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RESEARCH**

APPLICATION NUMBER:

209637Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA 209637

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Submission Date: 5th December, 2016

Submission Type; Code: NDA 505(b)(1); Standard

Brand Name: Ozempic

Generic Name: Semaglutide

Dosage Form and Strength: 1.34 mg/mL of semaglutide in a pre-filled disposable pen injector that delivers 0.25 mg, 0.5 mg, or 1 mg per injection

1.34 mg/mL of semaglutide in a pre-filled disposable pen injector that delivers 1 mg per injection

Route of Administration: Subcutaneous

Proposed Indication: As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus

Applicant: Novo Nordisk Inc.

Associated IND: IND 079754

OCP Review Team: Shalini Wickramaratne Senarath Yapa, Ph.D., Justin Earp, Ph.D., Lian Ma Ph.D., Manoj Khurana, Ph.D.

OCP Final Signatory: Chandrahas G Sahajwalla, Ph.D.

1. Executive Summary

This addendum will serve to provide the clinical pharmacology conclusions regarding the proposed dosing regimen considering the advisory committee's feedback on the observed retinopathies in the cardiovascular outcomes trial.

The clinical pharmacology review was placed in DARRTs on 8/22/2017 by Dr. Shalini Wickramaratne Senarath Yapa. In this review two quantitative analyses supported the hypothesis that rapid changes to glucodynamics in conjunction with semaglutide administration in patients with diabetes led to an increased risk of retinopathy:

- 1) The reviewer's multivariate time-to-event analysis of the adverse events dataset for the cardiovascular outcomes trial 3744 suggested that retinopathies increased with increasing dose as well as with increasing baseline HbA1c and decreased with baseline body-mass index.
- 2) The results of the applicant's analysis that evaluated whether EAC-confirmed diabetic retinopathies could be attributed to the initial rapid decline in blood glucose. The applicant concluded that:

“The effect of the change in HbA1c at week 16 was found to be statistically significant with a HR of 1.26 for a 1%-point reduction in HbA1c at week 16. This supports the theory that a rapid decline in blood glucose contributed to the mechanisms underlying the development of diabetic retinopathy complications in those with a prior history of diabetic retinopathy.”

(Source: Applicant's Summary of Clinical Safety, page 160-163)

Regarding the first point, the review team decided to use results from a separate analysis because the “retinopathy NEC” events (used in the Clin Pharm review) were not adjudicated for retinopathy specifically and included a larger grouping of events related to the eye. The results of a similar multivariate time-to-event analysis on the adjudicated retinopathies are presented in the statistical review by Dr. Ya-Hui Hsueh on 8/29/2017. The adjudicated events had an equal number of events in each semaglutide arm (n=25 per arm) reducing the overall evidence of dose response. However, the fact remains that the rate of adjudicated retinopathies in the semaglutide arm (50/1648) was 76% higher than that for the placebo arm (29/1649).

Regarding the second point, the applicant's analysis demonstrates an appearance of increased risk of retinopathy for patients that have a rapid initial decline in baseline HbA1c. Their analysis also indicated that prior retinopathy history was an important factor for increased risk of retinopathy. This was briefly discussed by the advisory committee, and dismissed as “exploratory”. It appeared that the consensus regarding these events is that they are attributed to the disease.

Additional data are required to evaluate the hypothesis that slower changes in glucodynamics can limit the occurrence of retinopathies. In the current diabetes environment where diabetic

retinopathy is a standard complication, with the paucity of data, it is not possible to conclude that this is associated with semaglutide induced changes to glucodynamics. As such, no changes can be recommended to the applicant's dosing regimen.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed submission NDA 209637 for semaglutide and found the applicant's proposed dosing regimen acceptable.

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/s/

JUSTIN C EARP
12/03/2017

LIAN MA
12/03/2017

MANOJ KHURANA
12/04/2017

CHANDRAHAS G SAHAJWALLA
12/04/2017

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Table of Contents

1. Executive Summary	4
1.1 Recommendations	4
1.2 Post-Marketing Requirements and Commitments	6
2. Summary of Clinical Pharmacology Assessment	6
2.1 Pharmacology and Clinical Pharmacokinetics	6
2.2 Dosing and Therapeutic Individualization	13
2.2.1 General dosing	13
2.2.2 Therapeutic individualization	13
2.3 Outstanding Issues	13
2.4 Summary of Labeling Recommendations	13
3. Comprehensive Clinical Pharmacology Review	14
3.1 Overview of the Product and Regulatory Background	14
3.1.1 What pertinent regulatory background or history contributed to the current assessment of the clinical pharmacology of this drug?	14
3.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?	15
3.1.3 What are the proposed mechanism of action and therapeutic indication of semaglutide?	17
3.1.4 What are the proposed dosages and routes of administration?	17
3.2 General Pharmacology and Pharmacokinetic Characteristics	17
3.2.1 Pharmacokinetics	17
3.2.2 Pharmacodynamics	33
3.2.3 Body weight	45
3.2.4 QTc prolongation	48
3.3 Clinical Pharmacology Questions	48
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?	48

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?.....	52
3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?.....	55
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?.....	62
3.3.5 Is the clinical formulation of semaglutide used in the clinical pharmacology program similar to the to-be-marketed formulation?.....	80
4. Labeling Recommendations.....	84
5. Appendices.....	91
5.1 Key Highlights of Clinical Pharmacology Studies Cited in the QBR.....	91
5.2 Summary of Bioanalytical Method Validation	94
5.2.1 Semaglutide.....	94
5.2.2 Concomitantly Administered Drugs in Drug Interaction Studies	107
5.3 Population PK Analysis	109
5.4 Study NN9535-3616: Renal impairment study: Original Analysis	123
5.5 Applicant’s Analysis of Retinopathies with regards to change from baseline HbA1c	126

1. Executive Summary

This is an original NDA submitted by Novo Nordisk Inc. on December 5th, 2016, seeking marketing approval for semaglutide as an adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 diabetes mellitus (T2DM). Semaglutide is proposed to be marketed under the tradename of Ozempic.

Semaglutide is a (b) (4) long-acting analogue of human glucagon-like peptide-1 (GLP-1), with a 94% sequence homology to human GLP-1. Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, a target receptor for native GLP-1. GLP-1 is an endogenous incretin hormone that stimulates insulin secretion and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner.

Following subcutaneous (SC) administration, semaglutide has a relatively long terminal half-life ($t_{1/2}$) which allows for once weekly dosing. The Applicant claimed that the prolonged action profile of semaglutide is due to the following mechanisms: delayed absorption from the subcutis, increase binding to albumin (decrease in renal clearance and protection from metabolic degradation), and an increase in enzymatic stability (against dipeptidyl peptidase 4 (DPP-4) enzymes).

Semaglutide formulation is a clear and colorless 1.34 mg/mL solution for injection available in a pre-filled disposable pen injector.

The clinical pharmacology development program conducted to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of semaglutide included 16 clinical pharmacology studies. Majority of the clinical pharmacology Phase 1 studies were conducted in healthy subjects (including first in human study, bioequivalence studies, metabolism study, QTc study, renal and hepatic impairment studies, drug-drug interaction studies, and studies in Japanese subjects) and the remaining studies were in patients with T2DM (PD studies, and 1 drug-drug interaction study). A Phase 1 PD study was conducted in obese, non-diabetic subjects. The Phase 2 dose-finding study was conducted in patients with T2DM. Pharmacokinetic data from 5 Phase 3a studies was used to perform population PK and exposure-response analyses. The program was supported by results from 9 *in vitro* human biomaterial studies.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of NDA 209637 for semaglutide and found it acceptable to support approval. OCP has the following recommendations and comments:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	<p>HbA1c reduction from Phase 3a studies provides primary evidence of effectiveness for the proposed dosing regimen.</p> <p>The PK and PD (an increase in insulin secretion and a decrease in glucagon secretion in a glucose-dependent manner after treatment with semaglutide) of semaglutide in patients with T2DM provided supportive evidence for effectiveness.</p>
General dosing instructions	<p>Semaglutide is to be administered once weekly, at any time of the day, with or without meals, and injected subcutaneously in the abdomen, in the thigh, or in the upper arm.</p> <p>The starting dose of semaglutide is 0.25 mg once weekly, after 4 weeks the dose should be increased to 0.5 mg once weekly. If further improvement in glycemic control is needed, after 4 weeks, the dose of semaglutide may be increased to 1 mg once weekly. The maximum recommended dose is 1 mg once weekly.</p> <p>The clinical pharmacology review identified a dose-retinopathy relationship for a higher incidence of retinopathies with the 1.0 mg dose compared to the 0.5 mg dose. The incidence of retinopathies is a concern and will be discussed at the upcoming advisory committee meeting for semaglutide in October 2017. The applicant conducted an analysis that suggests that patients with a faster drop in HbA1c were more prone to retinopathy, particularly in patients with prior retinopathy history and longer duration of prior diabetes history. Given the continuing discussion regarding the occurrence of retinopathies with increasing dose the final dosing recommendation will be made in an addendum to this review following the advisory committee meeting in October 2017.</p>
Dosing in patient subgroups	<p>No separate dose/dosing regimen is recommended in any patient subgroups due to intrinsic (age, sex, race, ethnicity, body weight, renal impairment, hepatic impairment) and extrinsic factors. Semaglutide does delay gastric emptying; therefore caution should be exercised when oral medications</p>

	are concomitantly administered with semaglutide.
Labeling	No major labelling issues. Refer to Section 4.
Bridge between the to-be-marketed and clinical trial formulations	<p>The to-be-marketed drug product formulation (1.34 mg/mL) was used in all pivotal Phase 3a studies and in the majority of the clinical pharmacology studies.</p> <p>During the clinical pharmacology development program, despite no changes to the formulation of semaglutide drug product, different concentrations of drug substance (1, 3, 10 mg/mL) and a change to the drug substance manufacturing processes (b) (4) was implemented. Bioequivalence was established (based on the primary pharmacokinetic endpoints) between the 2 drug product formulations (b) (4) drug substance and between drug product strengths of 1 mg/mL, 3 mg/mL, and 10 mg/mL.</p> <p>A faster absorption of semaglutide was observed with the highest drug product strength (10 mg/mL).</p>

1.2 Post-Marketing Requirements and Commitments

None.

2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor. A summary of the PK and PD characteristics of semaglutide is presented below.

Pharmacokinetics of semaglutide

Semaglutide demonstrated dose independent pharmacokinetic characteristics from 0.5 mg and 1.0 mg subcutaneous doses. Some of the key pharmacokinetic parameters of 1.0 mg SC semaglutide at steady-state in patients with T2DM are presented in the Table below.

PK Parameters	Geometric Mean (CV%)
$t_{\max,SS}$ ¹	36 – 59.8 hr (1.5 – 2.5 days)
$t_{1/2,SS}$	149-150 hr (6.2 days)
CL/F _{SS}	0.051 – 0.052 L/hr
V _{SS} /F	11.24 – 13.92 L

¹Median

The estimated terminal $t_{1/2,SS}$ of semaglutide indicates that steady-state will be achieved following 4-5 weeks of once weekly dosing in patients with T2DM.

In healthy subjects, the absolute bioavailability of semaglutide was estimated to be 89% after SC administration of 0.5 mg single dose of semaglutide.

Protein binding of semaglutide

In *in vitro* studies, the fraction unbound (f_u) of semaglutide in human plasma was <1%. Therefore the plasma protein binding of semaglutide in human plasma was >99%, and similar across the species tested (rabbit, monkey, minipig, mouse, rat). In plasma, albumin was the primary protein for binding of semaglutide.

Metabolism and excretion of semaglutide

In an *in vitro* study, following incubation of semaglutide with human neutral endopeptidase 24.11 (NEP), a total of 19 metabolites were structurally characterized. These metabolites are proposed to be products of initial NEP cleavage sites in the peptide backbone of semaglutide (4 metabolites were products from 1 proteolytic cleavage at one of the following sites: Ser¹⁸-Tyr¹⁹, Tyr¹⁹-Leu²⁰, Glu²⁷-Phe²⁸, and Trp³¹-Leu³²) and smaller peptides formed after additional proteolytic degradation.

In an *in vivo* mass balance study, following administration of a single SC dose of 0.5 mg [³H]-semaglutide to healthy subjects, 7, 22, and 7 components were detected in plasma, urine, and feces, respectively, of which components P4 in plasma and U22 in urine was identified as intact semaglutide. In plasma, metabolite P3B was identified as a peptide metabolite formed after proteolytic cleavage in semaglutide between Tyr¹⁹ and Leu²⁰ and products P3C-I, P3C-II, and P3C-III were characterized as semaglutide isomers.

In urine, metabolite U6 and U7 was identified as the free Lys²⁶ amino acid bound to the ADO-linker with di-butyric (C4) and di-hexanoic (C6) acid side chains, respectively, and are most

likely formed after several proteolytic cleavages of the semaglutide peptide backbone and sequential beta-oxidation of the di-fatty acid side chain.

The major excretion route of semaglutide-related materials was via the urinary (53% of administered dose) and fecal (18.6% of administered dose) routes. Approximately 3% of the dose was excreted as intact semaglutide in urine.

Pharmacodynamics of semaglutide in patients with T2DM

Pharmacodynamic effects of 1 mg semaglutide at steady-state on glycodynamics were demonstrated as follows:

An improvement in insulin secretion, during both the first (0-10 min) and second (10-120 min) phase insulin secretion, was observed following treatment with semaglutide when compared to placebo in patients with T2DM.

Following a meal stimulation test, there was a reduction in fasting glucose (22%), in AUC_{0-5 hr} postprandial glucose (20-29%), and in the overall 24 hr glucose profile (22%) in patients with T2DM treated with semaglutide compared to placebo. Likewise, a reduction in fasting (8%), AUC_{0-5 hr} postprandial (14-15%), and overall 24 hr profile (12%) glucagon was observed in patients with T2DM following semaglutide treatment compared to placebo. For insulin, an increase in fasting insulin was observed (30%) in patients treated with semaglutide compared to placebo, however no treatment effect of semaglutide when compared to placebo was evident for AUC_{0-5 hr} postprandial insulin.

For overall 24 hour insulin profile, the primary analysis revealed no treatment difference of semaglutide compared to placebo, however in a sensitivity analysis, which excluded patients who were non-compliant with meals, an 8-15% increase in insulin was observed after semaglutide treatment compared to placebo. Such observations for overall (primary analysis) and postprandial insulin are likely to be attributed to the lower postprandial demand for insulin in patients treated with semaglutide as a result of lower glucose concentrations and an increase in insulin sensitivity. In the Phase 3a studies, semaglutide treatment overall decreased insulin resistance (HOMA-IR indices) from baseline and throughout the trial.

Under hyperglycemic conditions, following a IV injection of arginine, an increase in insulin levels was observed during 0-10 min and 0-30 min periods following treatment with semaglutide compared to placebo (at end-of-treatment). The estimated treatment ratio (semaglutide/placebo) for mean change from baseline to end-of-treatment was 2.82 and 4.42 (significant) for the 0-10 min and 0-30 min time periods, respectively. The results suggest an improvement in maximal insulin secretory capacity in patients with T2DM treated with semaglutide when compared to placebo.

In patients with T2DM, an increase in insulin secretion rate with increasing plasma glucose levels (5-12 mmol/L) in a glucose-dependent manner was observed following treatment with semaglutide compared to placebo. For glucagon, a more pronounced glucose-dependent decrease in glucagon concentration was observed with increasing plasma glucose levels after treatment with semaglutide compared to placebo in patients with T2DM. Thereby, semaglutide improves insulin secretory response (β -cell responsiveness) and lowers glucagon secretion to elevated glucose concentrations in a glucose-dependent manner.

The insulin secretion rate-glucose concentration profile after semaglutide treatment in patients with T2DM was similar to that observed in healthy subjects (no treatment). The glucagon concentration-time profile for patients with T2DM was more similar to that of healthy subjects (no treatment) as compared to patients with T2DM treated with placebo.

Treatment with semaglutide (1 mg SC semaglutide at steady-state) did not compromise the overall counter-regulation of plasma glucose levels during hypoglycemia in patients with T2DM when compared to placebo. Semaglutide treatment compared to placebo did not alter the counter-regulatory responses of increased glucagon and did not impair the reduction in C-peptide levels in patients with T2DM.

Body weight

A body weight reduction of ~4-5 kg was evident in patients with T2DM and in obese, non-diabetic subjects following 12 weeks of treatment with semaglutide. In obese, non-diabetic subjects the reduction in body weight was likely attributed to appetite and energy intake rather than due to energy expenditure.

The PK of semaglutide appears to be correlated with body weight. There was a 0.73- and 1.4-fold increase compared to the population estimate over the 95% confidence interval of body weights in the population. No dose adjustments are recommended based on this covariate, due to the nature of the dosing regimen, starting low and increasing dose based on glycemic response.

QT/QTc

No significant QTc prolongation effect of semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) was detected in the TQT study. The largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean difference between semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

Age, sex, race, ethnicity

Age, sex, race, and ethnicity did not alter the PK of semaglutide sufficiently to warrant a dose adjustment based on any of these factors. The range of effect on the estimate of AUC was 2 –

6% different for these 4 factors. See Appendix 5.3 for technical details of the population PK analysis.

Renal and hepatic impairment

No dose adjustment of semaglutide is proposed for patients with T2DM with renal (mild, moderate, severe, end-stage) and hepatic (mild, moderate, severe) impairment.

In subjects with renal impairment (moderate, severe, end-stage), following adjustment for imbalances in age, sex, and body weight, the overall exposure of semaglutide, $AUC_{0-\infty}$, was 10-16% higher when compared to subjects with normal renal function. For subjects with mild renal impairment, $AUC_{0-\infty}$ was comparable (adjusted for imbalances) to that of subjects with normal renal function. On average, maximum concentrations of semaglutide were 11-20% lower (adjusted for imbalances) in subjects with renal impairment compared to subjects with normal renal function. In subjects with end-stage renal impairment, hemodialysis did not appear to affect the exposure of semaglutide. Results from the population PK analysis of the Phase 3 studies (NN9535-3623, NN9535-3626, NN9535-3624, NN9535-3744 and NN9535-4091) indicate little difference between patients with mild (1.06-fold increase in AUC), moderate (1.05-fold increase in AUC), and severe renal impairment (1.09-fold increase in AUC) and patients with normal renal function

In subjects with hepatic impairment (mild, moderate, severe), the overall exposure of semaglutide ($AUC_{0-\infty}$) was comparable to subjects with normal hepatic function (estimated ratio of mean $AUC_{0-\infty}$ was close to 1). On average, subjects with severe hepatic impairment had a 15% higher maximum concentration of semaglutide compared to subjects with normal hepatic function; however these results are likely to have been driven by an extreme C_{max} value from a single subject. Maximum concentrations of semaglutide were comparable for subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function (estimated ratio of mean C_{max} was close to 1).

Relative bioavailability from different injection sites

The population PK analysis suggested that BA decreased approximately 3% for injection into the thigh compared to the abdominal skin and that BA decreased approximately 8% for injection into the upper arm compared to in the abdominal skin.

Drug-drug interactions

No clinically relevant drug-drug interactions were observed between semaglutide and any of the evaluated co-administered drugs, therefore no dose adjustments are proposed when co-administered with semaglutide.

In vitro studies showed semaglutide to have a very low potential to inhibit or induce cytochrome P450 enzymes, and to inhibit drug transporters (P-gp, BCRP, OCT2, OAT1, OAT3). Semaglutide did partially inhibit OATP1B1 and OATP1B3, however the potential for clinically relevant interactions between semaglutide and OATP1B1/1B3 transporters is considered to be low.

Several drug-drug interactions were evaluated to assess to what extent the delay in gastric emptying by semaglutide would impact the PK profiles of concomitantly administered drugs. Drugs commonly used by patients with T2DM with different solubility and permeability properties and/or narrow therapeutic indices were selected; warfarin (Biopharmaceutics Classification System (BCS) Class I/II, narrow therapeutic index), atorvastatin (Class II), metformin (Class III), digoxin (Class II/IV, narrow therapeutic index).

In addition, the impact on the PK profiles of a low dose combination oral contraceptive, ethinylestradiol (EE) and levonorgestrel (LN), was also assessed. The impact of semaglutide on the exposure (AUC and C_{max}) of concomitantly administered drugs is presented in the Table below.

Geometric mean maximum concentration (C_{max}) of atorvastatin was approximately 38% lower when co-administered under semaglutide steady-state conditions compared to administration alone. The Applicant reports that the observed decrease in C_{max} is unlikely to be of clinical relevance as the efficacy of atorvastatin has been shown to be poorly correlated with peak concentrations.

For both EE and LN, a higher exposure, 11% and 20%, respectively, was observed when co-administered with semaglutide compared to administration alone. The Applicant overall concludes that no clinically relevant changes in the overall exposure of EE and LN was observed. The drug-drug interaction assessment for warfarin also showed no major changes in the overall or maximum anticoagulant effect of warfarin when co-administered with semaglutide.

Semaglutide	Co-administered Drug (Dose)	Time of Administration Relative to Semaglutide	AUC	C _{max}
0.25 mg, 0.5 mg, 1 mg. Each dose administered once weekly for 4 weeks. One or two additional doses of 1 mg administered at steady-state	Atorvastatin (40 mg, SD)	Before semaglutide dosing and at steady-state of 1 mg semaglutide (around t _{max})	↔	↓38%
	Digoxin (0.5 mg, SD)		↔	↓7%
	Metformin (MD, 500 mg twice a day for 3.5 days)		↔	↓10%
	Warfarin (25 mg, SD):			
	S-Warfarin		↔	↓9%
	R-warfarin		↔	↓7%
	Oral contraceptive:			
	Ethinylestradiol (MD, 0.03 mg once daily for 8 days)		↑11%	↔
	Levonorgestrel (MD, 0.15 mg once daily for 8 days)		↑20%	↔

↔ No change; 2-5% change

SD: Single-dose; MD: Multiple-dose

To-be-marketed formulation vs. clinical trial formulations

The proposed to-be-marketed formulation of semaglutide, 1.34 mg/mL (b) (4), was used in all Phase 3a studies and in a majority of Phase 1 studies. Despite no changes in the formulation of semaglutide drug product, different concentrations of drug substance (1, 3, 10 mg/mL) and changes in the drug substance manufacturing processes (b) (4) occurred during the development program.

Bioequivalence (BE) was established between drug product strengths 1 mg/mL, 3 mg/mL, 10 mg/mL based on the primary PK endpoint (AUC_{0-∞}) and between (b) (4) semaglutide based on the primary PK endpoints (AUC_{0-tlast}, C_{max}). For drug product strength, a faster absorption of semaglutide was evident with increase in product strengths. For the key

supportive secondary PK endpoint of C_{max} , only comparison of 1 mg/mL vs. 3 mg/mL product strengths met the pre-defined acceptance criteria.

The drug product strength of 10 mg/mL was used in 3 Phase 1 studies, and the Applicant reports that overall the efficacy and safety of semaglutide in this program is based on the pivotal Phase 3a studies which used the to-be-marketed formulation of semaglutide. No formal BE assessment was conducted with the to-be-marketed formulation (1.34 mg/mL); the Applicant reports that the results generated for product strengths 1 mg/mL and 3 mg/mL is representative of the to-be-marketed formulation of semaglutide.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Semaglutide is proposed to be administered once weekly, at any time of the day, with or without meals, and can be injected subcutaneously in the abdomen, thigh, or upper arm. The proposed dosing regimen for semaglutide is 0.25 mg once weekly via SC administration as a starting dose, after 4 weeks the dose should be increased to 0.5 mg once weekly. If further improvement in glycemic control is required, then after 4 weeks, the dose may be increased to 1 mg once weekly. The maximum recommended dose is 1 mg once weekly. No dose adjustments are recommended based on age, sex, race, ethnicity, body weight, in patients with renal impairment, and in patients with hepatic impairment.

2.2.2 Therapeutic individualization


No therapeutic individualization of semaglutide is recommended.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

Label Section	Recommendations
12.1 Mechanism of Action	 (b) (4)

	(b) (4)
12.2 Pharmacodynamics	(b) (4) <ul style="list-style-type: none"> ▪ Add “The effect of OZEMPIC on cardiac repolarization was tested in a through QTc trial. At a dose 1.5 times the proposed maximum recommended dose, semaglutide does not prolong the QT interval to any clinically relevant extent”.
12.3 Pharmacokinetics	<ul style="list-style-type: none"> ▪ Add “Primary route of elimination for OZEMPIC is via metabolism”.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

3.1.1 What pertinent regulatory background or history contributed to the current assessment of the clinical pharmacology of this drug?

Novo Nordisk Inc. has developed semaglutide, a human glucagon-like peptide-1 (GLP-1) receptor agonist, for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. During the clinical development of semaglutide, 7 key regulatory interactions with Novo Nordisk Inc. occurred:

- End of Phase 2 meeting (June 9th, 2010) to discuss the Phase 3 development program
- Type C meeting (written responses provided on May 18th, 2012) to discuss changes to the Applicant’s CMC, preclinical and planned Phase 3 programs
- Type C meeting (written responses provided on March 25th, 2013) to discuss nonclinical development program
- Type C meeting (written responses provided on August 16th, 2014) to discuss FDA’s advice letter regarding study NN9535-3744 (SUSTAIN 6)
- Type C meeting (written responses provided on June 12th, 2015) to discuss data format and standards for the clinical and nonclinical data to be include in the NDA

- Type C meeting (written responses provided on November 13th, 2015) to discuss the human factor/usability validation test protocol for the PDS290 pen injector
- Type C meeting (written responses provided on April 15th, 2016) to discuss the (b) (4) starting material for the manufacture of semaglutide drug substance for an NDA scheduled for submission in December 2016
- Pre-NDA meeting (written responses provided on 29th July, 2016 and September 1st, 2016) to discuss the submission of the NDA

Novo Nordisk Inc. submitted the NDA for semaglutide under Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations on December 5th, 2016.

3.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Semaglutide is a (b) (4) long-acting analogue of human glucagon-like peptide-1 (GLP-1), with a 94% sequence homology to human GLP-1. Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target receptor for native GLP-1. GLP-1 is an endogenous incretin hormone that stimulates insulin secretion and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner. The incretin based approach for management of T2DM is based on the current understanding that in this patient population there is a decrease response to endogenous incretins.

Following SC administration, semaglutide has a relatively long terminal $t_{1/2}$ of around 1 week which enables once weekly SC dosing. The Applicant claimed that the mechanisms by which semaglutide has a prolonged action profile is by 1) delayed absorption from the subcutis, 2) increase binding to albumin which results in a decrease in renal clearance and protection from metabolic degradation, and 3) an increase in stability against DPP-4 enzymes.

Drug substance: Semaglutide is an Aib⁸, Arg³⁴-GLP-1(7-37) analogue substituted on the ϵ -amino group of the lysine residue in position 26 with an (S)-22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl side chain. The side chain consists of two 8-amino-3,6-dioxaoctanoic acid (ADO) spacers, one γ -glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). The molecular formula of semaglutide is C₁₈₇H₂₉₁N₄₅O₅₉. The structural formula of semaglutide is presented in Figure 1. The theoretical average molecular weight of semaglutide is 4113.58 g/mol. Semaglutide is produced (b) (4) and chemical modifications.

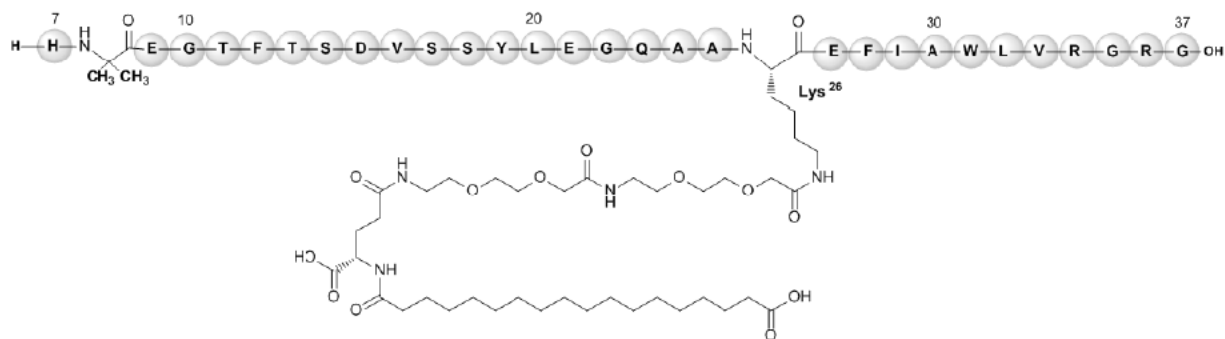


Figure 1: Chemical structure of semaglutide

(Source: Quality Overall Summary, Introduction, page 2)

Drug product: Semaglutide 1.34 mg/mL solution for injection, the drug product intended for market, is a clear and colorless solution. Semaglutide 1.34 mg/mL solution for injection will be marketed as a pre-filled disposable pen injector (1.5 mL cartridge assembled in PDS290 pen-injector for semaglutide 1.34 mg/mL). The composition of semaglutide 1.34 mg/mL solution for injection is outlined in Table 1.

Table 1: Composition of semaglutide 1.34 mg/mL solution for injection

Name of ingredients	Quantity per ml	Function	Reference to standards
Active substance			
Semaglutide	1.34 mg	Active drug substance	Novo Nordisk A/S
Excipients			
Disodium phosphate, dihydrate	1.42 mg	(b) (4)	USP, Ph. Eur.
Propylene glycol	14.0 mg	(b) (4)	USP, JP, Ph. Eur.
Phenol	5.50 mg ^a	(b) (4)	USP, JP, Ph. Eur.
Hydrochloric acid	q.s. ^b	pH adjustment	USP, JP, Ph. Eur.
Sodium hydroxide	q.s. ^b	pH adjustment	USP, JP, Ph. Eur.
Water for injections	(b) (4) ml	(b) (4)	USP, JP, Ph. Eur.
(b) (4)			

^aTo reach pH 7.4

(Source: Quality Overall Summary, Description and Composition of the Drug Product, page 2)

Two variants of the PDS290 pen-injector for semaglutide are as follows:

- PDS290 pen-injector for semaglutide 1.34 mg/mL (0.25 mg/0.5 mg/1 mg), which delivers doses of 0.25 mg, 0.5 mg, or 1 mg
- PDS290 pen-injector for semaglutide 1.34 mg/mL (1 mg), which only delivers doses of 1 mg

3.1.3 What are the proposed mechanism of action and therapeutic indication of semaglutide?

The mechanism of action of semaglutide in reducing blood glucose is via stimulation of insulin secretion and lowering of glucagon secretion, both in a glucose-dependent manner. Another mechanism involved in the reduction of blood glucose is a minor delay in gastric emptying in the early postprandial phase.

The proposed indication for semaglutide is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

3.1.4 What are the proposed dosages and routes of administration?

The proposed dosing regimen is as follows: the starting dose of semaglutide is 0.25 mg once weekly via SC injection and after 4 weeks the dose should be increased to 0.5 mg once weekly. If further improvement in glycemic control is needed, after 4 weeks, the dose of semaglutide may be increased to 1 mg once weekly. The maximum recommended dose is 1 mg once weekly.

Semaglutide is proposed to be administered once weekly, at any time of the day, with or without meals, and can be injected subcutaneously in the abdomen, in the thigh, or in the upper arm. The injection site can be changed without dose adjustments. Patients can change the day of weekly administration as long as the time between 2 doses is at least 2 days (>48 hrs).

3.2 General Pharmacology and Pharmacokinetic Characteristics

3.2.1 Pharmacokinetics

3.2.1.1 Single dose: Healthy subjects

Single dose PK of semaglutide for the (b) (4) semaglutide drug product (1.34 mg/mL) is described below since this is the to-be-marketed drug product (used in the confirmatory Phase 3a studies and in a majority of the clinical pharmacology program). A single dose of 0.5 mg semaglutide was administered via the SC route (lifted skin fold of the thigh) in healthy subjects. Blood samples were collected up to Day 29 following dose administration to characterize the PK of semaglutide (refer to Appendix 5.1 for description of Study NN9535-4010).

The mean plasma concentration-time profile for semaglutide is presented in Figure 2. Following SC administration, semaglutide was slowly absorbed into the systemic circulation and maximum concentrations were achieved between 24 to 122 hrs (~1 to 5 days; median: 95.6 hrs (~4 days)). The geometric mean terminal $t_{1/2}$ for semaglutide was 155.1 hrs (~6.5 days). The overall PK variability for C_{max} , $AUC_{0-t_{last}}$, $AUC_{0-\infty}$ was low (CV%: 19-24%).

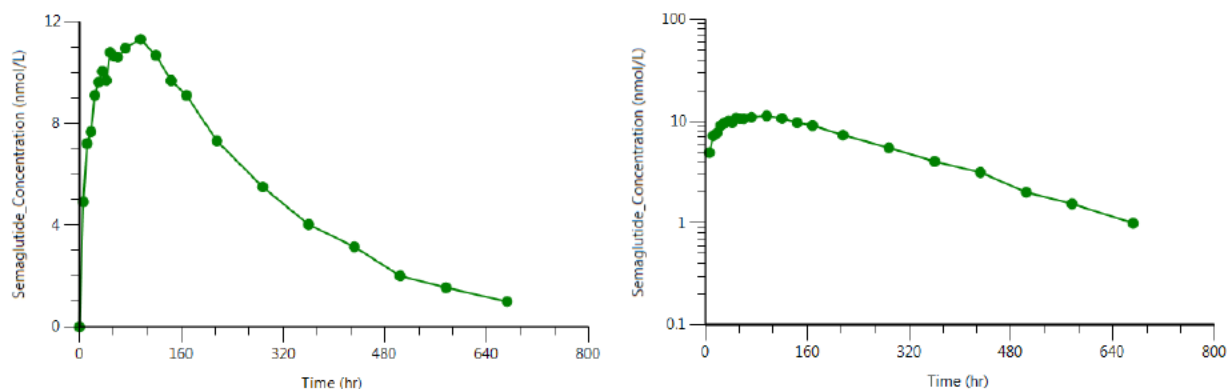


Figure 2: Mean plasma concentration-time profile of semaglutide after single SC dose of 0.5 mg in healthy subjects

(Source: Profile plotted from data from Clinical study report NN9535-4010, page 100-102)

Pharmacokinetics of semaglutide following a single SC dose of 0.5 mg in healthy subjects is presented in Table 2.

Table 2: Pharmacokinetic parameters of semaglutide after single SC dose of 0.5 mg in healthy subjects

PK Parameters	Geometric Mean (CV%) (n=27)
$AUC_{0-\infty}$ (nmol·hr/L)	3670 (24)
AUC_{0-last} (nmol·hr/L)	3424 (24)
C_{max} (nmol/L)	11.5 (18.9)
t_{max} (hr) ¹	95.62 (24, 121.77)
$t_{1/2}$ (hr)	155.1 (10.27)
CL/F (L/hr)	0.033 (23.54)
V_z/F (L)	7.41 (17.75)

¹Median (range)

(Source: Clinical study report NN9535-4010, page 71, 73, and 96)

Of note, the Applicant did conduct a Phase 1 study (NN9535-1820) in healthy subjects following administration of single SC doses of semaglutide ranging from 0.625 to 20 µg/kg. The results from this study are not reported in the Clinical Pharmacology review as the bioanalytical method used to quantify semaglutide plasma concentrations was influenced by matrix effect (Refer to Appendix 5.2).

The absolute bioavailability after SC administration of 0.5 mg semaglutide was estimated to be 89% (estimated treatment ratio (SC/IV) of geometric mean $AUC_{0-\infty}$ was 0.89 [0.83; 0.94]_{95%CI}) (refer to Appendix 5.1 for description of Study NN9535-3687). Similar geometric mean $t_{1/2}$ (143 hr (SC), 137 hr (IV)), clearance (0.035 L/hr (SC), 0.031 L/hr (IV)), and volume of distribution (7.22 L (SC), 6.16 L (IV)) of semaglutide was evident following SC (0.5 mg) and IV (0.25 mg) dosing. Similar terminal $t_{1/2}$ of semaglutide following IV and SC administration suggests the absence of flip-flop kinetics after SC dosing.

3.2.1.2 Multiple-dose: Healthy Subjects and Patients with T2DM

Healthy Subjects

Geometric mean plasma concentration-time profiles of semaglutide at steady-state following administration of the last dose of 0.5 mg and 1 mg semaglutide in healthy Caucasian and Japanese subjects is presented in Figure 3 (refer to Appendix 5.1 for description of Study NN9535-3634). No difference in the PK of semaglutide was observed between the 2 subject populations (Caucasian and Japanese).

In healthy Caucasian and Japanese subjects for both doses, maximum concentrations of semaglutide at steady-state were achieved between 30 to 36 hrs (1.3 to 1.5 days) post-dose. Geometric mean terminal $t_{1/2,SS}$ for semaglutide was 145 to 159 hr (6-6.6 days) and 163 to 167 hrs (6.7-6.9 days) following 0.5 mg and 1 mg semaglutide, respectively. The estimated terminal $t_{1/2,SS}$ of semaglutide indicates that steady-state will be achieved following 4-5 weeks of once weekly dosing in healthy Caucasian and Japanese subjects.

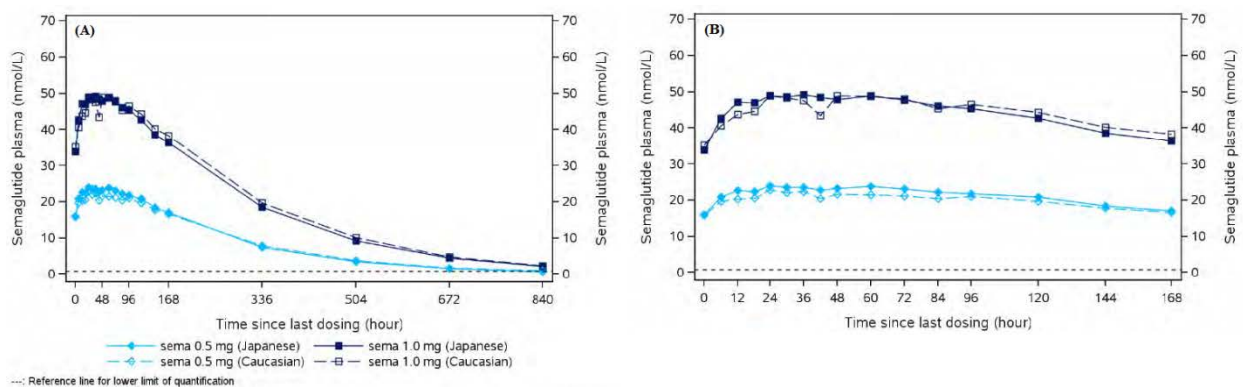


Figure 3: Geometric mean concentration-time plasma profile of semaglutide at steady-state following administration of 0.5 mg and 1 mg semaglutide in healthy Caucasian and Japanese subjects (A) Up to 840 hr after the last dose, (B) Up to 168 hr (dosing interval) after the last dose

(Source: Clinical study report NN9535-3634, page 92 and 95)

Geometric mean trough concentrations of semaglutide (7 days after the 4th dose at each dose level) are presented in Table 3. An increase in C_{trough} with an increase in semaglutide dose was evident in both Caucasian and Japanese subjects.

Table 3: Trough concentrations of semaglutide after administration of 0.25, 0.50, and 1.0 mg for 4 weeks in healthy Caucasian and Japanese subjects

	Semaglutide Dose			
	Caucasian subjects		Japanese subjects	
	0.5 mg (n=7-8)	1.0 mg (n=6-8)	0.5 mg (n=8)	1.0 mg (n=8)
7 days after the 4 th dose of 0.25 mg: Geometric mean (CV%) C _{trough} (nmol/L)	7.95 (8.0)	8.27 (14.9)	7.71 (19.4)	7.96 (15.2)
7 days after the 4 th dose of 0.50 mg: Geometric mean (CV%) C _{trough} (nmol/L)	16.38 (5.2)	16.85 (17)	16.23 (21.5)	17.05 (14.2)
7 days after the 4 th dose of 1.0 mg: Geometric mean (CV%) C _{trough} (nmol/L)	15.78 (5.0) ¹	35.15 (19.7)	15.98 (19.7) ¹	33.89 (14.4)

¹For the 0.5 mg semaglutide dose, C_{trough} is representative of 7 days after the 4th dose of 0.5 mg
(Source: Clinical study report NN9535-3634, page 101)

Pharmacokinetics of semaglutide at steady-state following administration of the last dose of 0.5 mg and 1 mg semaglutide in healthy Caucasian and Japanese subjects are presented in Table 4. At steady-state, a dose-dependent increase in AUC_{0-168hr,SS} (estimated treatment ratio: 2.22 [1.89, 2.60]_{95%CI} and 2.08 [1.80, 2.40]_{95%CI} for Caucasian and Japanese subjects, respectively) and C_{max,SS} (2.13 [1.82, 2.50]_{95%CI} and 2.06 [1.78, 2.38]_{95%CI} for Caucasian and Japanese subjects, respectively) was evident following administration of 0.5 mg and 1 mg semaglutide. The Applicant reports that these results are in accordance with demonstration of dose-proportionality.

Table 4: Pharmacokinetic parameters of semaglutide at steady-state following administration of the last dose of 0.5 mg and 1 mg semaglutide in healthy Caucasian and Japanese subjects

PK Parameters	Geometric mean (CV%)			
	Caucasian subjects 0.5 mg (n=7)	Caucasian subjects 1.0 mg (n=6)	Japanese subjects 0.5 mg (n=8)	Japanese subjects 1.0 mg (n=8)
AUC _{0-168hr,SS} (nmol·hr/L)	3371 (2.4)	7490 (17.9)	3583 (17.8)	7449 (12.2)
C _{max,SS} (nmol/L)	23.7 (7.5)	50.6 (17.5)	25.1 (17.8)	51.6 (11.1)
t _{max,SS} (hr) ¹	36 (24, 72)	30 (24, 72)	30 (12, 72)	36 (18, 96)
t _{1/2,SS} (hr)	159 (9.0)	167 (13.2)	145 (8.0)	163 (10.9)
CL/F _{SS} (L/hr)	0.036 (2.4)	0.032 (17.9)	0.034 (17.8)	0.033 (12.2)
V _Z /F _{SS} (L)	8.25 (11.1)	7.84 (19.6)	7.11 (12.8)	7.69 (14.0)

¹Median (range)

(Source: Clinical study report NN9535-3634, page 93 and 96)

Results from another study (Study NN9535-3652) in healthy subjects, showed that at steady-state, the geometric mean AUC_{0-168hr,SS} of semaglutide was 3081 (20 CV%) nmol·hr/L and 6077 (20 CV%) nmol·hr/L for the 0.5 mg and 1 mg doses, respectively (refer to Appendix 5.1 for description of study). The geometric mean C_{max,SS} of semaglutide was 22.1 (20.7 CV%) nmol/L and 42.7 (20.9 CV%) nmol/L for the 0.5 mg to 1 mg doses, respectively. Overall, the PK variability was low (CV%: 20-20.9 for C_{max,SS} and AUC_{0-168hr,SS}). These results are comparable to the exposure of semaglutide at steady-state (AUC_{0-168hr,SS} and C_{max,SS}) in healthy subjects reported in Study NN9535-3634.

Scatter plots of AUC_{0-168hr,SS}, AUC_{0-48hr,SS}, and C_{max} vs. semaglutide dose are presented in Figure 4. Dose-proportionality assessment showed that AUC_{0-48hr,SS} and C_{max,SS} increased in proportion to an increase in dose (estimated doubling constant for AUC_{0-48hr,SS} of 2.01 [1.99,2.04]_{95%CI}, p=0.3277 and C_{max} of 2.00 [1.97, 2.03]_{95%CI}, p=0.9017). For AUC_{0-168hr,SS}, a statistically significant deviation from dose-proportionality was observed (estimated doubling constant of 2.02 [2.00, 2.04]_{95%CI}, p=0.0474). However, the Applicant reports that since the estimated doubling constant was 2.02 [2.00, 2.04]_{95%CI} that this deviation was not considered to be clinically relevant. A sensitivity analysis, excluding subjects who were non-compliant, were in agreement with the primary analysis (note that no statistically significant deviation from dose-proportionality was observed for AUC_{0-168hr,SS}).

In healthy subjects the increase in semaglutide exposure (AUC and C_{max}) at steady-state with increasing dose was consistent with dose-proportionality.

