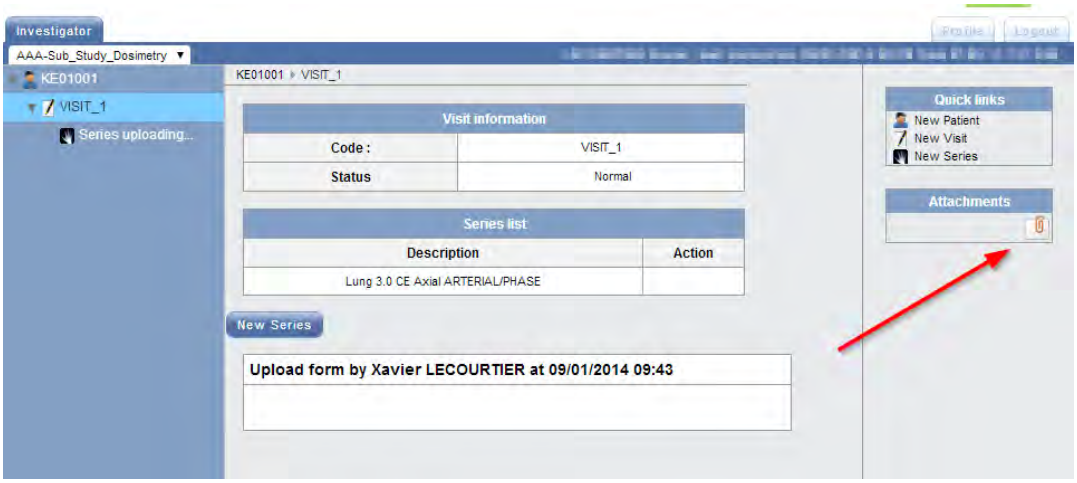
Image transfer for the dosimetry substudy

The evaluations made in the dosimetry substudy, in a subset of 20 study patients treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, are based on the reading and interpretation of WB planar and SPECT images (in addition to other non-imaging data) which are uploaded by the Investigator into the IRC platform and read by the Substudy Central Lab (IEO, Milan - Italy). In this regard, the IRC platform is used only for the image transfer. No quality control is performed on these images by the IRC. Images are uploaded by the investigator into the specific CRF of the Platform by selecting the appropriate modalities, as displayed in Figure 3 and 4, in the same way as conducted for the images uploaded in the main study.

The platform also allows the attachment of other files (Word, pdf, and Excel formats) which contain non-imaging data (e.g. calibration data; radiation detected in blood and urine) as needed for the dosimetry analysis.

Figure 3: Selection of the CRF section for the upload of substudy images

Figure 4: Screenshot for the upload of substudy images



The Substudy Central Lab finally downloads images for central analysis, after being alerted by the Investigational site or the CRO. Substudy images are QC checked by the Substudy Central Lab. Specific accounts are created by the IRC for the upload / download of the Substudy images. The process of Substudy data management and analysis is described in the Substudy Manual (Refer to NETTER-1 Substudy Manual).

Dosimetry data are elaborated at the Substudy Central Lab and outcomes on irradiation to specific critical organs (in particular, bone marrow and kidneys) released as soon as available. A final report with all patients data on radiation accumulation at all target organs and tumor lesions will be provided for inclusion in the clinical study database.

3.5.2 Image Display and Interpretation

3.5.2.1 Selection of images for interpretation, display sequence, and randomization

The selection and evaluation of the images previously uploaded by the Investigator are made independently by the central reader(s), and the evaluation is performed according to RECIST 1.1 criteria. The selection of the target lesions must be made with reference to the receptor positive tumors on somatostatin receptor scintigraphy with Octreoscan™. There is no pre-selection of images made by either the QC person, or the readers (either first reader, or adjudicator). There is no use of any supportive clinical information in the read. Information on local assessment (PD, SD, PR or CR) is given to the IRC QC person only, without detailed information on which lesions have been identified as target by the investigational site. Data on specific lesions are reported in the clinical eCRF of the main study, but central readers do not have access to the eCRF.

During the data review, readers complete a specific reading form attached to the image data in the electronic system. These data are kept on file by the IRC. In case of the need for adjudication, an email alert is automatically triggered to call an appointed adjudicator.

If the discrepancy is in relation to the screening process, the adjudicator performs a blinded analysis of the two contrasting assessments (local and central readers). If local assessment claiming tumor

progression during eligibility screening is confirmed the adjudicator, the adjudicator's analysis replaces the assessment of the first central reader and the patient is included in the study, otherwise, the adjudicator confirms the invalid PD status of the patient (see Figure 5).

If the discrepancy is in relation to follow-up data, the adjudicator will review the images independently of the previous assessments, but using targets defined during previous analyses. If local assessment shows same response as the adjudicator's, the adjudicator's analysis replaces the assessment of the first central reader. If a different response vs the local assessment is confirmed by the adjudicator (as also assessed by the first central reader), the adjudicator is also considered the reference over the first central reader (see Figure 6).The Investigator receives only the result of the adjudication, by email. The database is updated with the results of both the central reader's and the adjudicator's review.

The IRC is responsible of the quality control on the raw imaging database.

3.5.2.2 Number of readers and their background qualifications

The Quality Controller is familiar with Web browsing, medical imaging and quality control. Careful attention is assigned to the Quality Controller to warrant that the same radiologist reads successive examinations of the same patient.

Readers and adjudicators are familiar with Web browsing and medical imaging. They have expertise in Nuclear Medicine, scintigraphy evaluation and CT/MRI RECIST assessments in line with protocol requirements. A limited number of readers (up to 4) and of adjudicators (up to 2) is made available by the IRC for central reading.

3.5.2.3 Reader training and qualification

IRC performs annual interviews with their employees about their knowledge, experience and qualifications. The results are rated and documented, and serve as basis for an employee specific training according to their actual position (as per IRC internal SOP named "personal interview procedure").

During the course of hardware and software validation, all involved personnel are trained and this training is documented. The IRC, either directly or through third parties, is further responsible for the selection and training of the central readers, who have to be approved by the Sponsor. Central readers are initially trained by the Medical Director on the specific protocol, on RECIST 1.1, on the use of the Keosys platform, on the study specific eCRF, and undergo documented periodic training. IRC performs inter-readers and intra-reader assessments of variability, which are made available to the Sponsor or the appointed CRO.

3.5.2.4 Timing of image evaluation and the evaluation process

The IRC performs the image analysis and communicates the final results to the investigator site within 5 working days. Prompt interpretation of images is important for determining trial eligibility and to identify and document study events (tumor progression).

The read process is illustrated in the following Figures (Figure 5: Screening of the patient; Figure 6: Follow-up evaluation; Figure 7: Octreoscan™ adjudication process).

