CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209637Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	209637
Priority or Standard	Standard
Submit Date(s)	December 5, 2016
Received Date(s)	December 5, 2016
PDUFA Goal Date	December 5, 2017
Division/Office	DMEP
Reviewer Name(s)	Andreea Ondina Lungu
Review Completion Date	November 22, 2017
Established/Proper Name	Semaglutide
(Proposed) Trade Name	Ozempic
Applicant	Novo Nordisk
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Dosing Regimen(s)	0.5 mg and 1 mg once weekly
Applicant Proposed Indication(s)/Population(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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Glossary

AC	advisory committee
ACE	angiotensin converting enzyme
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DPP-4	Dipeptidyl peptidase-4
DUN	dispensing unit number
EAC	Event Adjudication Committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ER	extended release
FAS	full analysis set

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	fasting plasma glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide 1
GLP-1 RA	GLP-1 receptor agonist
GRMP	good review management practice
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term
ICH	International Council for Harmonization
IGlar	insulin glargine
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL	Low density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
MESI	Medical Event of Special Interest
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effects model repeated measures
NA	not applicable
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NN	Novo Nordisk
NNMQ	Novo Nordisk MedDRA Query
OAD	oral antidiabetic drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OW	once weekly
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment

PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Medical Dictionary for Regulatory Activities Preferred Term
RA	receptor agonist
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
Sema	semaglutide
SGLT2	Sodium-dependent glucose co-transporter-2
Sita	sitagliptin
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	Medical Dictionary for Regulatory Activities System Organ Class
SU	sulfonylurea
T1/2	terminal half-life
TEAE	treatment emergent adverse event
T2DM	type 2 diabetes mellitus
TG	triglycerides
TZD	thiazolidinedione
VAI	voluntary action indicated

1. Executive Summary

1.1. Product Introduction

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) studied for once-weekly subcutaneous (s.c.) administration in patients with type 2 diabetes mellitus (T2DM). Semaglutide is based on (b) (4) acylation technology (b) (4) with important structural modifications to obtain a longer half-life, making it suitable for OW dosing. The applicant proposes two therapeutic doses of s. c. semaglutide for commercialization: 0.5 mg once weekly (OW), and 1 mg OW. To minimize gastrointestinal adverse events, a fixed dose escalation regimen was employed in the clinical trials. All patients received a dose of 0.25 mg for 4 weeks. The dose was then increased to 0.5 mg. After an additional 4 weeks, the dose was increased to 1 mg for patients randomized to receive 1 mg of semaglutide.

Semaglutide is to be marketed in a prefilled disposable pen-injector which is already used by the applicant for other approved drug products (Saxenda®, Levemir®, Tresiba®, Ryzodeg®, and Norditropin®)

The proposed trade name for OW s.c. semaglutide is OZEMPIC.

The applicant proposes the following indication for the s.c. semaglutide:

> *OZEMPIC is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus*

1.2. Conclusions on the Substantial Evidence of Effectiveness

The semaglutide phase 3 development program is comprised of 5 multi-national efficacy trials, 2 efficacy trials conducted solely in Japan, and one safety trial (a 2 year outcomes trial to rule out excessive cardiovascular [CV] risk)).

The clinical trials conducted to support efficacy were conducted on a variety of background therapies. These included monotherapy, in combination with metformin (with or without other oral antidiabetic drugs [OADs]), in combination with OADs, and in combination with basal insulin. In all the trials, subjects treated with semaglutide demonstrated improved glycemic control as shown by a reduction in HbA1c from baseline (comparator-adjusted range: -0.27% to -1.56%). A similar reduction in HbA1C was seen in the 2-year cardiovascular outcomes trial (SUSTAIN 6).

In summary, semaglutide is efficacious as a glycemic lowering agent in patients with T2DM.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Diabetes mellitus is a serious disease that affects 22 million people in the United States. Diabetes mellitus can lead to macrovascular and microvascular complications that can reduce the quality of life and longevity of afflicted patients. There are currently 12 classes of diabetes medications approved for the treatment of type 2 diabetes mellitus including GLP-1 receptor agonists.

Semaglutide would be the 7th product in the GLP-1 receptor agonist class, and would be the 5th once weekly GLP-1 receptor agonist.

Semaglutide phase 3 development program is comprised of 5 multi-national efficacy trials, one cardiovascular outcomes trial (CVOT) of short duration (not an efficacy trial – outcomes trial to rule out excessive CV risk pre-marketing), and 2 Japanese safety trials. The development program appears generally adequate to evaluate efficacy of semaglutide in patients with T2DM as monotherapy and on different antidiabetic background medications (including commonly used therapies, such as metformin, sulfonylureas (SU), and insulin).

In all the efficacy trials, as well as the Japanese trials, semaglutide showed a dose-dependent reduction on HbA1c, sustained over the duration of the trials. This reduction was statistically superior to placebo as monotherapy and on a background of basal insulin. Semaglutide was also statistically superior to sitagliptin on a background of OADs including metformin and SU. Additionally, semaglutide was statistically superior to insulin in study 3625 (open label vs insulin glargine). While the design and conduct of this trial makes conclusions of clinical superiority to insulin glargine questionable, the clinical program provides evidence that semaglutide is efficacious in improving glycemic control in patients with T2DM.

Overall, the semaglutide safety profile was generally consistent with the known safety profile for GLP-1 RAs, with gastrointestinal adverse events being the most common adverse events, and potential for hypoglycemia on a background of insulin and/or insulin secretagogues.

Findings from the development program, particularly the findings from the CVOT, support concluding that there is no increased risk for adverse cardiovascular outcomes with semaglutide. However, findings from the CVOT suggested a new risk that was not previously seen with other GLP-1 RAs.

A significant increased risk for diabetic retinopathy complications was observed with semaglutide (50 [3.0%] patients) as compared with placebo (29 [1.8%] patients, HR: 1.76, 95% CI [1.11; 2.78]) in the CVOT. The treatment difference appeared early and continued throughout the trial. This finding may be a consequence of rapid improvements in glycemic control with semaglutide (similar to what was seen in the Diabetes Control and Complication Trial) and this mechanism has been supported by Dr Wiley Chambers, the FDA ophthalmology consultant. Though long-term data on retinopathy or other clinical outcomes are not available for semaglutide, it is expected that good glycemic control improves clinical outcomes (i.e., reduced microvascular complications) in the long run.

The clinical benefits of semaglutide outweigh the risks. The safety profile is similar to other approved GLP-1 RAs, with the exception of a finding of increased risk for diabetic retinopathy complications. The finding is perplexing as therapies that improve glycemic control are expected to reduce microvascular complications of diabetes (including retinopathy), but this appears similar to what has been reported with rapid glucose lowering. It is expected that long-term good glycemic control will improve clinical outcomes. Even if the increased risk for retinopathy does not resolve, there are other clinical outcomes where patients should see a benefit. Additionally, diabetic retinopathy is monitorable and there are effective therapies to manage this complication. This risk can be mitigated with close monitoring.

I recommend approval of semaglutide for improving glycemic control in patients with T2DM.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2014, the Center for Disease Control estimated that 22 million people in the United States have diabetes • Diabetes is associated with multiple complications including macrovascular and microvascular complications which may shorten and affect the quality of life of patients • Studies have shown that improving glycemic control in patients with diabetes improved clinical outcomes (e.g., reduction in retinopathy) • Many diabetic patients also have additional risk factors such as smoking, obesity, hypertension and hyperlipidemia which contribute to their overall health burden	• Diabetes is a serious condition associated with chronic morbidity and premature death • Glycemic control of diabetes improves microvascular complications
Current Treatment Options	• Twelve classes of drugs, including 5 GLP1-RAs, are FDA approved in the United States to improve glycemic control in patients type 2 diabetes	• There are multiple effective treatment options available for the treatment of type 2 diabetes, including other members of the GLP-1RA class administered once weekly
Benefit	• Semaglutide reduced HbA1c in a dose-dependent manner in all phase 3 trials, across a variety of backgrounds • Patients on semaglutide were more likely to achieve glycemic targets • Semaglutide led to sustained weight loss in patients with T2DM	• The efficacy pertaining to glycemic benefit was seen across all phase 3 trials. • Both doses of semaglutide improved glycemic control as measured by change from baseline in HbA1c and proportion achieving a HbA1c target • Additional findings which may be desireable for patients include reduction in weight. •

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety database reflects the expected use in the patient population. • Semaglutide safety is overall consistent with the GLP1RA drug class. Gastrointestinal adverse events were more common with semaglutide. Semaglutide by itself does not appear to increase the risk for hypoglycemia, but it is expected to lead to an increased risk for hypoglycemia when used in combination with sulfonylurea or insulin. Increases in serum amylase and lipase were seen but an increase in pancreatitis was not seen. Increases in heart rate were seen, but an increase in arrhythmia events was not seen. • Though there were numerically more lung, breast, and skin cancers with semaglutide, it is not possible to draw meaningful conclusions due to the small number of events and presence of confounders. • There was a higher incidence of ALT >5xULN with semaglutide. However, the additional liver function safety data does not suggest an increase in drug induced liver injury with semaglutide • In the 2-year CVOT, semaglutide was not associated with increased cardiovascular risk. An unexpected and important safety finding observed in the development program was an increase in the incidence of of diabetic retinopathy complications with semaglutide. While it is possible that this is a result of rapid glucose lowering with semaglutide, this cannot be confirmed with the present body of data, and longer studies may be needed to determine whether this increase ultimately converts to a benefit on retinopathy as might be expected with a glucose lowering drug.	• The safety profile of semaglutide is generally consistent with other GLP-1 RAs. • An increased risk for diabetic retinopathy complications was seen, though this may be a consequence of rapid lowering of glucose. Long-term it is expected that improved glycemic control will lead to improved outcomes for microvascular complications (which include retinopathy). This was discussed at an Advisory Committee meeting that took place on October 18, 2017, and the committee did not view this as a barrier to approval. There is a body of literature that shows that improved glycemic control is beneficial for microvascular complications such as retinopathy in the long run, despite the initial worsening in diabetic retinopathy. Further, progression in diabetic retinopathy can be monitored and treated. • The risks associated with semaglutide can be adequately managed through labeling.

1.4. Patient Experience Data

Not applicable. Validated patient experience data (e.g., experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition) were not submitted nor reviewed as part of this review.

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis resulting in chronic hyperglycemia that is associated with significant morbidity and mortality due to microvascular and macrovascular pathologies, and is a major cause of hospitalization, blindness, renal failure, amputations and cardiovascular (CV) disease. With Type 1 diabetes mellitus, patients lose the ability to secrete endogenous insulin and require exogenous insulin replacement. With T2DM, patients have varying degrees of insulin resistance and are unable to maintain euglycemia with endogenous insulin secretion.

There is no cure for T2DM, but therapies aimed at improving glycemic control are available. Currently approved therapies in T2DM aim to improve glycemic control by improving insulin resistance, enhancing insulin secretion, or increasing glucose excretion. One such therapeutic approach is through the incretin pathway, which is the pathway relevant for the semaglutide application.

2.2. Analysis of Current Treatment Options

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors

- Glucagon-like peptide-1 receptor agonists (GLP-1 RA)
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, some drug classes may be poorly tolerated by some patients or have limited usefulness in certain populations. For example, sulfonylureas (SU) and insulin are associated with a high risk for hypoglycemia, thiazolidinedione's (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors are contraindicated in patients with severe renal dysfunction. Additionally, progressive β-cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time requiring the addition of other agents. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies and concomitant treatment options for T2DM.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Semaglutide is a new molecular entity (NME), not currently marketed in the US for any indication. However, the drug product constitutes a modification of a currently approved product, liraglutide, and is the 7th member in the GLP-1 RA class of antidiabetic drugs.

3.2. Summary of Presubmission/Submission Regulatory Activity

Presubmission regulatory activities are summarized below.

June 9, 2010	End of Phase 2 Meeting: Discussion of the phase 3 program as it pertains to the glycemic lowering indication. Regarding

	(b) (4) [redacted]
May 18, 2012	Type C Meeting – Written responses further discussing the phase 3 program
March 25, 2013	Type C Meeting – Written responses and comments on the cardiovascular safety study (study 3744)
July 15, 2013	FDA advice letter including discussion of the premarketing CV outcomes study (study 3744). The applicant designed this study specifically to rule out the 1.8 CV risk margin premarketing, (b) (4) [redacted]
February 17, 2014	FDA advice letter regarding various aspects of the phase 3 development program
August 16, 2014	Type C Meeting – Seeking clarification on FDA advice letters dated July 15, 2013, and February 17, 2014 regarding study 3744 (SUSTAIN 6, premarket CV outcomes trial) (b) (4) [redacted]
June 12, 2015	Type C Meeting to discuss the data format and standards for the clinical and nonclinical data to be included in the semaglutide NDA
July 30, 2015	Advice request regarding the inclusion of the data from the oral semaglutide program in the sq semaglutide NDA
September 15, 2015	Agreed iPSP
November 13, 2015	Type C Meeting to discuss the device and human factors studies

3.3. Foreign Regulatory Actions and Marketing History

Semaglutide is not currently approved for use in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical

Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The inspection for this NDA consisted of five domestic and five foreign clinical sites as well as the sponsor, and the contract research organization. The inspection of two clinical investigators listed below revealed regulatory violations. The inspection of the sponsor and the remaining clinical investigators revealed no regulatory violations.

The two investigators with violations were as follows:

- Gustavo Frechtel, Site 122, Argentina, randomized 30 subjects in the CVOT (trial 3744) – The violation was 'Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND' - Voluntary action indicated (Dr. Frechtel responded to the observations on 6/15/2017 with appropriate corrective and preventive actions).
- Eddie Armas, Site 412, US (Florida), randomized 11 subjects in trial 3623. The violation was 'Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The site created its own source documentation templates based on the protocol requirements. Per the source documents, the site verifies subject compliance with taking their weekly injection by reviewing the subject diary where subjects record the date they took each injection. However, the subject diary does not have a space for every dose that is required to be taken, therefore this method is ineffective in verifying subject compliance' – Voluntary action indicated (Dr. Armas responded to the observations May 10, 2017 with corrective and preventive actions deemed to be acceptable).

In addition, Novo Nordisk informed the FDA on July 5, 2017 during the review of application NDA 209637 that the Event Adjudication Committee (EAC) adjudicators were unblinded to treatment in four open-label trials in the SUSTAIN program. This was not revealed nor discovered during the sponsor inspection. A review of (b) (4) (the contract research organization tacked with handling the adjudication packages) identified violations for which voluntary action was indicated (VAI). The events from the open-label trials were re-adjudicated by blinded adjudicator employed by the applicant. While some differences in adjudication were observed, they were mostly originating from a difference in the definition of benign neoplasms, and did not change my evaluation of the safety of semaglutide.

The OSI review concluded that, in general, based on the inspections of the 10 clinical sites, the sponsor, and the CRO, the inspectional findings support validity of data as reported by the sponsor under this NDA.

Please see OSI review by Dr Cynthia Kleppinger for details regarding the inspections performed and results.

4.2. Product Quality

Semaglutide is based on [redacted] (b) (4) acylation technology [redacted] (b) (4) with important structural modifications to obtain a longer half-life, making it suitable for OW dosing. The extended half-life of the semaglutide molecule is obtained by high affinity, specific binding to the fatty acid binding sites on albumin, and protection from DDP-4 inactivation. The drug product is to be administered subcutaneously once weekly, at the same doses, and with the same device that was used in the clinical program.

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

Please see CMC review by Dr Suong Tran for details.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Dr Federica Basso, the pharmacology and toxicology reviewer, has provided the following summary of the nonclinical data:

> 'In vitro and in vivo pharmacology studies have demonstrated that semaglutide potently activates the human GLP-1 receptor. Dose-related increase in glucose-dependent insulin secretion, and decrease in glucose levels were observed in rats, diabetic mice, and minipigs. The toxicity profile of semaglutide was evaluated in mice, rats, and monkeys for up to 3, 6 and 12 month duration, respectively. In all species dose levels were limited by pharmacologically mediated reductions in food intake and body weight. A dose- escalation approach was utilized in the pivotal toxicology studies to minimize the initial treatment-related effects on body weight.
>
> Mild focal C-cell hyperplasia, C-cell nests, and dilated ultimobranchial ducts were observed after 3-month of dosing in mice starting at 17X the clinical exposure. Liver necrosis and centrilobular hypertrophy were observed at higher doses, mostly in males (175X MRHD). Minimal to moderate Brunner's gland hypertrophy was noted in nearly all treated rats at the clinical exposure. This finding was reversible and was not considered adverse, given the absence of associated inflammatory or degenerative changes. In monkey, there were no definitive signs of toxicity other than the expected effects on body weight and food consumption. ECG abnormalities (a bigeminal rhythm with two episodes of sinus

tachycardia in Week 13 and a continuous left bundle branch block-like recording that persisted from Week 26 to Week 52) and slight multifocal myocardial vacuolation and degeneration, with karyomegaly, in the left ventricle were observed in one high-dose female and male, respectively (27X MRHD). A relationship to treatment could not be excluded; NOAEL for cardiac effects was established at 5-fold the clinical exposure. No adverse microscopic lesions were observed in the monkey thyroid at doses up to 27X MRHD.

In two-year carcinogenicity studies in mice and rats, a statistically significant increase in the incidence of C-cell adenoma and combined C-cell adenoma and carcinomas was observed in both species. These tumors occurred at the clinical exposure in rats and at 2X and 5X the clinical exposure in female and male mice, respectively. C-cell carcinomas were statistically significantly increased in male rats at ≥0.025 mg/kg/day (0.7X the clinical exposure). A numerical increase in C-cell carcinoma was noted in mice (n=2, 2, 2 in LD, MD and HD male mice; n=1, 2, 2 in LD, MD and HD female mice). C-cell tumors are known class effects of GLP-1R agonists and have been reported in two-year rodent studies with other long acting GLP-1R agonists. The human relevance of these tumors is unknown.

A standard development and reproductive toxicology program was conducted in rats, rabbits, and monkeys. In combined fertility and embryonic development studies in rats, no effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all doses, together with a small reduction in the number of corpora lutea. Both findings occurred at the clinical exposure, but were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight. Decrease in maternal body weight gain, embryofetal mortality, growth retardation, skeletal (scapula, long bones, ribs, digits, vertebrae and cranial bones) and visceral (cardiac blood vessels) malformations were observed in rats at approximately the clinical exposure. Mechanistic studies showed that semaglutide caused embryotoxicity in rats through a GLP-1 receptor-mediated impaired function of the inverted yolk sac. However, involvement of additional mechanisms leading to embryotoxicity in rats cannot be completely excluded.

In embryofetal development studies, marked maternal body weight loss and/or decrease in body weight gain were observed in rabbits and monkeys at the clinical exposure. Increased post-implantation loss, skeletal malformations in the sternebra and digits, and visceral malformations in the kidney and liver were observed in rabbits at the clinical exposure. A direct drug-related effect on fetal development cannot be ruled out. Sporadic malformations were noted in monkeys at $\geq$5X clinical exposure (shifts in the alignment of the vertebrae, ribs and sternebra at the cervico-thoracic border and blood accumulation under the skull causing misshapen right brain hemisphere), but were considered secondary to the effect on maternal body weight. No treatment related embryotoxic effects were noted in monkeys at the clinical exposure.

In a pre- and post-natal development study in monkeys, early pregnancy losses observed at 3X the clinical exposure were most likely related to maternal weight loss during the first trimester. There were no treatment related external abnormalities or histopathological findings in the offspring at doses up to 7X the clinical exposure.
Administration of semaglutide to juvenile SD rats for 11 weeks, from postnatal day 21 to 97, caused reduction in food consumption, body weight gain, and delayed sexual maturation at the clinical exposure. There were no consequential effects upon fertility or reproductive performance at doses up to 2X the clinical exposure.'

Please see full Pharmacology and Toxicology review by Dr Basso for details.

4.5. Clinical Pharmacology

Semaglutide is a GLP-1 RA developed for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The GLP-1 receptor is the target for native GLP-1, which is an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from beta cells and suppresses glucagon from alpha cells in the pancreas. Non-pancreatic effects of GLP-1 include slowing of gastric emptying, reduction of food intake, and an increase in satiety, all of which contribute to improved glycemic control and decreased body weight.

As a class, GLP-1 receptor agonists mimic the activities of physiologic GLP-1. They are categorized as either short-acting compounds (exenatide and lixisenatide) or as long-acting compounds (albiglutide, dulaglutide, exenatide long-acting release, and liraglutide). The pharmacokinetic differences between these drugs are reported to lead to differences in their pharmacodynamic profiles. The short-acting GLP-1 RAs are reported to primarily lower postprandial blood glucose levels through inhibition of gastric emptying, whereas the long-acting compounds are reported to have a stronger effect on fasting glucose levels, which is thought to be mediated predominantly through their insulinotropic and glucagonostatic actions.

Following subcutaneous (SC) administration, semaglutide has a relatively long terminal half-life (t1/2) 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).

The clinical pharmacology development program conducted to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of semaglutide included 16 clinical

pharmacology studies. These studies were reviewed by the Office of Clinical Pharmacology, and were found adequate to support approval of semaglutide.

Please see Clinical Pharmacology review by Dr Shalini Wikramatne Senarath Yapa and Dr. Justin Earp for details.

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Hearth (CDRH) was consulted to to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of semaglutide. The CDRH consultant recommended approval as follows:

"The application for Semaglutide 1.34 mg/ml solution for assembled in a PDS290 pen-injector NDA 209637 is approvable from the perspective of the applicable Quality System Requirements:
(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
(2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination. However, CDRH recommends that the applicant and manufacturer that are listed in the inspectional guidance that follows be inspected post approval since they are subject to, but have not been inspected for 21CFR820, Part 4 regulatory requirements for Combination Products."

Please see CDRH consult by Christopher Brown for details.

4.7. Consumer Study Reviews

Human factors studies conducted to evaluate the usability of the device and the ability to differentiate between the two proposed pen injectors were reviewed by Dr. Susan Rimmel of the Division of Medication Error Prevention and Analysis. See Dr. Rimmel's review for discussion of those studies.

5. Sources of Clinical Data and Review Strategy

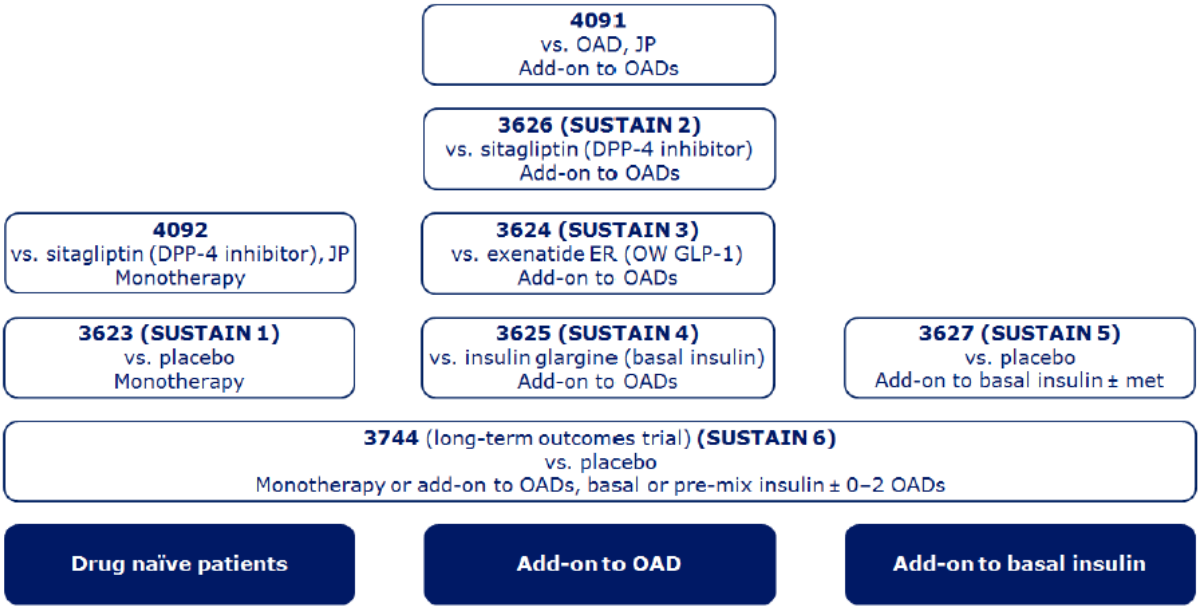
5.1. Table of Clinical Studies

The semaglutide development program included 8 clinical trials and enrolled patients from 45 countries, with approximately one third of the patients coming from the US (Table 1).

Semaglutide was investigated as monotherapy versus placebo and as combination therapy with basal insulin±metformin versus placebo. Active comparator trials include trials against

sitagliptin, exenatide ER, and insulin glargine. Additionally, two active-controlled, open-label (OL) trials were performed in Japan. A limited, 2-year cardiovascular outcomes trial (CVOT) compared semaglutide vs placebo on a background ranging from monotherapy to OADs, basal or pre-mixed insulin. This last trial was only for evaluation of cardiovascular outcomes and general safety of semaglutide, not for any glycemic lowering claim.

Figure 1 Semaglutide Phase 3 Development Program



Abbreviations: Exe ER: exenatide extended release; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; JP: Japan; met: metformin; OAD: oral anti-glycaemic drug; OW: once-weekly; T2D: type 2 diabetes.

Source: Figure 1-2 ISS

The number of patients exposed in the phase 3 trials included a total of 8,093 patients of whom 4,792 patients received at least one dose of semaglutide.

The duration of treatment in the phase 3 trials ranged from 30 to 104 weeks. The maintenance treatment period was 6 months for the following efficacy trials: 3623 monootherapy vs placebo), 3625 (vs insulin glargine on a background of OADs), and 3627 (vs placebo on a background of basal insulin+metformin). Other studies have a 56 week duration: 3626 (vs sitagliptin on a background of OADs), and 3624 (vs exenatide ER on a background of OADs). The duration of the CVOT was 104 weeks.

Two maintenance doses of semaglutide, 0.5 and 1.0 mg were studied in all phase 3 trials, except for trial 3624 (vs Exenatide ER), where only the maintenance dose of 1.0 mg was studied. To mitigate gastrointestinal side effects, all semaglutide-treated patients followed a fixed dose escalation regimen starting at 0.25 mg for 4 weeks before escalating to 0.5 mg as maintenance dose or another 4 weeks before escalating to 1 mg maintenance dose.

Not all trials were blinded. Placebo-controlled trials (trials 3623, 3627 and 3744) were double-blinded. Double-blinding was obtained by matching volume of injection/dose groups (0.5 mg and 1.0 mg). No blinding of dose (0.5 mg vs 1.0 mg) was performed. A double-blind trial design was attained for trial 3626 vs Sita (OADs) via a double-dummy treatment scheme.

An OL trial design was employed for some trials. The insulin-comparator trial - trial 3625 vs glargine (OADs) was conducted as an open-label comparator trial due to the complexity of blinding of insulin given the need to titrate insulin dose level. Additionally, due to the complexity of preparing a placebo version of Exenatide ER, trial 3624 was conducted as an open-label trial. Both Japanese safety trials were OL.

Table 1 Listing of Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety						
3623	Semaglutide vs placebo monotherapy	1) Semaglutide (0.5 mg, 128; 1.0 mg, 130) 2) Placebo (0.5 mg and 1.0 mg, 129) 3) 2:2:1:1, double-blind	Change from baseline to week 30 in HbA1c	30 weeks	387	Multinational (incl. US); T2DM; HbA1c of 7.0−10.0%; no treatment with glucose lowering agents in 90 days prior to screening; eGFR ≥30 mL/min/1.73 m2
3624	Semaglutide vs Exenatide ER (OADs background)	1) Semaglutide (1.0 mg, 404) 2) Exenatide ER (2.0 mg, 405) 3) 1:1, open-label	Change from baseline to week 56 in HbA1c	56 weeks	809	1) Multinational (incl. US); T2DM; HbA1c of 7.0−10.5%; eGFR ≥60 mL/min/1.73 m2 2) Stable treatment with 1–2 OADs (Met, TZD, SU)
3625	Semaglutide vs insulin glargine (OADs background)	1) Semaglutide (0.5 mg, 362; 1.0 mg, 360) 2) Insulin glargine (starting	Change from baseline to week 30 in HbA1c	30 weeks	1082	1) Multinational (incl. US); T2DM; HbA1c of 7.0−10.0 %; eGFR ≥30 mL/min/1.73 m2 2) Stable treatment with Met or Met/SU, insulin naïve

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		dose 10 units, 360) 3) 1:1:1, open-label				
3626	Semaglutide vs sitagliptin (OADs background)	Semaglutide 0.5 mg and 1 mg sq weekly Sitagliptin 100 mg orally daily 2:2:1:1, double-blind, double-dummy	Change from baseline to week 56 in HbA1c	56 weeks	1225	1) Multinational; T2DM; HbA1c of 7.0−10.5%; eGFR ≥60 mL/min/1.73 m2 2) Stable treatment with Met, TZD or Met/TZD
3627	Semaglutide vs placebo (basal insulin background)	1) Semaglutide (0.5 mg, 132; 1.0 mg, 131) 2) Placebob (0.5 mg and 1.0 mg, 133) 3) 2:2:1:1, double-blind	Change from baseline to week 30 in HbA1c	30 weeks	396	1) Multinational (incl. US); T2DM; HbA1c of 7.0−10.0%; eGFR ≥30 mL/min/1.73 m2 2) Stable treatment with basal insulin alone or in combination with Met
Studies to Support Safety						
3744	Semaglutide vs placebo cardiovascular outcomes study	1) Semaglutide (0.5 mg, 826; 1.0 mg, 822) 2) Placebo (0.5 mg, 824; 1.0 mg, 825) 3) 1:1:1:1, double-blind	Time from randomisation to first occurrence of a MACE, defined as cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke	104 weeks	3297	1) Multinational (incl. US); T2DM; HbA1c ≥7.0%; ≥50 years and clinical evidence of CVD or ≥60 years and subclinical evidence of CVD 2) Standard-of-care, e.g. noninvestigational glucose lowering medications adjusted to maintain target glycemic control (avoiding other GLP-1 RAs, DPP-IV inhibitors or pramlintide)
Other studies pertinent to the review of efficacy or safety – Studies in Japanese population						

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
4091	Semaglutide vs OADs (OADs background)	1) Semaglutide (0.5 mg, 239; 1.0 mg, 241) 2) Additional OAD (120) 3) 2:2:1, open-label	Number of treatment emergent adverse events during 56 weeks of treatment	56 weeks	600	1) Japan; T2DM; HbA1c 7.0−10.5%; eGFR ≥30 mL/min/1.73 m2 2) Stable treatment with diet and exercise or in combination with OAD monotherapy (either of SU, glinide, α-GI or TZD) within approved Japanese labelling
4092	Semaglutide vs sitagliptin (monotherapy	1) Semaglutide (0.5 mg, 103; 1.0 mg, 102) 2) Sitagliptin (100 mg, 103) 3) 1:1:1, open-label	Number of treatment emergent adverse events during 30 weeks of treatment	30 weeks	308	1) Japan; T2DM; HbA1c of 6.5−9.5% or 7.0−10.5%; eGFR ≥60 mL/min/1.73 m2 2) On stable OAD monotherapy at a half-maximum dose or below and HbA1c 6.5−9.5%, or on diet and exercise therapy and HbA1c 7.0−10.5%
Source: Reviewer generated using the tabular listing of clinical trials provided by the applicant						

5.2. Review Strategy

The applicant submitted five multi-national efficacy phase 3 trials, one CVOT, and two OL Japanese trials as evidence of efficacy and safety in patients with T2DM.

The efficacy review of the semaglutide program was performed by individual trial review (not including the Japanese trials) and by comparisons across trials. For the individual trial review, the reviewer focused on the individual clinical trial reports, protocols and statistical analysis plan; this review is located in sections 6.2 to 6.7. For the review across trials, the reviewer used the summary of clinical efficacy, and clinical overview documents provided in the submission. The integrated review of effectiveness is located in section 7.

Safety was assessed in individual studies as well as using pools of studies. These pools included:

- Phase 3 pool excluding CVOT
- Placebo pool

In addition, the CVOT was reviewed separately.

A more detailed discussion of the approach to the review of safety is located in section 8.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 3623 – SUSTAIN 1

6.1.1. Study Design

Overview and Objective

Study title: Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve patients with T2DM

Primary objective: To demonstrate superiority of once-weekly dosing of two dose levels of semaglutide versus placebo on glycemic control after 30 weeks of treatment in drug-naïve patients with T2DM.

Secondary objective: To compare the effects of once-weekly dosing of two dose levels of semaglutide versus placebo after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

Trial Design

The trial was randomized, double-blind, parallel-group, placebo-controlled, multinational, multicenter, four arm trial. There was a 2 week screening period, followed by a 30 week randomized treatment period, and a 5 week follow up period (Figure 2).

A total of 390 drug-naïve adults with T2DM treated with diet and exercise for at least 30 days before screening were planned for randomization.

Key inclusion/exclusion criteria:

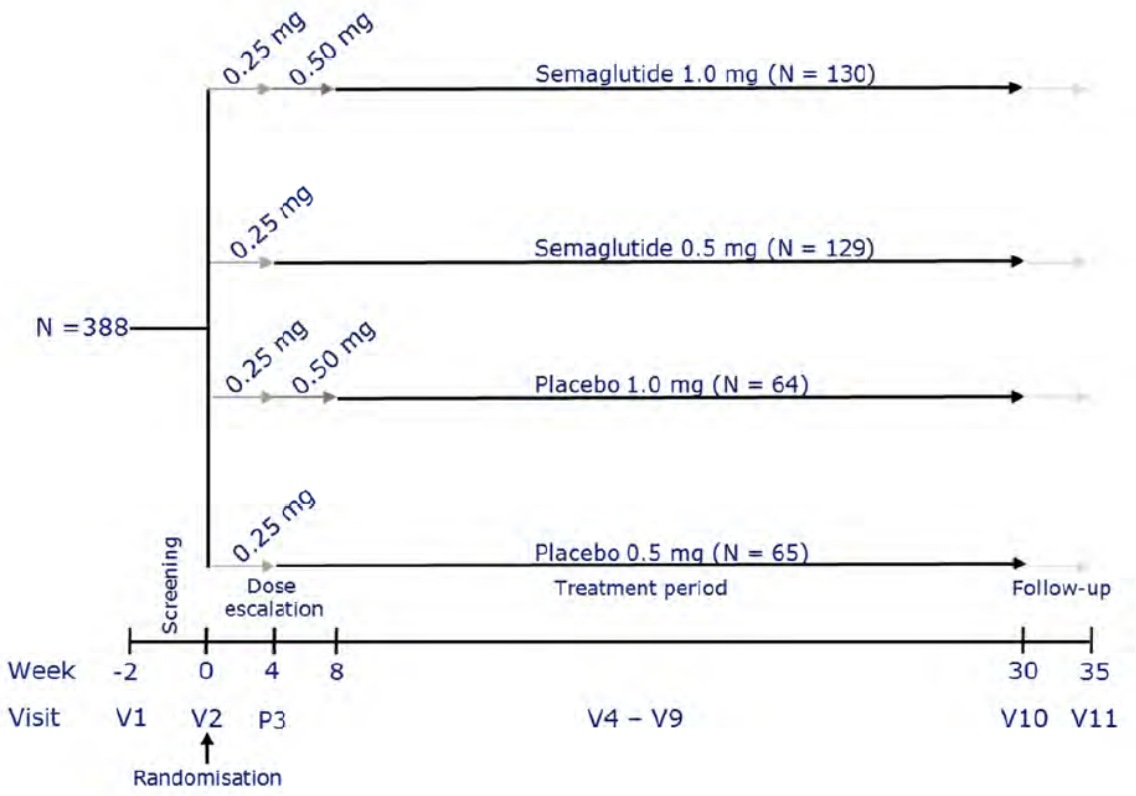
- Inclusion criteria included adult patients with T2DM, HbA1c 7-10%, treated with diet and exercise for at least 30 days prior to screening.

- Exclusion criteria included treatment with any glucose lowering agent within 90 days before screening, history of pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function (eGFR <30 mL/min/1.73 m2 per MDRD formula), acute coronary or cerebrovascular event within 90 days before randomization, heart failure (New York Heart Association class IV), known proliferative retinopathy or maculopathy.

Dose selection/Study treatments:

Semaglutide and placebo was administered by once-weekly s.c. injections. Injections could be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial. Randomization was 2:2:1:1 to treatment with either semaglutide 0.5 mg, semaglutide 1 mg, semaglutide placebo 0.5 mg or semaglutide placebo 1.0 mg once weekly. To mitigate tolerability concerns, the patients followed a fixed dose escalation scheme. All subjects started at 0.25 mg once weekly for 4 weeks than increased the dose to 0.5 mg once weekly. The 0.5 mg dose was then continued for the duration of the trial (for subjects randomized to an arm expected to receive 0.5 mg once weekly), or for 4 weeks before increasing to 1 mg once weekly (for subjects randomized to an arm expected to receive 1 mg once weekly)

Figure 2 Trial Design SUSTAIN 1



Abbreviations: N: number of subjects randomised, V: visit, P: phone visit.

Source: Figure 9-1 study report

Dose modification/discontinuation:
Once the final treatment dose was reached, no dose modifications were to occur per protocol. If treatment discontinuation occurred for safety reasons, the treatment could be re-initiated except if suspicion of pancreatitis lead to the discontinuation of treatment in the first place.

Administrative structure:
The trial was monitored by a Data Monitoring Committee (DMC), but only as it pertained to the major adverse cardiovascular events (MACE). There was no Steering Committee.

Procedures and schedule:
The patients had in person visits at screening, randomization, weeks 4, 8, 12, 16, 23, 30, and 35. Phone visits occurred at weeks 2 and 6. Detailed proceedings can be found in Table 2.
Of note, funduscopy or fundus photography was to be performed at randomization, or within 90 days of randomization.

Table 2 Trial Flowchart SUSTAIN 1

Trial Periods	Screen	Rand	Treatment period							End-of-treatment[1]	Follow-up[1]	End-of-treatment premature discontinuation[2]	Follow-u prematur discontinuat
Visit (V) or Phone (P) number	V1	V2	P3	V4	P5	V6	V7	V8	V9	V10	V11	V10A	V11A
Time of visit Weeks	-2	0	2	4	6	8	12	16	23	30	35		
Visit window Days	±7		±3	±3	±3	±3	±3	±3	±7	±7	+7		
SUBJECT RELATED INFO /ASSESSMENTS													
Informed consent	x												
In/exclusion criteria	x	x											
Randomisation		x											
Withdrawal criteria			x	x	x	x	x	x	x	x			
Concomitant illness and medical history	x												
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x												
Diabetes history	x												
History of CV disease	x												
History of gallbladder disease	x												
Smoking habits	x												
Fundoscopy/Fundus photography[3]		x											
Height		x											
EFFICACY													
Body weight		x		x		x	x	x	x	x		x	
Waist circumference		x		x		x	x	x	x	x		x	
Blood pressure	x	x		x		x	x	x	x	x		x	
HbA_{1c}	x	x		x		x	x	x	x	x		x	
Fasting plasma glucose		x		x		x	x	x	x	x		x	
Fasting insulin and proinsulin		x					x			x		x	
Fasting C-peptide		x					x			x		x	
Fasting glucagon		x					x			x		x	
Lipids		x					x			x		x	
SMPG 7 point profile		x					x			x		x	
SAFETY													
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG		x								x	x	x	x
Physical examination	x									x		x	
Pulse	x	x		x		x	x	x	x	x		x	
Anti-semaglutide antibodies[4]		x						x		x	x	x	x
Creatinine (including eGFR)	x			x		x	x	x	x	x		x	
Biochemistry		x		x		x	x	x	x	x		x	
Haematology		x		x		x	x	x	x	x		x	
Calcitonin	x							x		x		x	
Pregnancy test[5]	x	x		x		x	x	x	x	x	x	x	x
Urinalysis		x						x		x		x	
Urine Albumin to creatinine ratio		x								x		x	
Semaglutide PK				x		x		x		x		x	

Notes: [1] V10 (End-of-Treatment) and V11 (Follow-Up) are applicable for all randomised subjects. Subjects who had discontinued trial product prematurely were to attend V10 and V11 according to their initially scheduled week 30 and week 35 visits.

[2] Subjects discontinuing trial product prematurely were to be asked to attend two additional visits to undergo assessments: End-of-Treatment-premature discontinuat (V10A) and Follow-up -premature discontinuation (V11A). V10A was to be scheduled at discontinuation of the trial product. V11A was to be scheduled 5 weeks af discontinuation of trial product (+ 7 days visit window).

[3] Fundoscopy/fundus photography was to be performed at V2 or within 90 days prior to V2 if no deterioration in visual function since last assessment.

[4] Antibody sampling was preferably to be done pre-dose. For both fasting and non-fasting visit, where the injection takes place on the day of site visit, trial product h not to be taken before blood sampling. For visit 10 and 11: Not applicable if taken at a premature discontinuation visit.

[5] For women of child bearing potential: For all site visits a serum pregnancy test had to be performed. Urine pregnancy test was to be performed at any time during t trial if a menstrual period is missed, or as required by local law.

Abbreviations: Screen: screening, rand: randomisation, V: visit, P: phone visit, CV: cardiovascular, ECG: electrocardiogram, eGFR: estimated glomerular filtration SMPG: self-monitored plasma glucose, PK: pharmacokinetic, IV/WRS: interactive voice/web response system.

Source: Modified from Table 9-6 study report

Concurrent medications:
The patients were treatment naïve, no other antidiabetic medications were allowed except for rescue medication.

Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
No other diabetic medications were allowed 90 days before screening and during the trial, except rescue medication.

Patients with unacceptable hyperglycemia per the applicant were to be offered treatment intensification at the investigator's discretion, and in accordance with ADA/European Association for the Study of Diabetes guidance.

The following criteria were used for assessing the need for rescue medications (fasting plasma glucose - FPG – based, confirmed by local or central laboratory):

- 270 mg/dL from baseline to week 6
- 240 mg/dL from week 6 to week 12
- 200 mg/dL from week 12 to end of trial

Per the protocol, metformin was to be the first choice of rescue medication unless contraindicated. GLP-receptor agonists, DPP-IV inhibitors and pramlintide were not allowed as rescue medication. Rescue medication was to be prescribed as add-on to randomized treatment and patients were to continue to follow the protocol-specified visit schedule.

Patient completion, discontinuation, or withdrawal
The trial product could be discontinued in case of a safety concern, unacceptable intolerability, or at the request of a patient.

The trial product had to be discontinued in case of violation of any inclusion/exclusion criteria, pregnancy or intention to become pregnant, suspicion of acute pancreatitis, and withdrawal of informed consent.

Patients were to be encouraged to stay in the trial irrespective of lack of adherence to randomized treatment, lack of adherence to visit schedule, missing assessments, trial product discontinuation due to AEs, unwillingness to cope with injection regimen, and development of comorbidities or clinical outcomes. Thus, these circumstances were not to be considered as valid reasons for withdrawal from the trial as opposed to discontinuation of trial product.

Patients who agreed to provide information related to morbidities of relevance for the assessments of cardiovascular outcomes and/or other trial endpoints at end-of-trial were not to

be considered withdrawn from the trial.

Patients who considered withdrawing the informed consent were, as a minimum, to be encouraged to complete the end-of-treatment and follow-up visits.
Only patients who declined any further contact with the site in relation to the trial and who therefore did not agree to report information of relevance for the assessments of CV outcomes and/or other trial endpoints at end-of-trial were to be considered as withdrawn from the trial.

Study Endpoints

Primary endpoint:

- Change from baseline in HbA1c to week 30.

Secondary endpoints:

- Change in body weight from baseline to week 30[1]
- Change from baseline to week 30 in the following parameters:
    - FPG
    - Self-measured plasma glucose, 7-point profile
    - Mean 7-point profile
    - Mean post prandial increment (over all meals)
    - Insulin, C-peptide, pro-insulin, glucagon, pro-insulin/insulin ratio, homeostasis model assessment of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) (all fasting)
    - Fasting blood lipids (total cholesterol, LDL-cholesterol, VLDL-cholesterol,
    - HDL-cholesterol, triglycerides, free fatty acids)
    - BMI, waist circumference
    - Systolic and diastolic blood pressure
- Patients who achieve (yes/no) after 30 weeks of treatment:
    - HbA1c<7.0%
    - HbA1c≤6.5%
    - Weight loss ≥5%
    - Weight loss ≥10%
    - HbA1c<7.0% without severe or blood glucose (BG)-confirmed symptomatic hypoglycemia and no weight gain
- Safety outcomes

[1] Secondary endpoint with control for type 1 error

Statistical Analysis Plan

Per the applicant, the sample size calculation was based on the primary endpoint (change in HbA1c after 30 weeks of treatment) and the confirmatory secondary endpoint (change in body weight after 30 weeks of treatment). For the sample size calculations, it was pre-specified that the placebo groups were to be pooled, thereby assuming that there was no correlation between the change in HbA1c after 30 weeks and the administered placebo volume. For the primary endpoint, using a 1-sided CI with a confidence level of 97.5% and assuming a true difference of 0.5% and a standard deviation (SD) of 1.1% in change in HbA1c after 30 weeks of treatment, the applicant concluded that 103 patients per group would give 90% power to conclude superiority when comparing two treatments.

Before data were released for statistical analysis, a blinded review of all data was to take place to identify protocol deviations that may potentially have affected the results.

Definition of the analysis sets

- Full analysis set (FAS) included all randomized patients who had received at least 1 dose of randomized semaglutide (s.c.) or placebo. Patients in the FAS were to contribute to the evaluation based on their treatment assigned at randomisation. Efficacy analyses were based on FAS.

- Safety analysis set (SAS) included all randomized patients who had received at least 1 dose of randomized semaglutide (s.c.) or placebo. Patients in the SAS contributed to the evaluation based on the treatment the patient received. Safety analyses were based on SAS.

Definition of observation periods

- 'In-trial' observation period represents the period after randomization in which patients were considered trial participants (the last follow-up visit, 5 weeks after the last dose of medication). For patients who withdrew consent and did not attend the follow-up visit, their 'in-trial' period ended at the time of consent withdrawal.
- 'On-treatment' observation period is a subset of the 'in-trial' period and only includes the period when the patients were expected to be treated and exposed to the trial product. For adjudicated events this corresponded to the treatment emergent period.
- 'On-treatment without rescue medication' period included observations recorded from the first dose of trial product until the occurrence of initiation of rescue medication, or the end-date of the 'on-treatment' period.

Missing data:

- For continuous endpoints, last observation carried forward (LOCF) was used
- For endpoints subjected to statistical analysis, missing values were imputed by predictions from the statistical analysis model.

Protocol Amendments

There were three amendments (2 local amendments, and 1 global amendment) to the original protocol finalized on July 9, 2013. The global amendment was dated February 4, 2014, and, per the applicant, the main objective was to update the definition of hypoglycemia and to include an additional hypoglycemic endpoint (severe, or BG-confirmed symptomatic hypoglycemia) and associated statistical analysis.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant states that the study was conducted in accordance with ICH GCP.

Financial Disclosure

The applicant submitted adequate financial disclosures for the investigators that participated in this trial. There were a total of 424 investigators, out of which one reported financial disclosures.

Patient Disposition

Of the 652 patients screened, 264 (41%) were screening failures, thus 388 patients were randomized at a 2:2:1:1 ratio to receive semaglutide or placebo treatment at 2 different doses (0.5 mg, and 1 mg). Most screening failures (241/264) were due to patients not meeting the inclusion criterion of HbA1c levels being within 7−10% (both values included). Nine patients were recorded as having exclusion criteria as a reason for screen failure, where 15 patients had the reason listed as “other”, most of these patients withdrew consent or did not show up for the randomization visit.

Of the 388 patients randomized in the trial, 387 patients were exposed to trial products representing 128 patients exposed to semaglutide 0.5 mg, 130 patients exposed to semaglutide 1 mg and 129 patients exposed to placebo. One patient was randomized in error and never exposed to trial product. A total of 359 patients (93%) completed the trial and 340 patients (88%) completed the treatment. Of the 47 patients that discontinued the treatment early, the most commonly listed cause is “other”, for 21 patients, followed by “adverse event” for 18 patients, and 7 patients with protocol violations.

A larger proportion of patients who discontinued due to adverse events was observed with

semaglutide compared to placebo, however no dose dependence was observed.