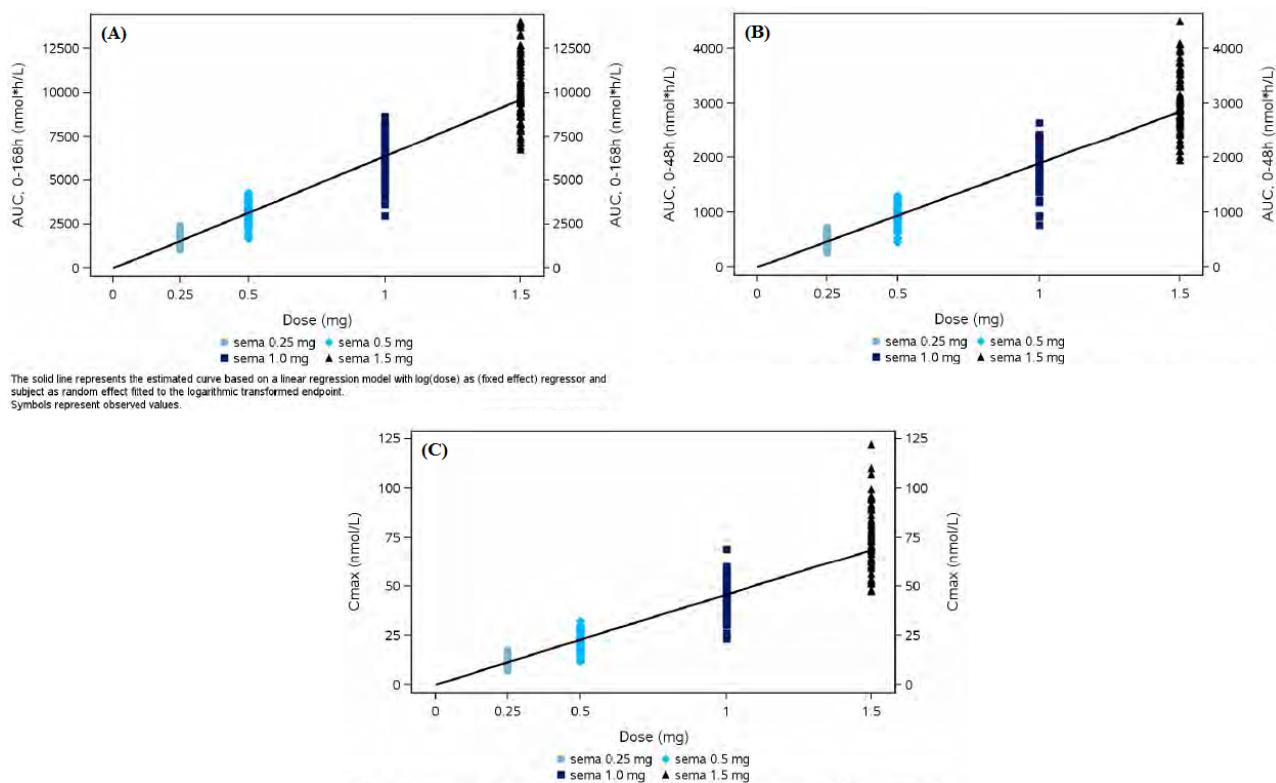


Figure 4: At steady-state, PK parameters, (A) $AUC_{0-168hr,SS}$, (B) $AUC_{0-48hr,SS}$, (C) $C_{max,SS}$ versus semaglutide dose in healthy subjects

(Source: Clinical study report NN9535-3652, page 532-534)

Patients with T2DM

Geometric mean plasma concentration-time profiles of semaglutide at steady-state following administration of the 5th dose at the 1 mg dose level in patients with T2DM is presented in Figure 5 (Study NN9535-3635) and Figure 6 (Study NN9535-3684) (refer to Appendix 5.1 for description of Studies NN9535-3635, -3684). Geometric mean semaglutide concentrations appeared to increase within 0 – 12 hrs post-dose and 0 - 24 hrs post-dose in Studies NN9535-3635 and NN9535-3684, respectively, after which the concentrations reached a plateau followed by a steady decline in concentration.

Maximum concentrations of semaglutide were achieved between 4 to 165 hrs (median: 36 hrs (1.5 days)) and between 18 to 121 hrs (median 59.8 hrs (2.5 days)) post-dose in Studies NN9535-3635 and NN9535-3684, respectively. Geometric mean terminal $t_{1/2,SS}$ for semaglutide was 149 hrs (~6.2 days) and 150 hrs (~6.3 days) in Studies NN9535-3635 and NN9535-3684,

respectively. The estimated terminal $t_{1/2,ss}$ of semaglutide indicates that steady-state will be achieved following 4-5 weeks of once weekly dosing in patients with T2DM.

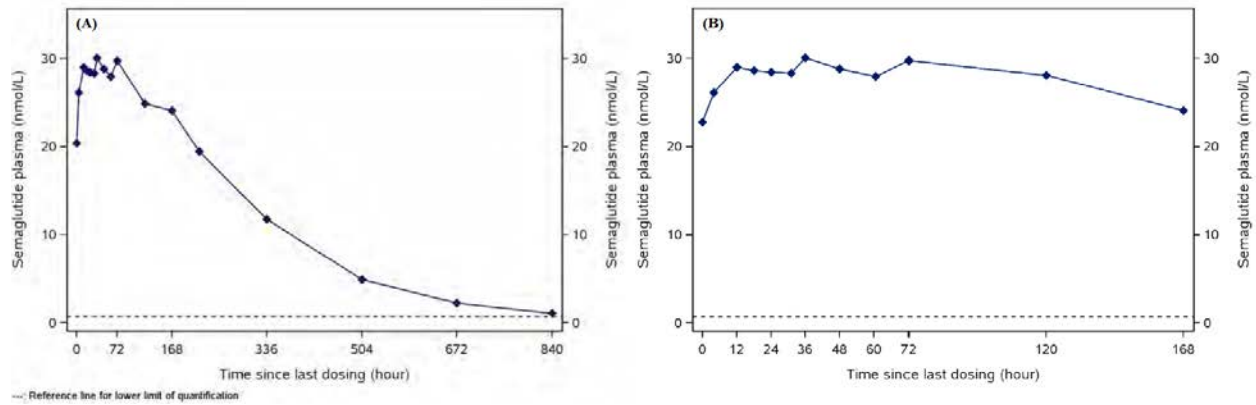


Figure 5: Geometric mean concentration-time plasma profile of semaglutide at steady-state following administration of 1 mg semaglutide dose in patients with T2DM in Study NN9535-3635, (A) Up to 840 hr (35 days) after the 5th dose, (B) Up to 168 hr (dosing interval) after the 5th dose

(Source: Clinical study report NN9535-3635, page 131 and 616)

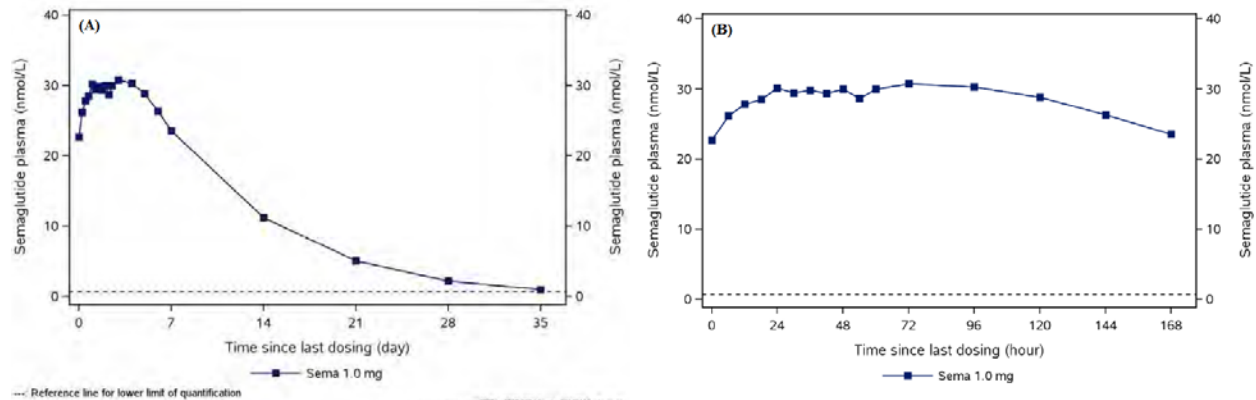


Figure 6: Geometric mean concentration-time plasma profile of semaglutide at steady-state following administration of 1 mg semaglutide dose in patients with T2DM in Study NN9535-3684, (A) Up to 35 days after the 5th dose, (B) Up to 168 hr (dosing interval) after the 5th dose

(Source: Clinical study report NN9535-3684, page 168 and 518)

Geometric mean trough concentrations of semaglutide (after dosing at each dose level) increased in a dose-dependent manner (Table 5).

Table 5: Trough concentrations of semaglutide after administration of 0.25, 0.50, and 1.0 mg for 4 weeks in patients with T2DM in Studies NN9535-3635 and NN9535-3684

	Semaglutide Dose		
	0.25 mg	0.50 mg	1.0 mg
NN9535-3635 (n=36-37): Geometric mean (CV%) C_{trough} (nmol/L)¹	6.12 (27.4)	11.71 (26.4)	22.79 (23.9)
NN9535-3684 (n=37): Geometric mean (CV%) C_{trough} (nmol/L)²	5.71 (36.3)	12.10 (22)	22.77 (21.4)

¹Trough concentrations measured after dosing at each dose level

²Trough concentrations measured 7 days after the 4th dose at each dose level

(Source: Clinical study report NN9535-3635, page 129; Clinical study report NN9535-3684, page 167)

Pharmacokinetics of semaglutide at steady-state following administration of the 5th dose at the 1 mg dose level in patients with T2DM is presented in Table 6.

Table 6: Pharmacokinetic parameters of semaglutide at steady-state following administration of the 5th dose of 1 mg semaglutide in patients with T2DM in Studies NN9535-3635 and NN9535-3684

PK Parameters	Geometric mean (CV%)	
	1.0 mg	
	NN9535-3635 (n=34-36)	NN9535-3684 (n=37)
AUC_{0-168hr,SS} (nmol·hr/L)	4684 (18.8)	4811 (20.2)
C_{max,SS} (nmol/L)	32.2 (19.1)	33.3 (20.8)
t_{max,SS} (hr)¹	36 (4, 165)	59.8 (18.1, 121.3)
t_{1/2,SS} (hr)	149 (10.9)	150 (11)
CL/F_{SS} (L/hr)	0.052 (18.8)	0.051 (20.2)
V_z/F_{SS} or V_{SS}/F(L)²	11.24 (18.6)	13.92 (23.7)

¹Median (range)

²V_z/F_{SS} in Study NN9535-3635 and V_{SS}/F in Study NN9535-3684

(Source: Clinical study report NN9535-3635, page 130; Clinical study report NN9535-3684, page 511)

Dose-proportionality can be inferred from the population PK analysis as linear between the dose of 0.5 mg and 1.0 mg. A linear PK model was implemented as the final model and post hoc estimates of C_{avg} and AUC suggest linear PK between the 0.5 and 1.0mg doses. See below

Summary of model-derived semaglutide steady-state exposures from the population PK analysis of trials 3623, 3624, 3626, 3744 and 4091.

		Maintenance dose	
		0.5 mg	1.0 mg
No of subjects	N (%)	634 (39.3%)	978 (60.7%)
	Geometric mean (95%CI)	15.8 (15.6-16.1)	29.8 (29.4-30.2)
C_{avg} (nmol/L)	Range	[8.3-30.2]	[14.8-61.3]
	Median	15.8	30.0
	95% range	[10.1-24.6]	[18.8-46.9]
	Geometric mean (95%CI)	2660 (2614-2707)	5006 (4934-5079)
AUC (h*nmol/L)	Range	[1388-5080]	[2485-10299]
	Median	2663	5034
	95% range	[1689-4134]	[3166-7875]
	Geometric mean (95%CI)	2660 (2614-2707)	5006 (4934-5079)

(Source: Applicant's Population PK Report, Table 5)

Interpatient variability in CL (population mean of 0.048 L/hr) at steady-state in patients with T2DM was 13% based on the population PK analysis of data from studies NN9535-3623, NN9535-3626, NN9535-3624, NN9535-3744 and NN9535-4091. Although this number should be interpreted with caution as the shrinkage around the estimate of between subject variability for CL is 25% suggesting a slightly larger actual number for between subject variability.

Healthy subjects vs. Patients with T2DM

Steady-state exposure of semaglutide ($AUC_{0-168hr,SS}$ and $C_{max,SS}$) following 1 mg once weekly SC dosing appeared to be lower in patients with T2DM when compared to healthy subjects. The Applicant reports that these observations are likely due to patients with T2DM having a higher body weight when compared healthy subjects. This is supported by population PK analysis which demonstrated that semaglutide exposure was inversely related to body weight (higher body weight resulted in lower exposure) (Refer to Section 3.3.3).

3.2.1.3 Volume of distribution and protein binding properties of semaglutide

Semaglutide is extensively bound to plasma proteins (>99%). In patients with T2DM, the apparent volume of distribution at steady-state (1 mg semaglutide) following SC dosing is in the range of 11.2-13.9 L.

Protein binding properties of semaglutide

Protein binding properties of semaglutide in animals and humans was evaluated in 2 *in vitro* studies using surface plasmon resonance (SPR) biosensor technology (Biacore T100 or T200 instrument). The studies were conducted using different assay conditions. Binding assays were conducted at 37°C using a range of diluted plasma samples from animals and human. Kinetic analysis based on a 1:1 binding model was used to determine percentage fraction unbound (f_u) and dissociation constant (K_D) of semaglutide in plasma.

In the first study, percentage f_u and K_D of semaglutide was determined in CD-1 mouse, wistar hannover and sprague dawley rat, NZ white rabbit, gottingen minipig, cynomolgus monkey, and human plasma. A 1:1 binding model was utilized to evaluate the binding between semaglutide and plasma proteins. Mean percentage f_u of semaglutide in plasma and K_D of semaglutide binding to plasma albumin across species is presented in Table 7. The reported K_D values was estimated on the assumption that albumin was the 1 plasma protein resulting in the 1:1 binding of semaglutide in plasma. In all species the mean percentage f_u in plasma was in the range of 0.1-0.6%, except for in rabbit (f_u of 0.036%). When assuming the 1:1 binding of semaglutide was to plasma albumin, the K_D of semaglutide was in the range of 0.1-3 μ M across species.

Table 7: Percentage f_u in plasma and K_D of semaglutide binding to albumin (ranked with increasing f_u ; decreasing affinity) across species

Species	Sex	Fraction unbound (%)	Albumin K_D (μ M)
		Mean \pm SD	Mean \pm SD
Rabbit (New Zealand White)	F	0.036 \pm 0.011	0.14 \pm 0.05
Monkey (Cynomolgus)	M + F	0.14 \pm 0.06	0.72 \pm 0.30
Human	M + F	0.19 \pm 0.04	1.07 \pm 0.25
Minipig (Göttingen)	F	0.22 \pm 0.19	1.37 \pm 1.19
Mouse (CD-1)	M + F	0.46 \pm 0.22	1.78 \pm 0.88
Rat (Wistar Hannover and Sprague Dawley)	M + F	0.63 \pm 0.19	2.80 \pm 0.87

(Source: Study number 208380, study report, page 24)

In the second study, percentage f_u and K_D of semaglutide and liraglutide was determined in CD-1 mouse, sprague dawley rat, NZ white rabbit, cynomolgus monkey, and human plasma. Mean percentage f_u of semaglutide and liraglutide across species is presented in Table 8. Mean percentage f_u in plasma is <1% in all species for both semaglutide and liraglutide. In human

plasma, the percentage f_u was higher for semaglutide (0.36%) compared to liraglutide (0.10%). Assuming 1:1 binding of semaglutide and liraglutide to plasma albumin, the mean K_D across species was in the range of 0.27 – 2.19 μM and 0.50 – 1.64 μM for semaglutide and liraglutide, respectively.

Table 8: Percentage f_u in plasma for semaglutide and liraglutide across species

	Gender	Fraction unbound (%)	
		Semaglutide Mean \pm CV%	Liraglutide Mean \pm CV%
Mouse (CD-1)	M/F	0.28 \pm 17.4	0.13 \pm 16.0
Rat (Sprague Dawley)	M/F	0.19 \pm 18.8	0.38 \pm 12.2
Rabbit (New Zealand White)	F	0.07 \pm 20.1	0.14 \pm 23.8
Monkey (Cynomolgus)	M/F	0.46 \pm 20.4	0.17 \pm 20.7
Human	M/F	0.36 \pm 14.8	0.10 \pm 13.9

(Source: Study number 213228, study report, page 15)

For binding of semaglutide and liraglutide in human serum albumin (assuming 1:1 binding to albumin), it was shown that semaglutide (K_D 0.59 \pm 0.12 μM) binds to albumin with a stronger affinity than liraglutide (K_D 5.08 \pm 3.06 μM). In fatty acid free albumin, the percentage f_u and K_D was 0.03 \pm 0 % and 0.18 \pm 0.03 μM , respectively, for semaglutide and 0.57 \pm 0.07% and 4.08 \pm 0.47 μM , respectively, for liraglutide. The unbound fraction of semaglutide following binding studies with human serum albumin (0.17 \pm 0.02%) and binding in plasma (0.36 \pm 0.05%), suggests that human albumin is the primary binding sites for semaglutide.

Results from *in vitro* studies suggest that the plasma protein binding of semaglutide is >99% in all species tested and that albumin is the primary protein for binding of semaglutide in plasma. Additionally, the observed mean blood to plasma ratio of [^3H]-semaglutide related material from the *in vivo* mass balance study suggests that [^3H]-semaglutide is primarily distributed in plasma (Refer to Section 3.2.1.4).

Volume of distribution of semaglutide in patients with T2DM and healthy subjects

In patients with T2DM, the apparent volume of distribution at steady-state (1 mg semaglutide) following SC administration was 11.24 L (18.6 CV%) and 13.92 L (23.7 CV%) in Studies NN9535-3635 and NN9535-3684, respectively. This is consistent with the population PK analysis V_d of 12.2 L using data from the Phase 3 trials 3623, 3624, 3626, 3744, and 4091 in patients with T2DM. In healthy subjects, the apparent volume of distribution at steady-state following SC administration was 7.11-8.25 L and 7.69-7.84 L for 0.5 mg and 1 mg semaglutide, respectively. The lower apparent volume of distribution in healthy subjects is likely to be

attributed to the lower body weight in this population compared to patients with T2DM. The volume of distribution following IV administration of single dose of 0.25 mg semaglutide to healthy subjects was 6.16 L (22.1 CV%).

These results suggest that semaglutide primarily circulates in the plasma. This is further supported by findings from the *in vitro* binding studies.

3.2.1.4 Elimination properties (metabolism and excretion) of semaglutide

In humans, semaglutide is metabolized following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The major excretion route of semaglutide-related materials was via the urinary (53% of administered dose) and fecal (18.6% of administered dose) routes. Expired air was found to be a minor excretory route (3.2%). In urine, intact semaglutide was identified, and accounted for 3.1% of the administered dose. In patients with T2DM, the apparent clearance and terminal $t_{1/2}$ at steady-state (1 mg semaglutide) following SC dosing is in the range of 0.051-0.052 L/hr and 149-150 hrs (~ 6 days), respectively.

***In vitro* metabolism studies**

In vitro metabolism of [³H]-Tyr-semaglutide and [³H]-Oct-semaglutide was assessed following incubation in rat, monkey, and human hepatocytes.

Wistar rat, cynomolgus monkey, and human hepatocyte monolayer cells were incubated with 10 nM and 1 μM of [³H]-Tyr-semaglutide for 4 and 24 hrs at 37°C. Results show that semaglutide was metabolically stable in this *in vitro* system since 100% of [³H]-Tyr-semaglutide remained unchanged in all monkey and human hepatocyte incubations and >99% of [³H]-Tyr-semaglutide remained unchanged in all rat hepatocyte incubations.

Sprague Dawley rat, cynomolgus monkey, and human cryopreserved hepatocytes were incubated with 10 nM and 1000 nM of [³H]-Oct-semaglutide for 4 hrs at 37°C. A total of 10 components were detected following incubation at the 1000 nM concentration level. Following incubation with 1000 nM of [³H]-Oct-semaglutide, the amount of parent compound remaining was 83.7%, 96%, and 94.5% in the rat, monkey and human hepatocytes, respectively. Following incubation with [³H]-Oct-semaglutide, 2 metabolites were formed in human hepatocytes similar to that present in rat hepatocytes. No metabolites were observed in monkey hepatocytes.

The Applicant concludes that limited metabolism was observed in rat, monkey, and human hepatocytes and no unique human metabolites were observed.

The Applicant assessed the *in vitro* metabolism of semaglutide by human neutral endopeptidase 24.11 (NEP), a reported target enzyme that metabolizes native GLP-1. Incubations were conducted with NEP (25 μg/mL) and semaglutide (5 μM) in potassium phosphate buffer at 37°C for 24 hrs. At 6 hr, 10 metabolites were characterized and 4 metabolites were products from 1

proteolytic cleavage at one of the following sites: Ser¹⁸-Tyr¹⁹, Tyr¹⁹-Leu²⁰, Glu²⁷-Phe²⁸, and Trp³¹-Leu³². The Applicant proposes that these sites are the initial NEP cleavage sites in the peptide backbone of semaglutide. At 24 hr, 15 metabolites were characterized as smaller peptides formed after additional proteolytic degradation.

Mass balance study (metabolism and excretion)

Study NN9535-3789, a mass balance study, was conducted to determine the metabolism and excretion characteristics of [³H]-semaglutide (Figure 7) following a single SC dose of 0.5 mg [³H]-semaglutide (up to 500 µCi) in healthy male subjects (refer to Appendix 5.1 for description of study).

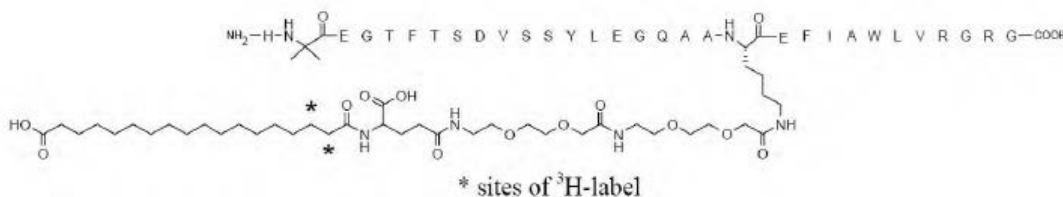


Figure 7: Structure of [³H]-semaglutide

(Source: NN9535-3789, Clinical study report, page 30)

Pharmacokinetics of semaglutide

Geometric mean concentration-time profile of semaglutide in plasma is presented in Figure 8. Maximum concentrations of semaglutide (geometric mean: 10.9 nmol/L) was achieved at 56 hr following dose administration. The estimated geometric mean terminal t_{1/2} for semaglutide is 168.3 hrs (~7 days).

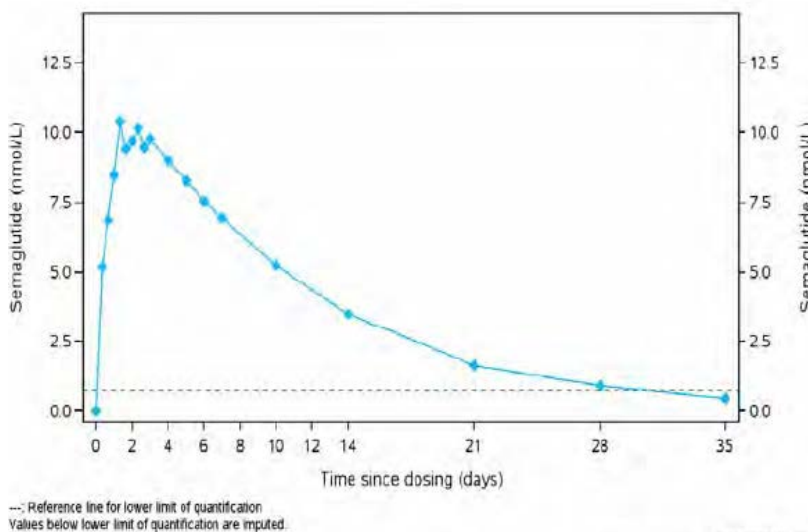


Figure 8: Geometric mean concentration-time profile for semaglutide in plasma

(Source: NN9535-3789, Clinical study report, page 91)

Metabolite profile of semaglutide in plasma, urine and feces

Plasma, urine, and feces samples were collected until the defined end criterion level was achieved (<0.5% of the administered dose was excreted in 2 consecutive samples).

In plasma, 7 components were detected. The primary component (P4) was [³H]-semaglutide which accounted for 82.6% of total radioactivity based on AUC_{last}. Six metabolites (P1-P3 and P5-P7) were detected in plasma, metabolite P3 was the most abundant metabolite accounting for 7.68% of all [³H]-semaglutide related material.

In urine, 22 components were detected. Six of these metabolites each accounted for more than 1% of the administered dose (U6, U7, U9, U10, U12, U22). The two most abundant metabolites (U6, U7) each accounted for ~14% of the administered dose. One component (U22) which accounted for 3.12% of the administered dose was considered likely to be semaglutide since it had the same retention time as semaglutide.

In feces, 7 metabolites were detected. Each metabolite accounted for 0.11-1.49% of the administered dose. Semaglutide was not detected in feces.

Analysis for structural identification of the most abundant metabolites in plasma (P3 and P2 (accounting for 3.90% of all [³H]-semaglutide related material)) and urine (U6, U7) was conducted (Study no: 214379). Structural identification was also conducted with the components proposed to be semaglutide (P4, U22). The proposed metabolic pathways for plasma and urine metabolites following SC dosing of semaglutide in healthy male subjects is presented in Figure 9.

Presence of intact semaglutide was verified in both plasma (P4) and urine (U22). Metabolite P3B was identified as a peptide metabolite formed after proteolytic cleavage in semaglutide between Tyr¹⁹ and Leu²⁰. Products P3C-I, P3C-II, and P3C-III were characterized as semaglutide isomers. Metabolite U6 and U7 was identified as the free Lys²⁶ amino acid bound to the ADO-linker with di-butyric (C4) and di-hexanoic (C6) acid side chains, respectively. These 2 metabolites are most likely formed after several proteolytic cleavages of the semaglutide peptide backbone and sequential beta-oxidation of the di-fatty acid side chain.

For P2, the Applicant reports that none of the molecular ions from the analytical analysis of HPLC fraction P2 was possible to match with structures from hydrolysis and beta-oxidation products or isomer formation.

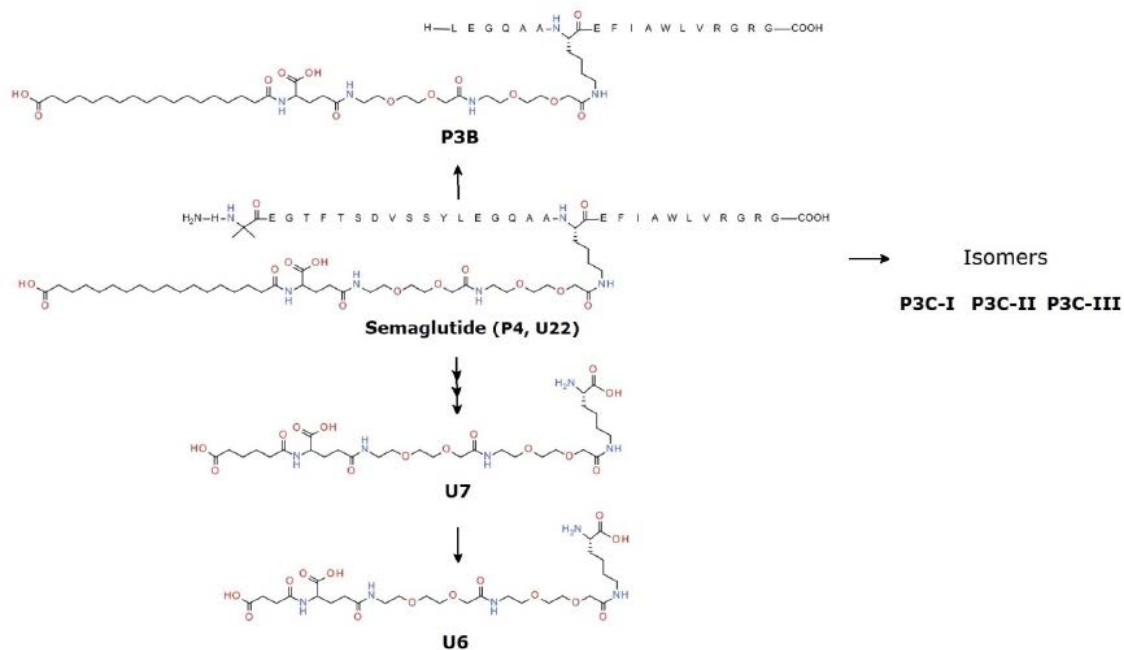


Figure 9: Proposed metabolic pathways for plasma and urine metabolites following SC dosing of semaglutide in healthy male subjects

(Source: Study number 214379, Study report, page 28)

Excretion of radioactivity in urine, feces and expired air

Collected urine and feces samples are referred to as ‘intact samples’ and freeze-dried samples are referred to as ‘dry samples’. Both intact and dry samples were assessed to distinguish between radioactivity corresponding to [³H]-semaglutide related materials and radioactivity related to volatile compounds (mainly tritiated water).

The geometric mean cumulative excretion of [³H]-semaglutide related material in intact and dry urine samples at Day 56 was 52.96% (8.20 CV%) and 39.56% (4.76 CV%), respectively, of the administered dose. The geometric mean cumulative excretion of [³H]-semaglutide related material in intact and dry fecal samples at Day 56 was 18.56% (19.85 CV%) and 16.75% (18.80 CV%), respectively, of the administered dose. The difference between total excretion in intact and dry samples is likely to be attributed to volatile components, most likely tritiated water. The geometric mean cumulative excretion of [³H]-semaglutide related material in expired air samples at Day 56 was 3.16% (8.95 CV%) of the administered dose. The total excretion of [³H]-semaglutide related material in intact urine, intact feces, and expired air was 75.07% (5.19) (geometric mean (CV%)) of the administered dose.

The results indicate that the major excretory routes of [³H]-semaglutide related material is the urinary and fecal route. Expired air was found to be a minor excretory route.

Pharmacokinetics of [³H]-semaglutide related material in plasma

Geometric mean concentration-time profile for [³H]-semaglutide related material in intact and dry plasma is presented in Figure 10. In both intact and dry samples, peak concentrations of [³H]-semaglutide related material (geometric mean: 11.5 and 11.6 nmol equiv/L, respectively) was achieved after 56 hrs post-dose. The estimated geometric mean t_{1/2} for [³H]-semaglutide related material was 201.2 hr and 180.5 hr in intact and dry samples, respectively.

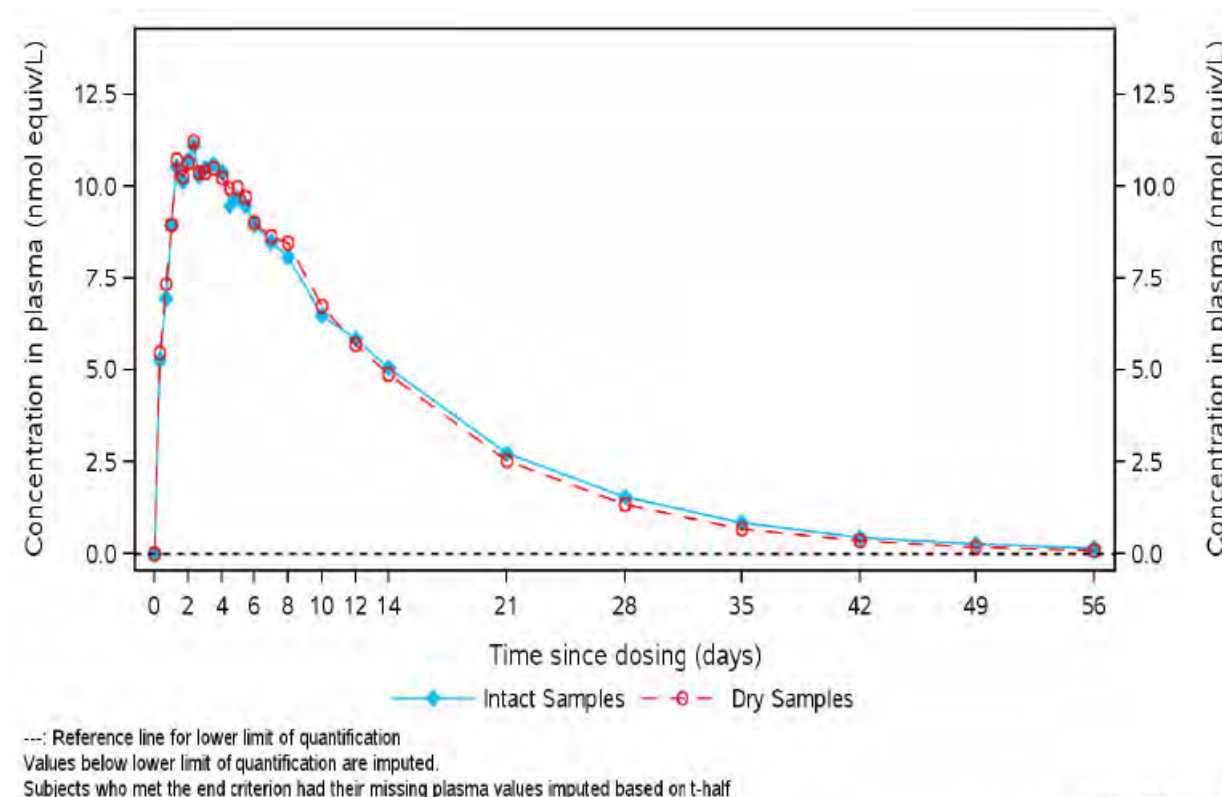


Figure 10: Geometric mean concentration-time profile for [³H]-semaglutide related material in intact and dry plasma

(Source: NN9535-3789, Clinical study report, page 86)

Blood to plasma ratio of [³H]-semaglutide related material

The blood to plasma ratio of [³H]-semaglutide related material was assessed to estimate the binding of [³H]-semaglutide related material to blood cells. The mean blood to plasma ratio of total [³H]-semaglutide related material in intact samples ranged from 0.53 to 0.66 and in dry samples ranged from 0.51-0.57 (relatively constant) throughout the sampling period (Day 35). On the day of dosing, the mean hematocrit was estimated to be 0.45 which indicates that 1 mL of blood contains 0.55 mL plasma. The Applicant reports that since the blood to plasma ratio of

total [³H]-semaglutide related material is close to this ratio of 0.55 and given that the primary component circulating in plasma was intact semaglutide, that the data indicates that [³H]-semaglutide was primarily distributed in plasma.

Elimination of semaglutide in patients with T2DM and healthy subjects

In patients with T2DM, the apparent clearance at steady-state (1 mg semaglutide) following SC administration was 0.052 L/hr (18.8 CV%) (NN9535-3635) and 0.051 L/hr (20.2 CV%) (NN9535-3684). This value is also consistent with the population PK estimate CL of 0.048 L/hr using data from the Phase 3 trials 3623, 3624, 3626, 3744, and 4091 in patients with T2DM. In healthy subjects, the apparent clearance at steady-state following SC administration was 0.034-0.036 L/hr and 0.032-0.033 L/hr for 0.5 mg and 1 mg semaglutide, respectively. A higher apparent clearance of semaglutide was observed in patients with T2DM when compared to healthy subjects.

In patients with T2DM, the terminal $t_{1/2}$ at steady-state (1 mg semaglutide) following SC administration was 149 hr (10.9 CV%) (NN9535-3635) and 150 hr (11 CV%) (NN9535-3684). In healthy subjects, the terminal $t_{1/2}$ at steady-state following SC administration was 145-159 hr and 163-167 hr for 0.5 mg and 1 mg semaglutide, respectively. Despite differences in the apparent clearance, comparable terminal $t_{1/2}$ was observed across the 2 patient/subject populations (range: 6.0 to 6.9 days) following SC dosing of semaglutide.

The elimination and terminal $t_{1/2}$ following administration of a IV (0.25 mg) and SC (0.5 mg) single dose of semaglutide to healthy subjects was 137 hr (12.8 CV%) and 143 hr (10.4 CV%), respectively, suggesting the absence of flip-flop kinetics following SC administration.

3.2.2 Pharmacodynamics

3.2.2.1 β -cell function and postprandial glucose

Study NN9535-3635 assessed the effect of 1 mg SC semaglutide at steady-state on the following PD endpoints:

- First and second phase insulin secretion in patients with T2DM (IV glucose tolerance test (IVGTT))(primary objective),
- Fasting and postprandial glucose, insulin, C-peptide, glucagon in patients with T2DM (meal stimulation test) (secondary objective),
- Maximal insulin secretory capacity in patients with T2DM (arginine stimulation test under hyperglycemic conditions) (secondary objective),
- β -cell insulin secretion (β -cell responsiveness) in patients with T2DM when compared to healthy subjects (graded glucose infusion test) (secondary objective)

Patients with T2DM were randomized (1:1 ratio) to receive either semaglutide treatment or matching placebo for 12 weeks (n=75 randomized, n=37-38/treatment arm). Dose escalation regimen for semaglutide or matching placebo was as follows: 0.25 mg once weekly for 4 weeks followed by 0.5 mg once weekly for 4 weeks. Thereafter, 1 mg semaglutide or matching placebo was administered once weekly for 4 weeks (maintenance period). Pharmacodynamic assessments were conducted at baseline and at the end-of-treatment (EoT, during the week after the 5th dose of semaglutide 1 mg was administered). Healthy subjects (n=12) enrolled in the study received no treatment.

Effect of semaglutide on insulin secretion

Geometric mean concentration-time profile for insulin following administration of an IV bolus injection of glucose (IVGTT) at baseline and EoT in patients with T2DM is presented in Figure 11. The estimated treatment ratio (semaglutide/placebo) for change from baseline to EoT in first phase insulin secretion ($AUC_{0-10min,insulin}$) was 3.02 [2.53; 3.60]_{95%CI} (p<0.0001) and in second phase insulin secretion ($AUC_{10-120min,insulin}$) was 2.10 [1.86; 2.37]_{95%CI} (p<0.0001). The results show an increase in insulin secretion during both the first and second phase insulin secretion after treatment (EoT) with semaglutide when compared to placebo. For semaglutide, the increase in insulin secretion was greater in the first phase compared to the second phase of insulin secretion.

For insulin secretion rate (ISR), the estimated treatment ratio (semaglutide/placebo) for change from baseline to EoT was 2.93 [2.50; 3.43]_{95%CI} (p<0.0001) and 1.75 [1.60; 1.91]_{95%CI} (p<0.0001) for first phase ($AUC_{ISR,0-10min}$) and second phase ($AUC_{ISR,10-120min}$) insulin secretion, respectively.

These results are supported by observations of an increase in the levels of C-peptide (estimated treatment ratio of 1.73 [1.59; 1.88]_{95%CI} and 1.74 [1.61; 1.87]_{95%CI} for $AUC_{0-10min,C-peptide}$ and $AUC_{10-120min,C-peptide}$, respectively) and a decrease in levels of glucagon (estimated treatment ratio of 0.90 [0.85; 0.96]_{95%CI} and 0.90 [0.85; 0.95]_{95%CI} for $AUC_{0-10min,glucagon}$ and $AUC_{10-120min,glucagon}$, respectively) during both the first and second phase in patients treated with semaglutide when compared to placebo. The Applicant concludes that an improvement in insulin secretion is evident in patients with T2DM treated with semaglutide compared to placebo.

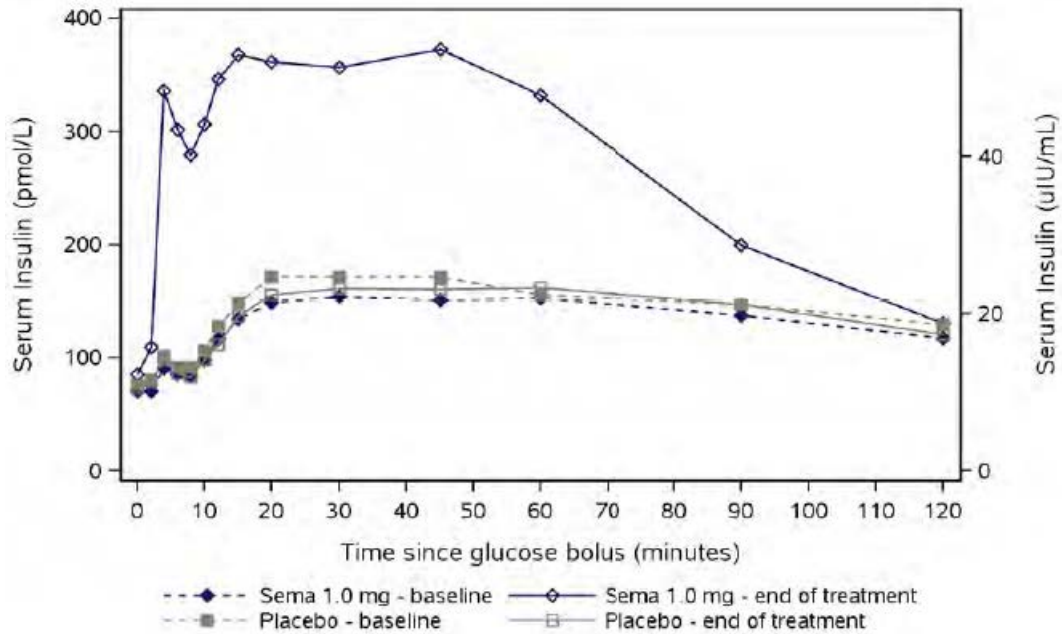


Figure 11: Geometric mean concentration-time profile for insulin following administration of semaglutide and placebo at baseline and end-of-treatment in patients with T2DM (IVGTT)

(Source: Clinical study report NN9535-3635, page 107)

Effect of semaglutide on overall, postprandial, and fasting glycemic parameters

Geometric mean concentration-time profile (24 hr) for glucose, insulin, C-peptide, and glucagon during the meal stimulation test (3 standardized meals (breakfast, lunch dinner)) at baseline and EoT in patients with T2DM is presented in Figure 12. Overall, a decrease in glucose and glucagon was evident after treatment (EoT) with semaglutide when compared to placebo. Subsequent to meal consumption, semaglutide treatment (EoT) induced lower insulin peak concentrations in patients with T2DM.

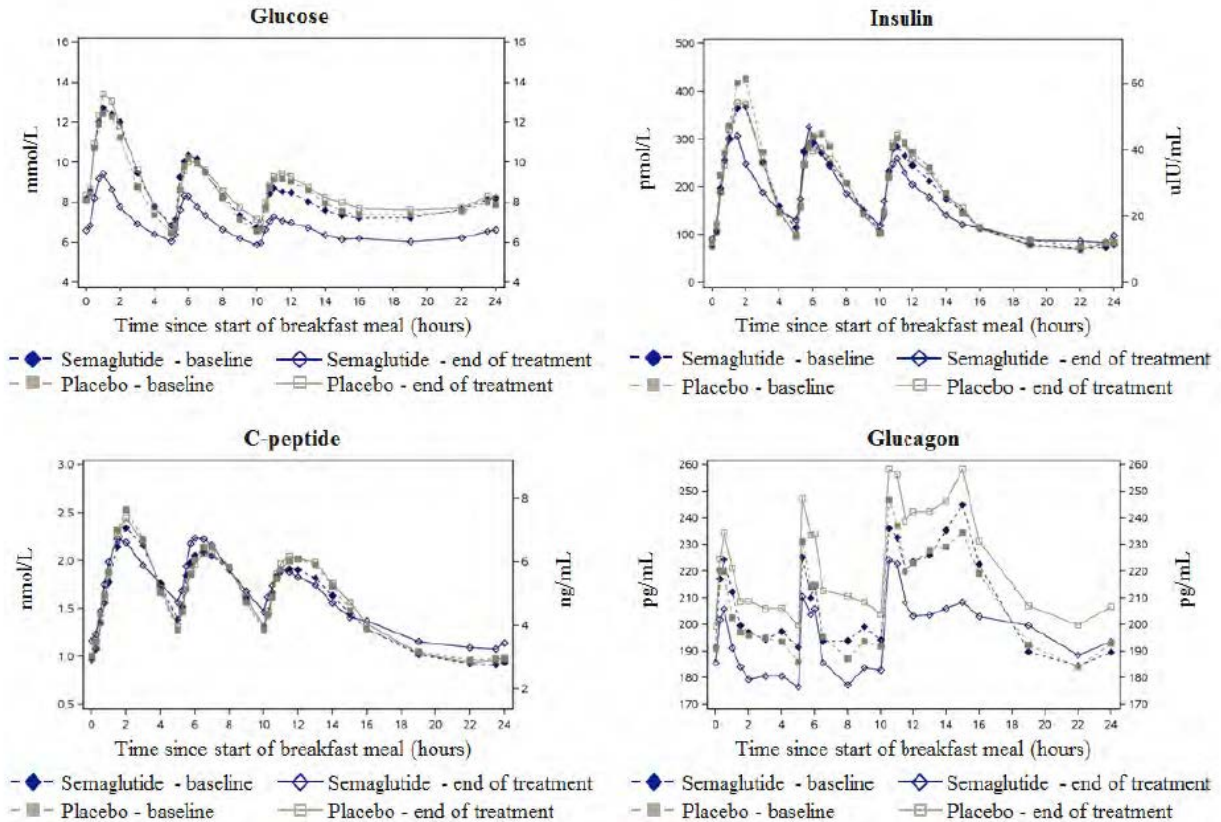


Figure 12: Geometric mean concentration-time profile (24 hr) for glucose, insulin, C-peptide, glucagon following administration of semaglutide and placebo at baseline and end-of-treatment in patients with T2DM (meal stimulation test)

(Source: Clinical study report NN9535-3635, page 113)

A forest plot of estimated treatment ratio (semaglutide/placebo) for change from baseline to EoT in 24 hr glucose, insulin, C-peptide, and glucagon (AUC_{0-24hr} during a meal test day) in patients with T2DM is presented in Figure 13. For the full 24 hr profiles (includes fasting and postprandial concentrations) the estimated treatment ratio (semaglutide/placebo) for glucose and glucagon was 0.78 [0.74; 0.82]_{95%CI} ($p < 0.0001$) and 0.88 [0.83; 0.93]_{95%CI} ($p < 0.0001$), respectively, confirming a decrease in glucose and glucagon following treatment with semaglutide compared to placebo (EoT). For insulin, no treatment effect was evident following treatment with semaglutide compared to placebo (EoT) (estimated treatment ratio: 1.01 [0.93; 1.10]_{95%CI} ($p = 0.8243$)). An increase in C-peptide was evident following treatment with semaglutide compared to placebo (EoT) (estimated treatment ratio: 1.05 [1.00; 1.10]_{95%CI} ($p = 0.0458$)).