Figure 5: Screening evaluation process

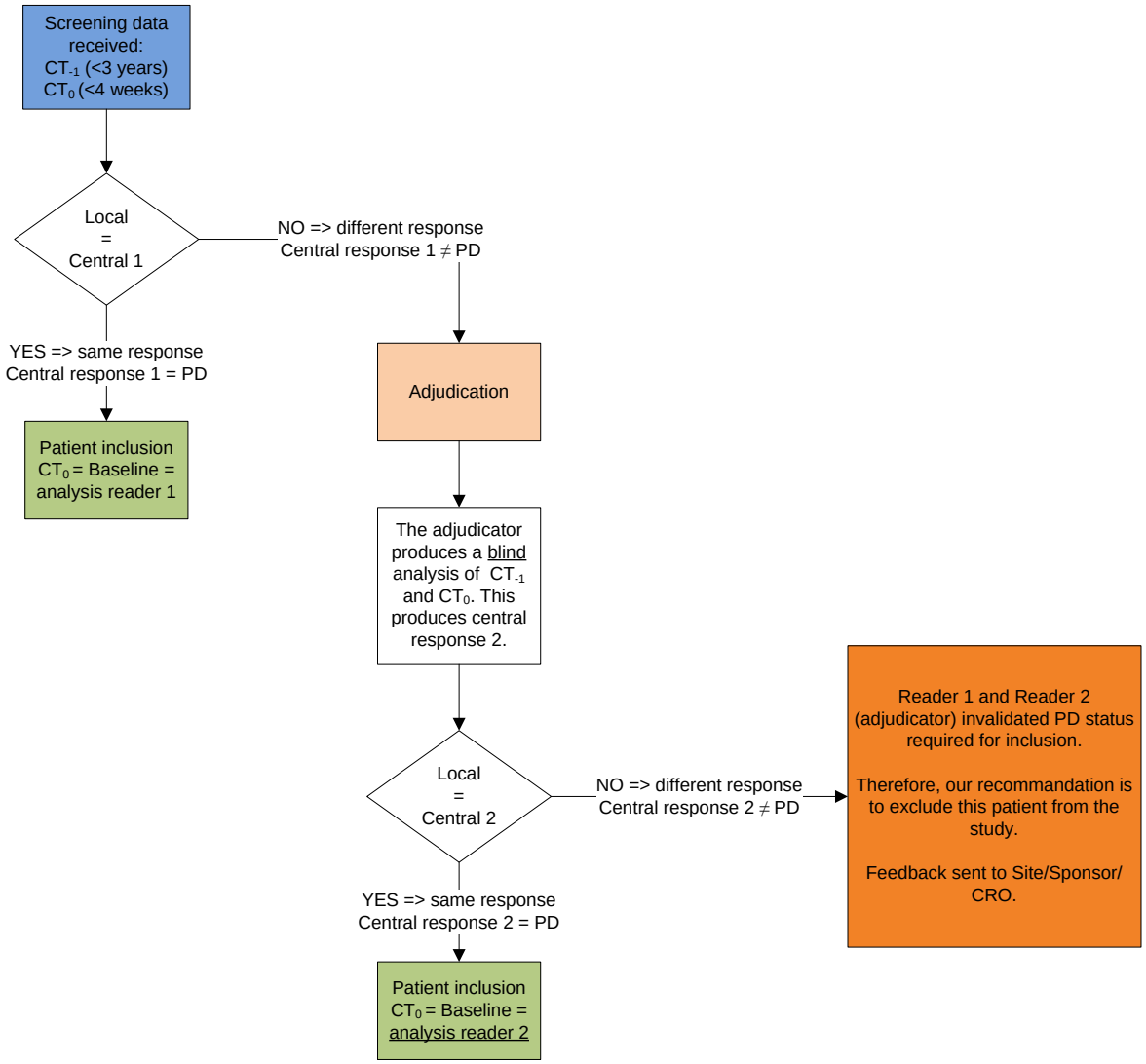


Figure 6: Follow-up evaluation process

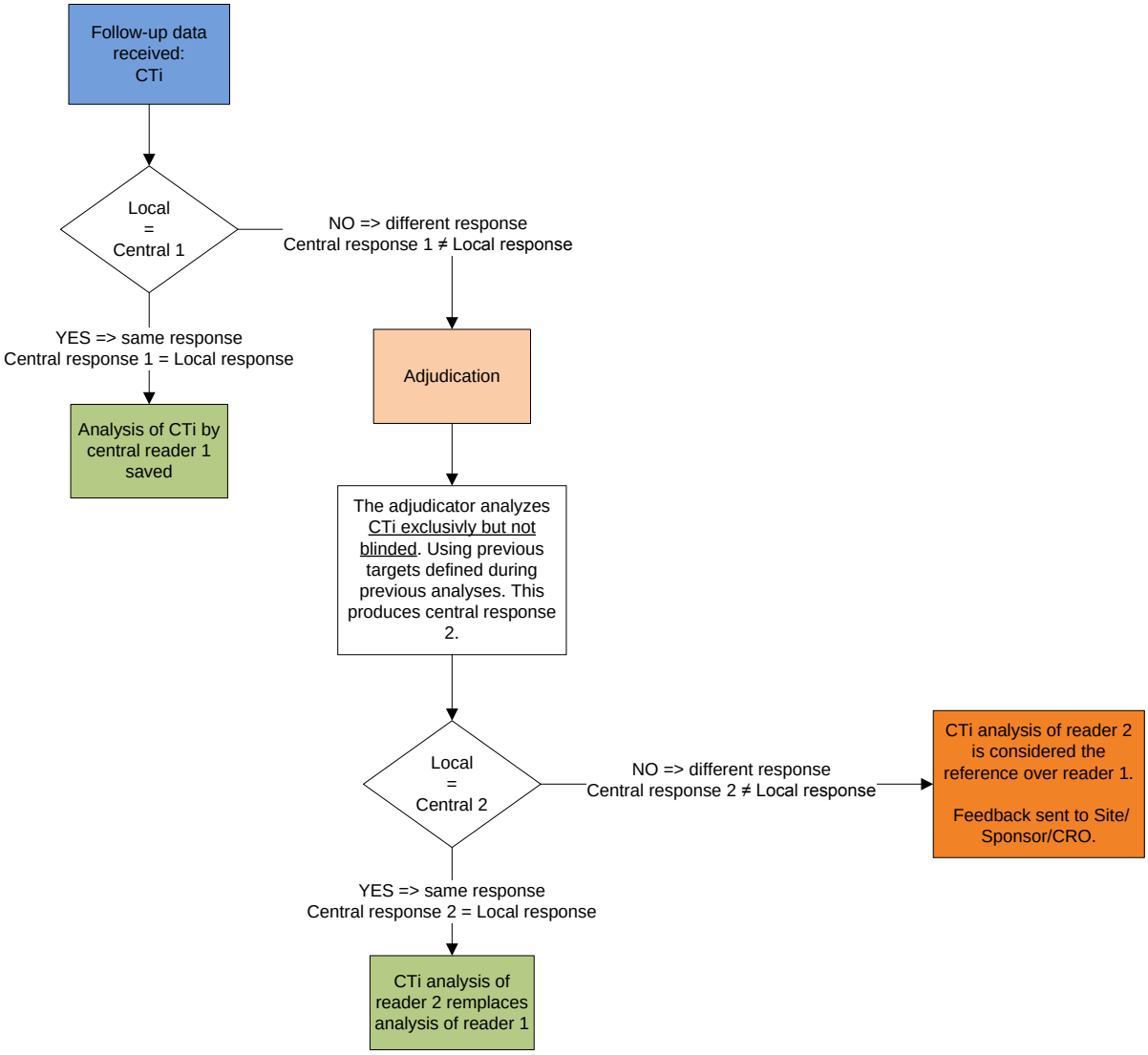
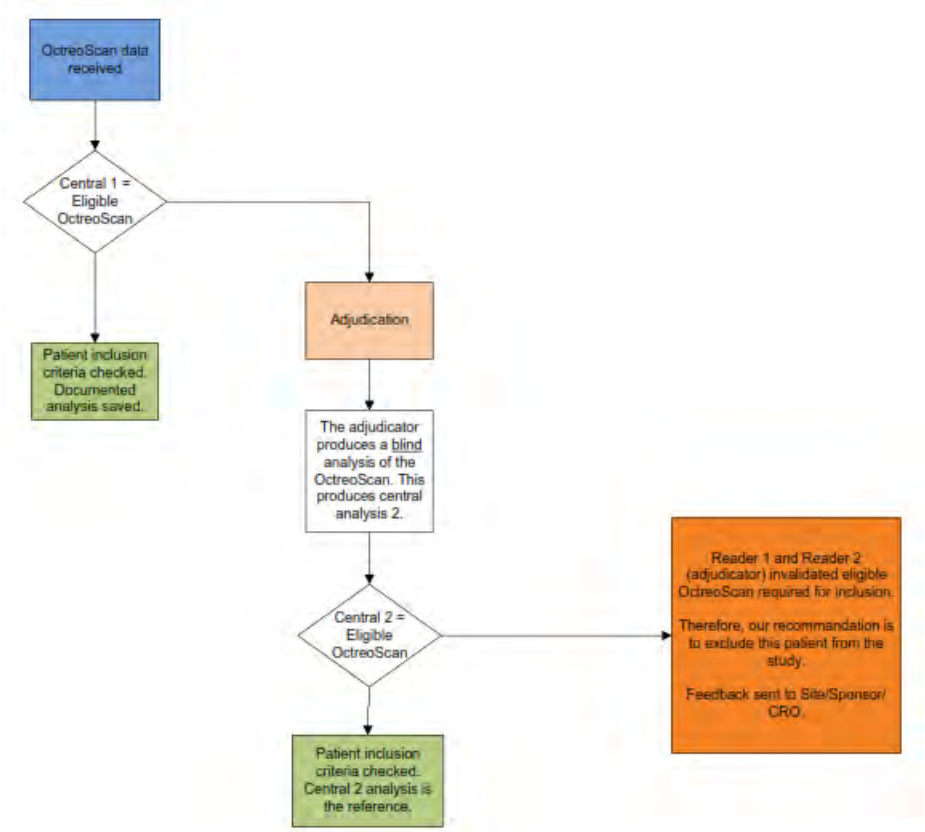


Figure 7: Octreoscan™ adjudication process



The central reading process of the CT/MRI scans is based on the independent evaluation of the central readers.