Table 3 Patient Disposition Summary SUSTAIN 1

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)	Total N (%)
Screened				652
Screening failures				264 (40.5)
Withdrawn before randomisation				0 (0)
Randomised	129	130	129	388
Exposed	128 (99.2)	130 (100)	129 (100)	387 (99.7)
Safety analysis set	128 (99.2)	130 (100)	129 (100)	387 (99.7)
Full analysis set	128 (99.2)	130 (100)	129 (100)	387 (99.7)
Treatment completers [1]	111 (86.7)	114 (87.7)	115 (89.1)	340 (87.9)
Without rescue medication	105 (82.0)	109 (83.8)	89 (69.0)	303 (78.3)
With rescue medication	6 (4.7)	5 (3.8)	26 (20.2)	37 (9.6)
Premature treatment discontinuation - primary reason [2]	17 (13.3)	16 (12.3)	14 (10.9)	47 (12.1)
Pregnancy			1 (0.8)	1 (0.3)
Protocol violation	4 (3.1)	2 (1.5)	1 (0.8)	7 (1.8)
Violation of the inclusion and/or exclusion criteria	4 (3.1)	2 (1.5)	1 (0.8)	7 (1.8)
Intention of becoming pregnant				
Adverse event	8 (6.3)	7 (5.4)	3 (2.3)	18 (4.7)
Gastrointestinal AEs	3 (2.3)	3 (2.3)		6 (1.6)
Pancreatitis				
Other AEs	5 (3.9)	4 (3.1)	3 (2.3)	12 (3.1)
Other	5 (3.9)	7 (5.4)	9 (7.0)	21 (5.4)
Trial completers [3]	119 (92.2)	123 (94.6)	117 (90.7)	359 (92.5)
Premature withdrawal from trial in relation to or after premature treatment discontinuation - primary reason	9 (7.0)	7 (5.4)	10 (7.8)	26 (6.7)
Withdrawal by Subject	2 (1.6)		2 (1.6)	4 (1.0)
Lost to follow-up	3 (2.3)	2 (1.5)	5 (3.9)	10 (2.6)
Death				
Missing follow-up information [4]	4 (3.1)	5 (3.8)	3 (2.3)	12 (3.1)
Premature withdrawing from trial after treatment completion - primary reason	1 (0.8)		2 (1.6)	3 (0.8)
Withdrawal by Subject				
Lost to follow-up	1 (0.8)		2 (1.6)	3 (0.8)
Death				
Missing follow-up information [4]				

Notes: [1]: Completion of treatment according to end-of-trial form. [2]: Includes only exposed subjects and is based on the primary reason for treatment discontinuation according to the end-of-trial form. [3]: Subjects with a follow-up visit. [4]: Subjects with no reason/date for withdrawal but without the follow-up visit.
Abbreviations: N: Number of subjects, %: For treatment completers and treatment non-completers percentages are based on exposed subjects. For trial completers and withdrawals percentages are based on randomised subjects.

Source: Table 10-1 Study Report

Protocol Violations/Deviations

A total of 24 protocol deviations covering treatment compliance and adherence were reported by the applicant. There were 22 protocol violations at patient level (2 were at site level): 6 in placebo, 7 in semaglutide 0.5 mg, and 9 in the semaglutide 1 mg. A total of 3 patients received concomitant medication that was not allowed – 2 patients received a GLP-1 RA (1 patient with semaglutide 1 mg at visit 10 and 1 patient with semaglutide 0.5 mg between visit 10 and 11), and one patient received metformin (patient on semaglutide 1 mg at visit 7).

It is unlikely that these protocol violations impacted the outcome of the trial.
There were more men enrolled in the trial, although this was not balanced between treatment groups as the semaglutide 0.5 mg and 1.0 mg groups and the placebo group had 46.9%, 61.5% and 54.3% men, respectively. Of the 8 countries in which the trial was conducted, most

patients were recruited from the United States (32%), Japan (15.8%), the Russian Federation (13.4%) and Canada (10.1%), while the remaining countries each contributed <10% of the patients. Most patients were White (64.3%) or Asian (21.4%), with 29.7% being Hispanics or Latinos of ethnicity. Different races were comparably distributed across the 3 groups. At baseline, the mean age of all patients was 53.7 years with most patients (81.9%) falling within the age group of 18−64 years.

The mean body weight across the 3 groups was 91.9 kg with the semaglutide 1 mg group having a higher mean body weight at baseline (96.9 kg) compared with semaglutide 0.5 mg (89.8 kg) and placebo (89.1 kg). A minority of patients (11.9%) had a BMI within the normal range of 18.5-25 kg/m2, while most patients had a BMI>25 kg/m2. The mean BMI was 32.9 kg/m2 across the 3 groups with BMI distributions being similar across the 3 treatment groups.

The mean HbA1c level was 8.05%, similar across the 3 groups. The average duration for which a patient had diabetes prior to entering this trial was 4.2 years (median: 1.9 years). 63.8% of patients had normal renal function, 31.3% had mild renal impairment, and 4.9% of patients had moderate renal impairment. The mean estimated GFR was 99.02 mL/min/1.73 m2 and was similar for the 3 groups.

Details on the demographic information are presented in Table 4 and Table 5 below.

Table 4 Demographics and Baseline Characteristics for Categorical Variables - FAS – SUSTAIN 1

Demographic Parameters	Placebo (N=129) n (%)	Treatment Group		Total (N=387) n (%)
		Semaglutide 0.5 mg (N=128) n (%)	Semaglutide 1 mg (N=130) n (%)	
Sex				
Male	59 (45.7)	68 (53.1)	50 (38.5)	177
Female	70 (54.3)	60 (46.9)	80 (61.5)	210
Age				
Mean years (SD)	53.9 (11.0)	54.6 (11.1)	52.7 (11.9)	53.7 (11.3)
Median (years)	54.0	53.5	55.0	54.0
Min, max (years)	18; 80	30; 80	26; 80	18; 80
Age Group				
18-64 years	105 (81.4)	102 (79.7)	110 (84.6)	317
65-74 years	21 (16.3)	20 (15.6)	16 (12.3)	57
75-84 years	2 (1.6)	6 (4.7)	4 (3.1)	12
≥ 85 years	1 (0.8)	0 (0.0)	0 (0.0)	1
Race				
White	78 (60.5)	83 (64.8)	88 (67.7)	249
Black or African American	9 (7.0)	11 (8.6)	11 (8.5)	31
Asian	32 (24.8)	26 (20.3)	25 (19.2)	83

Demographic Parameters	Placebo (N=129) n (%)	Treatment Group		Total (N=387) n (%)
		Semaglutide 0.5 mg (N=128) n (%)	Semaglutide 1 mg (N=130) n (%)	
American Indian or Alaska Native	1 (0.8)	0 (0.0)	0 (0.0)	1
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0
Other	9 (7.0)	8 (6.3)	6 (4.6)	23
Ethnicity				
Hispanic or Latino	36 (27.9)	34 (26.6)	45 (34.6)	115
Not Hispanic or Latino	93 (72.1)	94 (73.4)	85 (65.4)	272
Region (optional)				
United States	36 (27.9)	41 (32.0)	47 (36.2)	124 (32.0)
Rest of the World				
Canada	10 (7.8)	16 (12.5)	13 (10.0)	39 (10.1)
Italy	12 (9.3)	5 (3.9)	10 (7.7)	27 (7.0)
Japan	23 (17.8)	19 (14.8)	19 (14.6)	61 (15.8)
Mexico	13 (10.1(	10 (7.8)	10 (7.7)	33 (8.5)
Russian Federation	17 (13.2)	17 (13.3)	18 (13.8)	52 (13.4)
South Africa	11 (8.5)	8 (6.3)	7 (5.4)	26 (6.7)
United Kingdom	7 (5.4)	12 (9.4)	6 (4.6)	25 (6.5)
Africa				

Source: Reviewer generated using Tables 10-2 study report

Table 5 Demographics and Baseline Characteristics for Continuous Variables - FAS – SUSTAIN 1

	Sema 0.5 mg	Sema 1.0 mg	Placebo	Total
Number of subjects	128	130	129	387
Age (years)				
N	128	130	129	387
Mean (SD)	54.6 (11.1)	52.7 (11.9)	53.9 (11.0)	53.7 (11.3)
HbA1c (%)				
N	128	130	129	387
Mean (SD)	8.09 (0.89)	8.12 (0.81)	7.95 (0.85)	8.05 (0.85)
Fasting plasma glucose (mg/dL)				
N	125	129	127	381
Mean (SD)	174.1 (49.89)	178.5 (44.99)	174.4 (49.85)	175.7 (48.19)
Duration of Diabetes (years)				
N	127	129	129	385
Mean (SD)	4.85 (6.11)	3.65 (4.89)	4.06 (5.48)	4.18 (5.52)
Body mass index (kg/m2)				
N	128	130	129	387
Mean (SD)	32.46 (7.62)	33.92 (8.43)	32.40 (6.86)	32.93 (7.68)
MDRD GFR 'estimated' (mL/min/1.73 m^2)				
N	128	130	129	387
Mean (SD)	95.91 (26.23)	100.9 (27.74)	100.2 (24.97)	99.02 (26.37)

Notes: The baseline value is defined as the latest pre-dosing value.
Body mass index is calculated based on baseline measurement of body weight and height.
Abbreviations: N: Number of subjects, SD: Standard deviation, CV: Coefficient of variation, MDRD: Modification of diet in renal disease, GFR: glomerular filtration rate

Source: Modified from Table 10-3 study report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The most common condition reported as medical history was surgical and medical procedures (36%), infections and infestations (10%) and gastrointestinal disorders (6%) and these medical histories were represented to a similar degree across the 3 groups.

Besides T2DM, which was an inclusion criterion for the trial, the most frequently reported concomitant illnesses across the 3 treatment groups were hypertension (47.0%), dyslipidemia (26.4%), obesity (22.0%), osteoarthritis (13.7%) and seasonal allergy (10.9%). The number of patients with dyslipidemia was similarly distributed across the 3 treatment groups.

More patients with semaglutide 1 mg (25.4%) had obesity as a concomitant illness, compared with semaglutide 0.5 mg (21.9%) and placebo (18.6%).

At randomization, the fundoscopy findings were normal for most the patients (80−81% of the patients in all treatment groups). The proportion of patients with 'abnormal, not clinically significant' and 'abnormal, clinically significant' was comparable between the semaglutide 0.5 mg (16% and 3%, respectively), the semaglutide 1 mg (18% and 2%, respectively) and placebo groups (19% and 1−2%, respectively).

Of the 387 randomized and dosed patients, the majority (210 patients, 54.3%) had a history of hypertension, of which 20 patients (5.2%) had a confirmed left ventricular hypertrophy.

Baseline concomitant medications were generally similar between the treatment groups. The most frequently used concomitant medications were statins (26.1%), ACE inhibitors (20.2%), platelet aggregation inhibitors excluding heparin (15.5%), and angiotensin II agonists (12.9%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Rescue medication (biguanides and sulfonylureas - SU) was administered to a total of 39 patients, with fewer patients with semaglutide 0.5 mg (6 patients) and 1.0 mg (6 patients), compared with placebo (27 patients). Biguanides were administered to more patients with placebo (24 patients) compared with semaglutide 0.5 mg (6 patients) and 1.0 mg (6 patients). Sulfonylureas were administered to more patients with placebo (4 patients) compared with semaglutide 0.5 mg (1 patient) and 1.0 mg (none).

Efficacy Results – Primary Endpoint

Statistical analyses for efficacy were performed on the full analysis set (FAS). Of the 388 patients randomized in the trial, one patient with semaglutide 0.5 mg was not exposed to treatment, as the patient was randomized in error, since laboratory results for an exclusion

criterion parameter were not reported. No patients were excluded from any of the analyses sets.

The applicant reported the results for the main efficacy endpoint on the FAS using the on treatment without rescue medication observation period. The two placebo arms were pooled for the efficacy analyses. The applicant used MMRM method using the on-treatment data for the primary analysis.

In the MMRM analysis, from a mean baseline level of 8.05%, HbA1c levels decreased by 1.45 %-points and 1.55 %-points with semaglutide 0.5 mg and 1.0 mg, respectively at week 30. With placebo, a minimal decrease in HbA1c of 0.02 %-points was seen at week 30. Statistical superiority of semaglutide in reducing HbA1c levels from baseline to week 30 was demonstrated for both doses of semaglutide compared with placebo.

Table 6 HbA1c – Primary Statistical Analysis- FAS - SUSTAIN 1

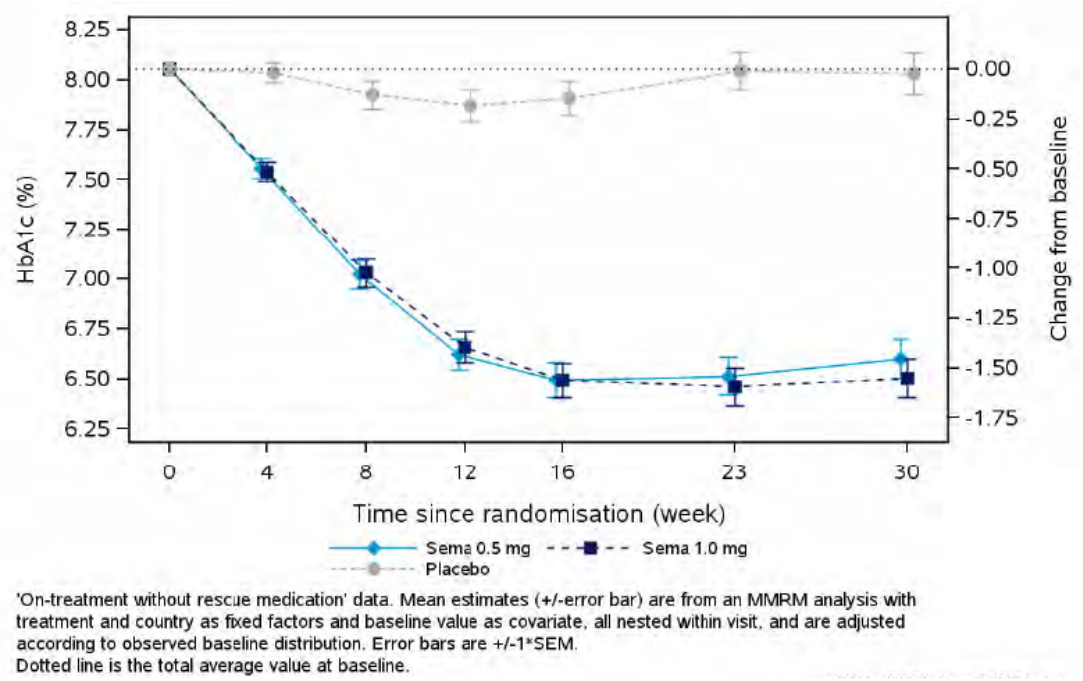
	FAS	N	Estimate	SE	95% CI	p-value
HbA1c (%)						
Mean at visit 10 (week 30)						
Sema 0.5 mg	128	102	6.60	0.10		
Sema 1.0 mg	130	104	6.50	0.10		
Placebo	129	84	8.03	0.10		
Change from baseline at visit 10 (week 30)						
Sema 0.5 mg	128	102	-1.45	0.10		
Sema 1.0 mg	130	104	-1.55	0.10		
Placebo	129	84	-0.02	0.10		
Treatment difference at visit 10 (week 30)						
Sema 0.5 mg - Placebo			-1.43		[-1.71 ; -1.15]	<.0001
Sema 1.0 mg - Placebo			-1.53		[-1.81 ; -1.25]	<.0001

Notes: Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.
Abbreviations: N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.

Source: Table 11-1 study report

HbA1c levels declined from initiation of treatment until week 16 followed by an apparent plateau that continued until the end of the 30-week treatment period with both semaglutide doses (Figure 3). The Placebo arm did not have any significant HbA1c changes over the course of the study.

Figure 3 HbA1c (%) Changes Over Time by Treatment Week – FAS- SUSTAIN 1



Source: Figure 11-1 study report

It is not clear that the way the applicant chose to perform the primary analysis in this study is a fair assessment of efficacy, as in the MMRM analysis the data is assumed to be missing at random and that may not be the case here. A sensitivity analysis including values after rescue – "in trial" period, yields similar results, although the response is somewhat attenuated.

Table 7 HbA1c - "In Trial" Observation Period – FAS – SUSTAIN 1

	FAS	N	Estimate	SE	95% CI	p-value
HbA1c (%)						
Mean at visit 10 (week 30)						
Sema 0.5 mg	128	119	6.65	0.10		
Sema 1.0 mg	130	121	6.46	0.10		
Placebo	129	116	7.81	0.10		
Change from baseline at visit 10 (week 30)						
Sema 0.5 mg	128	119	-1.41	0.10		
Sema 1.0 mg	130	121	-1.59	0.10		
Placebo	129	116	-0.25	0.10		
Treatment difference at visit 10 (week 30)						
Sema 0.5 mg - Placebo			-1.16		[-1.43 ; -0.88]	<.0001
Sema 1.0 mg - Placebo			-1.34		[-1.61 ; -1.07]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Analysis of observed 'in-trial' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.
Mean estimates are adjusted according to observed baseline distribution.

Source: Table 14.2.6 study report

The FDA analysis using multiple imputations using retrieved dropouts yielded similar results. Please see Biometrics review by Dr Jiwei He for details on the FDA statistical evaluation.

Data Quality and Integrity

Datasets and study documents appear adequate; I did not identify any issues.

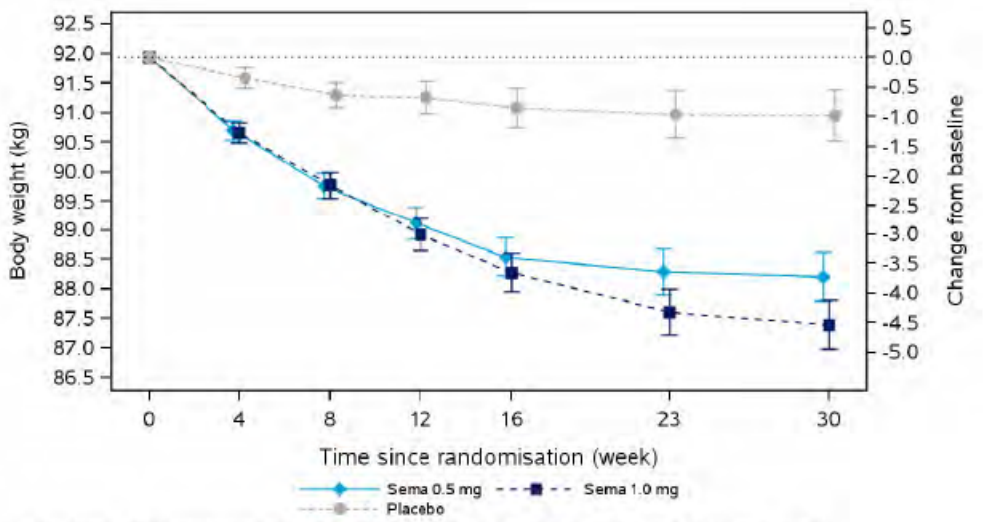
Efficacy Results – Secondary and other relevant endpoints

Change in body weight

Although a higher baseline body weight was seen with semaglutide 1 mg (96.9 kg) compared with semaglutide 0.5 mg (89.8 kg) and placebo (89.1 kg), the difference was small.

A placebo-adjusted weight loss of 2.7 kg (3.12%) and 3.56 kg (3.9%) was reported with semaglutide 0.5 mg and 1.0 mg, respectively, following 30 weeks of treatment. Most of the weight loss with semaglutide was observed in the first 16 weeks after initiation of the treatment. The differences in body weight were statistically superior for both semaglutide doses vs placebo. Sensitivity analyses were consistent with the primary analysis.

Figure 4 Body Weight Change Over Time – FAS – SUSTAIN 1



'On-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment and country as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
All visits but the week 16 and 23 visits were done in fasting state.
Dotted line is the total average value at baseline.

Source: Figure 11-5 study report

HbA1c treatment targets

A higher proportion of patients achieved a target HbA1c ≤6.5% after 30 weeks with either of the semaglutide doses (semaglutide 0.5 mg – 59%, semaglutide 1 mg – 60%) compared to placebo (13%). Similarly, a higher proportion of patients on semaglutide achieved a HbA1c target of <7% (semaglutide 0.5 mg – 74%, semaglutide 1 mg – 72%) compared to placebo (25%).

An HbA1c<7% without severe or BG-confirmed symptomatic hypoglycemia and no weight gain was obtained for more patients exposed to semaglutide 0.5 mg (66%) and semaglutide 1 mg (65%) when compared with placebo (19%).

Overall there does not appear to be a dose-response for either of the observed effects.

Table 8 Patients Achieving Various HbA1c Targets at Week 30- FAS – SUSTAIN 1

	FAS	N	R	Estimate	SE	95% CI	p-value
HbA1c <=6.5% (AACE)							
Estimated odds at visit 10 (week 30)							
Sema 0.5 mg	128	128	76	1.56	0.32		
Sema 1.0 mg	130	130	78	1.79	0.36		
Placebo	129	129	17	0.10	0.03		
Estimated odds ratio at visit 10 (week 30)							
Sema 0.5 mg / Placebo				15.99		[7.82 ; 32.68]	<.0001
Sema 1.0 mg / Placebo				18.34		[8.96 ; 37.54]	<.0001
HbA1c <7.0% (ADA)							
Estimated odds at visit 10 (week 30)							
Sema 0.5 mg	128	128	95	3.75	0.89		
Sema 1.0 mg	130	130	94	3.48	0.78		
Placebo	129	129	32	0.22	0.05		
Estimated odds ratio at visit 10 (week 30)							
Sema 0.5 mg / Placebo				16.92		[8.44 ; 33.89]	<.0001
Sema 1.0 mg / Placebo				15.70		[8.00 ; 30.83]	<.0001
HbA1c <7.0% without severe or BG confirmed symptomatic hypoglycaemia and without weight gain							
Estimated odds							
Sema 0.5 mg	128	128	85	2.25	0.47		
Sema 1.0 mg	130	130	85	2.21	0.45		
Placebo	129	129	25	0.18	0.04		
Estimated odds ratio							
Sema 0.5 mg / Placebo				12.69		[6.57 ; 24.52]	<.0001
Sema 1.0 mg / Placebo				12.45		[6.46 ; 23.99]	<.0001

Notes: Analysis of 'on-treatment without rescue medication' data. The binary endpoint is analysed using a logistic regression model with treatment and country as fixed factors and the baseline HbA1c value as covariate. Before analysis, missing data are imputed from a mixed model for repeated measures with treatment and country and baseline value, all nested within visit.
The composite binary endpoint is analysed using a logistic regression model with treatment and country as fixed factors and the baseline weight and HbA1c values as covariates. Before analysis, missing HbA1c and body weight data are imputed from separate mixed models for repeated measurements with treatment and country and parameter specific baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.
Abbreviations: N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval, SE: standard error, ADA: American Diabetes Assocoation, AACE: American Association of Clinical Endocrinologists.

Source: Table 11-3 study report

Weight loss targets

Patients achieving a weight loss of ≥5% or ≥10% were identified based on a binary (yes/no) outcome. A weight loss target of at least 5% was seen for 37% and 45% of patients with semaglutide 0.5 mg and 1.0 mg, respectively, and for 7% of patients on placebo. A weight loss target of at least 10%, this was seen for 8% and 13% of patients with semaglutide 0.5 mg and 1.0 mg, respectively, and for 2% of patients on placebo.

Dose/Dose Response

The placebo-adjusted HbA1C reduction was greater with semaglutide 1 mg compared to 0.5 mg.

Durability of Response

Most of the effect on HbA1c and weight was observed in the first 16 weeks of treatment, and sustained for the duration of the study (week 30).

Persistence of Effect

Not applicable. The effect after discontinuation of study drug was not assessed.

Additional Analyses Conducted on the Individual Trial

Sensitivity analyses are discussed above in the context of the primary analysis for the primary and secondary endpoints. They were generally consistent with the results of the primary analysis.

6.2. Study 3626 – SUSTAIN 2

6.2.1. Study Design

Overview and Objective

Study title: Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin and/or TZD in patients with type 2 diabetes

Primary objective: To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycemic control after 56 weeks of treatment.

Secondary objective: To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 56 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

Trial Design

This was a 56-week, randomized, double-blind, double-dummy, active-controlled, parallel-group, multicenter, multinational, four-armed trial investigating the efficacy and safety of semaglutide 0.5 mg and 1.0 mg once weekly versus sitagliptin 100 mg once daily in patients

with T2DM who had not achieved adequate glycemic control on metformin, TZD or a combination of metformin/TZD.

The trial was carried out in 18 countries in Europe, South and North America, Asia and South Africa.

Key inclusion/exclusion criteria:
Similar to those in SUSTAIN-1 with the following differences:

Inclusion criteria allowed for HbA1c of 7 to 10.5% and stable treatment for a period of 90 days prior to screening with either metformin ≥ 1500 mg (or maximum tolerated dose), pioglitazone ≥ 30 mg (or maximum tolerated dose), rosiglitazone ≥ 4 mg (or maximum tolerated dose) or a combination of either metformin/pioglitazone or metformin/rosiglitazone (doses as for individual therapies).

Dose selection/Study treatments:
Dose and dose escalation of semaglutide was similar to SUSTAIN-1.

Sitagliptin and sitagliptin placebo were provided as tablets and administered orally once daily at any time of the day irrespective of meals. The dose of sitagliptin was 100 mg without dose escalation.

Table 9 Dose Escalation Regimen SUSTAIN 2

Trial periods		Screening	Treatment			Follow up
			Dose escalation	Dose escalation/ Maintenance	Maintenance	
Visits in each period		Visits 1-2	Visits 2-3	Visits 3-5	Visits 5-13	Visits 13-14
Duration of each period		2 weeks	4 weeks	4 weeks	48 weeks	5 weeks
Treatment arm	**N**					
Semaglutide 0.5 mg and Sitagliptin placebo	400	Screening	Semaglutide 0.25 mg, 1.34 mg/mL and Sitagliptin 0 mg	Semaglutide 0.5 mg, 1.34 mg/mL and Sitagliptin 0 mg	Semaglutide 0.5 mg, 1.34 mg/mL and Sitagliptin 0 mg	Follow up
Semaglutide 1.0 mg and Sitagliptin placebo	400	Screening	Semaglutide 0.25 mg, 1.34 mg/mL and Sitagliptin 0 mg	Semaglutide 0.5 mg, 1.34 mg/mL and Sitagliptin 0 mg	Semaglutide 1.0 mg, 1.34 mg/mL and Sitagliptin 0 mg	Follow up
Sitagliptin 100 mg and Semaglutide placebo (1.0 mg)	200	Screening	Sitagliptin 100 mg and Semaglutide placebo 0 mg/mL	Sitagliptin 100 mg and Semaglutide placebo 0 mg/mL	Sitagliptin 100 mg and Semaglutide placebo, 0 mg/mL	Follow up
Sitagliptin 100 mg and Semaglutide placebo (0.5 mg)	200	Screening	Sitagliptin 100 mg and Semaglutide placebo 0.mg/mL	Sitagliptin 100 mg and Semaglutide placebo 0mg/mL	Sitagliptin 100 mg and Semaglutide placebo 0 mg/mL	Follow up

Notes: Semaglutide 0.25 mg, 0.5 mg, and 1.0 mg corresponded to 190µL, 370µL and 740µL, respectively.

Source: Table 9-1 study report

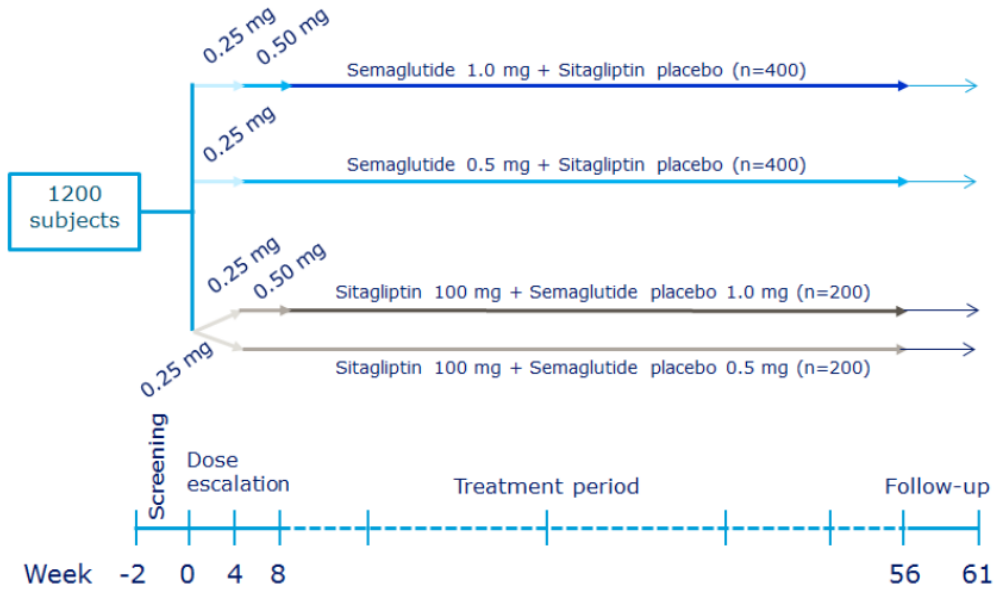
Assignment to treatment:

The trial period consisted of a 2-week screening period, a 56-week randomized treatment period (including a dose escalation period followed by a maintenance period) and a 5-week follow-up period.

Randomization was 2:2:1:1 as follows:

- Semaglutide 0.5 mg once weekly + sitagliptin placebo once daily
- Semaglutide 1 mg once weekly + sitagliptin placebo once daily
- Sitagliptin 100 mg once daily + semaglutide placebo 1 mg once weekly
- Sitagliptin 100 mg once daily + semaglutide placebo 0.5 mg once weekly

Figure 5 Trial Design SUSTAIN 2



Source: Figure 9-1 study report

Dose modification/discontinuation:
Similar to SUSTAIN-1.

Administrative structure:
Similar to SUSTAIN-1 with addition of an external Event Adjudication Committee (EAC) to adjudicate selected AEs (fatal events, acute coronary syndrome, cerebrovascular event, coronary revascularization procedures, heart failure requiring hospitalization, neoplasms, thyroid disease, and pancreatitis).

Procedures and schedule:
The patients had in person visits at screening, randomization, weeks 4, 8, 12, 16, 23, 30, 40, 48, 56, and 61. Phone visits occurred at weeks 6 and 35. Detailed study proceedings can be found in the study protocol submitted as part of this NDA.

Of note, funduscopy or fundus photography was to be performed at randomization, or within 90 days of randomization.

Concurrent medications:
Upon inclusion, patients were to continue pre-trial background antidiabetic medications throughout the entire trial, at the pre-trial dose and frequency of administration: metformin ≥

1500 mg (or maximum tolerated dose), pioglitazone ≥ 30 mg (or maximum tolerated dose), rosiglitazone ≥ 4 mg (or maximum tolerated dose).

Details of all concomitant therapies, including diabetes medication, were recorded in the eCRF at trial entry. Changes were to be recorded at each visit.

Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
Similar to SUSTAIN 1 with exception that choice of rescue medication was at the investigator's discretion.

Patient completion, discontinuation, or withdrawal
Similar to SUSTAIN 1.

Study Endpoints

Similar to SUSTAIN-1 with notable difference of assessment at week 56 rather than week 30, and additional exploratory secondary endpoints.

Statistical Analysis Plan

The sample size was calculated based on the primary endpoint, and the confirmatory secondary endpoint (change in weight at week 56).

To control the overall type 1 error rate, the non-inferiority and superiority hypotheses were tested hierarchically according to the following pre-specified test sequence:

1. Non-inferiority in change in HbA1c for semaglutide 1 mg vs. sitagliptin
2. Non-inferiority in change in HbA1c for semaglutide 0.5 mg vs. sitagliptin
3. Superiority in change in HbA1c for semaglutide 1 mg vs. sitagliptin
4. Superiority in change in body weight for semaglutide 1 mg vs. sitagliptin
5. Superiority in change in body weight for semaglutide 0.5 mg vs. sitagliptin
6. Superiority in change in HbA1c for semaglutide 0.5 mg vs. sitagliptin

Non-inferiority was to be concluded if the upper limit of the two-sided 95% CI for the estimated difference in HbA1c at week 56 between semaglutide and sitagliptin was less than 0.3%. The noninferiority analysis set was to be based on full analysis set.

In the analysis, the two sitagliptin groups (sitagliptin + semaglutide 0.5 mg placebo and sitagliptin + semaglutide 1 mg placebo) were pooled as no correlation between HbA1c change after 56 weeks and placebo volume was assumed.

The primary endpoint was analysed using an MMRM. The MMRM includes treatment and country as fixed factors and the baseline HbA1c as a covariate.

Protocol Amendments

There were seven amendments to the protocol: five local amendments and two global amendments.

Table 10 Protocol Amendments SUSTAIN 2

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
1	08 August 2013	Before	Japan	Updated with local requirements to clarify the planned number of subjects to be randomized in Japan (120 subjects); exclusion criteria to give examples of contraception methods appropriate in Japan; and addition of the local guidelines for diabetes care as one of the best possible care
2	30 August 2013	Before	Sweden	Updated with local requirements to implement the requirement for a changed definition on adequate contraceptive measures for trial subjects in Sweden
3	24 September 2013	Before	All countries	Updated with current storage conditions for sitagliptin and sitagliptin-placebo
4	26 September 2013	Before	Portugal	Updated with local requirements to clarify the adequate contraceptive measures applicable to Portugal
5	16 January 2014	After	Mexico	Updated with local requirements to clarify the planned number of subjects to be randomised in Mexico (55 subjects instead of 40)
6	04 February 2014	After	All countries	Updated with the following: – hypoglycaemia definition to include only severe hypoglycaemic episodes and symptomatic episodes with PG below 3.1 mmol/L – binary endpoint whether a subject had an episode in connection to the updated hypoglycaemia definition above – rescue medication criteria to clarify use and measurement of FPG – associated statistical analysis with the updated hypoglycaemia definition – minor corrections and updates for general clarification
7	04 June 2014	After	India	Updated with local requirements specific to India to reflect exclusion of subjects based on BMI (< 18.5 kg/m^2)

Abbreviations: FSFV = first subject first visit.

Source: Table 9-11 study report

Data Quality and Integrity: Sponsor's Assurance

The investigators were required to have been trained in GCP. Training of the investigators in the protocol was carried out through training sessions at the investigator meetings as well as an e-learning session, in order to ensure compliance and standardize performance across the trial. All principal investigators provided written commitments to comply with GCP and conduct the trial per the protocol, prior to participation in the trial. The trial was monitored by Novo Nordisk via on-site visits, telephone calls, and regular inspection of the eCRFs.

6.2.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with ICH GCP.

Financial Disclosure

The applicant submitted adequate financial disclosure documents. Of the 440 total investigators that participated in the trial, 2 had financial disclosures.

Patient Disposition

1796 patients were screened, 1231 randomized, and 1225 exposed to study medication. Of the 565 screening failures, the majority (448 patients) were due to failure in meeting inclusion criterion 4 (HbA1c level); while 62 patients met exclusion criterion 10 (impaired renal function).

Of the 410, 410, and 411 patients randomized to semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin groups, respectively, 409, 409, and 407 patients were exposed.

The overall proportion of patients completing treatment was generally lower with semaglutide than with sitagliptin (semaglutide 0.5 mg [87.0%], semaglutide 1 mg [85.1%], and sitagliptin [92.1%]). However, the proportion of patients completing the treatment without receiving rescue medication was higher with both semaglutide groups than with sitagliptin (semaglutide 0.5 mg [81.7%], semaglutide 1 mg [82.9%], and sitagliptin [72.5%]).

For a total of 146 (11.9%) patients, treatment was discontinued prematurely; the proportion of which was higher with both doses of semaglutide than with sitagliptin (semaglutide 0.5 mg [13.0%], semaglutide 1 mg [14.9%], and sitagliptin [7.9%]). AEs were the main reason for the premature discontinuation in a greater proportion of patients with semaglutide 0.5 mg (8.1%) and semaglutide 1 mg (10.0%) than with sitagliptin (2.9%).

Table 11 Patient Disposition SUSTAIN 2

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Sitagliptin N (%)	Total N (%)
Screened				1796
Screening failures				565 (31.5)
Withdrawn before randomisation				0
Randomised	410	410	411	1231
Exposed	409 (99.8)	409 (99.8)	407 (99.0)	1225 (99.5)
Safety analysis set	409 (99.8)	409 (99.8)	407 (99.0)	1225 (99.5)
Full analysis set	409 (99.8)	409 (99.8)	407 (99.0)	1225 (99.5)
Per protocol analysis set	365 (89.0)	361 (88.0)	385 (93.7)	1111 (90.3)
Treatment completers [1]	356 (87.0)	348 (85.1)	375 (92.1)	1079 (88.1)
Without rescue medication	334 (81.7)	339 (82.9)	295 (72.5)	968 (79.0)
With rescue medication	22 (5.4)	9 (2.2)	80 (19.7)	111 (9.1)
Premature treatment discontinuation - primary reason [2]	53 (13.0)	61 (14.9)	32 (7.9)	146 (11.9)
Pregnancy	0	0	0	0
Protocol violation	4 (1.0)	4 (1.0)	6 (1.5)	14 (1.1)
Violation of the inclusion and/or exclusion criteria	4 (1.0)	4 (1.0)	6 (1.5)	14 (1.1)
Intention of becoming pregnant	0	0	0	0
Adverse event	33 (8.1)	41 (10.0)	12 (2.9)	86 (7.0)
Gastrointestinal adverse events	19 (4.6)	31 (7.6)	1 (0.2)	51 (4.2)
Pancreatitis	2 (0.5)	1 (0.2)	3 (0.7)	6 (0.5)
Other adverse events	12 (2.9)	9 (2.2)	8 (2.0)	29 (2.4)
Other	16 (3.9)	16 (3.9)	14 (3.4)	46 (3.8)
Trial completers [3]	387 (94.4)	388 (94.6)	388 (94.4)	1163 (94.5)
Premature withdrawal from trial in relation to or after premature treatment discontinuation - primary reason	23 (5.6)	21 (5.1)	23 (5.6)	67 (5.4)
Withdrawal by Subject	10 (2.4)	11 (2.7)	10 (2.4)	31 (2.5)
Lost to follow-up	5 (1.2)	2 (0.5)	4 (1.0)	11 (0.9)
Death	2 (0.5)	1 (0.2)	3 (0.7)	6 (0.5)
Missing follow-up information [4]	2 (0.5)	1 (0.2)	3 (0.7)	6 (0.5)
Other	4 (1.0)	6 (1.5)	3 (0.7)	13 (1.1)
Premature withdrawing from trial after treatment completion - primary reason	0	1 (0.2)	0	1 (0.1)
Withdrawal by Subject	0	0	0	0
Lost to follow-up	0	0	0	0
Death	0	0	0	0
Missing follow-up information [4]	0	1 (0.2)	0	1 (0.1)
Other	0	0	0	0

N: Number of subjects, %: For treatment completers and treatment non-completers, percentages are based on exposed subjects
For trial completers and withdrawals percentages are based on randomised subjects.
[1]: Completion of treatment according to end-of-trial form. [2]: Includes only exposed subjects and is based on the primary reason for treatment discontinuation according to the end-of-trial form.
[3]: Subjects with a follow-up visit. [4]: Subjects with no reason/date for withdrawal but without the follow-up visit

Source: Table 10-1 study report

Protocol Violations/Deviations

In total, there were 96 important trial-site level protocol deviations, and 1591 important patient-level protocol deviations as summarized below.

Table 12 Summary of Important Protocol Deviations SUSTAIN 2

Protocol deviation category	Site-level PDs	Subject-level PDs				
		Sema 0.5 mg	Sema 1.0 mg	Sitagliptin	Screening failures	Total
Informed consent	10	45	59	39	48	191
Inclusion/exclusion/ randomisation criteria	3	15	23	19	6	63
Withdrawal criteria	0	0	0	1	0	1
Trial product handling	20	21	28	26	4	79
Treatment compliance	1	45	41	43	0	129
Assessment deviations	7	283	280	315	1	879
Other	55	72	99	76	2	249
Total	96	481	530	519	61	1591

Abbreviation: PD = protocol deviation; sema = semaglutide.

Source: Table 10-4 study report

Review of the details provided for the listed protocol deviations did not raise concerns that they impacted the trial conduct, safety or efficacy assessments.

Premature treatment discontinuation due to protocol violations happened in 1.0% in semaglutide 0.5 mg, 1.2% in semaglutide 1 mg, and 1.5% in sitagliptin.

Table of Demographic Characteristics

The mean age of the study participants was 55 years, approximately half of the patients were women, and 65.8% were white. The baseline HbA1c was 8.07%, and the mean duration of diabetes was 6.58 years.

Generally, the baseline demographic characteristics were matched between the treatment groups.

Table 13 Demographics and Baseline Characteristics for Categorical Variables – FAS- SUSTAIN 2

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Sitagliptin N (%)	Total N (%)
Number of subjects	409	409	407	1225
Age group				
N	409 (100.0)	409 (100.0)	407 (100.0)	1225 (100.0)
18–64 years	333 (81.4)	332 (81.2)	328 (80.6)	993 (81.1)
65–74 years	69 (16.9)	70 (17.1)	71 (17.4)	210 (17.1)
75–84 years	7 (1.7)	7 (1.7)	8 (2.0)	22 (1.8)
>= 85 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex				
N	409 (100.0)	409 (100.0)	407 (100.0)	1225 (100.0)
Female	202 (49.4)	204 (49.9)	199 (48.9)	605 (49.4)
Male	207 (50.6)	205 (50.1)	208 (51.1)	620 (50.6)
Race				
N	409 (100.0)	409 (100.0)	407 (100.0)	1225 (100.0)
White	279 (68.2)	279 (68.2)	281 (69.0)	839 (68.5)
Black or African American	18 (4.4)	24 (5.9)	17 (4.2)	59 (4.8)
Asian	106 (25.9)	99 (24.2)	102 (25.1)	307 (25.1)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	6 (1.5)	7 (1.7)	7 (1.7)	20 (1.6)
Ethnicity				
N	409 (100.0)	409 (100.0)	407 (100.0)	1225 (100.0)
Hispanic or Latino	69 (16.9)	67 (16.4)	73 (17.9)	209 (17.1)
Not Hispanic or Latino	340 (83.1)	342 (83.6)	334 (82.1)	1016 (82.9)
Renal function				
N	409 (100.0)	409 (100.0)	407 (100.0)	1225 (100.0)
Normal	260 (63.6)	268 (65.5)	275 (67.6)	803 (65.6)
Mild renal impairment	149 (36.4)	139 (34.0)	130 (31.9)	418 (34.1)
Moderate renal impairment	0 (0.0)	1 (0.2)	2 (0.5)	3 (0.2)
Severe renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
End stage renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not known	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate, Hkg: Hong Kong.
Baseline information is defined as the measurement at the latest assessment before dosing
The renal function categories are based on the MDRD eGFR
One subject did not have a recording of eGFR at baseline and therefore the renal function status is unknown. Three subjects had a moderate renal function at baseline. These four subjects were therefore randomised in error.

Source: Modified after table 10-2 study report

Table 14 Demographics and Baseline Characteristics for Continuous Variables – FAS- SUSTAIN 2

	Sema 0.5 mg	Sema 1.0 mg	Sitagliptin	Total
Number of subjects	409	409	407	1225
Age (years)				
N	409	409	407	1225
Mean (SD)	54.8 (10.2)	56.0 (9.4)	54.6 (10.4)	55.1 (10.0)
Median	55.0	56.0	55.0	55.0
Geometric mean (CV)	53.8 (19.82)	55.1 (18.02)	53.6 (20.33)	54.2 (19.44)
Min ; Max	27 ; 83	24 ; 78	23 ; 80	23 ; 83
HbA1c (%)				
N	409	409	407	1225
Mean (SD)	8.01 (0.92)	8.04 (0.93)	8.17 (0.92)	8.07 (0.93)
Median	7.80	7.80	7.90	7.90
Geometric mean (CV)	7.96 (11.22)	7.99 (11.27)	8.12 (10.99)	8.02 (11.19)
Min ; Max	5.90 ; 11.00	5.90 ; 11.40	6.50 ; 11.30	5.90 ; 11.40
Duration of Diabetes (years)				
N	409	409	407	1225
Mean (SD)	6.44 (4.66)	6.70 (5.56)	6.60 (5.08)	6.58 (5.11)
Median	5.30	5.40	5.40	5.40
Geometric mean (CV)	4.64 (115.76)	4.66 (118.08)	4.82 (105.12)	4.71 (112.88)
Min ; Max	0.30 ; 24.30	0.30 ; 39.20	0.30 ; 34.00	0.30 ; 39.20

Source: Table 10-3 study report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

If no funduscopy was available within 90 days, funduscopy was performed at randomization. The majority of patients (67%) had no retinopathy, the rest had either findings that were 'abnormal, not clinically significant' (26.0% and 25.7%, left and right eye respectively), or 'abnormal, clinically significant' (6.4% and 6.9%, left and right eye respectively).

Hypertension was reported in 53.6% of patients, dyslipidemia in 31.2%, obesity in 26.2%, hyperlipidemia in 12.2%, and diabetic neuropathy in 12.1%. 12.33% of patients were recorded as having ischemic heart disease at baseline, 2.78% had a history of myocardial infarction, 5.22% had a history of heart failure, and 1.71% had a history of ischemic stroke.

Only one patient had a history of pancreatitis at baseline, in the semaglutide 0.5 mg group.

These comorbidities were generally evenly distributed between the treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was monitored throughout the trial through monitoring of drug accountability. Additionally, semaglutide plasma concentrations were measured regularly during the trial, however, sitagliptin concentration was not measured.

As trial design required that patients had to be on metformin and/or TZD, the use of metformin was reported by 99.1% patients in all treatment groups, while 5.4% patients were on TZD (pioglitazone). Use of SUs (gliclazide or glimepiride) was reported by 1 patient in the semaglutide 0.5 mg group and 1 patient in the sitagliptin group.

HMG CoA reductase inhibitors (38.1%), ACE inhibitors (25.4%), platelet aggregation inhibitors excluding heparin (19.4%), and angiotensin II antagonists (18.0%) were the other most frequently used concomitant medications.

More patients in the sitagliptin group (85 patients) received rescue medication compared with patients treated with semaglutide 0.5 mg (25 patients) and semaglutide 1 mg (10 patients). The most frequently administered rescue medications included SUs (19 in patients treated with semaglutide 0.5 mg, 8 in semaglutide 1 mg group, and 64 in the sitagliptin group); biguanides (5 in patients treated with semaglutide 0.5 mg, 1 in semaglutide 1 mg group, and 13 in the sitagliptin group); and long-acting insulins (1 in a patient treated with semaglutide 0.5 mg, 1 in semaglutide 1 mg group, and 11 in the sitagliptin group).

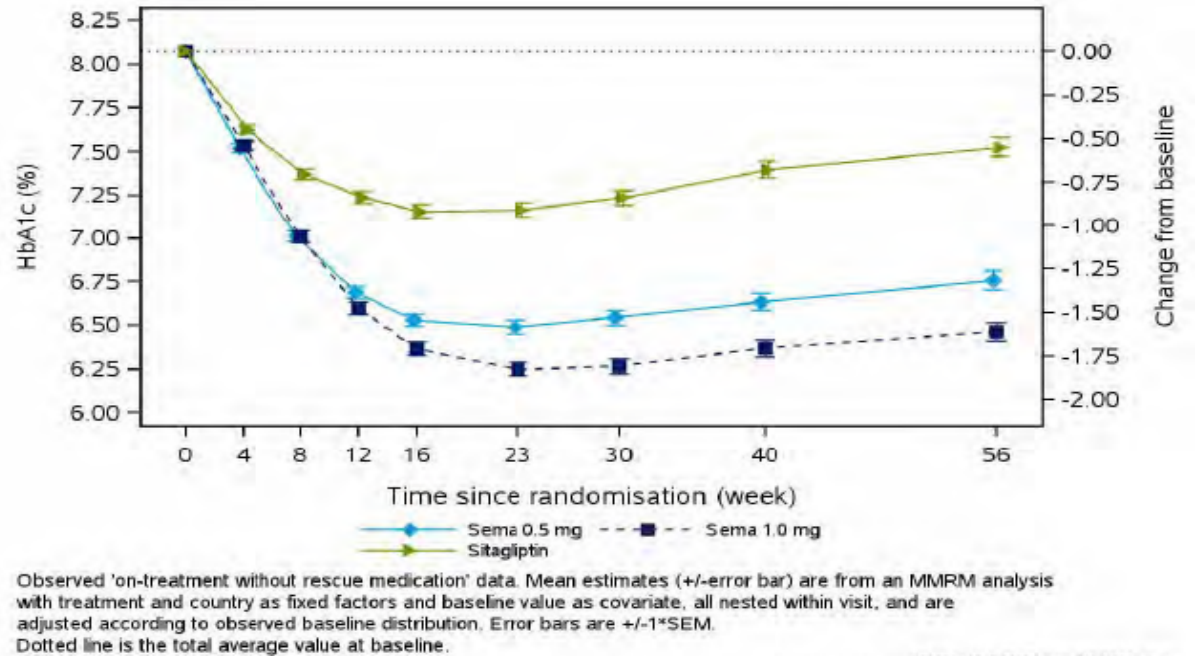
In both semaglutide treatment groups, the proportion of patients who received rescue medication slowly increased from randomization through week 40, after which the rate reached a plateau.

Efficacy Results - Primary Endpoint

Change in HbA1c

At baseline, HbA1c levels were similar among the semaglutide 0.5 mg, semaglutide 1 mg and sitagliptin groups (8.01%, 8.04%, and 8.17%, respectively). At week 56, HbA1c levels decreased by 1.32%- points and 1.61%-points with semaglutide 0.5 mg and 1.0 mg, respectively, compared with a 0.55%-points decrease with sitagliptin. Non-inferiority, followed by statistical superiority of both semaglutide doses compared to sitagliptin was established.

Figure 6 Mean HbA1c (%) by Treatment Week – FAS – SUSTAIN 2



Source: Figure 11-1 study report

Table 15 Mean HbA1c Changes at 56 Weeks – FAS – SUSTAIN 2

	FAS	N	Estimate	SE	95% CI	p-value
HbA1c (%)						
Mean at visit 13 (week 56)						
Sema 0.5 mg	409	328	6.76	0.05		
Sema 1.0 mg	409	331	6.46	0.05		
Sitagliptin	407	285	7.53	0.05		
Change from baseline at visit 13 (week 56)						
Sema 0.5 mg	409	328	-1.32	0.05		
Sema 1.0 mg	409	331	-1.61	0.05		
Sitagliptin	407	285	-0.55	0.05		
Treatment difference at visit 13 (week 56)						
Sema 0.5 mg - Sitagliptin			-0.77		[-0.92 ; -0.62]	<.0001
Sema 1.0 mg - Sitagliptin			-1.06		[-1.21 ; -0.91]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Modified from Table 11-1 study report

The FDA's preferred analysis using retrieved dropouts yielded results that were similar to the primary pre-specified MMRM analysis.