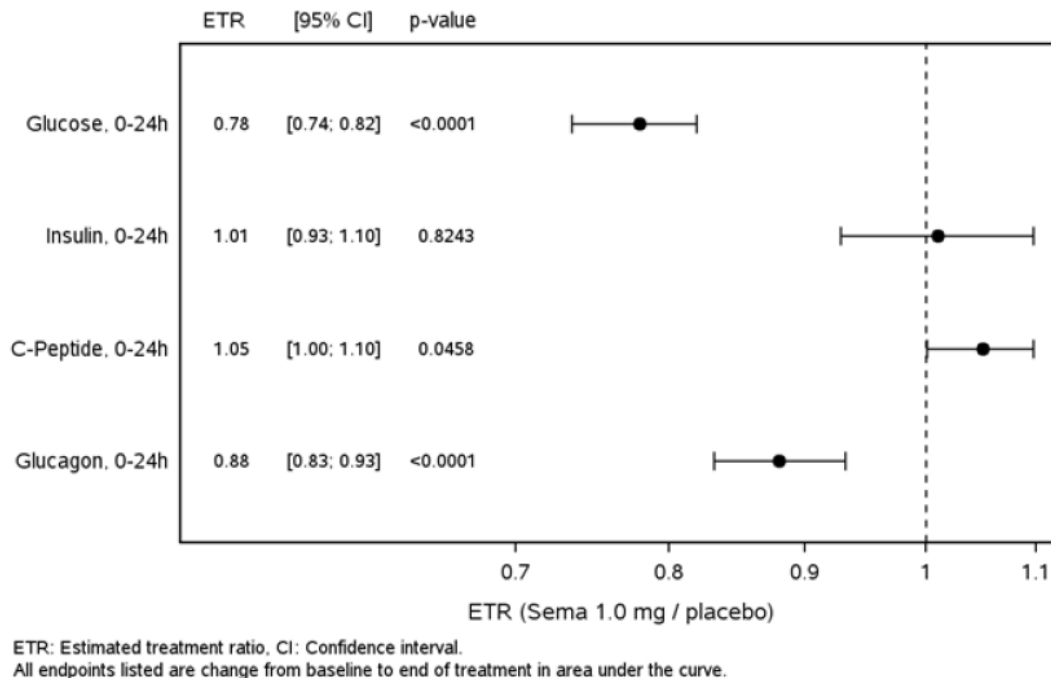


Figure 13: Forest plot of estimated treatment ratio (semaglutide/placebo) for change from baseline to EoT in 24 hr glucose, insulin, C-peptide, and glucagon (AUC_{0-24hr} during a meal test day) in patients with T2DM

(Source: Clinical study report NN9535-3635, page 114)

During the meal stimulation test, meals were not completely consumed by 38 patients. Sensitivity analysis was conducted by excluding (1) patients with incomplete meals and (2) patients with less than 80% meal completion. The estimated treatment ratio (semaglutide/placebo) for change from baseline to EoT for insulin and C-peptide was 1.15 [1.03; 1.28]_{95%CI} (p=0.0165) and 1.12 [1.06; 1.18]_{95%CI} (p=0.0003), respectively, following the first sensitivity analysis and 1.08 [0.99; 1.18]_{95%CI} (p=0.0946) and 1.09 [1.04; 1.14]_{95%CI} (p=0.0004), respectively, following the second sensitivity analysis. When compared to the primary analysis, an increase in insulin was observed especially when subjects with incomplete meals were excluded from the analysis. For glucose and glucagon the overall results from the sensitivity analysis was comparable to that of the primary analysis.

The effect of semaglutide (at steady-state) on individual meal response (AUC_{0-5 hr} postprandial) was investigated in a post hoc analysis (estimated treatment ratio for change from baseline to EoT). After each meal, the level of postprandial glucose (estimated treatment ratio after breakfast, lunch, dinner of 0.71 [0.67; 0.76]_{95%CI}, 0.79 [0.74; 0.85]_{95%CI}, 0.80 [0.75; 0.86]_{95%CI}, respectively) and postprandial glucagon (estimated treatment ratio after breakfast, lunch, dinner of 0.86 [0.82; 0.91]_{95%CI}, 0.86 [0.81; 0.91]_{95%CI}, 0.85 [0.79; 0.91]_{95%CI}, respectively) decreased in patient with T2DM after treatment with semaglutide compared to placebo. After each meal, no significant treatment effect on postprandial insulin (estimated treatment ratio after breakfast,

lunch, dinner of 0.95 [0.84; 1.07]_{95%CI}, 1.05 [0.94; 1.18]_{95%CI}, 0.90 [0.81; 1.01]_{95%CI}, respectively) and postprandial C-peptide (estimated treatment ratio after breakfast, lunch, dinner of 1.03 [0.96; 1.10]_{95%CI}, 1.06 [0.99; 1.14]_{95%CI}, 0.97 [0.91; 1.04]_{95%CI}, respectively) was evident following treatment with semaglutide as compared to placebo.

The effect of semaglutide (at steady-state) on fasting glycemic parameters was investigated in a post hoc analysis (estimated treatment ratio for change from baseline to EoT) with data obtained in the fasting state (values obtained prior to any meal consumption, nominal time = 0 min). In the fasting state, insulin (estimated treatment ratio: 1.30 [1.11; 1.53]_{95%CI}) and C-peptide (estimated treatment ratio: 1.23 [1.14; 1.32]_{95%CI}) increased and glucose (estimated treatment ratio: 0.78 [0.74; 0.83]_{95%CI}) and glucagon (estimated treatment ratio: 0.92 [0.86; 0.99]_{95%CI}) decreased after treatment with semaglutide when compared to placebo. The Applicant concludes that the effect of semaglutide treatment on insulin response was more pronounced in the fasting state; however for glucagon response the effect was evident in both the fasting and postprandial states.

The Applicant reports that observations of no treatment effect of semaglutide on overall and postprandial insulin and C-peptide concentrations (postprandial only) as compared to placebo is due to the lower postprandial demand for insulin in patients treated with semaglutide as a result of lower glucose concentrations and an increase in insulin sensitivity.

Assessment for insulin resistance (HOMA-IR indices) in patients with T2DM receiving either 0.5 mg and/or 1 mg maintenance doses of semaglutide was conducted in the Phase 3a studies. In all studies, treatment with semaglutide overall decreased the HOMA-IR indices from baseline to throughout the study. Compared to the comparators, this decrease in HOMA-IR indices was significantly larger following treatment with both semaglutide 0.5 mg and 1 mg doses (except in Studies NN9535-3623 and NN9535-4091 where no significant effect was observed with semaglutide 0.5 mg compared to the comparator). These results support an overall reduction in insulin resistance following treatment with semaglutide and generally to a larger extent than that observed with the comparators. These findings support the Applicant's statement of an increase in insulin sensitivity following treatment with semaglutide.

Effect of semaglutide on maximal insulin secretory capacity

Geometric mean concentration-time profile for insulin and glucagon and geometric mean ISR-time profile during the arginine stimulation test (IV injection of arginine under hyperglycemic conditions) at baseline and EoT in patients with T2DM is presented in Figure 14. An increase in insulin levels was observed at the 0-10 min (first test period) and 0-30 min (full test period) time periods following treatment with semaglutide when compared to placebo (EoT). For insulin, the estimated treatment ratio (semaglutide/placebo) for mean change from baseline to EoT was 2.82 [2.39; 3.32]_{95%CI} (p<0.0001) and 4.42 [3.74; 5.22]_{95%CI} (p<0.0001) for the 0-10 min and 0-30 min time periods, respectively.

Consistent with observations for insulin, the ISR increased after treatment with semaglutide compared to placebo (EoT) in both time periods (estimate treatment ratio for change from baseline to EoT of 1.69 [1.49; 1.92]_{95%CI} (p<0.0001) for AUC_{0-10min} and 2.69 [2.38; 3.05]_{95%CI} (p<0.0001) for AUC_{0-30 min}). The effect was greater in the full test period (0-30 min) for both insulin and ISR when compared to the first test period (0-10 min).

For glucagon a decrease in concentration levels was evident following treatment with semaglutide when compared to placebo (EoT) in both time periods (estimate treatment ratio for change from baseline to EoT of 0.80 [0.75; 0.87]_{95%CI} (p<0.0001) for AUC_{0-10min} and 0.82 [0.78; 0.87]_{95%CI} (p<0.0001) for AUC_{0-30 min}).

The Applicant concludes that an improvement in maximal insulin secretory capacity is evident in patients with T2DM treated with semaglutide compared to placebo.

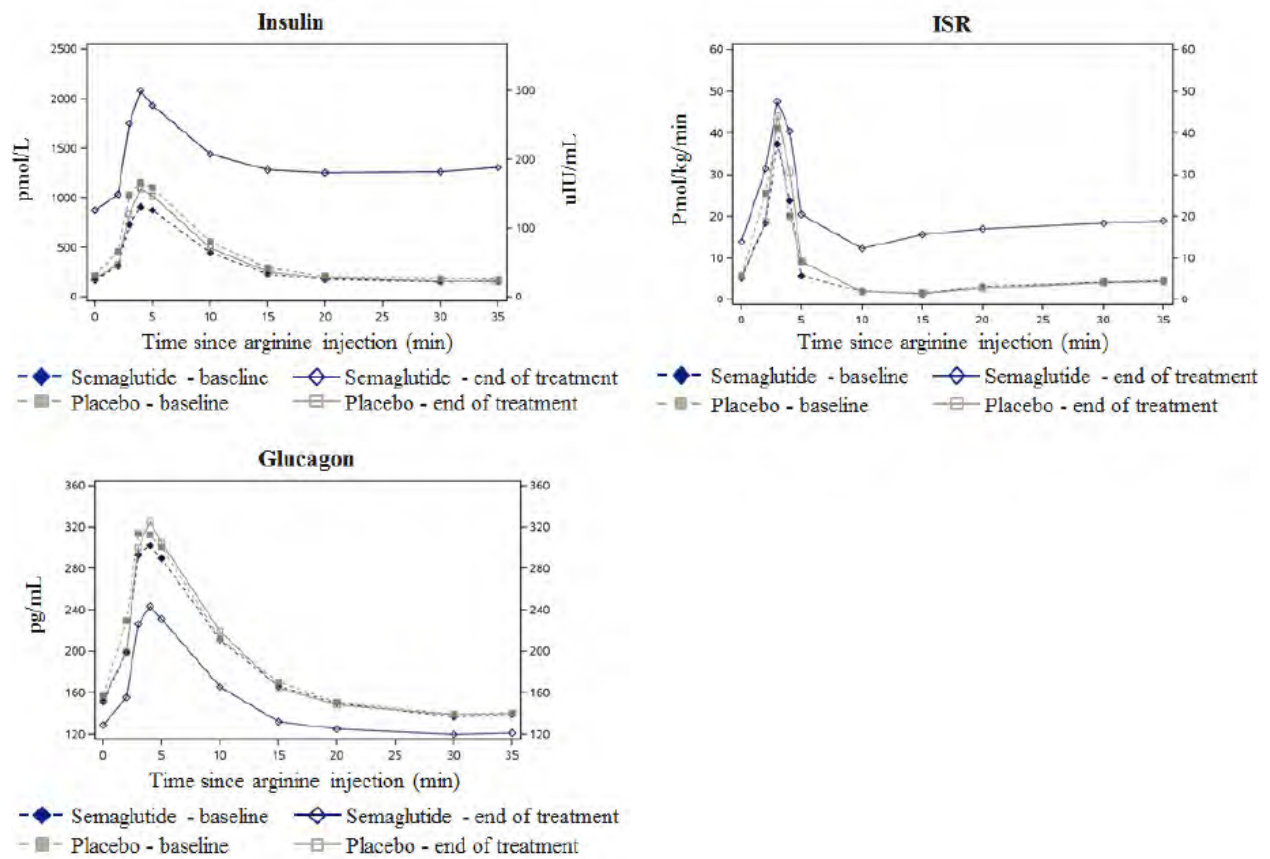


Figure 14: Geometric mean concentration-time profile for insulin and glucagon and geometric mean ISR-time profile following administration of semaglutide and placebo at baseline and end-of-treatment in patients with T2DM (arginine stimulation test)

(Source: Clinical study report NN9535-3635, page 117)

Effect of semaglutide on β -cell responsiveness

Geometric mean ISR-glucose concentration profile during the graded glucose infusion test in patients with T2DM at baseline and EoT and in healthy subjects (no treatment) at baseline is presented in Figure 15. Geometric mean ISR increased with increasing plasma glucose concentrations (5-12 mmol/L) in a glucose-dependent manner in patients with T2DM following treatment with semaglutide when compared to placebo (EoT). The estimated treatment ratio (semaglutide/placebo) for mean change from baseline to EoT for $AUC_{ISR,5-12\text{mmol/L glucose}}$ was 2.45 [2.16; 2.77]_{95%CI} ($p < 0.0001$) and for the slope of mean ISR vs. glucose concentration curve was 2.78 [2.44; 3.16]_{95%CI} ($p < 0.0001$) which indicates an improvement in β -cell responsiveness following treatment with semaglutide when compared to placebo. No significant treatment effect of semaglutide was observed on insulin clearance (estimated treatment ratio for mean change from baseline to EoT of 0.93 [0.79; 1.09]_{95%CI} ($p = 0.3515$)).

Geometric mean glucagon concentration-time profile during the graded glucose infusion test in patients with T2DM at baseline and EoT and in healthy subjects (no treatment) at baseline is presented in Figure 16. A more pronounced glucose-dependent decrease in glucagon concentrations was observed with increasing concentrations of glucose (represented by increase in time since graded glucose infusion) in patients with T2DM following treatment with semaglutide compared to placebo (EoT). In patients with T2DM, a slight decrease in glucagon ($AUC_{\text{glucagon},5-12\text{mmol/L glucose}}$) was observed after treatment with semaglutide when compared to placebo (EoT) (estimated treatment ratio for mean change from baseline to EoT of 0.87 [0.82; 0.93]_{95%CI} ($p < 0.0001$)).

The ISR-glucose concentration profile after semaglutide treatment (EoT) in patients with T2DM was similar to that observed in healthy subjects (no treatment). Additionally, the geometric mean estimates for $AUC_{ISR,5-12\text{mmol/L glucose}}$, slope of mean ISR vs. glucose concentration curve, and insulin clearance were similar between patients with T2DM treated with semaglutide and healthy subjects when compared to patient with T2DM treated with placebo. The glucagon concentration-time profile at the EoT for patients with T2DM treated with semaglutide was more similar to that of healthy subjects (no treatment) as compared to patients with T2DM treated with placebo.

The Applicant concludes that semaglutide improves insulin secretory response (β -cell responsiveness) and lowers glucagon secretion to elevated glucose concentrations in a glucose-dependent manner. Following semaglutide treatment, the insulin secretion rate in patients with T2DM was comparable to that in healthy subjects.

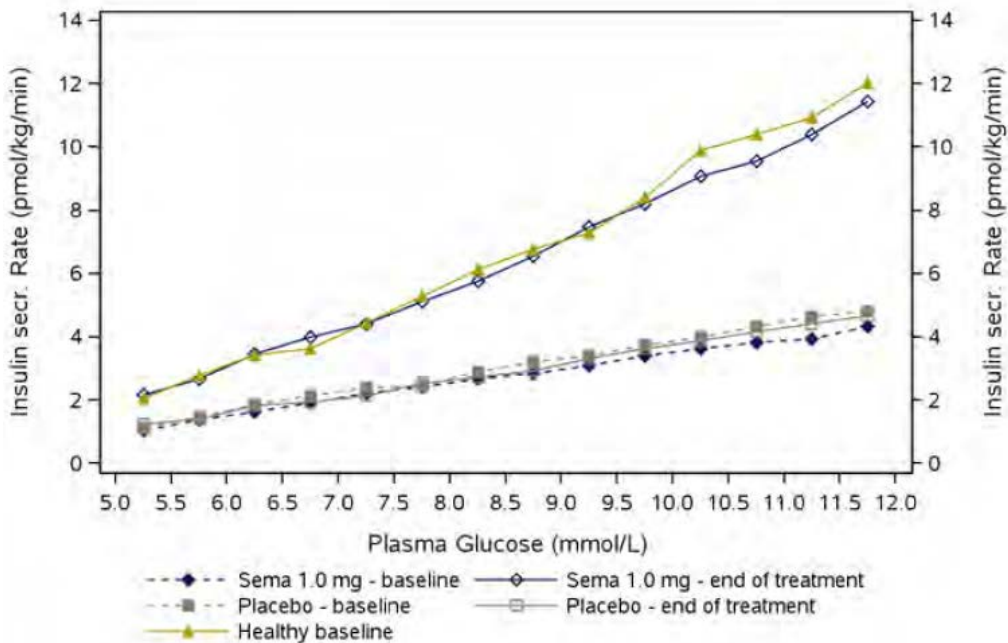


Figure 15: Geometric mean ISR-glucose concentration profile following administration of semaglutide and placebo in patients with T2DM at baseline and end-of-treatment and in healthy subjects (no treatment) at baseline (graded glucose infusion test)

(Source: Clinical study report NN9535-3635, page 121)

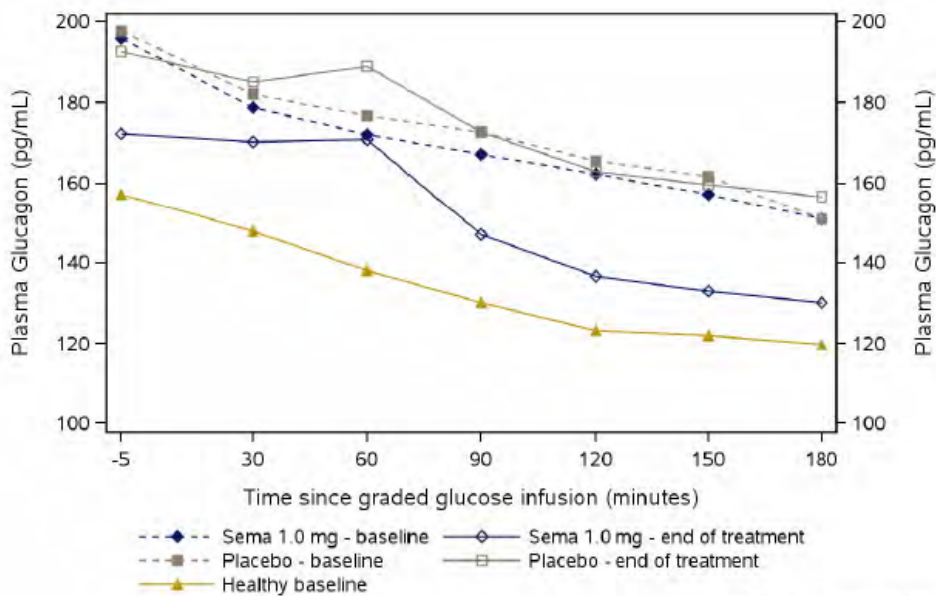


Figure 16: Geometric mean glucagon concentration-time profile following administration of semaglutide and placebo in patients with T2DM at baseline and end-of-treatment and in healthy subjects (no treatment) at baseline (graded glucose infusion test)

(Source: Clinical study report NN9535-3635, page 508)

Overall, the Applicant concludes that treatment with semaglutide in patients with T2DM improves insulin secretion in response to increasing glucose concentrations in all investigated β -cell stimuli tests. The study showed that semaglutide improves β -cell responsiveness in patients with T2DM to a similar level to that observed in healthy subjects (with no treatment). The improvement in glycemic response is due to a combined effect of semaglutide to stimulate insulin secretion and lower glucagon secretion in a glucose-dependent manner as compared to placebo.

3.2.2.2 Postprandial glucose and gastric emptying

As reported in Section 3.3.4.4, a delay in gastric emptying during the early postprandial phase was observed following treatment with semaglutide compared to placebo. The Applicant investigated the impact of this delay in gastric emptying on postprandial glucose concentrations following treatment with semaglutide.

Study NN9535-3685 investigated the effect of 1 mg SC semaglutide or matching placebo at steady-state on the *ad libitum* energy intake in obese, non-diabetic subjects (refer to Section 3.2.3). A secondary objective of this study was to compare the effect of semaglutide and placebo on postprandial glucose metabolism during a standardized breakfast meal. For glucose, the postprandial increment for the first hour of the meal test (iAUC_{0-1hr}) was lower in subjects treated with semaglutide compared to placebo (estimated treatment difference (semaglutide/placebo) of -0.56 [-0.88; -0.23]_{95%CI} (p=0.0018)). When gastric emptying was included as a covariate in the statistical analysis the treatment difference between semaglutide and placebo was lowered (estimated treatment difference of -0.33 [-0.70; -0.05]_{95%CI} (p=0.0829)). This suggests that the delay in gastric emptying in the early postprandial phase following administration of semaglutide contributes to the observed lower postprandial increase in glucose (iAUC_{0-1hr}) in the first hour following a meal.

3.2.2.3 Hypoglycemic counter-regulation

Study NN9535-3684 investigated the effect of 1 mg SC semaglutide at steady-state on the hypoglycemic counter-regulation in patients with T2DM (refer to Appendix 5.1 for description of study).

Geometric mean glucagon concentrations during the hypoglycemic clamp and recovery phase following administration of 1 mg SC semaglutide (steady-state) and matching placebo in patients with T2DM is presented in Figure 17. Geometric mean glucagon concentrations at ambient plasma glucose level (before clamp) and at target plasma glucose of 5.5 mmol/L and 3.5 mmol/L was 23%, 23%, and 29% lower, respectively, in patients treated with semaglutide compared to placebo. At nadir (target 2.5 mmol/L; observed mean plasma glucose level of 2.9 mmol/L), geometric mean glucagon concentrations were comparable in both treatment groups (93.78 pg/mL vs. 95.97 pg/mL (placebo)).

An increase in geometric mean glucagon plasma concentrations from target plasma glucose of 5.5 mmol/L to nadir (target 2.5 mmol/L) was observed in patients treated with semaglutide and placebo. The estimated absolute increase in mean glucagon concentrations was comparable after treatment with semaglutide and placebo in patients with T2DM (estimate treatment difference (ETD) (semaglutide-placebo): 5.2 pg/mL [-7.7; 18.1]_{95%CI}). However, given the lower glucagon concentrations in patients treated with semaglutide at the target plasma glucose level of 5.5 mmol/L, the estimated relative increase in mean glucagon concentrations was 28% higher in patients treated with semaglutide compared to placebo (estimate treatment ratio (semaglutide/placebo): 1.28 [1.04; 1.56]_{95%CI}). The within subject variability between the 2 treatments for absolute change in glucagon concentrations from target plasma glucose of 5.5 mmol/L to nadir was overall low in the majority of the patients.

During the recovery phase from hypoglycemia, the estimated time to reach target plasma glucose of 4 mmol/L from nadir (target of 2.5 mmol/L) was comparable in patients treated with semaglutide and placebo (estimated treatment ratio (semaglutide/placebo): 0.95 [0.89; 1.02]_{95%CI}). A decrease in glucagon concentrations was observed from nadir to recovery (Figure 17), with this decrease in glucagon concentrations greater in patients treated with semaglutide compared to placebo (ETD (semaglutide-placebo): -8.3 pg/mL [-21.3; 4.6]_{95%CI}, estimate treatment ratio (semaglutide/placebo): 0.85 [0.74; 0.98]_{95%CI}). After recovery, the geometric mean glucagon concentration level was 17% lower in patients treated with semaglutide compared to placebo.

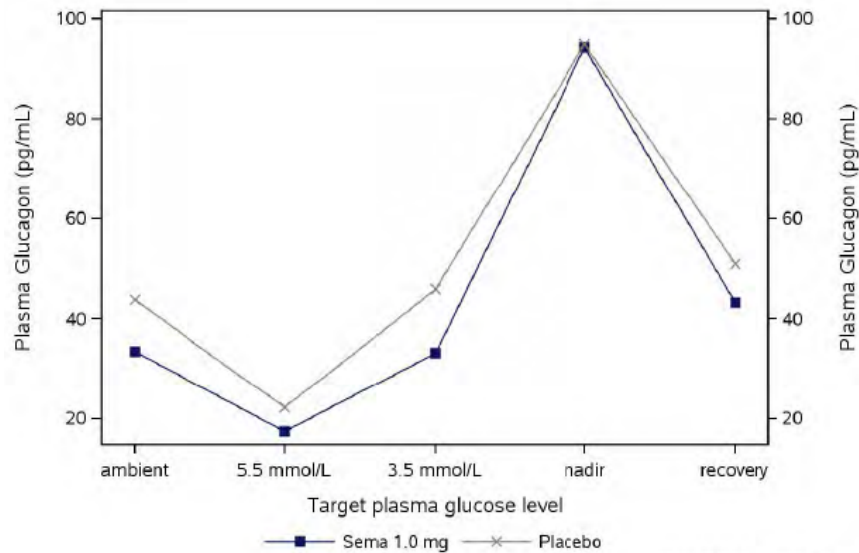


Figure 17: Geometric mean glucagon concentration during the hypoglycemic clamp and recovery phase following administration of 1 mg SC semaglutide (at steady-state) or placebo in patients with T2DM

(Source: Clinical study report NN9535-3684, page 261)

Assessment for responses to other counter-regulatory hormones was also evaluated during the stepwise hypoglycemic clamp. Overall, geometric mean concentrations of adrenaline, noradrenaline, cortisol, and growth hormones appeared to increase from target plasma glucose of 5.5 mmol/L to nadir (target 2.5 mmol/L). However, a trend towards lower increase from target plasma glucose of 5.5 mmol/L to nadir in mean concentrations of adrenaline, noradrenaline, and cortisol was evident in patients treated with semaglutide compared to placebo. For growth hormone, the increase in concentration was higher in patients treated with semaglutide compared to placebo.

Geometric mean C-peptide concentrations during the hypoglycemic clamp and recovery phase following treatment with 1 mg SC semaglutide (steady-state) and matching placebo in patients with T2DM is presented in Figure 18. In both treatment groups, geometric mean C-peptide concentrations decreased from target plasma glucose of 5.5 mmol/L to nadir (target of 2.5 mmol/L). At target plasma glucose of 5.5 mmol/L, 3.5 mmol/L, and nadir (target of 2.5 mmol/L) the geometric mean C-peptide concentrations were 2.1-, 1.8-, and 1.7-fold higher in patients treated with semaglutide compared to placebo. Given these observations, the overall decrease in mean C-peptide concentrations was greater in patients treated with semaglutide compared to placebo (ETD (semaglutide-placebo): -0.40 nmol/L [-0.49; -0.31]_{95%CI}, estimate treatment ratio (semaglutide/placebo): 0.80 [0.73; 0.87]_{95%CI}).

During the recovery phase from hypoglycemia, the slight increase in mean C-peptide concentrations from nadir to recovery was comparable in patients treated with semaglutide and placebo (ETD (semaglutide-placebo): -0.02 nmol/L [-0.06; 0.01]_{95%CI}, estimated treatment ratio (semaglutide/placebo): 0.92 [0.83; 1.02]_{95%CI}). After recovery, the geometric mean C-peptide concentrations were 56% higher in patients treated with semaglutide compared to placebo.

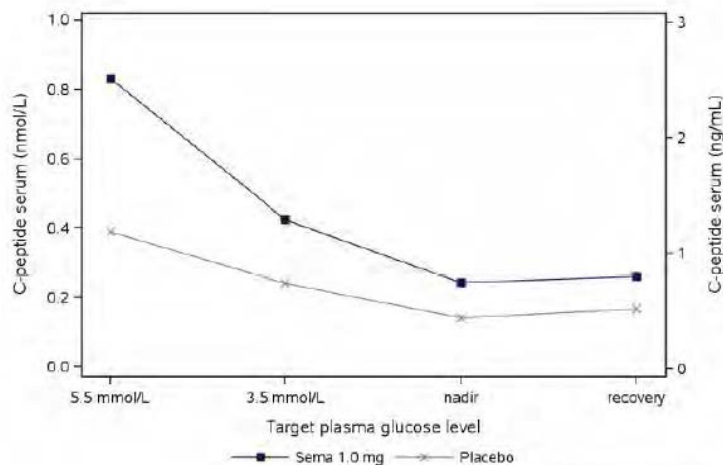


Figure 18: Geometric mean C-peptide concentrations during the hypoglycemic clamp and recovery phase following administration of 1 mg SC semaglutide (at steady-state) or placebo in patients with T2DM

(Source: Clinical study report NN9535-3684, page 130)

The Applicant concludes that under the studied conditions, treatment with semaglutide (highest maintenance dose at steady-state) did not compromise the overall counter-regulation of plasma glucose during hypoglycemia in patients with T2DM when compared to placebo.

3.2.3 Body weight

The effect of semaglutide on body weight was assessed in patients with T2DM and in obese, non-diabetic subjects. Semaglutide was administered for 12 weeks as follows: dose escalation regimen of 0.25 mg once weekly for 4 weeks followed by 0.5 mg once weekly for 4 weeks and thereafter 1 mg semaglutide once weekly for 4 weeks (maintenance period). The effect on body weight was assessed after a 5th dose of 1 mg SC semaglutide. The change from baseline to end of treatment in body weight after 12 weeks of treatment with semaglutide and placebo is presented in Table 9.

Table 9: Change from baseline to end of treatment in body weight (kg) in patients with T2DM and obese, non-diabetic subjects after 12 weeks of treatment with semaglutide and placebo

Population	Study Number	n	Treatment	Baseline	Change from Baseline
				Mean (SD)	Mean (SD)
T2DM patients	NN9535-3635 ¹	75	Semaglutide 1 mg	93.2 (14.2)	-4.2 (2.5)
			Placebo	90.0 (14.6)	-0.1 (1.6)
	NN9535-3684 ²	38	Semaglutide 1 mg	88.5 (11.0)	-3.7 (2.7)
			Placebo	86.9 (11.4)	0.3 (2.8) ⁴
Obese subjects	NN9535-3685 ³	30	Semaglutide 1 mg	101.7 (10.5)	-5.0 (2.4)
			Placebo	100.8 (11.3)	1.0 (2.4) ⁴

¹Phase 1 study; Patients treated with diet and exercise and/or metformin monotherapy

²Phase 1 study; Patients treated with metformin monotherapy

³Phase 1 study; Subjects were excluded from the study if they were on 1) any medication that could decrease and increase body weight, 2) excessive consumption of a diet deviating from normal diet, currently on a weight loss program, and 3) excessive participation in strenuous exercise

⁴Studies NN9535-3684 and NN9535-3685 are crossover in design, therefore the increase in body weight for the placebo group should be interpreted with caution due to possible carry over effect of patients/subjects treated with semaglutide in the first treatment period

(Source: Study NN9535-3635, Clinical study report, page 251 and 253; Study NN9535-3684, Clinical study report, page 947 and 950; Study NN9535-3685, Clinical study report, page 421 and 422)

Study NN9535-3685 investigated the potential mechanisms by which semaglutide lowers body weight in obese, non-diabetic subjects after 12 weeks of semaglutide and placebo treatment. In this subject population, a decrease in mean body fat mass, body lean mass, and body fat

percentage from baseline to week 12 was evident following treatment with semaglutide when compared to placebo. In the semaglutide treatment group, a larger reduction in mean body fat mass (mean (SD): -3.52 kg (2.1)) compared to mean body lean mass (mean (SD): -1.11 kg (1.14)) was observed.

In obese, non-diabetic subjects following a standardized breakfast meal, a 35% reduction in *ad libitum* energy intake during a lunch meal was observed in subjects who were treated with semaglutide compared to placebo. A lower energy intake during both *ad libitum* evening meal (17.9% reduction) and *ad libitum* snack box (22.5% reduction) was also evident in subjects treated with semaglutide compared to placebo. Overall, for all *ad libitum* meals, an approximately 24% lower energy intake was observed in subjects treated with semaglutide compared to placebo.

Energy expenditure was assessed using resting metabolic rate (RMR) and respiratory quotient (RQ). In a post-hoc analysis, the mean RMR was significantly lower in subjects treated with semaglutide compared to placebo (treatment difference: -601.9 kJ/24 hr [-958.9; -244.9]_{95%CI}, p=0.0019). When body lean mass (at week 12) was included as a covariate in the statistical model, a lower RMR (not a statistically significant difference) was observed in subjects treated with semaglutide compared to placebo (treatment difference: -507.5 kJ/24 hr [-1060.6; 45.6]_{95%CI}). This suggests that only a minor part of the lower RMR for subjects treated with semaglutide compared to placebo can be explained by treatment effect on body lean mass. Mean RQ was lower in subjects treated with semaglutide compared to placebo; however this difference was not significant. This observation suggests that there is no difference in oxidation of macronutrients after semaglutide treatment.

Subjective ratings for sensation of appetite parameters (hunger, satiety, fullness, and prospective food consumption), thirst, nausea, and well-being was assessed using Visual Analogue Scale (VAS) ratings following 12 weeks of semaglutide and placebo treatment. Subjects rated their sensation before the standardized breakfast meal (fasting rating (fasted state)) and during the 5 hr postprandial period (mean postprandial increment in ratings). The effect of semaglutide on fasting and postprandial appetite parameters, thirst, nausea, and well-being after 12 weeks of treatment is presented in Figure 19.

Fasting ratings showed the following: overall appetite score (a composite endpoint of the 4 individual appetite ratings (satiety, fullness, hunger, prospective food consumption)) was higher, hunger and prospective food consumption scores were lower, fullness score was higher after semaglutide treatment compared to placebo and no significant difference was observed for satiety score between both treatments. Overall a similar pattern was observed for mean postprandial increment in ratings (postprandial period), with only the increments of satiety rating being significantly higher in subjects treated with semaglutide compared to placebo. For thirst, nausea, and well-being no difference was evident between the 2 treatments in both the fasting

state and postprandial period. Overall the results indicate a lower appetite during both fasting and postprandial periods for subjects treated with semaglutide compared to placebo.

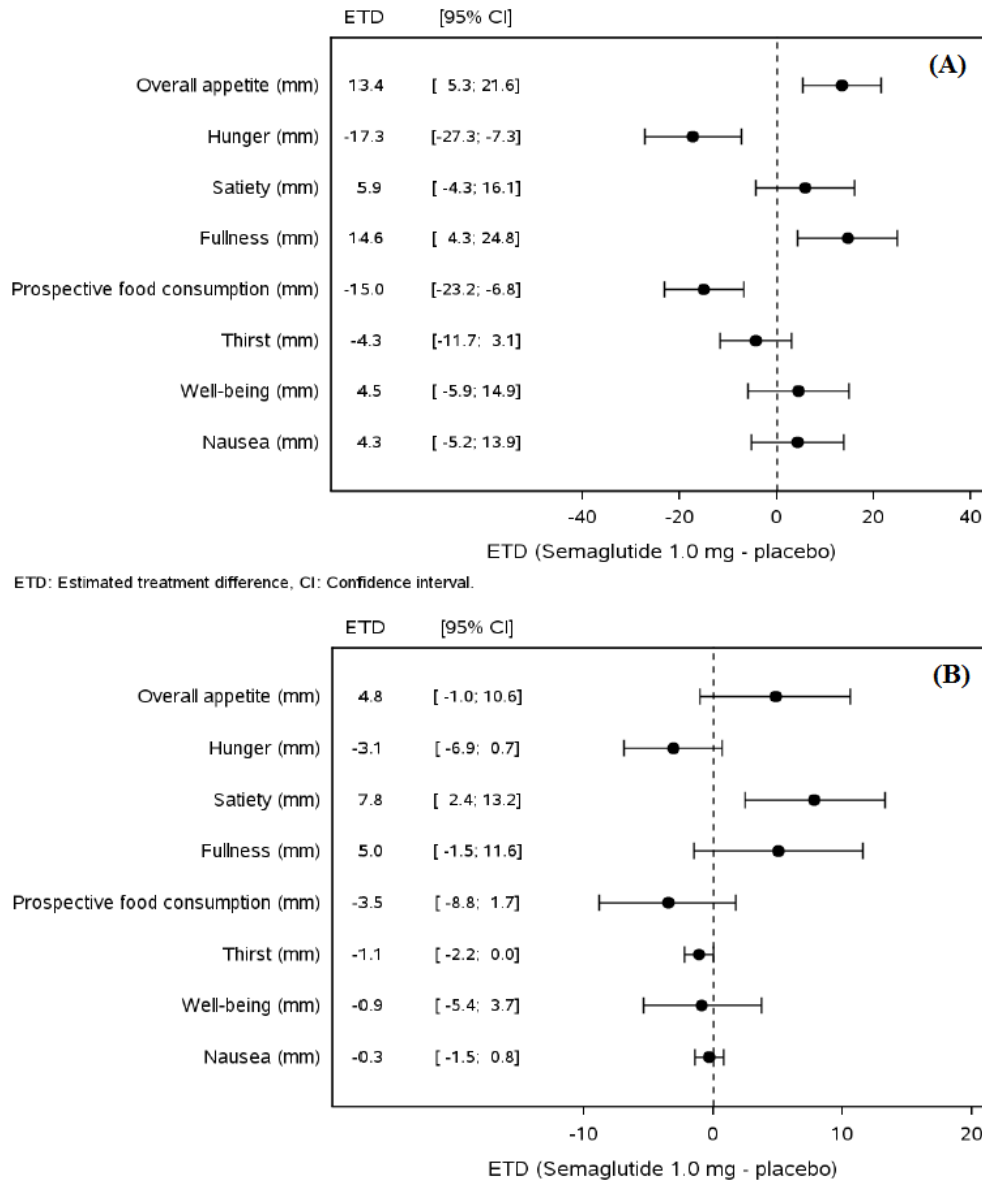


Figure 19: Effect of semaglutide on (A) fasting and (B) postprandial appetite, thirst, well-being, nausea in obese, non-diabetic subjects (VAS) after 12 weeks of treatment with semaglutide and placebo

(Source: Study NN9535-3685, Clinical study report, page 147)

The Applicant concludes that following 12 weeks of treatment with semaglutide, a body weight loss of ~4-5 kg was evident in patients with T2DM and in obese, non-diabetic subjects. The study conducted in obese, non-diabetic subjects suggests that the effect of semaglutide in lowering body weight is more related to appetite and energy intake than to energy expenditure.

3.2.4 QTc prolongation

No significant QTc prolongation effect of semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated. For further information refer to the QT-IRT review.

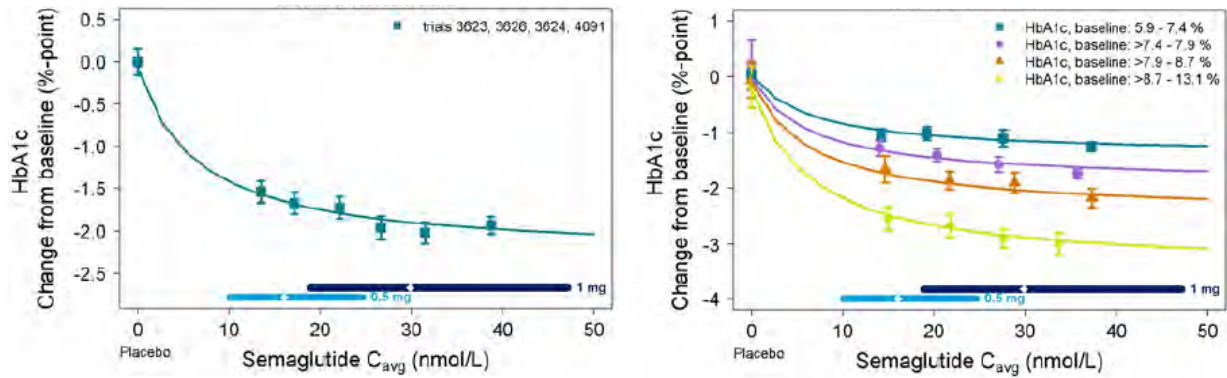
3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

This application hosts a wealth of pivotal and supportive evidence of effectiveness for semaglutide. HbA1c reduction and body weight loss, appear to be correlated with semaglutide dose/exposure (see below). Additional measures of glucodynamics from the phase 2 study also provide supportive evidence of efficacy. Given the need for different treatment goals (in HbA1c reduction) depending on disease severity, the availability of multiple dose levels that achieve exposures across the range of possible treatment effects is ideal.

Phase 3 Trials in Patients with Type 2 Diabetes:

Figure 20 (left panel) indicates there is a clear exposure-response relationship between semaglutide average concentration (C_{avg}) and change from baseline HbA1c reduction. The right panel indicates baseline HbA1c influences the potential treatment effect. Patients with higher HbA1c baseline values have the greatest amount of possible reduction (~3%) compared to patients with lower starting values (~1%), therefore they appear to exhibit the greatest treatment benefit. This is consistent with the behavior of other products in this class.



Cross-reference: Modified from [Modelling report \(M 5.3.3.5\), Figure 8A and 9A](#)

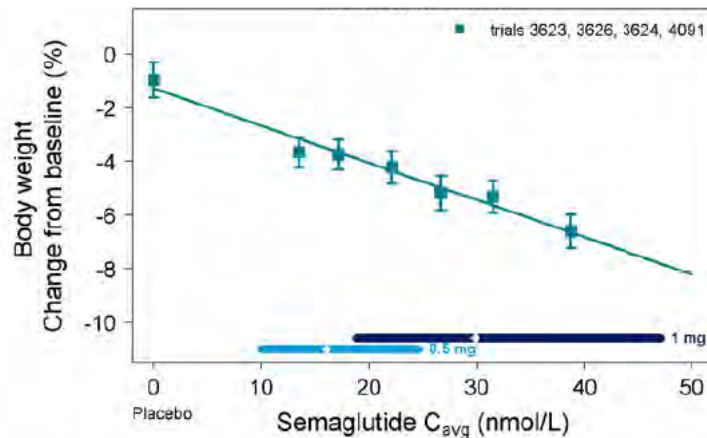
Notes: Data are mean HbA_{1c} values with 95% CI obtained after 30 weeks of treatment versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nM). The lines through data represent covariate-adjusted model-derived exposure-response relations for each trial population. Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges.

Figure 20: HbA_{1c} change from baseline versus exposure of semaglutide for all subjects (left panel) stratified by baseline HbA_{1c} (right panel) after 30 weeks of treatment in subjects with T2DM – trials 3623, 3626, 3624 and 4091

(Source: Applicant’s Summary of Clinical Pharmacology)

Additionally, the response in HbA_{1c} increased with increasing semaglutide exposure over the range of C_{avg} values obtained from administration of 0.5 and 1.0 mg semaglutide (Table 1). This suggest there is additional treatment benefit when increasing the dose from 0.5 mg semaglutide to 1.0 mg semaglutide.

Body weight loss from baseline until week 30 increased in a linear fashion with increasing semaglutide exposure and did not appear to level-off at the highest exposures obtained with 0.5 and 1.0 mg semaglutide (Figure 21).



Cross-reference: [Modelling Report \(M 5.3.3.5\), Figure 12A](#)

Notes: Data are mean values of body weight loss with 95% CI versus exposure expressed as quantiles of C_{avg} plus placebo (at C_{avg} of 0 nmol/L). The line through data represents covariate-adjusted model-derived estimates. Horizontal lines with diamonds along the x-axis represent medians and 95% exposure ranges.