The independent central readers do not have access to the local evaluation; they receive automatic notifications when the scans need to be evaluated. As soon as the central reading is available, the central lab web platform, Imagys, automatically compares it with the local assessment (Progressive Disease). In case of discrepancies between Investigator and IRC on the evaluation of the real-time progression of disease, a third IRC evaluator ("the Adjudicator") will perform a final assessment for final adjudication (Refer to NETTER-1 Study Protocol, Section 4.4.1, and Core Image Manual Amendment, Section 5.3). The IRC Adjudicator then evaluates the scan and provide a final assessment (the Adjudicator does not have access to the local evaluation, only to the first central assessment).

If the discrepancy persists:

- Investigator assessment: non-PD; central assessment: PD. The "treatment/assessment" phase of the study is terminated and the patient should proceed to the long term follow-up assessment period. The investigator may request the continuation of treatment and assessments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate until the cumulative dose limit has been reached and/or Sandostatin LAR provided by the Sponsor according to randomization; 12-week local tumor assessments; safety assessments as in the treatment/assessment phase of the study) until progression has been documented by the Investigator, thereafter, the patient will proceed to the long term follow-up assessment phase.
- Investigator assessment: PD; central assessment: non-PD. The "treatment/assessment" phase of the

study should be continued as planned. However, the Investigator may decide to withdraw the patient from the "treatment/assessment phase" because of unethical continuation of the study in his/her opinion, and start the follow-up phase of the study. Such cases should be limited as much as possible and discussed with the local CRO representative before withdrawing the patient.

In case of adjudication due to disagreement between the IRC and the site assessment, the discrepancy is documented, and, for the Primary End-Point analysis, only the adjudication IRC assessment is considered.

The final central response (eventually as the result of the adjudication process) is communicated to the Investigator by email, and the Investigator is requested to report this outcome into the eCRF.
Additional information on the process of image reading is reported in Section 2.5.2.1.

3.5.2.5 Imaging case report forms

Images are uploaded by the Investigators into the IRC platform by opening the screen for the selection of the required protocol, and by attaching the DICOM folders and providing additional information including:

- patient code ID
- visit information
- the local (as assessed at the investigational site) assessment (CR - PR - SD - PD), without specifications on the target lesion selected (information available to the IRC QC person only)

Figures 8, 9 and 10 provide screenshots of the main CRF page of the IRC Platform, the process of file selection, the upload of the local RECIST assessment, respectively.

Additional description of the CRF functionalities is reported in the Quality Controller User's Guide and in the Investigator User's Guide.

Specific training was provided to Investigators on the use of the CRF for the image upload.

Figure 8: IRC Platform – main CRF page

Figure 9: IRC Platform – files selection

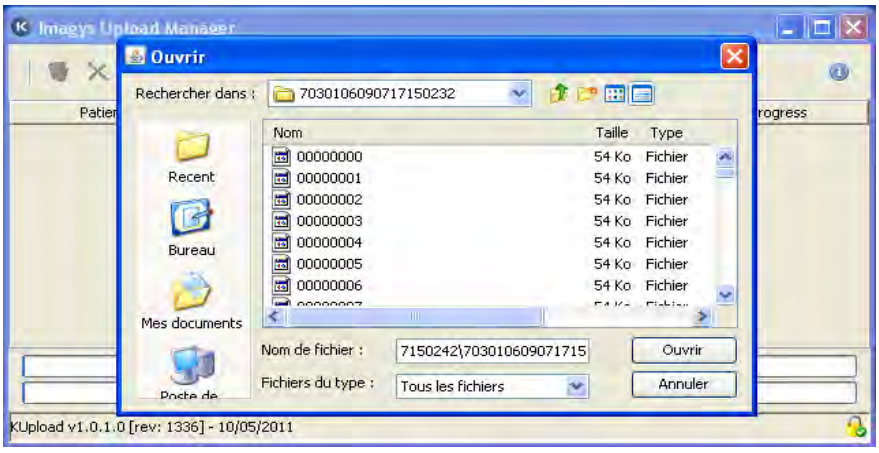
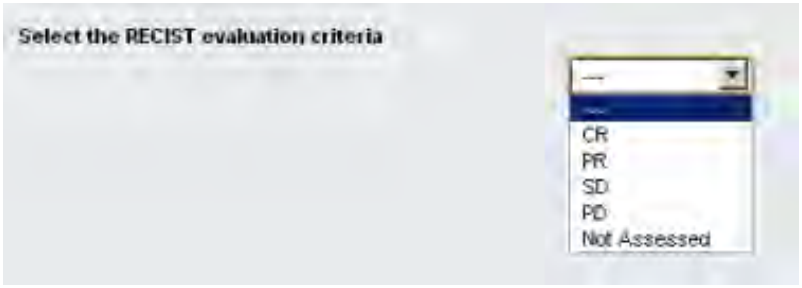


Figure 10: IRC Platform – local RECIST information



3.5.2.6 Imaging data lock process

The final IRC assessment will be transmitted to the investigator who will report the result in the clinical database via the eCRF which will be subsequently locked according to study procedures.

3.5.2.7 Quality control of the image display and interpretation process

Information on the technical equipment and the reader interpretation process is provided in Section 2.4.1.1 and 2.5.2.4.

The process of image interpretation is controlled by way of reader performance metrics (inter-, intra-reader variability), as reported in Section 2.5.2.3.

3.6 Imaging Data Transfer Process to the Sponsor

The final central review determination (CR, PR, SD or PD), as the result of the adjudication process, is communicated to the Investigator by email within 5 days of the images upload. The Investigator is requested to report this outcome into the main eCRF of the study , which becomes immediately part of the clinical data-base.

The original information on tumor progression as assessed by the IRC is also transferred to the clinical database at the end of the study. These data will represent the data-set for the statistical analysis of the tumor response-related study end-points (IRC images assessment).

Supportive data are collected separately as described in Section 2.9.

3.7 Archiving of Images

Case report forms and assessment tabulations represent source data and are retained by the IRC for potential inspection and auditing.

Images are retained by the IRC within its platform during the study and until images and all information on tumor response is transferred to the CRO. The CRO will transfer to Sponsor a copy of all images at the end of the study, after closure of the database.

Back-up storage is guaranteed. Archiving is performed in a manner conducive to a clear audit trail, including date and time recording. The IRC is responsible for the long-term archiving within its platform of images and supporting data provided by the Investigators. Copy of images and supporting data are returned to the Sponsor (via CRO) at the end of the study.

3.8 Monitoring Plans

The Sponsor or designee (e.g. delegated CRO) is responsible for periodic monitoring of the study to ensure that patients human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and ICH GCP, and that the data reported by the Investigator or designee are accurate, complete, and verifiable with the source documents. The Sponsor or delegated CRO is responsible for assigning (a) Clinical Study Monitor(s), who will monitor the study in accordance with the monitoring guidelines.
The Sponsor or delegated CRO implements and maintains QA and QC systems and written SOPs for clinical trial monitoring.

The Sponsor will arrange to inspect or audit the study at the IRC, clinical sites, and CRO facilities during the conduct of the NETTER-1 trial. The auditor is independent from the clinical monitoring and project management team at the Sponsor's site.