Please see Biometrics review by Dr Jiwei He for details regarding the FDA analyses.

Data Quality and Integrity - Reviewers' Assessment

Datasets and study documents appear adequate; I did not identify any issues.

Efficacy Results - Secondary and other relevant endpoints

Change in body weight

Mean body weight at baseline was similar among the three treatment groups, with an average of 89.48 kg. Semaglutide treatment lead to a dose-dependent weight loss compared to placebo, most of the weight loss occurring in the first 12 weeks.

Table 16 Body Weight Changes from Baseline to Week 56 – FAS – SUSTAIN 2

	FAS	N	Estimate	SE	95% CI	p-value
Body weight (kg)						
Change from baseline at visit 13 (week 56)						
Sema 0.5 mg	409	330	-4.28	0.25		
Sema 1.0 mg	409	334	-6.13	0.25		
Sitagliptin	407	290	-1.93	0.26		
Treatment difference at visit 13 (week 56)						
Sema 0.5 mg - Sitagliptin			-2.35		[-3.06 ; -1.63]	<.0001
Sema 1.0 mg - Sitagliptin			-4.20		[-4.91 ; -3.49]	<.0001
Body Weight (%)						
Change from baseline (%-points) at visit 13 (week 56)						
Sema 0.5 mg	409	330	-4.89	0.28		
Sema 1.0 mg	409	334	-6.82	0.28		
Sitagliptin	407	290	-1.87	0.28		
Treatment difference (%-points) at visit 13 (week 56)						
Sema 0.5 mg - Sitagliptin			-3.02		[-3.80 ; -2.24]	<.0001
Sema 1.0 mg - Sitagliptin			-4.95		[-5.73 ; -4.18]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Analysis of observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.
All visits but the week 23, 40 and 48 visits were done in fasting state.

Source: Table 11-2 study report

From a mean baseline in body weight of 89.48 kg across the three groups, the estimated change from baseline in body weight at week 56 was -4.28 kg (-4.89%-points) with semaglutide 0.5 mg, - 6.13 kg (-6.82%-points) with semaglutide 1 mg, and -1.93 kg (-1.87%-points) with sitagliptin.

HbA1c treatment targets

At week 56, a greater proportion of patients achieved HbA1c ≤6.5%, and <7% with semaglutide compared to sitagliptin.

The composite HbA1c treatment target of achieving HbA1c <7% without severe or blood glucose-confirmed symptomatic hypoglycemia and without weight gain was reached by a greater proportion of patients treated with semaglutide than with sitagliptin (63% of patients with semaglutide 0.5 mg, 74% with semaglutide 1 mg and 27% with sitagliptin).

Table 17 Patients Achieving Various HbA1c Targets at Week 56 – FAS – SUSTAIN 2

	FAS	N	R	Estimate	SE	95% CI	p-value
HbA1c ≤6.5% (AACE)							
Estimated odds at visit 13 (week 56)							
Sema 0.5 mg	409	409	215	1.01	0.11		
Sema 1.0 mg	409	409	270	2.07	0.24		
Sitagliptin	407	407	83	0.23	0.03		
Estimated odds ratio at visit 13 (week 56)							
Sema 0.5 mg / Sitagliptin				4.39		[3.15 ; 6.12]	<.0001
Sema 1.0 mg / Sitagliptin				8.99		[6.36 ; 12.72]	<.0001
HbA1c <7.0% (ADA)							
Estimated odds at visit 13 (week 56)							
Sema 0.5 mg	409	409	282	2.31	0.27		
Sema 1.0 mg	409	409	321	4.39	0.59		
Sitagliptin	407	407	148	0.55	0.06		
Estimated odds ratio at visit 13 (week 56)							
Sema 0.5 mg / Sitagliptin				4.16		[3.02 ; 5.74]	<.0001
Sema 1.0 mg / Sitagliptin				7.92		[5.59 ; 11.22]	<.0001
HbA1c <7.0% without severe or BG confirmed symptomatic hypoglycaemia and without weight gain							
Estimated odds							
Sema 0.5 mg	409	409	256	1.65	0.18		
Sema 1.0 mg	409	409	304	3.24	0.40		
Sitagliptin	407	407	109	0.34	0.04		
Estimated odds ratio							
Sema 0.5 mg / Sitagliptin				4.84		[3.51 ; 6.68]	<.0001
Sema 1.0 mg / Sitagliptin				9.52		[6.75 ; 13.43]	<.0001

N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval, SE: Standard error, ADA: American Diabetes Association, AACE: American Association of Clinical Endocrinologists. Analysis of 'on-treatment without rescue' data. The binary endpoint is analysed using a logistic regression model with treatment and country as fixed factors and the baseline HbA1c value as covariate. Before analysis, missing data are imputed from a mixed model for repeated measures with treatment and country and baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.

Source: Table 11-3 study report

Weight loss response

At week 56, a greater proportion of patients achieved a weight loss of ≥5% or ≥10% with semaglutide than with sitagliptin. At least 5% weight loss was observed in 46% and 62% of patients treated with semaglutide 0.5 mg and 1.0 mg, respectively, and 18% of patients treated with sitagliptin. Furthermore, 13%, 24%, and 3% of patients treated with semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively, achieved the stricter ≥10% weight loss criterion.

Various other secondary endpoints were explored by the applicant but I will not discuss them in this review as they are not relevant in this context.

Dose/Dose Response

For all outcomes, there did seem to be a dose-response with the higher semaglutide dose achieving better results compared to the lower dose.

Durability of Response

While most of the response was noticed in the first 12 weeks, the results were sustained for the remaining of the study.

Persistence of Effect

Not applicable

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.3. Study 3624 – SUSTAIN 3

6.3.1. Study Design

Overview and Objective

Study title: Efficacy and safety of semaglutide once-weekly versus exenatide ER 2.0 mg once-weekly as add-on to 1-2 oral antidiabetic drugs (OADs) in patients with type 2 diabetes.

Primary objective: To compare the effect of semaglutide 1 mg once-weekly versus exenatide ER 2.0 mg once-weekly on glycemic control after 56 weeks of treatment.

Secondary objectives:
To compare the effect of semaglutide 1 mg once-weekly versus exenatide ER 2.0 mg once-weekly after 56 weeks of treatment on:

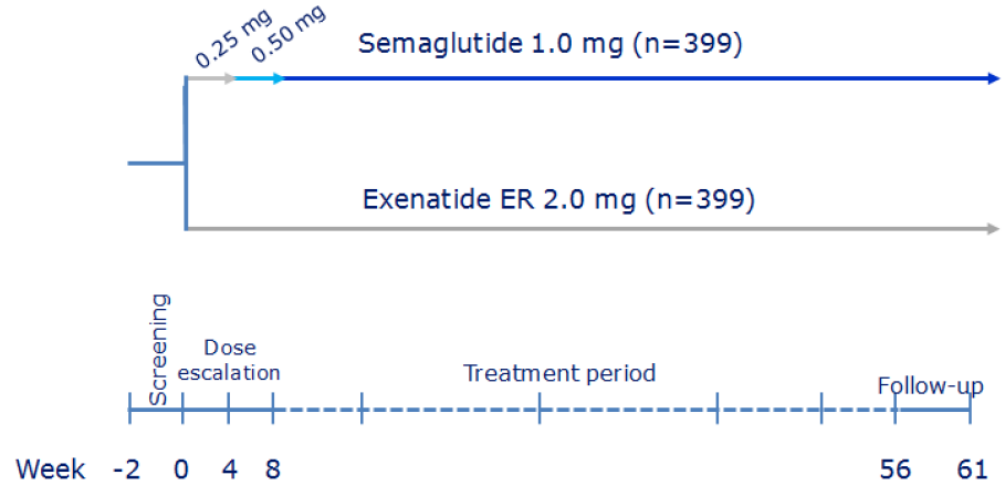
- Inducing and maintaining weight loss
- Other parameters of efficacy, safety and tolerability

Trial Design

This was a 56-week randomized, open-label, active-controlled, parallel-group, multi-national, multicenter, two-armed, efficacy and safety trial that compared once-weekly semaglutide 1 mg against once-weekly exenatide ER 2.0 mg.

The trial comprised a 2-week screening period, a 56-week treatment period, including an 8-week dose-escalation period (semaglutide only), and a 5-week off-drug follow-up period.

Figure 7 Trial Design SUSTAIN 3



Source: Figure 9-1 study report

In total, 138 sites in 12 countries randomized patients: Argentina: 4 sites; Croatia: 5 sites; Finland: 5 sites; France: 7 sites; Germany: 7 sites; Greece: 5 sites; Italy: 6 sites; Netherlands: 8 sites; Serbia: 5 sites; Switzerland: 5 sites; United Kingdom: 6 sites; and United States: 75 sites.

Since this was an open label trial, no blinding procedures were in place.

A total of 798 male and female patients with T2DM were planned for enrolment.

Key Inclusion/Exclusion Criteria:
Similary to SUSTAIN-1 with the following differences:

Inclusion criteria allowed for baseline HbA1c 7-10.5% and allowed for stable diabetes treatment with 1-2 OADs (metformin ≥ 1500 mg or maximum tolerated dose and/or TZD and SUs ≥ half of maximum dose allowed according to national label) for at least 90 days prior to screening.

Dose selection/Study treatments:
The applicant decided to only compare the highest dose of semaglutide proposed for marketing (1mg weekly) to the currently marketed long acting exenatide. The explanation for only choosing one semaglutide date was as follows: “The 1.0 mg semaglutide dose was chosen based on careful evaluations to strike a satisfactory balance between efficacy and safety.”

Dose escalation for semaglutide was similar to SUSTAIN-1.

Subjects receiving exenatide ER received the approved 2 mg dose once weekly. There is no dose titration for exenatide ER.

Dose modification/discontinuation:
Similar to SUSTAIN-1.

Administrative structure:
Similar to SUSTAIN-2.

Procedures and schedule:
Similar to SUSTAIN-2. For detailed procedures see Table 18.

Table 18 Trial Flow Chart SUSTAIN 3

Trial periods	Screening	Randomisation	Treatment period										EoT[1]	F-U[1]	Premature discontinuation[2]	
															EoT	F-U
Visit at site (V) or phone call (P)	**V1**	**V2**	**V3**	**P4**	**V5**	**V6**	**V7**	**V8**	**V9**	**P10**	**V11**	**V12**	**V13**	**V14**	**V13A**	**V14A**
Time of visit (weeks)	**-2**	**0**	**4**	**6**	**8**	**12**	**16**	**23**	**30**	**35**	**40**	**48**	**56**	**61**		
Visit window (days)	±7		±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS																
Informed consent	x															
Inclusion and exclusion criteria	x	x														
Randomisation		x														
Withdrawal criterion			x	x	x	x	x	x	x	x	x	x	x		x	
Concomitant illness and medical history	x															
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x															
Diabetes history	x															
History of gallbladder disease	x															
Smoking habits	x															
Fundoscopy/fundosphotography[3]		x														
Height		x														
EFFICACY																
Body weight		x	x		x	x	x	x	x		x	x	x		x	
Waist circumference		x	x		x	x	x	x	x		x	x	x		x	
Blood pressure	x	x	x		x	x	x	x	x		x	x	x		x	
HbA_{1c}	x	x	x		x	x	x	x	x		x		x		x	
Fasting plasma glucose		x	x		x	x	x		x				x		x	
Fasting insulin and proinsulin		x	x		x	x	x		x				x		x	
Fasting C-peptide		x	x		x	x	x		x				x		x	
Fasting glucagon		x	x		x	x	x		x				x		x	
Lipids		x							x				x		x	
hsCRP		x											x		x	
SMPG 7-point profile		x											x		x	
SAFETY																
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG		x							x				x	x	x	x
Physical examination	x												x		x	
Pulse rate	x	x	x		x	x	x	x	x		x	x	x		x	
Anti-semaglutide antibodies[4]		x					x		x		x		x	x	x	x
Anti-exenatide antibodies[4]		x					x		x		x		x	x	x	x
Creatinine (including eGFR)	x		x		x	x	x	x	x		x		x		x	
Biochemistry		x	x		x	x	x	x	x		x		x		x	
Haematology		x	x		x	x	x	x	x		x		x		x	
Calcitonin	x						x		x		x		x		x	
Pregnancy test[5]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis		x					x		x		x		x		x	
Urine Albumin to creatinine ratio		x											x		x	

Abbreviations: PRO = patient-reported outcomes; IV/WRS = interactive voice/web response system; PK = pharmacokinetics; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; ECG = electrocardiogram; EoT = end-of-trial; F-U = follow-up; SMPG = self-monitored plasma glucose.

1. Visit 13 (end-of-treatment) and visit 14 (follow-up) were applicable for all randomised subjects. Subjects who discontinued trial product prematurely were also to attend visit 13 and visit 14 according to their initially-scheduled week 56 and week 61 visits.
2. Subjects who discontinued trial product prematurely were to be asked to attend two additional visits to undergo assessments at end-of-treatment (visit 13A) and follow-up (visit 14A). Visit 13A was to be scheduled at discontinuation of the trial product; visit 14A was to be scheduled 5 weeks after discontinuation of trial product (+7 days visit window).
3. Fundoscopy/fundosphotography performed within 90 days before visit 2 was acceptable if results were available for evaluation at the visit 2 and if there was no deterioration in visual function since last assessment.
4. Blood sampling for antibody assessment was preferably to be done prior to dosing. For fasting and non-fasting visits, where the injection took place on the day of a site visit, trial product was not to be administered before blood sampling.
5. For visits 13 and 14: Not applicable if taken at a premature discontinuation visit (visits 13A or 14A).

Source: Modified from Table 9-3 study report

Concurrent medications:

Required background medication taken prior to trial enrolment was to continue throughout the trial; at least one and no more than two of the following were required:

- Metformin (maximum dose: ≥ 1500 mg or maximum tolerated dose)
- Thiazolidinedione (maximum dose: ≥ half of maximum dose allowed by the local label)
- Sulfonylureas (maximum dose: ≥ half of maximum dose allowed by the local label)

Background medications were to be maintained at the stable, pre-trial dose and frequency during the treatment period, unless rescue medication was needed. Sulfonylurea dose could be reduced in case of hypoglycemia.

Treatment compliance
Compliance was assessed by monitoring of drug accountability.

Rescue medications
Similar to SUSTAIN-2. GLP-1 RAs, DPP-4 inhibitors and pramlintide were not allowed.

Patient completion, discontinuation, or withdrawal
Similar to SUSTAIN-1.

Study Endpoints

Primary and confirmatory secondary endpoints were similar to SUSTAIN-2.

Statistical Analysis Plan

The primary and secondary endpoints were evaluated in a pre-specified and hierarchical, three-hypothesis test sequence. The hypotheses tested the following for semaglutide 1 mg vs. exenatide ER 2 mg at week 56:

1. Non-inferiority on change in HbA1c
2. Superiority on change in HbA1c
3. Superiority on change in body weight.

To advance to the next, the preceding test criterion had to be met.

Non-inferiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in HbA1c at week 56 between semaglutide 1 mg and exenatide ER 2.0 mg was less than 0.3%. Both the non-inferiority, and the superiority analysis, were based on the full analysis set (FAS).

The primary endpoint was analyzed using a MMRM. The MMRM includes treatment and country as fixed factors and the baseline HbA1c as a covariate. The confirmatory secondary endpoint (change in body weight at week 56 weeks) was analyzed using the same type of model as the primary endpoint, but with baseline body weight as the covariate.

Protocol Amendments

There were 4 amendments to the protocol as seen below.

Table 19 Amendments to the Protocol SUSTAIN 3

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
1	08-Oct-2013	Before	Greece	Addition of new trial sites.
2	04-Feb-2014	After	Global	Update for the definition of hypoglycaemia, including an additional hypoglycaemia endpoint and the associated statistical analysis. In addition, the rescue medication criteria were updated and minor updates for general clarification were made.
3	05-Feb-2014	After	The Netherlands	Addition of new trial sites.
4	25-Mar-2014	After	Greece	Removal of site

Source: Table 9-8 study report

Data Quality and Integrity: Sponsor's Assurance

The investigators were required to have been trained in ICH GCP. Training of the investigators in the protocol was carried out through training sessions at the investigator meetings as well as an e-learning session, to ensure compliance and standardize performance across the trial. All principal investigators provided written commitments to comply with ICH GCP and conduct the trial per the protocol, prior to participation in the trial. The trial was monitored by Novo Nordisk by on-site visits, telephone calls and regular inspection of the eCRFs.

6.3.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with ICH GCP.

Financial Disclosure

Of the 695 investigators, 7 had disclosable information. Of these 7, 5 had the financial disclosure forms, and 2 had certificate of due diligence.

Patient Disposition

In total, 1171 patients were screened; of these, 813 patients were randomized and 358 patients were screening failures

Of the 358 screening failures, the majority, 239, did not meet the inclusion criteria that pertained to HbA1c, and 53 met the exclusion criteria “impaired renal function”. The remaining screening failures were due to not meeting other inclusion criteria, or meeting various exclusion criteria, and 18 were labeled “other”.

Table 20 Patient Disposition Summary SUSTAIN 3

	Sema 1.0 mg N (%)	Exenatide ER N (%)
Randomised	**406**	**407**
Exposed	**404 (99.5)**	**405 (99.5)**
Safety analysis set	404 (99.5)	405 (99.5)
Full analysis set	404 (99.5)	405 (99.5)
Per protocol analysis set	347 (85.5)	333 (81.8)
Treatment completers [1]	**322 (79.7)**	**320 (79.0)**
Without rescue medication	300 (74.3)	281 (69.4)
With rescue medication	22 (5.4)	39 (9.6)
Premature treatment discontinuation - primary reason [2]	**82 (20.3)**	**85 (21.0)**
Pregnancy	0	1 (0.2)
Protocol violation	15 (3.7)	21 (5.2)
Violation of the inclusion and/or exclusion criteria	15 (3.7)	21 (5.2)
Adverse event	39 (9.7)	29 (7.2)
Gastrointestinal AEs	18 (4.5)	9 (2.2)
Pancreatitis	3 (0.7)	3 (0.7)
Other AEs	18 (4.5)	17 (4.2)
Other	27 (6.7)	34 (8.4)
NA	1 (0.2)	0
Trial completers [3]	**374 (92.1)**	**369 (90.7)**
Premature withdrawal from trial in relation to or after premature treatment discontinuation - primary reason	**32 (7.9)**	**37 (9.1)**
Withdrawal by Subject	16 (3.9)	19 (4.7)
Lost to follow-up	10 (2.5)	9 (2.2)
Death	2 (0.5)	0
Missing follow-up information [4]	2 (0.5)	4 (1.0)
Other	2 (0.5)	5 (1.2)
Premature withdrawing from trial after treatment completion	**0**	**1 (0.2)**
Lost to follow-up	0	1 (0.2)

Exenatide ER: Exenatide Extended release, N: Number of subjects, NA : Not available. %: For treatment completers and treatment non-completers percentages are based on exposed subjects. For trial completers and withdrawals percentages are based on randomised subjects.
[1]: Completion of treatment according to end-of-trial form.
[2]: Includes only exposed subjects and is based on the primary reason for treatment discontinuation according to the end-of-trial form.
[3]: Subjects with a follow-up visit.
[4]: Subjects with no reason/date for withdrawal but without the follow-up visit.

Source: Table 10-1 study report

Of the 406 and 407 patients randomized to semaglutide 1 mg and exenatide ER 2 mg, respectively, 404 and 405 patients were exposed. All exposed patients were included in the FAS and in the SAS.

The overall proportion of patients completing the treatment was similar between the semaglutide 1 mg (79.7%) and exenatide ER 2 mg (79.0%) groups. The proportion of patients completing the treatment without receiving rescue medication was greater with semaglutide 1 mg (74.3%) than with exenatide ER 2 mg (69.4%).

For a total of 167 (20.4%) patients, treatment was discontinued prematurely; the proportion of patients was similar between the semaglutide 1 mg (20.3%) and exenatide ER 2 mg (21.0%) groups. AEs were the reason for the premature discontinuation in a greater proportion of patients with semaglutide 1 mg (9.7%) than with exenatide ER 2 mg (7.2%); the AEs included

GIAEs (4.5% and 2.2% of patients, respectively), AEs potentially related to pancreatitis (0.7% and 0.7%) and 'Other' (i.e. not GIAEs or pancreatitis; 4.4% and 4.2%).

A total of 743 (91.4%) patients completed the trial; 374 (92.1%) patients with semaglutide 1 mg and 369 (90.7%) patients with exenatide ER 2 mg. Thus, 63 (7.7%) patients in total did not complete the trial; 30 (7.4%) patients with semaglutide 1 mg and 33 (8.1%) patients with exenatide ER 2 mg. With semaglutide 1 mg, 3.9% of the patients withdrew electively from the trial, compared with 4.7%with exenatide ER 2 mg. Two (0.5%) patients treated with semaglutide 1 mg died during the trial vs. none with exenatide ER 2 mg. Other reasons for withdrawal from the trial were 'Other' and 'Lost to follow-up'. In total, 10 (2.5%) patients in each treatment group were lost to follow-up.

Protocol Violations/Deviations

A total of five important protocol deviations (PDs)were recorded at trial level: one in 'trial product handling' (a calibrated thermometer used in lieu of a min/max thermometer for monitoring of the trial product temperature), one in 'assessment deviations' (initially excess, followed by insufficient blood samples were drawn for evaluation of the anti-semaglutide, and anti-exenatide, antibodies), and three on the "other' category (technical difficulties reporting MESIs within the 4 week period after identification during January 23, 2014, and March 17, 2014, revising an error in the paper CRF, rectification of the DMC responsibilities).

At country level, one PD was recorded for Argentina, where cooler bags were given to the patients before ethical approval of the trial.

There were 152 important trial-site level PDs and 1134 important patient-level PDs. The 152 important site-level PDs were categorized as follows: 'Assessment deviations', 7 PDs; 'Inclusion/exclusion/randomization criteria, 2 PDs; 'Informed consent', 7 PDs, 'Treatment compliance', 1 PD; 'Trial product handling', 25 PDs; 'Other', 110 PDs.

The patient level PDs are summarized below.

Table 21 Summary of Important Patient-Level Protocol Deviations SUSTAIN 3

Protocol deviation category	Sema 1.0 mg	Exenatide ER	Screening failures	Total
Informed consent	55	63	13	131
Inclusion/exclusion/randomisation criteria	28	29	1	58
Trial product handling	16	17	1	34
Treatment compliance	43	21	0	64
Assessment deviations	393	333	5	731
Other	41	74	1	116
Total	576	537	21	1134

Abbreviation: sema = semaglutide
Source: Table 10-4 study report

I evaluated these protocol deviations and concluded that it is unlikely that they impacted the trial results, or patient safety.

Table of Demographic Characteristics

The mean age was around 56 years and similar between the treatment groups. Of the 12 countries in which the trial was conducted, the United States was the country with the most patients (313 [38.7%] patients in total).

The vast majority of patients were White (83.9% in total); 7.2% in total were Black or African American and 1.7% in total were Asian. Most patients were of 'non- Hispanic or Latino' ethnicity (75.6%).

Most patients (32.6% in total) and more with exenatide ER 2 mg (34.6%) than with semaglutide 1 mg (30.7%) were obese.

The majority of patients (64.0% in total) had normal renal function; 35.8% in total had mild renal impairment. The proportion of patients with mild renal impairment was greater with semaglutide 1 mg (38.1%) compared with exenatide ER 2 mg (33.6%).

At baseline, mean HbA1c was similar between the two treatment groups 8.36% and 8.33% and with semaglutide 1 mg and exenatide ER 2 mg, respectively. The duration of diabetes was also similar between the two treatment groups (around 9 years).

Table 22 Demographics and Baseline Characteristics for Categorical Variables – FAS – SUSTAIN 3

	Sema 1.0 mg N (%)	Exenatide ER N (%)	Total N (%)
Number of subjects	404	405	809
Age group			
N	404 (100.0)	405 (100.0)	809 (100.0)
18-64 years	316 (78.2)	298 (73.6)	614 (75.9)
65-74 years	78 (19.3)	90 (22.2)	168 (20.8)
75-84 years	10 (2.5)	17 (4.2)	27 (3.3)
Sex			
N	404 (100.0)	405 (100.0)	809 (100.0)
Female	185 (45.8)	177 (43.7)	362 (44.7)
Male	219 (54.2)	228 (56.3)	447 (55.3)
Race			
N	404 (100.0)	405 (100.0)	809 (100.0)
White	341 (84.4)	338 (83.5)	679 (83.9)
Black or African American	28 (6.9)	30 (7.4)	58 (7.2)
Asian	8 (2.0)	6 (1.5)	14 (1.7)
American Indian or Alaska Native	2 (0.5)	1 (0.2)	3 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	2 (0.5)	2 (0.2)
Other	3 (0.7)	5 (1.2)	8 (1.0)
NA	22 (5.4)	23 (5.7)	45 (5.6)
Ethnicity			
N	404 (100.0)	405 (100.0)	809 (100.0)
Hispanic or Latino	91 (22.5)	106 (26.2)	197 (24.4)
Not Hispanic or Latino	313 (77.5)	299 (73.8)	612 (75.6)
Renal function			
N	403 (99.8)	405 (100.0)	808 (99.9)
Normal	249 (61.6)	269 (66.4)	518 (64.0)
Mild renal impairment	154 (38.1)	136 (33.6)	290 (35.8)
Moderate renal impairment	0 (0.0)	0 (0.0)	0 (0.0)
Severe renal impairment	0 (0.0)	0 (0.0)	0 (0.0)
End stage renal impairment	0 (0.0)	0 (0.0)	0 (0.0)
NA	1 (0.2)	0 (0.0)	1 (0.1)

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate, NA: Not Applicable.
Baseline information is defined as the measurement at the latest assessment before dosing.
Body mass index is calculated based on baseline measurement of body weight and height.
The renal function categories are based on the MDRD eGFR
N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate, NA: Not Applicable.
Baseline information is defined as the measurement at the latest assessment before dosing.
Body mass index is calculated based on baseline measurement of body weight and height.
The renal function categories are based on the MDRD eGFR

Source: Adapted from Table 10-2 study report

Table 23 Demographics and Baseline Characteristics for Continuous Variables– FAS – SUSTAIN 3

	Sema 1.0 mg	Exenatide ER	Total
Number of subjects	404	405	809
Age (years)			
N	404	405	809
Mean (SD)	56.4 (10.3)	56.7 (11.1)	56.6 (10.7)
Median	57.0	57.0	57.0
Geometric mean (CV)	55.4 (20.30)	55.5 (21.85)	55.4 (21.07)
Min ; Max	20 ; 82	21 ; 83	20 ; 83
HbA1c (%)			
N	404	405	809
Mean (SD)	8.36 (0.95)	8.33 (0.96)	8.35 (0.95)
Median	8.20	8.20	8.20
Geometric mean (CV)	8.31 (11.20)	8.28 (11.33)	8.29 (11.26)
Min ; Max	6.70 ; 11.10	6.50 ; 11.20	6.50 ; 11.20
Duration of Diabetes (years)			
N	404	405	809
Mean (SD)	9.02 (5.95)	9.40 (6.71)	9.21 (6.34)
Median	8.10	8.10	8.10
Geometric mean (CV)	6.95 (95.32)	7.20 (95.56)	7.07 (95.39)
Min ; Max	0.40 ; 37.10	0.30 ; 54.00	0.30 ; 54.00
Body mass index (kg/m2)			
N	403	405	808
Mean (SD)	33.97 (7.23)	33.57 (6.23)	33.76 (6.75)
Median	32.46	32.58	32.51
Geometric mean (CV)	33.27 (20.20)	33.02 (18.10)	33.15 (19.17)
Min ; Max	21.05 ; 72.84	21.22 ; 55.75	21.05 ; 72.84
MDRD GFR 'estimated' (mL/min/1.73 m^2)			
N	403	405	808
Mean (SD)	100.5 (24.68)	100.5 (22.54)	100.5 (23.62)
Median	97.00	99.00	98.00
Geometric mean (CV)	97.71 (23.84)	98.09 (22.47)	97.90 (23.15)
Min ; Max	60.00 ; 208.0	60.00 ; 194.0	60.00 ; 208.0

Exenatide ER: Exenatide Extended release, N: Number of subjects, SD: Standard deviation.
CV: Coefficient of variation, MDRD: Modification of diet in renal disease.
GFR: Glomerular filtration rate.
The baseline value is defined as the latest pre-dosing value.
Body mass index is calculated based on baseline measurement of body weight and height.

Source: Adapted from Table 10-3 study report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Medical history and concomitant illnesses were relatively balanced between the two treatment groups.

Frequent and clinically relevant concomitant illnesses included (proportion of patients with semaglutide 1 mg vs. exenatide ER 2.0 mg) hypertension (65.6% vs. 67.4%), hyperlipidemia (24.8% vs. 21.2%), dyslipidemia (15.8% vs. 18.8%), obesity (16.3% vs. 17.3%), gastroesophageal reflux disease (9.7% vs. 11.9%), diabetic neuropathy (6.2% vs. 6.9%), hepatic steatosis (5.7% vs. 6.2%) and cholelithiasis (3.0% vs. 1.0%).

Funduscopy was performed at screening if no recent normal funduscopy results were available. At baseline, 77.7% of the patients in the semaglutide arm, and 80% of patients in the exenatide arm, had no changes observed on the funduscopic exam.

There were no major differences between the treatment arms regarding the cardiovascular history. Only 2.48 % of patients in the semaglutide arm, and 3.21% of patients in the exenatide arm reported a history of myocardial infarction (MI). While the patient populations in the two arms appears different regarding stroke (0.74% with semaglutide, and 1.73% with exenatide), it is likely that the difference is due to chance as the number of patients with event are very small. Frequently reported histories of cardiovascular disease included (proportion of patients with semaglutide 1 mg vs. exenatide ER 2.0 mg) hypertension (70.8% vs. 70.6%), disorder of cardiac rhythm or cardiac conduction (9.9% vs. 8.9%) and ischemic heart disease (7.7% vs 9.9%).

No clinically relevant differences in histories of gallbladder disease at screening were observed between the semaglutide 1 mg (16.8%) and exenatide ER 2.0 mg (16.1%) groups. A history of gallstone disease (cholelithiasis) was reported at screening by 59 (14.6%) and 56 (13.8%) of the patients in the semaglutide 1 mg and exenatide ER 2.0 mg groups, respectively. A history of cholecystitis was reported at screening by 24 (5.9%) and 25 (6.2%) of the patients in the semaglutide 1 mg and exenatide ER 2.0 mg groups, respectively; 21 (5.2%) of the cholecystitis cases in both treatment groups were acute, whereas the remaining cases were chronic.

In the semaglutide 1 mg group, 15 patients (3.7%) reported a history of both cholecystitis and gallstone disease (cholelithiasis), compared with 16 (4.0%) patients with exenatide ER 2.0 mg. A history of pancreatitis (acute) was reported at screening by 1 (0.25%) patient in the semaglutide 1 mg group and by 2 (0.49%) patients in the exenatide ER 2.0 mg group.

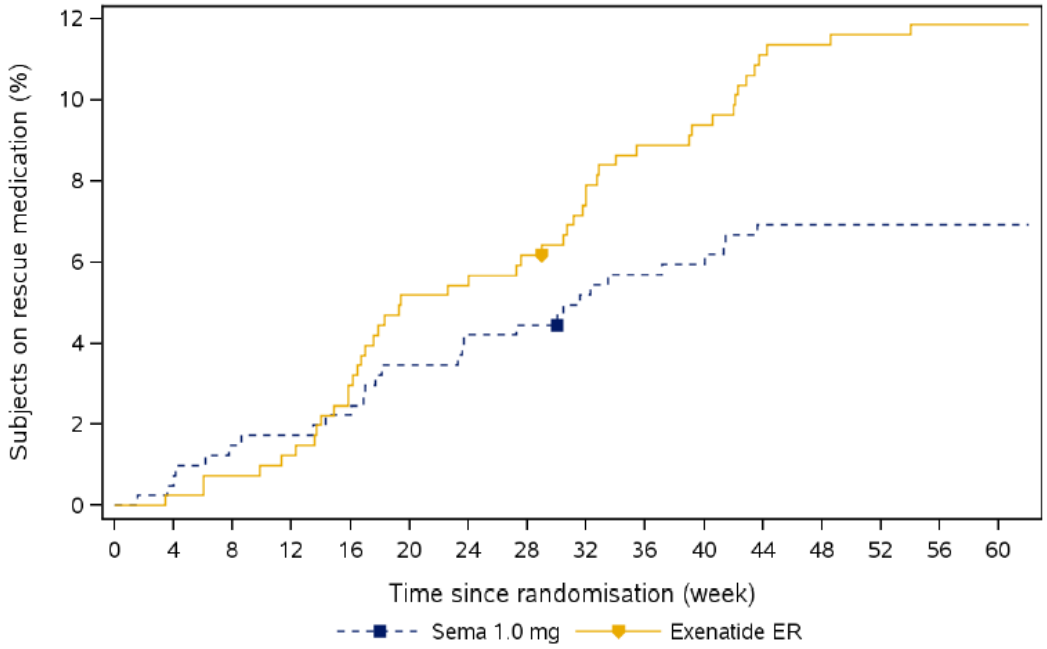
Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Use of biguanides (metformin) was reported by around 96% of the patients in each treatment group. Use of SUs was reported by a smaller proportion of patients in the semaglutide 1 mg group (44.8%) compared with the exenatide ER 2.0 mg group (51.4%), whereas the opposite was seen for thiazolidinediones (3.2% vs. 1.5%).

A total of 14 patients were randomized in error in violation of the protocol due to use of nonallowed antidiabetic medications; important patient-level protocol deviations were filed for all 14 cases, 13 of which led to premature treatment discontinuation.

Fewer patients with semaglutide 1 mg (29 patients) received rescue medication compared with exenatide ER 2.0 mg (48 patients). The most frequently administered rescue medications included SUs (18 [4.5%] patients with semaglutide 1 mg and 26 [6.4%] patients with exenatide ER 2.0 mg), long-acting insulins (8 [2.0%] and 8 [2.0%] patients) and metformin (7 [1.7%] and 9 [2.2%] patients).

Figure 8 Time from Randomization to Initiation of Rescue Medication (Weeks) – FAS – SUSTAIN 3



Exenatide ER: Exenatide Extended release. Denominator is number of subjects in the full analysis set.
Source: Figure 10-3 study report

Semaglutide plasma concentrations were measured regularly during the trial in part to assess compliance, however the exenatide concentrations were not measured. The protocol deviations for the 'treatment compliance' category were recorded for 43 patients in the exenatide arm, and only 21 patients in the semaglutide arm. None of these protocol deviations lead to treatment discontinuation.

Efficacy Results - Primary Endpoint

Change in HbA1c

At baseline, the HbA1c levels were similar between the semaglutide 1 mg and exenatide ER 2.0 mg groups (8.36% and 8.33%, respectively).

At week 56, the estimated mean change from baseline in HbA1c was -1.54 %-points with semaglutide 1 mg and -0.92 %-points with exenatide ER 2.0 mg. Non-inferiority, followed by statistical superiority, was established for semaglutide when compared to exenatide. The results of the primary analysis are shown in Table 24 below.

Table 24 Change in HbA1c from Baseline to Week 56 SUSTAIN 3

	FAS	N	Estimate	SE	95%CI	p-value
HbA_{1c} (%)						
Mean at week 56						
Sema 1.0 mg	404	291	6.81	0.06		
Exenatide ER	405	271	7.43	0.06		
Change from baseline at week 56						
Sema 1.0 mg	404	291	-1.54	0.06		
Exenatide ER	405	271	-0.92	0.06		
Treatment difference at week 56						
Sema 1.0 mg - Exenatide ER			-0.62		[-0.80;-0.44]	<.0001

Exenatide ER: Exenatide Extended release, N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Table 11-1 study report

The applicant also performed sensitivity analyses, and the results were supportive of the primary analysis.

Data Quality and Integrity - Reviewers' Assessment

The datasets and the study documents were adequate. I did not identify any quality or integrity issues.

Efficacy Results - Secondary and other relevant endpoints

Change in body weight

At baseline, the body weight was similar between the semaglutide and exenatide groups (96.2 kg and 95.4 kg, respectively).

At week 56, the estimated mean change from baseline in body weight was -5.63 kg (-5.98%) with semaglutide and -1.85 kg (-1.79%) with exenatide. The treatment difference was -3.78 kg, with a 95% CI (-4.58; -2.98).

With semaglutide the body weight decreased until week 30; after plateauing from week 30 to week 48, body weight again decreased through week. With exenatide, the body weight decreased until week 16; subsequently, it remained stable until week 30, where after it slightly increased until week 40 and then remained stable below the baseline through week 56.

Additional supportive secondary outcomes were reported by the applicant. Selected outcomes are summarized below:

- The HbA1c treatment targets were reached by greater proportions of patients at week 56 with semaglutide 1 mg compared with exenatide ER 2.0 mg; the estimated odds for reaching all three targets were significantly higher with semaglutide 1 mg than with exenatide ER 2.0 mg:
  – ≤6.5% HbA1c (AACE) was reached by 47.0% and 22.0% of the patients with semaglutide 1 mg and exenatide ER 2.0 mg, respectively; the estimated treatment odds ratio was 3.73 [2.66;5.23]95%CI.
  – <7.0% HbA1c (ADA) was reached by 66.8% and 39.8% of the patients with semaglutide 1 mg and exenatide ER 2.0 mg, respectively; the estimated treatment odds ratio was 3.88 [2.80;5.38]95%CI.
- The composite HbA1c treatment target (<7% without severe or blood glucose-confirmed symptomatic hypoglycemia and without weight gain) was reached by 56.9% and 28.6% of the patients with semaglutide 1 mg and exenatide ER 2.0 mg, respectively; the estimated treatment odds ratio was 4.03 [2.90;5.59]95%CI.

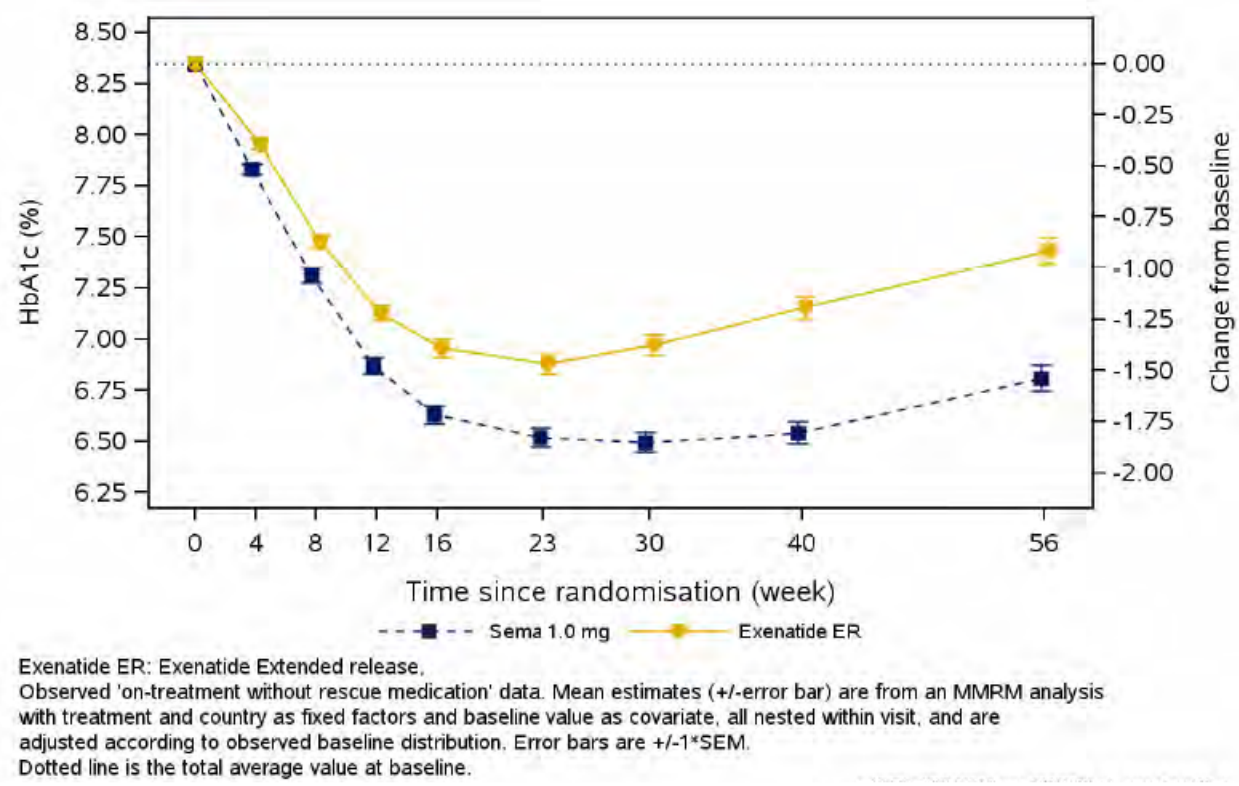
Dose/Dose Response

Not applicable, only one dose of each product was tested.

Durability of Response

In both treatment arms, HbA1c decreased from baseline until weeks 23-30, followed by an increase, however remaining below baseline levels at the end of the 56 weeks.

Figure 9 HbA1c (%) by Treatment Week - Mean Plot - Estimated – FAS – SUSTAIN 3



Exenatide ER: Exenatide Extended release,
Observed 'on-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment and country as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
Dotted line is the total average value at baseline.

Source: Figure 11-1 study report

Persistence of Effect

Not applicable. Effect after discontinuation of study drug was not assessed.

Additional Analyses Conducted on the Individual Trial

The applicant conducted various sensitivity analyses, all supportive of the primary analysis.

6.4. Study 3625 – SUSTAIN 4

6.4.1. Study Design

Overview and Objective

Title: Efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulfonylurea in insulin-naïve patients with type 2 diabetes

Primary objective

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily on glycemic control after 30 weeks of treatment in insulin-naïve patients with type 2 diabetes.

Secondary objective
To compare the effects of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily after 30 weeks of treatment on:

- Inducing and maintaining weight loss
- Other parameters of efficacy, safety, tolerability and patient reported outcomes

Trial Design

This was a randomized, open-label, active-controlled, parallel-group, multicenter, multinational, three-armed trial comparing two doses of semaglutide (0.5 mg and 1.0 mg) once-weekly versus insulin glargine once-daily.

A total of 1047 patients were planned for enrollment.

Key inclusion/exclusion criteria:
Similar to SUSTAIN-1 with the following difference:

Inclusion criteria allowed for stable diabetes treatment with metformin or metformin and SU (metformin ≥1500 mg or maximum tolerated dose and SU ≥ half of maximum allowed dose according to national label) for at least 90 days before screening.

Dose selection/Study treatments:
Randomization: 1:1:1 to treatment with either 0.5 mg semaglutide or 1.0 mg semaglutide once weekly or insulin glargine once daily for 30 weeks. Patients were stratified based on their pre-trial OAD at screening (metformin or metformin and SU) to ensure an approximately equal distribution of patients treated by metformin or metformin and SU in the 3 treatment arms.

Subjects randomized to either dose of semaglutide followed a dose escalation similar to that used in SUSTAIN-1.

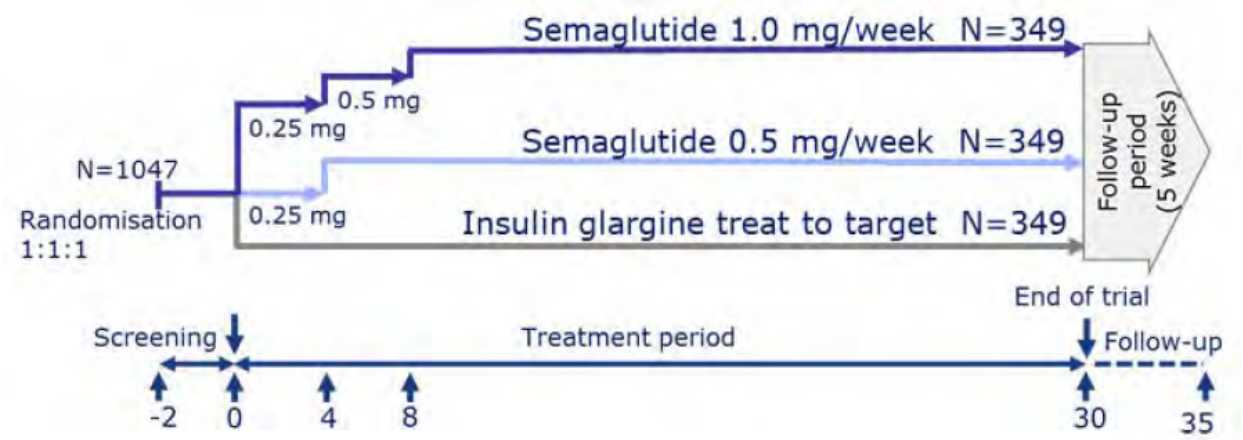
For the glargine arm, patients were started on 10 units daily (variable time of administration). During the treatment period, the dose of insulin was to be titrated by the investigator based on the lowest value of the patient's fasting self-monitored blood glucose (SMBG) 3 days prior to visits and phone contacts (which occurred at weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 19, 23, 26, and 30). Insulin titration was to be conducted according to the information presented below, however there was no central supervision to confirm that the investigators followed the protocol concerning insulin titration.

Table 25 Recommended Insulin Titration SUSTAIN 4

Lowest pre-breakfast SMBG (mg/dL)	Adjustment in insulin glargine (IU)
<56	-4 (for doses >45 IU, suggest dose reduction of 10%)
≥56 - <71	-2 (for doses >45 IU, suggest dose reduction of 5%)
≥71 - <100	No adjustment
≥100 - <120	+0-2 (at the discretion of the investigator)
≥120 - <140	+2
≥140 - <180	+4
≥180	+6-8 (at the discretion of the investigator)

Source: Tables 9-2 and 9-3 study report

Figure 10 Study Design SUSTAIN 4



Source: Figure 9-1 study report

Table 26 Dose-Escalation Regimen SUSTAIN 4

Trial periods		Screening	Period 1	Period 2	Period 3	Follow-up
Alias for trial period		Screening	Dose escalation T-T-T	Dose escalation/T-T-T/Maintenance	Maintenance T-T-T	Follow-up
Visits in each period		Visit 1−2	Visit 2-6	Visit 6-8	Visit 8−16	Visit 16−17
Duration of each period		2 weeks	4 weeks	4 weeks	22 weeks	5 weeks
Treatment	**N**					
Semaglutide 0.5 mg	349	Screening	Semaglutide 0.25 mg (1.34 mg/mL)	Semaglutide 0.5 mg (1.34 mg/mL)		Follow-up
Semaglutide 1.0 mg	349	Screening	Semaglutide 0.25 mg (1.34 mg/mL)	Semaglutide 0.5 mg (1.34 mg/mL)	Semaglutide 1.0 mg (1.34 mg/mL)	Follow-up
Insulin glargine	349	Screening	Insulin glargine (Lantus®) 100 IU/mL, initial dose 10 IU, then T-T-T			Follow-up

T-T-T, treat to target.

Source: Table 9-1 study report

Dose modification/discontinuation:
Similar to SUSTAIN-1

Administrative structure:
Similar to SUSTAIN-1.

Procedures and schedule:
Selected study procedures are presented below.

Table 27 Study Procedures SUSTAIN 4

Trial periods	Screening	Randomisation	Treatment period										EoT[1]	F-U[1]	Premature discontinuation[2]	
															EoT	F-U
Visit at site (V) or phone call (P)	V1	V2	V3	P4	V5	V6	V7	V8	V9	P10	V11	V12	V13	V14	V13A	V14A
Time of visit (weeks)	-2	0	4	6	8	12	16	23	30	35	40	48	56	61		
Visit window (days)	±7		±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS																
Informed consent	x															
Inclusion and exclusion criteria	x	x														
Randomisation		x														
Withdrawal criterion			x	x	x	x	x	x	x	x	x	x	x		x	
Concomitant illness and medical history	x															
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x															
Diabetes history	x															
History of gallbladder disease	x															
Smoking habits	x															
Fundoscopy/fundosphotography[3]		x														
Height		x														
EFFICACY																
Body weight		x	x		x	x	x	x	x		x	x	x		x	
Waist circumference		x	x		x	x	x	x	x		x	x	x		x	
Blood pressure	x	x	x		x	x	x	x	x		x	x	x		x	
HbA_{1c}	x	x	x		x	x	x	x	x		x		x		x	
Fasting plasma glucose		x	x		x	x	x		x				x		x	
Fasting insulin and proinsulin		x	x		x	x	x		x				x		x	
SMPG 7-point profile		x											x		x	
SAFETY																
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG		x							x				x	x	x	x
Physical examination	x												x		x	
Pulse rate	x	x	x		x	x	x	x	x		x	x	x		x	
Anti-semaglutide antibodies[4]		x					x		x		x		x	x	x	x
Anti-exenatide antibodies[4]		x					x		x		x		x	x	x	x
Creatinine (including eGFR)	x		x		x	x	x	x	x		x		x		x	
Biochemistry		x	x		x	x	x	x	x		x		x		x	
Haematology		x	x		x	x	x	x	x		x		x		x	
Calcitonin	x						x		x		x		x		x	
Pregnancy test[5]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis		x					x		x		x		x		x	
Urine Albumin to creatinine ratio		x											x		x	

ECG = electrocardiogram; EoT = end-of-trial; F-U = follow-up; SMPG = self-monitored plasma glucose.

1. Visit 13 (end-of-treatment) and visit 14 (follow-up) were applicable for all randomized subjects. Subjects who discontinued trial product prematurely were also to attend visit 13 and visit 14 according to their initially-scheduled week 56 and week 61 visits.