(Source: Applicant's Population PK Modeling Report, Figure 12)

Figure 21. Body weight change from baseline versus exposure of semaglutide after 30 weeks of treatment in subjects with T2DM – trials 3623, 3626, 3624 and 4091

Phase 2 Trials in Patients with Type 2 Diabetes:

Subjects who were treated with semaglutide had an observed reduction in HbA1c after 12 weeks of treatment of approximately 1%-point, from baseline values of 7.3–7.6%, whereas no pronounced change was observed during treatment with placebo (Table 10). This lower median response of approximately 1% reduction is attributed to lower baseline HbA1c values in the phase 2 trials compared to the phase 3 trials.

Table 10: Effect of semaglutide on HbA1c (%) in subjects with type 2 diabetes after 12 weeks of treatment – trials 3635, 3684, and 3819.

Trial ID	Treatment	N at baseline	Baseline	End of treatment	Change from baseline
			Mean (SD)	Mean (SD)	Mean (SD)
3635	Semaglutide 1.0 mg	37	7.3 (0.8)	6.4 (0.7)	-0.9 (0.4)
	Placebo	38	7.3 (0.7)	7.4 (0.9)	0.1 (0.5)
3684	Semaglutide 1.0 mg	38 (b)	7.6 (1.0)	6.5 (0.6)	-1.1 (0.7)
	Placebo (a)	37 (b)	7.3 (1.1)	7.6 (1.0)	0.4 (0.8)
3819	Semaglutide 1.0 mg	43	7.3 (0.8)	6.2 (0.3)	-1.1 (0.6)

Notes: ^a The change in HbA_{1c} levels for subjects when treated with placebo should be interpreted with caution due to the carry over effect of subjects treated with semaglutide in the first treatment period; there appeared to be a minor increase in HbA_{1c} level during treatment with placebo for subjects when treated with semaglutide in the first treatment period; ^b Trial 3684 was a cross-over trial, a total of 38 subjects were enrolled.

(Source: Applicant's Summary of Clinical Pharmacology, Table 3-16)

Mean concentration–time glucose, insulin, C-peptide and glucagon profiles were obtained over 24 hours in subjects with T2DM, at baseline and at semaglutide 1.0 mg/placebo steady state in trial 3635. The profiles covered three standardized meals; breakfast, lunch and a protein-rich dinner (Section 3.2.2.2). The profiles are presented in Figure 12.

The effect of semaglutide on fasting glucose concentrations was assessed in subjects with T2DM and in subjects with obesity. In subjects with T2DM, the observed lowering effects of semaglutide on fasting glucose were consistent across trials, ending at approximately 6.5 mmol/L (Table 11). In trial 3635, semaglutide lowered fasting glucose by 1.6 mmol/L [29 mg/dL], whereas placebo treatment had no effect (Appendix 5.3, Table 35 and 36). As compared to placebo, semaglutide lowered the fasting glucose by 22% (ETR: 0.78 [0.74; 0.83]_{95% CI})

Table 11: Effect of semaglutide on fasting glucose (mmol/L) in subjects with type 2 diabetes after 12 weeks of treatment – trials 3635, 3684, and 3819

Table 3–17 Effect of semaglutide on fasting glucose (mmol/L) in subjects with T2D after 12 weeks of treatment – trials 3635, 3684 and 3819

Trial ID	Treatment	N at baseline	Baseline	End of treatment
			Geometric mean (CV)	Geometric mean (CV)
3635	Semaglutide 1.0 mg	37	8.15 (19.5)	6.59 (18.1)
	Placebo	38	8.05 (16.9)	8.43 (19.2)
3684	Semaglutide 1.0 mg	38 (a)	8.98 (23.9)	6.69 (18.5)
	Placebo	37 (a)	8.84 (26.5)	8.73 (26.0)
3819	Semaglutide 1.0 mg	43	8.25 (20.0)	6.38 (16.6)

Notes: ^a Trial 3684 was a cross-over trial, a total of 38 subjects were enrolled.

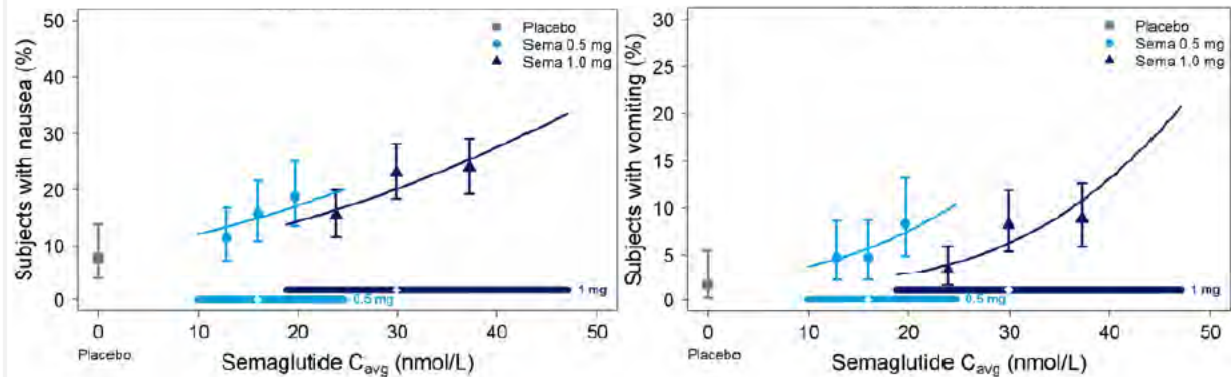
(Source: Applicant’s Summary of Clinical Pharmacology, Table 3-17)

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is acceptable for the general patient population with regards to providing reduction in HbA1c as described in the previous section. However, at this time it is not possible to conclude that 1.0 mg dose is acceptable in patients with prior retinopathy history due to 1) the exposure safety relationship for retinopathies described below and 2) the applicant’s analysis in appendix 5.5. The acceptability of this regimen is based on the flexibility afforded by the ability to start low and increase the dose for lack of efficacy or decrease the dose for tolerability issues. Based on results of an applicant’s analysis a slower titration in dose may be warranted in patients with prior retinopathy history. Given the ongoing discussion regarding retinopathies following semaglutide treatment in light of the upcoming advisory committee meeting, the clinical pharmacology recommended dosing will be revisited in an addendum to follow this advisory committee meeting in October 2017. The efficacy assessment for the 0.5 and 1.0 mg dose is discussed above and the exposure-response for safety assessment is described in this section.

Exposure-response for GI related adverse events:

Overall, the proportion of subjects reporting nausea and vomiting increased with semaglutide exposure (Figure 22), whereas reporting of diarrhea and constipation appeared to be largely independent of exposure (Modelling Report (M 5.3.3.5), Figure 18C and 19C). Further, the proportion of subjects reporting nausea and vomiting at a given exposure was slightly lower at maintenance doses of 1.0 mg compared to 0.5 mg.



Cross-reference: [Modelling Report \(M 5.3.3.5\)](#), [Figure 16C](#) and [17C](#)

Notes: Data are mean response values with 95% CI versus exposure expressed as concentration quantiles (plus placebo at 0 nmol/L). Lines through data represent covariate-adjusted model-based estimates for each treatment. Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges.

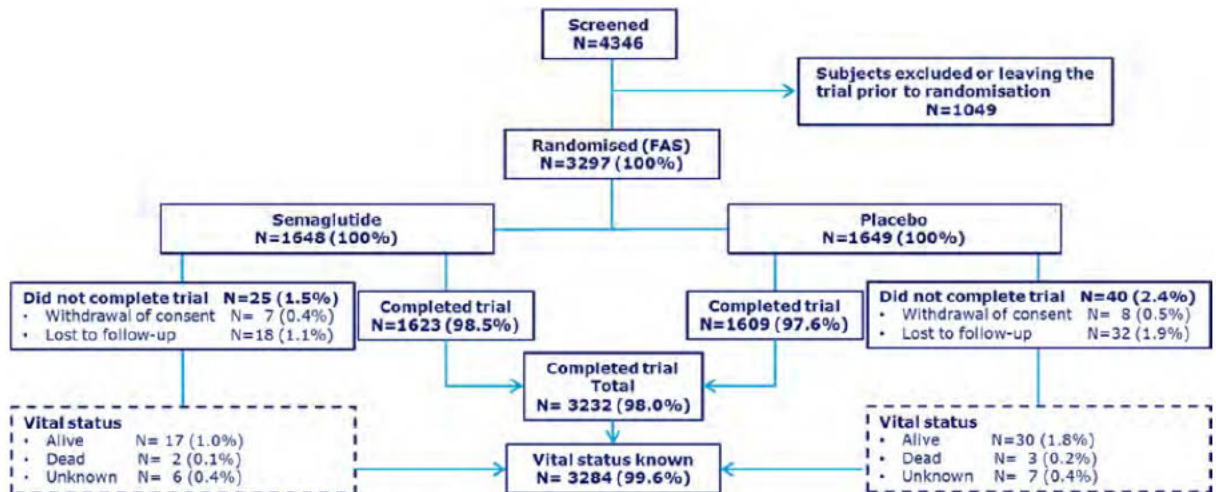
Figure 22: Proportions of subjects exhibiting nausea (left panel) and vomiting (right panel), at any time during 30 weeks of treatment versus semaglutide exposure (C_{avg}) by treatment in subjects with T2DM – trials 3623, 3626, 3624 and 4091

(Source: Applicant's Summary of Clinical Pharmacology, Figure 3-31)

Exposure-response for retinopathies:

Dose-response analyses were conducted to evaluate whether semaglutide concentrations correlated with increased risk of retinopathy. The analysis encompassed dose and retinopathy data from only the two-year cardiovascular outcomes trial (3744) with a prospective assessment for retinopathies at 1 year. The CVOT trial included diabetes patients at higher risk of CV events and with higher baseline HbA1c concentrations and had a total incidence of 79 retinopathies. PK data were not collected in this trial.

The trial population was subjects with T2DM with inadequate glycaemic control ($HbA1c \geq 7\%$) at high CV risk. The trial included subjects ≥ 50 years of age at screening with clinical evidence of CV disease and subjects ≥ 60 years of age at screening with subclinical evidence of CV disease. Subjects could be anti-hyperglycaemic drug naïve, or treated with 1 or 2 OAD(s), or treated with human NPH insulin or long-acting insulin analogue or pre-mixed insulin, alone or in combination with 1 or 2 OAD(s). The recruitment strategies required inclusion of subjects with moderate or severe chronic kidney disease.



Trial completer: a subject that either attend the last follow-up visit or dies while considered an active trial participant.
 FAS: full analysis set

Figure 23: CONSORT Diagram for subject disposition

(Source: Applicant’s Cardiovascular Outcomes Trial Report, Figure 10-1)

The reviewer’s graphical presentation of retinopathies by treatment and over time by treatment (Figure 24) suggest there is a trend for increasing chance of retinopathies with increasing semaglutide dose.

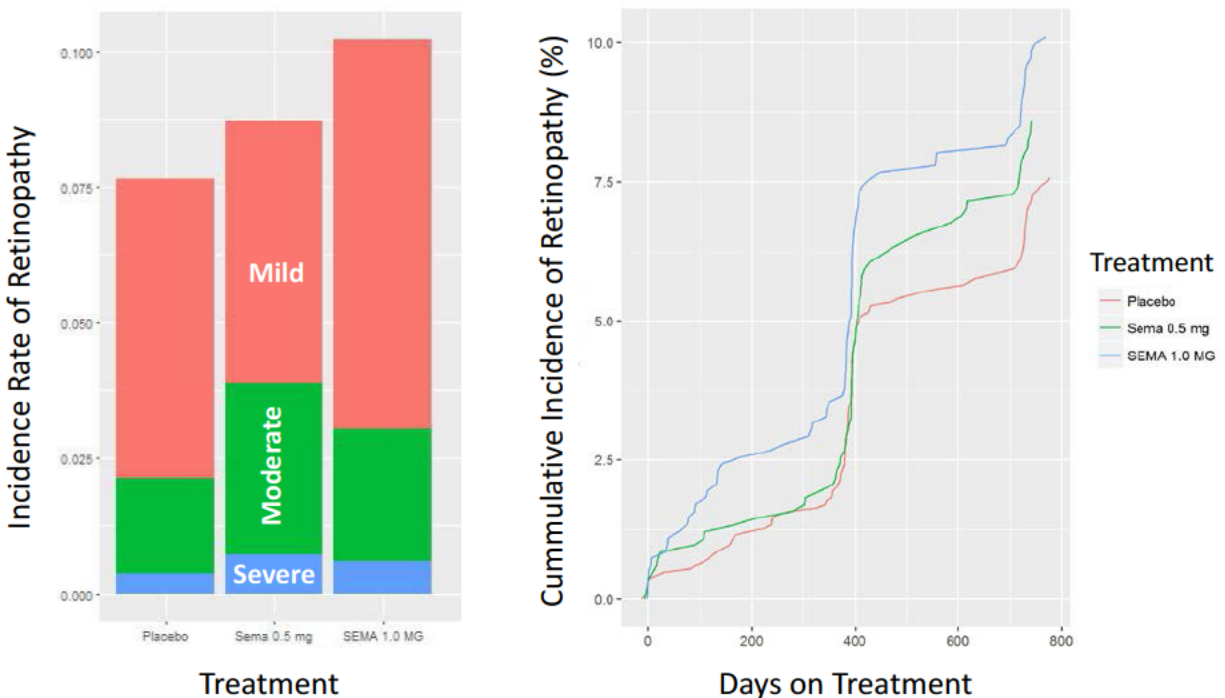


Figure 24: Incidence of Retinopathies appears to increase with increasing semaglutide dose. The left panel indicates the proportion of each dose group that had mild, moderate, and severe adverse events. The right panel depicts the cumulative incidence of retinopathies over the duration of the cardiovascular outcomes trial. The abrupt increase at 1 year is likely due to the prospectively planned eye evaluation at 1 year.

The results of the multivariate cox-proportional hazards analysis (Table 12) also suggest there is a significant effect of Dose and Baseline HbA1c towards causing retinopathies and an opposite effect of BMI on the probability of retinopathy. Age, race, sex, country and eGFR were also evaluated but did not evidence a significant correlation with retinopathy incidence.

Table 12: Final cox-proportional hazards multivariate model for retinopathies in the cardio-vascular outcomes trial 3744

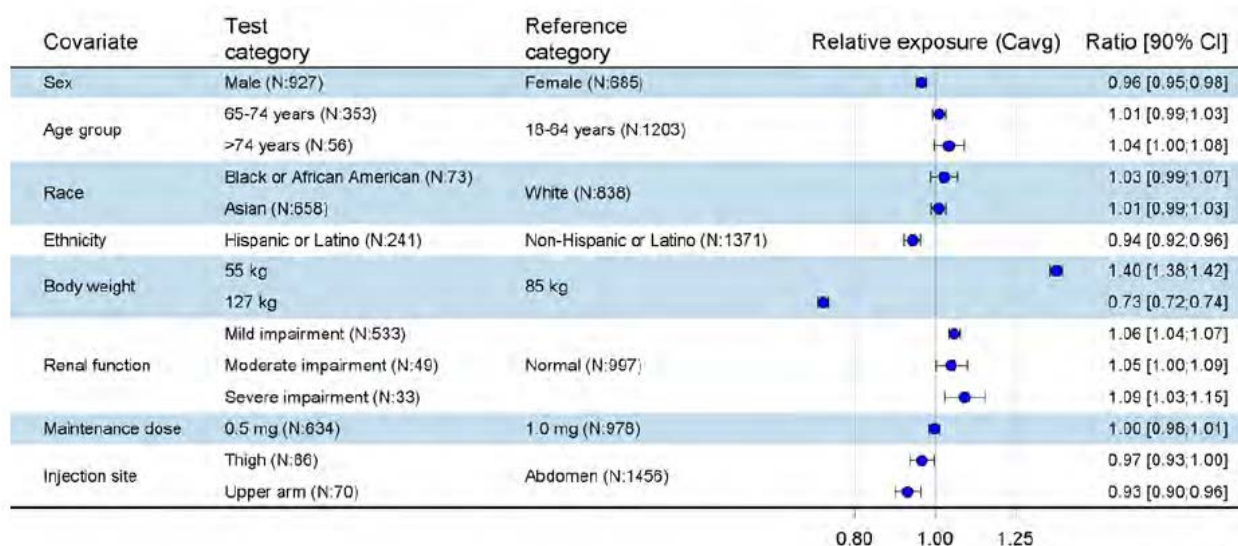
	coef	exp(coef)	se(coef)	p-value
Dose	0.3290	1.3895	0.1400	0.0188
Baseline HbA1c	0.1852	1.2035	0.0340	5.30E-08
Baseline BMI	-0.0355	0.9651	0.0103	0.00057

The presence of a significant dose-response relationship in the context of other adverse events in combination with the applicant’s analysis (Appendix 5.5) suggests that a longer duration at lower doses before increasing the semaglutide dose for efficacy reasons may be warranted. Additionally the label must indicate the risk of retinopathy after treatment.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No, the proposed dosing regimen is based on response to treatment and tolerability which inherently takes into account interpatient differences in PK/PD for efficacy and safety. Therefore dosing adjustments based on exposure alone may be unnecessary. That being said, for most covariates of semaglutide exposure, there were very minimal effects (Figure 25). Body weight had the largest degree of change in clearance with the 95% confidence interval of effect on clearance falling between 73% and 140% relative to the population PK value of clearance.

Figure 25: Forest plot of covariate analysis for semaglutide exposure expressed as steady-state dose-normalized average semaglutide concentrations relative to a reference subject



(Source: Applicant's Population PK Report, Figure 1)

No alternative dosing regimen for semaglutide is required in T2DM patients with renal impairment and hepatic impairment.

No studies have been conducted by the Applicant to characterize the PK of semaglutide in pediatric patients.

Does renal impairment affect semaglutide pharmacokinetics?

Study NN9535-3616, a multicenter, single-dose, parallel-group, open-label study, was conducted to investigate the PK of semaglutide in 5 groups of subjects with normal renal function, and mild, moderate, severe, and end-stage renal impairment. Healthy subjects or patients with T2DM (n=9 in the renal impairment groups) were enrolled in the study (n=11/normal renal function group and n=8-16/renal impairment groups completed the study). The study was a 'reduced/staged study design'. Stage 1 of the study was conducted in subjects with normal renal function and subjects with severe and end-stage renal impairment (on hemodialysis). Only if the pre-defined 'no-effect' criterion was not met would Stage 2 of the study be conducted in subjects with mild and moderate renal impairment. Subjects were administered a single dose of 0.5 mg of semaglutide via a SC injection into the anterior region of the thigh. Demographic characteristics pertaining to body weight and sex was planned to be balanced between the 5 groups, and age was planned to be kept within an age range (as close as possible between the groups).

During review of Study NN9535-3616, the Reviewer noted that the classification of subjects into renal function/impairment groups was based on the creatinine clearance (CL_{CR}) classification from the previous Guidance for Industry (May 1998). The previous Guidance for Industry was

used since the study was initiated in February 2009. The Reviewer requested that the Applicant re-classify subjects based on the classification criteria for CL_{CR} outlined in the new Guidance for Industry (March 2010). Preceding this, the primary and secondary PK endpoints were to be reanalyzed. In the retrospective analysis, all statistical analyses are reported as 90%CI in comparison to the statistical analysis for the primary PK endpoint in the original submission which was reported as 95%CI (AUC_{0-last} and C_{max} was reported as 90%CI). Results from the reanalysis are only reported below (refer to Appendix 5.4 for results from the original analysis).

Table 13 outlines the allocation of subjects into renal function/impairment groups based on the estimation of CL_{CR} (glomerular filtration rate) using the Cockcroft & Gault formula based on the previous and current Guidance for Industry. In total 9 out of the 54 subjects changed renal function groups based on the current CL_{CR} classification criteria (3 subjects from normal renal function to mild impairment, 5 subjects from mild to moderate impairment, 1 subject from severe impairment (not requiring dialysis) to end-stage renal disease).

Table 13: Classification of renal function/impairment groups

Stage	Renal function group	Guidance for Industry (May 1998) ¹		Guidance for Industry (March 2010) ²	
		CL_{CR} (mL/min)	N	CL_{CR} (mL/min)	N
1	Normal	>80	14	≥90	11
2	Mild impairment	>50 – ≤80	10	60-89	8
3	Moderate impairment	>30 – ≤50	11	30-59	16
4	Severe impairment	≤30	10	15-29	9
5	End Stage Renal Disease (ESRD)	Requiring dialysis	9	<15 not on dialysis/ Requiring dialysis	10

Notes: CL_{CR} : estimated creatinine clearance based on the Cockcroft-Gault equation; N = number of subjects in PK analysis set.

(Source: Response to FDA IR 20170728, page 4)

The primary PK endpoint of the study was systemic exposure ($AUC_{0-\infty}$); the results of the statistical comparison of $AUC_{0-\infty}$ are presented in Table 14.

Table 14: Statistical analysis of the primary PK endpoint ($AUC_{0-\infty}$) and secondary PK endpoint (C_{max})

	Mild/ Normal (n=7-8/11)	Moderate/ Normal (n=15-16/11)	Severe/ Normal (n=9/11)	End-stage ² / Normal (n=10/11)
$AUC_{0-\infty}$: Primary analysis¹				
Point estimate of ratio	1.00	1.10	1.16	1.13
90% CI	0.86, 1.15	0.97, 1.26	1.01, 1.32	0.99, 1.28
C_{max}: Primary analysis¹				
Point estimate of ratio	0.88	0.88	0.89	0.80
90% CI	0.69, 1.11	0.71, 1.10	0.71, 1.12	0.65, 0.99

¹Statistical analysis was conducted using analysis of covariance (ANCOVA) with renal function group and sex as categorical factors and age and log (body weight) as continuous covariates. If 90% CI was within the pre-defined range of [0.70; 1.43] then 'no-effect' was concluded.

²Subjects with end-stage renal impairment did not undergo hemodialysis procedures during the 0-48 hr post-dose period (Source: Response to FDA IR 20170728, page 6)

Based on the primary analysis, the 'no-effect' criterion (90% CI for the ratio of $AUC_{0-\infty}$ contained within pre-defined range of 0.70 to 1.43) for semaglutide exposure was met for subjects with mild, moderate, severe, end-stage renal impairment and subjects with normal renal function. The primary analysis has been adjusted for age, sex, and body weight since an imbalance in the distribution of these demographic characteristics was evident among the 5 groups. Male subjects were the predominate sex in 4 groups, except for in the moderate renal impairment group (male to female, 1:1 ratio). Subjects with normal renal function (mean (SD): 53 (9.6) yrs and 87.3 (20.5) kg) and end-stage renal impairment (mean (SD): 50.1 (9.3) yrs and 94.6 (17.1) kg) were younger in age and had a larger body weight than the remaining 3 groups (mean range: 61.2 to 65.9 yrs and 74.4 to 81.6 kg).

After adjustment for demographic characteristics, a weak relationship between CL_{CR} and $AUC_{0-\infty}$ was evident, with observations of low creatinine clearance to higher $AUC_{0-\infty}$ ($p = 0.0414$). The Applicant reports that these observations are not considered to be clinically relevant since it corresponds to a 14% higher AUC in subjects with a creatinine clearance of 10 mL/min compared to subjects with a normal creatinine clearance (90 mL/min).

For C_{max} , a secondary PK endpoint, the 'no-effect' criterion was met only for subjects with moderate and severe renal impairment and subjects with normal renal function (Table 14). Overall, a 11-20% lower C_{max} in subjects with renal impairment was evident compared to

subjects with normal renal function. No linear relationship was observed between CL_{CR} and C_{max} ($p=0.0859$ adjusted analysis).

Across the 5 renal function/renal impairment groups, the apparent clearance of semaglutide was comparable (range (geometric mean): 0.039 to 0.049 L/hr). The terminal $t_{1/2}$ was comparable in the normal renal function group and mild and moderate renal impairment groups (range (geometric mean): 178 to 187 hr) and longer in the severe renal impairment group (geometric mean $t_{1/2}$ of 219 hr) and end-stage renal impairment group (geometric mean $t_{1/2}$ of 243 hr).

The Applicant reports that dialysis did not appear to affect the PK of semaglutide as the point estimate of the ratio (end-stage renal impairment/normal renal function; adjusted for demographic characteristics) without hemodialysis (AUC_{0-48} : 0.82 [0.65, 1.02]_{90%CI}) was overall comparable to the point estimate of the ratio during hemodialysis (AUC_{48-96} : 0.95 [0.79, 1.13]_{90%CI}).

The unbound fraction of semaglutide was low and similar across the normal renal function and renal impairment groups (normal renal function group, mean $f_u = 0.0006$, renal impairment groups, mean $f_u = 0.0007$).

The Reviewer notes that in a majority of subjects the percent extrapolation of AUC was greater than 20%. This is likely to be attributed to the relatively short PK sampling period in the study (20 days, approximately $3 \times t_{1/2}$). The short sampling period is likely to be due to challenges in recruitment and retention of this subject population in the study. Despite this, the overall results from the Phase 1 study are also supported by findings from Phase 3a studies in patients with T2DM with renal impairment.

Results from the population PK analysis of the phase 3 studies (NN9535-3623, NN9535-3626, NN9535-3624, NN9535-3744 and NN9535-4091) indicate little difference between patients with mild (1.06-fold increase in AUC), moderate (1.05-fold increase in AUC), and severe renal impairment (1.09-fold increase in AUC) and patients with normal renal function. See Appendix 5.3 for further details.

Renal impairment does not impact the PK of semaglutide in a clinically relevant manner and thereby dose adjustments of semaglutide are not needed in patients with T2DM with renal impairment. Based on the totality of results from the Phase 1 and Phase 3a studies the Applicant's conclusions are reasonable.

Does hepatic function affect semaglutide pharmacokinetics?

Study NN9535-3651, a multicenter, single-dose, parallel-group, open-label study, was conducted to investigate the PK of semaglutide in 4 groups of subjects with normal hepatic function and mild, moderate, and severe hepatic impairment. Healthy subjects or patients with T2DM ($n=2$ in

the hepatic impairment groups) were enrolled in the study (n= 18/normal hepatic function and n= 6-10/hepatic impairment groups completed the study). Subjects were administered a single-dose of 0.5 mg of semaglutide via a SC injection into the anterior aspect of the thigh. Demographic characteristics pertaining to age, gender, and body weight was planned to be balanced between the 4 groups (groups were comparable with respect to age, body weight, and gender (least balanced group with respect to gender was the moderate hepatic impairment group (8:2 female to male)). Subjects were allocated into the 3 hepatic impairment groups based on the Child-Pugh classification (Table 15).

Table 15: Classification of hepatic function/impairment groups

	Points Scored for Observed Findings		
	1	2	3
Encephalopathy*	None	1 or 2	3 or 4 [#]
Ascites	Absent	Slight	Moderate
Serum bilirubin (μmol/L) or serum bilirubin (mg/dL)	< 34.2 <2	34.2–51.3 2–3	>51.3 >3
Serum albumin (g/L) or serum albumin (g/dL)	> 35 >3.5	28–35 2.8–3.5	<28 <2.8
Prothrombin time (sec prolonged)	<4	4–6	>6

*Grade 0: normal consciousness, personality, neurological examination, electro encephalogram.

*Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.

*Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.

*Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

*Grade 4: unrousable coma, no personality/behaviour, decerebrate, slow 2–3 cps delta activity.

#Subjects with encephalopathy grade 3 and 4 are excluded.

Conversion from points to groups of different degrees of hepatic impairment:

- Child-Pugh Grade A, mild hepatic impairment (5–6 points)
- Child-Pugh Grade B, moderate hepatic impairment (7–9 points)
- Child-Pugh Grade C, severe hepatic impairment (10–15 points)

(Source: Clinical study report NN9535-3651, page 31)

The primary PK endpoint was systemic exposure ($AUC_{0-\infty}$); the results of the statistical comparison of $AUC_{0-\infty}$ are presented in Table 16.

Table 16: Statistical analysis of the primary PK endpoint ($AUC_{0-\infty}$) and secondary PK endpoint (C_{max})

	Mild/Normal (n=8/17 ¹)	Moderate/Normal (n=10/17 ¹)	Severe/Normal (n=7/17 ¹)
$AUC_{0-\infty}$: Primary analysis^{2,3}			
Point estimate of ratio	0.95	1.02	0.97
90% CI	0.77, 1.16	0.93, 1.12	0.84, 1.12
C_{max}: Secondary analysis²			
Point estimate of ratio	0.99	1.02	1.15
90% CI	0.80, 1.23	0.88, 1.18	0.89, 1.48

¹For statistical analysis of C_{max} the normal hepatic function group had n=18 subjects

²Statistical analysis was conducted using a linear normal model (ANOVA) with log(body weight) and age as continuous covariates and gender and hepatic function group as categorical factors.

³If the 90% CI was within the pre-defined range of [0.70; 1.43] then 'no-effect' was concluded

(Source: Clinical study report NN9535-3651, page 81 and 84)

The estimated ratios of the mean $AUC_{0-\infty}$ for each hepatic impairment groups and normal hepatic function group was close to 1. For all hepatic impairment groups, the 90% CI for the estimated ratio of the mean total exposure of semaglutide was within the pre-defined 'no-effect' criterion of 0.70 to 1.43. No trend was observed for total exposure of semaglutide and hepatic function/impairment groups (Figure 26). No statistically significant association between $AUC_{0-\infty}$ and serum albumin, serum total bilirubin, and plasma prothrombin time prolongation was observed.

For C_{max} , a secondary PK endpoint, the estimated ratios of the mean C_{max} for the mild and moderate hepatic impairment groups and normal hepatic function group was close to 1. Peak concentration of semaglutide was 15% higher in subjects with severe hepatic impairment compared to subjects with normal hepatic function, and the 90% CI for estimated ratio of mean C_{max} was 0.89, 1.48. The Applicant reports that these observations are due to a single subject having an extreme C_{max} value. Following a sensitivity analysis, which excluded the extreme C_{max} value, the estimated ratio of the mean C_{max} for subjects with severe hepatic impairment and subjects with normal hepatic function was close to 1 (1.05 [0.88, 1.25]_{90%CI}). No trend was observed for peak concentration of semaglutide and hepatic function/impairment groups (Figure 26). No statistically significant association between C_{max} and serum albumin, serum total bilirubin, and plasma prothrombin time prolongation was evident.

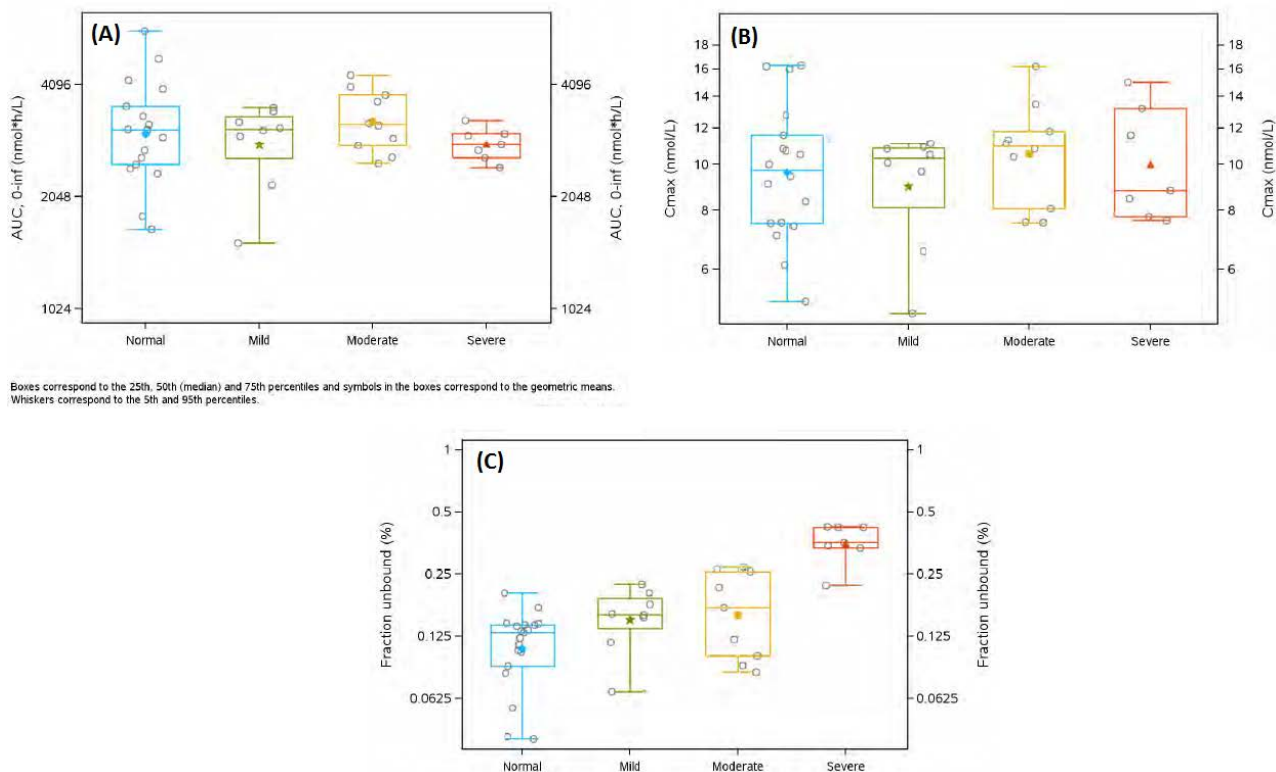


Figure 26: (A) Total exposure of semaglutide, (B) peak concentrations of semaglutide, and (C) fraction unbound (based on *in vitro* assessment) stratified by hepatic function/impairment groups

(Source: Clinical study report NN9535-3651, page 80, 87, 89)

The estimated mean fraction unbound of semaglutide (based on *in vitro* settings) was low across the hepatic function/impairment groups (0.12%, 0.16%, 0.17%, and 0.36% in the normal hepatic function, mild, moderate, and severe hepatic impairment groups, respectively). Under *in vitro* setting an increase in fraction unbound of semaglutide was evident with increasing degree of hepatic function (Figure 26). The Applicant reports that these results need to be interpreted with caution as *in vitro* setting is not likely to be predictive of the *in vivo* protein binding properties of semaglutide.

The Applicant concludes that hepatic impairment does not impact the exposure of semaglutide and thereby dose adjustments of semaglutide are not needed in patients with T2DM with hepatic impairment; the Reviewer is in agreement with the Applicant's conclusions.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No clinically relevant drug-drug interactions were observed between semaglutide and any of the evaluated co-administered drugs, therefore no dose adjustments are proposed when co-

administered with semaglutide. *In vitro* studies showed semaglutide to have a very low potential to inhibit or induce cytochrome P450 enzymes, and to inhibit drug transporters (P-gp, BCRP, OCT2, OAT1, OAT3). Semaglutide did partially inhibit OATP1B1 and OATP1B3, however the potential for clinically relevant interactions between semaglutide and OATP1B1/1B3 transporters is considered to be low.

Different Injection Sites

The population PK analysis suggested that BA decreased approximately 3% for injection into the thigh compared to the abdominal skin and that BA decreased approximately 8% for injection into the upper arm compared to in the abdominal skin. See appendix 5.3 for further details.

Cytochrome P450 inhibition potential of semaglutide

The potential inhibitory effect of semaglutide on human drug metabolizing cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5) was assessed *in vitro* using cryopreserved human hepatocytes. CYP-dependent activities were determined via monitoring the enzyme specific metabolite formation of individual marker substrates. For each CYP isozyme, formation of metabolite of the marker substrate in absence (0 μ M, solvent control) and presence of semaglutide (0.0005, 0.0015, 0.005, 0.015, 0.05, 1.5, 5 μ M for CYP1A2, -2B6, -2C8, -2C9, -2C19, -2D6 and 0.04, 0.12, 0.4, 1.2, 4, 12, 40 μ M for CYP3A4/5) was measured in duplicates. Both direct inhibition and time-dependent inhibition was assessed. Incubations with a selective inhibitor for each isozyme (both direct inhibition positive control and metabolism-dependent inhibition positive control) was conducted for confirmation of enzymatic activity.

Semaglutide IC₅₀ values (concentration of an inhibitor that causes a 50% decrease in enzyme activity) for direct and time-dependent inhibitions of CYP isozymes are presented in Table 17. Under the experimental conditions examined, semaglutide showed little or no evidence of direct or time-dependent inhibition of any of the CYP enzymes investigated, as evident by a lack of any concentration-dependent decrease in enzyme activity. The IC₅₀ values of >5 μ M for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and >40 μ M for CYP3A4/5 reported are the highest concentrations evaluated for each CYP isozyme.

Table 17: Semaglutide IC₅₀ for direct and time-dependent inhibitions of CYP isozymes

CYPs	Marker Substrate (μM) ¹	Isoform-Catalyzed Reaction	Direct Inhibition ² (IC ₅₀)	Time-Dependent Inhibition ² (IC ₅₀)
1A2	Phenacetin (40 μM)	O-dealkylation	>5 μM	>5 μM
2B6	Bupropion (50 μM)	Hydroxylation	>5 μM	>5 μM
2C8	Amodiaquine (7 μM)	N-dealkylation	>5 μM	>5 μM
2C9	Diclofenac (6 μM)	4'-hydroxylation	>5 μM	>5 μM
2C19	S-Mephenytoin (40 μM)	4'-hydroxylation	>5 μM	>5 μM
2D6	Dextromethorphan (7.5 μM)	O-demethylation	>5 μM	>5 μM
3A4/5	Testosterone (70 μM)	6β-hydroxylation	>40 μM	>40 μM
3A4/5	Midazolam (4 μM)	1'-hydroxylation	>40 μM	>40 μM

¹Concentrations of marker substrates were based on the K_m or S₅₀ values that were determined previously using human liver microsomes. For amodiaquine, a concentration of substrate exceeding the previously determine K_m value in human liver microsomes was used.

²When an IC₅₀ value falls outside the concentration range studies, the IC₅₀ value are reported to be greater than the highest concentration of semaglutide evaluated.

(Source: Summarized data, Study number XT135105, page 17, 36, 39)

For CYP2C8, CYP2C9, and CYP3A4/5 (as measured by midazolam) isozymes, semaglutide appeared to increase the enzyme activity and increase the enzyme's effectiveness with increasing concentrations of semaglutide (Figure 27). The Applicant reports that it is not uncommon to see non-Michaelis Menten kinetics for CYP enzymes *in vitro*, however the clinical relevance of this observation remains inconclusive.

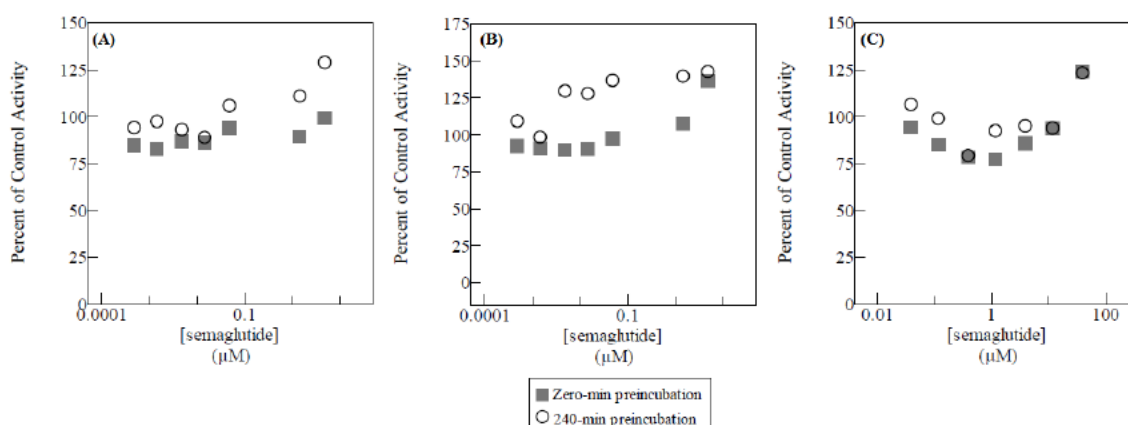


Figure 27: Inhibition of (A) CYP2C8, (B) CYP2C9, (C) CYP3A4/5 (midazolam) in human hepatocytes by semaglutide: IC₅₀ determination

(Source: Study number XT135105, page 30, 31, 35)

The Applicant concludes that semaglutide at concentrations up to either 5 μM or 40 μM (for CYP3A4/5) had little or no evidence of direct or time-dependent inhibition of any of the CYP enzymes studied (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5). The Applicant reports that *in vitro* studies showed semaglutide to have a very low potential to inhibit cytochrome P450 enzymes and we agree with the Applicant's conclusions.

Cytochrome P450 induction potential of semaglutide

The potential inductive effects of semaglutide on human drug metabolizing cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP3A4/5) was assessed *in vitro* using 3 preparations of cryopreserved human hepatocytes. The CYP isozyme inducer and marker substrate pairs were as follows:

- Omeprazole (50 μM) and phenacetin (100 μM), respectively, for CYP1A2
- Phenobarbital (750 μM) and bupropion (500 μM), respectively, for CYP2B6
- Rifampin (20 μM) and midazolam (30 μM), respectively, for CYP3A4/5

Cultured human hepatocytes were treated once daily for 3 consecutive days with dimethyl sulfoxide (DSMO, 0.1% v/v, vehicle control), flumazenil (25 μM , negative control), 1 of 8 concentrations of semaglutide (0.03, 0.1, 0.3, 1, 3, 5, 10, or 15 μM) or 1 of 3 human CYP inducers. Twenty-four hours following treatment, the hepatocyte cells were incubated *in situ* with marker substrates for the analysis of phenacetin *O*-dealkylation, bupropion hydroxylation, and midazolam 1'-hydroxylation (in triplicates). The effect of semaglutide on CYP1A2, CYP2B6, and CYP3A4 mRNA levels (in triplicates) and potential of semaglutide to cause cytotoxicity was also assessed.

The effect of semaglutide on human CYP isozyme activity and mRNA levels is presented in Table 18. Under the experimental conditions examined, semaglutide had little or no effect (>0.5-fold change and <2.0-fold change) on CYP1A2, CYP2B6, and CYP3A4/5 activity and mRNA levels regardless of semaglutide concentrations (ranging from 0.03 to 15 μM). Treatment of cultured human hepatocytes with up to 15 μM semaglutide showed little or no increase in release of lactate dehydrogenase (LDH, <5%), marker for cytotoxicity.

Table 18: Effect of semaglutide treatment on CYP enzyme activity and mRNA levels

CYPs	Substrate (µM)	Marker Substrate (Isoform-Catalyzed Reaction)	Enzyme Activity: Fold Change in Activity ³	Enzyme mRNA Levels: Fold Change
1A2	Semaglutide (0.03 to 15 µM)	Phenacetin, 100 µM (<i>O</i> -dealkylation)	Little or no effect; 0.670- to 1.06-fold change	Little or no effect; 0.631- to 1.17-fold change
	Flumazenil (25 µM) ¹		Little or no effect; 0.798- to 1.03-fold change	Little or no effect; 0.685- to 1.07-fold change
	Omeprazole (50 µM) ²		Increase; 16.1- to 51.3-fold change	Increase; 29.2- to 66.3-fold change
2B6	Semaglutide (0.03 to 15 µM)	Bupropion, 500 µM (Hydroxylation)	Little or no effect; 0.686- to 1.58-fold change	Little or no effect; 0.681- to 1.31-fold change
	Flumazenil (25 µM) ¹		Little or no effect; 0.815- to 1.07-fold change	Little or no effect; 0.746- to 0.973-fold change
	Phenobarbital (750 µM) ²		Increase; 4.35- to 11.6-fold change	Increase; 6.04- to 10.6-fold change
3A4/5	Semaglutide (0.03 to 15 µM)	Midazolam, 30 µM (1'-hydroxylation)	Little or no effect; 0.742- to 1.44-fold change	Little or no effect; 0.805- to 1.51-fold change
	Flumazenil (25 µM) ¹		Little or no effect; 0.892- to 1.16-fold change	Little or no effect; 0.732- to 1.60-fold change
	Rifampin (20 µM) ²		Increase; 5.41- to 15.1-fold change	Increase; 12.7- to 48.4-fold change

¹Negative control

²Positive control

³CYP1A2: Phenacetin *O*-dealkylation activity; CYP2B6: Bupropion hydroxylation activity; CYP3A4/5: Midazolam 1'-hydroxylation activity

(Source: Summarized data, Study number XT153005, page 17-19, 26-28, 30, 36-47)

The Applicant concludes that treatment of cultured human hepatocytes with semaglutide concentrations up to 15 μM caused little or no change in the enzymatic activity or on the mRNA levels of CYP1A2, CYP2B6, and CYP3A4/5. The Applicant reports that *in vitro* studies showed semaglutide of having a very low potential to induce cytochrome P450 enzymes and we agree with the Applicant's conclusions.

Transporter inhibition potential of semaglutide

The potential inhibitory effect of semaglutide on human ATP-binding cassette (ABC) transporters (P-gp and BCRP) and human solute carrier (SLC) transporters (OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) was investigated in an *in vitro* setting.