The Sponsor may delegate the CRO for specific inspection / auditing activities at the IRC.

3.9 Data Transfer and Archiving

Copies (identical to the originals) of all data pertaining to the process and the outcomes of the central imaging assessments must be returned to the Sponsor at the end of the study. Such data include (but it is not limited to):

- images received at, and managed by, Keosys for central assessments (CT/MRI, planar whole body scintigraphy and SPECT images for patients in the substudy),
- supporting documentation pertaining the single subjects (*as detailed below*).

The delegated CRO will operate on behalf of the Sponsor in this process.

Images and supporting documentation are returned to the Sponsor with data collected "by patient", at the patient's completion of the main treatment phase of the study.

Images and supporting documentation must be provided on suitable electronic support (HD, DVD). Images will be provided within folders containing the same original DICOM files as uploaded by the Investigator.

Images and supporting documentation must not contain patient identification notations (neither the patient's name, nor initials, nor birth date), but identification information on the type of scan, site/patient ID code and the visit number of reference (the date of the examination may either be reported in the file name, or be reported separately in a log with all details for each patient).

Therefore, image files must be named using the following format:

- sitecode#_patient#_Week#

For example: "BE01001_Incl_-1" or "BE01001_Incl_Octreoscan", or "BE01001_W000"
Each folder will contain sub-folders with the DICOM files (file extension .dcm).

A log with details for each patient and additional comments as needed ("supporting documentation"), should be attached to the files that are sent to the CRO.

The supporting documentation pertaining to the single subjects includes

- read outcome information;
- dates of visit by visit assessments;
- central readers identification;
- the specific reading form completed by readers, which is attached to the image data in the electronic system;
- quality-control checks upon critical software functions and notes on deviations;
- comments.

Shipments to the CRO will be made in batches including completed cases (subjects), at shipment intervals no longer than two months from the date of any patient's study ending.

General documentation on the platform and the process will also be provided, including:

- description of the platform/system characteristics, validation, reading process within the central lab;
- deviations detected in the general process either within the IRC procedures, or as sites' deviations (*NB: single patients' deviations are to be reported in the patients' supporting documentation*);
- information on central readers / adjudicators (CVs, training records, inter-readers and intra-reader assessments of variability);
- outcomes of the sites' qualification process.

The IRC is advised to keep its "original" images for archival purposes and as documentation for possible audits. The appointed CRO will cross-check data provided by Keosys with data available in the

clinical study data-base for consistency (e.g. read outcome information). The CRO will in turn provide AAA with all images / files received from Keosys, in due time.

3.10 Analysis and Interpretation of Image Information

If a patient does not have centrally assessed disease progression and is living, the patient will be regarded as censored in the context of a time to event analysis at the date of last evaluable tumor assessment. The final primary analysis of PFS will be performed when the planned number of 74 PFS events (centrally assessed progressions or deaths) is observed.

Additional PFS data are collected after the Primary End-Point has been reached during the treatment/assessment phase, or during the long term follow-up phase in case of a discrepancy in the evaluation of the progression of disease (Refer to NETTER-1 Study Protocol, Section 4.4.1). This additional PFS data will be collected and analyzed descriptively.

When a case is complete (i.e. after disease progression is centrally confirmed), the locked file (including all information available at the central reading center) is returned to the CRO (Section 2.9). A final review is then conducted by an independent radiologist and nuclear medicine specialist, member of a well-recognized nuclear medicine organization. This radiologist is blinded to the patient treatment arm. The objective of the review is to confirm that all steps of the collection, quality control, and assessment process have been conducted according to the study protocol and the Imaging Charter.

As discussed in the SAP, the primary efficacy analysis will be based on the full analysis data set of all randomized patients. A per protocol analysis will also be performed on the evaluable patients data set. Evaluability will be determined by an independent reviewer (Anders Sundin, MD, PhD, Professor and Senior Consultant at the Department of Radiology, Uppsala University Hospital, Sweden).

The following information (blind on the treatment arm and anonymised) will be provided to support his final assessment:

- All images generated during the study, including somatostatin receptors scintigraphy used to assess the lesions, images available before inclusion to confirm eligibility and data on cases which have been rejected or disputed by the IRC,
- Reports on all discrepancies (target lesions or outcome) between the local and central readers,
- Protocol violations for each case (including violation of inclusion / exclusion criteria),
- Previous anti-tumor treatments and procedures, incl. local ablation, microwave, embolization, as well as any prior surgical toraco-abdomino-pelvic procedures,
- Clinical anamnesis, including number and localization of metastases and co-morbidities at baseline,
- Previous radiology reports,
- Data on all parameters at inclusion, including date of first diagnosis, TNM and Ki67 levels.

No information on hematology or renal function (unless part of the inclusion/exclusion criteria), biochemistry / chemical markers (unless part of the inclusion/exclusion criteria), safety and adverse events, or clinical status at the time of case finalisation, will be provided.

This final assessment enables confirmation of eligibility in the per-protocol analysis of the primary end-point. Should a case not be selected for the statistical analysis, the reasons will be fully documented,

and the non-selected case will nevertheless be included in the clinical study report.

The reasons for non-eligibility include images of inadequate quality which casts doubt on the outcome of the readings, questionable decisions in selecting target lesions, for instance conflicting with RECIST 1.1, or other reasons which impact the relevance of the information assessment within the frame of the clinical trial protocol.

The confirmation of eligibility will be formally notified by the independent reviewer to the CRO statistician through the *Case Assessment Excel Spreadsheet* which includes the key elements to support the decision on per-protocol eligibility. After final decision at the blind data review meeting, the Spreadsheet will be printed, dated and signed by the independent reviewer before the database lock. All cases will be analysed (ITT), but only those "confirmed" in the overall assessment process will be part of the "per protocol" analysis.

The confirmation of eligibility, as formally notified with the completion of the Case Assessment Spreadsheet, will trigger the imaging data lock process and the statistical analysis of the primary end-point, PFS.

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NETTER-1 Dosimetry Substudy Manual

NETTER-1 Substudy Manual

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Appendix IV: Pharmacokinetics and dosimetry data analysis

Statistical Analysis Plan

Study AAA-III-01

APPENDIX IV

DOSIMETRY AND PHARMACOKINETICS DATA ANALYSIS

Version 1.0

18-DEC-2014

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Table of contents

List of Abbreviations

Abbreviations	Description of abbreviations
^{177}Lu	Lutetium-177
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
BED	Biologically Effective Dose
CI	Confidence Interval
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraaacetic Acid
ECG	Electrocardiogram
FWHM	Full Width at Half Maximum
GBq	Giga Becquerel (Bq = unit of radioactivity)
Gy	Gray (unit of radiation exposure; equal to 100 rad)
HPLC	High-Performance Liquid Chromatography
HR	Heart Rate
ICH	International Conference on Harmonization
IEO	European Institute of Oncology
i.v.	Intravenous
LAR	Long Acting Release
mCi	MilliCurie (unit of radioactivity; 1 mCi = 37 MBq)
ND	Number of Decays
PK	Pharmacokinetics
PRRT	Peptide Receptor Radionuclide Therapy
RP	Reverse Phase (HPLC)
RT	Retention Time
SAP	Statistical Analysis Plan
SPECT	Single-Photon Emission Computerized Tomography
WB	Whole Body

1 Sub-study plan

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and methodology to be used to conduct the analysis of data generated in the sub-study of the NETTER-1 clinical trial.

The purpose of this Appendix to the SAP is to ensure the appropriate analysis of the sub-study data by using pre-specified statistical approaches prior to the database lock. It is based on the current version of the NETTER-1 clinical study protocol, version 4.0 dated March 25, 2014 and version 4.1, dated June 5, 2014. The two protocol versions do not differ for the procedures related to sub-study.

This Appendix to the SAP is a detailed technical extension of the clinical Study Protocol and follows the principles of the International Conference on Harmonization (ICH) Guidelines E3, E6 and E9 and the relevant Working Instructions and Standard Operating Procedures.