2. Subjects who discontinued trial product prematurely were to be asked to attend two additional visits to undergo assessments at end-of-treatment (visit 13) and follow-up (visit 14A). Visit 13 was to be scheduled at discontinuation of the trial product; visit 14A was to be scheduled 5 weeks after discontinuation of trial product (+7 days visit window).

3. Fundoscopy/fundus photography performed within 90 days before visit 2 was acceptable if results were available for evaluation at the visit 2 and if there was no deterioration in visual function since last assessment.

4. Blood sampling for antibody assessment was preferably to be done prior to dosing. For fasting and non-fasting visits, where the injection took place on the day of a site visit, trial product was not to be administered before blood sampling.

5. For visits 13 and 14: Not applicable if taken at a premature discontinuation visit (visits 13 or 14A).

Source: Excerpted from table 9-3 study report

Funduscopy was to be performed at randomization by the investigator or per local practice. The fundoscopy/fundus photography evaluations were to follow these categories:

- Normal
- Abnormal
- Was the result clinically significant? (No/Yes)

If fundoscopy/fundus photography had been performed within 90 days before visit 2 the procedure did not need to be repeated, unless worsening of visual function had occurred since the last examination. The results of the fundoscopy/fundus photography had to be available prior to randomization.

In case a patient underwent a thyroidectomy (partial or total) for any reason during the trial, the patient was to be asked to inform the investigator prior to the operation. In addition to the examination of the thyroid tissue routinely made by the hospital pathology laboratory, the pathology slides of the thyroid tissue were to be sent centrally for a second review by a pathologist with expertise in thyroid and C-cell pathology. The central pathologist was to be blinded to both randomized treatment and the diagnosis from the hospital pathology laboratory. Both the hospital pathology report and the central pathology report were to be reviewed by the EAC. There was also a procedure that involved genetic testing for the RET gene mutations associated with MEN2 syndrome in appropriate cases, unless forbidden by the local law.

Rescue medication:
Criteria to initiate rescue medication were similar to SUSTAIN-1.

If the mean3-day fasting SMBG, or any fasting glucose measured by a local or central lab, were above the limits, the patient was called for an unscheduled visit and a confirmatory FPG had to be obtained by the local or central laboratory. If confirmation was obtained, the patient was offered intensification of the diabetes regimen at the discretion of the investigator (in accordance to ADA and European guidelines). For the patients in the glargine arm, increase of insulin glargine was not considered rescue if it was per the titration algorithm.

Treatment compliance:
Patient compliance was assessed by monitoring of drug accountability.

Study Endpoints

Similar to SUSTAIN-1.

Statistical Analysis Plan

Testing strategy was hierarchical as follows:

- Non-inferiority in change in HbA1c for semaglutide 1 mg vs insulin glargine
- Superiority in change in body weight for semaglutide 1 mg vs insulin glargine
- Non-inferiority in change in HbA1c for semaglutide 0.5 mg vs insulin glargine
- Superiority in change in HbA1c for semaglutide 1 mg vs insulin glargine
- Superiority in change in body weight for semaglutide 0.5 mg vs insulin glargine
- Superiority in change in HbA1c for semaglutide 0.5 mg vs insulin glargine

The chosen non-inferiority margin was 0.3%.

Analysis sets:
- FAS: included all randomized patients who received at least one dose of semaglutide or glargine
- PP analysis set: all FAS patients who fulfilled the following criteria:
  – had not violated any inclusion criteria
  – had not fulfilled any exclusion criteria
  – had a non-missing HbA1c measurement at screening and/or randomization
  – had at least 23 actual weeks of exposure
  – had at least one non-missing HbA1c measurement after 23 actual weeks of exposure

When establishing non-inferiority in change in HbA1c the analysis was based on the FAS and supplemented by an analysis with the PP analysis set as supportive evidence. The FAS was used in the analysis when concluding superiority.

The primary statistical analyses were based on FAS using data observed from the "on treatment without rescue" observation period. The primary endpoint was analyzed using MMRM which included treatment, country, pre-trial OAD as fixed factors, and baseline HbA1c as covariate.

For the confirmatory secondary endpoint, the same model was applied, the only difference being that baseline body weight was used as a covariate.

MMRM assumes that the data is missing at random, although this may not be the case in this open-label trial, therefore I am not sure that MMRM is the appropriate way to analyze data in this situation.

Analyses of various safety endpoints will be discussed in the safety section of this review.

Please see Biometrics review for comments and the FDA's statistical analyses.

Protocol Amendments

There were three local amendments to the protocol.

Table 28 Protocol Amendments SUSTAIN 4

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
1	25 March 2014	Before	Slovakia	Requirement to reimburse all medication required by the trial protocol
2	08 May 2014	Before	Germany	Update of exclusion criteria number 3 upon request from BfArm
3	02 July 2014	Before	Germany	Update of exclusion criteria number 11 upon request from BfArm

Abbreviations: FSFV: fist subject first visit.

Exclusion criteria 3 refers to appropriate birth control methods and only applies to Germany, exclusion criteria 11 refers to the limitation in eGFR appropriate for enrollment for the patients from Germany (eGFR < 60 ml/min/1.73m^2 vs <30 ml/min/1.73m^2 for the rest of the participants)
Source: Table 9-11 study report

Data Quality and Integrity: Sponsor's Assurance

In all, 16 internal audits and 3 external inspections were performed at 22 trial sites, per the applicant, and no major issues have been identified. However, after the NDA was submitted, the applicant informed the FDA that the EAC was inadvertently unblinded for this study (and for all open label studies). The events were blindly re-adjudicated by the applicant during the NDA review.

6.4.2. Study Results

Compliance with Good Clinical Practices

The applicant stated that the trial was conducted in accordance with ICH GCP.

Financial Disclosure

Of the 999 investigators participating in the trial, 5 had disclosable financial information, and all 5 had disclosure information forms.

Patient Disposition

Of the 1610 patients screened, 521 (32%) were screening failures and the remaining 1089 patients were randomized at a 1:1:1 ratio to receive semaglutide at one of two different doses or insulin glargine treatment.

The majority of screening failures (401/521) were patients not meeting the inclusion criterion of HbA1c levels being within 7-10%. Patients meeting an exclusion criterion accounted for 72 screening failures.

Of the 1089 patients randomized, 1082 patients were exposed to trial products. Seven patients that were randomized were not exposed to trial products for reasons such as withdrawal by patient and loss to follow-up. In total, there were 362 patients exposed to semaglutide 0.5 mg, 360 patients exposed to semaglutide 1 mg, and 360 patients exposed to insulin glargine. A total of 1020 patients (94%) completed the trial and 952 patients (88%) completed the treatment. The proportion of patients completing the treatment was higher with insulin glargine compared to semaglutide. There were 924 patients (85%) that completed the treatment without rescue medication.

Table 29 Patients Disposition SUSTAIN 4

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	IGlar N (%)
Screened			
Screening failures			
Withdrawn before randomisation			
Randomised	362	362	365
Exposed	362 (100)	360 (99.4)	360 (98.6)
Safety analysis set	362 (100)	360 (99.4)	360 (98.6)
Full analysis set	362 (100)	360 (99.4)	360 (98.6)
Per protocol analysis set	314 (86.7)	308 (85.1)	336 (92.1)
Treatment completers [1]	313 (86.5)	305 (84.7)	334 (92.8)
Without rescue medication	299 (82.6)	296 (82.2)	329 (91.4)
With rescue medication	14 (3.9)	9 (2.5)	5 (1.4)
Premature treatment discontinuation- primary reason [2]	49 (13.5)	55 (15.3)	26 (7.2)
Pregnancy		1 (0.3)	1 (0.3)
Protocol violation	12 (3.3)	13 (3.6)	2 (0.6)
Violation of the inclusion and/or exclusion criteria	12 (3.3)	13 (3.6)	2 (0.6)
Intention of becoming pregnant			
Adverse event	19 (5.2)	27 (7.5)	5 (1.4)
Gastrointestinal AEs	10 (2.8)	17 (4.7)	
Pancreatitis	1 (0.3)		
Other AEs	8 (2.2)	10 (2.8)	5 (1.4)
Other	18 (5.0)	14 (3.9)	18 (5.0)
Trial completers [3]	335 (92.5)	342 (94.5)	343 (94.0)
Premature withdrawal from trial in relation to or after premature treatment discontinuation - primary reason	24 (6.6)	19 (5.2)	20 (5.5)
Withdrawal by Subject	11 (3.0)	8 (2.2)	11 (3.0)
Lost to follow-up	2 (0.6)	1 (0.3)	2 (0.5)
Death	2 (0.6)		2 (0.5)
Missing follow-up information [4]	9 (2.5)	10 (2.8)	5 (1.4)
Premature withdrawing from trial after treatment completion - primary reason	3 (0.8)	1 (0.3)	2 (0.5)
Withdrawal by Subject			
Lost to follow-up			
Death			
Missing follow-up information [4]	3 (0.8)	1 (0.3)	2 (0.5)

IGlar: Insulin glargine, N: Number of patients, %: For treatment completers and treatment non-completers percentages are based on exposed patients. For trial completers and withdrawals percentages are based on randomized patients. [1]: Completion of treatment according to end-of-trial form. [2]: Includes only exposed patients and is based on the primary reason for treatment discontinuation according to the end-of-trial form. [3]: Patients with a follow-up visit. [4]: Patients with no reason/date for withdrawal but without the follow-up visit.
Source: Adapted from Table 10-1 study report

A greater proportion of patients treated with semaglutide 1 mg discontinued treatment prematurely compared with those in the 0.5 mg and insulin glargine groups.

Additionally, a greater proportion of patients were administered rescue medication with semaglutide 0.5 mg (14 patients) compared with semaglutide 1 mg (9 patients) or insulin glargine (5 patients).

Protocol Violations/Deviations

There were no protocol deviations identified at trial level.

Protocol deviations at country level: Macedonia, missing health authority approval for updated patient information/informed consent.

Protocol deviation sat trial site and patient level: 154 important trial site PDs and 1130 patient-level PDs

- Trial site deviations – I reviewed all deviations as submitted by the sponsor, most of them are versions of monitoring frequency changes, none of them likely to impact the results of the study
- Patient level deviations will be discussed below.

Table 30 Summary of Important Protocol Deviations at Patient Level SUSTAIN 4

Protocol deviation category	Sema 0.5 mg	Sema 1.0 mg	Insulin glargine	Screening failures	Total
Informed consent	24	26	23	30	103
Inclusion/exclusion/randomisation criteria	23	19	17	2	61
Trial product handling	8	5	7	0	20
Treatment compliance	47	59	24	0	130
Assessment deviations	259	278	159	3	699
Other	37	27	49	4	117
Total	398	414	279	39	1130

Abbreviation: sema= semaglutide

Source: Table 10-4 study report

Informed consent deviations: 103 patient level deviations, 30 of which were in screening failures. The remaining 73 PDs concerned 72 randomized patients. The applicant states that, except for 2 patients, the informed consent was signed prior to any trial-related activity, and that all IC PDs were resolved by corrective actions.

Inclusion/exclusion/randomization criteria deviations: A total of 61 important patient-level PDs concerning 55 patients were reported, 2 of which concerned screening failures. 20/61 of the

PDs were reported in patients failing inclusion criteria (most failed the inclusion criterion referring to background therapy). 6 PDs pertained to exclusion criteria, 15 PDs to stratification criteria, and 12 PDs to missing screening/randomization results.

Trial product handling: 20 patient level PDs, most of which (8 PDs) were due to trial products that were incorrectly stored and dispensed and/or administered. There were no adverse events reported in these patients related to the use of trial product.

Treatment compliance: 130 patient-level PDs were reported, of which 43 were associated with patients receiving a wrong dose of trial medication due to a prescribing error. An additional 42 PDs were due to patients receiving a wrong dose due to patient non-compliance or patient error.

Assessment deviations: 699 patient-level PDs were reported, 465 due to one or more of an assessment was missing, and 177 were injection of the trial product the day of the visit (<8 hours between last injection and time of laboratory samples).

Other: 117 patient-level PDs were reported, 36 were due to entry in the patient diary or PRO questionnaire done by persons other than the patient or the patient's designated caregiver, 33 due to missing or incomplete source data, and 20 due to PRO questionnaires not dispensed appropriately.

Although some imbalances in protocol deviations are noted between the semaglutide arms and comparator, they are unlikely to impact the results of the trial.

After database lock, one additional patient-level and 22 site-level PDs were identified. The patient-level PD was in the 'other' category and due to missing source data. One site-level PD was related to trial product handling and the remaining 21 site-level PDs were due to monitoring visits conducted outside the visit window defined by the protocol.

Table of Demographic Characteristics

The demographic characteristics were similar between the treatment groups. Details are presented in the tables below. The average age was 56 years, the largest proportion of patients was from the US (45.7%), and the majority of the patients were white (77.1%). The majority of patients were overweight or obese. Baseline HbA1c was 8.17%. The duration of diabetes differed slightly among the groups, with a mean duration of 7.8 years in the semaglutide 0.5 mg group, 9.3 years in the semaglutide 1 mg group, and 8.6 years in the insulin glargine group.

Table 31 Demographics and Baseline Characteristics for Categorical Variables – FAS – SUSTAIN 4

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	IGlar N (%)	Total N (%)
Number of subjects	362	360	360	1082
Oral antidiabetic treatment				
Metformin	176 (48.6)	175 (48.6)	172 (47.8)	523 (48.3)
Metformin and SU	186 (51.4)	185 (51.4)	188 (52.2)	559 (51.7)
Age group				
18-64 years	278 (76.8)	281 (78.1)	281 (78.1)	840 (77.6)
65-74 years	72 (19.9)	61 (16.9)	67 (18.6)	200 (18.5)
75-84 years	12 (3.3)	18 (5.0)	12 (3.3)	42 (3.9)
>= 85 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex				
Female	165 (45.6)	178 (49.4)	165 (45.8)	508 (47.0)
Male	197 (54.4)	182 (50.6)	195 (54.2)	574 (53.0)
Country				
United States	165 (45.6)	162 (45.0)	168 (46.7)	495 (45.7)
Race				
American Indian or Alaska Native	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)
Asian	42 (11.6)	39 (10.8)	38 (10.6)	119 (11.0)
Black or African American	32 (8.8)	34 (9.4)	33 (9.2)	99 (9.1)
Native Hawaiian or Other Pacific Island	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	279 (77.1)	279 (77.5)	276 (76.7)	834 (77.1)
Other	3 (0.8)	3 (0.8)	5 (1.4)	11 (1.0)
NA	5 (1.4)	5 (1.4)	7 (1.9)	17 (1.6)
Ethnicity				
Hispanic or Latino	61 (16.9)	74 (20.6)	78 (21.7)	213 (19.7)
Not Hispanic or Latino	301 (83.1)	286 (79.4)	281 (78.1)	868 (80.2)
NA	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Smoker status				
Current smoker	50 (13.8)	50 (13.9)	60 (16.7)	160 (14.8)
Never smoked	213 (58.8)	217 (60.3)	222 (61.7)	652 (60.3)
Previous smoker	99 (27.3)	93 (25.8)	78 (21.7)	270 (25.0)
Renal function				
N	362 (100.0)	360 (100.0)	360 (100.0)	1082 (100.0)
Normal	210 (58.0)	221 (61.4)	221 (61.4)	652 (60.3)
Mild Renal Impairment	138 (38.1)	117 (32.5)	123 (34.2)	378 (34.9)
Moderate Renal Impairment	14 (3.9)	22 (6.1)	16 (4.4)	52 (4.8)
Severe Renal Impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
End stage Renal Impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

IGlar: Insulin glargine, N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate, SU:Sulphonylurea, NA: Not applicable. The renal function categories are based on the MDRD eGFR. Baseline value is defined as the latest pre-dosing value. Subjects were stratified based on their pre-trial oral antidiabetic treatment at screening (metformin or metformin and SU).

Source: Adapted from Table 10-2 study report

Table 32 Demographics and Baseline Characteristics for Continuous Variables – FAS – SUSTAIN 4

	Sema 0.5 mg	Sema 1.0 mg	IGlar	Total
Number of subjects	362	360	360	1082
Age (years) Mean (SD)	56.5 (10.3)	56.7 (10.4)	56.2 (10.6)	56.5 (10.4)
HbA1c (%) Mean (SD)	8.13 (0.85)	8.25 (0.94)	8.13 (0.88)	8.17 (0.89)
Duration of Diabetes (years) Mean (SD)	7.77 (5.14)	9.34 (7.17)	8.61 (6.29)	8.57 (6.28)
Body mass index (kg/m2) Mean (SD)	33.11 (6.45)	32.96 (6.51)	32.95 (6.51)	33.01 (6.49)
MDRD GFR 'estimated' (mL/min/1.73 m^2) Mean (SD)	97.89 (25.94)	97.95 (27.55)	99.66 (26.46)	98.50 (26.64)

IGlar: Insulin glargine,
MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate.

Source: Adapted from Table 10-3 study report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Medical history and concomitant illnesses

Common concomitant illnesses included hypertension (65.4%), hyperlipidemia (27.4%), and obesity (21.3%). There were slightly greater proportions of patients with hypertension in the semaglutide 0.5 mg and 1.0 mg groups (both 66.9%) compared to the insulin glargine group (62.5%). In addition, the proportions of hyperlipidemia were also slightly higher in the semaglutide 0.5 mg (28.7%) and 1.0 mg groups (28.3%) compared to the insulin glargine group (25.3%). A history of myocardial infarction was reported among 4.0% of patients, while heart failure was reported among 1.9%. Among all patients in the trial, 14.3% had a history of gallbladder disease at screening. The proportions of patients with this history were 14.9%, 14.7%, and 13.3% in the semaglutide 0.5 mg, 1.0 mg, and insulin glargine groups, respectively. A slightly larger proportion (7.8%) of patients in the semaglutide 1 mg group had a history of cholecystitis compared to the 0.5 mg group (6.4%) and insulin glargine group (6.4%). History of gallstone disease differed slightly among the treatment groups with proportions of 12.2%, 10.8%, and 9.7% in the semaglutide 0.5 mg, 1.0 mg, and insulin glargine groups, respectively. A total of four patients (0.4%) had a history of pancreatitis at screening, with three of these patients in the semaglutide 0.5 mg group and one patient in the 1.0 mg group

There were similar distributions of obese patients across the treatment groups at screening.

Table 33 Common Concomitant Illnesses at Baseline SUSTAIN 4

Dictionary Derived Term	Glargine N=360	Sema 0.5 mg N=362	Sema 1.0 mg N=360
Hypertension	227 (63.06%)	243 (67.13%)	242 (67.22%)
Hyperlipidemia	93 (25.83%)	104 (28.73%)	103 (28.61%)
Dyslipidemia	65 (18.06%)	63 (17.40%)	67 (18.61%)
Hypercholesterolemia	43 (11.94%)	41 (11.33%)	45 (12.50%)
CV history	49 (13.61%)	40 (11.05%)	40 (11.11%)

Source: Reviewer generated using Jreview, ADSL and medical history datases

Retinal examination was to be performed at randomization by the investigator, or according to local practice. Fundoscopy evaluations were categorized by the investigator as either 'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant'. Approximately 80% of patients in each treatment group had normal funduscopic examinations.

Almost all patients were on metformin, and over 50% were on SU. Lipid and antihypertensive medications were balanced between the treatment groups.

Table 34 Frequently Used Concomitant Medications at Baseline SUSTAIN 4

Medication Class	Glargine N=360	Sema 0.5 mg N=362	Sema 1.0 mg N=360
Biguanides	359 (99.72%)	362 (100.00%)	360 (100.00%)
Sulfonylureas	187 (51.94%)	186 (51.38%)	185 (51.39%)
HMG coa reductase inhibitors	176 (48.89%)	168 (46.41%)	180 (50.00%)
ACE inhibitors	131 (36.39%)	129 (35.64%)	144 (40.00%)
Platelet aggregation inhibitors excl. heparin	99 (27.50%)	106 (29.28%)	104 (28.89%)
Beta blocking agents, selective	66 (18.33%)	73 (20.17%)	59 (16.39%)
Dihydropyridine derivatives	64 (17.78%)	50 (13.81%)	59 (16.39%)
Angiotensin II antagonists	52 (14.44%)	73 (20.17%)	46 (12.78%)
Thiazides	36 (10.00%)	46 (12.71%)	40 (11.11%)
Fibrates	24 (6.67%)	31 (8.56%)	26 (7.22%)
Other lipid modifying agents	20 (5.56%)	26 (7.18%)	23 (6.39%)

Source: Reviewer generated using Jreview, ADSL and concomitant medications dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patient compliance was assessed by monitoring of drug accountability. As seen in the protocol deviations section, only a small proportion of patients were reported with compliance issues.

Rescue medications:

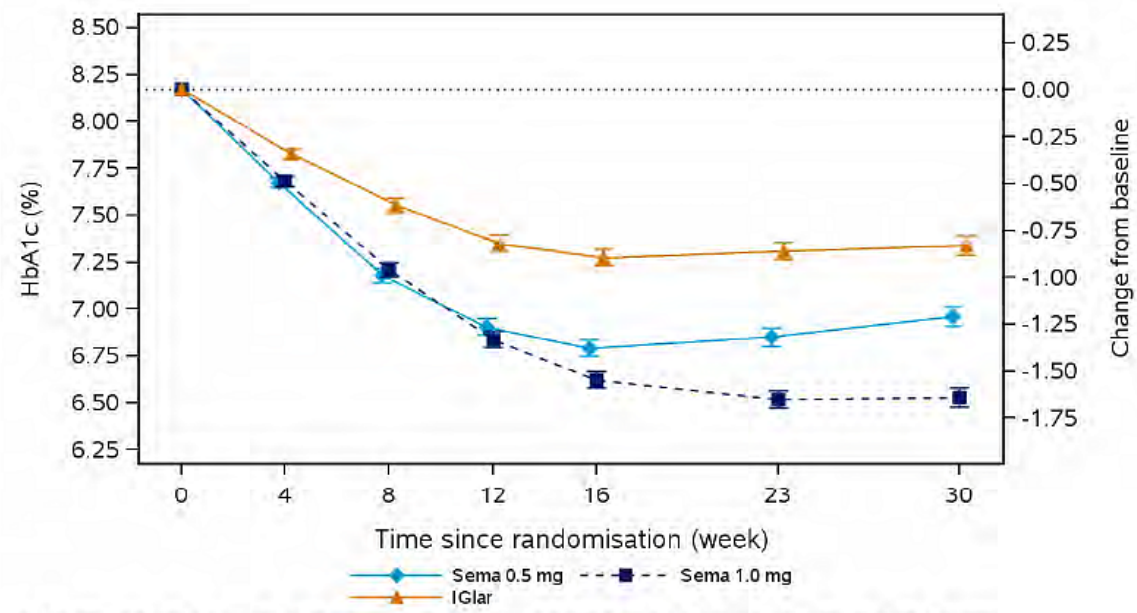
A total of 28 patients were administered rescue medication. Of these, 14 were in the semaglutide 0.5 mg group, 9 were in the 1.0 mg group, and 5 were in the insulin glargine group. Sulfonylureas were most commonly used as rescue medications.

Efficacy Results - Primary Endpoint

Change in HbA1c at 30 weeks

The baseline HbA1c levels were similar among the three treatment groups with a mean baseline HbA1c level of 8.17%. A decrease in HbA1c was observed in all treatment arms from baseline to week 16, followed by a plateau for glargine and semaglutide 0.5 mg. In the semaglutide 1 mg the HbA1c reduction continued until week 23, followed by plateau.

Figure 11 Mean HbA1c (%) by Treatment Week - SUSTAIN 4



IGlar: Insulin glargine. Observed 'on-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM. Dotted line is the total average value at baseline.

Source: Figure 11-1 study report

Primary statistical analysis: HbA1c levels decreased by 1.21%-point and 1.64%-point with semaglutide 0.5 mg and 1.0 mg, respectively, and by 0.83%-point with insulin glargine. The applicant concluded that both semaglutide doses were superior to placebo based on these results.

Table 35 HbA1c – Primary Statistical Analysis – FAS – SUSTAIN 4

	FAS	N	Estimate	SE	95% CI	p-value
HbA1c (%)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	362	288	6.96	0.05		
Sema 1.0 mg	360	283	6.53	0.05		
IGlar	360	322	7.34	0.05		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	362	288	-1.21	0.05		
Sema 1.0 mg	360	283	-1.64	0.05		
IGlar	360	322	-0.83	0.05		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - IGlar			-0.38		[-0.52 ; -0.24]	<.0001
Sema 1.0 mg - IGlar			-0.81		[-0.96 ; -0.67]	<.0001

IGlar: Insulin glargine, N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Table 11-1 study report

More patients on semaglutide achieved the pre-defined treatment targets, and the response was dose-dependent.

Table 36 Patients Achieving HbA1c Response after 30 Weeks of Treatment – FAS – SUSTAIN 4

	FAS	N	R	Estimate	SE	95% CI	p-value
HbA1c <=6.5% (AACE)							
Estimated odds at visit 16 (week 30)							
Sema 0.5 mg	362	362	135	0.55	0.06		
Sema 1.0 mg	360	360	195	1.25	0.14		
IGlar	360	360	63	0.18	0.03		
Estimated odds ratio at visit 16 (week 30)							
Sema 0.5 mg / IGlar				3.02		[2.11 ; 4.33]	<.0001
Sema 1.0 mg / IGlar				6.86		[4.76 ; 9.89]	<.0001
HbA1c <7.0% (ADA)							
Estimated odds at visit 16 (week 30)							
Sema 0.5 mg	362	362	208	1.35	0.15		
Sema 1.0 mg	360	360	264	3.26	0.43		
IGlar	360	360	137	0.56	0.07		
Estimated odds ratio at visit 16 (week 30)							
Sema 0.5 mg / IGlar				2.39		[1.73 ; 3.28]	<.0001
Sema 1.0 mg / IGlar				5.78		[4.08 ; 8.19]	<.0001
HbA1c <7.0% without severe or BG confirmed symptomatic hypoglycaemia and without weight gain							
Estimated odds							
Sema 0.5 mg	362	362	169	0.85	0.09		
Sema 1.0 mg	360	360	231	2.02	0.24		
IGlar	360	360	56	0.16	0.02		
Estimated odds ratio							
Sema 0.5 mg / IGlar				5.39		[3.72 ; 7.81]	<.0001
Sema 1.0 mg / IGlar				12.88		[8.73 ; 19.02]	<.0001

IGlar: Insulin glargine, N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval, FAS: full analysis set, BG: Blood glucose. Analysis of 'on-treatment without rescue medication' data. The binary endpoint is analysed using a logistic regression model with treatment, country and stratum as fixed factors and the baseline weight and HbA1c values as covariates. Before analysis, missing HbA1c and body weight data are imputed from separate mixed models for repeated measures with treatment, country, stratum and parameter specific baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.

Source: Table 11-3 study report

Data Quality and Integrity - Reviewers' Assessment

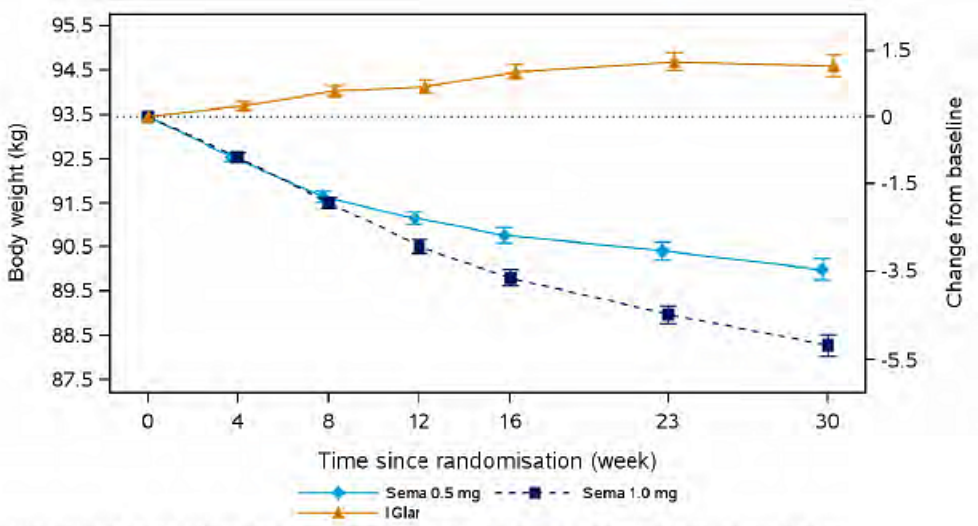
I did not identify any issues with the data submitted by the applicant.

Efficacy Results - Secondary and other relevant endpoints

Change in body weight at week 30

Baseline body weight was similar between the treatment groups, with a mean of 93.5 kg. After 30 weeks of treatment, a mean weight loss of 3.47 kg and 5.17 kg was achieved for the semaglutide 0.5 mg and 1.0 mg groups, respectively, while a weight increase of 1.15 kg was reported for the insulin glargine group.

Figure 12 Mean Body Weight (kg) by Treatment Week - FAS – SUSTAIN 4



IGlar: Insulin glargine. Observed 'on-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
All visits were done in fasting state.
Dotted line is the total average value at baseline.

Source: Figure 11-5 study report

Table 37 Change in Body Weight – SUSTAIN 4

	FAS	N	Estimate	SE	95% CI	p-value
Body weight (kg)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	362	292	89.98	0.24		
Sema 1.0 mg	360	284	88.27	0.24		
IGlar	360	325	94.60	0.23		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	362	292	-3.47	0.24		
Sema 1.0 mg	360	284	-5.17	0.24		
IGlar	360	325	1.15	0.23		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - IGlar			-4.62		[-5.27 ; -3.96]	<.0001
Sema 1.0 mg - IGlar			-6.33		[-6.99 ; -5.67]	<.0001
Body Weight (%)						
Mean of baseline (%) at visit 16 (week 30)						
Sema 0.5 mg	362	292	96.18	0.25		
Sema 1.0 mg	360	284	94.54	0.25		
IGlar	360	325	101.41	0.24		
Change from baseline (%-points) at visit 16 (week 30)						
Sema 0.5 mg	362	292	-3.82	0.25		
Sema 1.0 mg	360	284	-5.46	0.25		
IGlar	360	325	1.41	0.24		
Treatment difference (%-points) at visit 16 (week 30)						
Sema 0.5 mg - IGlar			-5.23		[-5.92 ; -4.54]	<.0001
Sema 1.0 mg - IGlar			-6.88		[-7.57 ; -6.18]	<.0001

IGlar: Insulin glargine, N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Analysis of observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.
All visits were done in fasting state.

Source: Table 11-2 study report

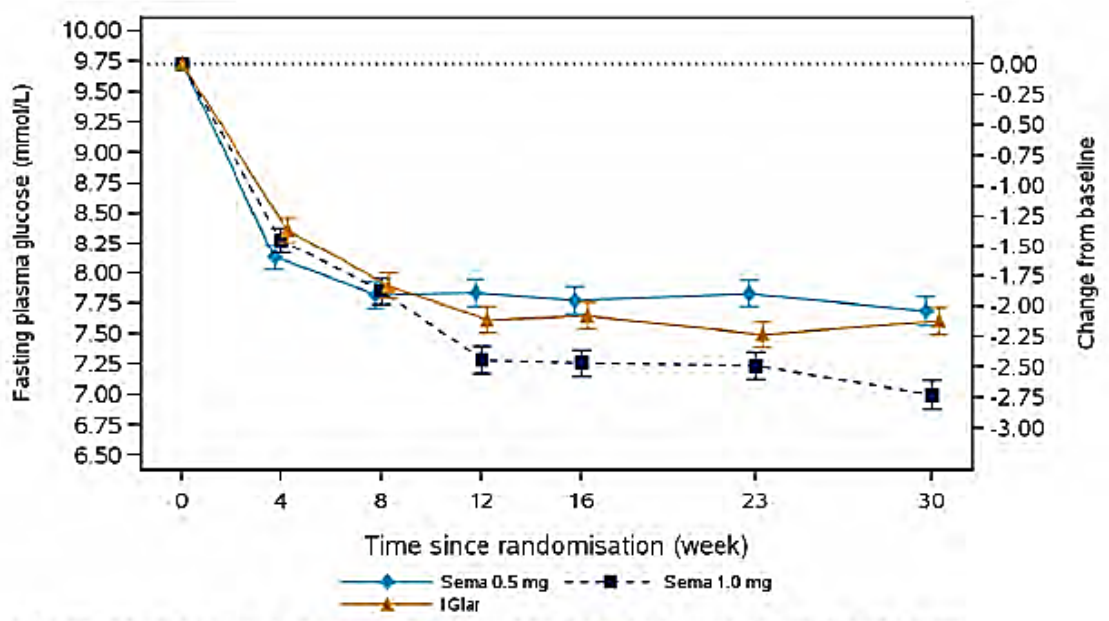
Patients achieving a weight loss response of ≥5% or ≥10% were classified according to a binary (yes/no) outcome.

A weight loss response of ≥5% was achieved for a greater proportion of patients treated with semaglutide 0.5 mg (37.0%) and 1.0 mg (50.8%) compared to insulin glargine (4.7%). Weight loss response ≥10%, this was obtained for 1.7% of insulin glargine-treated patients, while 7.7% and 15.8% of patients in the semaglutide 0.5 mg and 1.0 mg dose groups, respectively.

Fasting plasma glucose

The baseline FPG was similar between the treatment groups. All treatment groups experienced a decrease in FPG over the first 12 weeks, followed by a plateau. At the end of the 30 weeks, only the semaglutide 1 mg arm had a statistically significant difference in the FPG response compared to insulin glargine.

Figure 13 Mean Fasting Plasma Glucose (mmol/L) by Treatment Week – FAS – SUSTAIN 4



IGlar: Insulin glargine. Observed 'on-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM. Dotted line is the total average value at baseline.

Source: Figure 11-4 study report

Table 38 Fasting Plasma Glucose – SUSTAIN 4

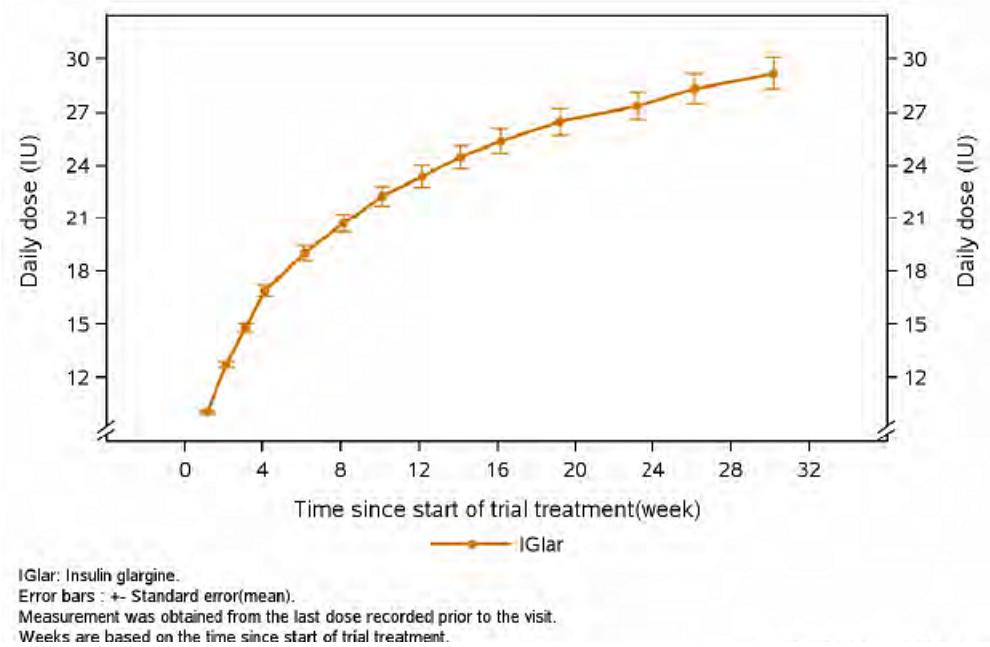
	FAS	N	Estimate	SE	95% CI	p-value
Fasting plasma glucose (mg/dL)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	362	282	138.53	2.14		
Sema 1.0 mg	360	280	126.06	2.15		
IGlar	360	319	137.08	2.03		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	362	282	-36.74	2.14		
Sema 1.0 mg	360	280	-49.21	2.15		
IGlar	360	319	-38.18	2.03		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - IGlar			1.45		[-4.34 ; 7.23]	0.6242
Sema 1.0 mg - IGlar			-11.02		[-16.85 ; -5.20]	0.0002

Source: Adapted from table 11-5

Interestingly, the FPG plateaued in the insulin glargine arm despite a continuous increase in the insulin dose after week 12, although the slope of the increase was less in the later part of the study. Also, it is possible that despite the treat-to-target approach to insulin titration, the insulin adjustments were still insufficient, and a better HbA1c reduction could have been achieved with more aggressive titration. Based on the continuous increase in the insulin dose

over the course of the trial, the full potential of insulin treatment does not appear to have been reached.

Figure 14 Mean Insulin Dose (Actual) in Units by Treatment Week – SUSTAIN 4

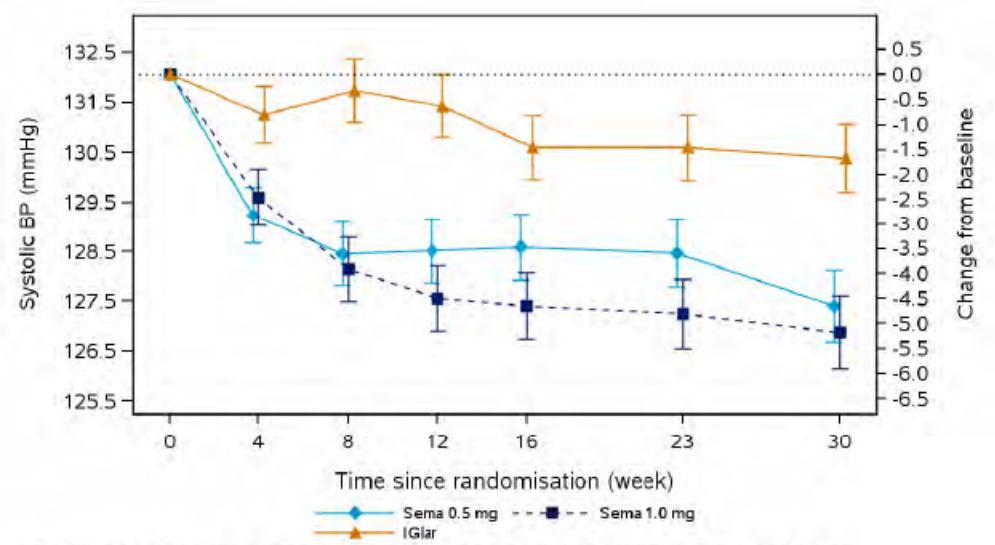


Source: Figure 14.2.38 study report

Blood pressure

Mean diastolic and systolic blood pressures at baseline were 80 mmHg and 132 mmHg, respectively, with the three groups being comparable. There were fluctuations in diastolic blood pressure between baseline and week 30 for all three treatment groups with no notable differences between semaglutide and insulin glargine.

Figure 15 Systolic Blood Pressure (mmHg) Over Time - SUSTAIN 4



IGlar: Insulin glargine. Observed 'on-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM. Dotted line is the total average value at baseline.

Source: Adapted from Figure 11-28 study report

Table 39 Systolic Blood Pressure – FAS – SUSTAIN 4

	FAS	N	Estimate	SE	95% CI	p-value
Systolic BP (mmHg)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	362	293	127.41	0.72		
Sema 1.0 mg	360	285	126.88	0.73		
IGlar	360	327	130.38	0.68		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	362	293	-4.65	0.72		
Sema 1.0 mg	360	285	-5.17	0.73		
IGlar	360	327	-1.68	0.68		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - IGlar			-2.97		[-4.92 ; -1.03]	0.0028
Sema 1.0 mg - IGlar			-3.50		[-5.46 ; -1.54]	0.0005

IGlar: Insulin glargine, N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratum as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Adapted from Table 11-15 study report

Dose/Dose Response

Semaglutide 1 mg dose was more efficacious compared to semaglutide 0.5 mg dose for all the endpoints.

Durability of Response

The decrease in HbA1c with semaglutide 0.5 mg was gradual in the first 16 weeks, followed by a slight upslope from 16 to 30 weeks. Since the study was only 30 weeks long, it is not clear whether this uptrend would have continued, or what the long-term persistence of effect would have been.

For semaglutide 1 mg, a gradual decrease in HbA1c was observed for the first 23 weeks, followed by a plateau. Again, it is not clear how long the effect would persist due to the duration of the study.

Despite the slight uptrend in the later part of the study for the lower semaglutide dose, my interpretation of the efficacy results is that the glycemic lowering was maintained up to the end of the 30 weeks.

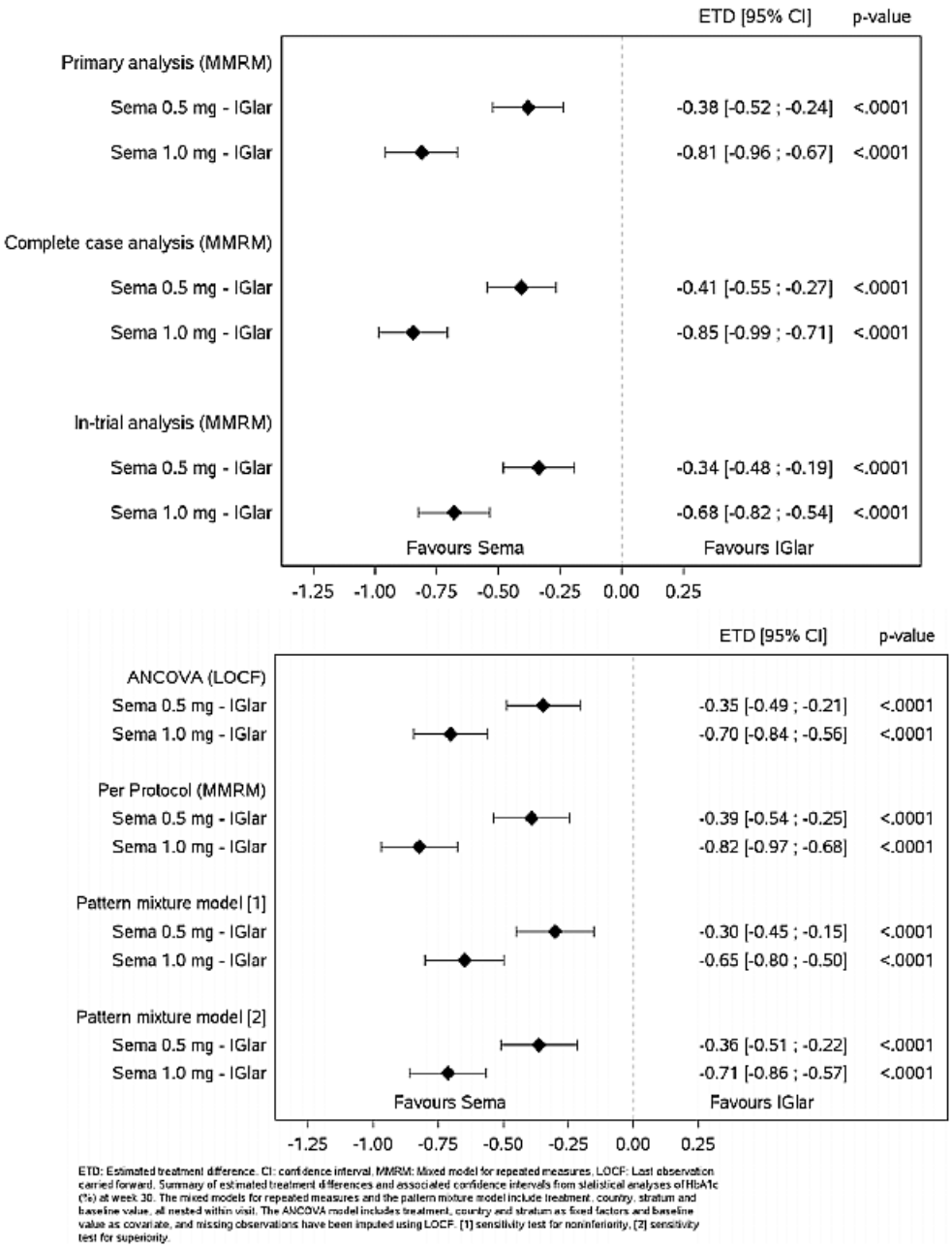
Persistence of Effect

Not applicable. Effect after discontinuation of study drug was not assessed.

Additional Analyses Conducted on the Individual Trial

Sensitivity analyses for the primary endpoint were generally supportive of the primary analysis, as shown in Figure 16 below.

Figure 16 HbA1c (%) - Statistical Analyses - Forest Plot - SUSTAIN 4



Source: Figure 11-3 study report

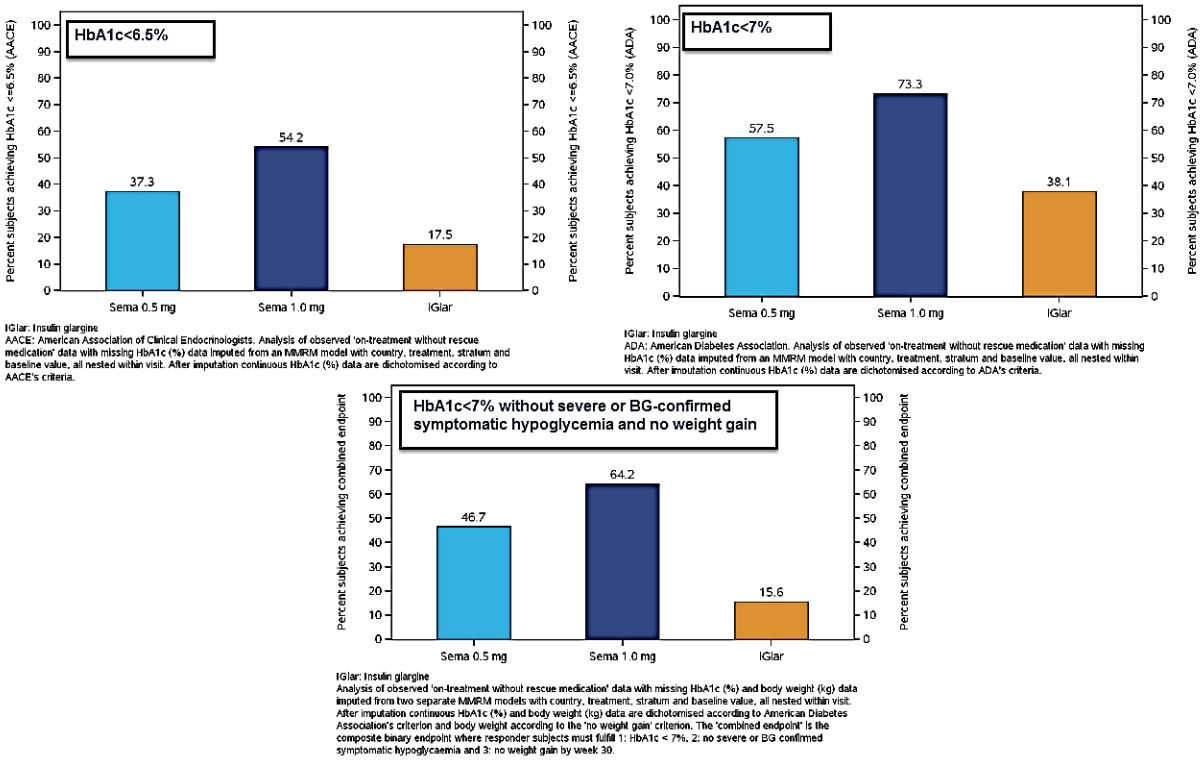
The applicant also analyzed the data to evaluate the proportion of patients in each treatment group that reached various treatment targets as follows:

- Patients reaching an HbA1c level ≤6.5% (AACE)
- Patients reaching an HbA1c level <7% (ADA)

- Patients reaching an HbA1c level <7% without severe or BG-confirmed symptomatic hypoglycemia and no weight gain

The results are presented in Figure 17 below.

Figure 17 Proportion of Patients Achieving Specific Targets SUSTAIN 4



Source: Adapted from figures 11-9, 11-10, 11-11 study report

For all these targets, it appears that more patients on semaglutide achieved them compared to the patients on insulin glargine, and a dose response was seen between the two semaglutide doses.

However, these results should eeeb interpreted with caution since it is not clear that insulin treatment was optimized in SUSTAIN 4.

6.5. Study 3627 – SUSTAIN 5

6.5.1. Study Design

Overview and Objective

Study title: Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in patients with T2DM.

Primary objective
To demonstrate superiority of once-weekly dosing of two dose levels (0.5 mg and 1.0 mg) of semaglutide versus placebo on glycemic control in patients with T2DM on basal insulin.

Secondary objectives
To compare the effect of once-weekly dosing of two dose levels of semaglutide (0.5 mg and 1.0 mg) versus placebo in patients with T2DM on basal insulin with regards to:
- Inducing and maintaining weight loss
- Other parameters of efficacy, safety, tolerability and patient reported outcomes (PROs)

Trial Design

Multinational, multi-center, randomized, double-blind, parallel-group, placebo-controlled, four-armed trial. The trial period consisted of a 2-week screening period, followed by a 30-week randomized treatment period and a 5-week follow-up period.