The inhibition of P-gp function (bidirectional transport across Caco-2 cells) and BCRP function (bidirectional transport across MDCKII-BCRP and control MDCKII cells) by semaglutide (0.6 and 6 μM) was assessed using digoxin as a P-gp probe substrate and prazosin as a BCRP probe substrate. Valspodar and Ko143 were used as positive control inhibitors of P-gp and BCRP transporters, respectively. The inhibition of OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 function (HEK293 cells; accumulation of the probe substrate into transporter and control cells) by semaglutide (0.5 and 5 μM for OATP1B1/1B3; 0.05 and 0.5 μM for OAT1, OAT3, OCT2) was assessed using the following probe substrates, estradiol-17 β -glucuronide for OATP1B1/1B3, *p*-aminohippurate for OAT1, estrone-3-sulfate for OAT3, and metformin for OCT2 transporters. Rifampin, probenecid, and quinidine were used as positive control inhibitors of the OATP1B1/1B3, OAT1/3, and OCT2 transporters, respectively. Each incubation experiment was conducted in the absence and presence of 0.1% BSA, since non-specific binding of semaglutide to incubation equipment was reduced with 0.1% BSA.

The potential of semaglutide to inhibit P-gp, BCRP transporters and OATP1B1/1B3, OCT2, OAT1/3 transporters are presented in Table 19 and 20, respectively. Under the experimental conditions examined, results suggest that semaglutide is not an inhibitor of P-gp (<3% inhibition for both doses), BCRP (<20% inhibition for both doses), OCT2 (<25% inhibition, not concentration-dependent), OAT1 (<32% inhibition, not concentration-dependent), and OAT3 (<16% inhibition, not concentration-dependent) transporters. However, results do suggest that semaglutide may inhibit human SLC transporters, OATP1B1 (0% and 44% inhibition for the 0.5 and 5 μM doses, respectively) and OATP1B3 (20% and 67% inhibition for the 0.5 and 5 μM doses, respectively (absence of BSA); 2% and 22% inhibition for the 0.5 and 5 μM doses, respectively (presence of BSA)).

Table 19: Inhibition of P-gp and BCRP transporters in the presence of semaglutide and respective positive controls

Transporters	Probe Substrate	Inhibitor	Efflux Ratio ¹ of Solvent Control Compared to Inhibitor	% Inhibition ⁴
P-gp	Digoxin (10 µM)	Semaglutide (0.6 and 6 µM)	No/minor reduction	<u>Absence, presence BSA:</u> <3%
		Valspodar (1 µM)	Reduced from 50.6 ² to 1.81	<u>Absence BSA:</u> 98%
			Reduced from 46.0 ² to 1.34	<u>Presence BSA:</u> 99%
BCRP	Prazosin (1 µM)	Semaglutide (0.6 and 6 µM)	No/minor reduction ³	<u>Absence, presence BSA:</u> <20%
		Ko143 (1 µM)	Reduced from 7.18 ² to 1.04 ³	<u>Absence BSA:</u> 99%
			Reduced from 6.95 ² to 1.12 ³	<u>Presence BSA:</u> 98%

¹Efflux Ratio: P_{app} (basal to apical)/ P_{app} (apical to basal)

²Efflux ratio of solvent control

³Based on corrected efflux ratio

⁴Absence BSA = low concentration of BSA (0.0001%) and Presence BSA = 0.1% BSA

P_{app} : Apparent permeability

(Source: Summarized data, Study number XT158008, page 30-31, 35-38)

Table 20: Inhibition of OATP1B1/1B3, OCT2, and OATP1/3 in the presence of semaglutide and respective positive controls

Transporters	Probe Substrate	Inhibitor	%Inhibition of Transporter-Specific Uptake Rate of Probe Substrate by Inhibitor Compared to Solvent Control ¹
OATP1B1	Estradiol-17 β -glucuronide (50 nM)	Semaglutide (0.5 and 5 μ M)	<u>Absence BSA</u> : 0% (0.5 μ M) and by 44% (5 μ M) <u>Presence BSA</u> : No inhibition (0.5 and 5 μ M) ²
		Rifampin (10 μ M)	<u>Absence BSA</u> : by 93% <u>Presence BSA</u> : by 96%
OATP1B3	Estradiol-17 β -glucuronide (50 nM)	Semaglutide (0.5 and 5 μ M)	<u>Absence BSA</u> : by 20% (0.5 μ M) and by 67% (5 μ M) <u>Presence BSA</u> : by 2% (0.5 μ M) and by 22% (5 μ M) ²
		Rifampin (10 μ M)	<u>Absence BSA</u> : by 98% <u>Presence BSA</u> : by 100%
OCT2	Metformin (10 μ M)	Semaglutide (0.05 and 0.5 μ M)	<u>Absence and presence BSA</u> : by <25%, not concentration-dependent
		Quinidine (300 μ M)	<u>Absence BSA</u> : by 80% <u>Presence BSA</u> : by 65%
OAT1	<i>p</i> -aminohippurate (1 μ M)	Semaglutide (0.05 and 0.5 μ M)	<u>Absence BSA</u> ³ : by <32%, not concentration-dependent
		Probenecid (100 μ M)	<u>Absence BSA</u> ³ : by 88%
OAT3	Estrone-3-sulfate (0.05 μ M)	Semaglutide (0.05 and 0.5 μ M)	<u>Absence BSA</u> ³ : by <16%, not concentration-dependent
		Probenecid (100 μ M)	<u>Absence BSA</u> ³ : by 94%

¹Absence BSA = low concentration of BSA (0.0001%) and Presence BSA = 0.1% BSA

²The Applicant reports that the reduced inhibition in the presence of BSA (0.1%) may be attributed to a reduction in the free concentration of semaglutide due to protein binding

³Due to the lower uptake of the probe substrate in the presence of BSA (0.1%), the inhibition of semaglutide and positive control was only conducted in the absence of BSA. The Applicant reports that the lower uptake of the probe substrate in the presence of BSA (0.1%) is most likely attributed to a reduction in the free concentration due to protein binding.

(Source: Summarized data, Study number XT158008, page 31-32, 39-43)

The IC₅₀ determination for OATP1B1/1B3 inhibition by semaglutide was assessed in the presence of semaglutide (0.1 to 10 μM), estradiol-17β-glucuronide (50 nM, probe substrate), and rifampin (10 μM) and cyclosporine (1 μM) (positive control inhibitors).

For OATP1B1, the transporter-specific uptake of estradiol-17β-glucuronide into OATP1B1-expressing cells was reduced from 1.27 pmol/mg/min to 0.506 pmol/mg/min, thereby a 60% inhibition, in the presence of semaglutide. The calculated IC₅₀ value for OATP1B1 was 3.50 μM (Figure 28(A)). In the presence of 10 μM semaglutide and 0.1% BSA, the uptake of estradiol-17β-glucuronide into OATP1B1-expressing cells was reduced from 1.63 pmol/mg/min to 0.920 pmol/mg/min (a 44% inhibition).

For OATP1B3, in the presence of semaglutide the transporter-specific uptake of estradiol-17β-glucuronide into OATP1B3-expressing cells was reduced from 0.214 pmol/mg/min to 0.0606 pmol/mg/min, thereby a 72% inhibition. The calculated IC₅₀ value for OATP1B3 was 2.95 μM (Figure 28(B)). In the presence of 10 μM semaglutide and 0.1% BSA, the uptake of estradiol-17β-glucuronide into OATP1B3-expressing cells was reduced from 0.152 pmol/mg/min to 0.0870 pmol/mg/min (a 43% inhibition).

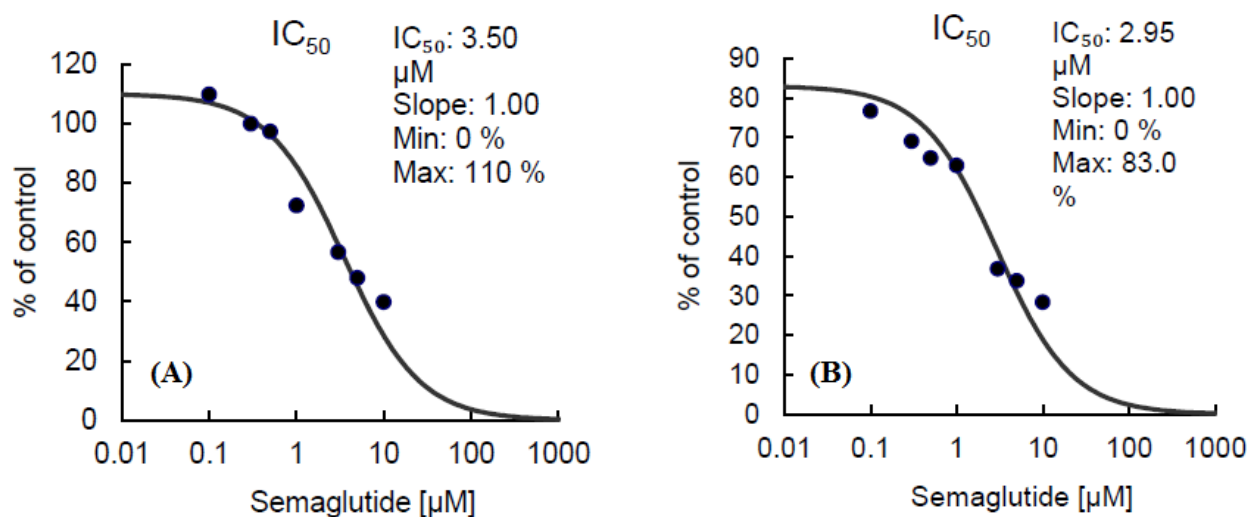


Figure 28: IC₅₀ determination profiles for semaglutide for (A) OATP1B1 transporter and (B) OATP1B3 transporter

(Source: Study number XT158008, page 57-58)

The Applicant concludes that under the conditions evaluated, semaglutide is not an inhibitor of human ABC transporters P-gp and BCRP, nor is it an inhibitor of the human SLC transporters OCT2, OAT1, and OAT3. Semaglutide however did partially inhibit OATP1B1 and OATP1B3 transporters with an IC₅₀ value of 3.50 μM (3500 nmoL/L) and 2.95 μM (2950 nmoL/L), respectively. The Applicant reports that the potential for clinically relevant interactions of semaglutide on OATP1B1/1B3 transporters is considered to be low since the estimated IC₅₀

values are approximately 100-fold above the expected steady-state C_{\max} for semaglutide (~33 nmol/L at 1 mg once weekly dosing). Therefore, semaglutide is not expected to cause any clinically relevant drug-drug interactions related to inhibition of human drug transporters and we agree with the Applicant's conclusions.

Effect of semaglutide on the pharmacokinetics of co-administration drugs

A known effect of GLP-1 and GLP-1 analogues is a potential delay in gastric emptying which could influence the PK of concomitantly administered drugs. The Applicant evaluated the effect of semaglutide on gastric emptying as part of a randomized, single-center, multiple-dose, double-blind, two-period, placebo-controlled, cross-over trial in obese, non-diabetic subjects. Subjects were randomized (1:1 ratio) to receive either 1 of 2 different treatment orders, semaglutide followed by placebo treatment or placebo followed by semaglutide treatment (n=30 randomized).

Each treatment period was 12 weeks in duration and subject were administered semaglutide 0.25 mg once weekly for 4 weeks, followed by 0.5 mg once weekly for 4 weeks, and followed by 1 mg semaglutide once weekly for 4 weeks or matching placebo. Subjects received a 5th dose of 1 mg semaglutide/placebo at the end of the 12 week period (at steady-state conditions). This dose was administered 12 hrs prior to start of a 5 hr standardized meal test. The standardized meal had a total energy content of 600 kcal (macronutrient composition: 30 E% fat, 15 E% protein, 55 E% carbohydrate). For assessment of gastric emptying, paracetamol (1500 mg) was included in the yoghurt part of the meal. Subjects were instructed to consume the meal within 15 minutes.

Mean plasma concentration-time profiles for paracetamol after 12 weeks of treatment with semaglutide or placebo are presented in Figure 29. Statistical analysis for the PK endpoints for assessment of gastric emptying (supportive secondary endpoints of the study) is presented in Table 21.

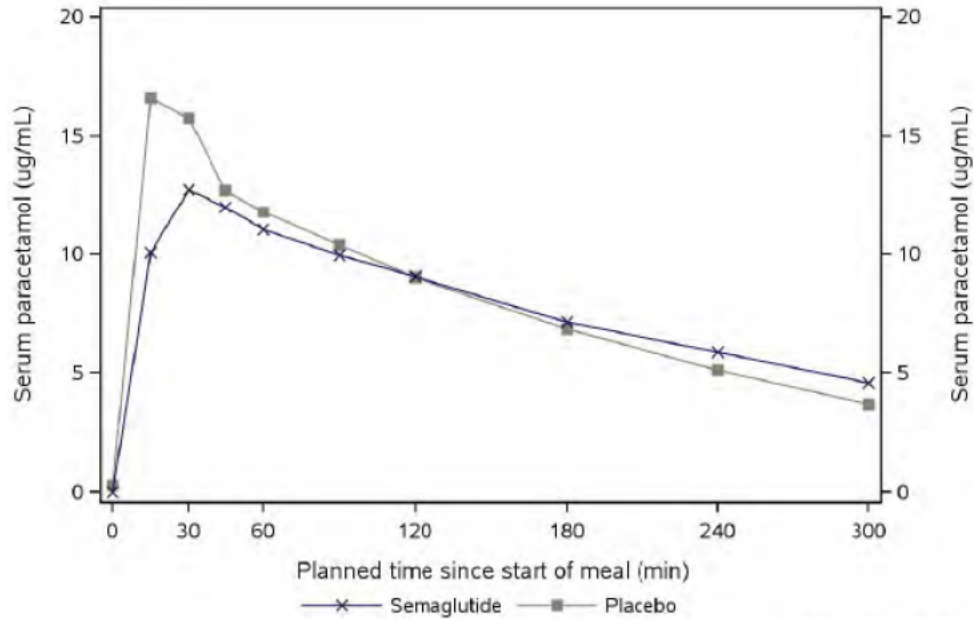


Figure 29: Mean paracetamol plasma concentration-time profile after 12 weeks of treatment with semaglutide or placebo in obese, non-diabetic subjects (note the y-axis legend should read plasma paracetamol and not serum paracetamol)

(Source: Clinical study report NN9535-3685, page 171)

Table 21: Statistical analysis for PK endpoints for paracetamol

PK Parameter	n (semaglutide/placebo)	Treatment Ratio ¹ (semaglutide/placebo): Point estimate	95% CI	p-value
AUC _{0-1hr}	28/28	0.73	0.61, 0.87	0.0012
AUC _{0-5hr}	28/28	0.94	0.88, 1.01	0.1081
C _{max}	28/28	0.77	0.67, 0.88	0.0006

¹Linear mixed model with treatment and treatment period as fixed effect and subject as random effect

(Source: Clinical study report NN9535-3685, page 172)

Peak concentrations of paracetamol were 23% lower and early exposure of paracetamol (1 hr post-dose) was 27% lower in subjects treated with semaglutide compared to placebo. Total exposure of paracetamol (5 hr post-dose) was comparable in subjects treated with semaglutide and placebo. A sensitivity analysis for AUC_{0-5hr}, which excluded data from a subject who received an incorrect dispensing unit number (DUN), 4 subjects who did not complete the meal, and 1 subject who had a positive baseline value for paracetamol, showed similar results to that of the primary analysis. Median time to peak concentrations of paracetamol was 0.5 hr and 0.29 hr after start of the standardized meal in subjects treated with semaglutide and placebo, respectively.

The results suggested a delay in gastric emptying during the early postprandial phase for subjects treated with semaglutide compared with placebo; however no overall delay in gastric emptying was evident over the postprandial period.

Based on these observations, several drug-drug interactions were conducted to assess the extent to which the delay in gastric emptying by semaglutide would impact the PK profiles of concomitantly administered drugs.

Summary of the drug-drug interaction study designs are presented in Table 22.

Table 22: Summary of pharmacokinetic drug-drug interaction study design

Study Design	Patient Population	Co-administered Drug (BCS Class Classification)	Dose	Dosing Duration	n
Single-center, open-label, one sequence cross-over trial	Healthy subjects (male and female)	Semaglutide	0.25 mg, 0.5 mg, 1 mg	Each dose administered once weekly for 4 weeks initiating with the 0.25 mg dose. Two additional 1 mg doses was administered at steady-state	31 (exposed to the treatments); 26 (completed study)
		Atorvastatin (Low solubility, high permeability, Class II)	40 mg	Single-dose administered before semaglutide dosing and at steady-state of 1 mg semaglutide (around t_{max} of semaglutide)	
		Digoxin (Low solubility, permeability not easily determined Class II/IV; narrow therapeutic index)	0.5 mg		
Single-center, open-label, one sequence cross-over trial	Healthy subjects (male and female)	Semaglutide	0.25 mg, 0.5 mg, 1 mg	Each dose administered once weekly for 4 weeks initiating with the 0.25 mg dose. Two additional 1 mg doses was	24 (exposed to the treatments); 23 (completed)

				administered at steady-state	study
		Metformin (High solubility, low permeability, Class III)	500 mg	500 mg twice a day for 3.5 days to achieve steady-state conditions. Metformin was administered before semaglutide dosing and at steady-state of 1 mg semaglutide (around t_{max} of semaglutide)	
		Warfarin (Low/high solubility, high permeability, Class I/II; narrow therapeutic index)	25 mg	Single-dose administered before semaglutide dosing and at steady-state of 1 mg semaglutide (around t_{max} of semaglutide)	
Single-center, open-label, one sequence cross-over trial	Postmenopausal female patients with T2DM treated with diet and exercise alone and/or metformin monotherapy	Semaglutide	0.25 mg, 0.5 mg, 1 mg ¹	Each dose administered once weekly for 4 weeks initiating with the 0.25 mg dose. One additional 1 mg dose was administered at steady-state	43 (exposed to the treatments); 39 (completed study)
		EE and LN (low dose combination oral contraceptive)	0.03 mg of EE and 0.15 mg of LN	0.03 mg of EE and 0.15 mg of LN once daily for 8 days to achieve steady-state conditions. EE and LN was administered before semaglutide dosing and at steady-state of 1 mg semaglutide (around t_{max} of semaglutide)	

¹Actual doses administered were 0.24 mg, 0.51 mg, and 0.99 mg (due to the dosing device and injection volumes permitted)

BCS: Biopharmaceutics Classification System; EE: Ethinlyestradiol; LN: Levonorgesterol

(Source: Information summarized from Clinical study report NN9535-3818, Clinical study report NN9535-3817, Clinical study report NN9535-3819)

Geometric mean plasma concentration-time profiles for atorvastatin and digoxin administered alone and co-administered with semaglutide at steady-state are presented in Figure 30.

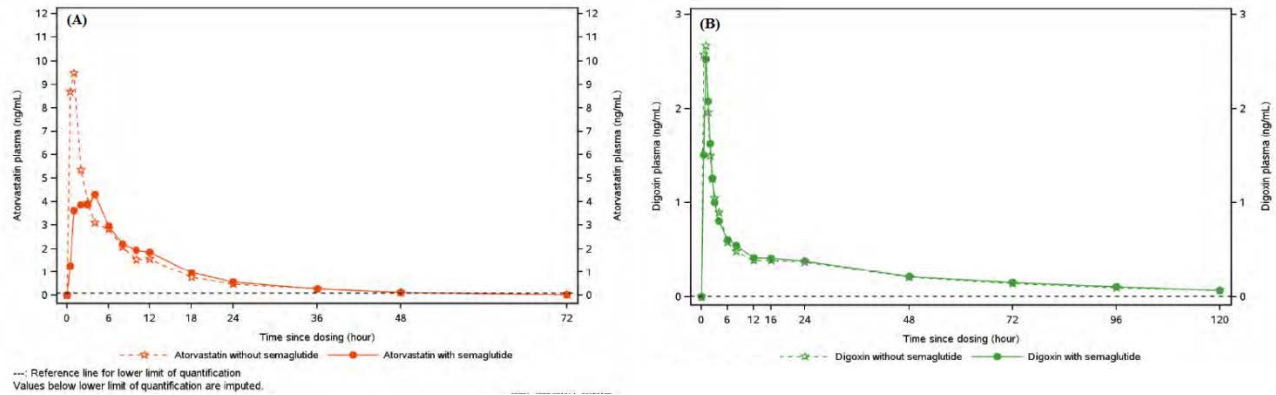


Figure 30: Geometric mean (A) atorvastatin and (B) digoxin plasma concentration-time profiles after single dose administration without semaglutide and with semaglutide (at steady-state)

(Source: Clinical study report NN9535-3818, page 81 and 84)

Geometric mean and mean plasma concentration-time profiles for metformin and warfarin administered alone and co-administered with semaglutide at steady-state are presented in Figure 31.

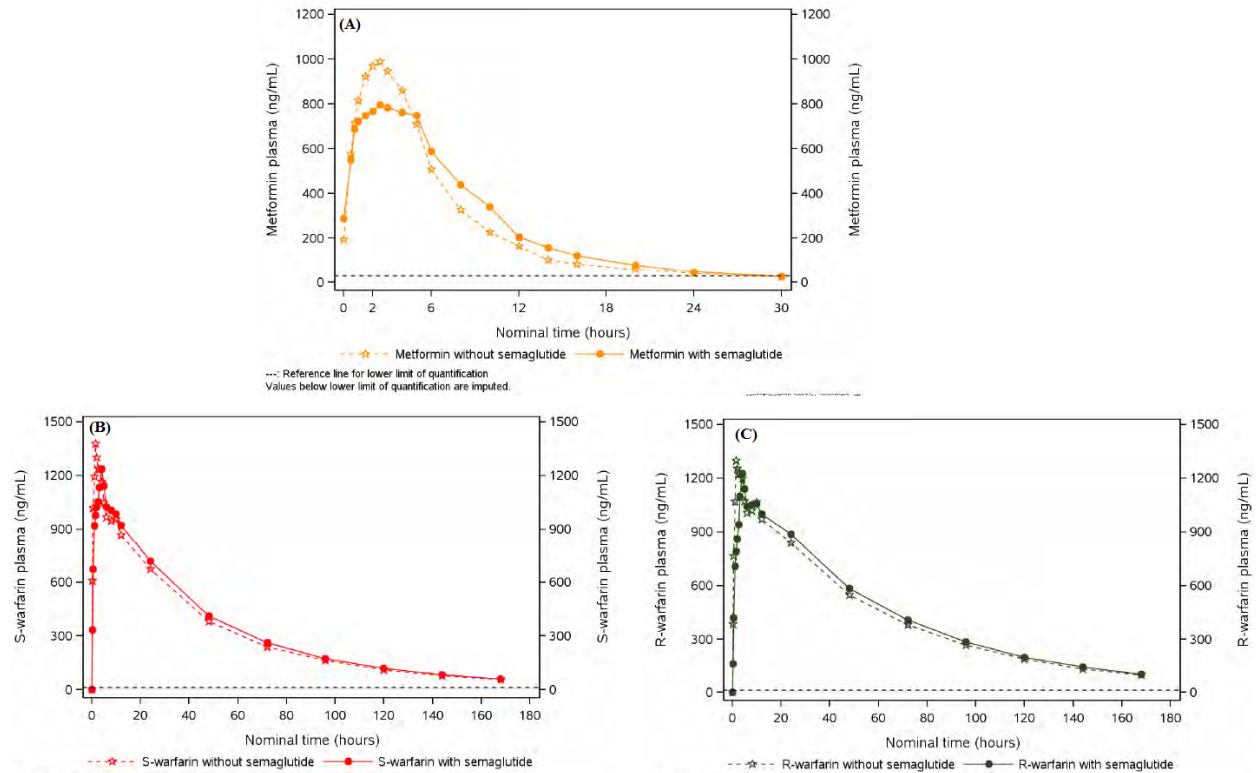


Figure 31: (A) Geometric mean plasma concentration-time profile for metformin after multiple dose administration, (B) mean plasma concentration-time profile for S-warfarin, and (C) geometric mean plasma concentration-time profile for R-warfarin after single dose of warfarin without semaglutide and with semaglutide (at steady-state)

(Source: Clinical study report NN9535-3817, page 83 and 86)

Mean plasma concentration-time profiles for EE and LN administered alone and co-administered with semaglutide at steady-state are presented in Figure 32.

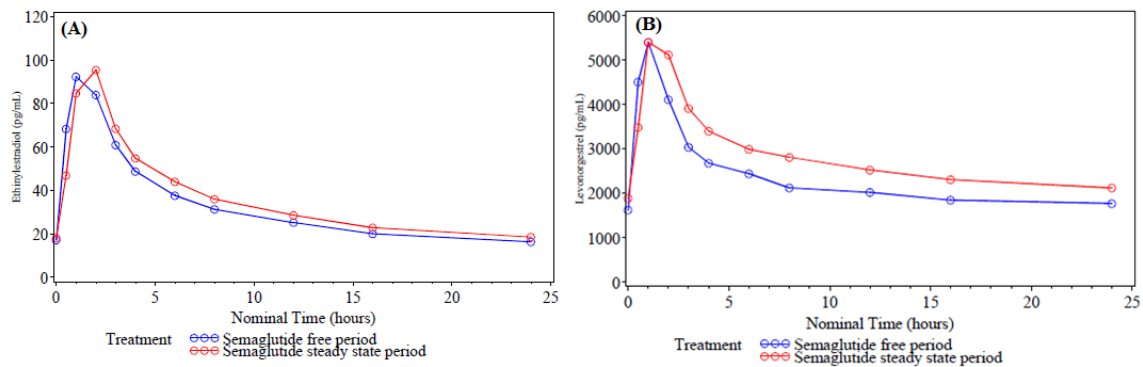


Figure 32: Mean 24 hr plasma concentration-time profiles of (A) EE and (B) LN after multiple dose administration without semaglutide and with semaglutide (at steady-state)

(Source: Clinical study report NN9535-3819, page 72)

Statistical analysis of the primary PK endpoint (AUC_{0-t}) and supportive secondary PK endpoint (C_{max}) from all studies are summarized in Table 23.

Table 23: Statistical analysis for primary PK endpoint (AUC_{0-t}) and supportive secondary PK endpoint (C_{max}) by co-administered drugs

Drug	PK Parameter	n (with/without semaglutide)	Treatment Ratio (with/without semaglutide): Point estimate ¹	90% CI
Atorvastatin	$AUC_{0-72hr,SD}$ ²	26/26	1.02	0.93, 1.12
	$C_{max,SD}$ ³	26/26	0.62	0.47, 0.82
Digoxin	$AUC_{0-120hr,SD}$	26/26	1.02	0.97, 1.08
	$C_{max,SD}$ ³	26/26	0.93	0.84, 1.03
Metformin	$AUC_{\tau,SS}$ ⁵	22/22	1.03	0.96, 1.11
	$C_{max,SS}$ ³	22/22	0.90	0.83, 0.98
S-Warfarin ⁴	$AUC_{0-168hr,SD}$	22/22	1.05	0.99, 1.11
	$C_{max,SD}$ ³	22/22	0.91	0.85, 0.98
R-Warfarin ⁴	$AUC_{0-168hr,SD}$	22/22	1.04	0.98, 1.10
	$C_{max,SD}$ ³	22/22	0.93	0.87, 1.00
Ethinylestradiol	$AUC_{\tau,SS}$ ⁶	37/37	1.11	1.06, 1.15
	$C_{max,SS}$ ³	37/37	1.04	0.98, 1.10
Levonorgestrel	$AUC_{\tau,SS}$ ⁶	40/40	1.20	1.15, 1.26
	$C_{max,SS}$ ³	40/40	1.05	0.99, 1.12

¹ANOVA model with treatment of semaglutide (with or without) and subjects as fixed factors

² AUC_{0-72hr} represents the area under the curve from 0 to last quantifiable observations during the 72 hrs (Response to IR, Resp_Req_Clin_Pharm_20170519, page 15)

³Supportive secondary PK endpoint

⁴Warfarin consists of 2 enantiomers: S-warfarin and R-warfarin

⁵tau was 12 hours

⁶tau was 24 hours

SS: At steady-state; SD: Single-dose

(Source: Results summarized from Clinical study report NN9535-3818, Clinical study report NN9535-3817, Clinical study report NN9535-3819)

Single-dose administration of atorvastatin (40 mg) at steady-state of semaglutide resulted in the ‘no-effect’ criterion for the primary PK endpoint of AUC_{0-72hr} being met as the 90% CI for the estimated ratio of AUC_{0-72hr} (with/without semaglutide) was within the pre-specified limit of 0.80 to 1.25. For atorvastatin, mean C_{max} was approximately 38% lower when co-administered under semaglutide steady-state conditions compared to administration alone. Time to peak concentration of atorvastatin (t_{max}) was delayed when atorvastatin was co-administered under semaglutide steady-state conditions compared to when administered alone (median values: 2 hr and 0.74 hr, respectively). The Reviewer concurs with the conclusion that the observed decrease in C_{max} is unlikely to be of clinical relevance as the efficacy of atorvastatin has been shown to be poorly correlated with C_{max} .

Single-dose administration of digoxin (0.5 mg) at steady-state of semaglutide resulted in the ‘no-effect’ criterion for the primary PK endpoint of $AUC_{0-120hr}$ being met as the 90% CI for the estimated ratio of $AUC_{0-120hr}$ (with/without semaglutide) was within the pre-specified limit of 0.80 to 1.25. For digoxin, mean C_{max} were comparable when co-administered under semaglutide steady-state conditions compared to administration alone.

Administration of metformin under steady-state conditions (500 mg twice a day for 3.5 days) with steady-state of semaglutide resulted in the ‘no-effect’ criterion for the primary PK endpoint of $AUC_{\tau,SS}$ and key secondary endpoint of $C_{max,SS}$ being met as the 90% CI for the estimated ratio of $AUC_{\tau,SS}$ and C_{max} (with/without semaglutide) was within the pre-specified limit of 0.80 to 1.25. A sensitivity analysis, excluding 2 subjects who were non-compliant with semaglutide treatment, showed similar results to that of the primary analyses (estimated ratio: 1.07 [1.00, 1.14]_{90%CI} for $AUC_{\tau,SS}$ and 0.94 [0.88, 1.01]_{90%CI} for $C_{max,SS}$).

Single-dose administration of warfarin (25 mg) at steady-state of semaglutide resulted in the ‘no-effect’ criterion for the primary PK endpoint of $AUC_{0-168hr}$ and key secondary endpoint of C_{max} for both S-warfarin and R-warfarin being met as the 90% CI for the estimated ratio of the respective $AUC_{0-168hr}$ and C_{max} (with/without semaglutide) was within the pre-specified limit of 0.80 to 1.25. A sensitivity analysis, excluding 2 subjects who were non-compliant with semaglutide treatment, showed similar results to that of the primary analyses (estimated ratio for $AUC_{0-168hr}$: 1.07 [1.02, 1.12]_{90%CI} for S-warfarin and 1.06 [1.01, 1.12]_{90%CI} for R-warfarin; estimated ratio for C_{max} : 0.93 [0.87, 1.00]_{90%CI} for S-warfarin and 0.96 [0.90, 1.02]_{90%CI} for R-warfarin). For both S-warfarin and R-warfarin the time to peak concentration was delayed when warfarin was co-administered under semaglutide steady-state conditions compared to when administered alone (S-warfarin: median t_{max} was 3 hr and 1 hr, respectively; R-warfarin: median t_{max} was 3.5 hr and 1.5 hr, respectively).

An additional key supportive secondary endpoint of the study was estimation of the international normalized ratio (INR) response of warfarin when co-administered with semaglutide compared to without semaglutide (Figure 33). The estimated ratio (with/without semaglutide) of $iAUC_{INR,0-}$

$_{168hr}$ (incremental) and maximum observed INR response for warfarin was 1.05 [0.87, 1.28] $_{90\%CI}$ and 1.04 [0.99, 1.10] $_{90\%CI}$, respectively. Sensitivity analysis overall showed comparable results to that of the primary analysis. No major changes in the overall or maximum anticoagulant effect of warfarin were observed when co-administered with semaglutide.

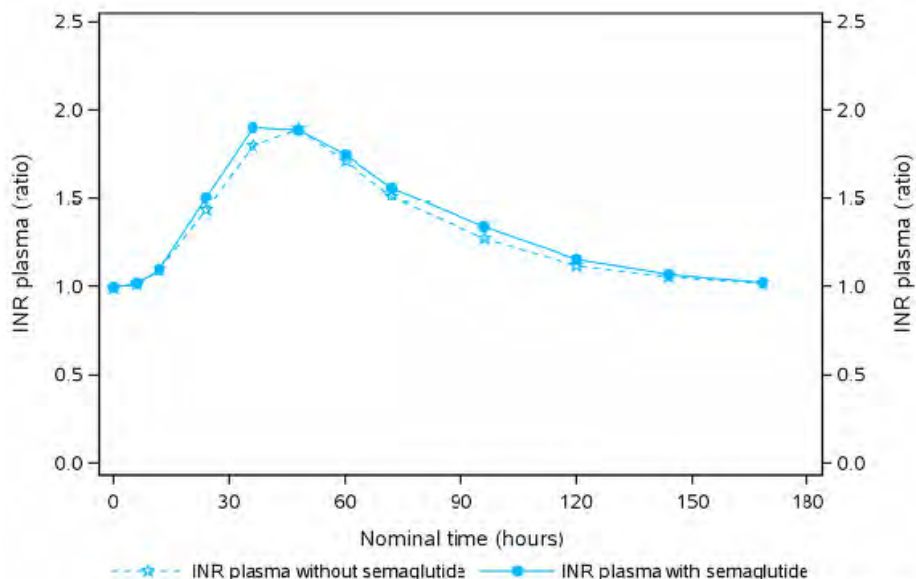


Figure 33: Mean INR plasma profile for warfarin when co-administered without and with semaglutide (at steady-state)

(Source: Clinical study report NN9535-3817, page 94)

Administration of EE under steady-state conditions (0.03 mg once daily for 8 days) with steady-state of semaglutide resulted in the ‘no-effect’ criterion for the primary PK endpoint of $AUC_{\tau,SS}$ ($\tau=24$ hr) being met as the 90% CI for the estimated ratio of $AUC_{\tau,SS}$ (with/without semaglutide) was within the pre-specified limit of 0.80 to 1.25. However, the ‘no-effect’ criterion was not met for the primary PK endpoint of $AUC_{\tau,SS}$ ($\tau=24$ hr) for LN under steady-state conditions (0.15 mg once daily for 8 days) since the 90% CI for the estimated ratio of $AUC_{\tau,SS}$ was outside the pre-specified limit (90%CI: 1.15, 1.26). Overall, for both EE and LN, a larger exposure (11% and 20%, respectively) was observed when co-administered with semaglutide compared to administration alone. For EE and LN, similar peak concentrations ($C_{max,SS}$) were observed when administered with and without semaglutide.

Inclusion of body weight (mean change from screening to follow-up visit for body weight was - 5.0 kg) as a covariate in the statistical model (post hoc analysis) explained some of the increase in exposure of LN (estimated ratio: 1.09 [1.01, 1.17] $_{90\%CI}$), however opposing results were observed for EE exposure (estimate ratio: 1.16 [1.07, 1.25] $_{90\%CI}$). Body weight had no appreciable influence on the estimates for $C_{max,SS}$ for both EE and LN. The Applicant overall

concludes that no clinically relevant changes in the overall exposure of EE and LN were observed in the study.

No clinically relevant drug-drug interactions were observed between semaglutide and any of the evaluated co-administered drugs and therefore no dose adjustments is required when co-administered with semaglutide. The proposed labelling language pertaining to the potential drug-drug interaction for orally administered medications is reasonable.

3.3.5 Is the clinical formulation of semaglutide used in the clinical pharmacology program similar to the to-be-marketed formulation?

The Applicant reports that throughout the clinical development program there were no changes to the formulation of semaglutide drug product. However, different concentrations of drug substance [REDACTED] (b) (4) based drug substance manufacturing processes were implemented during the clinical development program. In the Phase 1 and 2 studies, drug product strengths of 1, 3, 10, and 1.34 mg/mL [REDACTED] (b) (4) semaglutide were used. In the Phase 3a studies, drug product strength of 1.34 mg/mL with [REDACTED] (b) (4) semaglutide was administered to patients; this is the to-be-marketed drug product.

Studies were conducted to establish BE between (1) different drug product strengths (1, 3, and 10 mg/mL) and (2) different manufacturing processes for semaglutide [REDACTED] (b) (4). Bioequivalence was established between drug product strengths 1 mg/mL and 3 mg/mL and between [REDACTED] (b) (4) semaglutide. For the 10 mg/mL drug product strength, the primary PK endpoint (exposure) met the pre-defined acceptance criteria for comparisons 1 mg/mL vs. 10 mg/mL and 3 mg/mL vs. 10 mg/mL, however higher maximum concentrations of semaglutide and earlier t_{max} was observed for the 10 mg/mL drug product strength when compared to the lower strengths.

Drug product strengths

Mean geometric plasma concentration-time profiles for semaglutide stratified by drug product strengths are presented in Figure 34 (refer to Appendix 5.1 for description of Study NN9535-3687). Time to maximum concentrations appeared to occur earlier and maximum concentrations were higher with increasing drug product strength (median t_{max} of 60, 41.9, 12 hr and geometric mean C_{max} of 11.3, 13.1, and 16.2 nmol/L for 1 mg/mL, 3 mg/mL, and 10 mg/mL strengths, respectively). Terminal $t_{1/2}$ of semaglutide was similar for the different drug product strengths (geometric mean $t_{1/2}$ of 147, 152, 149 hrs for 1 mg/mL, 3 mg/mL, and 10 mg/mL strengths, respectively).

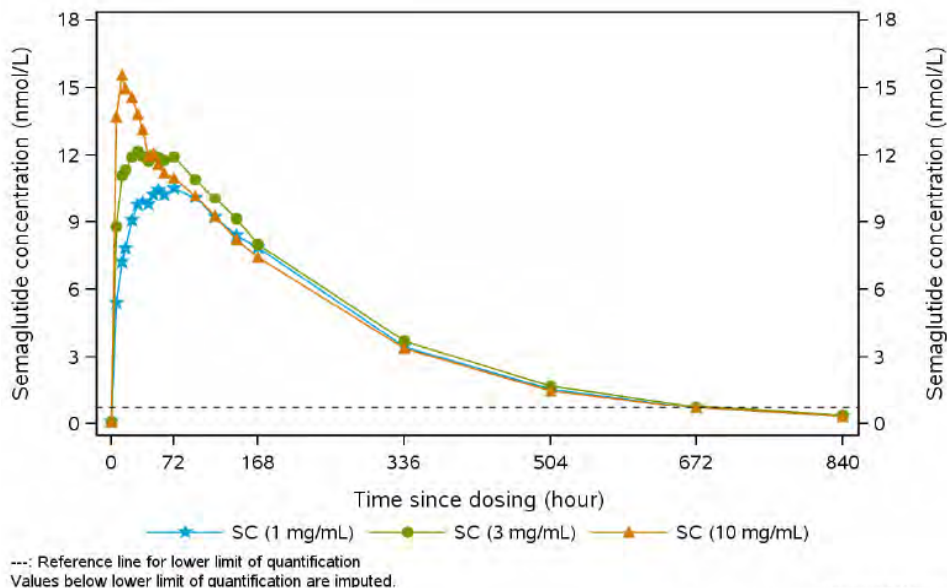


Figure 34: Mean geometric plasma concentration-time profiles for semaglutide following a 0.5 mg SC dose stratified by drug product strength (1, 3, 10 mg/mL)

(Source: Clinical study report NN9535-3687, page 94)

Statistical analysis for the primary PK endpoint ($AUC_{0-\infty}$) and key supportive secondary PK endpoint (C_{max}) is presented in Table 24. Bioequivalence was demonstrated between 2 drug product strengths of semaglutide (1 vs. 3 mg/mL, 1 vs. 10 mg/mL, 3 vs. 10 mg/mL) since the 90%CI for the treatment ratio for $AUC_{0-\infty}$ was within the pre-defined acceptance criteria of 80 to 125%. The Applicant concludes that total exposure of semaglutide is not affected by drug product strengths in the range of 1 to 10 mg/mL.

Table 24: Statistical analysis for primary PK endpoint and key supportive secondary PK endpoints of semaglutide

Drug Product Strength Comparison ²	n	Treatment Ratio: Point estimate ¹	90%CI
Primary PK Endpoint: AUC_{0-∞}			
1 vs. 3 mg/mL	20/18	1.02	0.99, 1.05
1 vs. 10 mg/mL	20/20	0.97	0.94, 1.01
3 vs. 10 mg/mL	18/20	0.96	0.92, 0.99
Key Supportive Secondary PK Endpoint: C_{max}			
1 vs. 3 mg/mL	20/18	0.91	0.84, 1.00
1 vs. 10 mg/mL	20/20	0.71	0.65, 0.78
3 vs. 10 mg/mL	18/20	0.78	0.72, 0.85

¹Linear normal model with semaglutide strength and period as fixed effect and a random subject effect

²For the 3 mg/mL drug product strength the dose administered was 0.51 mg; all relevant PK parameters were adjusted for the higher dose administered (from 0.51 mg to 0.50 mg)

(Source: Clinical study report NN9535-3687, page 96 and 104)

Maximum concentrations of semaglutide are affected by different drug product strengths with the results suggesting a faster absorption of semaglutide with increasing drug product strengths. For C_{max}, only the drug product strength comparison 1 mg/mL vs. 3 mg/mL met the pre-defined acceptance criteria.

Drug product strength of 10 mg/mL was used in three Phase 1 studies (NN9535-1820 (first-in-human), NN9535-3616 (renal impairment), NN9535-1821 (Phase 2 dose finding)) and the overall efficacy and safety of semaglutide in this drug development program is based on the pivotal Phase 3a studies which used the drug product strength of 1.34 mg/mL (to-be-marketed). Despite BE assessment not being conducted with the 1.34 mg/mL drug product strength, the comparison of product strengths 1 mg/mL and 3 mg/mL encompasses the strength of the to-be-marketed product (1.34 mg/mL) and thereby results generated are representative of the to-be-marketed product.

Despite BE not been met for C_{max} of drug product strength of 10 mg/mL compared to the 2 lower strengths, the total exposure of semaglutide was comparable for all 3 drug product strengths. For semaglutide, the exposure-response (HbA1c) relationship is related to the total exposure rather than maximum concentrations of semaglutide (Refer to Section 3.3.1), and this study showed that the total exposure of semaglutide was similar for all 3 drug product strengths.

(b) (4) *drug substance*

Study NN9535-4010 was conducted to establish BE between semaglutide drug product (1.34 mg/mL) based on drug substance from 2 manufacturing processes (b) (4) (refer to Appendix 5.1 for description of study). A single dose of 0.5 mg semaglutide (b) (4) and 0.5 mg semaglutide (b) (4) was administered via the SC route to healthy subjects in a 2-period, cross-over design.

Statistical analysis for the primary PK endpoints is presented in Table 25. Bioequivalence was demonstrated between semaglutide (b) (4) and semaglutide (b) (4) since the 90%CI for the treatment ratio for the primary PK endpoints ($AUC_{0-tlast}$, C_{max}) was within the pre-defined acceptance criteria of 80 to 125%. The Applicant concludes that BE was demonstrated between (b) (4) manufactured semaglutide and we are in agreement with the Applicant's conclusions.

Table 25: Statistical analysis for primary PK endpoints of semaglutide

PK Parameter	n	Treatment Ratio	90%CI
	(b) (4)	(b) (4); Point estimate ¹	
$AUC_{0-tlast}$ ²	27/27	1.04	1.02, 1.06
C_{max}	27/27	1.04	0.99, 1.08

¹Linear normal model with production method, period, sequence, and subject within sequence as fixed effect

² $AUC_{0-tlast}$: AUC from time 0 until the last quantifiable measurement

(Source: Clinical study report NN9535-4010, page 72)

4. Labeling Recommendations

The following are the preliminary labeling recommendations relevant to clinical pharmacology for NDA 209637. The ~~red-strikeout font~~ is used to show the proposed text to be deleted and underline blue font is used to show text to be included.

HIGHLIGHTS OF PRESCRIBING INFORMATION

DRUG INTERACTIONS

- OZEMPIC delays gastric emptying. May impact absorption of concomitantly administered oral medications (b) (4)

(b) (4)

7. DRUG INTERACTIONS

(b) (4) Oral Medications

(b) (4) OZEMPIC causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, OZEMPIC did not affect the absorption of orally administered medications to any clinically relevant degree [see *Clinical Pharmacology (12.3)*]. Nonetheless, ~~C~~caution should be exercised when oral medications are concomitantly administered with OZEMPIC.

8. USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

No dose adjustment of OZEMPIC is recommended for patients with renal impairment (b) (4)

(b) (4)

(b) (4)

In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in [OZEMPIC semaglutide](#) pharmacokinetics (PK) was observed [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment of OZEMPIC is recommended for patients with hepatic impairment. In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in [OZEMPIC semaglutide](#) pharmacokinetics (PK) was observed [*see Clinical Pharmacology (12.3)*].

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Semaglutide is a [Glucagon-Like Peptide-1 \(GLP-1\)](#) analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

~~GLP-1 is a physiological hormone that has multiple actions in glucose-mediated by the GLP-1 receptors.~~ (b) (4)

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. (b) (4)

The principal mechanism of protraction resulting in the long half-life of [semaglutide](#) is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the [dipeptidyl peptidase 4 \(DPP-4\)](#) enzyme.

(b) (4)

12.2 Pharmacodynamics

OZEMPIC Semaglutide (b)(4) fasting and postprandial blood glucose and reduces body weight (b)(4). All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with **OZEMPIC semaglutide** 1 mg.

Fasting and Postprandial Glucose

Semaglutide reduced fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with **OZEMPIC semaglutide** 1 mg resulted in reductions in glucose in terms of absolute change from baseline and relative reduction compared to placebo (%) for fasting glucose 29 mg/dL (22%), 2 hour postprandial glucose 74 mg/dL (36%), mean 24 hour glucose concentration 30 mg/dL (22%). (b)(4)

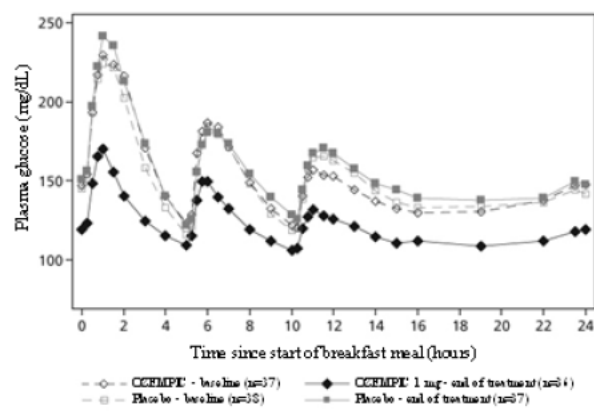


Figure 1. Mean 24 hour plasma glucose profiles (standardized meals) in patients with type 2 diabetes before (baseline) and after 12 weeks of treatment with **OZEMPIC semaglutide or placebo**

(b)(4) Insulin Secretion

Both first- and second-phase insulin secretion were increased in patients with type 2 diabetes treated with OZEMPIC compared with placebo.

Glucagon Secretion

OZEMPIC Semaglutide lowered the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, treatment with **OZEMPIC semaglutide** resulted in the following relative reductions in glucagon compared to placebo, fasting glucagon (8^{(b)(4)}%), postprandial glucagon response (14-15%), and mean 24 hour glucagon concentration (12%).

Glucose dependent insulin and glucagon secretion

[OZEMPIC Semaglutide](#) lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With [OZEMPIC semaglutide](#), the insulin secretion rate in patients with type 2 diabetes was (b) (4) to that of healthy subjects (see Figure 2).

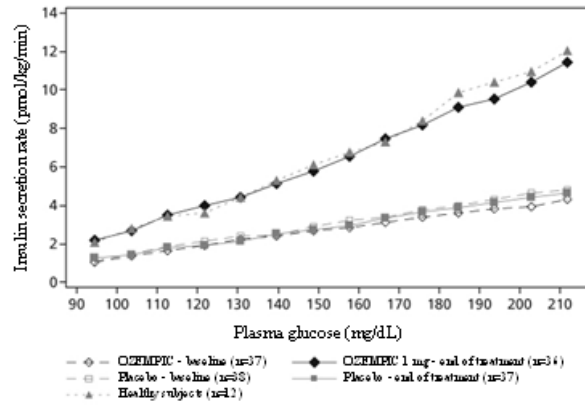


Figure 2. Mean insulin secretion rate versus glucose concentration in patients with type 2 diabetes during graded glucose infusion before (baseline) and after 12 weeks of treatment with [OZEMPIC semaglutide](#) or placebo and in untreated healthy subjects

During induced hypoglycemia, [OZEMPIC semaglutide](#) compared to placebo did not alter the counter regulatory responses of increased glucagon, and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Gastric emptying

[OZEMPIC Semaglutide](#) caused a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

(b) (4)

Cardiac electrophysiology (QTc)

The effect of [OZEMPIC semaglutide](#) on cardiac repolarization was tested in a through QTc trial. [At a dose 1.5 times the proposed maximum recommended dose, semaglutide does not prolong the QT interval to any clinically relevant extent.](#) (b) (4)

12.3 Pharmacokinetics

(b) (4)

Absorption

Absolute bioavailability of [OZEMPIC semaglutide](#) was 89%.

Distribution

The mean [apparent](#) volume of distribution of [OZEMPIC semaglutide](#) following [subcutaneous s.c.](#) administration in patients with type 2 diabetes was approximately 12.5 L. [OZEMPIC Semaglutide](#) was extensively bound to plasma albumin (>99%).

Elimination

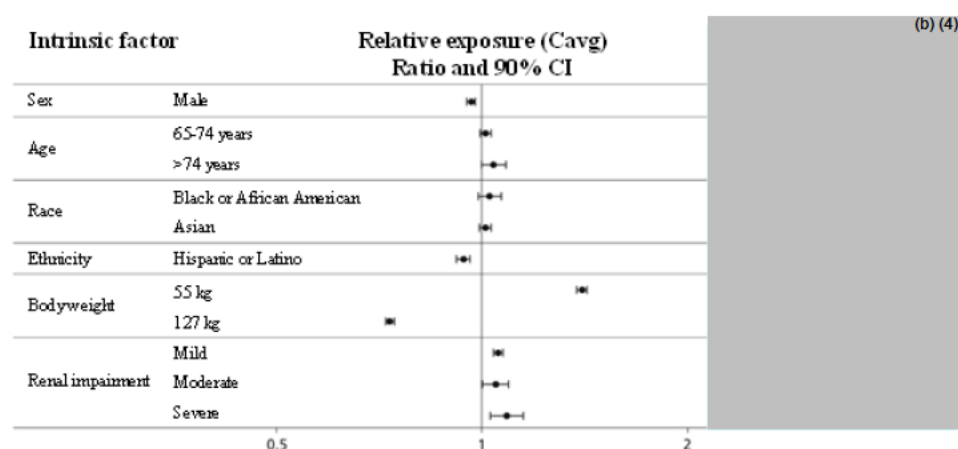
(b) (4) [Metabolism - Primary route of elimination for OZEMPIC is via metabolism.](#) [OZEMPIC Semaglutide](#) is metabolized following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

(b) (4) [Excretion -](#) The primary excretion routes of [OZEMPIC semaglutide](#) related material (b) (4) via the urine and feces. Approximately 3% of the dose was excreted as intact semaglutide via urine.

(b) (4)

Specific Populations

The effects of intrinsic factors on the pharmacokinetics of OZEMPIC semaglutide are shown in Figure 3.



OZEMPIC Semaglutide exposure (C_{avg}) relative to reference subject profile: non-Hispanic/non-Latino, White, female below 65 years, body weight 85 kg, with normal renal function. Population pharmacokinetic PK model also included maintenance dose and injection site as covariates. Body weight test categories (55 and 127 kg) represent the 5% and 95% percentiles in the dataset.

(b) (4)

Abbreviations: C_{avg}: average OZEMPIC semaglutide concentration. CI: Confidence interval.

Figure 3. Impact of intrinsic factors on OZEMPIC semaglutide exposure

Patients with Renal impairment - Renal impairment (b) (4) not impact the pharmacokinetics of OZEMPIC semaglutide in a clinically relevant manner. This was shown in a study with a single dose of 0.5 mg OZEMPIC semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, end-stage renal disease ESRD) compared with subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with renal impairment based on data from (b) (4) studies (Figure 3).

Patients with Hepatic impairment - Hepatic impairment (b) (4) not have any impact on the exposure of OZEMPIC semaglutide. The pharmacokinetics of OZEMPIC semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a study with a single-dose of 0.5 mg OZEMPIC semaglutide.

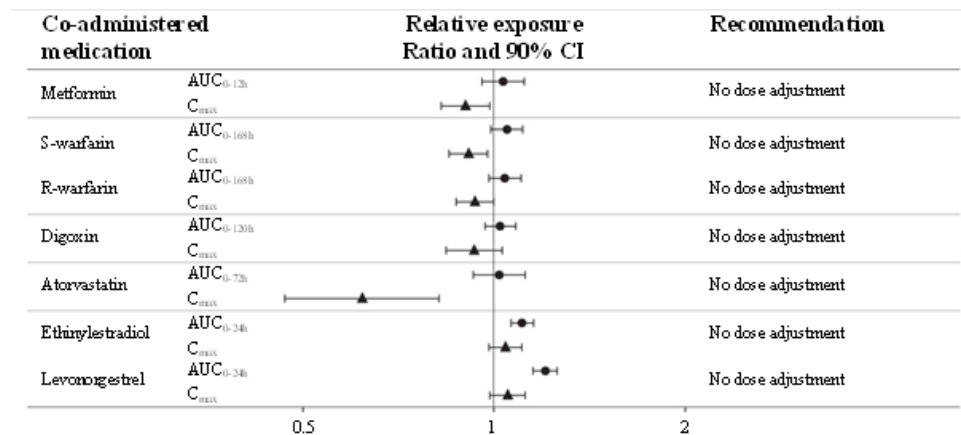
Pediatrics Patients - OZEMPIC-Semaglutide has not been studied in pediatric patients.

Drug Interactions Studies

In vitro studies have shown very low potential for OZEMPIC-semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

The delay of gastric emptying with [OZEMPIC semaglutide](#) may influence the absorption of concomitantly administered oral medicinal products. The potential effect of [OZEMPIC semaglutide](#) on the absorption of co-administered oral medications was studied in trials at OZEMPIC 1 mg steady state exposure.

No clinically relevant drug-drug interaction with OZEMPIC (Figure 4) was observed based on the evaluated medications, therefore no dose adjustment is required when co-administered with [OZEMPIC semaglutide](#).



Relative exposure in terms of AUC and C_{max} for each medication when given with [OZEMPIC semaglutide](#) compared to without [OZEMPIC semaglutide](#). Metformin and oral contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. Warfarin (S-warfarin/R-warfarin), digoxin and atorvastatin were assessed after a single dose. Abbreviations: AUC: area under the curve. C_{max}: maximum concentration. CI: confidence interval.

Figure 4. Impact of [OZEMPIC semaglutide](#) on the exposure of co-administered oral medications

5. Appendices

5.1 Key Highlights of Clinical Pharmacology Studies Cited in the QBR

Study Number	Description of Study
<p>NN9535-4010</p> <p>Single dose PK of semaglutide in healthy subjects; BE for (b) (4) drug substance</p>	<p>A randomized, single-center, double-blind, 2-period, cross-over study in healthy subjects (male and female, n=28 randomized) conducted to establish bioequivalence (BE) between semaglutide trial products based on drug substance from 2 different manufacturing processes (b) (4). A single dose of 0.5 mg semaglutide (b) (4) and 0.5 mg semaglutide (b) (4) was administered via the SC route (lifted skin fold of the thigh) to healthy subjects.</p>
<p>NN9535-3687</p> <p>Single dose PK of semaglutide in healthy subjects; BE for 3 different semaglutide drug product strengths</p>	<p>A randomized, single-center, single-dose, 2-period, incomplete cross-over study in healthy subjects (male and female, n=42 randomized) conducted to establish BE between 3 different semaglutide drug product strengths (1, 3, and 10 mg/mL) when semaglutide is administered in equimolar doses (Group A, n= 32, randomized) and to assess the absolute bioavailability (BA) of semaglutide (Group B, n=10, randomized). In Group A, subjects were randomized to receive a single dose of 0.5 mg semaglutide from 2 out of the 3 drug product strengths via SC administration (lifted skin fold of the abdomen) in a 2-period, incomplete cross-over design. In Group B, subjects received a single SC dose of 0.5 mg semaglutide and single IV dose of 0.25 mg semaglutide (drug product strength 1 mg/mL) in a 2-period cross-over design. For BA analysis, AUC_{0-∞} following IV administration of semaglutide was dose-adjusted from 0.25 mg to 0.5 mg. Blood samples were collected up to Day 35 following dose administration to characterize the PK of semaglutide.</p>
<p>NN9535-3634</p> <p>(Steady-state PK of semaglutide in healthy subjects)</p>	<p>The steady-state PK of semaglutide following multiple-dose SC administration (abdomen) of 0.5 mg and 1 mg semaglutide (1.34 mg/mL) was evaluated in healthy male Japanese and Caucasian subjects (n=44 randomized). Dose escalation regimen of semaglutide was as follows: (1) maintenance dose of 0.5 mg was achieved following administration of 0.25 mg once weekly for 4 weeks and (2) maintenance dose of 1 mg was achieved following administration of 0.25 mg once weekly for 4 weeks followed by 0.5 mg once weekly for 4 weeks. Thereafter, semaglutide 0.5 mg dose was administered once weekly for 9 weeks and semaglutide 1 mg dose was administered once weekly for 5 weeks to achieve steady-state conditions. Pre-dose blood samples were collected throughout the study and serial blood samples were collected after the first single dose administration of 0.25 mg and after the last dose administration (0.5 mg and 1 mg) to characterize the PK of semaglutide.</p>

<p>NN9535-3652 (Steady-state PK of semaglutide in healthy subjects)</p>	<p>Study was conducted in healthy subjects (male and female, n=168 randomized) to evaluate the effect of semaglutide on cardiac repolarization. The dose escalation regimen of semaglutide (1.34 mg/mL) administered via the SC route (thigh or abdomen) in 1 treatment arm (n=84 randomized, moxifloxacin placebo) was as follows: 0.25 mg once-weekly for 4 weeks, followed by 0.50 mg once-weekly for 4 weeks, followed by 1 mg once-weekly for 4 weeks, and followed by 1.5 mg once-weekly for 4 weeks. Semaglutide dose of 1.5 mg once weekly for 4 weeks was administered to obtain supra-therapeutic exposure levels. At each dose level, blood samples were collected up to 48 hrs after the last dose and a trough sample was collected 168 hr after the last dose to characterize the PK of semaglutide.</p>
<p>NN9535-3635, NN9535-3684 (Steady-state PK of semaglutide in patients with T2DM)</p>	<p>Steady-state PK of semaglutide following 1 mg once weekly SC dosing (thigh or abdomen) in patients with T2DM was investigated in Studies NN9535-3635 (male and female patients on diet and exercise and/or stable metformin background therapy, n=75 randomized) and NN9535-3684 (male and female patients on stable metformin background therapy, n=38 randomized). Steady-state was achieved following dose escalation regimen of semaglutide (1.34 mg/mL) as follows: 0.25 mg once-weekly for 4 weeks, followed by 0.50 mg once-weekly for 4 weeks, and followed by 1 mg once-weekly for 4 weeks (maintenance period). Pharmacokinetics of semaglutide at steady-state was assessed following administration of a 5th dose of semaglutide at the 1 mg dose level.</p>
<p>NN9535-3789 (Mass balance study)</p>	<p>A single-center, open-label, mass balance study, conducted to determine the absorption, metabolism, and excretion characteristics of [³H]-semaglutide following a single SC dose (thigh) of 0.5 mg [³H]-semaglutide (up to 500 µCi (administered range: 438.6 to 445.0 µCi)) in healthy male subjects (n=7; age range: 48 to 64 years). Plasma samples to characterize the PK of semaglutide were collected up to 5 weeks post-dose (~5 times the plasma t_{1/2} of semaglutide). Plasma, urine, and feces for assessment of radioactivity was collected until excreted levels of radioactivity had reached the defined end criterion level (>95% of excreta recovery or a total ³H-excretion (feces + urine) ≤0.5% of the administered dose in 2 consecutive 24 hr samples collected weekly) or until a maximum of 9 weeks post-dose. Blood and expired air for assessment of radioactivity was collected up to 5 weeks post-dose. Radioactivity was measured in both intact and dry matrix samples (except for in expired air samples). Plasma, urine, and feces for assessment of semaglutide metabolites were collected up to 9 weeks post-dose. Distribution of total radio-labeled material was characterized in plasma and blood.</p>
<p>Study NN9535-3684 (Hypoglycemic)</p>	<p>Patients were randomized (1:1 ratio) to receive semaglutide or matching placebo treatment in a 2-period cross-over design (n=38 randomized). Dose escalation regimen for semaglutide or matching placebo was as follows: 0.25 mg once</p>

counter-regulation)	weekly for 4 weeks followed by 0.5 mg once weekly for 4 weeks. Thereafter, 1 mg semaglutide or matching placebo was administered once weekly for 4 weeks (maintenance period). Approximately 48 hrs after administration of a 5 th dose of 1 mg semaglutide or matching placebo a stepwise hypoglycemic clamp was initiated. Pharmacodynamic endpoints was assessed during the hypoglycemic clamp at each of the targeted plasma glucose levels (5.5, 3.5, 2.5 mmol/L) and after recovery from hypoglycemia (plasma glucose \geq 4 mmol/L).
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5.2 Summary of Bioanalytical Method Validation

5.2.1 Semaglutide

5.2.1.1 Validation

Quantification of semaglutide in human plasma and human urine was determined using validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) methods. Validation methods reported below are based on the LC-MS/MS method and the reported PK of semaglutide in the Clinical Pharmacology review is based on concentrations determined with the LC-MS/MS method.

Early on in the clinical development program, semaglutide in human plasma was quantified using a luminescent oxygen channeling immunoassay (LOCI). Subsequently it was discovered that the LOCI assay was influenced by a matrix effect which impacted the quantification of semaglutide in plasma. Based on these observations, a new method, LC-MS/MS, was developed and validated which showed absence of matrix effect. When comparing the LOCI and LC-MS/MS methods, semaglutide concentrations were on average 2-fold higher with the LC-MS/MS method compared to the LOCI method.

Concentration of semaglutide in Studies NN9535-1820 (first-in-human), NN9535-1821 (Phase 2), NN9535-3633 (multiple dose, Caucasian/Japanese), and Study NN9535-3679 (BE – product strength) were determined using the LOCI method. Studies NN9535-3633 and NN9535-3679 were repeated and semaglutide concentrations in the new studies, NN9535-3634 and NN9535-3687, are based on the LC-MS/MS method. Reanalysis of semaglutide concentrations from Studies NN9535-1820 and NN9535-1821 was not conducted. The Applicant concludes that PK results based on the LOCI method should be interpreted with care.

Since semaglutide concentrations derived from the LOCI method may not be reliable due to matrix effect, the Clinical Pharmacology review does not contain PK data derived from the LOCI method. Therefore, the Reviewer has not included validation results from the LOCI method in the Clinical Pharmacology review.

Validation assessments for the LC-MS/MS method for quantification of semaglutide in human plasma and human urine are reported below.

LC-MS/MS Method: Human Plasma (Calibration range: 1.94-194 nM)

Concentration of semaglutide in human plasma (K₃EDTA) was quantified using a validated LC-MS/MS method. The method was validated for quantification of semaglutide in human plasma (K₃EDTA) over a concentration range of 1.94 – 194 nM. A weighting factor of 1/concentration was applied to the calibration curve. In brief, the analytical method was as follows:

To aliquots of 50 μ L of human plasma (K_3 EDTA), 350 μ L of internal standard (IS: ^{(b) (4)}
 was added, samples were mixed, centrifuged, and supernatants were injected into the LC-MS/MS system (HPLC system with an Applied Biosystems/MDS SCIEX API 4000 triple quadrupole mass spectrometer).

The assay was validated in accordance to appropriate regulatory guidances. The analytical method was validated in terms of sensitivity, accuracy, precision, dilution linearity, selectivity/matrix effect, recovery, impact of hemolysis, carry-over, stability (solution stability, short-term, freeze/thaw, long-term, post-preparative, whole blood), processed sample integrity, stress test, and impact of concomitantly administered drugs. Summary of the assay validation (validation report no: VAA91659, VAA95112; bioanalytical report no: AAA96048) is presented in Table 1.

Table 1: Summary of semaglutide PK assay validation (LC-MS/MS) in human plasma (calibration range 1.94-194 nM) (NNC 0113-0000-0217 refers to semaglutide)

Analyte	NNC 0113-0000-0217		
Matrix (Anticoagulant)	Human plasma (K_3 EDTA)		
Preservative	none		
SOP Number	SOP SM1-346A		
Assay Method	LC-MS/MS method following protein precipitation		
Detector	AB/MDS Sciex API 4000		
Assay Volume Required	0.05 mL		
Standard Curve Range	1.94 – 194 nM		
Regression Type	Linear (1/concentration)		
Quantification Method	Area Ratio		
Quality Control Samples		Precision (%)	Accuracy (%)
	QC 8	14.6	111.5
Inter-run	QC 24	11.2	99.9
	QC 125	9.3	99.8
	QC 640	6.5	100.2
	QC 8	6.0	116.7
Intra-run 02NNV (L1483)	QC 24	10.2	95.8
	QC 125	3.7	93.6
	QC 640	3.9	99.3
	QC 8	13.7	112.5
Intra-run 03NNV (L1483)	QC 24	11.9	105.3
	QC 125	9.2	101.6
	QC 640	7.8	97.6
	QC 8	10.9	97.3
Intra-run 09NNV (L1483)	QC 24	5.7	102.5
	QC 125	12.2	104.3
	QC 640	4.6	102.2
	QC 8	18.1	119.6
Intra-run 15NNV (L1388)	QC 24	14.4	96.6
	QC 125	7.6	99.8
	QC 640	8.8	101.8
<u>Stability for NNC 0113-0000-0217 in Matrix</u>			
Long-term Stability	33 days at -20°C (QC 24, QC 640 and DQC 8000)		
Short-term Stability	24 hours at room temperature (QC 24, QC 640 and DQC 8000)		
Freeze and Thaw Stability	3 cycles at -20°C / at -80°C (QC 24, QC 640 and DQC 8000)		
Post-preparative Stability	89 hours at 5°C (QC 24 and QC 640)		
Whole Blood Stability	Demonstrated for 2 hours at room temperature		
Selectivity	Acceptance criteria met		
Carry-over (carry-over 2 samples)	Acceptance criteria met		
Stress Test	Interference within acceptance		
Impact of Haemolysis	Interference > 20%, relative to LLOQ ^a Accuracy and precision within acceptance at QC 24, QC 125 and QC 640 level; accuracy > 120% at LLOQ level ^b		
Matrix Effect	Acceptance criteria met		
Recovery	Acceptance criteria met		

Dilution Integrity	Demonstrated up to 8000 ng/mL (dilution factor 20)
Processed Sample Integrity	Up to 176 hours at 5°C (QC 8, QC 24, QC 125 and QC 640)
Batch Size	192 injections
Impact Co-administered NNC 0113-0000-3363	Acceptance criteria met
Stock solution NNC 0113-0000-0217	
Short-term Stability	22 hours at 0.895 mg/mL (in solvent as provided by the Sponsor) at room temperature
Stock Solution (b) (4) (IS)	
Short-term Stability	24 hours at 26.9 g/mL (in solvent as provided by the Sponsor) at room temperature
Working Solution (b) (4) (IS)	
Long-term Stability	8 days at 13.5 µg/mL in methanol / formic acid / water, 80:0.2:20 (v/v/v) at -20°C
Short-term Stability	23 hours at 13.5 µg/mL in methanol / formic acid / water, 80:0.2:20 (v/v/v) at room temperature
Short-term Stability	24 hours at 108 ng/mL in ethanol at 5°C

- ^a Interference at the retention time of NNC 0113-0000-0217 in Human plasma (K₃EDTA) fortified with 5% whole blood (without spiking with NNC 0113-0000-0217) was observed in >50% of blank and STD 0 samples (two different Human plasma (K₃EDTA) lots were fortified with 5% whole blood); detailed data in [Table 19](#).
- ^b The mean accuracy at the LLOQ level, determined in two different Human plasma (K₃EDTA) lots, was outside acceptance; data are detailed in [Table 21](#). The precision ranged from 19.6% (matrix lot CM/09-1091) to 28.1% (matrix lot CM/09-1087).

Stability for NNC 0113-0000-0217 in Matrix at -20°C	
Stability at the QC low level (QC 24)	Demonstrated for up to 692 days
Stability at the QC high level (QC 640)	Demonstrated for up to 659 days
Stability at the DQC level (DQC 8000)	Demonstrated for up to 582 days
Stability for NNC 0113-0000-0217 in Matrix at -80°C	
Stability at the QC low level (QC 24)	Demonstrated for up to 322 days
Stability at the QC high level (QC 640)	Demonstrated for up to 385 days
Stability at the DQC level (DQC 8000)	Demonstrated for up to 385 days

Note:

- Co-administered compounds (ethinylestradiol and levonorgestrel): No impact demonstrated (acceptance criteria met)

QC8: 1.94 nM, QC24: 5.83 nM, QC125: 30.4 nM, QC640: 156 nM, QC8000: 1945 nM

(Source: Validation report number VAA91659, page 15-16; Validation report number VAA95112, page 13; Bioanalytical report number AAA96048; page 48)

Assessment for carry-over of semaglutide and IS was performed as follows:

Carry-over assessment for semaglutide was evaluated by assigning a carry-over blank sample 1 and carry-over blank sample 2 after each high QC level (156 nM). Since semaglutide is an adhesive compound the Applicant anticipated that the carry-over relative to LLOQ would be >20% in the carry-over blank sample 1 and therefore included a carry-over blank sample 2. Absolute and relative carry-over estimates of semaglutide in both blank samples are reported below.

Absolute and relative carry-over of semaglutide in human plasma (K₃EDTA)

	Absolute % Carry-Over ¹	Relative % Carry-Over ²
Carry-over blank sample 1 (4 runs, n=6 each)	≤0.47%	Response was ≤20% relative to the mean response of the LLOQ calibration standard for all n=6 samples for 2 out of the 4 runs. Response was ≤20% relative to the mean response of the LLOQ calibration standard for n=3/6 samples for 2 out of the 4 runs.
Carry-over blank sample 2 (4 runs, n=6 each)	≤0.29%	Response was ≤20% relative to the mean response of the LLOQ calibration standard for all n=6 samples for 3 out of the 4 runs. Response was ≤20% relative to the mean response of the LLOQ calibration standard for n=5/6 samples for 1 out of the 4 runs.

¹Absolute % carry-over: [area carry-over sample/area QC 156 nM] × 100

²Relative % carry-over: [area carry-over sample/STD LLOQ (mean) area] × 100

(Source: Response to May 19th Request – Clin Pharm, Submitted on 05/26/2017, page 4-5)

The acceptance criterion was specified only for carry-over blank sample 2 and the criterion was met.

The Applicant implemented the following actions to minimize carry-over in the analytical runs with clinical samples:

- Avoid low concentration samples right after high concentration samples (Study NN9535-3616)
- Calibration range for quantification of semaglutide in all remaining studies was lowered to a range of 0.729-60.8 nmol/L
- Carry-over in routine analysis of clinical samples was monitored and the following acceptance criteria for blank samples was applied:
 - at least 50% of the standard zero samples are free of interference at the retention time of the analytes of interest
 - at least 50% of the blank samples are free of interference at the retention time of the analytes of interest and at the retention time of the IS
 - at least two-thirds of all blank and standard zero samples meet the above described interference criteria.

(Source: Response to May 19th Request – Clin Pharm, Submitted on 05/26/2017, page 4-5)

Similar to semaglutide, carry-over assessment for IS in human plasma (K₃EDTA) was conducted with carry-over blank 1 and 2 samples (n=6 of each) after each high QC level (156 nM). Absolute % carry-over for carry-over blank 1 sample was ≤0.39%. Relative % carry-over for carry-over 2 blank sample met the acceptance criteria.

LC-MS/MS Method: Human Plasma (Calibration range: 0.729-60.8 nmol/L)

The LC-MS/MS method for quantification of semaglutide concentrations in human plasma (validation study no: VAA91659/VAA95112, calibration range: 1.94 – 194 nM (nmol/L)) was optimized and re-validated with a lower LLOQ level of 0.729 nmol/L; the overall concentration range was 0.729 – 60.8 nmol/L. A weighting factor of $1/\text{concentration}^2$ was applied to the calibration curve. In brief, the analytical method was as follows:

To aliquots of 100 μL of human plasma (K_3EDTA), aqueous IS (b) (4) was added, samples were mixed, centrifuged, and protein precipitated. Supernatants were evaporated to dryness, reconstituted and injected into the LC-MS/MS system (UPLC Waters Acquity system with an Applied Biosystems/MDS SCIEX API QTrap[®] 5500 mass spectrometer).

The assay was validated in accordance to appropriate regulatory guidances. The analytical method was validated in terms of sensitivity, precision, accuracy, dilution linearity, selectivity/matrix effect, recovery, impact of hemolysis, carry-over, stability (solution stability, short-term, freeze/thaw, long-term, whole blood), processed sample integrity, impact of concomitantly administered drugs, and stress test. Summary of the assay validation (validation study no: AA95860 and bioanalytical report no: AAA98749) is presented in Table 2.

Table 2: Summary of semaglutide PK assay validation (LC-MS/MS) in human plasma (calibration range 0.729 – 60.8 nmol/L)

Analyte	Semaglutide (NNC 0113-0000-0217)		
Matrix (Anticoagulant)	Human plasma (K ₃ EDTA)		
Preservative	none		
SOP Number	SOP SM1-362A		
Assay Method	LC-MS/MS method following protein precipitation		
Detector	Applied Biosystems/MDS SCIEX API QTrap® 5500		
Assay Volume Required	0.10 mL		
Standard Curve Range	0.729 – 60.8 nmol/L (3.00 – 250 ng/mL)		
Regression Type	Linear (1/concentration ²)		
Quantification Method	Area Ratio		
Quality Control Samples		Precision (%)	Accuracy (%)
Inter-run	QC 3	10.8	90.5
	QC 9	7.0	92.6
	QC 40	8.1	91.8
	QC 200	7.3	89.3
Intra-run 4	QC 3	12.1	85.5
	QC 9	8.1	95.0
	QC 40	3.9	88.7
	QC 200	6.5	88.5
Intra-run 5	QC 3	10.9	95.0
	QC 9	10.0	91.4
	QC 40	15.3	90.7
	QC 200	12.7	88.0
Intra-run 9	QC 3	10.0	85.2
	QC 9	3.6	89.5
	QC 40	3.0	92.4
	QC 200	5.4	89.2
Intra-run 10	QC 3	5.1	96.5
	QC 9	4.3	94.5
	QC 40	3.8	95.3
	QC 200	2.7	91.5
<u>Stability for Semaglutide in Matrix</u>			
Long-term Stability	144 days at -20°C (QC 9, QC 200 and DQC 1000) 24 days at -80°C (QC 9, QC 200 and DQC 1000)		
Short-term Stability	26 hours at room temperature (QC 9 and QC 200)		
Freeze and Thaw Stability	3 cycles at -20°C and 2 cycles at -80°C		
Whole Blood Stability	Demonstrated for 2 hours at room temperature		
Selectivity	Acceptance criteria met		
Carry-over (carry-over blank samples)	Acceptance criteria met		
Stress Test	Interference within acceptance		
Impact of Haemolysis	Interference > 20%, relative to LLOQ ^a Accuracy and precision within acceptance at QC 3, QC 9, QC 40 and QC 200 level.		

^a Interference at the retention time of Semaglutide was observed in one of the three different blank human plasma (K₃EDTA) lots fortified with 2% whole blood; detailed data in (Table 15).

Matrix Effect	Acceptance criteria met
Recovery	Acceptance criteria met
Dilution Integrity	Demonstrated up to 1000 ng/mL (dilution factor 5)
Processed Sample Integrity	Up to 173 hours at 5°C
Batch Size	Up to 192 injections
Impact Co-administered NNC 0113-0000-3363	No impact demonstrated
<u>Working Solution</u> (b) (4) (IS) Long-term Stability	Evaluated but not demonstrated for 538 ng/mL in Millipore water at room temperature; requires fresh preparation on the day of use.
Short-term Stability	Evaluated but not demonstrated for 538 ng/mL in Millipore water at room temperature; requires fresh preparation on the day, storage at room temperature and use between 1 h and 5 h after preparation.

Note:

- Stability of semaglutide in matrix: long term stability: 309 days at -20°C (2.19, 9.73, 48.6, 243 nmol/L)
- Co-administered compounds (paracetamol, acetylsalicylic acid, metformin HCL): No impact demonstrated (acceptance criteria met)

QC3: 0.729 nmol/L, QC9: 2.19 nmol/L, QC40: 9.73 nmol/L, QC200: 48.6 nmol/L, QC1000: 243 nmol/L

(Source: Validation study number AA95860, page 15-16; Bioanalytical report number AAA98749)

Assessment for recovery of semaglutide and IS was performed as follows:

Recovery of semaglutide from human plasma (K₃EDTA) was assessed by comparing the peak area of processed samples (protein precipitation) at each QC level (2.19, 9.73, 48.6 nmol/L, n=6) with peak area of processed (protein precipitation) blank matrix containing IS spiked with semaglutide (100% recovery) post-extraction (n=6). Recovery of semaglutide from human plasma met the acceptance criterion for the 2.19 nmol/L (recovery: 159%), 9.73 nmol/L (recovery: 154.9%), and 48.6 nmol/L (recovery: 171.8%) QC samples.

Recovery of IS from human plasma (K₃EDTA) was assessed by comparing the peak area of processed samples (protein precipitation) containing IS at the 9.73 nmol/L QC level (n=6) with peak area of processed sample (protein precipitation) at the 9.73 nmol/L QC level containing spiked IS (100% recovery) post-extraction (n=6). Recovery of IS from human plasma (recovery: 135.8%) met the acceptance criterion.

The Applicant reports that the observed recovery of >100% is likely attributable to non-specific binding of semaglutide and IS to tube surfaces during preparation of diluted solutions for the post-extraction samples. Recovery of >100% was not evident during the validation of the 1.94 – 194 nM method; the Applicant reports that this is likely due to the vehicle of diluted solutions being 100% ethanol.

LC-MS/MS Method: Human Plasma (Calibration range: 0.729-60.8 nmol/L; Stable labeled internal standard)

Partial re-validation of the LC-MS/MS method for quantification of semaglutide in human plasma (K₃EDTA) (validation study no: AA95860, calibration range: 0.729 – 60.8 nmol/L) was carried out to include a stable labeled internal standard in the method and for reduction of run time by gradient change of the UPLC method. In brief, the analytical method was as follows:

To aliquots of 100 µL of human plasma (K₃EDTA), aqueous labeled-IS (b) (4) () containing 0.5% BSA was added, samples were mixed, centrifuged, and protein precipitated. Supernatants were evaporated to dryness, reconstituted and injected into the LC-MS/MS system (UPLC system with an Applied Biosystems/MDS SCIEX API QTrap[®] 5500 mass spectrometer).

A weighting factor of 1/concentration² was applied to the calibration curve. The assay was validated in accordance to appropriate regulatory guidances. The analytical method was validated in terms of sensitivity, precision, accuracy, dilution linearity, selectivity/matrix effect, impact of hemolysis, carry-over, stability (solution stability, short-term, freeze/thaw, long-term), processed sample integrity, impact of concomitantly administered drugs, impact of end-stage renal disease, stress test, and automation step (Hamilton STAR). Summary of the assay validation (validation report no: VCA11388, VCA17145, VZZ44775, bioanalytical report no: ACA12337) is presented in Table 3.

Table 3: Summary of semaglutide PK assay validation (LC-MS/MS) in human plasma (calibration range 0.729 – 60.8 nmol/L, labeled internal standard)

Analyte	Semaglutide		
Matrix (Anticoagulant)	Human plasma (K ₃ EDTA)		
Preservative	N/AP		
SOP Number	SOP SM1-385A		
Assay Method	LC-MS/MS method following protein precipitation		
Detector	Applied Biosystems/MDS SCIEX API QTrap® 5500		
Assay Volume Required	0.10 mL		
Standard Curve Range	0.729 – 60.8 nmol/L (3.00 – 250 ng/mL)		
Regression Type	Linear (1/concentration ²)		
Quantification Method	Peak Area Ratio		
Quality Control Samples		Precision (%)	Accuracy (%)
Between-run (Watson runs 2, 3, 4)	LLOQ (QC 3)	6.8	100.2
	QC 9	3.9	99.9
	QC 40	3.3	99.7
	QC 200	3.3	98.0
Within-run (Watson run 3)	LLOQ (QC 3)	4.8	96.1
	QC 9	2.7	98.9
	QC 40	2.2	98.6
	QC 200	3.6	96.3
Selectivity	No interference, 10 matrix lots investigated		
Sensitivity	Within acceptance		
Matrix Effect	Within acceptance, 7 matrix lots investigated		
Carry-over	Within acceptance		
Stress test	No cross-well contamination		
Interference in haemolysed matrix	No interference observed		
Impact of haemolysis	No impact on precision and accuracy observed		
Processed Sample Integrity	Demonstrated for up to 172 hours at 5°C		
Performance of Acquity UPLC Iclass Binary Solvent Manager	Not demonstrated		
<u>Stability of Semaglutide</u> ^{(b) (4)} (IS):			
Short-term stability in solution	Demonstrated at room temperature for at least: <ul style="list-style-type: none"> • 20 hours at 1.20 mg/mL (as delivered by Sponsor) • 20 hours in methanol / water / formic acid (80:20:0.2 v/v/v) at 12.0 µg/mL • 29 hours in BSA / water (0.5:100 w/v) at 150 ng/mL 		
Long-term stability in solution	Demonstrated at -20°C for at least 65 days in methanol / water / formic acid (80:20:0.2 v/v/v) at 12.0 µg/mL		
<u>Stability of Semaglutide:</u>			
Long-term stability in matrix	Demonstrated at -20°C for at least 463 days in matrix (at low QC, high QC and DQC level)		
Batch Size	Up to 192 injections		

Evaluation for semaglutide in plasma	Conclusion
Impact due to co-administered Warfarin, Atorvastatin, Digoxin, Lisinopril, Omeprazole and Metformin	No impact demonstrated
Selectivity, matrix effect and accuracy in plasma from End-Stage Renal Disease (ESRD)	Acceptance criteria met
Freeze (up to 6 cycles at -20°C and 1 cycles at -80°C) / thaw stability	Stability demonstrated
Storage for up to 1021 days at -20°C	Stability demonstrated
Storage for up to 351 days at -80°C	Stability demonstrated

Hamilton MICROLAB STARlet 8-Channel and Hamilton MICROLAB STARlet 96-Channel:

Sensitivity	Demonstrated with a 420 µL aspiration setting for the Hamilton MICROLAB STARlet 96-Channel (no under-filling)
Dilution integrity	Verified at 243 nmol/L with 1:5 dilution
Stress test	No cross-well contamination for both 8-channel and 96-channel systems
Maximum batch size	2 analytical runs (2 96-well plates per run)

Note:

- Stability of semaglutide in matrix: short-term stability: up to 72 hrs at room temperature (2.19, 48.6, 243 nmol/L)

QC3: 0.729 nmol/L, QC9: 2.19 nmol/L, QC40: 9.73 nmol/L, QC200: 48.6 nmol/L, QC1000: 243 nmol/L

(Source: Validation report number VCA11388, page 13; Validation report number VCA17145, page 15; Bioanalytical report number ACA12337, page 23; Validation report number VZZ44775, page 11)

Assessment for recovery of semaglutide and labelled IS:

The Applicant reports that since non-specific binding in unextracted reference solutions influenced the recovery of semaglutide and IS (as observed in validation study number AA95860), that a dedicated recovery assessment was not conducted during the partial re-validation of the method.

Despite a recovery assessment not been conducted, the Applicant reports that the observed low variability (CV%) on absolute peak area for both semaglutide (7.7% to 7.8%) and labeled-IS (7.9% to 9.6%) when QC samples (2.19, 48.6 nmol/L, n=3) were spiked in 7 matrix lots of human plasma, shows consistent recovery for both analytes (refer to response to IR, Resp-Req-Clin-Pharm-20170519, page 8-11).

LC-MS/MS Method: Human Urine (Concentration range: 0.729-60.8 nmol/, Stable labeled internal standard)

Concentration of semaglutide in human urine was quantified using a validated LC-MS/MS method. Detergent Triton X-100 was added to blank human urine in order to prevent non-specific binding of analyte to polypropylene tubes (final matrix composition: human urine/1% Triton X-100 (9:1, v/v)). The method was validated for quantification of semaglutide in human urine/1% Triton X-100 (9:1, v/v) over a concentration range of 0.729 – 60.8 nmol/L which corresponds to a concentration range of 0.810 to 67.5 nmol/L in human urine. A weighting factor of $1/\text{concentration}^2$ was applied to the calibration curve. In brief, the analytical method was as follows:

To aliquots of 100 μL of human urine/1% Triton X-100 (9:1, v/v), labeled-IS ([N-15][C-13] GLP-1 analogs) containing 0.5% BSA was added, samples were mixed, and centrifuged. Supernatants were evaporated to dryness, reconstituted and injected into the LC-MS/MS system.

The assay was validated in accordance to appropriate regulatory guidances. The analytical method was validated in terms of sensitivity, accuracy, precision, dilution linearity, selectivity/matrix effect, carry-over, stability (solution stability, short-term, freeze/thaw, long-term), processed sample integrity, and stress test. Summary of the assay validation (validation report no: VCA11773 and VCA17145) is presented in Table 4.

Table 4: Summary of semaglutide PK assay validation (LC-MS/MS) in human urine/1% Triton X-100 (9:1, v/v) (calibration range 0.729 – 60.8 nmol/L, labeled internal standard)

Analyte	Semaglutide		
Matrix (Anticoagulant)	Human urine / 1% Triton X-100 (9:1, v/v)		
Preservative	N/AP		
SOP Number	SOP SM1-395A		
Assay Method	LC-MS/MS method following protein precipitation		
Detector	AB SCIEX QTrap® 5500		
Assay Volume Required	0.100 mL		
Standard Curve Range	0.729 – 60.8 nmol/L (3.00 – 250 ng/mL)		
Regression Type	Linear (1/concentration ²)		
Quantification Method	Peak Area Ratio		
Quality Control Samples		Precision (%)	Accuracy (%)
Between-run (Watson runs 6, 8, 9)	LLOQ (QC 3)	5.0	101.2
	QC 9	3.9	105.0
	QC 40	2.4	99.2
	QC 200	2.2	100.2
Within-run (Watson run 8)	LLOQ (QC 3)	4.6	103.2
	QC 9	3.9	102.7
	QC 40	3.0	99.1
	QC 200	2.9	99.1
Selectivity	No interference, 10 matrix lots investigated		
Sensitivity	Within acceptance		
Matrix Effect	9 out of 10 lots investigated within acceptance		
Carry-over	Within acceptance		
Stress test	No cross-well contamination		
Dilution Integrity	Demonstrated up to 1000 ng/mL (243 nmol/L) (dilution factor 5)		
Processed Sample Integrity	Demonstrated for up to 171 hours at 5°C		
<u>Stability of Semaglutide</u> ^{(b) (4)} IS:			
Short-term stability in solution	Demonstrated at room temperature for at least: Up to 6 hours in BSA / Water (0.5:100 w/v) at 120 ng/mL Up to 24 hours in BSA / Water (0.5:100 w/v) at 120 ng/mL		
<u>Stability of Semaglutide in matrix:</u>			
Long-term stability	Demonstrated at -20°C for at least 225 days in matrix (at low QC, high QC and DQC level) Demonstrated at -20°C for at least 226 days in matrix (at QC 8000)		
Short-term stability	At least 24 hours		
Freeze and thaw stability	3 cycles at -20°C 2 cycles at -80°C		
Batch Size	Up to 96 injections		
<u>Stability of Semaglutide in human urine / 1% Triton X-100 (9:1, v/v):</u>			
Long-term stability:	Demonstrated at -80°C for up to 105 days at low QC, high QC and DQC level		

QC3: 0.729 nmol/L, QC9: 2.19 nmol/L, QC40: 9.73 nmol/L, QC200: 48.6 nmol/L, QC1000: 243 nmol/L; QC8000: 1945 nmol/L (Source: Validation report number VCA11773, page 13; Validation report number VCA17145, page 17)

Assessment for recovery of semaglutide and IS:

Recovery of semaglutide and labeled-IS in human urine/1% Triton X-100 was not assessed. The Applicant's reasoning is that in human urine the albumin concentration is low, therefore

semaglutide is not expected to be bound to protein in the urine. The Applicant reports that the protein precipitation step in the sample preparation stage is not an extraction but rather a dilution of urine. Therefore, the recovery from urine is regarded as 100% (refer to response to IR, Resp-Req-Clin-Pharm-20170519, page 12).