In this Appendix to the SAP, a description of dosimetry and pharmacokinetic data pertaining to the sub-study portion of the NETTER-1 trial is provided. These represent exploratory objectives of the NETTER-1 study.

A dosimetry, pharmacokinetics and ECG substudy is conducted in a subset of 20 patients at selected sites with the objective to provide a more complete assessment of the safety aspects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. In addition, the pharmacokinetics of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and its metabolites will be investigated. Also the acute cardiac effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be assessed by way of a 24-hour Holter electrocardiogram (ECG) monitoring. Reference is made to Section 6.6 of the study protocol. Data will be collected according to the NETTER-1 sub-study Manual (Version 4.1 dated June 16, 2014).

According to protocol version 4.0, sub-study data are collected from patients who have been randomized to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, in addition to 30 mg Sandostatin LAR. In spite of all the efforts to increase the rate of patient enrolment in the substudy, the recruitment was not fulfilling expectations for an on-time completion. To further facilitate the enrolment, subsequent protocol Amendment 4.1 has allowed non-randomization for the patients newly enrolled in the substudy.
Dosimetry data (based on planar whole body (WB) and 3D single-photon emission computerized tomography (SPECT) scintigraphy, and blood / urine radioactivity levels) are analyzed at the Nuclear Medicine Dept of the European Institute of Oncology (IEO) (Milan- Italy) under the coordination of Dr. Marta Cremonesi. Dosimetry outcome data will be made available by IEO in MS Excel (.xls) files for data transfer into the clinical database within a SAS sub-study (dosimetry) dataset.

In addition to the dosimetry data assessed by IEO as per protocol, additional dosimetry data will be available from German centers not participating to the dosimetry substudy, but having performed similar analyses as requested by the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz - BfS). Those data will be part of the clinical dataset and will be analyzed separately.

Pharmacokinetic (PK) profiles from urines samples are assessed by the Radiopharmacy Dept of IEO (Milan – Italy) under the coordination of Dr. Marco Chinol and Dr. Stefano Papi. Urine samples will be analyzed for the determination of the rate and extent of elimination of ^{177}Lu-

$DOTA^0$-Tyr^3-Octreotate (the radiochemical status of the parent radionuclide and of its metabolites) by gamma-detector RP-HPLC. PK data will be made available by IEO in MS Excel (.xls) files for data transfer into the clinical database within a SAS sub-study (pharmacokinetics) dataset.

Electrocardiographic data are analyzed by iCardiac Technologies Inc (Rochester, NY - USA) for the determination of ECG parameters, including the QT/QTc interval. ECG data will be made available by iCardiac in .xls files for data transfer into the clinical database within a SAS sub-study (electrocardiographic) dataset. A specific SAP for ECG data has been prepared by iCardiac and included as Annex V to the NETTER-1 SAP.

1.1 Determination of sample size

20 patients will be enrolled in the sub-study.
No specific statistics-based calculation of the sample size was made.

2 Statistical and analytical procedure

2.1 Analysis variables

2.1.1 Demographic and baseline characteristics

Data from the specific eCRF pages will be used.

Dosimetry study
- date of birth, gender, body height and body weight

Pharmacokinetic study and metabolites characterization
- date of birth, gender

2.1.2 Variables on study

The following variables will be calculated.

Dosimetry study

Variables obtained from WB planar and SPECT images, as well as from blood/urine radioactivity, will be collected for the dosimetry analysis and reported in a separate document ("NETTER-1 Dosimetry Results Template") including data for each subject. This data will be used for the determination of the absorbed doses to target organs and tumor lesions, and for the biokinetics.

The analysis of data and radiation dosimetry calculations are performed at IEO.

The number of decays (ND) per unit injected activity, mathematically equivalent to the quantity of residence time (Stabin MG et al., 2005), will be calculated from multiexponential fits to the time–activity curves for spleen, kidneys, liver, testes, and remainder of body.

The time-activity curve for blood will be evaluated with rescaling for the individual blood mass based on patient gender, weight, and height. The ND in the red marrow (ND_{RM}) will be derived from the blood-based method (Cremonesi M et al., 2006; Forrer F et al., 2009): $ND_{RM} = ND_{blood} \times m_{RM} / m_{blood}$, where m_{RM} and m_{blood} are the individual red marrow and blood masses, and ND_{blood} is the ND in the blood. The red marrow mass will be derived assuming a fixed ratio of red marrow to

blood mass. The total absorbed dose to red marrow will be extrapolated from the blood curve. Absorbed doses to target organs will be calculated by entering the ND values for all the source organs in the OLINDA/EXM software and adjusting the doses reported by the software for individual weight and organ masses for kidneys, liver, spleen (determined from CT), and red marrow.

Whenever possible and for comparison purposes only, the patient specific red marrow mass will also be derived based on the individual volume of the lumbar vertebrae L2, L3, L4 (V_{L2-L4}) estimated from CT images (Ferrer L et al., 2010), according to the equation: $m_{RM} = 6.7\% V_{L2-L4}$. The dose to the red marrow will then be rescaled with the red marrow mass determined from the L2-L4 methods and compared with the previous one derived by proportionality with the blood volume.

Pharmacokinetic profiles

The Pharmacokinetic profiles will be assessed with the following procedure:

1. Determine the time-activity curves in the source organs by either numerical fitting of exponential curves to the data or by compartmental modeling to all organ uptake, blood and excretion data. A general code for numerical and compartmental modeling (the SAAM II software - http://www.saam.com) will be used (Cobelli C et al., 1998).

   The bi-exponential clearance pattern is assumed to be applied.

2. The time-activity curve in each source region will be integrated to determine the cumulated activity Ã [in MBq.h].

   A typical result of step 1 is a bi-exponential curve $A_{organ} = A_1 e^{-\lambda 1 t} + A_2 e^{-\lambda 1 t}$. The corresponding cumulated activity is:

   $$\tilde{A}_{organ} = \frac{A_1}{\lambda_1 + \lambda_p} + \frac{A_2}{\lambda_2 + \lambda_p}$$, with λ_p the physical decay constant of ^{177}Lu.

   If step 1 will not be successful, the cumulated activity will be calculated by applying the trapezoid method for numerical integration. Linear extrapolation to t = 0 will be performed by assuming A(0) = A(4).

3. The quotient of Ã and the injected activity IA will be calculated to yield the number of decays ND = Ã/IA (or residence time τ).

4. The fraction of administered activity that is excreted through the urinal pathway will be determined. A numerical fit (bi-exponential curve) to the urinary data will be performed to determine the fractions and elimination rates in the subsequent clearance stages:

   $$A_{Urine}(t) = A_0 - A_1 e^{-\lambda_1 t} - A_2 e^{-\lambda_2 t}$$

   A curve-fitting program, like SAAM II, will be used. The clearance stages are needed for the calculation of the bladder residence time.

5. The cumulated activity in the total body will be used to calculate the cumulated activity in the remainder of the body (source contribution to the bone marrow and other organs dose), by subtraction of the sum of the NDs in all known source organs from the total body NB:

$$\tau_{remainder} = \tau_{TB} - \sum_{source.organ.i} \tau_i$$

Radiation dosimetry calculation

Data for ^{177}Lu are available in the OLINDA/EXM (Stabin MG et al., 2005) software package. Alternatively, the S-factors can be also taken from the Radiation Dose Assessment Resource (RADAR) site (http://www.doseinfo-radar.com/RADARphan.html). By using these S-factors and the residence times for the source organs, the radiation dose to all target organs will be calculated.

For each target organ, the total dose /activity will be assessed as the sum of beta and photon radiation. For each tumour lesion, the total dose /activity will be assessed as the product of (number of disintegrations) x (dose factor for ND = 1 h).