A total of 390 adults with T2DM were planned for randomization

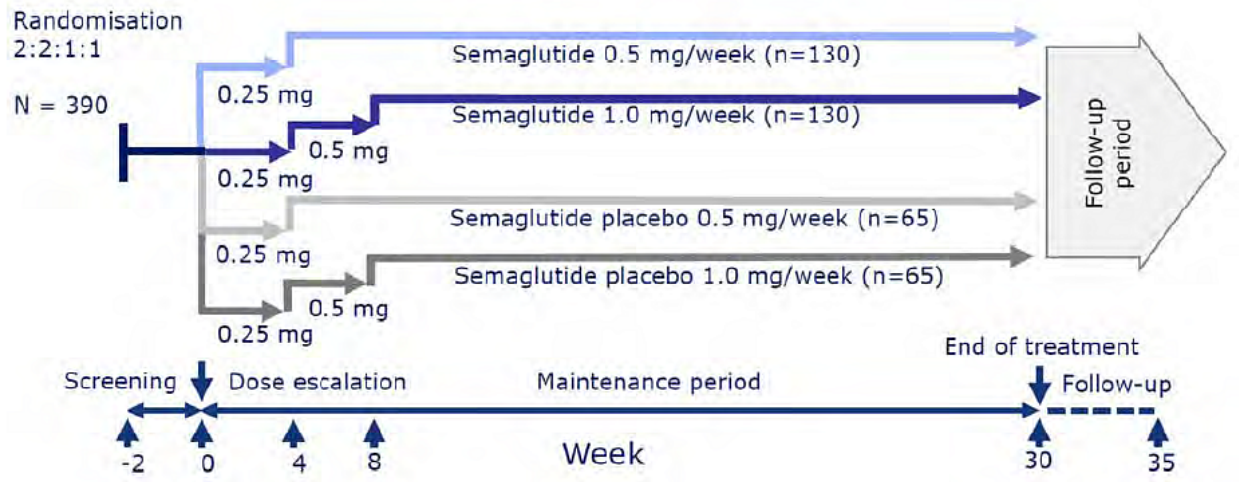
Key inclusion/exclusion criteria:
Similar to SUSTAIN-1 except for the following:

Inclusion criteria allowed for stable diabetes treatment with basal insulin (+/- 20% change in total daily dose), a minimum of 0.25 IU/kg/day and/or 20 IU/day of: insulin glargine, insulin detemir, insulin degludec and/or NPH insulin, alone or in combination with metformin (at least 1500 mg/day or maximum tolerated dose) for 90 days prior to screening.

Dose selection/Study treatments:
Eligible subjects were randomized 2:2:1:1 to treatment with either semaglutide 0.5 mg, semaglutide 1 mg, placebo 0.5 mg or placebo 1.0 mg once weekly for 30 weeks. The randomization was stratified according to HbA1c level at screening (≤8.0% or >8.0%) and use of metformin (yes or no).

Dose escalation was similar to that used in SUSTAIN-1.

Figure 18 Trial Design SUSTAIN 5



Source: Figure 9-1 study report

Table 40 Study Treatments SUSTAIN 5

Visits	**Visit 1–2**	**Visit 2–4**	**Visit 4–6**	**Visit 6–16**	**Visit 16–17**
Trial period	Screening	Dose escalation	Dose escalation / Maintenance	Maintenance	Follow-up
Duration of period	2 weeks	4 weeks	4 weeks	22 weeks	5 weeks
Treatment					
Semaglutide 0.5 mg	N/A	Semaglutide 0.25 mg	Semaglutide 0.5 mg		N/A
Semaglutide 1.0 mg		Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	
Placebo 0.5 mg		Placebo 0.25 mg	Placebo 0.5 mg		
Placebo 1.0 mg		Placebo 0.25 mg	Placebo 0.5 mg	Placebo 1.0 mg	

N/A: not applicable.

Source: Table 9-1 study report

Dose modification/discontinuation:
Similar to SUSTAIN-1

Administrative structure:
Similar to SUSTAIN-1.

Procedures and schedule:
See schedule of events in Table 41 below:

Table 41 Trial Procedures SUSTAIN 5

Trial Periods	Screening	Randomisation	Treatment													End of treatment	Follow-up	End of Treatment – premature discontinuation	Follow-up premature discontinuation
V (Visit)/P (Phone contact)	V1	V2	P3	V4	P5	V6	P7	P8	V9	P10	P11	V12	P13	V14	P15	V16	V17	V16A[2]	V17A[2]
Timing of visit (Weeks)	-2	0	2	4	6	8	10	11	12	13	14	16	19	23	26	30[1]	35[1]		
Visit window (Days)	±7		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS																			
Informed consent	X																		
In/exclusion criteria	X	X																	
Randomisation		X																	
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Concomitant illness and medical history	X																		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																		
Diagnosis of diabetes	X																		
Smoking habits	X																		
History of concomitant cardiovascular disease	X																		
History of gallbladder disease	X																		
Height		X																	
EFFICACY																			
Body weight		X		X		X			X			X		X		X		X	
Insulin dose		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
hsCRP		X							X							X		X	
Fasting plasma glucose		X		X		X			X			X		X		X		X	
HbA_{1c}	X	X		X		X			X			X		X		X		X	
Lipids		X							X							X		X	
Blood pressure	X	X		X		X			X			X		X		X		X	
7-point profile		X							X							X		X	
1-point profile		X	X	X	X	X	X	X	X	X	X	X		X					
SAFETY																			
Anti-semaglutide antibodies		X										X				X	X	X	X
Adverse events		X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X														X	X	X	X
Fundoscopy / Fundus photography		X																	
Physical examination	X															X		X	
Biochemistry		X		X		X			X			X		X		X		X	
Creatinine	X			X		X			X			X		X		X		X	
Haematology		X		X		X			X			X		X		X		X	
Calcitonin	X								X							X		X	
Urinalysis		X										X		X		X		X	
Urine albumin to creatinine ratio		X														X		X	

Source: Excerpted from Table 9-8 study report

Concurrent medications:

The only allowed diabetes background medications were basal insulin with or without metformin. The patients were to continue pre-trial background medication throughout the entire trial. The acceptable types of insulin are outlined in the inclusion criteria above.

Patients with HbA1c ≤8% at screening were to have the insulin dose reduced by 20% at start of trial product to limit the potential risk of hypoglycemia induced by the combination of insulin and semaglutide. The insulin dose could be up-titrated from week 10 to week 16 according to the table below (lowest FPG refers to lowest FPG of the 3 days prior to adjustment). Notably, the insulin was not to be titrated above the pre-randomization dose.

Table 42 Insulin Titration (HbA1c ≤8%) SUSTAIN 5

Lowest FPG		Adjustment of basal insulin (total daily dose) IU[#§]
mmol/L	mg/dL	
≥4.0 – <5.5	≥71 – <100	No adjustment
≥5.5 – <6.7	≥100 – <120	+0–2 (at the discretion of the investigator)
≥6.7 – <7.8	≥120 – <140	+2
≥7.8 – <10.0	≥140 – <180	+4
≥10.0	≥180	+6–8 (at the discretion of the investigator)

The insulin dose was not to be titrated above the pre-randomisation dose.

§ For insulin glargine, insulin detemir, and insulin degludec, the unit is U; for NPH insulin, the unit is IU. For the purpose of analysing insulin dose, U and IU are not differentiated in this document.

Source: Table 9-2 study report

For all patients, insulin could be down-titrated from week 0 to week 12, per Table 43 below.

Table 43 Insulin Down-Titration SUSTAIN 5

Lowest FPG		Adjustment of basal insulin (total daily dose) IU[§]
mmol/L	mg/dL	
<3.1	<56	-4 (for doses >45 IU, suggest dose reduction of 10%)
≥3.1 – <4.0	≥56 – <71	-2 (for doses >45 IU, suggest dose reduction of 5%)

§ For insulin glargine, insulin detemir, and insulin degludec, the unit is U; for NPH insulin, the unit is IU. For the purpose of analysing insulin dose, U and IU are not differentiated in this document.

Source: Table 9-3 study report

Otherwise basal insulin was to remain constant during the trial except for dose reduction for hypoglycemia.

Metformin was to be used in accordance with treatment guidelines or local label in the individual country at the discretion of the investigator. If patients were on metformin at screening, the dose was to remain stable during the trial (except if rescue criteria were fulfilled).

Treatment compliance:
Similar to SUSTAIN-1

Rescue medications:
Criteria for initiation of rescue medication was similar to SUSTAIN-1.

Treatment compliance:
Similar to SUSTAIN-1.

Study Endpoints

Similar to SUSTAIN-1 with additional exploratory secondary endpoints including insulin dose.

Statistical Analysis Plan

For the primary HbA1c endpoint and the confirmatory secondary body weight endpoint, superiority were planned to be tested for semaglutide 1 mg versus placebo and semaglutide 0.5 mg versus placebo. The superiority analysis was based on the FAS.

The conclusion of superiority with treatment of each semaglutide dose
versus placebo after 30 weeks was evaluated hierarchically according to the sequence given below (type 1 error for testing the four hypotheses 5% 2-sided):

- Superiority in change in HbA1c for semaglutide 1 mg vs placebo
- Superiority in change in HbA1c for semaglutide 0.5 mg vs placebo
- Superiority in change in body weight for semaglutide 1 mg vs placebo
- Superiority in change in body weight for semaglutide 0.5 mg vs placebo

The primary endpoint, and confirmatory secondary endpoint, were analyzed using MMRM. The MMRM included treatment, country, and the stratification variable (HbA1c at screening and use of metformin) as fixed factors and baseline HbA1c as covariate. This model assumed that the data are missing at random.

Reviewer'scomment: It is not clear that this is the best model to analyze the data, as missingness of data may be correlated to lack of compliance. The FDA biometrics team recommended that a retrieved dropout analysis would be best in this situation, please see biometrics review for details.

Protocol Amendments

There were 2 amendments to the original protocol, one local amendment in Germany, and one global amendment. Details are presented in Table 44 below.

Table 44 Protocol Amendments SUSTAIN 5

Amendment no.	Issue date	Timing of change (before or after FSFV on 01-Dec-2014)	Countries affected	Key changes
1	26 August 2014	Before	Germany	Changes in exclusion criteria 11 according to comments from Health Authorities in Germany to align with local SmPC for metformin.
2	18 December 2014	After	Global	Change and clarify the wording of Section 6.4, "Rescue criteria". Minor updates for general clarification had been done in Sections 5.3.2, 8.3.2.1, 9.3, 12.2 and 17.3. In addition, the new name of the central laboratory had been included in Attachment I.

Abbreviations: FSFV: first subject first visit. SmPC: Summary of Product Characteristics.
Source: Table 9-13 study report

None of these amendments is likely to have impacted the results of the study.

Data Quality and Integrity: Sponsor's Assurance

The trial was monitored by Novo Nordisk using on-site visits, telephone calls and regular inspection of the eCRFs. Four internal audits were performed, one in Germany, two in Japan, and one in the US.

6.5.2. Study Results

Compliance with Good Clinical Practices

The sponsor stated that the trial was conducted in accordance with ICH GCP.

Financial Disclosure

Of the 486 investigators that participated in the trial, 10 had disclosable financial interests, and all had the financial disclosure form submitted.

Patient Disposition

Of the 534 patients screened, 137 (25.7%) were screening failures, thus 397 patients were randomized at a 2:2:1:1 ratio to receive semaglutide or placebo treatment at 2 different doses. The majority of screening failures (98/137) were due to patients not meeting the inclusion criterion #4 of HbA1c levels being within 7−10% (both values included), and other common reasons for screening failures included inclusion criterion #3 (8/137), various exclusion criteria (28/137) other reasons (9/137).

Of the 397 patients randomized in the trial, 396 patients were exposed to trial products representing 132 patients exposed to semaglutide 0.5 mg, 131 patients exposed to semaglutide 1 mg and 133 patients exposed to placebo. One patient was randomized and then lost to follow-up without reporting a first drug date and therefore never considered exposed to trial product. A total of 380 out of 397 patients (95.7%) completed the trial and 353 out of 396 exposed patients (89.1%) completed the treatment

Table 45 Patient Disposition SUSTAIN 5

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)	Total N (%)
Screened				534
Screening failures				137 (25.7)
Withdrawn before randomisation				0 (0)
Randomised	132	132	133	397
Exposed	132 (100)	131 (99.2)	133 (100)	396 (99.7)
Safety analysis set	132 (100)	131 (99.2)	133 (100)	396 (99.7)
Full analysis set	132 (100)	131 (99.2)	133 (100)	396 (99.7)
Treatment completers [1]	118 (89.4)	115 (87.8)	120 (90.2)	353 (89.1)
Without rescue medication	115 (87.1)	114 (87.0)	101 (75.9)	330 (83.3)
With rescue medication	3 (2.3)	1 (0.8)	19 (14.3)	23 (5.8)
Premature treatment discontinuation - primary reason [2]	14 (10.6)	16 (12.2)	13 (9.8)	43 (10.9)
Pregnancy	1 (0.8)			1 (0.3)
Protocol violation	1 (0.8)		2 (1.5)	3 (0.8)
Violation of the inclusion and/or exclusion criteria	1 (0.8)		2 (1.5)	3 (0.8)
Intention of becoming pregnant				
Adverse event	6 (4.5)	10 (7.6)	1 (0.8)	17 (4.3)
Gastrointestinal AEs	2 (1.5)	5 (3.8)		7 (1.8)
Pancreatitis	1 (0.8)			1 (0.3)
Other AEs	3 (2.3)	5 (3.8)	1 (0.8)	9 (2.3)
Other	6 (4.5)	6 (4.6)	10 (7.5)	22 (5.6)
Trial completers [3]	127 (96.2)	127 (96.2)	126 (94.7)	380 (95.7)
Premature withdrawal from trial in relation to or after premature treatment discontinuation - primary reason	4 (3.0)	4 (3.0)	7 (5.3)	15 (3.8)
Withdrawal by Subject	2 (1.5)	2 (1.5)	1 (0.8)	5 (1.3)
Lost to follow-up	2 (1.5)	1 (0.8)	6 (4.5)	9 (2.3)
Death				
Missing follow-up information [4]		1 (0.8)		1 (0.3)
Premature withdrawing from trial after treatment completion - primary reason	1 (0.8)	1 (0.8)		2 (0.5)
Withdrawal by Subject				
Lost to follow-up	1 (0.8)	1 (0.8)		2 (0.5)
Death				
Missing follow-up information [4]				

N: Number of subjects, %: For treatment completers and treatment non-completers percentages are based on exposed subjects.
For trial completers and withdrawals percentages are based on randomised subjects.
[1]: Completion of treatment according to end-of-trial form. [2]: Includes only exposed subjects and is based on the primary reason for treatment discontinuation according to the end-of-trial form. [3]: Subjects with a follow-up visit. [4]: Subjects with no reason/date for withdrawal but without the follow-up visit.

Source: Table 10-1 study report

The treatment duration and the number of days a patient belonged to the 'in-trial' or 'on-treatment' observation periods were similar across the 3 groups, but the average time a patient

belonged to the 'on-treatment without rescue medication' observation period was longer with semaglutide (229.6 days for semaglutide 0.5 mg, 226.6 days for semaglutide 1 mg) compared with placebo (207.2 days).

Table 46 Observation Periods and Treatment Duration - FAS – SUSTAIN 5

	Sema 0.5 mg	Sema 1.0 mg	Placebo	Total
Number of subjects	132	131	133	396
In-trial observation period (days) [1]				
N	132	131	133	396
Mean (SD)	244.3 (21.4)	243.1 (26.4)	237.9 (40.5)	241.7 (30.6)
Median (Q1, Q3)	246.0 (246.0, 248.5)	246.0 (245.0, 249.0)	246.0 (246.0, 249.0)	246.0 (245.0, 249.0)
Min ; max	69 ; 287	26 ; 260	15 ; 276	15 ; 287
Total (years)	32244 (88.28)	31842 (87.18)	31643 (86.63)	95729 (262.1)
On-treatment observation period (days) [2]				
N	132	131	133	396
Mean (SD)	233.0 (40.6)	228.3 (49.9)	231.0 (46.3)	230.7 (45.7)
Median (Q1, Q3)	246.0 (243.0, 246.0)	246.0 (239.0, 246.0)	246.0 (242.0, 246.0)	246.0 (241.0, 246.0)
Min ; max	50 ; 253	26 ; 260	15 ; 254	15 ; 260
Total (years)	30754 (84.20)	29904 (81.87)	30718 (84.10)	91376 (250.2)
On-treatment without rescue medication observation period (days) [3]				
N	132	131	133	396
Mean (SD)	229.6 (45.6)	226.6 (52.7)	207.2 (69.6)	221.1 (57.7)
Median (Q1, Q3)	246.0 (242.5, 246.0)	246.0 (239.0, 246.0)	246.0 (232.0, 246.0)	246.0 (239.0, 246.0)
Min ; max	50 ; 253	26 ; 260	1 ; 254	1 ; 260
Total (years)	30306 (82.97)	29687 (81.28)	27553 (75.44)	87546 (239.7)
Treatment duration (days) [4]				
N	132	131	133	396
Mean (SD)	199.4 (40.0)	194.8 (48.5)	198.2 (41.4)	197.5 (43.4)
Median (Q1, Q3)	210.0 (210.0, 216.0)	210.0 (210.0, 213.0)	210.0 (210.0, 211.0)	210.0 (210.0, 213.0)
Min ; max	14 ; 224	14 ; 224	14 ; 224	14 ; 224
Total (years)	26326 (72.08)	25524 (69.88)	26367 (72.19)	78217 (214.1)

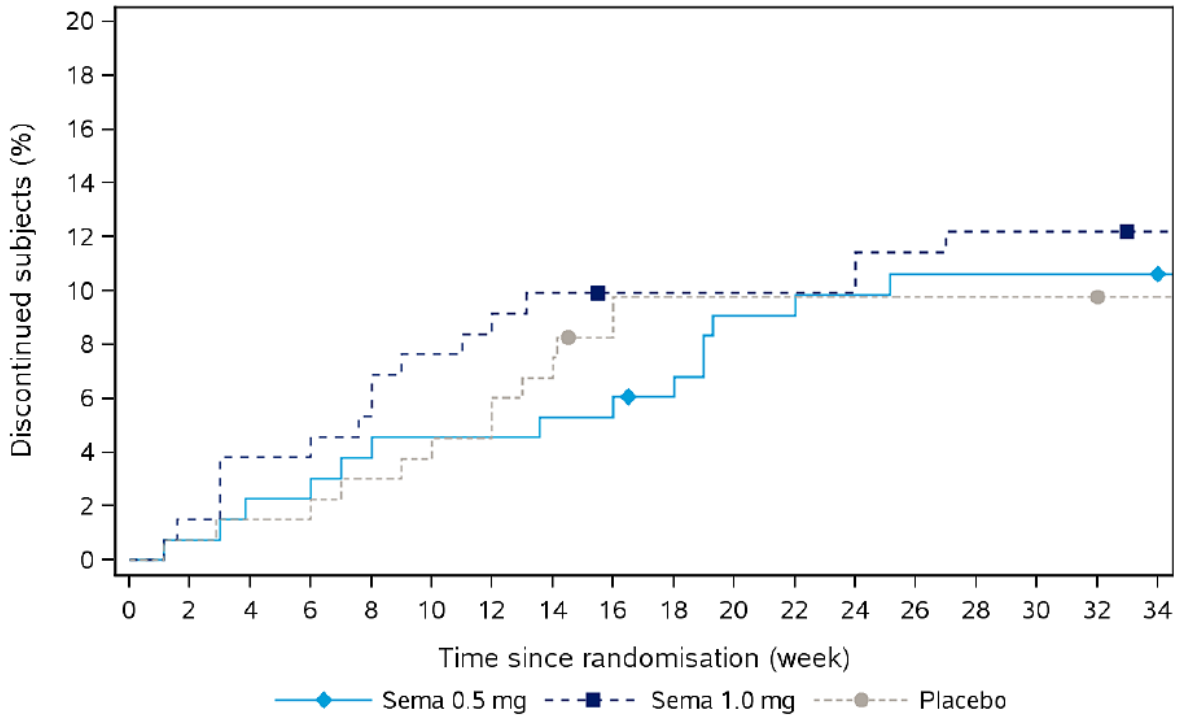
N: Number of subjects, SD: Standard deviation, Q1: 1st quartile, Q3: 3rd quartile.
[1]: The in-trial observation period denotes the time from randomisation to 'end-of-trial'. [2]: The 'on-treatment' observation period denotes the time from date of first dose to date of last dose plus 42 days, both inclusive. [3]: The 'on-treatment without rescue medication' observation period denotes the time period from the day of first randomised dose to the day of first initiation of rescue medic ation. [4]: Treatment duration is the time period from day of first randomised dose to day of last randomised dose plus 7 days.

Source: Table 14.1.7 study report

A total of 43 patients discontinued treatment prematurely across the 3 groups. The main reason for premature treatment discontinuation was adverse events for the semaglutide groups, and was 'Other' for the placebo group. Three patients discontinued the treatment due to inclusion/exclusion criteria protocol violations. A total of 17 patients discontinued treatment prematurely due to AEs (6 patients [4.5%] with semaglutide 0.5 mg, 10 patients [7.6%] with semaglutide 1 mg, 1 patient [0.8%] with placebo), among which 7 patients (2 for semaglutide 0.5 mg and 5 for semaglutide 1 mg) were due to GIAEs. The remaining 22 patients were due to 'Other' reasons (e.g. moving, lost to follow-up, patient's decision). In total, 15 patients withdrew from the trial at or after premature treatment discontinuation, and another 2 patients withdrew after treatment completion.

While there were no major differences between the arms regarding treatment discontinuations for the entire duration of the trial, the patients in the semaglutide 1 mg arm started discontinuations earlier in the study compared to semaglutide 0.5 mg or placebo.

Figure 19 Time from Randomization to Premature Treatment Discontinuation for Any Reason (Weeks) - FAS – SUSTAIN 5



Denominator is number of subjects in FAS.
Source: Figure 10-2 study report

Protocol Violations/Deviations

Protocol deviations at the trial site and patient level

There were 47 and 257 important PDs at the site level and patient level, respectively. The majority of the PDs at the site level were in the category of "Other" (44 PDs). Two PDs were in the category of "Inclusion/Exclusion criteria", and one PD was in the category of "Trial product handling".

Table 47 Summary of Important Protocol Deviations at Site Level and Patient Level SUSTAIN 5

Protocol deviation category	Site-level	Subject -level				
		Sema 0.5 mg	Sema 1.0 mg	Placebo	Screening failures	Total
Informed consent		2	2	1	0	5
Inclusion/exclusion/randomisation criteria	2	8	2	7	1	18
Withdrawal criteria		0	2	0	0	2
Trial product handling	1	4	2	2	0	8
Treatment compliance		14	12	9	0	35
Assessment deviations		46	53	57	0	156
Other	44	9	15	9	0	33
Total	47	83	88	85	1	257

Abbreviations: Sema: semaglutide.
Source: Table 10-7 study report

Informed consent: For all patients, an IC form was completed prior to any trial-related activity. There were 5 patient-level PDs (involving 5 patients) related to the IC (3 PDs related to incorrect or incomplete IS, one PD related to incorrect IC procedure, and one PD where the nurse wrote the investigator's name and date).

Inclusion/exclusion/randomization criteria

There were 2 site-level PDs and 18 patient-level PDs. The two site-level PDs concerned two sites ticking exclusion criteria #12 (Acute coronary or cerebrovascular event within 90 days before randomization) before randomization actually took place. These 2 PDs involved 5 patients, and all patients completed the trial.

A total of 18 patient-level PDs concerning 18 patients were reported. Twelve of those were related to exclusion criteria (one was screening failure). One was related to inclusion criteria, 4 were related to incorrect stratification, and one had randomization procedures performed 4 days prior to the randomization call.

Withdrawal criteria: There were 2 patient-level PDs for 2 patients who had high SMPG values, the confirmatory FPG tests were not completed as defined in the protocol. Neither patient received rescue medication, and both of them completed the trial.

Trial product handling

One site-level PD and 8 patient-level PDs were reported. The site-level PD concerned 4 patients from one site who were dispensed trial product stored out of the allowed temperature range. No patients withdrew due to these PDs, and all patients were included in the analyses. Three of the patients withdrew/discontinued treatment later during the trial due to other reasons (moving out of the country, AE, or lost to follow-up). The 8 patient-level PDs were as follows: 5 patients were dispensed incorrectly stored trial product, 2 patients were dispensed/administered the wrong trial product (one patient received semaglutide instead of placebo "for a few days" per the applicant, and another patient received the wrong dose of semaglutide of 8 weeks – 9 doses), and one patient did not receive directions for use of the trial product.

Treatment compliance

A total of 35 patient-level PDs (approximately 12% of all PDs) were reported, and these PDs occurred with similar frequencies across the 3 treatment groups:

- 27 patients received a wrong dose of trial medication due to a prescribing error, patient non- compliance or patient error (including dose escalation deviation)
- 2 patients missed more than 3 consecutive doses of trial product
- 5 patients received concomitant treatment not allowed according to the protocol: 4 patients received GLP-1 RA during the follow-up period, 1 patient self-administered a bolus insulin dose. All 5 patients completed treatment and were included in the analysis.
- 1 patient changed injection day several times during the trial

Assessment deviation

A total of 156 patient-level assessment deviations were reported (approximately 50% of all PDs):

- 34 PDs were related to missing all planned safety assessments at the trial visits where the last safety assessments should be performed (V16 + V17, or V16A + V17A).
- 57 PDs were related to missing one or more safety assessments for antibody, calcitonin, body measurements, vital signs and physical examination, blood samples, ECG, and urinalysis at certain visits.
- 14 PDs were related to missing serum pregnancy or home urine pregnancy test.
- 8 PDs were related to pregnancy tests performed on patients in menopause.
- 2 PDs were related to the principal investigator signing the laboratory report late.
- 4 PDs were related to patients not fasting at visit as per protocol and no retest was performed.
- 36 PDs were related to trial product injected prior to lab sampling.
- 1 PD was related to not entering elevated lipase value (considered adverse event) into the EDC within the required timeframe

Other

A total of 44 site-level PDs were reported (approximately 14% of all PDs):

- 2 PDs were related to patient diary not dispensed.
- 38 PDs were related to monitoring visits not within the interval defined by the protocol
- 3 PDs were related to source data missing (incl. diary) or incomplete
- 1 PD was related to a new study coordinator performing study related tasks before completion of the mandatory training

A total of 33 patient-level PDs were reported (approximately 11% of all PDs):

- 8 PDs were related to late reporting or late signing of SAEs or MESIs.
- 3 PDs were related to site staff entering information in the patients' diary.
- 7 PDs were related to patient diary not dispensed.
- 1 PD was related to monitoring visits not within the interval defined by the protocol.
- 1 PD was related to trial task performed by site staff not delegated the responsibility in the log of staff or delegation log
- 11 PDs were related to source data missing (incl. diary) or incomplete, among which missing diaries accounted for 9 PDs
- 2 PDs were related to patients randomized 10 days after visit 2 due to insufficient medication on site.

No PDs were identified after database lock.

Table of Demographic Characteristics

More men (56.1%) than women (43.9%) were enrolled in this trial. Of the 5 countries in which the trial was conducted, United States had the most patients (45.5%). The majority of patients were White (77.5%) or Asian (16.7%) with 11.6% of patients being Hispanic or Latino ethnicity. At baseline, the mean age of all patients was 58.8 years

The mean HbA1c level was 8.37%, and the mean duration of diabetes was 13.32 years. Normal renal function was seen for 50.8% of patients, mild renal impairment was seen for 40.4% of patients, while 8.8% of patients had moderate renal impairment. The mean eGFR was 91.3 mL/min/1.73 m2 and was similar for the 3 groups.

Table 48 Selected Demographics and Baseline Characteristics for Categorical Variables - FAS – SUSTAIN 5

	Sema 0.5 mg N	(%)	Sema 1.0 mg N	(%)	Placebo N	(%)	Total N	(%)
Number of subjects	132		131		133		396	
Stratum								
HBA1C <= 8.0% + METFORMIN	41	(31.1)	41	(31.3)	40	(30.1)	122	(30.8)
HBA1C <= 8.0% + No METFORMIN	8	(6.1)	8	(6.1)	9	(6.8)	25	(6.3)
HBA1C > 8.0% + METFORMIN	69	(52.3)	69	(52.7)	70	(52.6)	208	(52.5)
HBA1C > 8.0% + No METFORMIN	14	(10.6)	13	(9.9)	14	(10.5)	41	(10.4)
Age group								
18-64 years	93	(70.5)	102	(77.9)	86	(64.7)	281	(71.0)
65-74 years	32	(24.2)	26	(19.8)	43	(32.3)	101	(25.5)
75-84 years	7	(5.3)	3	(2.3)	3	(2.3)	13	(3.3)
>= 85 years	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)
Sex								
Female	58	(43.9)	54	(41.2)	62	(46.6)	174	(43.9)
Male	74	(56.1)	77	(58.8)	71	(53.4)	222	(56.1)
Country								
United States	60	(45.5)	59	(45.0)	61	(45.9)	180	(45.5)
Race								
American Indian or Alaska Native	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Asian	19	(14.4)	23	(17.6)	24	(18.0)	66	(16.7)
Black or African American	4	(3.0)	9	(6.9)	8	(6.0)	21	(5.3)
Native Hawaiian or Other Pacific Islander	1	(0.8)	0	(0.0)	0	(0.0)	1	(0.3)
White	108	(81.8)	98	(74.8)	101	(75.9)	307	(77.5)
Other	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)
Ethnicity								
Hispanic or Latino	15	(11.4)	12	(9.2)	19	(14.3)	46	(11.6)
Not Hispanic or Latino	117	(88.6)	119	(90.8)	114	(85.7)	350	(88.4)
Smoker status								
N	132	(100.0)	131	(100.0)	133	(100.0)	396	(100.0)
Current smoker	28	(21.2)	25	(19.1)	23	(17.3)	76	(19.2)
Never smoked	60	(45.5)	65	(49.6)	69	(51.9)	194	(49.0)
Previous smoker	44	(33.3)	41	(31.3)	41	(30.8)	126	(31.8)
Renal function								
Normal	65	(49.2)	70	(53.4)	66	(49.6)	201	(50.8)
Mild Renal Impairment	55	(41.7)	49	(37.4)	56	(42.1)	160	(40.4)
Moderate Renal Impairment	12	(9.1)	12	(9.2)	11	(8.3)	35	(8.8)
Severe Renal Impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
End stage Renal Impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate. The renal function categories are based on the MDRD eGFR. Baseline value is defined as the latest pre-dosing value. Subjects were stratified based on HbAlc level at screening (<=8.0% and > 8.0%) and use of metformin (yes and no).

Source: Modified from Table 10-2 study report

Table 49 Selected Demographics and Baseline Characteristics for Continuous Variables - FAS – SUSTAIN 5

	Sema 0.5 mg	Sema 1.0 mg	Placebo	Total
Number of subjects	132	131	133	396
Age (years) Mean (SD)	59.1 (10.3)	58.5 (9.0)	58.8 (10.9)	58.8 (10.1)
HbA1c (%) Mean (SD)	8.36 (0.83)	8.31 (0.82)	8.42 (0.88)	8.37 (0.84)
Duration of Diabetes (years) Mean (SD)	12.91 (7.59)	13.74 (7.82)	13.30 (7.98)	13.32 (7.79)
Body weight (kg) Mean (SD)	92.74 (19.57)	92.49 (22.23)	89.88 (21.06)	91.70 (20.97)
Body mass index (kg/m2) Mean (SD)	32.77 (6.01)	32.00 (6.41)	31.77 (6.05)	32.18 (6.16)
MDRD GFR 'estimated' (mL/min/1.73 m^2) Mean (SD)	91.88 (26.30)	91.06 (23.41)	90.97 (25.37)	91.30 (25.00)

N: Number of subjects
MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate.
The baseline value is defined as the latest pre-dosing value.

Source: Modified from Table 10-3 study report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Medical history/Concomitant illnesses

While some small differences can be seen between the treatment arms regarding the history of hypertension, lipid disorders, and CV history, the differences are small and unlikely to impact the results of the study. An explanation for these small observed differences could be the small sample size.

Table 50 Selected Medical History SUSTAIN 5

Dictionary Derived Term	Comparator N=133	Sema 0.5 mg N=132	Sema 1.0 mg N=131
Hypertension	90 (67.67%)	93 (70.45%)	81 (61.83%)
Hyperlipidemia	40 (30.08%)	43 (32.58%)	35 (26.72%)
Dyslipidemia	37 (27.82%)	26 (19.70%)	32 (24.43%)
Hypercholesterolemia	15 (11.28%)	21 (15.91%)	11 (8.40%)
CV history	22 (16.54)	29 (21.97)	19 (14.5)

Source: reviewer generated medical history and ADSL datasets

Funduscopy

Fundoscopy was performed at randomization, if no recent (within 90 days before visit 2) normal fundoscopy results were available. Funduscopy/fundus evaluations were categorized as

'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant' by the investigator.

At randomisation, the fundoscopy findings were normal for the majority of the patients (ranged from 63.6−68.9% for all groups). The proportions of patients with 'abnormal, not clinically significant' (ranged from 23.5−27.3% for all groups) and 'abnormal, clinically significant' (ranged from 8−10% for all groups) were comparable among the treatment groups.

Table 51 Baseline Funduscopy Results

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)
Number of subjects	132	131	133
Left eye fundoscopy - Observed 'in-trial' data			
Visit 2 (week 0)			
Normal	91 (68.9)	86 (65.6)	86 (65.2)
Abnormal and not clinically significant	31 (23.5)	32 (24.4)	34 (25.8)
Abnormal and clinically significant	10 (7.6)	13 (9.9)	12 (9.1)
Right eye fundoscopy - Observed 'in-trial' data			
Visit 2 (week 0)			
Normal	90 (68.2)	85 (64.9)	84 (63.6)
Abnormal and not clinically significant	32 (24.2)	33 (25.2)	36 (27.3)
Abnormal and clinically significant	10 (7.6)	13 (9.9)	12 (9.1)

Source: Modified from Table 14.3.6.12 study report

History of gallbladder disease/pancreatitis

Of the 396 randomized and dosed patients, 40 patients (10.1%) had a history of gallstone disease with a lower number of patients with placebo (10 patients) compared with semaglutide 0.5 mg (14 patients) and 1.0 mg (16 patients). A history of gallbladder disease was reported for 53 patients (13.4%) with fewer patients with placebo (15 patients) compared with semaglutide 0.5 mg (17 patients) and 1.0 mg (21 patients). Otherwise the semaglutide arms and comparator were balanced. No patient had a history of pancreatitis as expected from the enrollment criteria.

Table 52 History of Gallbladder Disease at Screening SUSTAIN 5

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)
Number of subjects	132	131	133
Pancreatitis	132(100.00)	131(100.00)	133(100.00)
No	132(100.00)	131(100.00)	133(100.00)
Yes	0(0.00)	0(0.00)	0(0.00)
Gallstone Disease	132(100.00)	131(100.00)	133(100.00)
No	118(89.39)	115(87.79)	123(92.48)
Yes	14(10.61)	16(12.21)	10(7.52)
Cholecystitis	132(100.00)	131(100.00)	133(100.00)
No	125(94.70)	125(95.42)	126(94.74)
Yes	7(5.30)	6(4.58)	7(5.26)
Acute	7(5.30)	4(3.05)	3(2.26)
Chronic	0(0.00)	1(0.76)	1(0.75)
Missing	0(0.00)	1(0.76)	3(2.26)
Gallbladder Disease	132(100.00)	131(100.00)	133(100.00)
No	115(87.12)	110(83.97)	118(88.72)
Yes	17(12.88)	21(16.03)	15(11.28)
Both	4(3.03)	1(0.76)	2(1.50)
Cholecystitis Only	3(2.27)	5(3.82)	5(3.76)
Gallstone Disease Only	10(7.58)	15(11.45)	8(6.02)

N: Number of subjects, %:Percentage of subjects.
Gallbladder disease is defined as Yes if at least one of Gallstone disease or Cholecystitis is Yes.

Source: Modified from Table 14.1.23 study report

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance is best represented by a discussion of protocol deviations for this category. For the PD category treatment compliance, a total of 35 protocol deviations were reported for 34 patients. These PDs were related to patients receiving a wrong dose of trial product, missed more than 3 consecutive doses, not following the dose escalation schedule, using GLP-1 RA during the follow-up period, using the trial product once daily instead of once weekly. The semaglutide arms has a higher number of patinets in this PD category (14 for semaglutide 0.5 mg, and 12 for semaglutide 1 mg), compared to placebo – 9 patients. The applicant did not consider any of these PDs to have potential to impact the sresults of the study.

Concomitant medications

Most patients (83.3%) were taking metformin at baseline (330 patients, 110 per treatment arm). One patient in the placebo arm was also taking glipizide. This last patient was randomized in error, and discontinued treatment prematurely.

Basal insulin: Insulin glargine was most commonly used (213/396 patients), balanced between the treatment groups. The geometric mean insulin glargine dose was higher with semaglutide 1 mg (41.50 IU) compared to the semaglutide 0.5 mg (37.87 IU) and placebo (38.07 IU) groups. Insulin detemir was the second most commonly used insulin type (75 patients), and the geometric mean dose was the highest in the semaglutide 0.5 mg group. Insulin degludec and NPH insulin showed some variations across the treatment groups in terms of the number of

patients using these insulins and the geometric mean insulin dose. Overall, the variations in insulin dose among the 3 treatment groups appeared to be driven by a few patients using exceptionally high insulin doses (300 IU or higher).

Table 53 Basal Insulin Dosing at Baseline – FAS – SUSTAIN 5

	Sema 0.5 mg	Sema 1.0 mg	Placebo	Total
Number of subjects	132	131	133	396
Insulin glargine (IU)				
N	76	70	67	213
Mean (SD)	42.63 (21.67)	50.34 (41.81)	43.43 (23.25)	45.42 (30.26)
Median	35.00	40.00	40.00	40.00
Geometric mean (CV)	37.87 (51.53)	41.50 (63.97)	38.07 (55.29)	39.09 (56.82)
Min ; Max	15.00 ; 100.0	14.00 ; 320.0	15.00 ; 124.0	14.00 ; 320.0
Insulin detemir (IU)				
N	20	27	28	75
Mean (SD)	56.05 (26.24)	40.07 (22.67)	39.96 (22.32)	44.29 (24.29)
Median	49.00	36.00	31.00	40.00
Geometric mean (CV)	51.22 (44.30)	35.81 (48.60)	35.21 (53.12)	39.15 (51.82)
Min ; Max	28.00 ; 120.0	20.00 ; 130.0	15.00 ; 100.0	15.00 ; 130.0
Insulin degludec(IU)				
N	10	19	14	43
Mean (SD)	63.80 (86.35)	30.26 (11.98)	35.50 (15.01)	39.77 (43.74)
Median	28.50	26.00	37.00	28.00
Geometric mean (CV)	40.85 (102.6)	28.54 (34.41)	32.12 (52.09)	32.24 (58.75)
Min ; Max	22.00 ; 300.0	20.00 ; 67.00	12.00 ; 60.00	12.00 ; 300.0
Neutral protamine hagedorn (NPH) insulin (IU)				
N	27	15	24	66
Mean (SD)	45.96 (33.35)	40.40 (22.31)	45.50 (32.51)	44.53 (30.52)
Median	30.00	28.00	32.00	30.00
Geometric mean (CV)	37.40 (68.49)	35.13 (58.44)	37.26 (67.85)	36.82 (64.93)
Min ; Max	20.00 ; 130.0	20.00 ; 80.00	20.00 ; 124.0	20.00 ; 130.0

N: Number of subjects, SD: Standard deviation, CV: Coefficient of variation.

Source: Table 10-4 study report

The most frequently used other concomitant medications were statins (HMG-CoA reductase inhibitors) (51.5%), ACE inhibitors plain (37.4%), platelet aggregation inhibitors excluding heparin (31.1%), beta blocking agents (22.2%), dihydropyridine derivatives (19.4%), angiotensin II antagonists plain (17.4%), and proton pump inhibitors (13.1%). There were no significant differences between the treatment groups.

After randomisation, initiation of concomitant medications was generally similar for the 3 treatment groups, except for the initiation of insulin and oral diabetes medications as rescue medication, which was higher with placebo.

Table 54 Selected Other Concomitant Medications SUSTAIN 5

Medication Class	Comparator	Sema 0.5 mg	Sema 1.0 mg

HMG coa reductase inhibitors	69 (51.88%)	62 (46.97%)	72 (54.96%)
ACE inhibitors	49 (36.84%)	55 (41.67%)	44 (33.59%)
Dihydropyridine derivatives	25 (18.80%)	24 (18.18%)	28 (21.37%)
Angiotensin II antagonists	21 (15.79%)	28 (21.21%)	22 (16.79%)
Thiazides	8 (6.02%)	11 (8.33%)	14 (10.69%)
Other lipid modifying agents	7 (5.26%)	8 (6.06%)	4 (3.05%)
Fibrates	10 (7.52%)	7 (5.30%)	2 (1.53%)
Total patients	133 (100.00%)	132(100.00%)	131 (100.00%)

Source: Reviewer generated using concomitant medications and ADSL datasets

Rescue medication was started in a higer proportion of patients on placebo (21 patients), compared to either semaglutide arm (3 patients on semaglutide 0.5 mg, and one patient on semaglutide 1 mg). Long acting insulin was used in most of these patients for rescue (2 patients with semaglutide 0.5 mg, 1 patient with semaglutide 1 mg, 13 patients with placebo).

Efficacy Results - Primary Endpoint

The applicant performed efficacy analyses on the full analysis set (FAS) using the 'on-treatment without rescue medication' observation period.

Change in HbA1c from baseline to week 30

Baseline HbA1c levels were similar across the 3 groups with a mean of 8.37%.

From a mean baseline level of 8.37%, HbA1c levels decreased by 1.45%-point and 1.85%-point with semaglutide 0.5 mg and 1.0 mg, respectively at week 30. With placebo, a negligible decrease in HbA1c of 0.09%-point was seen at week 30. Superiority of semaglutide in reducing HbA1c levels from baseline to week 30 was demonstrated for both doses of semaglutide compared with placebo. This may not be surprising since the insulin dose was mostly kept constant by the trial design.

Table 55 HbA1c (%) - Primary Statistical Analysis - FAS – SUSTAIN 5

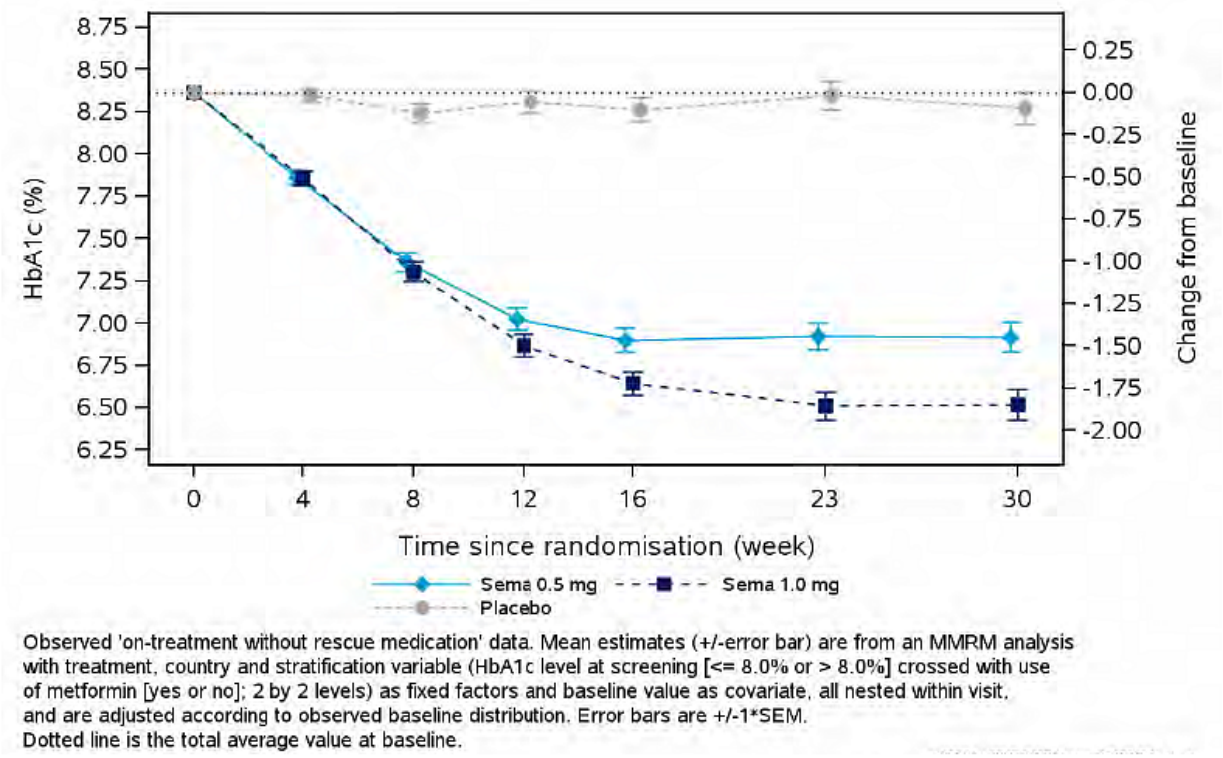
	FAS	N	Estimate	SE	95% CI	p-value
HbA1c (%)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	132	111	6.92	0.09		
Sema 1.0 mg	131	108	6.52	0.09		
Placebo	133	94	8.27	0.09		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	132	111	-1.45	0.09		
Sema 1.0 mg	131	108	-1.85	0.09		
Placebo	133	94	-0.09	0.09		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - Placebo			-1.35		[-1.61 ; -1.10]	<.0001
Sema 1.0 mg - Placebo			-1.75		[-2.01 ; -1.50]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval. Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Modified from Table 11-1 study report

HbA1c levels declined from baseline until week 16 followed by an apparent plateau that continued until the end of the 30-week treatment period in patients treated with semaglutide 0.5 mg, whereas an apparent plateau is seen in patients treated with semaglutide 1 mg from week 23. With placebo, HbA1c levels remained at a similar level from baseline to week 30.

Figure 20 Mean HbA1c (%) by Treatment Week - FAS – SUSTAIN 5



Source: Figure 11-1 study report

Data Quality and Integrity - Reviewers' Assessment

I did not identify any issues with the data integrity.

Efficacy Results - Secondary and other relevant endpoints

Confirmatory secondary endpoint: Change from baseline to week 30 in body weight

Mean body weight at baseline was similar across the 3 treatment groups (92.7 kg for semaglutide 0.5 mg, 92.5 kg for semaglutide 1 mg, and 89.9 for placebo). The weight was reduced in all treatment groups at week 30: by 3.67 kg (4.21%) and 6.42 kg (7.27%) with semaglutide 0.5 mg and 1.0 mg, respectively, compared to a reduction of 1.36 kg (1.30%) with placebo, at week 30.

Table 56 Body Weight - FAS – SUSTAIN 5

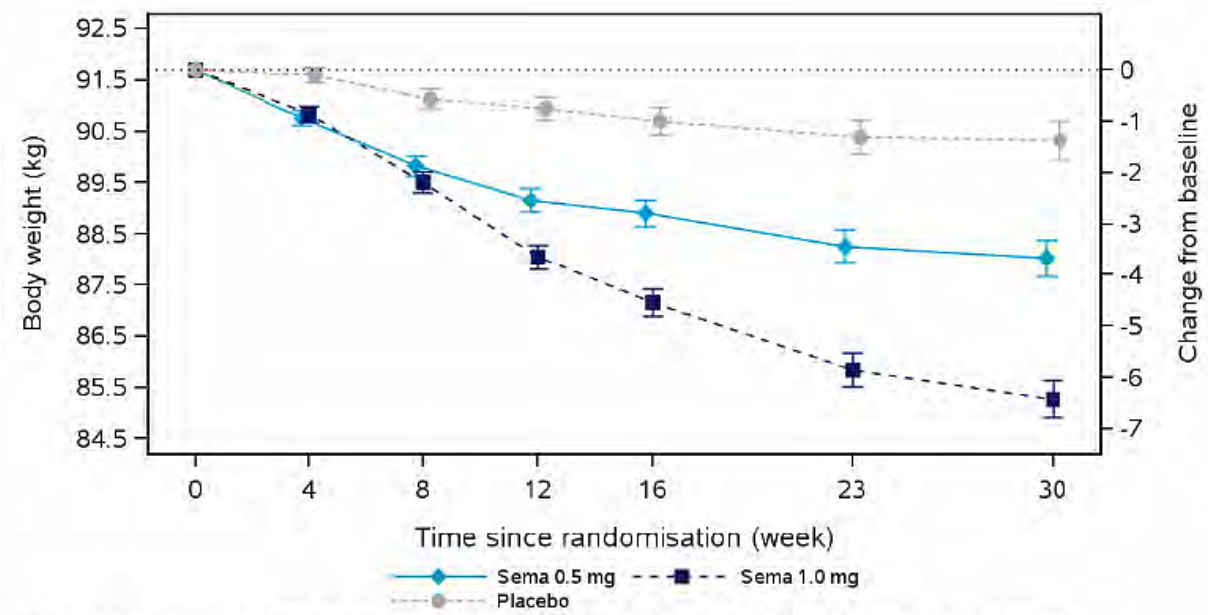
	FAS	N	Estimate	SE	95% CI	p-value
Body weight (kg)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	132	111	88.02	0.36		
Sema 1.0 mg	131	108	85.27	0.36		
Placebo	133	95	90.33	0.37		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	132	111	-3.67	0.36		
Sema 1.0 mg	131	108	-6.42	0.36		
Placebo	133	95	-1.36	0.37		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - Placebo			-2.31		[-3.33 ; -1.29]	<.0001
Sema 1.0 mg - Placebo			-5.06		[-6.08 ; -4.04]	<.0001
Body Weight (%)						
Mean of baseline (%) at visit 16 (week 30)						
Sema 0.5 mg	132	111	95.79	0.38		
Sema 1.0 mg	131	108	92.73	0.39		
Placebo	133	95	98.70	0.40		
Change from baseline (%) at visit 16 (week 30)						
Sema 0.5 mg	132	111	-4.21	0.38		
Sema 1.0 mg	131	108	-7.27	0.39		
Placebo	133	95	-1.30	0.40		
Treatment difference (%-points) at visit 16 (week 30)						
Sema 0.5 mg - Placebo			-2.90		[-3.99 ; -1.82]	<.0001
Sema 1.0 mg - Placebo			-5.97		[-7.06 ; -4.88]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Analysis of observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.
All visits were done in fasting state.