5.2.1.2 Bioanalytical Reports

Inter-assay accuracy and precision

Inter-assay accuracy and precision of QC samples and calibration standard samples for semaglutide (human plasma and human urine) was assessed in individual bioanalytical reports for the Phase 1 and Phase 3a studies which characterized the PK of semaglutide. Accuracy and precision assessments were performed in accordance to the regulatory guidances. In all bioanalytical reports, the inter-assay accuracy and precision of QC samples and calibration standards were within the acceptance criterion: accuracy within $\pm 15\%$ of the nominal concentration ($\pm 20\%$ at the LLOQ) and precision of $\leq 15\%$ ($\leq 20\%$ at the LLOQ).

Incurred sample reproducibility

For the Phase 1 and 3a studies, the method for quantification of semaglutide in human plasma was considered reproducible since the assessment for incurred sample reproducibility (ISR) met the acceptance criteria: 67% of the repeated sample results are within 20% of the original concentration (number of ISR samples = 7% of the study sample size). No ISR assessment was performed in the bioanalytical report for human urine (Study NN9535-3651) since semaglutide concentrations in human urine for all study samples were below the limit of quantification.

5.2.2 Concomitantly Administered Drugs in Drug Interaction Studies

Atorvastatin, ortho-hydroxyatorvastatin, para-hydroxatorvastatin: Quantitative assessment of atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxatorvastatin in human plasma was performed using a validated HPLC with MS/MS detection method (study ID: AHDP2). The calibration curve range for atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxatorvastatin was 0.100 to 75 ng/mL. The assay was validated in accordance to the appropriate regulatory guidances. The Applicant reports that the bioanalysis of patient samples for atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxatorvastatin was conducted according to current FDA guidelines and recommendations. For in-study validation, the between-batch precision (%CV) at low, mid-1, mid-2, high, dilution QC samples for atorvastatin was less than or equal to 9.07% and accuracy (%theoretical) range from 100.97% to 105.32%. For in-study validation, the between-batch precision (%CV) at low, mid-1, mid-2, high, dilution QC samples for ortho-hydroxyatorvastatin was less than or equal to 10.9% and accuracy (%theoretical) range from 101.32% to 103.31%. For in-study validation, the between-batch precision (%CV) at low, mid-1, mid-2, high, dilution QC samples for para-hydroxatorvastatin was less than or equal to 7.79% and accuracy (%theoretical) range from 98.91% to 104.29%. The Applicant reports that all patient samples were analyzed within the 323 days for atorvastatin and 294 days for ortho-hydroxyatorvastatin and para-hydroxatorvastatin demonstrated long-term storage stability in human plasma containing sodium heparin at -70°C.

Digoxin: Quantitative assessment of digoxin in human plasma was performed using a validated HPLC with MS/MS detection method (project code: QLW2). The calibration curve range for digoxin was 0.0100 to 10 ng/mL. The assay was validated in accordance to the appropriate regulatory guidances. The Applicant reports that the bioanalysis of patient samples for digoxin was conducted according to current FDA guidelines and recommendations. For in-study validation, the between-batch precision (%CV) at low, mid-1, mid-2, high, dilution QC samples for digoxin was less than or equal to 9.62% and accuracy (%theoretical) range from 93.37% to 98.49%. The Applicant reports that all patient samples were analyzed within the 286 days demonstrated long-term stability in human plasma containing dipotassium EDTA at -20°C.

Metformin: Quantitative assessment of metformin in human plasma was performed using a validated LC-MS/MS method (study: ZZ00904-01). The calibration curve range for metformin was 30 to 6000 ng/mL. The assay was validated in accordance to the appropriate regulatory guidances. The Applicant reports that the bioanalysis of patient samples for metformin was conducted according to current FDA guidelines and recommendations. For in-study validation, the between-batch precision (%CV) at low, mid, high QC samples for metformin was less than or equal to 5.5% and accuracy (%theoretical) range from 100.2% to 104.4%. The Applicant reports that patient samples were analyzed without exceeding the long-term stability.

Warfarin: Quantitative assessment of R-warfarin and S-warfarin in human plasma was performed using a validated LC-MS/MS method (study: ZZ21621-01). The calibration curve range for R-warfarin and S-warfarin was 12.5 to 2500 ng/mL. The assay was validated in accordance to the appropriate regulatory guidances. The Applicant reports that the bioanalysis of patient samples for R-warfarin and S-warfarin was conducted according to current FDA guidelines and recommendations. For in-study validation, the between-batch precision (%CV) at low, mid, high, QC samples for R-warfarin was less than or equal to 5.2% and accuracy (%theoretical) range from 100.0% to 102.9%. For in-study validation, the between-batch precision (%CV) at low, mid, high, QC samples for S-warfarin was less than or equal to 5.1% and accuracy (%theoretical) range from 100.3% to 102.7%. The Applicant reports that patient samples were analyzed without exceeding the long-term stability.

Ethinylestradiol (EE) and levonorgestrel (LN): Quantitative assessment of EE and levonorgestrel LN in human plasma was performed using a validated GS/MS method (project code: OX006, OX006B). The calibration curve range for EE was 2.5 to 250 pg/mL and for LN was 25 to 25000 pg/mL. The assay was validated in accordance to the appropriate regulatory guidances. The Applicant reports that the bioanalysis of patient samples for EE and LN was conducted according to current FDA guidelines and recommendations. For in-study validation, the between-batch precision (%CV) at low, mid, high, QC samples for EE was less than or equal to 8.5% and accuracy (%theoretical) range from 99.7% to 99.8%. For in-study validation, the between-batch precision (%CV) at low, mid, high, QC samples for LN was less than or equal to 7.6% and accuracy (%theoretical) range from 97.7% to 103.1%.

Acetaminophen (paracetamol): Quantitative assessment of acetaminophen in human plasma was performed using a validated LC-MS/MS method (study: 8226219). The calibration curve range for acetaminophen was 50 to 50000 ng/mL. The assay was validated in accordance to the appropriate regulatory guidances. The Applicant reports that the bioanalysis of patient samples for acetaminophen was conducted according to current FDA guidelines and recommendations. For in-study validation, the between-batch precision (%CV) at low, mid, high, QC samples for acetaminophen was less than or equal to 6.2% and accuracy (%theoretical) range from 99.7% to 104.7%. The Applicant reports that all patient samples were analyzed within the known long-term stability period of 646 days at -10°C to -30°C.

5.3 Population PK Analysis

Applicant's Analysis:

PK Data:

The population PK analysis was based on data from five phase 3a trials; 3623, 3626, 3624, 3744 and 4091. All trials were randomized, multi-center trials and their design is summarized in Table 5.3-1. The trials were global except for trial 4091 which was conducted in Japan.

Table 5.3-1. Clinical Trial Characteristics for Population PK Analysis

	Trial 3623 (SUSTAIN 1)	Trial 3626 (SUSTAIN 2)	Trial 3624 (SUSTAIN 3)	Trial 3744 (SUSTAIN 6)	Trial 4091 (SUSTAIN –Japan)
Blinding	Double-blind	Double-blind	Open label	Double-blind	Open label
Comparator	Placebo	Sitagliptin 100 mg	Exenatide ER 2.0 mg	Placebo	Additional OAD
Semaglutide maintenance dose	0.5, 1.0 mg	0.5, 1.0 mg	1.0 mg	0.5, 1.0 mg	0.5, 1.0 mg
Randomisation	2:2:1:1*	2:2:1:1**	1:1	1:1:1:1*	2:2:1***
Randomised	390	1200	798	3260	595
Subjects randomised to semaglutide	260	800	399	1630	476
Planned number of subjects with PK assessment	390	600	399	240	476
Planned number of subjects with PK assessment and randomized to semaglutide	260	400	399	120	476
Treatment duration	30 weeks	56 weeks	56 weeks	104 weeks	56 weeks
Background medication	None	1–2 OADs (either MET, PIO, ROSI or a combination of either MET/PIO or MET/ROSI. ‡	1–2 OADs (MET and/or thiazolidinedione and sulfonyleureas)	0–2 OADs, basal or premixed insulins ± 0-2 OADs. Background medication was allowed to change during the trial	0–1 OAD (either of SU, glimide, α-GI or TZD) ‡

*Relative proportions randomised to 0.5 mg semaglutide, 1.0 mg semaglutide, 0.5 mg placebo, 1.0 mg placebo.

Relative proportions randomised to 0.5 mg semaglutide: 1.0 mg semaglutide, sitagliptin with 0.5 mg semaglutide placebo, sitagliptin with 1.0 mg semaglutide placebo. *Relative proportions randomised to 0.5 mg semaglutide, 1.0 mg semaglutide, additional OAD.

‡ α-GI: α-glucosidase inhibitor; MET: metformin; PIO: pioglitazone; ROSI: rosiglitazone; SU: sulfonyleurea; TZD thiazolidinediones

(Source: Applicant's Population PK Report, Table 1)

Trial Populations:

Trials 3623, 3626 and 3624 were global trials of which trial 3623 and 3626 also included Japanese patients whereas trial 4091 was a trial conducted in Japan, including Japanese subjects only.

For trials 3623, 3626 and 3624, the inclusion and exclusion criteria were similar across trials. The trials included male and female subjects diagnosed with T2D and with an age ≥ 18 years at

the time of signing informed consent. For Japanese patients included in the global trials, the age requirement was ≥ 20 years at the time of signing informed consent.

In trial 3744 (a long-term cardiovascular outcome trial), subjects were in addition required to have either clinical evidence of cardiovascular disease and to be aged ≥ 50 years or to have subclinical evidence of cardiovascular disease and to be aged ≥ 60 years. In this trial, subjects undergoing chronic haemodialysis or chronic peritoneal dialysis were excluded but there were no restrictions on renal function. In the three remaining global trials (trials 3623, 3626 and 3624), subjects with impaired renal function (defined as $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ except for trial 3623 which defined $\text{GFR} < 30 \text{ ml/min/1.73 m}^2$) were excluded, i.e. only no or mild renal impairment was allowed. For trial 4091 subjects with severely impaired renal function defined as estimated glomerular filtration rate (eGFR) $< 30 \text{ mL/min/1.73 m}^2$ were excluded.

In trial 3744, there was no restriction for the degree of glycaemic control ($\text{HbA1c} \geq 7.0\%$ -points), whereas the three remaining global trials included subjects with HbA1c 7.0–10.5 %-points (trials 3626 and 3624) or 7.0–10.0%-points (trial 3623). The Japanese trial (trial 4091) included subjects with HbA1c of 7.0 - 10.5%-points and on stable treatment.

There were no restrictions on body weight or body mass index in any of the trials. Detailed inclusion and exclusion criteria can be found in the respective trial protocols.

Bioanalytical Assay/Lower Limit of Quantification:

Semaglutide concentrations were estimated in plasma by means of a validated liquid chromatography-mass spectrometry (LC/MS/MS) assay following protein precipitation. The lower limit of quantification (LLOQ) was 0.729 nmol/L.

Population PK Methods:

A pre-specified full model approach was used for the population PK analysis. This comprised a graphical, model-independent exploration of covariate effects on semaglutide exposure as well as estimation of a base model without covariates and of a full covariate model with all covariates included.

Base PK Model:

The base model was used for justifying the structural model and as a base for the covariate analysis. A one-compartment model with first-order absorption and elimination was used to describe semaglutide PK. The structural model was parameterised in terms of the following parameters:

- k_a (absorption rate constant for semaglutide).

- CL/F (apparent clearance for semaglutide).
- V/F (apparent volume of distribution for semaglutide).

The semaglutide absorption rate constant (k_a) was set to a value of 0.0286 h⁻¹ obtained from a PK model based on full PK profiles from clinical pharmacology trials in normoglycaemic and T2D subjects (Novo Nordisk, data on file). The assumption that k_a can be fixed without affecting the conclusions of the analysis, was verified by a sensitivity analysis.

Between-subject variability (log-normal; without correlation between parameters) was estimated for CL/F and V/F. No between-subject variability was included for k_a .

The model was estimated on un-transformed concentration values and a proportional error model was used to describe the residual variability. Models were estimated using first order conditional estimation with interaction (FOCE+I).

Full PK Model with Covariates:

The full model containing the covariates listed in Table 5.3-2 was used for obtaining point estimates and confidence intervals for potential effects of these covariates on semaglutide plasma exposure.

In addition to above covariates, the exposure versus time since first dose and effects of antibody status (presence of anti-semaglutide antibodies) on semaglutide exposure at steady-state were evaluated graphically. The antibody status was evaluated after 16, 30, 40, 44, 56, 80 and 104 weeks of treatment and subjects with anti-semaglutide antibodies on at least one occasion were included in the graphical evaluation as antibody positives.

Table 5.3-2.: Covariates for the population PK model.

Covariate	Values / Unit
Sex	Female, male
Age group*	18–64, 65–74, >74 year
Race**	White, Black or African American, Asian
Ethnicity	Non-Hispanic or Latino, Hispanic or Latino
Body weight	kg (continuous variable)
Renal function	Normal (eGFR ≥90 mL/min), mild (eGFR 60–89 mL/min), moderate (eGFR 30–59 mL/min), severe (eGFR <30 mL/min)
Maintenance dose level	0.5, 1.0 mg
Injection site	Abdomen, thigh, upper arm

* Less than 20 subjects were above 85 years. Hence, these were included in the >74 year age group. **Race groups with less than 20 subjects and subjects of unknown race were included in the Other group which was merged with the White group for the covariate analysis.

The full covariate PK model was parameterised as:

$$CL_i / F = CL_{typ} \cdot E_{dose} \cdot E_{weight} \cdot E_{sex} \cdot E_{age} \cdot E_{GFR} \cdot E_{race} \cdot E_{ethnicity} \cdot E_{inj.site} \cdot \exp(\eta_i)$$

$$E_{dose} = (\theta_{dose0.5mg})^{dose0.5mg}$$

$$E_{weight} = \left(\frac{weight}{85kg} \right)^{\theta_{wt}}$$

$$E_{sex} = (\theta_{male})^{male}$$

$$E_{age} = (\theta_{age65-74y})^{age65-74y} \cdot (\theta_{age\geq75y})^{age\geq75y}$$

$$E_{GFR} = (\theta_{GFRmild})^{GFRmild} \cdot (\theta_{GFRmoderate})^{GFRmoderate} \cdot (\theta_{GFRsevere})^{GFRsevere}$$

$$E_{race} = (\theta_{BlackAfrAm})^{BlackAfrAm} \cdot (\theta_{Asian})^{Asian} \cdot (\theta_{Other})^{Other}$$

$$E_{ethnicity} = (\theta_{Hispanic})^{Hispanic}$$

$$E_{inj.site} = (\theta_{Thigh})^{Thigh} \cdot (\theta_{Upperarm})^{Upperarm}$$

where CL_{typ} is the typical semaglutide clearance (CL/F) for a reference subject profile defined as non-Hispanic or Latino, White female below 65 years, with a body weight of 85 kg, with normal renal function, dosed in the abdomen with semaglutide 1.0 mg. The body weight selected as the reference weight (85 kg) corresponds to the approximate median body weight of the population, see Table 4. The symbol θ is used for the covariate effect parameters. For categorical covariate variables, data from subjects in categories with less than 20 subjects were included in the largest covariate group.

The percentage of the amount of the unexplained variability in CL/F (and hence, of the average exposure) which was explained by inclusion of covariates was estimated from the base and full models as

$$\% \text{ variability explained} = \frac{\Omega_{\text{base}} - \Omega_{\text{full}}}{\Omega_{\text{base}}} \cdot 100\% \quad (\text{Eq. 1})$$

where Ω_{base} and Ω_{full} are the unexplained variances for $\log(\text{CL}/F)$ from the base model and the full covariate model, respectively.

Results:

A total of 7397 PK observations from 1683 subjects in the semaglutide treatment arms were scheduled for PK assessment. Nineteen subjects were excluded due to missing PK data, and 33 subjects were excluded due to lack of PK assessments above LLOQ. Additionally, 8 subjects were excluded due to mismatch between dosing information and PK sampling, and 11 subjects were excluded due to inadequate recording of the dose administrations. The final population PK dataset comprised of 1612 subjects with 6781 assessments i.e. with a mean of 4.2 semaglutide concentration values per subject. A total of 4.2% of the subjects (8.3% of the PK observations) were excluded during data cleaning.

Table 5.3-3 provides a summary of subject characteristics across trials with regards to sex, age group, race, ethnicity, renal function and maintenance dose as categories and age, body weight, BMI, diabetes duration, and baseline HbA1c on continuous scale. The population was relatively well balanced with regards to sex and furthermore, covered a wide range of demographic characteristics. Age ranged from 20 years to 86 years, baseline HbA1c ranged from 5.9 % to 13.1% and body weight ranged from 39.7 kg to 198.3 kg. Mean diabetes duration was 8.1 years, ranging from 0 to 48.9 years.

For the PK covariate analysis, it was required that each category contained at least 20 subjects which reduced the dataset to comprise three specific race groups; Asian, Black or African American, and White. The race group American Indian or Alaska Native comprised 2 subjects and was included in the group of White, which was the largest race group (N=838). Subjects without registered race (Unknown, n=41) were treated likewise. The majority of subjects were below 65 years. The age group ≥ 85 years contained less than 20 subjects and was included in an age group ≥ 75 years with 56 subjects in total. More than 60% of the subjects had normal renal function, the remaining having either mild (33.1%), moderate (3%) or severe (2%) renal impairment.

Table 5.3-3: Baseline characteristics of subjects included in the population PK analysis. Categories are ordered with categorical variables followed by continuous variables.

Category	Group	3623	3626	3624	3744	4091	Total
All	N	237 (14.7%)	417 (25.9%)	366 (22.7%)	118 (7.3%)	474 (29.4%)	1612 (100%)
Sex	Male	128 (54%)	204 (48.9%)	193 (52.7%)	66 (55.9%)	336 (70.9%)	927 (57.5%)
	Female	109 (46%)	213 (51.1%)	173 (47.3%)	52 (44.1%)	138 (29.1%)	685 (42.5%)
Age group	18-64 years	195 (82.3%)	343 (82.3%)	285 (77.9%)	54 (45.8%)	326 (68.8%)	1203 (74.6%)
	65-74 years	34 (14.3%)	68 (16.3%)	72 (19.7%)	49 (41.5%)	130 (27.4%)	353 (21.9%)
	75-84 years	8 (3.4%)	6 (1.4%)	9 (2.5%)	13 (11.0%)	18 (3.8%)	54 (3.3%)
	≥85 years	0 (0%)	0 (0%)	0 (0%)	2 (1.7%)	0 (0%)	2 (0.1%)
Race	White	155 (65.4%)	284 (68.1%)	315 (86.1%)	84 (71.2%)	0 (0%)	838 (52.0%)
	Asian	50 (21.1%)	104 (24.9%)	7 (1.9%)	23 (19.5%)	474 (100%)	658 (40.8%)
	Black or African American	19 (8.0%)	26 (6.2%)	19 (5.2%)	9 (7.6%)	0 (0%)	73 (4.5%)
	American Indian or Alaska Native	0 (0%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	2 (0.1%)
	Unknown ¹	13 (5.5%)	3 (0.7%)	23 (6.3%)	2 (1.7%)	0 (0%)	41 (2.5%)
Ethnicity	Not Hispanic or Latino	169 (71.3%)	347 (83.2%)	290 (79.2%)	91 (77.1%)	474 (100%)	1371 (85.0%)
	Hispanic or Latino	68 (28.7%)	70 (16.8%)	76 (20.8%)	27 (22.9%)	-	241 (15.0%)
Renal function ²	Normal	143 (60.3%)	284 (68.1%)	226 (61.7%)	23 (19.5%)	321 (67.7%)	997 (61.8%)
	Mild	83 (35.0%)	133 (31.9%)	140 (38.3%)	34 (28.8%)	143 (30.2%)	533 (33.1%)
	Moderate	11 (4.6%)	0 (0%)	0 (0%)	28 (23.7%)	10 (2.1%)	49 (3%)
	Severe	0 (0%)	0 (0%)	0 (0%)	33 (28.0%)	0 (0.0%)	33 (2.0%)
Maintenance dose	Semaglutide 1.0 mg	118 (49.8%)	196 (47.0%)	366 (100%)	61 (51.7%)	237 (50.0%)	978 (60.7%)
	Semaglutide 0.5 mg	119 (50.2%)	221 (53%)	0 (0%)	57 (48.3%)	237 (50.0%)	634 (39.3%)
Age	Mean (SD)	53.2 (11.6)	55.8 (9.5)	56.3 (10.3)	65.4 (7.7)	58.4 (10.4)	57 (10.6)
	Range	[26-80]	[30-82]	[20-78]	[51-86]	[26-83]	[20-86]
Body weight	Mean (SD)	93.8 (24.9)	89.4 (20.4)	96.2 (22.2)	88.3 (19.7)	71.3 (15.5)	86.2 (22.5)
	Range	[39.8-185.3]	[49-151.6]	[49.9-198.3]	[51.5-166]	[39.7-142]	[39.7-198.3]
BMI	Mean (SD)	33.4 (8.3)	32.3 (6.1)	34.1 (7.3)	32.1 (5.9)	26.3 (4.7)	31.1 (7.1)
	Range	[16.4-71.8]	[19.6-53.3]	[21.0-72.8]	[21.1-52.5]	[16.3-53.5]	[16.3-72.8]
Duration of diabetes	Mean (SD)	4.2 (5.5)	6.9 (5.4)	8.9 (5.9)	15.5 (8.7)	8.7 (6.3)	8.1 (6.6)
	Range	[0-34.5]	[0.3-39.2]	[0.4-37.1]	[0.4-48.9]	[0.1-41.7]	[0-48.9]
HbA _{1c}	Mean (SD)	8.1 (0.9)	8 (0.9)	8.3 (0.9)	8.7 (1.4)	8.1 (0.9)	8.2 (1)
	Range	[6.4-10.2]	[5.9-10.7]	[6.7-11.1]	[6.8-12.7]	[6.7-13.1]	[5.9-13.1]

¹Subjects without information on race were from France (n=20), Mexico (n=13), Canada (n=2), USA (n=2), Australia (n=1), Norway (n=1), South Africa (n=1) and United Kingdom (n=1). ²Renal function based on eGFR defined as normal function: ≥90 ml/min, mild impairment: 60–89 ml/min, moderate impairment: 30–59 ml/min, severe: <30 ml/min.

The PK of semaglutide was successfully described by a one-compartment model with first order absorption and first order elimination. The parameter estimates for the full covariate model are shown in Table 5.3-4. Based on the full model, the apparent clearance and volume of distribution for a reference subject profile (non-Hispanic or Latino, White female below 65 years, with a body weight of 85 kg, with normal renal function, dosed in the abdomen with 1.0 mg semaglutide) was found to be 0.0478 L/h and 12.2 L, respectively. The between subject CV of clearance was 26.6% for the base model and 12.9% for the full model. In terms of variance, this corresponds to 75.8% of the variability being explained by the covariates.

Table 5.3-4. Parameter estimates from the full population PK model with covariate effects included.

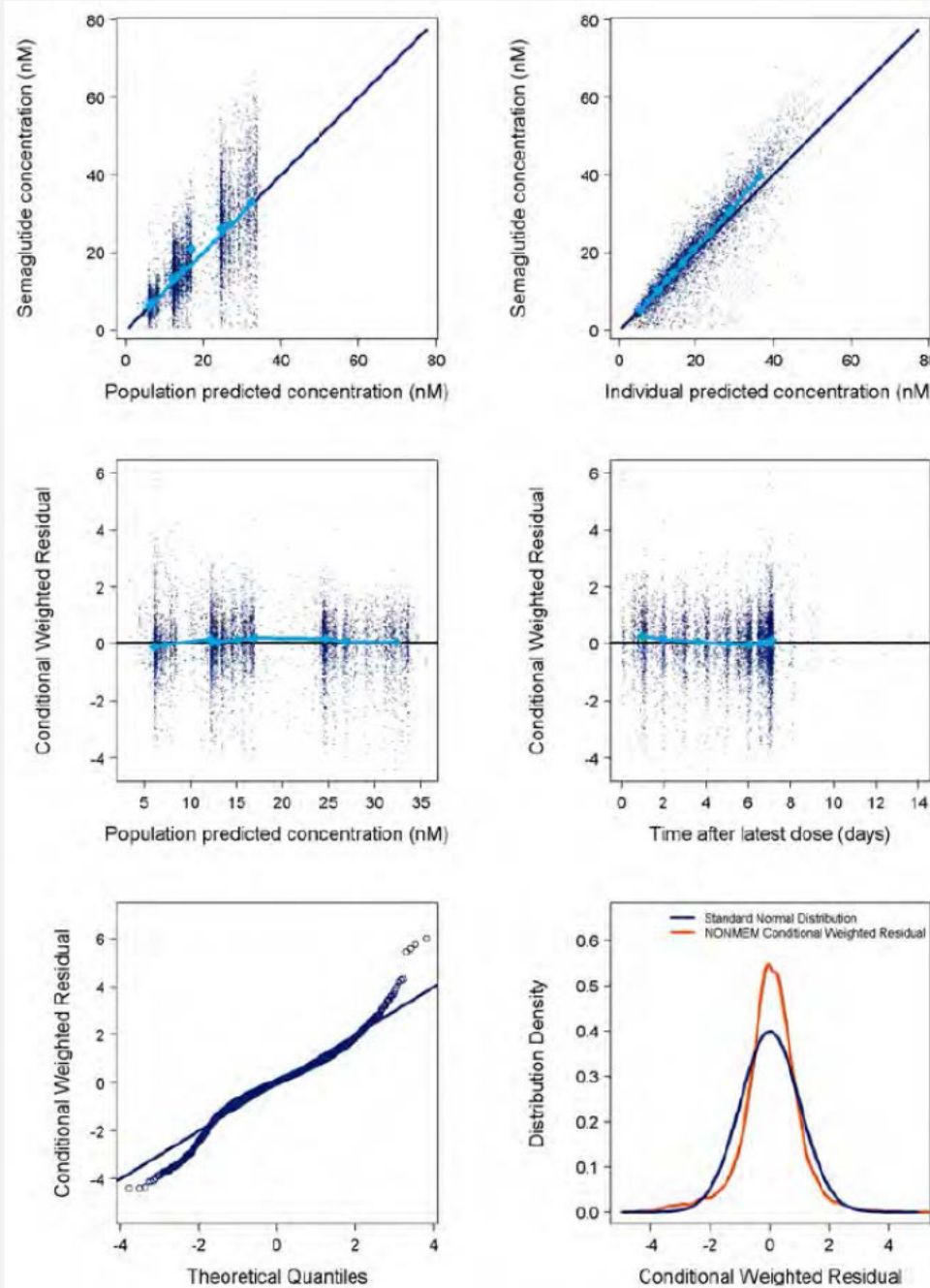
Parameter	Estimate	95% CI lower limit	95% CI upper limit	RSE (%)	IIV (%CV)	Shrinkage (%)
k_a (h^{-1})	0.0286	Fixed	Fixed	Fixed	NA	NA
CL/F (L/h)	0.0478	0.0468	0.0488	1.06	12.9	25
V/F (L)	12.2	12.1	12.4	0.487	37.3	58.1
Body weight	0.774	0.724	0.823	3.27	NA	NA
Sex - male	1.04	1.02	1.06	0.963	NA	NA
Age 65–74 y	0.988	0.966	1.01	1.11	NA	NA
Age >74 y	0.961	0.916	1.01	2.41	NA	NA
Maintenance dose 0.5 mg	1.00	0.984	1.02	0.855	NA	NA
Race - Black	0.974	0.912	1.04	3.28	NA	NA
Race - Asian	0.989	0.965	1.01	1.25	NA	NA
Ethnicity – Hispanic or Latino	1.06	1.03	1.1	1.62	NA	NA
Injection site - thigh	1.04	0.993	1.08	2.1	NA	NA
Injection site - upper arm	1.08	1.03	1.12	2.13	NA	NA
Renal - Mild impairment	0.948	0.930	0.965	0.963	NA	NA
Renal - Moderate impairment	0.955	0.900	1.01	2.95	NA	NA
Renal - Severe impairment	0.920	0.846	0.995	4.15	NA	NA
Proportional residual error (%CV)	23.8	NA	NA	NA	NA	8.0

RSE: Relative standard error. IIV: Inter-individual variation

The results of the model-based covariate analysis are summarized in Figure 25 as means and 90% CI for the average dose-normalised semaglutide exposure at steady-state (C_{avg}) for each covariate category relative to the reference subject profile. Due to the full model approach, the effect of each covariate was evaluated in addition to the combined effects of the other covariates. Covariate effects were considered to be of no relevance if the 90% CI of the relative exposure was within the 0.8 to 1.25 standard equivalence range.

The applicant's diagnostic plots for the base model are shown in Figure 5.3-1.

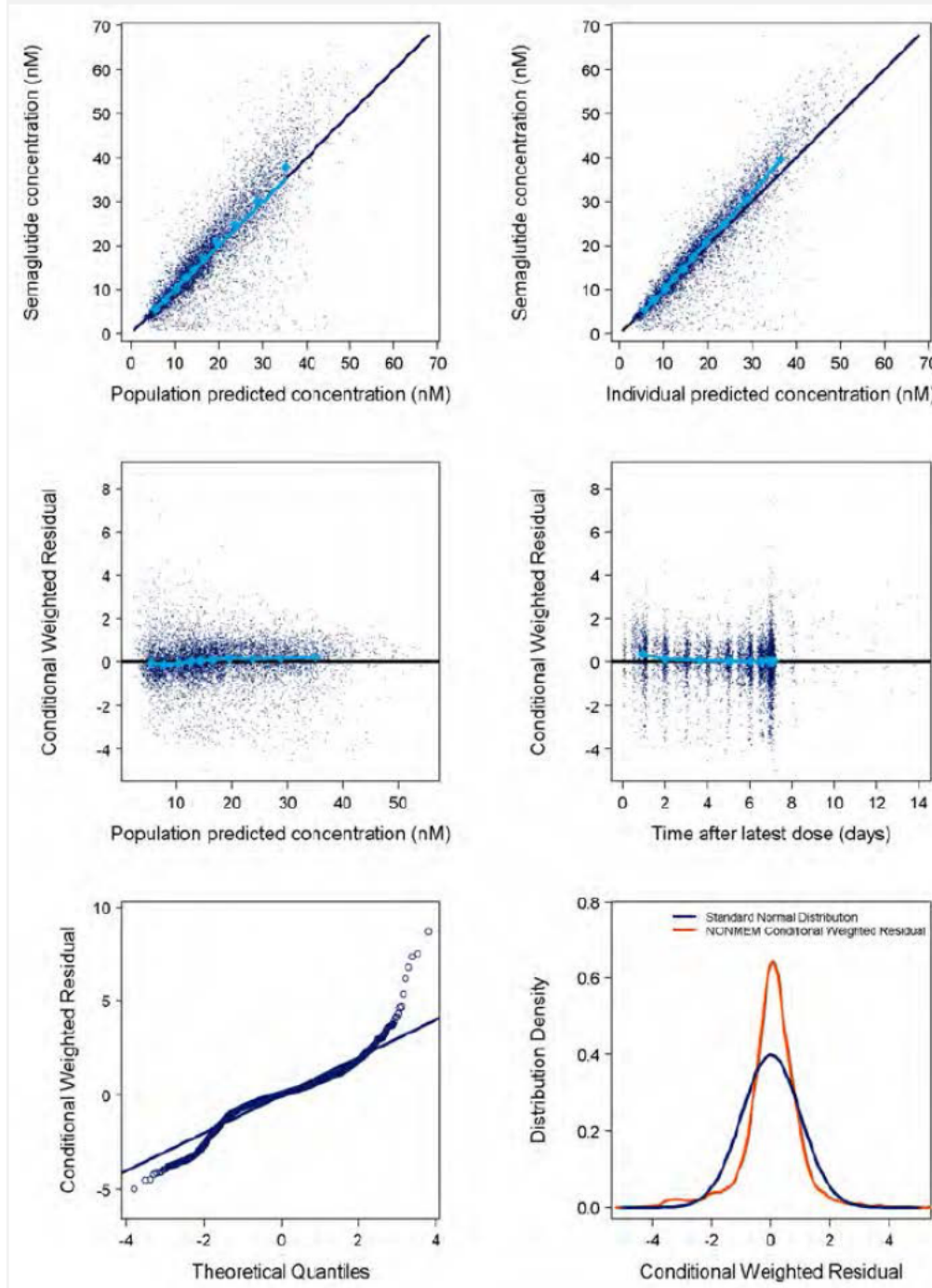
Figure 5.3-1. Diagnostic plots for the base PK model. Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals.



(Source: Applicant's Population PK Report, Figure 29)

The applicant's diagnostic plots for the full population PK model are shown in Figure 5.3-2.

Figure 5.3-2. Diagnostic plots for the base PK model. Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals.



(Source: Applicant's Population PK Report, Figure 32)

Reviewer’s Analysis and Comments:

The applicant’s population PK model is reasonable for describing semaglutide PK and establishing BW as a covariate and age, sex, race, ethnicity, and injection site as factors that do not affect the PK sufficiently to warrant dose adjustment.

The reviewer conducted additional NONMEM runs to evaluate the appropriateness of each covariate in the population PK model. Table 5.3-5 describes the change in objective function value and reduction in BSV after inclusion of each covariate on CL.

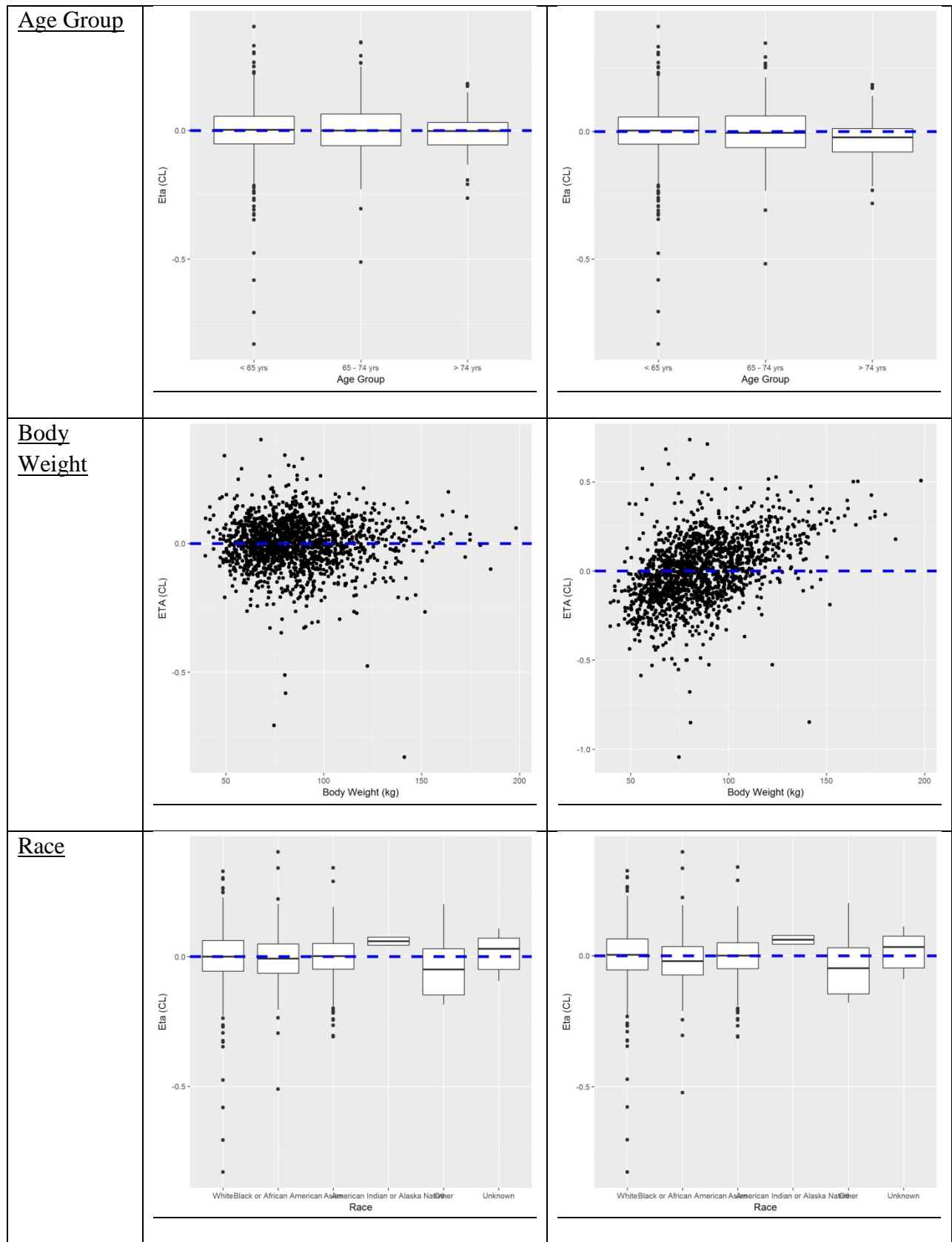
Table 5.3-5: Full PK model covariate evaluation based on change to objective function and between subject variability on clearance when removing the covariate of interest.

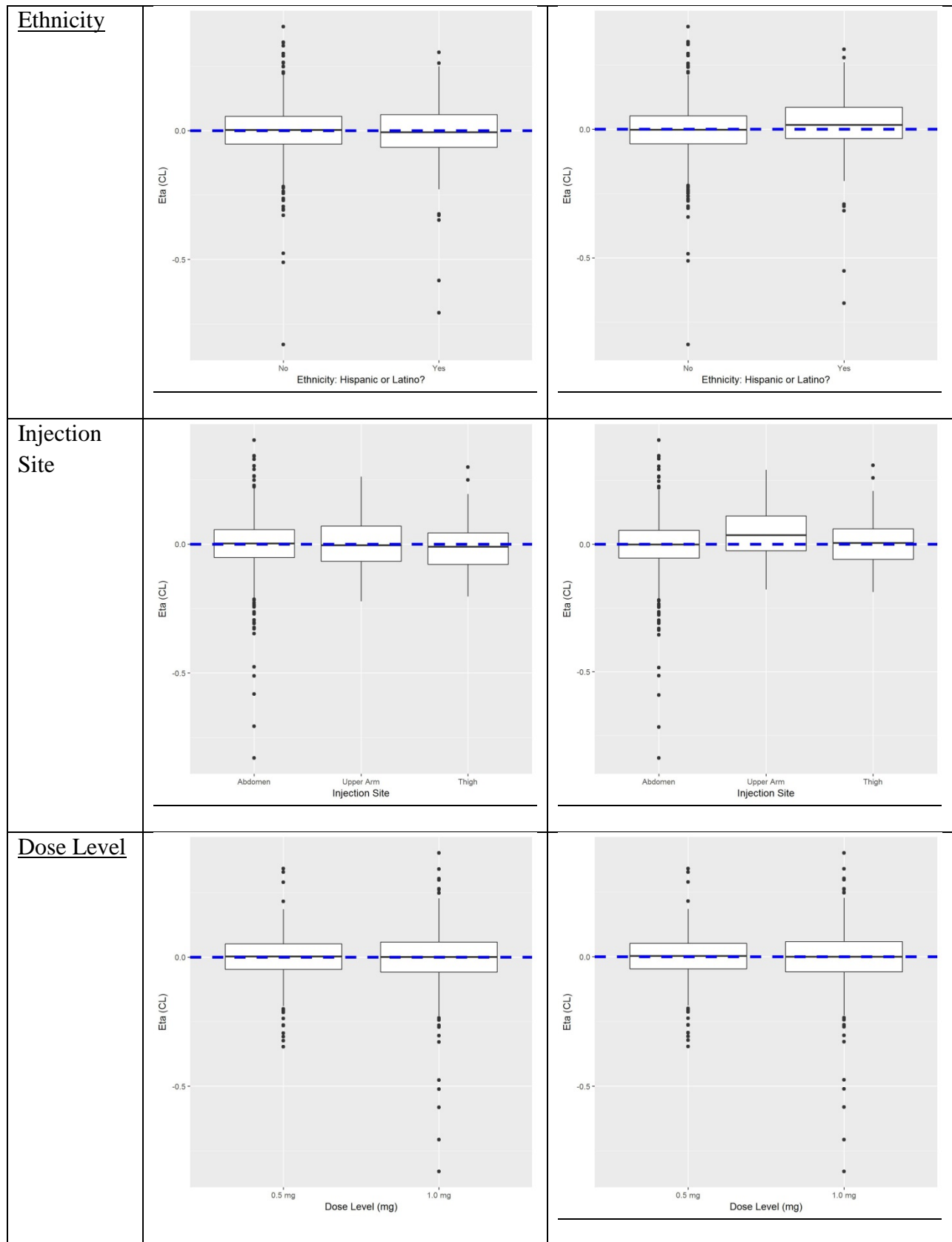
	Δ DF	OBJ	Δ OBJ	Δ BSV(CL) CV%	Shrinkage(CL) %
Sponsor's Full Model	0	26153.47	---	---	25.0
Full - Renal Impairment	3	26187.56	34.1	0.31	24.1
Full - Injection Site	2	26168.01	14.5	0.08	24.7
Full - Ethnicity	1	26173.83	20.4	0.00	25.0
Full - Race	2	26155.22	1.75	-0.08	24.9
Full - Dose Level	1	26153.46	-0.01	-0.04	25.0
Full - Age Group	2	26156.71	3.24	0.04	24.8
Full - Sex	1	26169.08	15.6	0.08	24.7
Full - Body Weight	1	26965.93	812	7.92	12.0

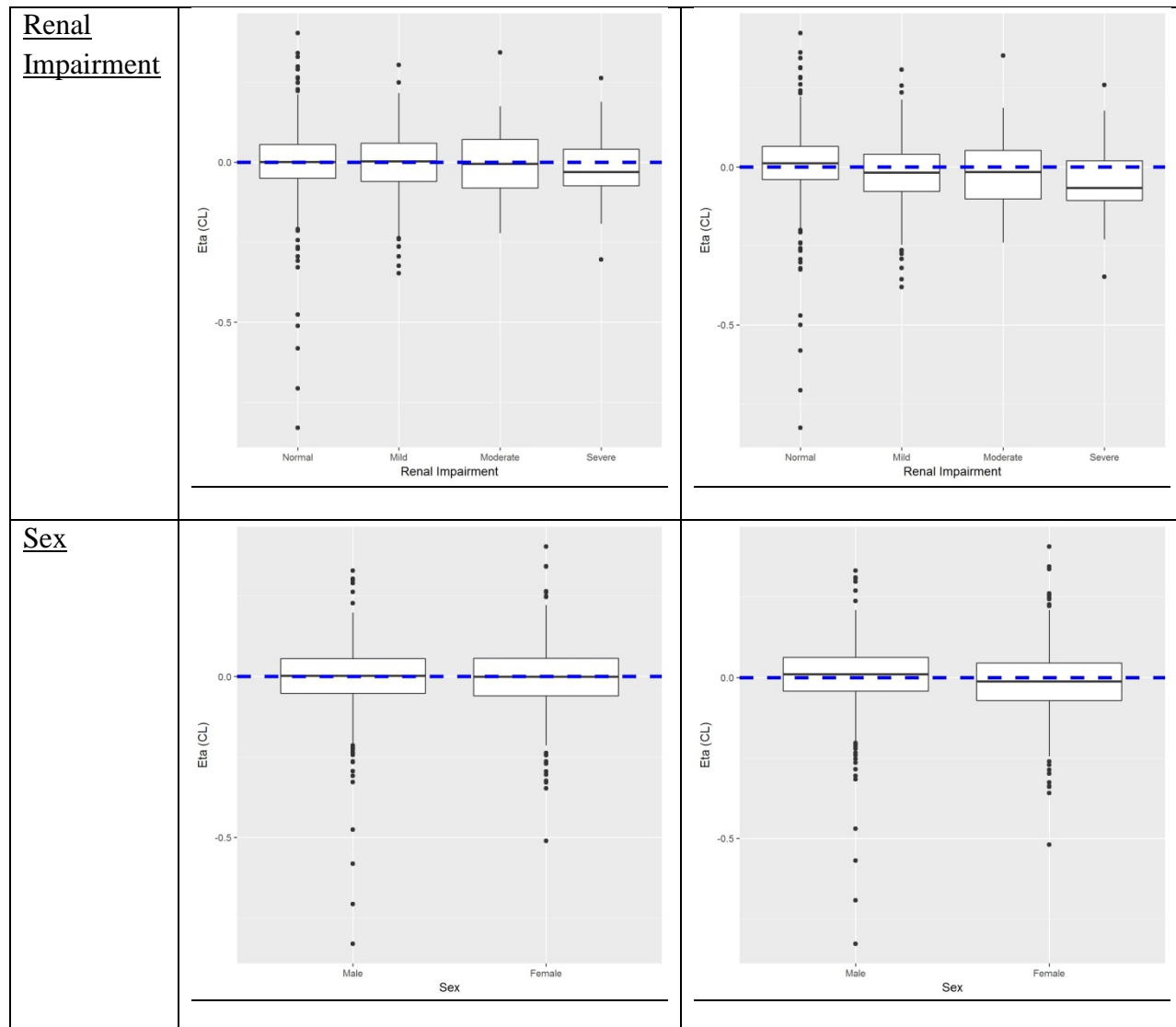
Figure 5.3-3 illustrates whether or not inclusion of the covariate improved was specified appropriately. Deviations from zero suggest there is a trend that is not accounted for correctly. As is consistent with the table above, only the inclusion of body-weight significantly improved the population PK model of semaglutide.