The following parameters will be analyzed and reported in the dosimetry dataset of the study:

- Absorbed radiation dose to single organs (kidneys, liver, spleen, bone marrow, testes, bladder walls, total body, other organs) and tumour lesions per unit activity (Gy/GBq)
- Cumulative absorbed radiation dose to single organs (kidneys, liver, spleen, bone marrow, testes, bladder walls, total body, other organs) and tumour lesions, in four cycles, for a total activity of 29.6 GBq (cumulative dose calculated under the hypothesis that the biokinetics is maintained for all cycles) (Gy)
- Decay constants λ (a_1 ; a_2 ; a_3)
- Effective half-life ($T½_{eff}$), to be calculated as ln2 / λ (*ln = natural logarithm*)
- Number of Decays (ND; also referred to as “time integrated activity” or “equivalent residence time”) per unit activity (h)
- Cumulative kidney Biologically Effective Dose (BED) (Gy), to be calculated as BED x 4 (*4 cycles*)

The corresponding dosimetry data listings are shown in Appendix 8.1.

For each patient, additional information will be collected:

- information on whether the cumulative bone marrow radiation dose has exceeded 3.7 Gy,
- information on whether the cumulative kidney radiation dose has exceeded 38 Gy of BED,
- information on the cycle number when dosimetry analysis was performed
  (it is anticipated that, in the event that dosimetry calculations are performed in relation to the 2nd or 3rd cycle of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, only the dose estimates for the kidney and the bone marrow can be used in the overall evaluation, as the tumour lesions, liver and spleen can be influenced by the prior therapy effect),
- presence of risk factors for kidney toxicity (e.g.: diabetes, essential arterial hypertension, hypercholesterolemia, obesity, smoking, familiar history of kidney disease).

Pharmacokinetic study and metabolites characterization in urines

Rate and extent of elimination of ^{177}Lu-DOTA^0-Tyr^3-Octreotate in urines will be determined as % of the administered dose, over partial time-periods (0-1 hr; 1-4 hrs; 4-16 hrs; 16-48 hrs) and as cumulative elimination.

The following parameters will be calculated for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and other metabolites identified in each patient:

- Proportion of each compound in each sample (% of the peak area out of the total area).
- Retention Time (RT - min).
- Full Width at Half Maximum (FWHM) of the principal peak, as an indicator of changes in the chemical state.
- Chromatogram resolution of each peak.
- Concentration (MBq/mL), i.e. quantitative determination of each compound, calculated in relation to the radioactivity detected.

2.2 Analysis populations

All subjects with consistent data will be analysed. Subjects with insufficient availability of data will be discarded from the analysis. However, data from all enrolled subjects will be included in the substudy report as well as the reasons for eventual removal from the analysis.

Dosimetry study

For the dosimetry analysis, the following data should be available as minimum, in order to consider the case as valid:

- Site/Patient identification (Site #; Patient screening #)
- data from at least 5 time points from the WB planar images
- bladder emptying before the first image

Pharmacokinetic study and metabolites characterization

For the pharmacokinetic analysis, the following data should be available as minimum, in order to consider the case as valid:

- Site/Patient identification (Site #; Patient screening #)
- Date and time of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration
- Unavailability of all samples requested

2.3 Data analysis

Results will be presented as listings containing all data available for each single parameter and as analytical outcomes.

Each variable will be analyzed descriptively and reported as follows: for descriptive analyses of continuous variables and of changes from baseline of these continuous variables, number of non-missing values (N), number of missing values, mean, 95% CI for the mean (where appropriate), standard deviation, minimum, lower quartile, median, upper quartile and maximum will be presented. Categorical variables will be presented in frequency tables, i.e. as frequencies and percentages.

The correlation between changes in serum creatinine / creatinine clearance (calculated by the Cockroft-Gault formula) assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative kidney Biological Effective Dose (BED) up to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated.

The correlation between changes in serum creatinine / creatinine clearance (calculated by the Cockroft-Gault formula) assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative absorbed doses for kidneys up to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated.

The correlation between changes in total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (AP), serum albumin assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative absorbed doses for liver up to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated. This analysis will be conducted separately for (1) patients with normal livers and (2) patients with liver metastases.

The correlation between changes in Hb, WBCs, neutrophils, lymphocytes, platelets assessed four weeks after the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion versus the cumulative absorbed doses for bone marrow to the last ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion will be determined. For this purpose the correlation coefficients according to Pearson and Spearman will be calculated.

Results obtained from the radiation dosimetry calculations will be kept at the site (with indication of the precise archiving location) and made available upon request of the Sponsor, its delegates (e.g. the appointed CRO), or Regulatory Authorities.

2.4 Data handling conventions

2.4.1 Missing values

No replacements will be made in case of missing data for either the dosimetry, or the pharmacokinetic, or the ECG study.

2.4.2 Transformation of data

The following derived parameters will be calculated according to the following criteria / formulas:

Dosimetry study
The methods for data analysis are described in the NETTER-1 sub-study Manual. For the definition of the time-activity curves (radiation pharmacokinetic profile), appropriate numerical and compartment modelling will be applied using the SAAM II software (Cobelli C et al, 1998). Radiation dosimetry calculation will be made with the OLINDA/EXM software (Stabin MG et al, 2005).

Pharmacokinetic study and metabolites characterization
Concentration (MBq/mL) will be calculated using the following formula (derived from the calibration curve): $C = (Area - 1524) / 40161$

3 General appearance of output

Data will be presented as tables, figures, listings.
Every table, listing or graph contains the study-specific project code (Study AAA-III-01) in the first line.

For each analysis, the analysis variable will be reported. If important details are necessary to understand the output, these should be given as well.
The total number of patients within each report reflects the number of patients within the collective the analysis is based on, so if missing values occur, their frequency is also presented.

The number of decimals presented refers to the original values. Minimum and maximum have as many decimals as the original values, the mean and the median and all other percentiles have one additional decimal, and the standard deviation has two additional decimals.
Percentage values will be printed with one decimal.
No p-values are expected.

The Output will be presented using Times New Roman as the standard type of font and text size 10. The page setup is landscape and the paper size is A4 with a margin of 2.5 cm all around.

4 Software documentation

Data analyses are performed using the following specific softwares:

Dosimetry study
For the radiation pharmacokinetic profile: SAAM II® software (Cobelli C et al, 1998).
For the radiation dosimetry calculation: OLINDA/EXM® software (Stabin MG et al, 2005).

Pharmacokinetic study
Perkin Elmer TotalChrom Workstation-v6®.

5 Coding systems utilized

No internationally recognized coding systems are applicable to either the dosimetry or the pharmacokinetic analysis.

6 References

Cobelli C, Foster DM. Compartmental models: theory and practice using the SAAM II software system. Adv Exp Med Biol 1998; 445:79-101.

Cremonesi M, Ferrari M, Bodei L, Tosi G, Paganelli G. Dosimetry in peptide radionuclide receptor therapy: a review. J Nucl Med 2006; 47:1467-75.

Ferrer L, Kraeber-Bodéré F, Bodet-Milin C, et al. Three methods assessing red marrow dosimetry in lymphoma patients treated with radioimmunotherapy. Cancer 2010; 116:1093-100.

Forrer F, Krenning EP, Kooij PP, et al. Bone marrow dosimetry in peptide receptor radionuclide therapy with [177Lu-DOTA(0),Tyr(3)]octreotate. Eur J Nucl Med Mol Imaging 2009; 36:1138-46.

NETTER-1 Dosimetry Results Template.

NETTER-1 Substudy Manual (Version 4.1 dated June 16, 2014).

Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med. 2005; 46:1023-7.

7 Signature Page

I have carefully read this statistical analysis plan and agree with the described methods and processing.