Source: Table 11-2 Study Report

The weight trends over time show a decrease in weight with no apparent plateau until week 30.

Figure 21 Mean Body Weight (kg) by Treatment Week - FAS – SUSTAIN 5



Observed 'on-treatment without rescue medication' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
All visits were done in fasting state.
Dotted line is the total average value at baseline.

Source: Figure 11-5 study report

Supportive secondary endpoints

HbA1c treatment targets

The applicant analyzed HbA1c responses grouped in the following 3 categories:

- Patients reaching an HbA1c level ≤6.5% (AACE)
- Patients reaching an HbA1c level <7% (ADA)
- Patients reaching an HbA1c level <7% without severe or BG-confirmed symptomatic hypoglycemia and no weight gain

For all these treatment targets, both doses of semaglutide were statistically superior to placebo, as most patients in the placebo group did not achieve the targets (not surprising since the study was designed to maintain pre-trial doses of background medications for the placebo group.

Table 57 Patients Achieving HbA1c Response after 30 Weeks of Treatment – FAS – SUSTAIN 5

	FAS	N	R	Estimate	SE	95% CI	p-value
HbA1c <7.0% (ADA)							
Estimated odds at visit 16 (week 30)							
Sema 0.5 mg	132	132	80	1.60	0.30		
Sema 1.0 mg	131	131	103	3.73	0.83		
Placebo	133	133	14	0.11	0.03		
Estimated odds ratio at visit 16 (week 30)							
Sema 0.5 mg / Placebo				14.68		[7.43 ; 29.02]	<.0001
Sema 1.0 mg / Placebo				34.28		[16.59 ; 70.83]	<.0001
HbA1c <=6.5% (AACE)							
Estimated odds at visit 16 (week 30)							
Sema 0.5 mg	132	132	54	0.66	0.13		
Sema 1.0 mg	131	131	80	1.52	0.29		
Placebo	133	133	6	0.04	0.02		
Estimated odds ratio at visit 16 (week 30)							
Sema 0.5 mg / Placebo				15.61		[6.47 ; 37.64]	<.0001
Sema 1.0 mg / Placebo				35.84		[14.72 ; 87.27]	<.0001
HbA1c <7.0% without severe or BG confirmed symptomatic hypoglycaemia and without weight gain							
Estimated odds							
Sema 0.5 mg	132	132	71	1.20	0.22		
Sema 1.0 mg	131	131	88	2.01	0.39		
Placebo	133	133	9	0.07	0.02		
Estimated odds ratio							
Sema 0.5 mg / Placebo				17.90		[8.26 ; 38.78]	<.0001
Sema 1.0 mg / Placebo				29.93		[13.65 ; 65.61]	<.0001

N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval, SE: standard error, ADA: American Diabetes Association, AACE: American Association of Clinical Endocrinologists.
For ADA and AACE targets: Analysis of 'on-treatment without rescue' data. The binary endpoint is analysed using a logistic regression model with treatment, country and stratification variable (HbA1c level at screening [<=8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and the baseline HbA1c value as covariate. Before analysis, missing data are imputed from a mixed model for repeated measures with treatment, country, stratum and baseline value, all nested within visit.
For composite target: Analysis of 'on-treatment without rescue medication' data. The binary endpoint is analysed using a logistic regression model with treatment, country, and stratification variable (HbA1c level at screening [<=8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and the baseline weight and HbA1c values as covariates. Before analysis, missing HbA1c and body weight data are imputed from separate mixed models for repeated measurements with treatment, country, stratum and parameter specific baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.
Source: Table 11-3 Study Report

Weight loss response

Patients achieving a weight loss of ≥5% or ≥10% were identified based on a binary (yes/no) outcome. Both semaglutide doses were statistically superior to placebo, as most patients in the placebo arm did not lose weight.

Table 58 Patients Achieving Weight Loss Targets after 30 Weeks of Treatment – FAS – SUSTAIN 5

	FAS	N	R	Estimate	SE	95% CI	p-value
Body Weight Loss >= 10%							
Estimated odds at visit 16 (week 30)							
Sema 0.5 mg	132	132	12	0.07	0.03		
Sema 1.0 mg	131	131	34	0.30	0.07		
Placebo	133	133	4	0.02	0.01		
Estimated odds ratio at visit 16 (week 30)							
Sema 0.5 mg / Placebo				3.18		[1.05 ; 9.63]	0.0405
Sema 1.0 mg / Placebo				12.80		[4.51 ; 36.33]	<.0001
Body Weight Loss >= 5%							
Estimated odds at visit 16 (week 30)							
Sema 0.5 mg	132	132	55	0.70	0.13		
Sema 1.0 mg	131	131	86	1.98	0.38		
Placebo	133	133	15	0.12	0.03		
Estimated odds ratio at visit 16 (week 30)							
Sema 0.5 mg / Placebo				5.91		[3.08 ; 11.31]	<.0001
Sema 1.0 mg / Placebo				16.59		[8.52 ; 32.30]	<.0001

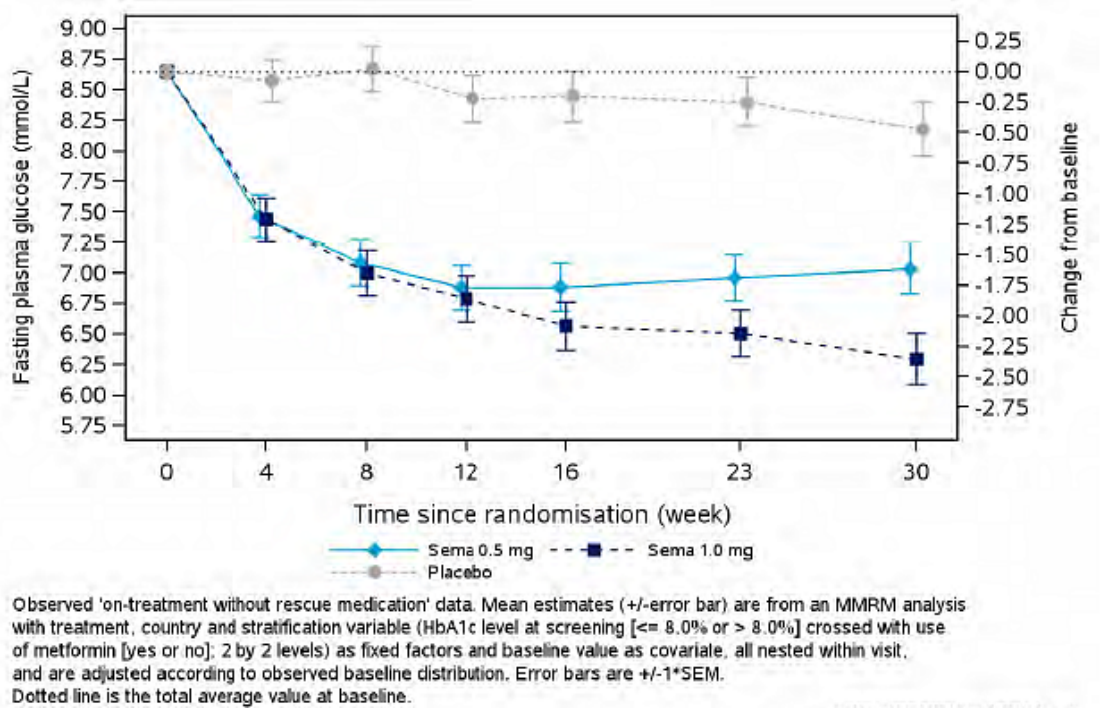
N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval. Analysis of 'on-treatment without rescue' data. The binary endpoint is analysed using a logistic regression model with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no], 2 by 2 levels) as fixed factors and the baseline weight value as covariate. Before analysis, missing data are imputed from a mixed model for repeated measures with treatment, country, stratum and baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.

Source: Table 11-4 Study Report

Fasting plasma glucose

Baseline levels of FPG were similar across the 3 treatment groups with a mean of 155.9 mg/dL. There was a minimal decrease over time in the FPG for the placebo group. The semaglutide 0.5 mg treatment resulted in a decline in FPG over the course of the first 12 weeks, followed by a plateau. The semaglutide 1 mg group followed a similar trend until week 12, and it continued to decrease until week 30 (although the rate of decline was lower). Both semaglutide arms were statistically significant better than placebo at reducing FPG at week 30.

Figure 22 Mean Fasting Plasma Glucose (mmol/L) by Treatment Week – FAS- SUSTAIN 5



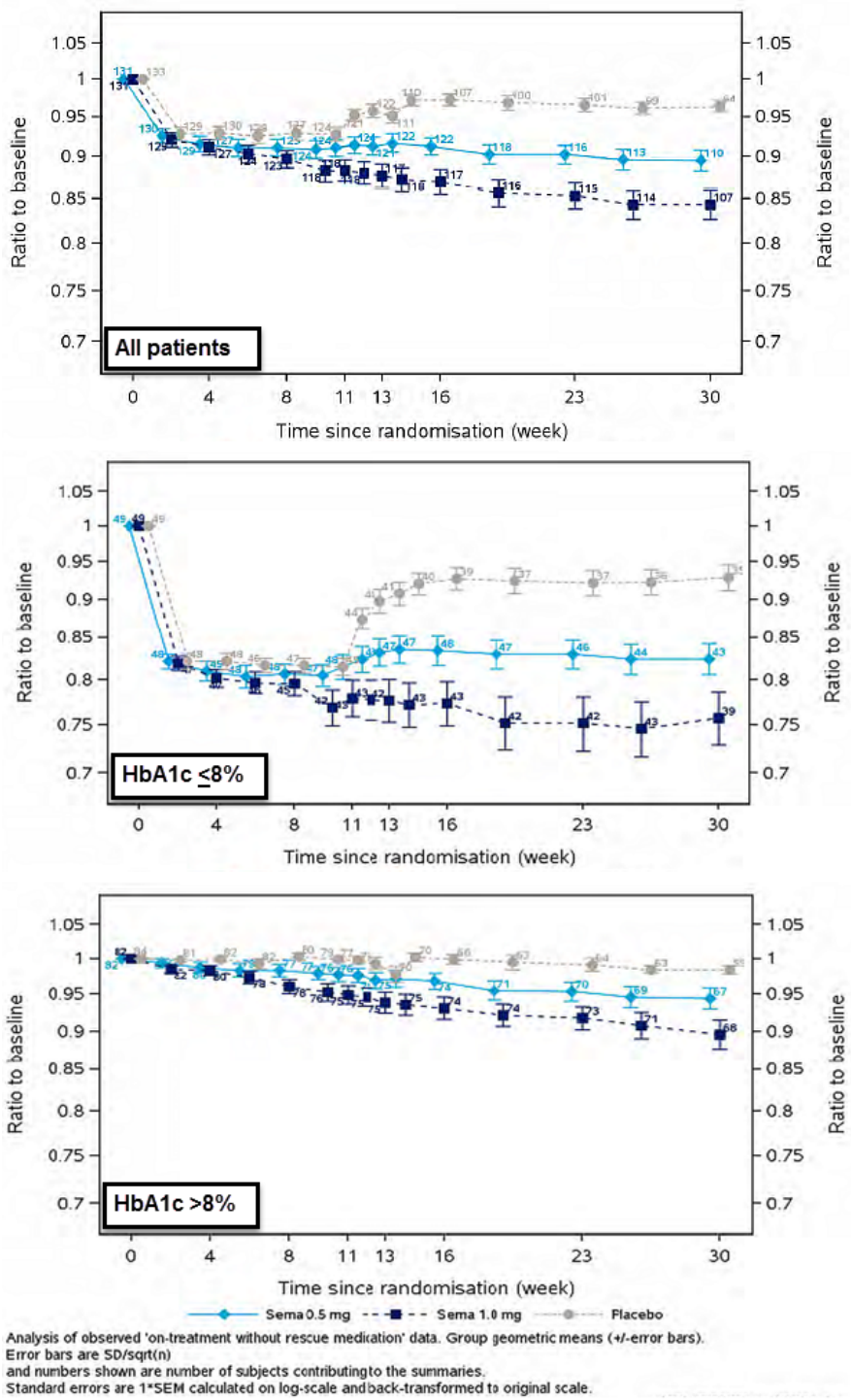
Source: Figure 11-14 Study Report

Basal Insulin dose

The profiles for insulin dose ratio to baseline are presented separately for the overall population, and for patients with HbA1c ≤8% (insulin reduction by 20% was required at the end of the study, followed by gradual up-titration if needed), and >8% (no insulin reduction needed when trial drug started).

Overall there was an initial decrease in the dose of basal insulin in the first 2 weeks, followed by a plateau in the semaglutide 0.5 mg arm, continued slight decrease in the semaglutide 1 mg arm, plateau in placebo, followed by a slight increase between weeks 12-14, then plateau again. Notably the basal insulin dose at the end of the trial (30 weeks) in the placebo group did not quite reach the baseline levels. As evidenced in the figure below, this trend is mostly the result of the basal insulin dose trends in the patients who started the study with a HbA1c ≤8%.

Table 59 Insulin Dose (Geometric Mean) by Treatment Arm and Treatment Week – FAS-SUSTAIN 5



Source: Figures 11-19, 11-20, and 11-21 Study Report

The applicant concludes that semaglutide resulted in a significant reduction in the insulin doses compared to placebo (6% and 12% with semaglutide 0.5 mg and 1 mg respectively).

It is not at all clear that this reduction is clinically meaningful.

Blood pressure

At baseline, blood pressure was similar across the 3 groups with a mean diastolic and systolic blood pressure of 78.99 mmHg and 134.76 mmHg, respectively. Both systolic and diastolic blood pressure demonstrated a downward trend during the 30-week treatment period for all 3 groups. The lowest blood pressure was observed around week 23 in all 3 groups. At week 30, diastolic blood pressure was at similar level for the 3 groups, while systolic blood pressure showed some separation among the 3 treatment groups with semaglutide 1 mg showing the greatest reduction.

Table 60 Blood Pressure Change from Baseline to Week 30 – FAS – SUSTAIN 5

	FAS	N	Estimate	SE	95% CI	p-value
Diastolic BP (mmHg)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	132	111	77.16	0.73		
Sema 1.0 mg	131	108	77.49	0.74		
Placebo	133	95	76.83	0.79		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	132	111	-1.84	0.73		
Sema 1.0 mg	131	108	-1.50	0.74		
Placebo	133	95	-2.17	0.79		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - Placebo			0.33		[-1.80 ; 2.45]	0.7606
Sema 1.0 mg - Placebo			0.66		[-1.47 ; 2.80]	0.5412
Systolic BP (mmHg)						
Mean at visit 16 (week 30)						
Sema 0.5 mg	132	111	130.46	1.26		
Sema 1.0 mg	131	108	127.49	1.27		
Placebo	133	95	133.77	1.34		
Change from baseline at visit 16 (week 30)						
Sema 0.5 mg	132	111	-4.29	1.26		
Sema 1.0 mg	131	108	-7.27	1.27		
Placebo	133	95	-0.99	1.34		
Treatment difference at visit 16 (week 30)						
Sema 0.5 mg - Placebo			-3.31		[-6.92 ; 0.31]	0.0728
Sema 1.0 mg - Placebo			-6.29		[-9.91 ; -2.66]	0.0007

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'on-treatment without rescue medication' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Table 11-17 Study Report

Dose/Dose Response

There did appear to be a dose-response for semaglutide for most endpoints studied, including the primary and confirmatory secondary endpoints.

Durability of Response

The maximum decrease in HbA1c occurred in the first 16 weeks with semaglutide 0.5 mg, and in the first 23 weeks for semaglutide 1 mg, and appeared to persist for the duration of the study for both semaglutide doses.

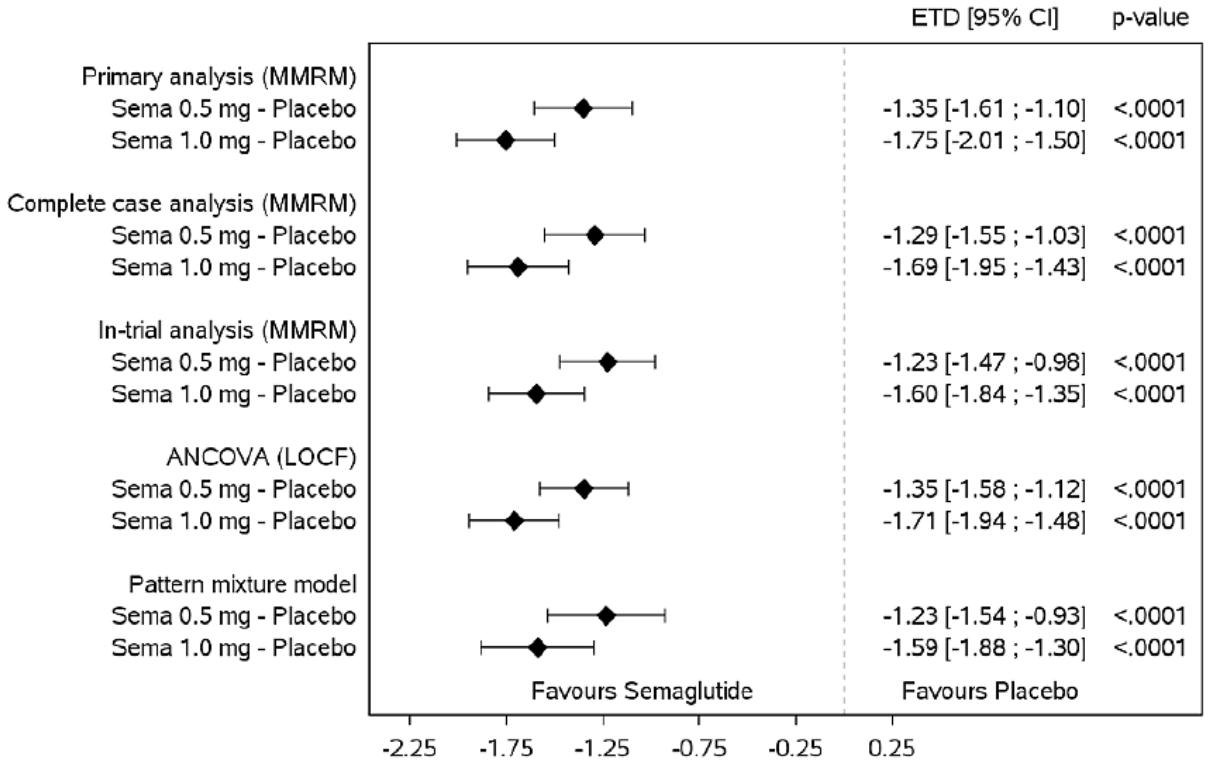
Persistence of Effect

Not applicable, patients not studied after end of trial.

Additional Analyses Conducted on the Individual Trial

The applicant conducted sensitivity analyses for the primary endpoint, and all were supportive of the primary endpoint. The results of these analyses are presented below.

Figure 23 HbA1c (%) - Sensitivity Analyses – FAS – SUSTAIN 5



ETD: Estimated treatment difference. CI: confidence interval. Summary of results from analyses of 'on-treatment without rescue medication' data. Estimated treatment ratios and associated confidence intervals are from mixed model for repeated measurements with treatment, country, stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) and baseline value, all nested within visit.

Source: Figure 11-3 Study Report

6.6. Study 3744 – SUSTAIN 6

6.6.1. Study Design

Overview and Objective

Study Title: A long-term, randomized, double-blind, placebo-controlled, multinational, multi-center trial to evaluate cardiovascular and other long-term outcomes with semaglutide in patients with type 2 diabetes.

Primary objective
To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to placebo in adults with type 2 diabetes. This is done by demonstrating that the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio for semaglutide versus placebo is less than 1.8 when comparing time to first occurrence of a major adverse cardiovascular event (MACE).

The primary objective was changed in global protocol amendment no. 4. The original primary objective read:

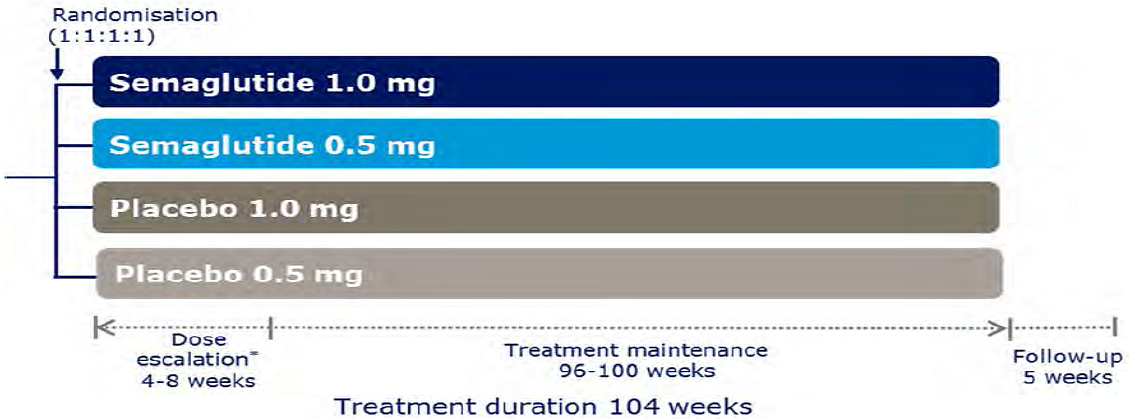
To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to a pooled comparator group (including placebo and active comparators) in adults with type 2 diabetes. This is done by demonstrating that the upper limit of the 95% CI of the hazard ratio for semaglutide versus comparators is less than 1.8 when comparing in a meta-analysis time to first occurrence of a major adverse cardiovascular event (MACE) using all MACEs accrued from all patients included in all of the confirmatory phase 3 clinical trials.

Secondary objectives
To assess the long-term safety and efficacy of semaglutide 0.5 mg and 1 compared to placebo, both added on to standard-of-care, in adults with type 2 diabetes at high risk of cardiovascular events.

Trial Design

This trial was a multi-center, multi-national, randomized, double-blind, parallel-group, controlled trial performed to establish the CV safety and long term outcomes of semaglutide compared to placebo, when added to standard-of-care, in men and women with T2DM at high risk of CV events.

Figure 24 Trial Design SUSTAIN 6



Source: Figure 9-1 Study Report

The trial duration was partly event-driven and as per protocol the trial was to be terminated when the projected number of patients with 3-component EAC-confirmed MACE was at least 122, and at the earliest 104 weeks after the last patient had been randomized. Due to a higher

actual accrual rate of EAC-confirmed MACE than anticipated, the projected number of MACE was reached earlier than predicted. Therefore, each patient was treated for 104 weeks with a post-treatment follow-up period of 5 weeks. Hence, the planned trial duration was 109 weeks per patient.

A total of 3260 adults with T2DM were planned for randomization.

Key Inclusion/Exclusion criteria:
The trial population was patients with T2DM with inadequate glycemic control (HbA1c ≥ 7%) at high CV risk. The trial included patients ≥ 50 years of age at screening with clinical evidence of CV disease and patients ≥ 60 years of age at screening with subclinical evidence of CV disease.

Inclusion criteria include
- Adult patients with T2DM with HbA1C ≥7% at screening
- Age ≥50 at screening and clinical evidence of CV disease ddefined as at least one of the below criteria
    a) prior MI.
    b) prior stroke or TIA.
    c) prior coronary, carotid or peripheral arterial revascularisation.
    d) >50% stenosis on angiography or imaging of coronary, carotid or lower extremity arteries.
    e) history of symptomatic coronary heart disease documented by e.g. positive exercise stress test or any cardiac imaging or unstable angina with ECG changes
    f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging
    g) chronic heart failure NYHA class II-III.
    h) chronic renal impairment, documented (prior to screening) by eGFR <60 mL/min/1.73m2 per MDRD.

OR
- Age ≥60 at screening and subclinical evidence of CV disease defined as meeting at least one of the below criteria:
    i) persistent microalbuminuria (30-299 mg/g) or proteinuria.
    j) hypertension and left ventricular hypertrophy by ECG or imaging.
    k) left ventricular systolic or diastolic dysfunction by imaging.
    l) ankle/brachial index <0.9.

Exclusion criteria include
- Use of GLP-1 RA, or pramlintide within 90 days prior to screening, or DPP-4 30 days prior to screening
- Treatment with insulin other than basal and pre-mixed insulin, within 90 days prior to screening - except for short-term use in connection with intercurrent illness.
- History of chronic pancreatitis, or idiopathic acute pancreatitis

- Acute coronary or cerebro-vascular event within 90 days prior to randomization
- End-stage liver disease
- Calcitonin ≥50 ng/L at screening.
- Personal or family history of MEN2 or familial medullary thyroid carcinoma
- Personal history of non-familial medullary thyroid carcinoma.

For complete inclusion/exclusion criteria please see study report.

Dose selection/study treatments:
Both doses of semalutide were studied. Dose titration was similar to that used in SUSTAIN-1.

Procedures and Schedule:

Patients were scheduled to attend the site once every month during the first 6 months and every 3 months during the rest of the trial, and to have monthly phone contacts with the investigator between the site visits.

Table 61 Study Flowchart SUSTAIN 6

Periods	Screen	Rand	Treatment period[12]																	End-of-treatment[1]	Follow-up[1]
Visit (V) **Phone (P)**	V 1	V 2	V 3	V 4	V 5	V 6	P 6x	V 7	P 8	V 9	P 10	V 11	P 12	V 13	P 14	V 15	P 16	V 17	P 18	V 25	V 26
Time of visit (weeks)	-2	0	2	4	8	16	23	30	38	44	50	56	62	68	74	80	86	92	98	104	109
Visit window (days)			± 3	± 3	± 3	± 3	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 14	± 7	+ 7
Informed consent	x																				
In/exclusion criteria	x	x																			
Randomisation		x[2]																			
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant ill & medical history	x																				
Concomitant med	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																				
Diabetes history	x																				
History of CV disease	x																				
History of gallbladder disease	x																				
Smoking habits	x																				
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundos copy /- photography		x[3]										x[4]								x[4]	
ECG		x						x				x				x				x	x
Physical examination	x																			x	
Blood pressure	x	x	x	x	x	x		x		x		x		x		x		x		x	
Anti-semaglutide antibodies		x						x		x		x				x				x[5]	x[5]
HbA_{1c}	x	x			x	x		x		x		x		x		x		x		x	
Fasting plasma glucose		x	x	x	x	x		x		x		x		x		x		x		x	
Fasting insulin + fasting pro-insulin		x						x				x				x				x	
Lipids		x						x		x		x				x				x	
Biochemistry		x	x	x	x	x		x		x		x		x		x		x		x	
Creatinine[6]	x[6]	x	x	x	x	x		x		x		x		x		x		x		x	
Haematology		x	x	x	x	x		x		x		x		x		x		x		x	
Calcitonin	x	x				x		x		x		x				x				x[5,7]	
Semaglutide PK[8]			x	x	x	x		x				x								x[5]	
Pregnancy test[9]	x																			x	
Urinalysis		x				x		x		x		x				x				x	
Insulin adjustment[10]			x	x	x	x															
SMPG[10]			x	x	x	x															
Drug accountability					x	x		x		x		x		x		x		x		x	
IV/WRS call	x	x			x	x		x		x		x		x		x		x		x	
Hand out DFU[11]		x			x	x		x		x		x		x		x		x		x	
Instruct in trial product use	x	x																			

[1] V25/End-of-treatment and V26/Follow-up are applicable for all randomized patients.
[2] Randomisation should take place within 2 weeks after V1/Screening.
[3] Funduscopy/fundus photography should be performed at V2 or within 90 days prior to V2 if no deterioration in visual function since last assessment.
[4] Funduscopy/fundus photography should be performed at Visit 11 and 25 or within 14 days prior to those visits.
[5] Not applicable if taken at premature discontinuation visit(s).
[6] Sampling for creatinine only, including eGFR calculation.
[7] If the last calcitonin value taken in the trial is ≥10 ng/L patient should preferably be referred to a thyroid specialist for further evaluation.
[8] Only applicable for patients included in the pharmacokinetic (PK) subgroup.
[9] Urine-stick pregnancy test should be performed at site at any time during the trial if a menstrual period is missed, or as required by local law.
[10] FOR PATIENTS TREATED WITH INSULIN AT THE TIME OF RANDOMISATION: In the initial 12 weeks after randomisation, patient will have the insulin dose adjusted based on 3 consecutive pre-breakfast (fasting overnight) SMPG values, preferably measured 3 consecutive days before each weekly phone contact/clinic visit. Therefore, the patient must be contacted by phone once weekly in the initial 12 weeks in the weeks where no clinic visit is planned.

[11] Written DFU must be given to the patient at visit 2. At subsequent dispensing visits DFU can be given orally and/or in writing as deemed necessary.
[12] Visits 19–24 were obsolete due to termination of trial after 109 weeks for each randomized patient, and visit 25 was rescheduled to take place after 104 weeks
Source: Modified from Table 9-5 Study Report

Table 62 Additional Visits SUSTAIN 6

Periods		End of Treatment[12] premature discontinuation	Follow Up[12] premature discontinuation
Visit (V) at site Phone (P) contacts		V25A	V26A
Time of visit (weeks)		Shortly after discontinuation of trial product	5 weeks after discontinuation of trial product
Visit window (days)		+7	+7
Withdrawal criteria		x	x
Concomitant medication		x	x
Adverse events		x	x
Hypoglycaemic episodes		x	x
ECG		x	x
Fundoscopy/fundus photography		x[13]	
Physical exam		x	
Blood pressure		x	
Pulse		x	
Body weight		x	
Waist circumference		x	
BLOOD SAMPLINGS			
Anti-semaglutide antibodies		x	x
HbA_{1c}		x	
Fasting plasma glucose		x	
Fasting insulin + fasting pro-insulin		x	
Lipids		x	
Biochemistry		x	
Creatinine (including eGFR)		x	
Haematology		x	
Calcitonin		x	
Semaglutide PK[14]		x	
Urinalysis		x	
Drug accountability		x	
IV/WRS call		x	
REMINDERS			
Dispense and/or collect diary		x	x
Attend visit fasting		x	x

[12] Subjects discontinuing trial drug prematurely will be asked to continue visit schedule and two additional visits; **End of Treatment-premature discontinuation** which should be scheduled shortly after discontinuation of trial drug and **Follow Up-premature discontinuation** which should be scheduled 5 weeks after discontinuation of trial drug.
[13] In case of premature termination of trial drug, fundoscopy/fundus photography should be performed at Visit 25A. It is acceptable to perform the fundoscopy/fundus photography after Visit 25A if the results are available at Visit 26A.
[14] Only applicable for subjects included in the PK subgroup.

Source: Excerpted from Table 9-5 Study Report

CV events used for the evaluation of the primary endpoint were pre-defined as medical events of special interest (MESIs). CV events related to the composite CV endpoints underwent event adjudication by the EAC.

All MESIs are outlined in the table below. Select MESIs were independently adjudicated in this study, including the components of the primary endpoint. MESIs, regardless of seriousness, were to be reported using both the AE form, SIF and the MESI form. The MESI form was tailored to collect specific information related to the individual MESIs. For MESIs qualifying for event adjudication, a source data collection form (event adjudication form) was also to be completed in the eCRF.

To avoid introducing bias in the conduct of the trial, Novo Nordisk exempted cases/AEs that were part of the MACE endpoints from un-blinding during regulatory reporting, even though the cases fulfilled the definition of SUSARs.

Events were evaluated based on pre-defined diagnostic criteria in accordance with the FDA Draft Definitions for Testing November 9, 2012- "Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials"

Table 63 Medical Events of Special Interest SUSTAIN 6

Event	Sent for adjudication
Fatal events (if not covered by another MESI)	X
ACS (myocardial infarction, unstable angina requiring hospitalisation)	X
Cerebrovascular events (stroke, transient ischemic attack)	X
Coronary revascularisation procedure	X
Peripheral arterial revascularisation procedure	
Hospitalisation for heart failure (Heart failure requiring hospital admission)	X
Nephropathy[a]	X
Diabetic retinopathy complications[b]	X
Cardiac arrhytmia	
Neoplasm, malignant and benign (excluding thyroid neoplasm)	X
Thyroid disease (including thyroid neoplasm or resulting in thyroidectomy)	X
Pancreatitis or clinical suspicion of pancreatitis	X
Acute gallstone disease	
Acute renal failure	
Severe episodes of hypoglycaemia	
Immunogenicity events (allergic reactions, immune complex disease, or anti-semaglutide antibody formation)	
Suspected transmission of an infectious agent via a trial product	
AEs leading to treatment discontinuation	
Medication errors concerning trial products • Administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Administration of a high dose with the intention to cause harm (e.g., suicide attempt). • Administration of an accidental overdose, defined as a higher dose than 1.1 mg/week (±24 hours), as 1.1 mg is the highest dose the subject will be able to take in 1 injection.	

Note: [a] New onset of persistent macroalbuminuria (>300 mg/g/24hrs), or persistent doubling of serum creatinine level and creatinine clearance per MDRD ≤45 mL/min/1.73m^2, or the continuous renal-replacement therapy (in the absence of an acute reversible cause), or death due to renal disease. [b] Need for retinal photocoagulation, or need for treatment with intravitreal agents, or vitreous haemorrhage, or diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible. [c] Will only be adjudicated in cases of thyroid neoplasm or resulting in thyroidectomy.

Abbreviations: ACS: acute coronary syndrome; AE: adverse event; MESI: medical events of special interest.

Source: Table 9-6 Study Report

Table 64 Adjudicated Adverse Events SUSTAIN 6

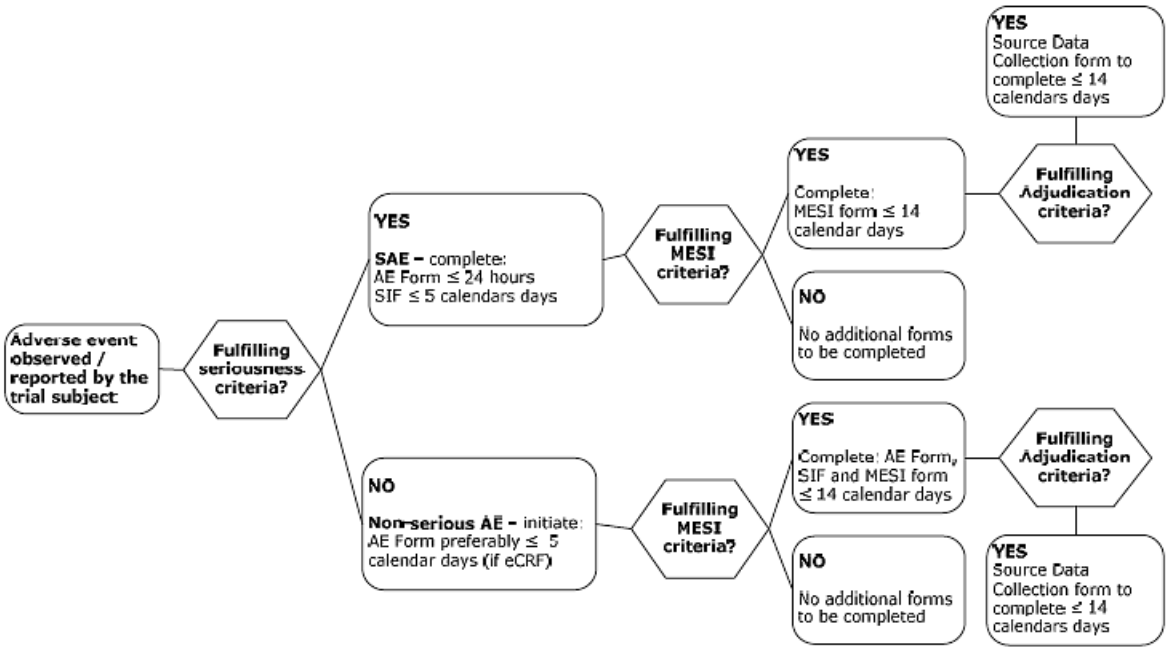
Adjudicated events	Speciality of assigned adjudicator
Fatal events • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	Cardiologist/neurologist[a]
ACS • MI, i.e., spontaneous MI, percutaneous coronary intervention related MI, coronary artery bypass graft surgery related MI and silent MI. • Unstable angina requiring hospitalisation.	Cardiologist[b]
Cerebrovascular event • Stroke • Transient ischemic attack	Neurologist
Coronary revascularisation procedure	Cardiologist
Heart failure requiring hospital admission	Cardiologist
Nephropathy	Nephrologists
Diabetic retinopathy complications	Ophthalmologists
Neoplasm (excluding thyroid neoplasm) • Malignant neoplasm • *In situ* neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behaviour	Oncologist
Thyroid disease (including thyroid neoplasm or resulting in thyroidectomy)	Endocrinologist and oncologist[c]
Pancreatitis or clinical symptoms leading to suspicion of pancreatitis • Acute pancreatitis • Chronic pancreatitis	Gastroenterologist

Notes: Based on information in EAC Charter (Appendix 16.1.13). [a] Fatal events were submitted to 2 neurologists if related to a neurological event and to 2 cardiologists for all other events. [b] Silent MI events (not reported by sites but identified via ECG screening) were submitted directly to full committee and reviewed by 3 cardiologists including the EAC chair to achieve consensus adjudication. [c] Thyroid Neoplasm/Disease events were submitted to 1 endocrinologist and 1 oncologist.

Abbreviations: ACS: acute coronary syndrome; EAC: event adjudication committee; ECG: electrocardiogram; MI: myocardial infarction.

Source: Table 9-7 Study Report

Figure 25 Initial Reporting of Adverse Events SUSTAIN 6



Source: Figure 9-2 study report

Fundoscopy/fundus photography

Fundoscopy/fundus photography was to be performed at visit 2 or within 90 days prior to visit 2 if the fundoscopy/fundus photography had been performed for any reason unrelated to this trial. In this case the fundoscopy/fundus photography did not need to be repeated, unless visual function had worsened since the last examination. It was to be documented in the medical records that the reason for performing the fundoscopy/fundus photography was not related to this trial. Furthermore, fundoscopy/fundus photography was to be performed at visits 11, 19 and 25. In case of premature discontinuation of trial product, fundoscopy/fundus photography was to be performed at visit 25A. It was acceptable to perform the fundoscopy/fundus photography after visit 25A provided the results were available at visit 26A.

Fundoscopy/fundus photography was to be performed by the investigator, a local ophthalmologist or an optometrist according to local practice. Dilation was not a requirement. Result of the fundoscopy/fundus photography was to be interpreted locally by the investigator. The interpretation followed the categories:

- Normal.
- Abnormal, not clinically significant.
- Abnormal, clinically significant.

Study Endpoints

The primary endpoint was:

- Time from randomization to first occurrence of a MACE, defined as CV death, non-fatal MI, or non-fatal stroke.

The primary endpoint was the only endpoint controlled for type 1 error.

Supportive secondary endpoints addressing the primary objective:

- Time from randomization to first occurrence of an expanded composite CV outcome, defined as either MACE, revascularisation (coronary and peripheral), unstable angina requiring hospitalisation or hospitalisation for heart failure.
- Time from randomization to each individual component of the expanded composite CV outcome.
- Time from randomization to first occurrence of all-cause death, non-fatal MI, or non-fatal stroke.

Confirmatory secondary endpoints addressing the secondary objective:

- Change from baseline to week 104 in body weight (kg).
- Change from baseline to week 30 in HbA1c for patients on premix insulin at baseline.
- Change from baseline to week 30 in HbA1c for patients on SU monotherapy at baseline.

Supportive secondary endpoints addressing the secondary objective:

- Occurrence of SAEs of cardiac arrhythmia and conduction disturbances.
- Time from randomisation to first occurrence of either a retinal photocoagulation, or treatment with intravitreal agents, or vitreous haemorrhage, or diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible).
- Time from randomisation to first occurrence of new or worsening nephropathy, defined as new onset of persistent macroalbuminuria (>300 mg/g), or persistent doubling of serum creatinine level and creatinine clearance per MDRD ≤45 mL/min/1.73m2, or the continuous renalreplacement therapy (in the absence of an acute reversible cause), or death due to renal disease).
- Change from baseline to last assessment during the treatment period in:
  – body weight and waist circumference.
  – HbA1c, FPG, fasting plasma insulin, HOMA-B, and pro-insulin to insulin ratio.
  – lipid profile, including total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and FFAs.
  – systolic and diastolic BP and pulse.
  – UACR.
- Proportion of patients achieving ≥5% and ≥10% body weight loss.
- Proportion of patients requiring addition of glucose-lowering medication.
- Incidence of hypoglycemia.
- Incidence of AEs and the following MESIs:

– neoplasm (malignant and benign).
– pancreatitis, or clinical suspicion of pancreatitis.
– acute gallstone disease (biliary colic or acute cholecystitis).
– thyroid disease.
– cardiac arrhythmia (specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement).
– acute renal failure.
– severe hypoglycemic episode.
– immunogenicity event (allergic reactions, immune-complex disease and lack of efficacy).
– medication errors concerning trial products.
– suspected transmission of an infectious agent via a trial product.
– AEs leading to treatment discontinuation.

- Laboratory parameters: haematology and biochemistry (including amylase and lipase), hormone (calcitonin) and urinalysis.
- Anti-semaglutide antibodies.
- Changes from baseline in ECG.
- Semaglutide plasma concentration in a subset of the population (N= approximately 60 patients with severe renal impairment (GFR value 15-29 mL/min/1.73m2), N= approximately 180 patients without severe renal impairment).
- Change from baseline to last assessment during the treatment period in SF-36v2TM PRO scores.

Some of the many secondary endpoints will be addressed in the safety section, and I will not discuss them under efficacy. The only secondary endpoint that I will discuss is the change in HbA1c from baseline to last assessment during the treatment period, as this may affect the interpretation of the primary endpoint.

Statistical Analysis Plan

Initially, a meta-analysis of all phase 3 trials was to be performed for MACE. However, following advice from the FDA, MACE analyses were based on this trial only.

The sample size calculation for this trial was an event driven calculation that included considerations from the planned analysis of MACEs and specific assumptions for the event rates in the “high risk” population included in this trial.

The primary objective was to confirm that semaglutide treatment did not excessively increase the CV risk as compared to placebo. This was to be done by demonstrating that the upper bound of the two-sided 95% CI of the HR for semaglutide versus placebo was less than 1.8 for

time to first occurrence of MACE. Assuming the same population MACE risk for the semaglutide and placebo groups (i.e., the population HR equals 1), a total minimum of 122 events were needed in order to have at least 90% power to ascertain that the upper two-sided 95% confidence limit for the HR was less than 1.8.

Based on further assumptions regarding the expected number of events (Table 65), the total sample size required in order to obtain 122 events in this trial was set to 3260, i.e. 815 patients were to be randomized to each of the 2 semaglutide dose arms and 1630 patients were to be randomized to placebo. The actual calculation was based on a mean time in the trial of 2.10 years, an event rate of 1.98% and a lost to follow up rate of maximum 10.0%.

Table 65 Assumptions Regarding Expected Number of Events SUSTAIN 6

Assumption	Comments
A population MACE event rate of approximately 2.0% per subject per year for subjects included in this trial	Based on experience from previous outcome trials in high risk populations, event rates are difficult to predict. Preliminary data on file from the on-going LEADER® trial (EX2211-3748), with very similar inclusion/exclusion criteria regarding CV risk, indicate that an event rate of 2% could be justified. The chosen event rate was judged as being conservative but not unrealistically low.
Subjects not lost to follow-up will have a mean time in the trial of 2.1 years	This assumption was based on an anticipated recruitment period of 9 months and a recruitment pattern similar to that observed in the LEADER® trial where 16%, 51% and 100%, were recruited after one, two and three thirds, respectively, of the recruitment period (~3, 6 and 9 months in this trial). In the assumption it had furthermore been taken into account that after first patient had been in the trial for 2.5 years a gradual close down of subjects might be initiated provided they had been in the trial for at least 2 years.
A maximum lost to follow-up rate of 10% (uniformly distributed between the semaglutide and placebo arms)	Assumption seemed to be conservative as compared to the preliminary lost to follow-up rate in the LEADER® trial.

Abbreviations: CV: cardiovascular; MACE: major adverse cardiovascular event.

Source: Table 9-11 Study Report

The following analysis sets were defined in the protocol:

- FAS: includes all randomized patients. The statistical evaluation of the FAS follows the ITT principle and patients contribute to the analyses 'as randomized'
- SAS: Includes all patients exposed to at least one dose of the trial product. The patients contribute to analyses 'as treated'

Before data were released for statistical analysis, a blinded review of all data was performed to identify PDs that may potentially have affected the results. Furthermore, extreme values and outliers were identified by the statistician during programming and data review, according to the ICH-E9 guideline, using a fake randomization.

The decision to exclude any patient or observation from the statistical analysis was the joint responsibility of the clinical study group. The patients or observations to be excluded and the reason for their exclusion were to be documented and signed by the relevant parties, prior to breaking the randomisation code and database release

Two observation periods were defined as follows:

- 'In-trial' observation period: the time-period from randomization until the follow-up visit at end-of-trial, unless the patient withdrew consent, was considered lost-to-follow-up or died. Patients contributed with data regardless of treatment adherence and analyses based on the in-trial observation period include data collected at or after the date of randomisation and up until and including the first of the following dates:
  - date of follow-up visit for patients who complete the trial by attendance of this visit.
  - date of death for patients who complete the trial by death during trial.
  - date of withdrawal for patients who withdraw IC.
  - date of last patient-investigator contact for patients who were lost to follow-up.
- 'On treatment' observation period: subset of the 'in trial' period. It represents the time period where the patients were considerd exposed to trial product.

Calculation of the time to event and censoring

For time to event endpoints, patients that did not experience an event were censored at the patient specific end-dates defined by the observation periods. This implies that the censoring time was the same across different time to event endpoints within an observation period. Time to event or censoring was calculated as time from the randomization date (as registered in the IV/WRS system) in an analysis based on the in-trial observation period and from the date of first dose of trial product in an analysis based on the on-treatment observation period.

Trial completers were defined as the patients that either attended the last follow-up visit, or who died while considered an active trial participant.

Treatment completers were defined as patients who did not permanently discontinue treatment prematurely.

A patient was considered lost to follow-up if the patient did not complete the trial and did not withdraw consent.

Patients, for which it was not possible to obtain vital status, were considered lost to follow-up for vital status.

The blinding of the randomized treatments was maintained until the database had been released for statistical analysis. No interim analyses or other analyses of unmasked or between group data were performed before the database was locked, with the exception of those highly confidential analyses performed by an external independent statistician to support the deliberations of the independent DMC or in direct response to a recommendation by the DMC.

Statistical analyses

The significance level used in all statistical analyses was 5% (two-sided).

In order to preserve the overall type 1 error, the confirmatory hypothesis of non-inferiority for the primary endpoint and the superiority hypotheses for the 3 confirmatory secondary endpoints were evaluated hierarchically according to the sequence below, starting with the first. In this testing sequence it was necessary to fulfil the test criteria, which was to reject the corresponding null hypothesis in order to go to the next step. If the corresponding null hypothesis was not rejected, the testing was to be stopped and no further hypotheses were to be tested.

The pre-specified hierarchical testing procedure was:

- Non-inferiority of semaglutide versus placebo for the primary endpoint.
- Superiority of semaglutide 1 mg versus placebo in change in body weight at week 104.
- Superiority of semaglutide 0.5 mg versus placebo in change in body weight at week 104.
- Superiority of semaglutide 1 mg versus placebo in change in HbA1c at week 30 for patients on premix insulin at baseline.
- Superiority of semaglutide 0.5 mg versus placebo in change in HbA1c at week 30 for patients on premix insulin at baseline.
- Superiority of semaglutide 1 mg versus placebo in change in HbA1c at week 30 for patients on SU monotherapy at baseline.
- Superiority of semaglutide 0.5 mg versus placebo in change in HbA1c at week 30 for patients on SU monotherapy at baseline.

The primary analysis was based on the FAS using the in-trial observation period.

Non-inferiority of semaglutide versus placebo was considered to be confirmed if the upper limit of the two-sided 95% CI for the HR was below 1.8

For the three confirmatory endpoints, 2 hypotheses were evaluated:

- Superiority for semaglutide 1 mg versus placebo.
- Superiority for semaglutide 0.5 mg versus placebo.

Protocol Amendments

There were 18 substantial amendments to the protocol, 2 global and 16 local amendments (Table 66).

APPEARS THIS WAY ON ORIGINAL

Table 66 Protocol Amendments SUSTAIN 6

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
1	23-Sep-2012	Before	Israel	All relevant sections regarding collection of blood sample for genetic testing in the protocol were deleted, due to long approval process for genetic testing in Israel.
2	17-Sep-2012	Before	Argentina	To reflect requirements from HA, it was specified that for Argentina, all diabetic treatments throughout the trial were covered by Novo Nordisk Pharma Argentina S.A.
3	13-Nov-2012	Before	United Kingdom	Following request from the MHRA it was specified that for women of childbearing potential two effective forms of contraception were to be used with their partners.
4	07-May-2013	After	Global	To accommodate a request from FDA and changes in FDA requirements the primary objective, the statistical section and other relevant sections were updated accordingly (see Section 9.8.2). Additional minor updates were made.
5	06-Mar-2013	After	Denmark	Change in PI at 1 site.
6	13-Mar-2013	After	Argentina	Information that trial product should be discontinued in case of occurrence of a SAE suspected to be related to the trial product was added as requested by HA.
7	01-Apr-2013	After	Turkey	Change in PI at 2 sites, addition of 2 new sites.
8	NA	NA	NA	Not in use, cancelled.
9	NA	NA	NA	Not in use, cancelled.
10	13-May-2013	After	Bulgaria	Addition of 1 new site.
11	07-Oct-2013	After	Israel	Dietary counselling was added as part of the retention strategy in Israel.
12	04-Nov-2013	After	Brazil	To reflect requirements from HA, changes in protocol Section 8.4 Laboratory Assessments and Section 8.7.6 Thyroidectomy, tissue sample and genetic testing were made.
13	13-May-2014	After	Global	The definition of hypoglycaemia was updated incl. related endpoints, associated statistical analysis and how to report (See Section 9.8.2). Additional minor updates for clarification.
14	18-Feb-2014	After	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.
15	04-Nov-2014	After	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.
16	29-Jan-2015	After	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.
17	04-Aug-2015	After	Bulgaria	New edition of patient chronicle, thank you letter and leaflet on maintaining good health to be submitted to HA/EC locally.
18	14-Oct-2015	After	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.