Figure 5.3-3: Covariate evaluation based on visual inspection of the relationship between residuals for individual clearance estimate and the covariate of interest. Deviations from zero suggest there is a relationship with the covariate that is not being characterized.

<u>Test Covariate</u>	<u>Full Model</u>	<u>Full Model w/out Test Covariate</u>







The reviewer's assessment based on the above sensitivity analysis of the applicant's full model is that the population PK characterization of semaglutide is acceptable.

5.4 Study NN9535-3616: Renal impairment study: Original Analysis

Study NN9535-3616, a multicenter, single-dose, parallel-group, open-label study, was conducted to investigate the PK of semaglutide in 5 groups of subjects with normal renal function, and mild, moderate, severe, and end-stage renal impairment. Healthy subjects or patients with T2DM (n=9 in the renal impairment groups) were enrolled in the study (n=14/normal renal function group and n=10-11/renal impairment groups completed the study). The study was a 'reduced/staged study design'. Stage 1 of the study was conducted in subjects with normal renal function and subjects with severe and end-stage renal impairment (on hemodialysis). Only if the pre-defined 'no-effect' criterion was not met would Stage 2 of the study be conducted in subjects with mild and moderate renal impairment. Subjects were administered a single dose of 0.5 mg of semaglutide via a SC injection into the anterior region of the thigh. Demographic characteristics pertaining to body weight and sex was planned to be balanced between the 5 groups, and age was planned to be kept within an age range (as close as possible between the groups). Subjects were allocated into the 5 renal function/impairment groups based on the estimation of creatinine clearance (glomerular filtration rate) using the Cockcroft & Gault formula (Table 1).

Table 1: Classification of renal function/impairment groups

Renal Group	Description	Estimated Creatinine Clearance (mL/min)
1 (N = 14)	Normal renal function	>80 mL/min
2 (N = 10)	Mild renal impairment	>50-≤80 mL/min
3 (N = 10)	Moderate renal impairment	>30-≤50 mL/min
4 (N = 10)	Severe renal impairment	≤30 mL/min
5 (N = 10)	End stage renal disease	Requiring dialysis

(Source: Clinical study report NN9535-3616, page 26)

The Reviewer notes that the study was initiated in 2009 and thereby the classification of renal function for subjects enrolled in the study (Table 1) was based on the previous 'Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling (May 1998)'.

The primary PK endpoint of the study was systemic exposure ($AUC_{0-\infty}$); the results of the statistical comparison of $AUC_{0-\infty}$ are presented in Table 2.

Table 2: Statistical analysis of the primary PK endpoint ($AUC_{0-\infty}$) and secondary PK endpoint (C_{max})

	Mild/ Normal (n=9-10/14)	Moderate/ Normal (n=10-11/14)	Severe/ Normal (n=10/14)	End-stage ² / Normal (n=9/14)
$AUC_{0-\infty}$: Primary analysis¹				
Point estimate of ratio	1.006	1.153	1.223	0.987
95% CI	0.833, 1.215	0.961, 1.384	1.018, 1.468	0.818, 1.192
$AUC_{0-\infty}$: Sensitivity analysis¹				
Point estimate of ratio	0.994	1.074	1.135	1.096
95% CI	0.849, 1.163	0.912, 1.265	0.974, 1.322	0.937, 1.283
C_{max}: Primary analysis¹				
Point estimate of ratio	0.953	0.878	0.948	0.721
90% CI	0.76, 1.20	0.70, 1.10	0.75, 1.19	0.57, 0.91
C_{max}: Sensitivity analysis¹				
Point estimate of ratio	0.902	0.794	0.859	0.818
90% CI	0.73, 1.11	0.64, 0.99	0.70, 1.06	0.66, 1.01

¹Statistical analysis was conducted using analysis of covariance (ANCOVA) in log-transformed scale with renal function as a fixed effect (primary analysis) and if applicable due to clinical reasons, with age, sex, log(body weight) as explanatory variable (sensitivity analysis). For $AUC_{0-\infty}$ if 95% CI was within the pre-defined range of [0.70; 1.43] then 'no-effect' was concluded. For C_{max} the 90% CI was analyzed and reported.

²Subjects with end-stage renal impairment did not undergo hemodialysis procedures during the 0-48 hr post-dose period (Clinical study report NN9535-3616, page 76 and 79)

Based on the primary analysis, semaglutide exposure was approximately 22% higher in subjects with severe renal impairment compared to subjects with normal renal function and the 'no-effect' criteria was not met (upper bound of the 95% CI for the ratio of $AUC_{0-\infty}$ was not within the pre-defined criteria of 0.70 to 1.43). The 'no-effect' criterion for semaglutide exposure was met for subjects with mild, moderate, end-stage renal impairment and subjects with normal renal function.

An imbalance in the distribution of age, sex and body weight was evident among the 5 groups. Male subjects were the predominate sex in all 5 groups and subjects with normal renal function (mean (SD): 54.6 (9.07) yrs and 84.9 (19.09) kg) and end-stage renal impairment (mean (SD):

48.2 (7.19) yrs and 97.2 (15.66) kg) were younger in age and had a higher body weight than the remaining 3 groups (mean range: 62.8 to 66.5 yrs and 78.1 to 80.1 kg).

A sensitivity analysis, adjusting for differences in age, sex and body weight, showed that for all comparisons the 95% CI for the ratio of $AUC_{0-\infty}$ was contained within the pre-defined ‘no-effect’ interval. After adjusting for demographic characteristics, a weak relationship between creatinine clearance and $AUC_{0-\infty}$ was evident, with observations of low creatinine clearance to higher $AUC_{0-\infty}$ ($p = 0.0414$). The Applicant reports that these observations are not considered to be clinically relevant since it corresponds to a 14% higher AUC in subjects with a creatinine clearance of 10 mL/min compared to subjects with a normal creatinine clearance (90 mL/min).

For C_{max} , a secondary PK endpoint, the ‘no-effect’ criterion was met for all comparisons except for subjects with end-stage renal impairment and subjects with normal renal function (Table 2). When accounting for imbalances in demographic characteristics (age, sex, body weight), a 10-20% lower C_{max} in subjects with renal impairment was evident compared to subjects with normal renal function. The 90% CI for the ratio of C_{max} was only within the pre-defined criterion for subjects with mild and severe renal impairment and subjects with normal renal function. No linear relationship was observed between creatinine clearance and C_{max} ($p = 0.1643$, unadjusted analysis, $p=0.0859$ adjusted analysis).

The Applicant reports that dialysis did not appear to affect the PK of semaglutide as the point estimate of the ratio (end-stage renal impairment/normal renal function) without hemodialysis (AUC_{0-48} : 0.722 [0.57, 0.91]_{90%CI}) was comparable to the point estimate of the ratio during hemodialysis (AUC_{48-96} : 0.815 [0.67, 0.99]_{90%CI}). After adjusting for demographic characteristics (age, sex, body weight) the point estimates for AUC_{0-48} (0.814 [0.66, 1.01]_{90%CI}; without hemodialysis) and AUC_{48-96} (0.930 [0.78, 1.10]_{90%CI}; during hemodialysis) were comparable.

The unbound fraction of semaglutide was low and similar across the renal function and renal impairment groups (normal renal function group, mean $f_u = 0.0006$, renal impairment groups, mean $f_u = 0.0007$).

The results show that renal impairment does not impact the PK of semaglutide in a clinically relevant manner.

5.5 Applicant's Analysis of Retinopathies with regards to change from baseline HbA1c

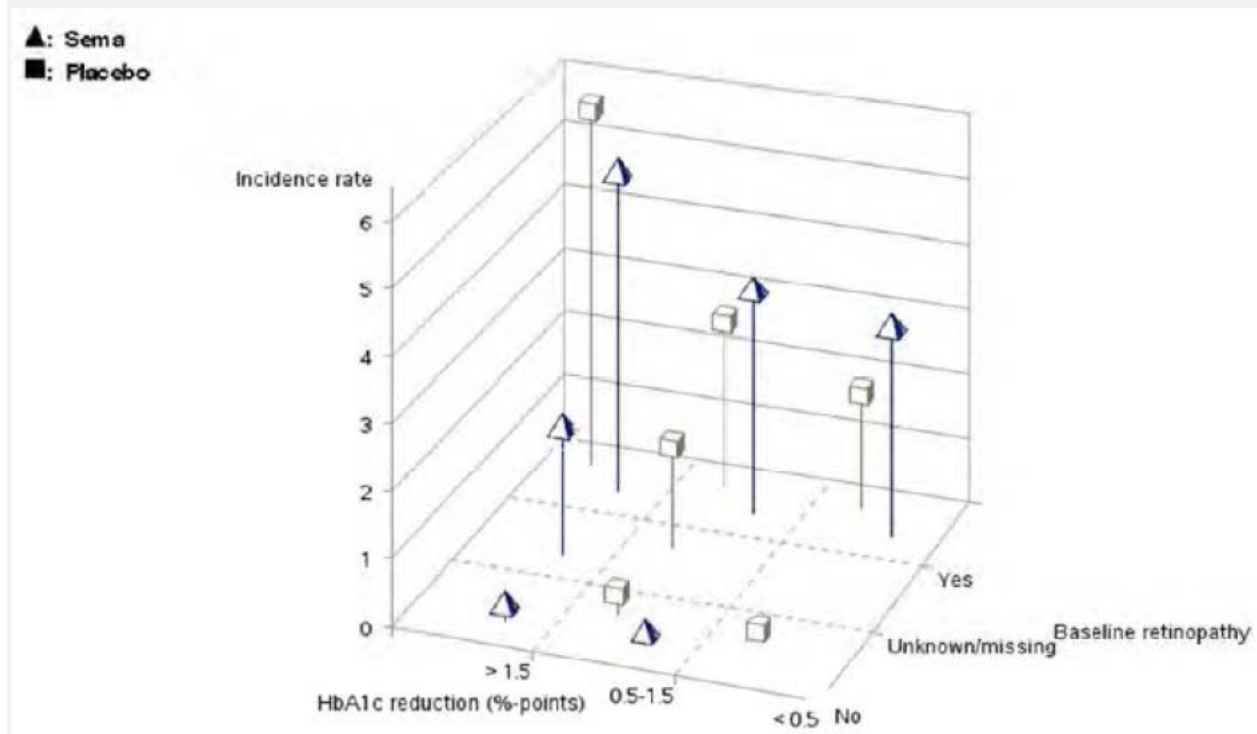
Source: Applicant's Summary of Clinical Safety, page 160-163

To evaluate whether the mechanism underlying the effect of semaglutide on EAC-confirmed events of diabetic retinopathy complications could be attributed to the initial rapid decline in blood glucose, a post hoc mediator analysis was performed.

In this analysis, the change in HbA1c at week 16 was chosen as a marker for the initial rapid decline in blood glucose. Week 16 was considered the most appropriate time point for assessment of the rate of the change in HbA1c for two reasons: 1) the full treatment effect on HbA1c was attained at this time point (Figure 2–24) and 2) the number of subjects discontinuing prematurely (higher with semaglutide than with placebo) was limited at this time point.

Figure 2–24 illustrates that the incidence rates of first EAC-confirmed event of diabetic retinopathy complications for different subgroups of subjects increased with increasing HbA1c reduction and were highest in the subjects with diabetic retinopathy at baseline. In subjects with similar reduction in HbA1c at week 16 and similar status of diabetic retinopathy at baseline, the incidence rates of first EAC-confirmed event of diabetic retinopathy complications between treatments (semaglutide versus placebo) were comparable.

Applicant's Figure 2–24 First EAC-confirmed event of diabetic retinopathy complications – observed risk times and incidence rates – by treatment, baseline history of diabetic retinopathy, and reduction in HbA1c at week 16 – FAS in-trial – CVOT



Note: The figure shows observed incidence rates for time to first EAC-confirmed event of diabetic retinopathy complications (vertical axis) for subgroups of subjects categorised by baseline diabetic retinopathy (yes, no, unknown/missing) and reduction in HbA1c (%-points) at week 16 (<0.5%-points, 0.5–1%-points, >1.5%-points), horizontal axes. Blue needles with pyramids are for semaglutide, grey needles with cubes are for placebo. Observed incidence rates per 100 PYR are calculated as 100 times the number of events divided by the total risk time. A subject's risk time is the time from randomisation until the subject's first EAC-confirmed event or censoring. Abbreviations: EAC: event adjudication committee; HbA1c: glycated haemoglobin; PYR: patient-years of risk time. Cross-reference: Trial 3744 (M 5.3.5.1), EOT Figure 15.2.862.

The post hoc mediator analysis was an unstratified Cox proportional hazards model which in addition to treatment (semaglutide, placebo) included 'change in HbA1c (% points) at week 16' and factors considered to be both predictive for a reduction in HbA1c as well as being risk factors for diabetic retinopathy. Such factors are known to potentially confound a mediator analysis, if they are not controlled for in the analysis. These factors were: 'HbA1c at baseline', 'retinopathy at baseline' ('Yes', 'No', 'Unknown/missing') and 'baseline duration of diabetes'. The results of the mediator analysis are presented in Table 2–39. The estimated treatment difference (in terms of HR) between semaglutide and placebo for time to first EAC-confirmed event of diabetic retinopathy complications was reduced from a statistically significant HR of 1.76 in the pre-specified analysis to a non-statistically significant HR of 1.22 in the mediator analysis (controlling for the effect of change in HbA1c at week 16) with a proportion of the treatment effect eliminated of 72%. Conversely, the effect of the change in HbA1c at week 16 was found to be statistically significant with a HR of 1.26 for a 1%-point reduction in HbA1c at week 16. This supports the theory that a rapid decline in blood glucose contributed to the mechanisms underlying the development of diabetic retinopathy complications in those with a prior history of diabetic retinopathy.

Applicant's Table 2-39 Time to first EAC-confirmed event of diabetic retinopathy complications – *post hoc* mediator analysis of change in HbA1c at week 16 – FAS in-trial –

CVOT.

Analysis	Estimate [95% C.I.]	p-value	Subjects with EAC-confirmed events of diabetic retinopathy complications in-trial vs. all subjects	
			Semaglutide	Placebo
Pre-specified analysis				
Total effect of treatment ^a	1.76 [1.11;2.78]	0.0159	50/1648	29/1649
Post hoc mediator analysis				
Controlled direct effect of treatment ^a	1.22 [0.71;2.09]	0.4793	50/1648	29/1649
Effect of change in HbA _{1c} (%-points) at week 16 ^b	1.26 [1.03;1.57]	0.0290	-	-
Proportion eliminated	0.72	-	-	-

a: HR for semaglutide vs. placebo; b: HR ratio for one unit larger reduction.

Note: The table summarises the results of a *post hoc* mediator analysis for time to first EAC-confirmed event of diabetic retinopathy complication together with the results of the pre-specified analysis. The mediator analysis assesses the effect of change in HbA_{1c} at week 16 on time to first EAC-confirmed event of diabetic retinopathy complication. This is analysed by an unstratified Cox proportional hazards model which in addition to treatment (semaglutide, placebo) as a fixed factor also includes 'change in HbA_{1c} (%-points) at week 16' and factors considered to be both predictive for a reduction in HbA_{1c} as well as being risk factors for diabetic retinopathy. Such factors are known to potentially confound a mediator analysis, if they are not controlled for in the analysis. These factors were: 'HbA_{1c} at baseline', 'retinopathy at baseline' ('Yes', 'No', 'Unknown/missing') and 'baseline duration of diabetes'. Missing values of HbA_{1c} were imputed as predicted values from a mixed model for repeated measures. 'Proportion eliminated' is calculated as: (total effect of treatment - controlled direct effect of treatment)/(total effect of treatment - 1), i.e. the absolute risk reduction from the mediator analysis divided by the total excess risk.

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; EAC: event adjudication committee; HbA_{1c}: glycated haemoglobin; HR: hazard ratio.

Cross-reference: modified from [Trial 3744 \(M 5.3.5.1\)](#), EOT Table 15.2.860.

The mediator analysis was also performed to evaluate the effect of controlling for the change in HbA_{1c} at weeks 8, 30, 44, 56, 68, 80, 92 and 104. When using the change in HbA_{1c} at week 8 in the statistical model as a measure of the initial reduction in blood glucose levels, the proportion of the treatment effect eliminated was lower than when using HbA_{1c} at week 16. This was as expected since HbA_{1c} reflects the average glycaemic control over the past 12 weeks, and it would therefore be unlikely that HbA_{1c} measured at week 8 fully reflects the actual treatment effect on glycaemic control during the 8 weeks. As opposed, HbA_{1c} at week 16 is expected to more fully reflect the actual treatment effect on glycaemic control during the initial months of treatment. Furthermore, the proportion of the treatment effect eliminated by the change in HbA_{1c} generally decreased with increasing treatment weeks after week 16.

Reviewer's Comments:

The applicant's post hoc analysis suggests that a rapid decline in HbA1c may lead to retinopathies for patients with a prior retinopathy history. This would suggest that a slower course of increasing the dose from 0.25 mg up to 1.0 mg may be warranted in high-risk patients. This topic will be revisited in the October 2017 addendum following the advisory committee meeting.

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/s/

SHALINI WICKRAMARATNE SENARATH YAPA
08/22/2017

JUSTIN C EARP
08/22/2017

LIAN MA
08/22/2017

MANOJ KHURANA
08/22/2017

CHANDRAHAS G SAHAJWALLA
08/22/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	NDA 209637	SDN	1
Applicant	Novo Nordisk Inc.	Submission Date	12/05/2016
Generic Name	Semaglutide	Brand Name	TBD
Drug Class	Long-acting glucagon-like peptide (GLP-1) receptor agonist		
Proposed Indications	<ul style="list-style-type: none"> ▪ As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus <div style="background-color: #cccccc; height: 20px; width: 100%; text-align: right; font-size: 8px;">(b) (4)</div>		
Proposed Dosage Regimen	Recommended starting dose is 0.25 mg once weekly (not a therapeutic dose); after 4 weeks the dose should be increased to 0.5 mg once weekly; after 4 weeks the dose may be increase to 1 mg once weekly to further improve glycemic control. Maximum recommended dose is 1 mg once weekly. Can be administered at any time of the day, with or without meals.		
Dosage Form	Pre-filled, multi-dose pen	Route of Administration	Subcutaneous (abdomen, thigh or upper arm)
OCP Division	DCP2	OND Division	DMEP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Shalini Wickramaratne Senarath Yapa, Ph.D.	Manoj Khurana, Ph.D.	
Pharmacometrics	Justin Earp, Ph.D.	Nitin Mehrotra, Ph.D.	
Genomics			
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	2/3/2017	74-Day Letter Date	2/17/2017
Review Due Date	8/2/2017	PDUFA Goal Date	12/5/2017
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes list comment(s):			
Is there a need for clinical trial(s) inspection?			
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes, explain:			

Clinical Pharmacology Package

Tabular Listing of All Human Studies Yes No Clinical Pharmacology Summary Yes No
 Bioanalytical and Analytical Methods Yes No Labeling Yes No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)	
In Vitro Studies			
<input checked="" type="checkbox"/> Metabolism Characterization	4	206642; 214064; 215514; 214379	
<input type="checkbox"/> Transporter Characterization			
<input checked="" type="checkbox"/> Distribution	2	208380; 213228	
<input checked="" type="checkbox"/> Drug-Drug Interaction	3	XT135105; XT158008; XT153005	
In Vivo Studies			
Biopharmaceutics			
<input checked="" type="checkbox"/> Absolute Bioavailability	1	NN9535-3687	
<input type="checkbox"/> Relative Bioavailability			
<input checked="" type="checkbox"/> Bioequivalence	2	NN9535-3679; NN9535-4010	
<input type="checkbox"/> Food Effect			
<input checked="" type="checkbox"/> Other	16	Bioanalytical methods (study numbers): 207163, 208465, 209028, 209082, 209099, 209507, 214299, AA91659, AA95112, AA95860, AA98749, CA11388, CA11773, CA12337, CA17145, ZZ44775	
Human Pharmacokinetics			
Healthy Subjects	<input checked="" type="checkbox"/> Single Dose	1	NN9535-1820
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input checked="" type="checkbox"/> Multiple Dose	6	NN9535-1821; NN9535-3623, NN9535-3626, NN9535-3624, NN9535-4091, NN9535-3744
<input checked="" type="checkbox"/> Mass Balance Study	1	NN9535-3789	
<input type="checkbox"/> Other (e.g. dose proportionality)			
Intrinsic Factors			
<input checked="" type="checkbox"/> Race	2	NN9535-3633; NN9535-3634	
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input checked="" type="checkbox"/> Hepatic Impairment	1	NN9535-3651	
<input checked="" type="checkbox"/> Renal Impairment	1	NN9535-3616	
<input type="checkbox"/> Genetics			
Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			
<input checked="" type="checkbox"/> Effects of Primary Drug	3	NN9535-3817; NN9535-3818; NN9535-3819	
Pharmacodynamics			
<input checked="" type="checkbox"/> Healthy Subjects	1	NN9535-3685	
<input checked="" type="checkbox"/> Patients	2	NN9535-3635; NN9535-3684	
Pharmacokinetics/Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			

<input checked="" type="checkbox"/> QT	1	NN9535-3652		
Pharmacometrics				
<input checked="" type="checkbox"/> Population Pharmacokinetics	1	SUSTAIN Modelling Report		
<input checked="" type="checkbox"/> Exposure-Efficacy	1	SUSTAIN Modelling Report		
<input checked="" type="checkbox"/> Exposure-Safety	1	SUSTAIN Modelling Report		
Total Number of Studies		In Vitro		In Vivo
			25	23
Total Number of Studies to be Reviewed		In Vitro	25	In Vivo
				23

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 351(k) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist

Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Filing Memo

See Attachment: Presentation slides from Filing meeting (date: 01/19/2017).



NDA 209637 Filing Meeting

Semaglutide injection

(Proposed proprietary name: Ozempic)

Sponsor: Novo Nordisk Inc.
Submitted: 5th December 2016
Filing meeting: 19th January 2017

OCP Review Team:

Shalini W.S. Yapa, Ph.D., Justin Earp, Ph.D.,
Nitin Mehrotra, Ph.D., Manoj Khurana, Ph.D.



Overview

- **Type of submission:** Section 505(b)(1)
- Semaglutide is a novel glucagon-like peptide-1 (GLP-1) receptor agonist
- **Proposed indications:**
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
- **Formulation, Dosage Form and Strengths:**
 - Semaglutide 1.34 mg/mL solution for injection
 - Prefilled, multi-dose pen that delivers doses of 0.25 mg, 0.5 mg
 - Prefilled, multi-dose pen that delivers a dose of 1 mg
- **Administration:**
 - SC injection in the abdomen, thigh or upper arm
- **Proposed dosing regimen:**
 - Starting dose of 0.25 mg OW, after 4 weeks the dose should be increased to 0.5 mg OW, after 4 weeks the dose may be increased to 1 mg OW
 - Maximum recommended dose - 1 mg OW

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2



Clinical Pharmacology Development Program

Phase 1 trials (Type)	Population, Sample Size	Description
1820 (PK/PD)	Healthy, 56	Dose escalation; SD; Safety, tolerability, PK, PD
3679 (PK/PD)	Healthy, 44	Equivalence – product strengths (concentrations of 1 mg/mL, 3 mg/mL, 10 mg/mL); SD
3687 (PK/PD)	Healthy, 42	Equivalence/BA; PK of SC injections (concentrations of 1 mg/mL, 3 mg/mL, 10 mg/mL) and absolute BA; SD
4010 (PK/PD)	Healthy, 28	Bioequivalence – 2 manufacturing processes (trial products based on semaglutide (b) (4) and semaglutide (b) (4) SD
3633 (PK/PD)	Healthy (Japanese, Caucasian), 84	Dose escalation; MD; Safety, tolerability, PK
3634 (PK/PD)	Healthy (Japanese, Caucasian), 44	Safety, tolerability, MD
3789 (PK/PD)	Healthy, 7	Absorption, metabolism, excretion; SD
3652 (PK/PD)	Healthy, 166	Effect on cardiac repolarization; MD
Special Populations		
3616 (PK/PD)	62	Renal impairment; SD; PK, tolerability
3651 (PK/PD)	44	Hepatic impairment; SD; PK, safety, tolerability
Drug-Drug Interaction		
3817 (PK/PD)	Healthy, 23	Metformin and warfarin; MD; PK and PD
3818 (PK/PD)	Healthy, 31	Atorvastatin and digoxin; MD; PK
3819 (PK/PD)	T2DM, 43	Oral contraceptive combination drug; MD; 13 weeks
Pharmacodynamics		
3635 (PK/PD)	T2DM (healthy subjects as comparators), 87	Effect on β -cell function; MD; 12 weeks
3684 (PK/PD)	T2DM, 37	Effect on hypoglycemia counter-regulation; MD; 26 weeks
3685 (PK/PD)	Obese, 30	Energy intake, appetite sensations, postprandial glucose, TG metabolism, gastric emptying; MD; 12 weeks

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3

Clinical Development Program



Phase 2 trial (Type)	Population, Sample Size	Description
1821 (Dose range)	T2DM, 411	Dose finding; Safety and efficacy; MD; 12 weeks

Phase 3 trials (Type)	Population, Sample Size	Description
3623 (Efficacy and safety)	T2DM (drug naïve), 387	Placebo-controlled; efficacy and safety; 30 weeks
3626 (Efficacy and safety)	T2DM (on metformin and/or thiazolidinedione (TZD)), 1225	Active-control (sitagliptin); efficacy and safety; 56 weeks
3624 (Efficacy and safety)	T2DM (on 1-2 OADs), 809	Active-control (exenatide ER); efficacy and safety; 56 weeks
4091 (Efficacy and safety)	T2DM (Japanese, on 1 OAD (sulphonylurea (SU), glinide, α -glucosidase inhibitor (α -GI) or TZD)), 600	Active-control (SU, glinide, α -GI or TZD); efficacy and safety; 56 weeks
3744 (Safety)	T2DM (on 1-2 OADs or insulin with or without 1-2 OADs, or T2DM drug naïve), 3297	Placebo-control; Evaluate CV and other long-term outcomes with semaglutide; 104 weeks

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4

Filing Conclusion



- Application is fileable from a clinical pharmacology perspective

Key Review Questions

- What are the PK characteristics of SC semaglutide and do they support the proposed dosing regimen? Does the data support the sponsor's claims?
- What are the clinically relevant DDI between semaglutide and co-administered drugs? Does the data support the sponsor's claims?
- What are the PD characteristics of SC semaglutide? How are they relevant to the efficacy of semaglutide? Does the PD data support the sponsor's claims?
- Does the exposure-response relationship for efficacy support the proposed dose of semaglutide?

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5

Semaglutide – Clinical Pharmacology

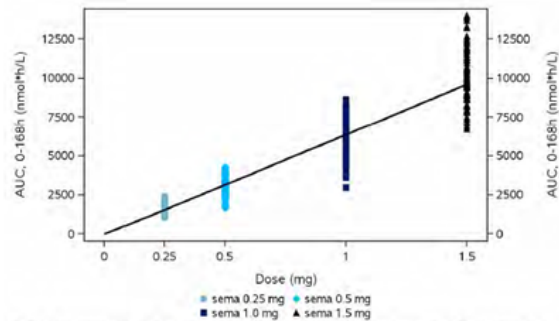
Pharmacokinetic Profile



Sponsor's claims:

- Absolute bioavailability ~89%
- C_{max} was reached 1 to 3 days post-dose
- Steady-state exposure was achieved following 4-5 weeks of OW dosing
- Elimination half-life of ~ 1 week
- Extensively bound to plasma protein, metabolized following proteolytic cleavage, primary excretion routes are via urine and feces
- Exposure increased in a dose-proportional manner (doses of 0.5 mg and 1 mg)

Individual AUC_{0-168h} of semaglutide at SS (trial 3652; healthy subjects)



Review Questions:

- What are the PK characteristics of SC semaglutide and do they support the proposed QW dosing regimen?
- Does the data support the sponsor's claims?

No Dose Adjustments Proposed for Any Intrinsic Factors/Specific Populations



Population PK analysis of semaglutide exposure in subjects with T2DM (trials 3623, 3626, 3624, 3744, 4091)

Covariate	Test category	Reference category	Relative exposure (C _{avg})	Ratio [90% CI]
Sex	Male (N:527)	Female (N:885)		0.99 [0.95, 0.98]
Age group	65-74 years (N:353)	18-64 years (N:1203)		1.01 [0.99, 1.03]
	>74 years (N:56)			1.04 [1.00, 1.08]
Race	Black or African American (N:73)	White (N:838)		1.03 [0.99, 1.07]
	Asian (N:658)			1.01 [0.99, 1.03]
Ethnicity	Hispanic or Latino (N:241)	Non-Hispanic or Latino (N:1371)		0.94 [0.92, 0.96]
Body weight	55 kg	85 kg		1.40 [1.38, 1.42]
	127 kg			0.73 [0.72, 0.74]
Renal function	Mild impairment (N:533)	Normal (N:997)		1.09 [1.04, 1.07]
	Moderate impairment (N:49)			1.05 [1.00, 1.09]
	Severe impairment (N:33)			1.09 [1.03, 1.15]
Maintenance dose	0.5 mg (N:634)	1.0 mg (N:976)		1.00 [0.98, 1.01]
Injection site	Thigh (N:86)	Abdomen (N:1456)		0.97 [0.93, 1.00]
	Upper arm (N:70)			0.93 [0.90, 0.96]

- Exposure inversely related to body weight
- In the exposure range associated with semaglutide 0.5 mg and 1 mg, all subjects, independent of body weight, achieved exposures adequate for a HbA1c lowering effect

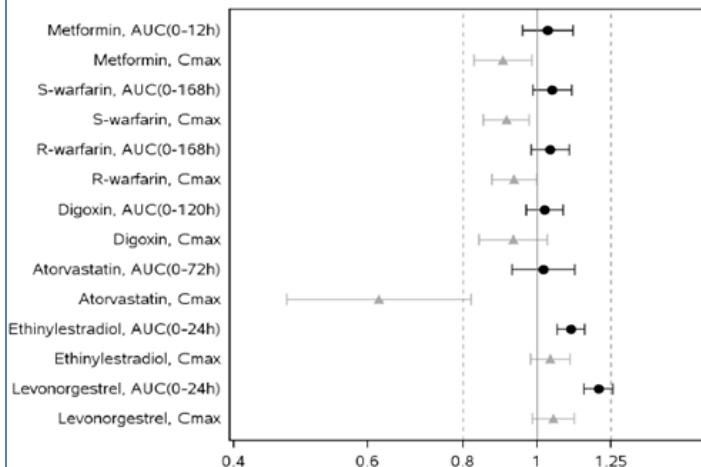
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8

No Specific Concern for Drug-Drug Interactions



Effect of semaglutide on co-administered oral drugs in subjects with T2DM and in healthy subjects (trial 3817, 3818, 3819)



Estimated ratio (with/without semaglutide) and 90% confidence interval
Metformin, ethinylestradiol and levonorgestrel assessed at steady state
Warfarin, digoxin and atorvastatin assessed after single dose

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9

Sponsor's Claims:

- CYP/Transporter:** Low potential for semaglutide to inhibit or induce CYP enzymes and inhibit drug transporters
- Delay in gastric emptying:** No clinically relevant DDI with semaglutide

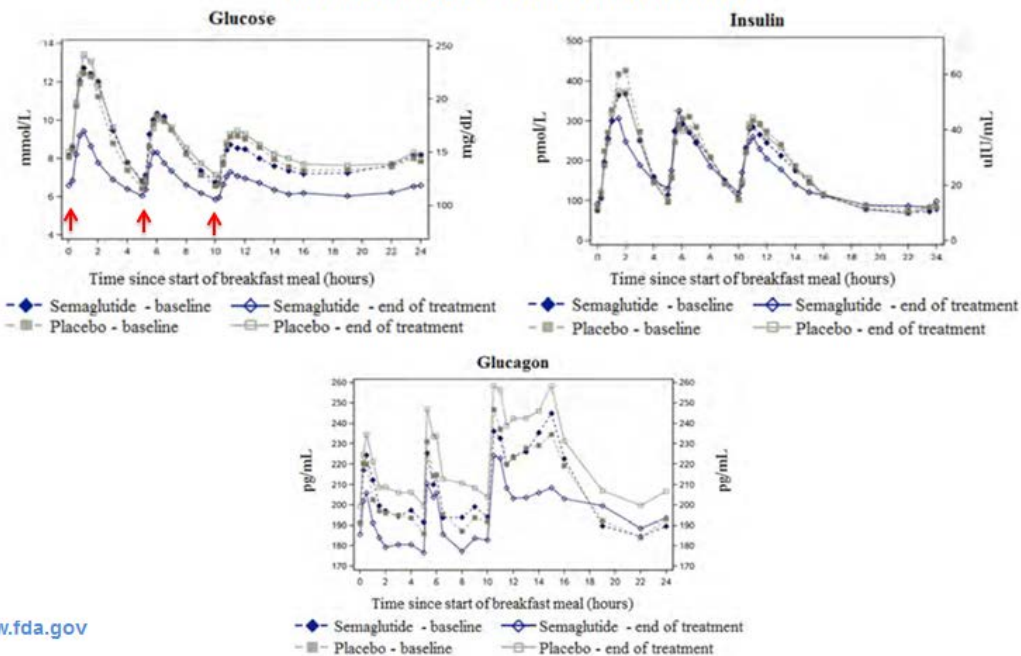
Review Question:

- What are the clinically relevant interactions between semaglutide and co-administered drugs?
- Does the data support the sponsor's claims?

Pharmacodynamic Profile – Clinical Relevance of Post-prandial Assessments Over 24-hr



24-hour glucose, insulin and glucagon profile after 12 weeks of treatment with semaglutide 1 mg or placebo in subjects with T2DM (trial 3635)



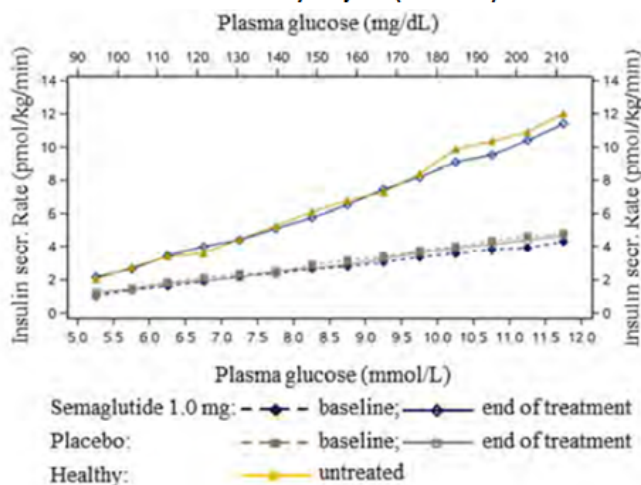
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10

Pharmacodynamic Profile – Clinical Relevance of Glucose Dependent Insulin Secretion



Insulin secretion rate vs. glucose concentrations during graded glucose infusion test in subjects with T2DM after 12 weeks of treatment and in healthy subjects (trial 3635)



Semaglutide improved insulin secretion response to elevated glucose levels in a glucose-dependent manner, with nearly comparable response at normoglycaemia

Review Questions:

- What are the PD characteristics of semaglutide?
- How are they relevant to the efficacy of semaglutide?
- Does the PD data support the sponsor's claims?

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11

Dose-Response Relationship: Phase 2 Dose Finding Trial

Sponsor's Claim: A dose-dependent decrease in mean HbA_{1c} change from baseline (FAS, LOCF) was shown across the 5 semaglutide dose levels (6 treatment arms) – Phase 2 trial (trial 1821)

Table 11-5 ANOVA of Change in HbA_{1c}, LOCF - Full Analysis Set

Comparison after 12 weeks of treatment (LOCF)				
Estimated Treatment Differences (%)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	-1.19	[-1.58 ; -0.80]	<.0001	Yes
Sema 0.8 mg T - Placebo	-0.95	[-1.33 ; -0.57]	<.0001	Yes
Sema 0.8 mg - Placebo	-0.97	[-1.35 ; -0.59]	<.0001	Yes
Sema 0.4 mg - Placebo	-0.61	[-0.98 ; -0.23]	0.0002	Yes
Sema 0.2 mg - Placebo	-0.41	[-0.79 ; -0.02]	0.0324	Yes
Sema 0.1 mg - Placebo	-0.09	[-0.46 ; 0.28]	0.9772	No

Dose-Response Relationship: Numerically Better Response with 1 mg Dose in Monotherapy Trial

Trial 3623 vs placebo (Monotherapy) - Phase 3a trial

Table 2-3 Efficacy results after 30 weeks of treatment – trial 3623

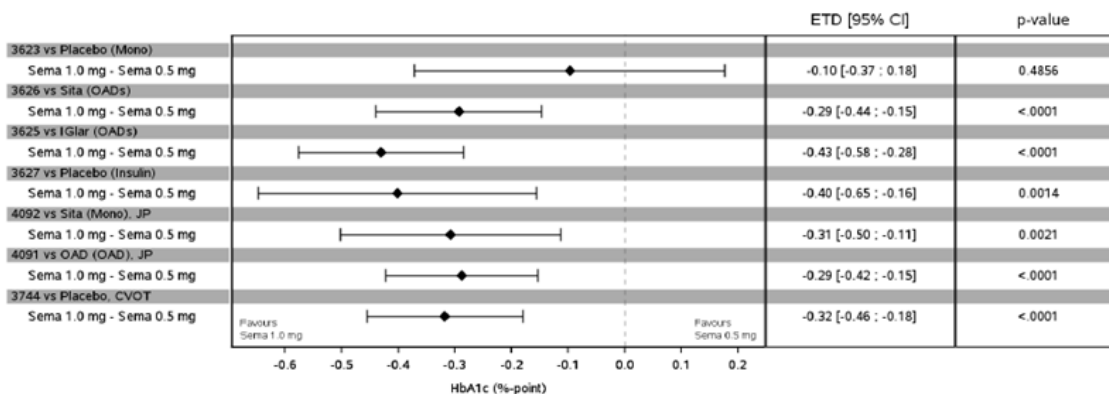
Parameter	Sema 0.5 mg (n=128)	Sema 1.0 mg (n=130)	PBO (n=129)	Sema 0.5 mg vs PBO	Sema 1.0 mg vs PBO
	Estimated change from baseline at week 30			Estimated treatment difference at week 30 [95% CI]	
HbA _{1c} ^a , %-points	-1.45	-1.55	-0.02	-1.43 [-1.71 ; -1.15]* ¹	-1.53 [-1.81 ; -1.25]* ¹
Body weight ^b , kg	-3.73	-4.53	-0.98	-2.75 [-3.92 ; -1.58]* ¹	-3.56 [-4.74 ; -2.38]* ¹
FGF ^c , mmol/L (mg/dL)	-2.51 (-45.20)	-2.34 (-42.09)	-0.55 (-9.92)	-1.96 [-2.49 ; -1.43]* (-35.28 [-44.87 ; -25.70]*)	-1.79 [-2.31 ; -1.26]* (-32.17 [-41.71 ; -22.64]*)
7-point SMPG mean, mmol/L (mg/dL)	-2.35 (-42.30)	-2.65 (-47.83)	-0.67 (-12.03)	-1.68 [-2.18 ; -1.18]* (-30.27 [-39.22 ; -21.32]*)	-1.99 [-2.48 ; -1.50]* (-35.80 [-44.62 ; -26.97]*)
7-point SMPG increment, mmol/L (mg/dL)	-0.75 (-13.50)	-1.08 (-19.51)	-0.34 (-6.13)	-0.41 [-0.87 ; 0.05] (-7.37 [-15.65 ; 0.91])	-0.74 [-1.19 ; -0.29]* (-13.38 [-21.52 ; -5.23]*)
Diastolic BP ^d , mmHg	-0.50	0.18	0.40	-0.89 [-2.81 ; 1.02]	-0.21 [-2.12 ; 1.69]
Systolic BP ^e , mmHg	-2.58	-2.74	-1.72	-0.86 [-4.15 ; 2.43]	-1.03 [-4.29 ; 2.24]
	Proportion (%) of subjects achieving the target at week 30			Estimated odds ratio at week 30 [95% CI]	
HbA _{1c} ≤ 6.5% ^f , %	59	60	13	15.99 [7.82 ; 32.68]*	18.34 [8.96 ; 37.54]*
HbA _{1c} < 7.0% ^f , %	74	72	25	16.92 [8.44 ; 33.89]*	15.70 [8.00 ; 30.83]*
HbA _{1c} < 7.0% without severe or BG confirmed symptomatic hypoglycaemia and without weight gain ^f , %	66	65	19	12.69 [6.57 ; 24.52]*	12.45 [6.46 ; 23.99]*

Dose-Response Relationship for 1 mg Dose Support from Add-on Trials



Sponsor's Claim: A significantly larger reduction in HbA1c from baseline to end-of-treatment was obtained with 1.0 mg vs. 0.5 mg dose in all trials (except in trial 3623 vs. placebo, monotherapy trial) - Phase 3a trials

HbA1c (%-point) – comparison of semaglutide 0.5 mg and 1.0 mg for Phase 3a trials excluding trial 3624



ETD: Estimated treatment difference. Exe ER: Exenatide Extended Release. OAD: Oral anti-diabetic drug. 95% CI: 95% confidence interval. Mono: Monotherapy. Sita: Sitagliptin. IGlar: Insulin Glargine. JP: Japan. CVOT: Cardiovascular outcomes trial. On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. The post-baseline data are analysed using the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline HbA1c as covariate, all nested within visit. Mean estimates are adjusted according to the observed baseline distribution.

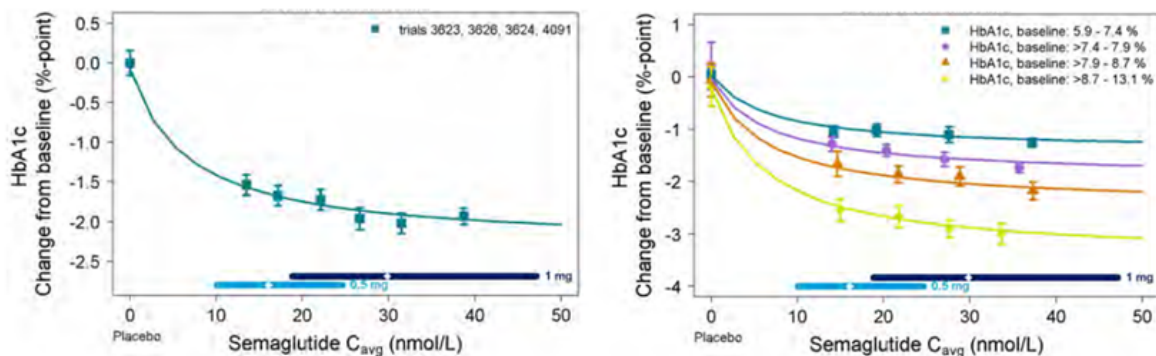
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14

Exposure-Response (HbA1c) Relationship



HbA1c change from baseline vs. exposure of semaglutide for all subjects (left panel) and stratified by baseline HbA1c (right panel) after 30 weeks of treatment in subjects with T2DM



Review Question: Does the exposure-response relationship for efficacy support the proposed dose of semaglutide?

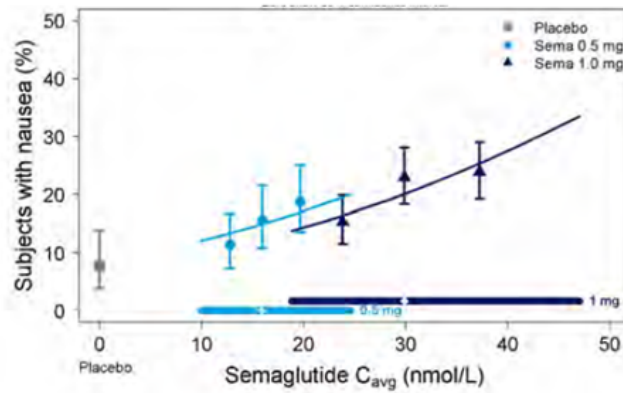
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15

Exposure-Safety (Nausea) Relationship



Proportion of subjects with nausea at any time vs. steady-state exposure by treatment (trials 3623, 3626, 3624, 4091)



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16

Summary



- Application is *fileable* from a clinical pharmacology perspective
- To be marketed and Phase 3 products are identical – no bridging needed
- No OSIS inspections

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17

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/s/

SHALINI WICKRAMARATNE SENARATH YAPA
02/01/2017

MANOJ KHURANA
02/01/2017