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8 Appendices

8.1 Dosimetry outcomes data

		1 cycle x 7.4 GBq	n cycles x 7.4 GBq
Absorbed dose to	**absorbed doses per unit activity**	**absorbed doses in the cycle**	**cumulative absorbed doses in n cycles (*)**
TARGET ORGANS	**(Gy/GBq)**	**(Gy)**	**(Gy)**
Kidneys	**0.00**	**0.00**	**0.00**
Liver	**0.00**	**0.00**	**0.00**
Red Marrow	**0.00**	**0.00**	**0.00**
Spleen	**0.00**	**0.00**	**0.00**
testes	**0.00**	**0.00**	**0.00**
Bladder Wall	**0.00**	**0.00**	**0.00**
Total Body	**0.00**	**0.00**	**0.00**
Other organs	**0.00**	**0.00**	**0.00**
TUMORS			
Lesion 1	**0.00**	**0.00**	**0.00**
Lesion 2	**0.00**	**0.00**	**0.00**
Lesion 3	**0.00**	**0.00**	**0.00**
Lesion 4	**0.00**	**0.00**	**0.00**
Lesion 5	**0.00**	**0.00**	**0.00**
Lesion 6	**0.00**	**0.00**	**0.00**
Lesion 7	**0.00**	**0.00**	**0.00**
Lesion 8	**0.00**	**0.00**	**0.00**
Lesion 9	**0.00**	**0.00**	**0.00**
Lesion 10	**0.00**	**0.00**	**0.00**

(*) cumulative dose = absorbed doses in the cycle multiplied by the number of Lutathera cycles performed

	Number of decays per unit activity (ND) (h)
Red Marrow	**0.00**
Kidneys	**0.00**
Liver	**0.00**
Spleen	**0.00**
Testes	**0.00**
Remainder Body	**0.00**
Bladder Wall	**0.00**
Total Body	
Lesion 1	**0.00**
Lesion 2	**0.00**
Lesion 3	**0.00**
Lesion 4	**0.00**
Lesion 5	**0.00**
Lesion 6	**0.00**
Lesion 7	**0.00**
Lesion 8	**0.00**
Lesion 9	**0.00**
Lesion 10	**0.00**

	decay constants			T½ eff		
	a1 (h-1)	a2 (h-1)	a3 (h-1)	λ1	λ 2	λ 3
blood	0	0.0	0.00	Ln2/a1	Ln2/a2	Ln2/a3
red marrow						
kidney - left	0	0.0		Ln2/a1	Ln2/a2	
kidney - right	0	0.0		Ln2/a1	Ln2/a2	
kidneys	0	0.0		Ln2/a1	Ln2/a2	
liver	0	0.0		Ln2/a1	Ln2/a2	
spleen	0	0.0		Ln2/a1	Ln2/a2	
testes	0	0.0		Ln2/a1	Ln2/a2	
Remainder Body	0	0.0		Ln2/a1	Ln2/a2	
bladder (cumul.)	0	0.0		Ln2/a1	Ln2/a2	
OLINDA input:	0.000					
Lesion 1	0.0	0.00		Ln2/a1	Ln2/a2	
Lesion 2	0.0	0.00		Ln2/a1	Ln2/a2	
Lesion 3	0.0	0.00		Ln2/a1	Ln2/a2	
Lesion 4						
Lesion 5						
Lesion 6						
Lesion 7						
Lesion 8						
Lesion 9						
Lesion 10						

Cumulative Kidney Biologically Effective Dose (BED)

	Lu dose	**$T_{1/2\ eff}$**	**Lu-177**	**dose**	**BED pz sp**	**BED std**
	GBq	h	Gy/GBq	Gy	Gy	Gy
cy 1	0.0	00.0	**0.00**	**0.0**	**0.0**	0
cy 2	0.0	00.0	**0.00**	**0.0**	**0.0**	0
cy 3	0.0	00.0	**0.00**	**0.0**	**0.0**	0
cy 4	0.0	00.0	**0.00**	**0.0**	**0.0**	0
tot	**00.0**			**0**	**0**	**0**

Appendix V: ECG data analysis

A multicenter, stratified, open, randomized, comparator-controlled, parallel-group, Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours.

(Protocol: AAA-III-01)

Analysis of ECGs from Continuous Recordings
Cardiac Substudy Statistical Analysis Plan (CS SAP)

Version: Final 1.0

Author: Meijian Zhou, PhD

Date: January 14, 2015

Review Page for Cardiac Substudy Statistical Analysis Plan (CS SAP)

Approval of CS SAP– Final Version

Distribution list of reviewers for this document prior to final sign-off.

Functional Zone Name	Reviewer's Name	Signature/Date
iCardiac-Cardiovascular Safety	Borje Darpo, MD, PhD	Jan 15, 2015
iCardiac Statistics	Meijian Zhou, PhD	15 Jan 2015
iCardiac Operations Protocol Lead	Brian Smith	15 Jan 2015

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

AIC	Akaike information criterion
bpm	Beats per minute
CI	Confidence Interval
C_{max}	Maximum plasma concentration
Δ	Change-from-baseline
ECG	Electrocardiographic
FDA	Food and Drug Administration
HR	Heart rate
ms	Millisecond
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PR	Time from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex (onset of ventricular depolarization)
QRS	Duration of the QRS complex in the ECG
QT	ECG interval between Q and T waves
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAD	Single ascending dose
SAP	Statistical analysis plan
SD	Standard Deviation
SE	Standard Error

2 AMENDMENTS FROM PREVIOUS VERSION(S)

None

3 INTRODUCTION

This cardiac substudy statistical analysis plan (CS SAP) will be used to evaluate the cardiac substudy data of the study protocol AAA-III-01, A multicenter, stratified, open, randomized, comparator-controlled, parallel-group, Phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours (the NETTER-1 Study). It was developed after review of the protocol AAA-III-01 (Protocol version 4.0, dated March 25, 2014, and Protocol version 4.1, dated June 5, 2014), and finalized prior to database lock/data analysis. This document defines the populations to be analyzed and provides full details of the statistical analyses, data displays, and algorithms to be used for data derivations to aid in the production of the statistical output and the statistical section of the Clinical Study Report in regard to ECG and QTc Analysis. Relevant subject characteristics as well as the electrocardiographic parameters that will be evaluated are described along with the specific statistical methods.

4 STUDY DESIGN

This is a multicenter, stratified, open, randomized, comparator-controlled, parallel-group, Phase III study. In this study, treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) will be compared to treatment with high dose (60 mg) Octreotide LAR in patients with metastatized or locally advanced, inoperable, somatostatin receptor positive, histologically proven midgut carcinoid tumours; these patients should be progressive under Octreotide LAR. Objective tumour response in both arms is assessed every 12±1 weeks from the randomization date according to RECIST Criteria.

Patients will be evaluated for safety and tolerability in accordance with the Visit Schedules for the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm and the Octreotide LAR arm.

A 20-patient Dosimetry, Pharmacokinetics, and ECG study has been performed in about 10 selected sites. This substudy of the Phase III clinical trial NETTER-1 is conducted in patients who have been determined to be eligible for the main study and have signed the specific informed consent, and who have been randomized to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment arm as per Protocol Amendment 4.0, or who have not been randomized but directly assigned to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm, specifically for the purpose of this substudy, as per Protocol Amendment 4.1.

Regarding the cardiac portion of the substudy, a 24-hour continuous ECG recording via 12-lead Holter machine is performed on the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Data recording starts two hours prior to the start of the amino acid infusion, continue during the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and after completion of the treatment procedure for a total of 24 hours.

5 ECG OBJECTIVES AND ENDPOINTS

5.1 Objectives

This plan addresses the secondary objective of the substudy to evaluate cardiac safety: determine the acute electrophysiological changes during treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (through 24-hour continuous ECG recording via 12-lead Holter monitoring). Accordingly, this objective is further divided into the following sub-objectives:

Primary:

- To evaluate the effect of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on cardiac repolarization as measured by the QTcF interval in the enrolled patients.

Secondary:

- To evaluate the effect of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on other ECG parameters.

5.2 ECG Endpoints

Primary:

- The primary endpoint is change-from-baseline QTcF.

Secondary:

- Change-from-baseline heart rate, PR, QRS, QT, QTcB, and RR;
- Categorical outliers defined as QTcF > 450, > 480, and > 500 ms at any time point and change-from-baseline QTcF > 30 and > 60 ms;
- Categorical analyses for change-from-baseline HR > 25% decrease and HR < 50 bpm, change-from-baseline HR > 25% and HR > 100 bpm, change-from-baseline PR > 25% increase and PR > 200 ms, and change-from-baseline QRS > 25% increase and QRS > 120 ms;
- Frequency of T-wave morphology changes and U-wave presence;
- Relationship between ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plasma concentration and ΔQTcF.