Note: Amendments in this table includes substantial amendments (Appendix 16.1.1).
Abbreviations: EC = ethics committee, FDA = US Food and Drug Administration, FSFV = first subject first visit, HA = health authorities, MHRA = Medicines and HealthCare products Regulatory Agency, NA = not applicable, PI = principal investigator, SAE = serious adverse event.

Source: Table 9-12 study report

In addition, there were 11 non-substantial amendments to the protocol, these concerned changes to protocol attachment II, updates to trial staff and sites, and contact information.

Data Quality and Integrity: Sponsor's Assurance

The trial was monitored by Novo Nordisk by on-site visits, telephone calls and regular inspection of the eCRFs with sufficient frequency (the intervals between visits did not exceed 8 weeks); for sites that had had LSLV, remote monitoring was allowed instead of on-site visits.

There were 53 internal audits and 11 external inspections performed for the trial. During a system audit, a number of non-compliances with GCP were identified at a site in Argentina (site 122).

6.6.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with ICH GCP.

Financial Disclosure

Of the total of 1285 investigators, 8 were NN employees, 29 had financial disclosure information, and one had financial disclosable information with certification of due diligence.

Patient Disposition

This trial followed the intention to treat (ITT) principle and extensive efforts were thus made to keep patients in the trial. Patients were encouraged to stay in the trial irrespective of lack of adherence to randomized treatment, lack of adherence to visit schedule, missing assessments, trial product discontinuation due to AEs, unwillingness to cope with injection regimen, development of co-morbidities or clinical outcomes. Patients randomized in error were not withdrawn from the trial, but were generally asked to discontinue the treatment with trial product.

Of the 4346 patients screened, 1049 patients were screening failures. Most screening failures (668/1049) were due to patients not meeting the inclusion criterion of an HbA1c ≥7% at screening. For 8 patients, the screening failure related to that IC was not obtained before any trialrelated activities (inclusion criterion 1). Patients not meeting the inclusion criteria of being ≥50 years of age at screening and clinical evidence of CV disease accounted for 86 screening failures. The exclusion criterion number 23 regarding any other factor likely to limit protocol compliance or reporting of AE at the discretion of the investigator accounted for 53 screening failures. For 16 patients, an acute coronary or cerebro-vascular event had occurred within the previous 14 days from visit 2 (exclusion criterion 7). Malignant neoplasm requiring

chemotherapy, surgery, radiation or palliative therapy had occurred for 20 patients in the previous 5 years (inclusion criterion 13). A total of 4 patients were screening failures as they simultaneously participated in any other clinical trial of an investigational agent. There were 3 patients with screening failures due to exclusion criterion number 24 relating to a female of childbearing potential who is pregnant, breast-feeding or intend to become pregnant or is not using adequate contraceptive methods. There were 151 screening failures categorized as 'other'.

3297 patients were randomized (1:1:1:1) to receive semaglutide 0.5 mg (826 patients), semaglutide 1 mg (822 patients), placebo 0.5 mg (824 patients) or placebo 1.0 mg (825 patients). Of these, 3286 patients (99.7%) were exposed to trial product, 1642 patients were exposed to semaglutide and 1644 patients were exposed to placebo.

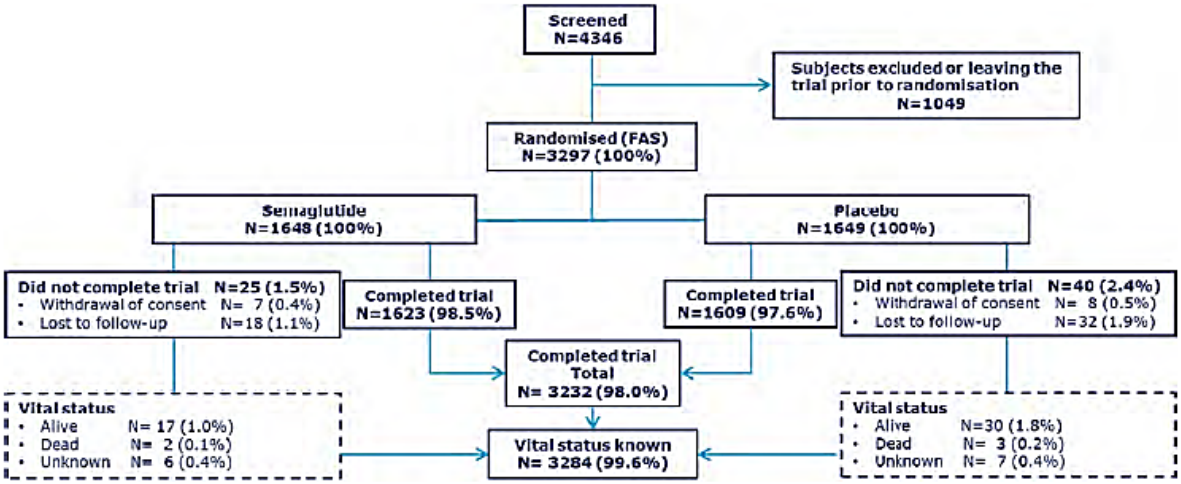
Trial completers were defined as patients that either attended the last follow-up visit (visit 26) or who died while considered active trial participants. According to this definition, 3232 patients (98.0%) completed the trial, with similar distributions between the semaglutide and placebo groups.

Treatment completers were defined as patients that did not permanently discontinue treatment prematurely. There were 2636 patients (80.0%) that completed the treatment, slightly fewer with semaglutide compared with placebo. Of the approximately 20% of patients that permanently discontinued treatment prematurely in this trial, the reason GI tolerability was more frequent with semaglutide 0.5 mg (5.7%) and 1.0 mg (9.4%) compared with placebo 0.5 mg (1.2%) and 1.0 mg (1.0%). Trial fatigue, suspicion of placebo, and introduction of disallowed medication was more frequent reasons for premature treatment discontinuation with placebo compared with semaglutide. The reasons Other (5.7%), and AEs other than GI (5.6%) were among the most prevalent reasons for premature treatment discontinuation, but these were similarly distributed between the semaglutide and placebo groups.

There were 7 patients with semaglutide and 8 patients with placebo that withdrew from the trial in relation to or after treatment discontinuation. There were 18 patients with semaglutide and 32 patients with placebo that were lost to follow-up. A patient was considered lost to follow-up if the patient did not complete the trial and did not withdraw consent. Attempts to obtain vital status were done up until DBL. Patients, for which vital status was not obtained in this way, were considered lost to follow-up for vital status. Thus, of the 3297 patients randomized in this trial, the last known vital status was unknown for a total of 13 patients; 6 with semaglutide and 7 with placeb

Appears this way on original

Figure 26 Patient Disposition Diagram SUSTAIN 6



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

Source: Figure 10-1 study report

Table 67 Patient Disposition – All Randomized Patients – SUSTAIN 6

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo 0.5 mg N (%)	Placebo 1.0 mg N (%)
Full analysis set (all randomised subjects)	826 (100.0%)	822 (100.0%)	824 (100.0%)	825 (100.0%)
Safety analysis set (all exposed subjects)	823 (99.6%)	819 (99.6%)	819 (99.4%)	825 (100.0%)
Treatment completers [1]	662 (80.1%)	635 (77.3%)	673 (81.7%)	666 (80.7%)
Trial completers	812 (98.3%)	811 (98.7%)	804 (97.6%)	805 (97.6%)
Subjects who died during the trial	30 (3.6%)	32 (3.9%)	32 (3.9%)	28 (3.4%)
Subjects who attended visit 26	782 (94.7%)	779 (94.8%)	772 (93.7%)	777 (94.2%)
Premature treatment discontinuers [2]	164 (19.9%)	186 (22.6%)	151 (18.3%)	159 (19.3%)
Gastrointestinal tolerability	47 (5.7%)	77 (9.4%)	10 (1.2%)	8 (1.0%)
Withdrawal of informed consent	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Adverse event other than related to gastrointestinal tolerability	51 (6.2%)	41 (5.0%)	38 (4.6%)	55 (6.7%)
Introduction of disallowed medication	3 (0.4%)	3 (0.4%)	8 (1.0%)	8 (1.0%)
Suspicion of placebo (without introduction of disallowed medication)	3 (0.4%)	3 (0.4%)	15 (1.8%)	10 (1.2%)
Randomised in error	12 (1.5%)	13 (1.6%)	16 (1.9%)	6 (0.7%)
Resistance to injections	2 (0.2%)		2 (0.2%)	
Trial fatigue	5 (0.6%)	5 (0.6%)	15 (1.8%)	11 (1.3%)
Other	40 (4.8%)	43 (5.2%)	46 (5.6%)	60 (7.3%)
Withdrawals in relation to or after treatment discontinuation [3]	2 (0.2%)	5 (0.6%)	4 (0.5%)	4 (0.5%)
Last known vital status for subjects not completing the trial	14 (1.7%)	11 (1.3%)	20 (2.4%)	20 (2.4%)
Subjects lost to follow-up [4]	12 (1.5%)	6 (0.7%)	16 (1.9%)	16 (1.9%)
Alive	9 (1.1%)	5 (0.6%)	14 (1.7%)	12 (1.5%)
Dead	1 (0.1%)			2 (0.2%)
Unknown	2 (0.2%)	1 (0.1%)	2 (0.2%)	2 (0.2%)
Withdrawals	2 (0.2%)	5 (0.6%)	4 (0.5%)	4 (0.5%)
Alive	1 (0.1%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Dead		1 (0.1%)	1 (0.1%)	
Unknown	1 (0.1%)	2 (0.2%)	1 (0.1%)	2 (0.2%)

N: Number of subjects, %: Percentages are based on randomised subjects, Visit 26: Follow-up visit
[1]: Subjects who were exposed, did not discontinue treatment prematurely, who did not withdraw from trial and who were not lost to follow-up before the last treatment visit. [2]: Subjects who were not exposed, but had given a reason for premature treatment discontinuation are also included. Reason is based on the primary reason for treatment discontinuation according to the premature discontinuation of trial product form or the end-of-trial form. [3] Covers all withdrawals. For some, withdrawal was also the reason for premature treatment discontinuation, and they are then also counted under [2]. Note that withdrawal implies treatment discontinuation, and this is the reason reported if no other reason for treatment discontinuation is given.
[4]: Subjects who did not complete the trial and did not withdraw from trial.

Source: Table 10-1 study report

The proportion of patients that permanently discontinued treatment prematurely for any reason was larger with pooled semaglutide compared with pooled placebo, and was larger with semaglutide 1 mg compared with semaglutide 0.5 mg. The treatment discontinuation with semaglutide was driven by AEs, mainly GI AEs. The proportion of patients that discontinued treatment prematurely due to withdrawal was low (<0.2%) and was similar across the four treatment groups.

There were 10 patients for which the actual treatment differed from the planned treatment, 5 patients with semaglutide and 5 patients with placebo. The changes were related to a different dose within treatment type, thus no patients received a different treatment type than planned.

Of the 308 patients that were stratified with an eGFR≤30 mL/min/1.73m2, 206 had an actual eGFR value >30 mL/min/1.73m2 and were thus incorrectly stratified. Of the 2989 patients that were stratified with an eGFR>30 mL/min/1.73m2, 5 patients had an actual eGFR value ≤30. mL/min/1.73m2.

Protocol Violations/Deviations

Protocol deviations

PDs were categorized as important/non-important and reported into different categories according to a set of pre-specified categories and subcategories. Important PDs were considered those that could significantly impact the completeness, accuracy and/or reliability of the trial data or that could significantly affect the patient's rights, safety or well-being.

In total, 5291 important PDs were closed before DBL. The important PDs were represented by 4 trial level PDs, 5 country level PDs, 649 site level PDs and 4633 patient level PDs. Overall, the important PDs were considered not to have an impact on trial conduct, patient safety or data interpretation.

Important PDs at trial level

Of the 4important PDs were reported; 1 reported as 'assessment deviation' (800 blood samples drawn fasting but after trial product administration) and 3 reported in the 'other' category. The ones categorized as 'other' were as follows:

- PD related to capturing the date of the last meal preceding an episode of hypoglycemia in the patient's diary, this was corrected by a protocol amendment.
- One PD was related to the CRA performing source data verification and verification of any critical data prior to the database lock. This change was communicated to affiliates and updated to the monitoring guidelines.

- One (1) PD was related to discrepancy in recording the insulin dose in the eCRF. As per the monitoring guideline, the total daily dose of insulin was to be entered on the concomitant medication form after the semaglutide maintenance dose was reached. As the patients were treated for 2 years, only the insulin dose taken at the day before each trial visit was captured in order to avoid numerous entries of insulin doses resulting from frequent dose changes. A protocol amendment was made to allow recording of only the insulin dose taken at the day before each trial visit, in electronic data capture and the same was updated to monitoring guidelines.

The applicant did not consider these PDs to have impacted the trial results, and I agree with the assessment.

Important PDs at country level

A total of 5 important PDs were reported: 2 in the 'assessment deviation' category and 3 in the 'other' category.

Assessment deviations:

- One PD related to missing and cancelled laboratory results in one country (affecting 9 patients) – the labs were sent to the central facility out of the stability period. Re-testing was performed.
- One PD was related to collection of additional laboratory results for eGFR. The eGFR was planned to be reported for every visit where serum creatinine was reported. Although no additionad blood sample was needed, an amendment was required to obtain ethics approval in the UK for the reporting of additional laboratory results for eGFR.

Other:

- One (1) PD was related to local affidavit signed after site initiation visit: the principal investigator and the trial site staff had signed a wrong version of the affidavit according to local regulation and at some of the sites the local affidavit was signed by sub-investigator and site staff after site initiation visit. A memo was created in this regard and CRAs were retrained.
- One (1) PD was related to late reporting of SUSARs to investigator. The CTA was retrained on the importance of timely SUSAR shipment and was made aware of the impact.
- One (1) PD was related to incomplete implementation of changes from the master patient diary version 2 (the "trial drug" had not been changed into "diabetes treatment" in the diary). Space for inserting information regarding details of the last trial drug dose taken prior to the next phone contact/site visit was missing for all

patients. As a corrective action, details of last trial drug dose taken prior to the next phone contact/next clinic visit were documented in the patients' medical records.

The important PDs at the country-level were not considered to have an overall impact on trial conduct, patient safety or data interpretation.

Important protocol deviations at trial site and patient level

There were 649 and 4633 important PDs at the level of trial site and patient, respectively, similarly distributed across the four treatment arms.

Table 68 Summary of Important Protocol Deviations at Site and Patient Level SUSTAIN 6

Protocol deviation category	Site-level	Subject-level					
		Screening failures	Sema 0.5 mg	Sema 1.0 mg	Placebo 0.5 mg	Placebo 1.0 mg	Total
Informed consent	55	52	68	93	96	94	403
Inclusion/exclusion/randomisation criteria	10	0	84	79	77	66	306
Withdrawal criteria	0	0	0	0	0	0	0
Trial product handling	77	3	25	43	26	32	128
Treatment compliance	11	0	102	102	107	135	446
Assessment deviations (incl. lab)	78	7	519	484	504	493	2007
Other	418	6	356	357	312	311	1343
Total	649	68	1154	1158	1122	1131	4633

Abbreviations: Sema: semaglutide.
Source: Table 10-19 study report

Informed consent

There were 55 PDs at site-level and 403 PDs at patient-level related to informed consent (IC). Of the 403 patient-level PDs, 52 PDs concerned 51 patients that were screening failures; the remaining 351 PDs concerned 309 randomized patients. Among the site-level PDs, more than half of the PDs (~65%) were related to incorrect/incomplete IC form or incorrect IC procedure; these site-level PDs concerned approximately 140 patients. The majority (80%) of the IC related patient-level PDs (concerning 297 patients) were either due to incorrect/incomplete IC form or incorrect IC procedure.

Inclusion/exclusion/randomization criteria

There were 10 site-level PDs and 306 patient-level PDs related to inclusion/exclusion/ randomization criteria.

The majority of the site-level PDs and approximately three-quarter of the patient-level PDs (222 PDs for 218 patients) were due to incorrect stratification (stratification based on evidence of CV disease/insulin treatment/severe renal impairment at baseline) captured in the IV/WRS. However, in statistical analyses where stratification was included, all 9 combinations of the three stratification factors were included based on the actual information collected through the eCRF.

Trial product handling

A total of 77 site-level PDs and 128 patient-level PDs related to trial product handling were identified. Twenty one (21) PDs concerning 22 patients were related to the wrong trial product/dispensing unit number (DUN) being dispensed and/or administered. Thirteen (13) of these patients did not administer the wrong DUN. The data for the 9 patients that administered the wrong trial product is outlined in the table below. The table also includes 2 additional patients captured with PD 'treatment compliance'.

Table 69 Patients Receiving the Wrong Trial Product/DUN SUSTAIN 6

Subject ID	Treatment	Wrong DUN(s) dispensed (trial product)	Doses taken
106001	Placebo 1.0 mg	500183, 520632, 532183 (placebo)	Administered, but doses unknown
106010	Semaglutide 0.5 mg	602274, 608117 (semaglutide 1.34 mg/ml)	Administered, but doses unknown
123004	Placebo 1.0 mg	571912 (semaglutide 1.34 mg/ml)	1 injection
255033	Placebo 1.0 mg	550564 (semaglutide 1.34 mg/ml)	6 injections
462014	Placebo 0.5 mg	840232 (semaglutide 1.34 mg/ml)	1 injection
481020	Placebo 0.5 mg	740495 (semaglutide 1.34 mg/ml)	4 injections
481033	Semaglutide 1.0 mg	752445 (placebo)	6 injections
633013	Placebo 0.5 mg	631289 (placebo)	Administered, but doses unknown
633016[a]	Placebo 0.5 mg	571845 (semaglutide 1.34 mg/ml)	Administered, but doses unknown
633017[a]	Semaglutide 1.0 mg	529317 (placebo)	Administered, but doses unknown
671009	Placebo 1.0 mg	591511 (placebo)	5 injections

Notes: [a]The PD related to these subject IDs was captured in the category 'treatment compliance'.
Abbreviations: DUN: dispensing unit number.

Source: Table 10-20 study report

Approximately 35% site-level PDs, and 21% of patient-level PDs, were in the subcategory 'other'. For the site-level PDs, the most common reasons included incorrect/missing temperature logs and incorrect handling/dispensing of trial products.

Treatment compliance

A total of 11 trial site-level PDs and 446 patient-level PDs related to treatment compliance were identified. The PDs were reported with a comparable frequency in the 4 treatment groups (slightly higher number of PDs [135] reported with placebo 1.0 mg arm).

Assessment deviations

A total of 78 site-level PDs and 2012 patient-level PDs were identified in the category 'assessment deviations' (including laboratory).

Among the site-level PDs, ~43% were related to missing one or more of the following assessments: PK samples, antibody samples, calcitonin samples, all other blood samples, ECG measurements, fundoscopy/fundus photography, body measurements, vital signs, physical examination and urinalysis from following visits: baseline and/or end of treatment and/or follow up (including premature discontinuation). General actions taken were: the investigator was reminded to ensure all laboratory sampling required per protocol were done, re-test was performed if a sample was missing and retraining of site staff was done.

A total of 22% of the site-level PDs were related to missing planned safety assessments at the trial visits, where the last safety assessments were to be performed (visit 25 and 26) and ~17% of PDs were related to laboratory reports not printed out and signed in the proper timeline (prior to the patients' next scheduled visits).

Approximately 52% of the patient-level PDs were related to missing one or more of the following assessments: PK samples, antibody samples, calcitonin samples, all other blood samples, ECG measurements, fundoscopy/fundus photography, body measurements, vital signs, physical examination and urinalysis from following visits: baseline and/or end of treatment and/or follow up (including premature discontinuation). Generally, the actions taken were: training site staff on protocol requirements, the investigator had been asked to explain again to the patients that they were to comply with the defined visits of the protocol, investigator was reminded to ensure all laboratory sampling required by the protocol and to perform retest if applicable.

Approximately 22% of the patient-level PDs were due to missing planned safety assessments at the visits 25 and 26, where the last safety assessments were to be performed, while ~15% of

the PDs were due to missing date and/or investigator signature on the laboratory report as defined by the protocol, including late signing and signing at the wrong page.

Other

At site-level, there were 418 important PDs. The majority (~53%) of these PDs concerned monitoring visits performed out of the protocol defined interval. In most cases, the monitor/in-house CRA/delegate was in contact with the site or a remote monitoring was done between site visits. The remaining site-level PDs concerned trial task performed by site staff not delegated the responsibility (~14%), other (~10%), missing or late reporting of SAEs/MESIs or technical complaints (~9%), recurrent late reporting of non-serious AE (~7%), entry in the patient diary done by persons other than the patient or the patient's designated caregiver (~3%), source data missing (including diary) or incomplete (~2%) and diary or PRO questionnaire not dispensed (<1%). At site-level, 4 PDs which concerned monitoring visits performed out of the protocol defined time window, were wrongly sub-categorised as fraud/misconduct (1 PD) and as randomisation code broken for reasons other than safety (3 PDs). There was no suspicion of fraud and no patient was unblinded in the trial for reasons other than safety. Therefore, these 4 PDs should be considered under the sub-category concerning monitoring visit window.

At the patient-level, there were 1343 important PDs. The majority (~57%) of these concerned delayed reporting of MESI/SAE or delayed signing off the relevant forms. These PDs were rectified as soon as possible, the IRB/IEC was notified, as applicable and the site staff was re-trained in the relevant protocol sections. There were 10 patient-level PDs concerning fraud/misconduct. Of these, 6 PDs at one site concerned forging signature of the principal investigator by the primary coordinator, on the IC form. Though the signature was forged, a medically qualified investigator was present during the consenting process for all these patients. For these 6 PDs, the local IRB concluded that a re-consent was unnecessary and that the original consent process was not invalid. The remaining 4 PDs were mistakenly sub-categorised as fraud, and they concerned laboratory report not been filed in medical records (1 PD) and missing investigator assessment and signature on visit/lab report (3 PDs). There was no suspicion of fraud/misconduct in these 4 PDs.

Even though, no patient was unblinded in this trial for reasons other than safety, there were 18 patient-level PDs wrongly categorised/sub-categorised as randomisation code broken for reasons other than safety. These 18 PDs concerned PDs related to 'assessment deviations' (8 PDs), 'IC' (1 PD), 'treatment compliance' (2 PDs) and missing or late reporting of SAEs/MESIs or technical complaints (7 PDs).

Patients randomized in other trials

Three (3) patient-level PDs (patient IDs 630018, 678013, and 712007) were due to patients participating both in trial 3744 and other Novo Nordisk sponsored trials at the same time. These patients were considered as duplicate patients. Patients were asked to discontinue trial products but to continue in the trial and none of the patients reported any EAC-confirmed MACE.

Four (4) patient-level PDs were due to patients participating both in trial 3744 as well as in clinical trials performed by other sponsors. Except for patient ID 282010 who discontinued trial product but continued in the trial, the rest of the patients agreed to stop participating in the other trials and resume treatment in this trial. There was one EAC confirmed MACE, an event of cerebellar hemorrhage reported in a patient (patient ID 147010) receiving placebo treatment.

Important protocol deviations closed or identified after database lock

2 additional PDs were identified, 1 at the site-level and 1 at the patient-level, both reported under the category 'other'. The site-level PD was related to monitoring visit performed out of the visit window; it was confirmed that the monitor was in contact with the site to ensure quality. The patient-level PD was due to an SAE reported late by the site.

Table of Demographic Characteristics

Overall, demographics and baseline characteristics were well matched between patients randomized to semaglutide 0.5 mg, semaglutide 1 mg, placebo 0.5 mg and placebo 1.0 mg.

The mean age at baseline was 64.6 years. The majority of patients were in the age groups between 50–74 years and slightly less than 10% were ≥75 years. A higher proportion of males (60.7%) than females were randomized, with a similar distribution between semaglutide and placebo groups.

Most patients were White (83.0%), and of non-Hispanic or Latino ethnicity (84.5%). Of the 20 countries in which the trial was conducted, the largest proportion of patients was recruited from the United States (34.5%). The proportion of patients per country was comparable between the semaglutide and placebo treatment groups.

The trial population were generally obese with a baseline mean BMI of 32.80 kg/m2 and more than 62% of patients in each treatment group had a mean BMI ≥30 kg/m2 at baseline.

The patient population had a mean HbA1c of 8.70%, and a relatively long mean duration of diabetes (13.89 years). Mean BP, pulse rate, lipids and smoking status were also well matched between the treatment groups.

Table 70 Selected Demographics and Baseline Characteristics for Continuous Variables – FAS – SUSTAIN 6

	Sema	Placebo	Total
Duration of Diabetes (years)			
N	1648	1649	3297
Mean (SD)	14.17 (8.20)	13.60 (8.02)	13.89 (8.11)
Body weight (kg)			
N	1646	1645	3291
Mean (SD)	92.33 (20.66)	91.86 (20.55)	92.09 (20.60)
Body mass index (kg/m2)			
N	1645	1645	3290
Mean (SD)	32.80 (6.23)	32.80 (6.16)	32.80 (6.20)
Systolic BP (mmHg)			
N	1648	1649	3297
Mean (SD)	136.0 (17.47)	135.3 (16.82)	135.6 (17.15)
Diastolic BP (mmHg)			
N	1648	1649	3297
Mean (SD)	76.99 (10.00)	77.10 (10.04)	77.05 (10.02)
Pulse rate (beats/min)			
N	1648	1649	3297
Mean (SD)	72.11 (11.05)	71.98 (10.77)	72.05 (10.91)
MDRD GFR 'estimated' (mL/min/1.73 m2)			
N	1648	1649	3297
Mean (SD)	75.88 (25.88)	76.39 (27.19)	76.13 (26.54)

Source: Modified from Table 15.1.15 study report

Table 71 Selected Demographics and Baseline Characteristics for Categorical Variables – FAS – SUSTAIN 6

	Sema N (%)	Placebo N (%)	Total N (%)
Number of subjects	1648	1649	3297
Age group			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
50-64 years	855 (51.9)	844 (51.2)	1699 (51.5)
65-74 years	636 (38.6)	641 (38.9)	1277 (38.7)
75-84 years	147 (8.9)	154 (9.3)	301 (9.1)
>= 85 years	10 (0.6)	10 (0.6)	20 (0.6)
Sex			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
Female	635 (38.5)	660 (40.0)	1295 (39.3)
Male	1013 (61.5)	989 (60.0)	2002 (60.7)
Country			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
United States	570 (34.6)	567 (34.4)	1137 (34.5)
Race			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
White	1384 (84.0)	1352 (82.0)	2736 (83.0)
Black or African American	108 (6.6)	113 (6.9)	221 (6.7)
Asian	121 (7.3)	152 (9.2)	273 (8.3)
American Indian or Alaska Native	3 (0.2)	7 (0.4)	10 (0.3)
Native Hawaiian or Other Pacific Islander	3 (0.2)	0 (0.0)	3 (0.1)
Other	29 (1.8)	25 (1.5)	54 (1.6)
Ethnicity			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
Hispanic or Latino	256 (15.5)	254 (15.4)	510 (15.5)
Not Hispanic or Latino	1392 (84.5)	1395 (84.6)	2787 (84.5)
Smoker status			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
Current smoker	204 (12.4)	202 (12.2)	406 (12.3)
Never smoked	754 (45.8)	739 (44.8)	1493 (45.3)
Previous smoker	690 (41.9)	707 (42.9)	1397 (42.4)
Unknown		1 (0.1)	1 (0.0)
Renal impairment			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
Normal	493 (29.9)	497 (30.1)	990 (30.0)
Mild	686 (41.6)	682 (41.4)	1368 (41.5)
Moderate	423 (25.7)	409 (24.8)	832 (25.2)
Severe	41 (2.5)	54 (3.3)	95 (2.9)
End stage	5 (0.3)	7 (0.4)	12 (0.4)
Insulin treatment			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
None	692 (42.0)	692 (42.0)	1384 (42.0)
Basal insulin	515 (31.3)	531 (32.2)	1046 (31.7)
Premix insulin	441 (26.8)	426 (25.8)	867 (26.3)
SU monotherapy			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
No	1589 (96.4)	1585 (96.1)	3174 (96.3)
Yes	59 (3.6)	64 (3.9)	123 (3.7)
Clinical evidence of CV disease			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
No	295 (17.9)	267 (16.2)	562 (17.0)
Yes	1353 (82.1)	1382 (83.8)	2735 (83.0)

Source: Modified from Table 15.1.14 Study Report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Medical history and concomitant illnesses

The most common concomitant illnesses reported for the trial population at baseline were hypertension (90.1%), dyslipidemia (33.2%), hyperlipidemia (29.0%), coronary artery disease (23.4%), obesity (23.5%), myocardial ischemia (23.3%) and osteoarthritis (20.0%).

Funduscopy

At randomisation, the fundoscopy findings were normal for approximately half of the patients across the semaglutide and placebo treatment groups. The proportions of patients with 'abnormal, not clinically significant' and 'abnormal, clinically significant' fundoscopy findings were approximately 40% and 10%, respectively and with minor variations across the semaglutide and placebo treatment groups.

Table 72 Baseline Funduscopy Results SUSTAIN 6

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo 0.5 mg N (%)	Placebo 1.0 mg N (%)	Total N (%)
Number of subjects	826	822	824	825	3297
Left eye ophthalmoscopy - Observed 'in-trial' data					
Visit 2 (week 0)					
Normal	396 (49.2)	432 (53.8)	448 (55.0)	435 (53.6)	1711 (52.9)
Abnormal and not clinically significant	325 (40.4)	291 (36.2)	279 (34.2)	311 (38.3)	1206 (37.3)
Abnormal and clinically significant	84 (10.4)	80 (10.0)	88 (10.8)	65 (8.0)	317 (9.8)
Right eye ophthalmoscopy - Observed 'in-trial' data					
Visit 2 (week 0)					
Normal	390 (48.3)	432 (53.9)	439 (53.9)	431 (53.1)	1692 (52.3)
Abnormal and not clinically significant	332 (41.1)	293 (36.5)	291 (35.7)	307 (37.8)	1223 (37.8)
Abnormal and clinically significant	85 (10.5)	77 (9.6)	84 (10.3)	74 (9.1)	320 (9.9)

Source: Modified from Table 15.3.6.16

History of cardiovascular disease

Of the 3297 patients randomized into the trial, the majority (83.0%) were enrolled based on clinical evidence of CV disease at baseline, while 17.0% were enrolled based only on subclinical evidence of CV disease. The distribution was comparable across semaglutide and placebo treatment groups. Proportions of patients (%) fulfilling each inclusion criterion were well-balanced across the semaglutide and placebo treatment groups.

Table 73 Total Number of Patients Fulfilling the Inclusion Criteria by Evidence of CV Disease – FAS – SUSTAIN 6

	Semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects in FAS	1648	1649	3297
Clinical evidence of cardiovascular disease, age≥50	1353 (82.1)	1382 (83.8)	2735 (83.0)
a) Prior myocardial infarction	529 (32.1)	542 (32.9)	1071 (32.5)
b) Prior stroke or prior transient ischaemic attack	257 (15.6)	259 (15.7)	516 (15.7)
c) Prior arterial revascularisation	694 (42.1)	721 (43.7)	1415 (42.9)
d) >50% stenosis on angiography	564 (34.2)	597 (36.2)	1161 (35.2)
e) History of symptomatic coronary heart disease	250 (15.2)	236 (14.3)	486 (14.7)
f) Asymptomatic cardiac ischemia	75 (4.6)	71 (4.3)	146 (4.4)
g) Chronic heart failure NYHA II-III	285 (17.3)	288 (17.5)	573 (17.4)
h) Chronic kidney disease	386 (23.4)	409 (24.8)	795 (24.1)
Together with another criterie for clinical evidence [a]	224 (13.6)	218 (13.2)	442 (13.4)
Chronic kidney disease alone [b]	162 (9.8)	191 (11.6)	353 (10.7)
Subclinical evidence of cardiovascular disease, age≥60	295 (17.9)	267 (16.2)	562 (17.0)
i) Microalbuminuria or proteinuria	159 (9.6)	149 (9.0)	308 (9.3)
j) Hypertension and left ventricular hypertrophy	125 (7.6)	108 (6.5)	233 (7.1)
k) Left ventricular systolic and diastolic dysfunction	78 (4.7)	77 (4.7)	155 (4.7)
l) Ankle/brachial index <0.9	34 (2.1)	25 (1.5)	59 (1.8)

Notes: Please note that a given subject might have several criteria fulfilled, including criteria belonging to different age groups. Chronic kidney disease corresponding to glomerular filtration rate 30-59 mL/min/1.73 m^2 per CKD-Epi. 'Age ≥ 60 years' group might include subjects also in the 'Age ≥50 years' group. According to inclusion criterion no 3 in the protocol subjects were either to have age ≥50 and at least one of the conditions a) to h) or age ≥60 and at least one of the conditions i) to l). Subjects with missing age information at time of randomisation are not included in either age category. [a] Chronic kidney disease in combination with one or more other criteria for clinical evidence of cardiovascular disease. [b] Chronic kidney disease alone.
Abbreviations: FAS: full analysis set, N: number of subjects, NYHA: New York Heart Association, %: percentage of subjects.
Source: Table 10-6 study report

Among the patients enrolled in the trial, the most predominant individual clinical evidence of CV disease at baseline were prior arterial revascularisation (42.9%), >50% stenosis on angiography (35.2%), prior MI (32.5%), chronic kidney disease (24.1%), chronic heart failure NYHA II-III (17.4%) and prior stroke or prior TIA (15.7%). The most frequent subclinical evidence of CV disease was microalbuminuria or proteinuria (9.3%). Patients often fulfilled more than one of the criteria for clinical or subclinical evidence of CV disease at baseline. If both clinical and subclinical evidence of CV disease were present, the patient was randomized based on clinical evidence.

No noteworthy differences in the CV disease history at screening between the semaglutide and placebo treatment groups were observed. Hypertension and ischaemic heart disease were among the most common CV diseases reported and were observed in 92.8% and 60.5% of patients, respectively.

Table 74 History of Cardiovascular Disease at Screening – FAS – SUSTAIN 6

	Semaglutide N (%)	Placebo N (%)	Total N (%)
Number of Subjects in FAS	1648	1649	3297
Ischaemic Heart Disease			
Yes	988 (60.0)	1006 (61.0)	1994 (60.5)
Asymptomatic (Silent) Cardiac Ischaemia	136 (8.3)	149 (9.0)	285 (8.6)
Stable Angina Pectoris	231 (14.0)	251 (15.2)	482 (14.6)
Unstable angina (symptoms at rest or severe and of new onset or crescendo pattern	125 (7.6)	117 (7.1)	242 (7.3)
Non-ST-Elevation Myocardial Infarction	180 (10.9)	184 (11.2)	364 (11.0)
ST-segment Elevation Myocardial Infarction	202 (12.3)	197 (11.9)	399 (12.1)
Unknown	114 (6.9)	108 (6.5)	222 (6.7)
No	660 (40.0)	642 (38.9)	1302 (39.5)
Unknown	0	1 (0.1)	1 (0.0)
Percutaneous Coronary Intervention [a]			
Yes	490 (29.7)	522 (31.7)	1012 (30.7)
No	493 (29.9)	480 (29.1)	973 (29.5)
Unknown	302 (18.3)	301 (18.3)	603 (18.3)
Coronary Artery Bypass Graft [a]			
Yes	288 (17.5)	289 (17.5)	577 (17.5)
No	493 (29.9)	480 (29.1)	973 (29.5)
Unknown	291 (17.7)	283 (17.2)	574 (17.4)
Myocardial Infarction			
Yes	530 (32.2)	542 (32.9)	1072 (32.5)
No	1118 (67.8)	1107 (67.1)	2225 (67.5)
Heart Failure			
Yes	381 (23.1)	396 (24.0)	777 (23.6)
NYHA I	91 (5.5)	97 (5.9)	188 (5.7)
NYHA II	241 (14.6)	240 (14.6)	481 (14.6)
NYHA III	44 (2.7)	49 (3.0)	93 (2.8)
Unknown	5 (0.3)	10 (0.6)	15 (0.5)
No	1267 (76.9)	1253 (76.0)	2520 (76.4)
Left Ventricular Diastolic Dysfunction			
Yes	354 (21.5)	316 (19.2)	670 (20.3)
No	977 (59.3)	970 (58.8)	1947 (59.1)
Unknown	317 (19.2)	363 (22.0)	680 (20.6)
Hypertension			
Yes	1543 (93.6)	1516 (91.9)	3059 (92.8)
Left Ventricular hypertrophy-No	549 (33.3)	562 (34.1)	1111 (33.7)
Left Ventricular hypertrophy-Yes	508 (30.8)	471 (28.6)	979 (29.7)
Left Ventricular hypertrophy-Unknown	486 (29.5)	483 (29.3)	969 (29.4)
No	105 (6.4)	133 (8.1)	238 (7.2)
Ischaemic Stroke			
Yes	178 (10.8)	205 (12.4)	383 (11.6)
No	1469 (89.1)	1443 (87.5)	2912 (88.3)
Unknown	1 (0.1)	1 (0.1)	2 (0.1)
Transient Ischaemic Attack			
Yes	98 (5.9)	94 (5.7)	192 (5.8)
No	1550 (94.1)	1554 (94.2)	3104 (94.1)
Unknown	0	1 (0.1)	1 (0.0)
Intracranial Artery Stenosis			
Yes	26 (1.6)	25 (1.5)	51 (1.5)
No	1622 (98.4)	1621 (98.3)	3243 (98.4)
Unknown	0	3 (0.2)	3 (0.1)
Carotid Artery Stenosis			
Yes	137 (8.3)	157 (9.5)	294 (8.9)
No	1511 (91.7)	1490 (90.4)	3001 (91.0)
Unknown	0	2 (0.1)	2 (0.1)
Peripheral Arterial Disease In Lower Extremities			
Yes	226 (13.7)	227 (13.8)	453 (13.7)
No	1422 (86.3)	1422 (86.2)	2844 (86.3)
> 50% Artery Stenosis			
Yes	567 (34.4)	600 (36.4)	1167 (35.4)
Intracranial Artery Stenosis	3 (0.2)	9 (0.5)	12 (0.4)
Carotid Artery Stenosis	71 (4.3)	84 (5.1)	155 (4.7)
Coronary Artery Bypass Graft [a]	472 (28.6)	495 (30.0)	967 (29.3)
Peripheral Artery Stenosis	77 (4.7)	73 (4.4)	150 (4.6)
No	1078 (65.4)	1045 (63.4)	2123 (64.4)
Unknown	3 (0.2)	4 (0.2)	7 (0.2)

Source: Modified from Table 10-7 study report

Baseline blood pressure and pulse were similar between the treatment groups, as were baseline lipid levels.

Table 75 Vital Signs at Baseline – FAS- SUSTAIN 6

	Semaglutide	Placebo	Total
Number of subjects in FAS	1648	1649	3297
Systolic BP (mmHg)			
N	1648	1649	3297
Mean (SD)	136.0 (17.47)	135.3 (16.82)	135.6 (17.15)
Min ; Max	84.00 ; 203.00	74.00 ; 204.00	74.00 ; 204.00
Diastolic BP (mmHg)			
N	1648	1649	3297
Mean (SD)	76.99 (10.00)	77.10 (10.04)	77.05 (10.02)
Min ; Max	46.00 ; 116.00	40.00 ; 110.00	40.00 ; 116.00
Pulse rate (beats/min)			
N	1648	1649	3297
Mean (SD)	72.11 (11.05)	71.98 (10.77)	72.05 (10.91)
Min ; Max	42.00 ; 149.00	40.00 ; 117.00	40.00 ; 149.00

Source: Table 10-8 study report

History of diabetes complications

A total of 969 subjects (29.4%) had a history of diabetic retinopathy at screening, reflected most often by non-proliferative diabetic retinopathy. Non-proliferative diabetic retinopathy at screening was reported by a higher proportion of subjects in the semaglutide treatment groups compared with the placebo treatment groups. An average of 40.5% of subjects had peripheral neuropathy at screening. An average of 44.3% of subjects across treatment groups had diabetic nephropathy, reflected most often by chronic renal failure or microalbuminuria.
Details on history of diabetes complications at screening are shown below.

Table 76 Diabetes Complications at Baseline SUSTAIN 6

	Semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects in FAS	1648	1649	3297
Diabetic retinopathy			
Yes	510 (30.9)	459 (27.8)	969 (29.4)
Nonproliferative [a]	402 (24.4)	348 (21.1)	750 (22.7)
Macular oedema	31 (1.9)	33 (2.0)	64 (1.9)
Laser therapy/treatment with intravitreal agents	57 (3.5)	43 (2.6)	100 (3.0)
Surgical treatment	5 (0.3)	5 (0.3)	10 (0.3)
Proliferative [a]	103 (6.3)	99 (6.0)	202 (6.1)
Macular oedema	16 (1.0)	15 (0.9)	31 (0.9)
Laser therapy/treatment with intravitreal agents	59 (3.6)	53 (3.2)	112 (3.4)
Surgical treatment	14 (0.8)	10 (0.6)	24 (0.7)
Unknown	5 (0.3)	12 (0.7)	17 (0.5)
Macular oedema	0	1 (0.1)	1 (0.0)
Laser therapy/treatment with intravitreal agents	2 (0.1)	2 (0.1)	4 (0.1)
No	1023 (62.1)	1089 (66.0)	2112 (64.1)
Unknown	115 (7.0)	101 (6.1)	216 (6.6)
Neuropathy [a]			
Yes	673 (40.8)	688 (41.7)	1361 (41.3)
Peripheral	659 (40.0)	676 (41.0)	1335 (40.5)
Autonomic	20 (1.2)	30 (1.8)	50 (1.5)
Unknown	2 (0.1)	0	2 (0.1)
No	914 (55.5)	909 (55.1)	1823 (55.3)
Unknown	61 (3.7)	52 (3.2)	113 (3.4)
Nephropathy			
Yes	722 (43.8)	739 (44.8)	1461 (44.3)
Microalbuminuria with normal serum creatinine/creatinine clearance	249 (15.1)	259 (15.7)	508 (15.4)
Macroalbuminuria or overt proteinuria, with normal serum creatinine/creatinine clearance	89 (5.4)	87 (5.3)	176 (5.3)
Chronic renal failure (elevated serum creatinine or reduced creatinine clearance)	388 (23.5)	397 (24.1)	785 (23.8)
Unknown	4 (0.2)	3 (0.2)	7 (0.2)
No	843 (51.2)	841 (51.0)	1684 (51.1)
Unknown	83 (5.0)	69 (4.2)	152 (4.6)
Macroangiopathy			
Yes	517 (31.4)	496 (30.1)	1013 (30.7)
No	1129 (68.5)	1148 (69.6)	2277 (69.1)
Unknown	2 (0.1)	5 (0.3)	7 (0.2)

Notes: [a] For neuropathy, nonproliferative diabetic retinopathy and proliferative diabetic retinopathy a subject might have more than one filled out.

Source: Table 10-13 study report

History of pancreatitis and gallbladder disease

Only a small proportion of patients had a history of clinical pancreatitis (0.6%), expected since history of idiopathic acute pancreatitis was an exclusion criteria. Gallstone disease and cholecystitis were reported in 13.2% and 8.1% of patients, respectively.

Table 77 History of Pancreatitis and Gallbladder Disease at Screening – FAS – SUSTAIN 6

	Semaglutide N (%)	Placebo N (%)	Total N (%)
Number of Subjects in FAS	1648	1649	3297
Pancreatitis			
Yes	10 (0.6)	9 (0.5)	19 (0.6)
Acute	10 (0.6)	9 (0.5)	19 (0.6)
No	1638 (99.4)	1639 (99.4)	3277 (99.4)
Unknown	0	1 (0.1)	1 (0.0)
Gallstone Disease			
Yes	210 (12.7)	225 (13.6)	435 (13.2)
No	1438 (87.3)	1424 (86.4)	2862 (86.8)
Cholecystitis			
Yes	139 (8.4)	128 (7.8)	267 (8.1)
Acute	86 (5.2)	87 (5.3)	173 (5.2)
Chronic	51 (3.1)	41 (2.5)	92 (2.8)
No	1507 (91.4)	1519 (92.1)	3026 (91.8)
Unknown	2 (0.1)	2 (0.1)	4 (0.1)
Gallbladder Disease			
Yes	277 (16.8)	285 (17.3)	562 (17.0)
Both	72 (4.4)	68 (4.1)	140 (4.2)
Cholecystitis Only	67 (4.1)	60 (3.6)	127 (3.9)
Gallstone Disease Only	137 (8.3)	156 (9.5)	293 (8.9)
No	1370 (83.1)	1363 (82.7)	2733 (82.9)

Notes: Gallbladder disease is defined as Yes if at least one of Gallstone disease or Cholecystitis is Yes.
Abbreviations: FAS: full analysis set, N: number of subjects, %: percentage of subjects.
Source: Table 10-14 study report

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Semaglutide plasma concentrations were measured regularly during the trial in a subgroup of patients. Based on observed semaglutide plasma concentrations in the PK subgroup and the number and nature of important PDs related to treatment compliance, the general treatment adherence in the trial was considered high.

Concomitant medications at baseline

Overall, use of concomitant medication at baseline was well-balanced across the semaglutide and placebo treatment groups.

More than 92% of patients received antihypertensive therapy at baseline including beta-blockers, calcium channel blockers, ACE-I and ARB. Approximately 76% of patients were treated with lipid lowering medication, mainly statins

Table 78 Cardiovascular Medication Ongoing at Baseline – FAS – SUSTAIN 6

	Semaglutide		Placebo		Total	
Number of subjects in FAS	1648		1649		3297	
Anti-hypertensive drugs	1553	(94.2)	1529	(92.7)	3082	(93.5)
Beta blockers	934	(56.7)	960	(58.2)	1894	(57.4)
Calcium channel blockers	519	(31.5)	536	(32.5)	1055	(32.0)
ACE inhibitors	829	(50.3)	813	(49.3)	1642	(49.8)
Angiotensin receptor blockers	548	(33.3)	563	(34.1)	1111	(33.7)
Others	123	(7.5)	135	(8.2)	258	(7.8)
Diuretics	624	(37.9)	636	(38.6)	1260	(38.2)
Loop diuretics	280	(17.0)	276	(16.7)	556	(16.9)
Thiazides	233	(14.1)	236	(14.3)	469	(14.2)
Thiazide-like diuretics	118	(7.2)	116	(7.0)	234	(7.1)
Aldosterone antagonists	97	(5.9)	97	(5.9)	194	(5.9)
Lipid lowering drugs	1263	(76.6)	1258	(76.3)	2521	(76.5)
Statins	1199	(72.8)	1200	(72.8)	2399	(72.8)
Ezetimibe	63	(3.8)	66	(4.0)	129	(3.9)
Other lipid lowering drugs	189	(11.5)	168	(10.2)	357	(10.8)
Anti-thrombotic medication	1252	(76.0)	1262	(76.5)	2514	(76.3)
Vitamin K antagonists	88	(5.3)	76	(4.6)	164	(5.0)
Direct thrombin inhibitors	9	(0.5)	9	(0.5)	18	(0.5)
Direct factor Xa inhibitors	3	(0.2)	10	(0.6)	13	(0.4)
ADP receptor inhibitors (excluding ASA)	339	(20.6)	357	(21.6)	696	(21.1)
Acetylsalicylic acid (ASA)	1051	(63.8)	1057	(64.1)	2108	(63.9)

Abbreviations: ACE: angiotensin-converting-enzyme, ADP: adenosine diphosphate, ASA: acetylsalicylic acid, FAS: full analysis set.

Source: Table 10-15 study report

Post-baseline, the proportion of patients requiring addition of CV medication was lower in the semaglutide 0.5 mg and 1.0 mg groups compared with the corresponding placebo group.