6 STATISTICAL METHODS

6.1 General Methodology

All statistical analysis of the study will be performed using the statistical software SAS for Windows Version 9.3 (SAS Institute, Inc., Cary, NC). Data collected from all patients enrolled in the substudy will be presented in data listings. Both absolute values and change from baseline for each subject will be given where applicable. All continuous data

will be listed with the same precision as will be presented in the database. Data listings will be sorted by subject ID, and time point. Missing values will be represented by an empty cell and no imputation will be made.

Continuous data will be summarized in tables using missing data count, mean, median, range, standard deviation (SD), standard error (SE), and 90% 2-sided confidence interval (CI; based on a t-distribution if not otherwise stated) by time points. All continuous data will be rounded to the nearest tenth. Categorical data (including the missing data category) will be summarized by timepoint using counts and percentages. Percentages will be rounded up or down to next integer percentage. Population counts for the substudy will be used as the denominator in the calculation of percentages unless otherwise specified.

If QTc prolongation is observed which is deemed to be related to plasma levels of the drug (or its metabolites), other contributing factors will be explored. Such factors will include: hypokalemia, hypomagnesemia, presence of heart disease and concomitant medication with drugs known to interfere with ECG parameters.

6.2 Analysis Sets

Safety Set: consists of all patients enrolled in the substudy, who received at least one dose of study drug.

QTc Analysis Set: contains all patients in the safety set who had measurements at baseline as well as on-treatment data with at least1 postdose time point with a QTcF value.

Pharmacokinetic (PK) Analysis Set: consists of all patients enrolled in the substudy, who received the study drug and have at least one valid PK concentration measurement for study drug.

PK/QTc Analysis Set: contain all patients in both the QTc analysis and the PK analysis sets with at least one pair of postdose PK and QTc data from the same timepoint.

6.3 Baseline

The predose timepoint will be used as the baseline for postdose timepoints for all ECG variables.

6.4 ECG parameters

6.4.1 QT Correction Formulae

The QT and preceding RR value for each beat will be used for heart rate correction.

Replicate ECGs (up to 10) will be extracted from the continuous digital 12-lead ECG recording at predose, middle of infusion, end of infusion, then after the end of infusion: 20 min, 40 min, 1 h, 2 h, 4 h, 8 h, and 24h. The median value from each extracted

replicate will be calculated, and then the mean of all available medians from a nominal time point will be used as the patient reportable value at that time point.

QTcF:

QT corrected according to Fridericia's formula is defined as $QTcF = QT/RR^{1/3}$.

QTcB:

QT corrected according to Bazett's formula is defined as $QTcB = QT/RR^{1/2}$.

6.4.2 Central Tendency Analysis

The primary analysis will be based on a linear mixed effect model with the change from baseline QTcF as the dependent variable, time (categorical) as factor, and baseline QTcF as covariate. Subject will be included in the model as random effect for the intercept. An unstructured covariance matrix will be specified for the repeated measures at post-dose timepoints within subject. If the model with unstructured covariance matrix fails to converge, other covariance matrix such as compound symmetry can be considered. The least-squares (LS) means and their two-sided 90 % CIs will be calculated from the model and graphically displayed.

For heart rate, PR, QRS, QT, QTcB, and RR interval similar figures will be presented based on descriptive statistics. All parameters mentioned above will further be summarized in tables using mean, SE, and 90% CI by timepoint.

6.4.3 Categorical Analysis

The analysis results for categorical outliers, T-wave morphology and U-wave presence will be summarized in frequency tables with counts and percentages for both number of subjects and number of timepoints. A subject or timepoint will be determined as an outlier subject/timepoint if the following criteria (which are assessed separately) are met for the ECG intervals:

- QTcF

Treatment value of > 500 ms when not present at baseline (new onset)
Treatment value of > 480 and ≤ 500 ms when not present at baseline (new onset)
Treatment value of > 450 and ≤ 480 ms when not present at baseline (new onset)
Change in QTc from baseline of > 30 and ≤ 60 ms
Change in QTc from baseline > 60 ms

- PR

Change of PR from baseline of more than 25% increase leading to PR > 200 ms

- QRS

Change of QRS from baseline of more than 25% increase leading to QRS > 120 ms

- HR

HR changes reflecting a more than 25% decrease from baseline to a HR < 50 bpm
HR changes reflecting a more than 25% increase from baseline to a HR > 100 bpm

For T-wave morphology and U-wave presence, the analysis will be focused on change from baseline, i.e. treatment-emergent changes.

All outliers will be summarized on the basis of incidence rates. If a subject experiences more than one episode of a particular outlier event, the subject will be counted only once for that event.

6.4.4 Concentration-QTc Analysis

The relationship between plasma concentration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and primary endpoint ΔQTcF will be quantified using a linear mixed effects modeling approach. The following 3 linear models will be considered:

1. Model 1 will be a linear model with an intercept
2. Model 2 will be a linear model with mean intercept fixed to 0 (with variability)
3. Model 3 will be a linear model with no intercept.

Time matched concentration will be included in the model as covariate and subject as a random effect for both intercept and slope, when applicable.

The model that best fits the data best will be used for predicting population average Δ QTcF and its corresponding upper 95% one-sided CI bound at the geometric mean maximum plasma concentrations or other concentrations of interest.

In addition to the above analysis, alternate dependent variables such as QTcF to derive the ΔQTcF endpoint may be considered.

The plot of the observed median-decile ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentrations and associated mean ΔQTcF (90% CI) together with the mean (90% CI) predicted ΔQTcF is used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Additional exploratory analyses (via graphical displays and/or model fitting) may include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

6.5 Sample Size

Assuming a 1-sided 0.05 significance level and a standard deviation of 20 ms for ΔQTcF, a total of 20 evaluable subjects who complete the substudy will be sufficient to achieve 80% power to exclude a prolongation of 20 ms or longer of the upper 1-sided 95% CI of the mean ΔQTcF for up to 9 post-dose timepoints, assuming that the prolongation is 3 ms for all post-dose timepoints.

7 TABLES, LISTINGS, AND FIGURES

7.1 Tables

Tables will be presented in section 14.3 of the report. The numbering therefore starts with 14.3.

7.1.1 ECG parameters

Number	Title	Comments
14.3-1.1	Baseline values with descriptive statistics	Number of subjects, mean, SD, SE, min, max, median and 90% CI for each ECG parameters will be given.
14.3-1.2	Absolute values across time points for QTcF	Based on descriptive statistics
14.3-1.3	Change-from-baseline across time points for QTcF	Mean, SE and 90% CI from the linear mixed effects model will be given.
14.3-1.4	Absolute values across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-1.5	Change-from-baseline across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-1.6	QTcF outliers per absolute category (> 450 ms; > 480 ms and > 500 ms)	
14.3-1.7	QTcF outliers per change-from-baseline category (> 30 ms; > 60 ms)	
14.3-1.8	Categorical analyses for heart rate, PR, and QRS	
14.3-1.9	T-wave morphology and U-wave presence: treatment emergent changes	
14.3-1.10	Exposure-response analysis of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate associated ΔQTcF	Fixed effect estimates and corresponding p-values will be given.
14.3-1.11	Predicted ΔQTcF interval at geometric mean peak ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentration	

7.2 Figures

7.2.1 ECG parameters

Number	Title	Comments
14.3-2.2	Absolute values across time points for QTcF	Based on descriptive statistics
14.3-2.3	Change-from-baseline across time points for QTcF	Based on linear mixed effects model
14.3-2.4	Absolute values across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-2.5	Change-from-baseline across time points for heart rate, PR, QRS, QT, QTcB and RR	Based on descriptive statistics
14.3-2.9	The relationship between ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentrations and ΔQTcF with 90% confidence interval.	Scatter plot of ΔQTc vs. concentration and regression line with CI.

7.3 Listings

7.3.1 ECG parameters

Number	Title	Comments
14.3-3.1	QT parameters – absolute values and change-from-baseline	Including QTcF, QTcB and QT
14.3-3.2	Other ECG parameters – absolute values and change-from-baseline	Including heart rate, PR, QRS and RR
14.3-3.3	T-wave morphology and U-wave presence listings	
14.3-3.4	ΔQTcF and time-matched plasma concentration for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for each subject	Data for concentration-QTc analysis