Table 79 Additional Cardiovascular Medication During the Trial – FAS – SUSTAIN 6

	Sema 0.5 mg N	(%)	Sema 1.0 mg N	(%)	Placebo 0.5 mg N	(%)	Placebo 1.0 mg N	(%)
Number of subjects in FAS	826		822		824		825	
Cardiovascular medication	305	(36.9)	291	(35.4)	372	(45.1)	346	(41.9)
Anti-hypertensive drugs	168	(20.3)	151	(18.4)	202	(24.5)	198	(24.0)
Beta blockers	45	(5.4)	48	(5.8)	57	(6.9)	50	(6.1)
Calcium channel blockers	45	(5.4)	46	(5.6)	74	(9.0)	79	(9.6)
ACE inhibitors	42	(5.1)	40	(4.9)	42	(5.1)	37	(4.5)
Angiotensin II receptor blockers	46	(5.6)	42	(5.1)	56	(6.8)	54	(6.5)
Others	38	(4.6)	20	(2.4)	28	(3.4)	33	(4.0)
Diuretics	103	(12.5)	87	(10.6)	150	(18.2)	130	(15.8)
Loop diuretics	53	(6.4)	37	(4.5)	83	(10.1)	76	(9.2)
Thiazides	28	(3.4)	26	(3.2)	40	(4.9)	26	(3.2)
Thiazide-like diuretics	15	(1.8)	10	(1.2)	18	(2.2)	28	(3.4)
Aldosterone antagonists	23	(2.8)	22	(2.7)	34	(4.1)	36	(4.4)
Lipid-lowering drugs	87	(10.5)	67	(8.2)	98	(11.9)	107	(13.0)
Statins	58	(7.0)	51	(6.2)	70	(8.5)	75	(9.1)
Ezetimibe	7	(0.8)	4	(0.5)	8	(1.0)	12	(1.5)
Others	31	(3.8)	16	(1.9)	31	(3.8)	26	(3.2)
Anti-thrombotic medication	108	(13.1)	118	(14.4)	137	(16.6)	118	(14.3)
Vitamin K antagonists	15	(1.8)	24	(2.9)	16	(1.9)	13	(1.6)
Direct thrombin inhibitors	5	(0.6)	5	(0.6)	5	(0.6)	6	(0.7)
Direct factor Xa inhibitors	20	(2.4)	15	(1.8)	25	(3.0)	18	(2.2)
ADP receptor inhibitors (excluding ASA)	45	(5.4)	54	(6.6)	58	(7.0)	58	(7.0)
Acetylsalicylic acid (ASA)	42	(5.1)	37	(4.5)	52	(6.3)	44	(5.3)

Notes: 'In-trial' data. Addition of cardiovascular medication is defined as treatment with any of the cardiovascular medications initiated during trial, if not used at randomisation.
Abbreviations: ASA: acetylsalicylic acid, FAS: full analysis set, N: number of subjects in the summary statistic, %: percentage of subjects
Source: Table 10-7 study report

The treatment groups were well-balanced at trial entry with respect to the use of OADs and insulin products. The most commonly used antidiabetic medication at baseline was metformin (approximately 73% of patients used biguanides) followed by insulin treatment (31.7% of patients were treated with basal insulin and 26.3% with premix insulin) and SUs (26.8% without insulin and 15.9% in combination with insulin). Only 2% of the patients did not use any diabetes medications at baseline, and 42% were insulin-naïve.

Table 80 Insulin and SU Therapy at Baseline – FAS – SUSTAIN 6

	Semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects in FAS	1648	1649	3297
Insulin treatment			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
Basal	515 (31.3)	531 (32.2)	1046 (31.7)
Premix	441 (26.8)	426 (25.8)	867 (26.3)
None	692 (42.0)	692 (42.0)	1384 (42.0)
SU monotherapy			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
Yes	59 (3.6)	64 (3.9)	123 (3.7)
No	1589 (96.4)	1585 (96.1)	3174 (96.3)
Combinations of insulin and SU			
N	1648 (100.0)	1649 (100.0)	3297 (100.0)
SU - with or without other antidiabetics (but no insulin)	450 (27.3)	435 (26.4)	885 (26.8)
Insulin - with or without other antidiabetics (but no SU)	708 (43.0)	680 (41.2)	1388 (42.1)
SU and insulin - with or without other antidiabetics	248 (15.0)	277 (16.8)	525 (15.9)
No SU and no Insulin - with or without other antidiabetics	242 (14.7)	257 (15.6)	499 (15.1)

Notes: Data sources are general concomintant medications entries together with visit specific entries for insulin and SU therapy during trial drug dose escalation
Abbreviations: FAS: full analysis set, SU: sulfonylureas

Source: Table 10-16 study report

Proportion of patients requiring additional glucose-lowering medication during the trial was lower with semaglutide 0.5 mg and 1.0 mg groups compared with the corresponding placebo group.

Table 81 Additional Diabetes Medication During the Trial – FAS – SUSTAIN 6

	Sema 0.5 mg N	Sema 0.5 mg (%)	Sema 1.0 mg N	Sema 1.0 mg (%)	Placebo 0.5 mg N	Placebo 0.5 mg (%)	Placebo 1.0 mg N	Placebo 1.0 mg (%)
Number of subjects in FAS	826		822		824		825	
Glucose-lowering medication	172	(20.8)	160	(19.5)	345	(41.9)	325	(39.4)
Insulin treatment	85	(10.3)	70	(8.5)	204	(24.8)	191	(23.2)
Basal insulin	31	(3.8)	20	(2.4)	98	(11.9)	93	(11.3)
Basal+bolus insulin	60	(7.3)	50	(6.1)	123	(14.9)	118	(14.3)
Addition of bolus insulin	2	(0.2)	5	(0.6)	7	(0.8)	1	(0.1)
Non-insulin glucose-lowering medication	104	(12.6)	111	(13.5)	199	(24.2)	197	(23.9)
Alpha glucosidase inhibitors	1	(0.1)	4	(0.5)	8	(1.0)	11	(1.3)
Biguanides	30	(3.6)	21	(2.6)	46	(5.6)	29	(3.5)
Glucose-lowering combination therapy	4	(0.5)	0		4	(0.5)	2	(0.2)
DPP4-inhibitors	14	(1.7)	22	(2.7)	32	(3.9)	21	(2.5)
GLP-1 receptor agonists	8	(1.0)	15	(1.8)	7	(0.8)	9	(1.1)
Meglitinides	7	(0.8)	4	(0.5)	14	(1.7)	13	(1.6)
SGLT-2 inhibitors	21	(2.5)	23	(2.8)	40	(4.9)	53	(6.4)
Sulfonylureas	29	(3.5)	32	(3.9)	60	(7.3)	67	(8.1)
Thiazolidinediones	7	(0.8)	7	(0.9)	30	(3.6)	28	(3.4)

Notes: 'In-trial' data. Addition of glucose-lowering medication is defined as treatment for more than three consecutive weeks with a glucose lowering agent not used at randomisation.
Abbreviations: DPP-4: dipeptidyl peptidase-4, FAS: full analysis set, GLP-1: glucagon like-peptide 1, N: number of subjects in the summary statistic, SGLT-2: sodium-dependent glucose transporter two, %: percentage of subjects
Source: Table 10-18 study report

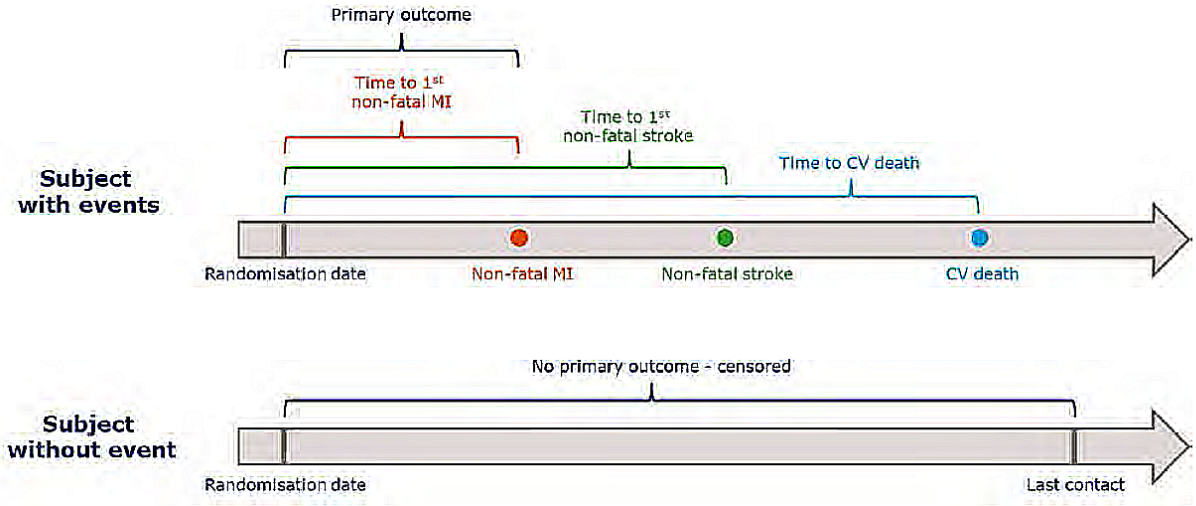
Efficacy Results - Primary Endpoint

Statistical analyses investigating efficacy were performed on the FAS (randomized patients), while safety analyses, including time to first event analyses, were performed on both the FAS and the SAS (randomized and exposed patients). For the efficacy and safety analyses, two different observation periods were defined; in-trial and on-treatment, respectively.

A total of 3297 patients (FAS) and 3286 patients (SAS) were randomized to semaglutide 0.5 mg (826 and 823 patients), semaglutide 1 mg (822 and 819 patients), placebo 0.5 mg (824 and 819 patients) or placebo 1.0 mg (825 and 825 patients).

When considering the majority of time a patient was treated with trial product, the randomized and actual treatment was different for 10 patients, but these changes occurred within treatment type, thus no patient changed treatment from semaglutide to placebo or vice versa. The primary endpoint was the time from randomization to first occurrence of a composite of the following CV endpoints: EAC-confirmed CV death (including undetermined cause of death), non-fatal MI or non-fatal stroke, together defined as MACE. Events with EAC-confirmed onset date between randomization and end of the in-trial observation period were included in the analyses. In case events had the same date of onset the priority for selecting the first event was: CV death (incl. undetermined cause of death) > non-fatal MI > non-fatal stroke.

Figure 27 Example of How Patients Contribute to Time to First MACE Analyses SUSTAIN 6



Source: Figure 11-1 study report

A total of 254 first MACE were reported during the trial. The proportion of patients with first MACE was lower with semaglutide than with placebo; a total of 108 patients (6.6%) experienced EAC-confirmed MACE with semaglutide versus 146 (8.9%) with placebo. The difference between groups in overall number of events is primarily attributable to a smaller number of first non-fatal MI and stroke events with semaglutide compared with placebo.

Table 82 EAC-Confirmed First MACE - FAS In-Trial SUSTAIN 6

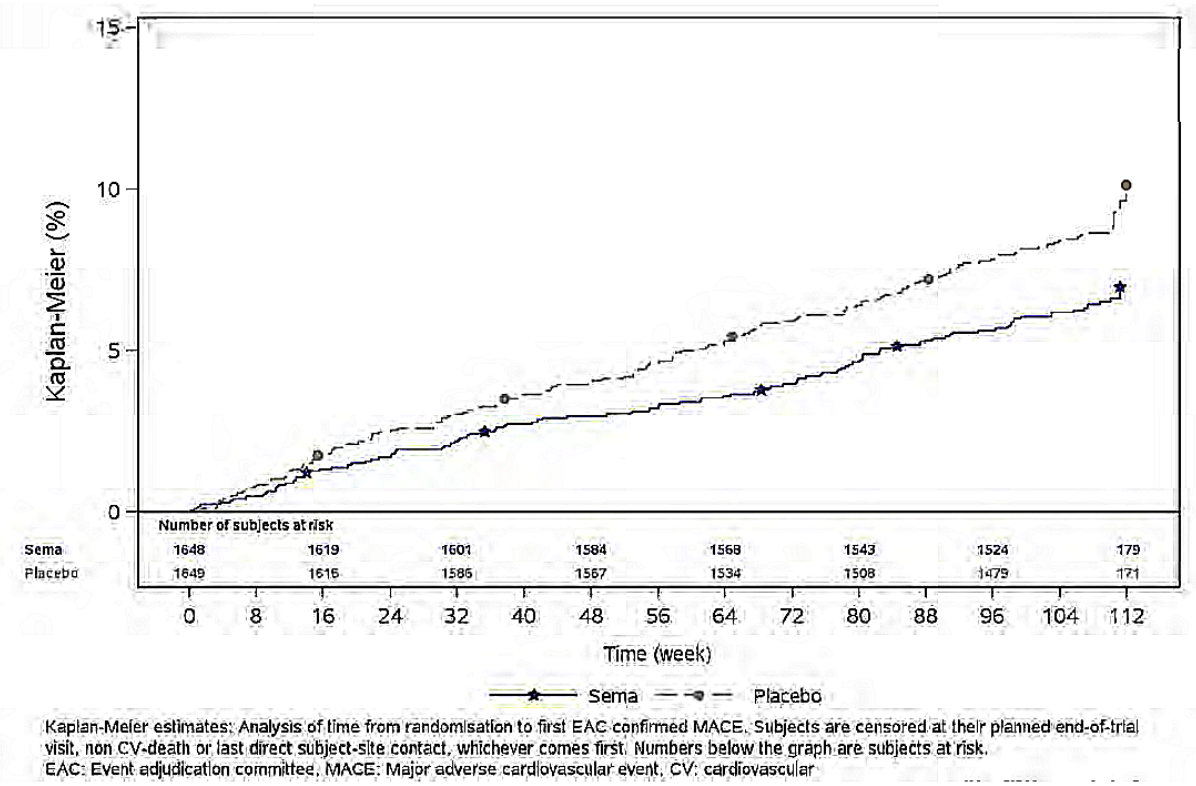
	Semaglutide N	(%)	Placebo N	(%)	Total N	(%)
Subjects	1648		1649		3297	
First MACE	108	(6.6)	146	(8.9)	254	(7.7)
Cardiovascular death	37	(2.2)	40	(2.4)	77	(2.3)
MI (non-fatal)	46	(2.8)	64	(3.9)	110	(3.3)
Stroke (non-fatal)	25	(1.5)	42	(2.5)	67	(2.0)

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: E: number of events; EAC: event adjudication committee; MACE: major adverse cardiovascular event; MI: myocardial infarction; N: number of subjects; %: percentage of subjects.

Source: Table 11-3 study report

Events had onset throughout the entire observation period, with no clustering of events over time as assessed from time of randomization. The Kaplan-Meier plot of time to first MACE, shows that the semaglutide and placebo curves separated shortly after trial initiation, and the lines continued to separate throughout the trial.

Figure 28 Plot of Time to First EAC-Confirmed MACE, Semaglutide Versus Placebo – FAS In-Trial SUSTAIN 6



Kaplan-Meier estimates: Analysis of time from randomisation to first EAC confirmed MACE. Subjects are censored at their planned end-of-trial visit, non CV-death or last direct subject-site contact, whichever comes first. Numbers below the graph are subjects at risk.
EAC: Event adjudication committee, MACE: Major adverse cardiovascular event, CV: cardiovascular

Notes: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first EAC-confirmed MACE. Subjects are censored at their planned end-of-trial visit, non-CV deaths or last direct subject-site contact, whichever comes first.
Abbreviations: EAC, event adjudication committee; sema, semaglutide.

Source: Figure 11-2 study report

The difference between semaglutide and placebo in time to first EAC-confirmed MACE among all randomized patients was analysed using a stratified Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor. The non-inferiority analysis was considered confirmatory. The estimated HR was 0.74 [0.58; 0.95]95%CI. Non-inferiority of semaglutide versus placebo was confirmed, with the upper bound of the 2-sided 95% CI for the HR being below 1.8. A post-hoc test for superiority provided a p-value of 0.0167.

Table 83 Time to First EAC-Confirmed MACE, Pre-Defined Test for Non-Inferiority and Post Hoc Test of Superiority; Semaglutide Versus Placebo - FAS In-Trial

Subjects with events (All subjects)	HR	95% CI	Test	p-value
Semaglutide/Placebo 108 (1648) / 146 (1649)	0.74	[0.58; 0.95]	Non-inferiority[a]:	<0.0001
			Superiority[a]:	0.0167

Notes: Analysis of time from randomisation to first EAC confirmed MACE. Subjects are censored at their planned end-of-trial visit, non-CV death or last direct subject-site contact, whichever comes first. Subjects without an event are censored at time of last contact (phone or visit) including unscheduled contacts.
[a] The test is based on the pre-specified Cox proportional hazard analysis using the two-sided Wald test, with treatment (semaglutide, placebo) as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomisation procedure (in total 9 levels).
Abbreviations: CI: confidence interval; EAC: event adjudication committee; FAS: full analysis set; HR: hazard ratio; MACE: major cardiovascular event.
Source: Table 11-4 study report

Post hoc analysis of time to first MACE reported in the on-treatment period showed consistent results with a HR of 0.73 (0.56; 0.96)95%CI and a p-value of 0.0253.

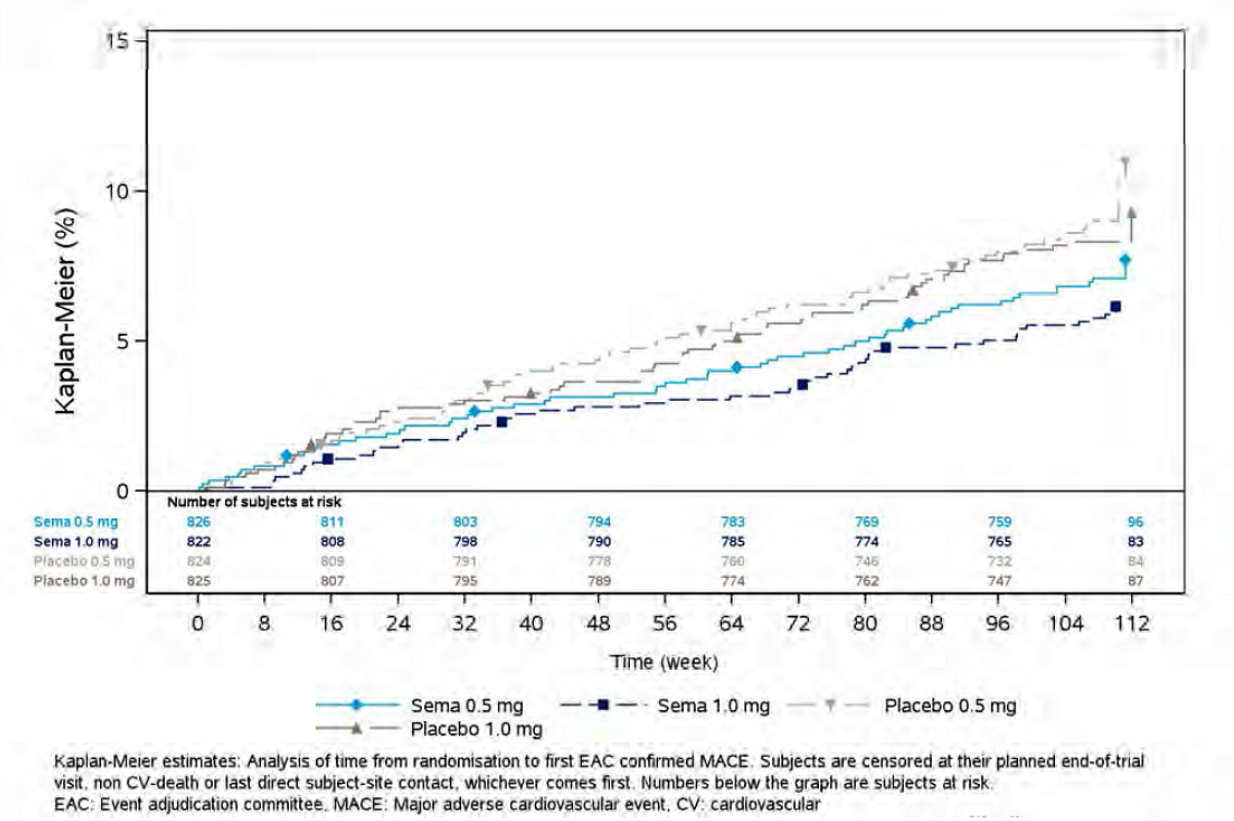
The semaglutide 0.5 mg vs placebo 0.5 mg and semaglutide 1 mg versus placebo 1.0 mg differences in time to first EAC-confirmed MACE among all randomized patients were analysed using a stratified Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor. Clinically relevant risk reductions relative to placebo were observed for both of the individual doses of semaglutide, with an apparent larger risk reduction with semaglutide 1 mg (HR: 0.71 [0.49; 1.02]95%CI) compared with semaglutide 0.5 mg (HR: 0.77 [0.55; 1.08]95%CI);

Table 84 EAC-Confirmed First MACE, Semaglutide by Dose Versus Placebo - FAS In-Trial – SUSTAIN 6

	Sema 0.5 mg			Sema 1.0 mg			Placebo 0.5 mg			Placebo 1.0 mg		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Subjects	826			822			824			825		
PYO	1708.4			1699.8			1694.9			1706.2		
First MACE	59	(7.1)		49	(6.0)		77	(9.3)		69	(8.4)	
CV death	19	(2.3)		18	(2.2)		20	(2.4)		20	(2.4)	
MI (non-fatal)	26	(3.1)		20	(2.4)		30	(3.6)		34	(4.1)	
Stroke (non-fatal)	14	(1.7)		11	(1.3)		27	(3.3)		15	(1.8)	
All MACE	59	(7.1)	69 4.0	49	(6.0)	60 3.5	77	(9.3)	79 4.7	69	(8.4)	86 5.0
CV death	21	(2.5)	21 1.2	23	(2.8)	23 1.4	21	(2.5)	21 1.2	25	(3.0)	25 1.5
MI (non-fatal)	26	(3.1)	32 1.9	21	(2.6)	26 1.5	30	(3.6)	30 1.8	34	(4.1)	45 2.6
Stroke (non-fatal)	16	(1.9)	16 0.9	11	(1.3)	11 0.6	28	(3.4)	28 1.7	16	(1.9)	16 0.9

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: CV: cardiovascular; E: number of events; EAC: event adjudication committee; MACE: major adverse cardiovascular event; MI: myocardial infarction; N: number of subjects; PYO: patient years of observation; R: event rate per 100 patient years of observation (PYO); %: percentage of subjects.
Source: Table 11-5 study report

Figure 29 Plot of Time to First EAC-Confirmed MACE, Semaglutide by Dose Versus Placebo - FAS In-Trial – SUSTAIN 6



Kaplan-Meier estimates: Analysis of time from randomisation to first EAC confirmed MACE. Subjects are censored at their planned end-of-trial visit, non CV-death or last direct subject-site contact, whichever comes first. Numbers below the graph are subjects at risk.
EAC: Event adjudication committee. MACE: Major adverse cardiovascular event, CV: cardiovascular

Notes: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first EAC-confirmed MACE. Subjects are censored at their planned end-of-trial visit, non-CV deaths or last direct subject-site contact, whichever comes first.
Abbreviations: sema, semaglutide.
Source: Figure 11-3 study report

Data Quality and Integrity - Reviewers' Assessment

The applicant submitted datasets and multiple documents addressing the study results. I did not find any issues with the data quality.

Efficacy Results - Secondary and other relevant endpoints

<u>Supportive secondary endpoints addressing the primary objective</u>

Time from randomization to first occurrence of an expanded composite CV outcome, defined as either MACE, revascularisation (coronary and peripheral), unstable angina requiring hospitalisation or hospitalisation for heart failure.

All the outcomes except peripheral revascularisation were based on EAC-confirmed events. Hence, EAC-reported onset dates are used for all adjudicated events, whereas investigator-reported onset date is used for peripheral revascularisation.

In case several events in a single patient had the same date of onset, the priority for selecting the first event was: CV death (including undetermined cause of death) > non-fatal acute MI > non-fatal silent MI > non-fatal stroke > hospitalisation for heart failure > hospitalisation for UAP > coronary revascularisation> peripheral revascularisation.

All events

The proportion of patients with events and the event rates were generally lower with semaglutide than with placebo. Revascularization, hospitalisation for heart failure and non-fatal MIs were the most frequent EAC-confirmed events, both with semaglutide and placebo.

Table 85 Expanded Cardiovascular Composite Endpoint (all events), Semaglutide Versus Placebo - FAS In-Trial – SUSTAIN 6

	Semaglutide				Placebo				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1648				1649				3297			
PYO	3408.2				3401.1				6809.3			
Expanded CV outcome	199	(12.1)	330	9.7	264	(16.0)	410	12.1	463	(14.0)	740	10.9
CV death	44	(2.7)	44	1.3	46	(2.8)	46	1.4	90	(2.7)	90	1.3
MI (non-fatal)	47	(2.9)	58	1.7	64	(3.9)	75	2.2	111	(3.4)	133	2.0
Stroke (non-fatal)	27	(1.6)	27	0.8	44	(2.7)	44	1.3	71	(2.2)	71	1.0
Revascularisation	83	(5.0)	96	2.8	126	(7.6)	146	4.3	209	(6.3)	242	3.6
UAP requiring hosp.	22	(1.3)	24	0.7	27	(1.6)	28	0.8	49	(1.5)	52	0.8
Hosp. for heart failure	59	(3.6)	81	2.4	54	(3.3)	71	2.1	113	(3.4)	152	2.2

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: CV: cardiovascular; E: number of events; EAC: event adjudication committee; MI: myocardial infarction; N: number of subjects; PYO: patient years of observation; R: event rate per 100 patient years of observation (PYO); UAP: unstable angina pectoris; %: percentage of subjects
Source: table 11-10 study report

First events

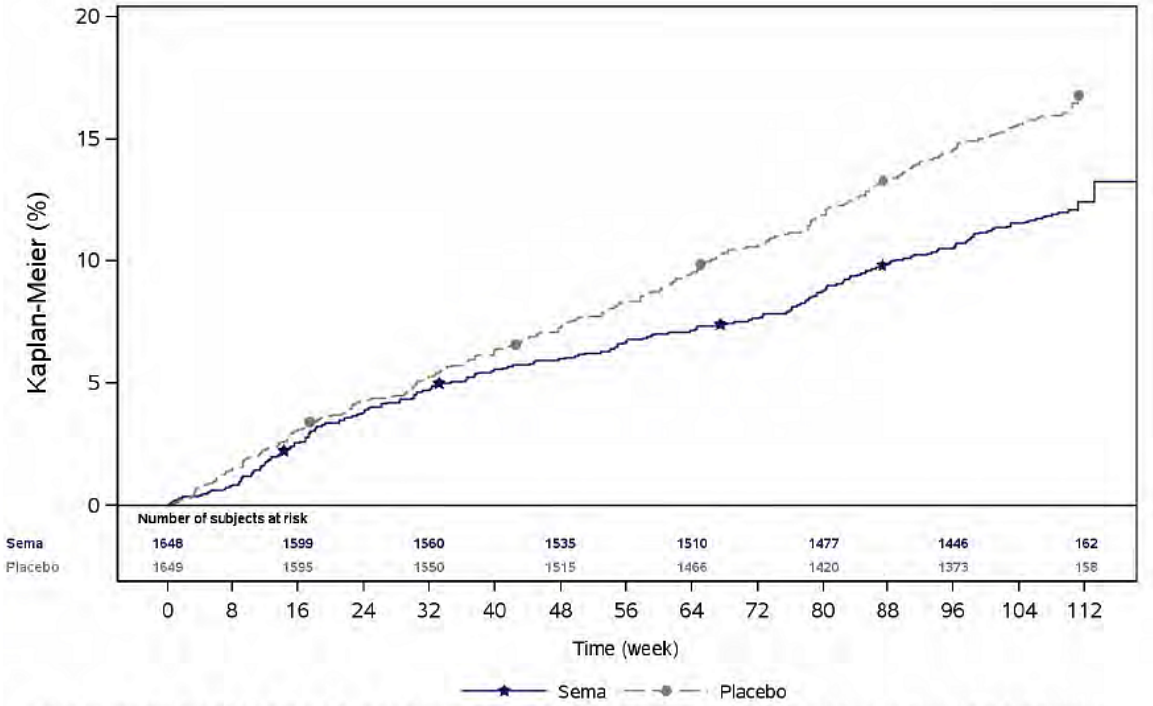
The proportion of patients with first events and the event rates were lower with semaglutide than with placebo; a total of 199 patients (12.1%) experienced events within the expanded CV composite endpoint with semaglutide versus 264 (16.0%) with placebo. The estimated HR was 0.74 [0.62; 0.89] 95%CI.

Table 86 First Events for Expanded Cardiovascular Composite Endpoint, Semaglutide Versus Placebo - FAS In-Trial – SUSTAIN 6

	Semaglutide N	(%)	Placebo N	(%)	Total N	(%)
Number of subjects	1648		1649		3297	
First expanded CV outcome	199	(12.1)	264	(16.0)	463	(14.0)
CV death	27	(1.6)	31	(1.9)	58	(1.8)
MI (non-fatal)	42	(2.5)	61	(3.7)	103	(3.1)
Stroke (non-fatal)	25	(1.5)	41	(2.5)	66	(2.0)
Revascularisation	43	(2.6)	70	(4.2)	113	(3.4)
UAP requiring hosp.	18	(1.1)	22	(1.3)	40	(1.2)
Hosp. for heart failure	44	(2.7)	39	(2.4)	83	(2.5)

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: CV: cardiovascular; E: number of events; EAC: event adjudication committee; hosp.: hospitalisation; MI: myocardial infarction; N: number of subjects; UAP: unstable angina pectoris; %: percentage of subjects
Source: Table 11-11 study report

Figure 30 Plot of Time to First Expanded Composite CV Outcome, Semaglutide Versus Placebo - FAS In-Trial – SUSTAIN 6



Kaplan-Meier estimates: Analysis of time from randomisation to first expanded cardiovascular outcome. Subjects are censored at their planned end-of-trial visit, non CV-death or last direct subject-site contact, whichever comes first. Numbers below the graph are subjects at risk.
CV: cardiovascular

Notes: Numbers below the figure represents number of subjects at risk. Cumulative incidence estimates: Analysis of time from randomisation to first expanded composite CV outcome with CV death modelled as competing risk. Subjects are censored at their planned end-of-trial visit, non-CV deaths or last direct subject-site contact, whichever comes first.
Abbreviations: CV: cardiovascular; EAC: event adjudication committee; sema: semaglutide.
Source: figure 11-13 study report

The number of events for the extended CV outcome are presented below by semaglutide dose. In addition to the components of the primary endpoint, the following endpoints are presented: revascularization, unstable angina requiring hospitalization, and hospitalization for heart failure. Patients on semaglutide do not appear to have a higher incidence for these ebvents compared to placebo. The hospitalization for heart failure endpoint will also be discussed in the safety section of this review.

Table 87 First and All Expanded Cardiovascular Composite Endpoint, Semaglutide by Dose Versus Placebo - FAS In-Trial- SUSTAIN 6

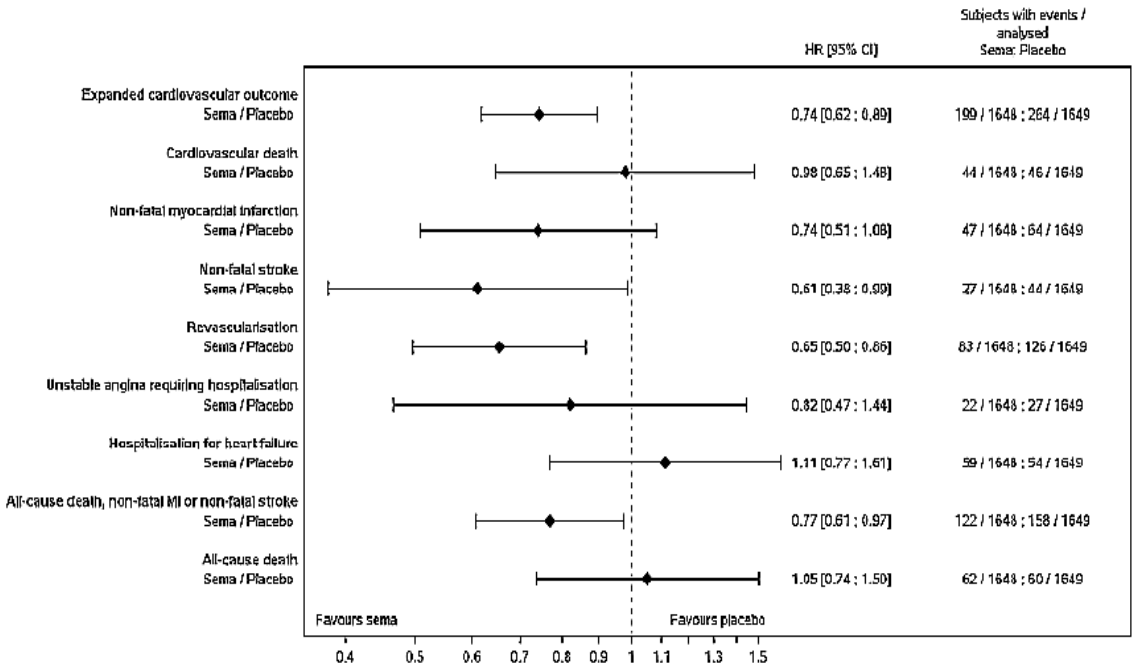
	Sema 0.5 mg				Sema 1.0 mg				Placebo 0.5 mg				Placebo 1.0 mg			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	826				822				824				825			
PYO	1708.4				1699.8				1694.9				1706.2			
First exp. outcome	109	(13.2)			90	(10.9)			137	(16.6)			127	(15.4)		
CV death	14	(1.7)			13	(1.6)			13	(1.6)			18	(2.2)		
MI (non-fatal)	24	(2.9)			18	(2.2)			29	(3.5)			32	(3.9)		
Stroke (non-fatal)	14	(1.7)			11	(1.3)			27	(3.3)			14	(1.7)		
Revascularisation	21	(2.5)			22	(2.7)			31	(3.8)			39	(4.7)		
UAP requiring hosp.	10	(1.2)			8	(1.0)			14	(1.7)			8	(1.0)		
Hosp. for HF	26	(3.1)			18	(2.2)			23	(2.8)			16	(1.9)		
Expanded outcome	109	(13.2)	187	10.9	90	(10.9)	143	8.4	137	(16.6)	202	11.9	127	(15.4)	208	12.2
CV death	21	(2.5)	21	1.2	23	(2.8)	23	1.4	21	(2.5)	21	1.2	25	(3.0)	25	1.5
MI (non-fatal)	26	(3.1)	32	1.9	21	(2.6)	26	1.5	30	(3.6)	30	1.8	34	(4.1)	45	2.6
Stroke (non-fatal)	16	(1.9)	16	0.9	11	(1.3)	11	0.6	28	(3.4)	28	1.7	16	(1.9)	16	0.9
Revascularization	45	(5.4)	54	3.2	38	(4.6)	42	2.5	63	(7.6)	70	4.1	63	(7.6)	76	4.5
UAP requiring hosp.	12	(1.5)	13	0.8	10	(1.2)	11	0.6	16	(1.9)	17	1.0	11	(1.3)	11	0.6
Hosp. for HF	37	(4.5)	51	3.0	22	(2.7)	30	1.8	29	(3.5)	36	2.1	25	(3.0)	35	2.1

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: CV: cardiovascular; E: number of events; EAC: event adjudication committee; exp: expanded; HF: heart failure; MI: myocardial infarction; N: number of subjects; PYO: patient years of observation; R: event rate per 100 patient years of observation; sema: semaglutide; UAP: unstable angina pectoris; %: percentage of subjects.
Source: table 11-12 study report

Time from randomization to each individual component of the expanded composite CV outcome.

The numbers of events with semaglutide and placebo are shown for the expanded MACE and composite CV outcome endpoints as well as for each of the individual components, and the associated hazard ratios. Most of these endpoints have a hazard ratio favoring semaglutide. CV death, and all-cause death, andn hospitalization for heart failure, appear to be balanced between semaglutide and placebo.

Figure 31 Forest Plot on Time to First Expanded Composite CV Outcome and Individual Components, Semaglutide Versus Placebo – FAS In-Trial – SUSTAIN 6



HR: Estimated hazard ratio CI: confidence interval. Summary of results from analyses of time to components of expanded cardiovascular outcome. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with treatment (semaglutide, placebo) as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomisation procedure (in total 9 levels).

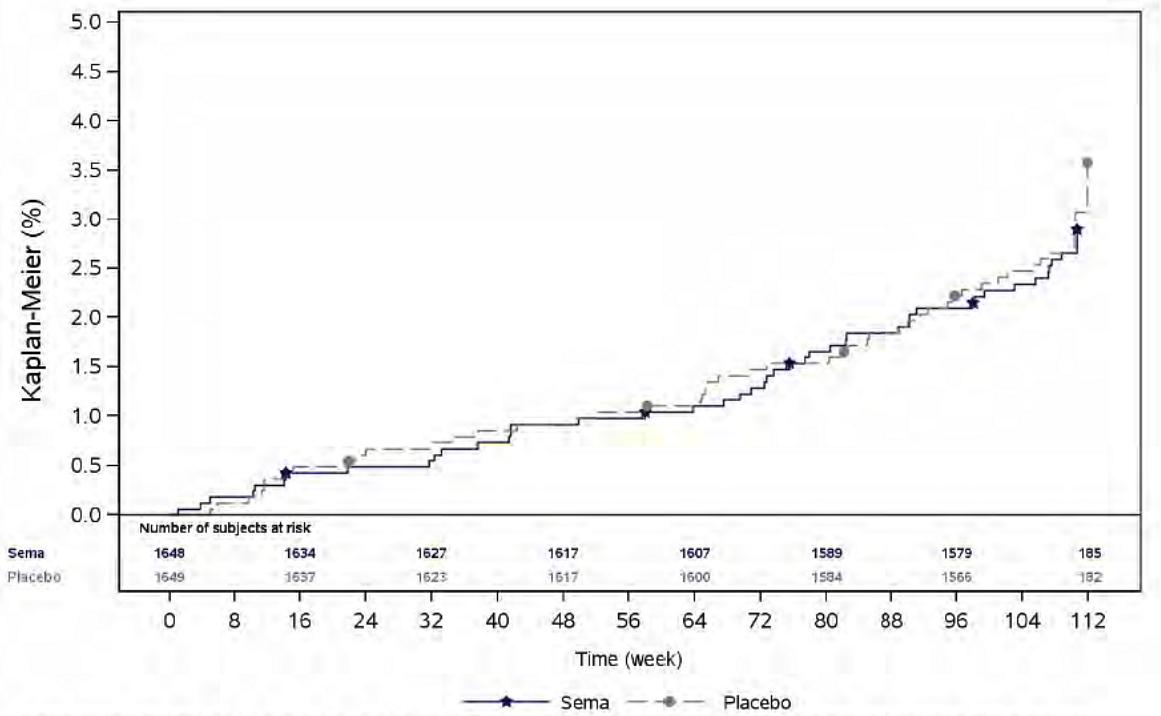
Notes: Summary of results from analysis of expanded CV outcome and components. Estimated HRs and associated CIs are from a Cox proportional hazards model with treatment (semaglutide; placebo) as a fixed factor and stratified by all possible combinations of the three stratification factors used in the randomisation procedure (in total 9 levels).
Abbreviations: CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio; sema: semaglutide.

Source: Figure 11-15 study report

CV death

Deaths classified by the EAC as CV deaths included deaths due to undetermined causes. A total of 44 CV deaths with semaglutide and 46 CV deaths with placebo were confirmed by the EAC for the in-trial period, and the analysis of treatment difference showed an HR of 0.98 [0.65; 1.48]95% CI, suggesting no difference between the treatment arms. The Kaplan-Meier time to event plot also shows no difference between semaglutide and placebo.

Figure 32 Kaplan Meier Plot of Time to First EAC-Confirmed CV Death – FAS In–Trial – SUSTAIN 6



Kaplan-Meier estimates: Analysis of time from randomisation to EAC confirmed cardiovascular death. Subjects are censored at their planned end-of-trial visit, non CV-death or last direct subject-site contact, whichever comes first. Numbers below the graph are subjects at risk.
EAC: Event adjudication committee

Note: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first outcome. Subjects are censored at their planned end-of-trial visit, deaths or last direct subject-site contact, whichever comes first.
Abbreviations: EAC:event adjudication committee; sema: semaglutide

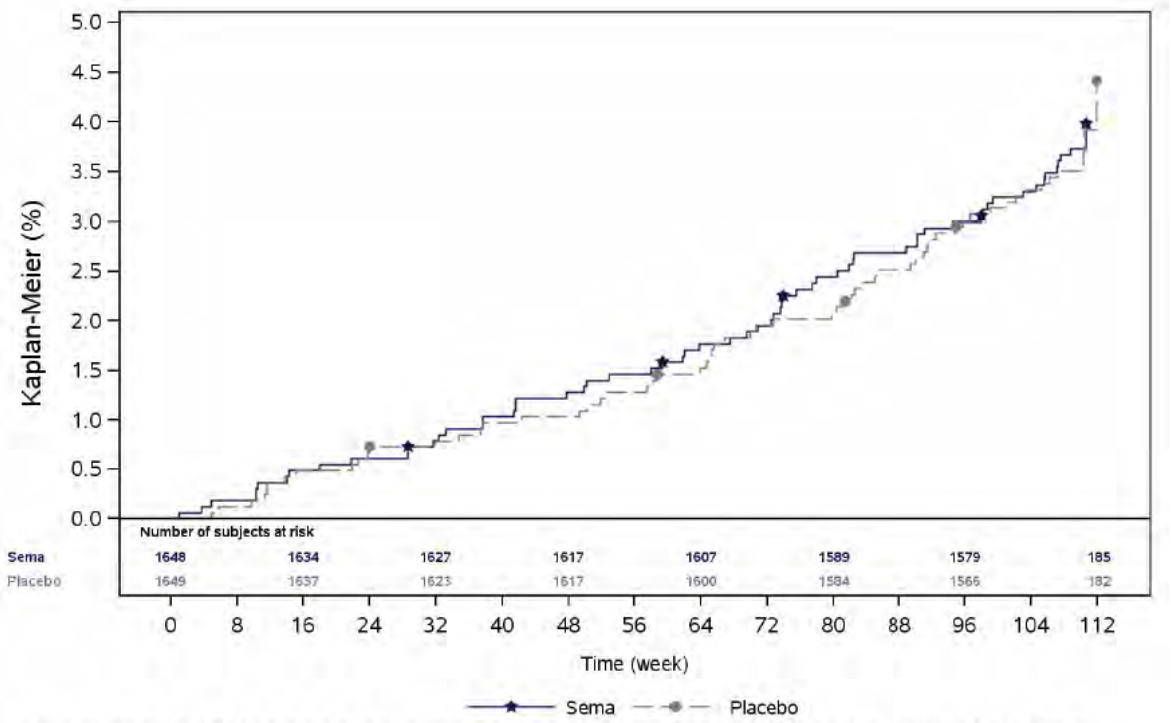
Source: Figure 11-16 study report

Time from randomization to first occurrence of all-cause death, non-fatal MI, or non-fatal stroke.

All-cause death

As seen for CV death, no difference was observed between the treatment arms regarding all-cause death. A total of 62 all-cause deaths were confirmed with semaglutide versus 60 with placebo. The analysis of treatment difference also showed no difference, with a HR of 1.05 [0.74; 1.50]95%CI; p=0.7854. No effect of semaglutide dose level was apparent.

Figure 33 Kaplan Meier Plot of Time to EAC-Confirmed All-Cause Death – FAS In–Trial – SUSTAIN 6



Kaplan-Meier estimates: Analysis of time from randomisation to first EAC confirmed all-cause death. Subjects are censored at their planned end-of-trial visit or last direct subject-site contact, whichever comes first. Numbers below the graph are subjects at risk.
EAC: Event adjudication committee

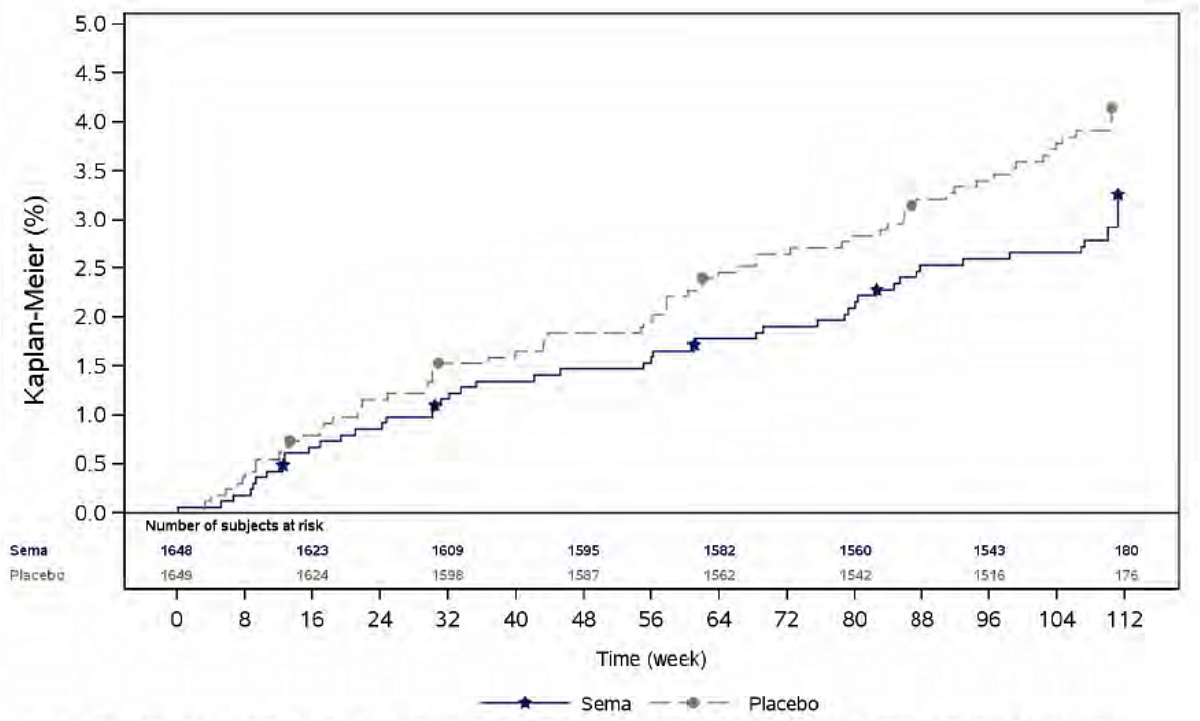
Note: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first outcome. Subjects are censored at their planned end-of-trial visit, deaths or last direct subject-site contact, whichever comes first.
Abbreviations: EAC:event adjudication committee; sema: semaglutide.

Source: Figure 11-27 study report

Non-fatal MI

A total of 47 first non-fatal MIs (acute and silent) were confirmed with semaglutide versus 64 with placebo. The analysis of treatment difference showed a HR of 0.74 [0.51; 1.08]95% CI, p=0.1194. The estimated cumulative risk of non-fatal MI at week 104 was 2.7% with semaglutide and 3.8% with placebo.

Figure 34 Kaplan Meier Plots of Time to First EAC-Confirmed Non-Fatal MI – FAS In–Trial – SUSTAIN 6



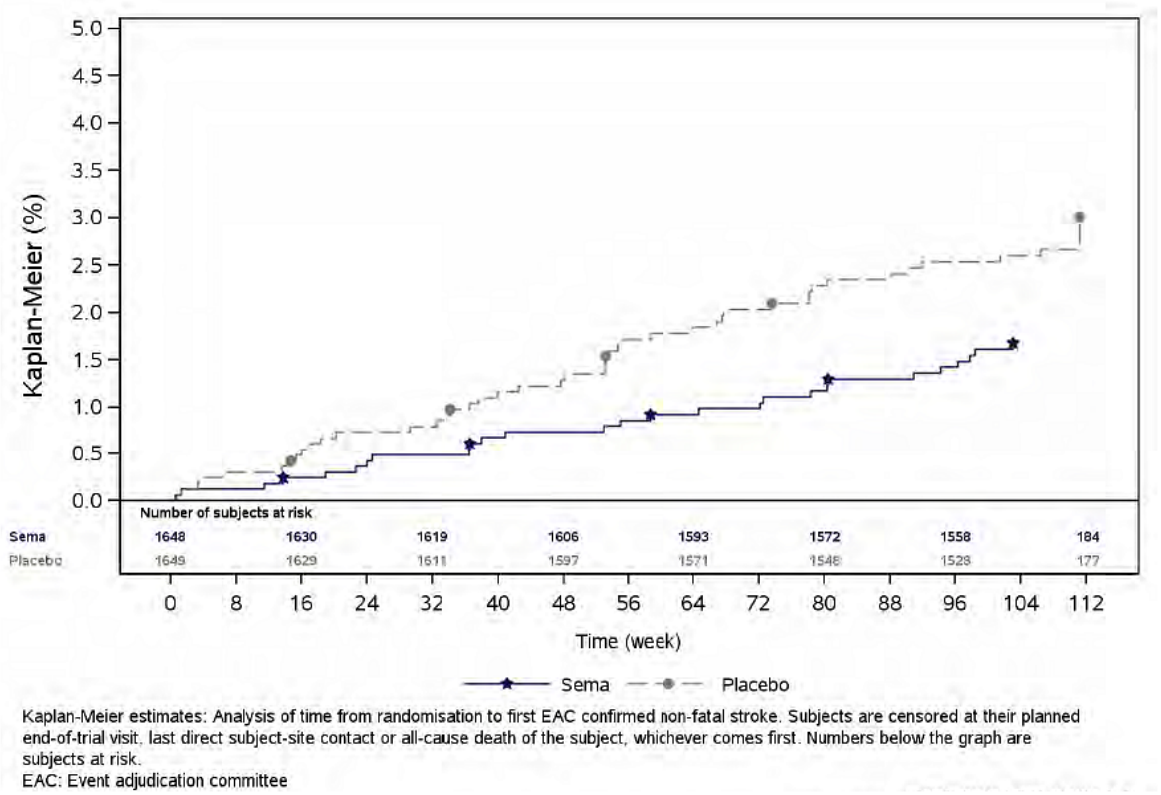
Kaplan-Meier estimates: Analysis of time from randomisation to first EAC confirmed non-fatal myocardial infarction. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact or all-cause death of the subject, whichever comes first. Numbers below the graph are subjects at risk.
EAC: Event adjudication committee

Note: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first outcome. Subjects are censored at their planned end-of-trial visit, deaths or last direct subject-si contact, whichever comes first.
Abbreviations: EAC:event adjudication committee; sema: semaglutide
Source: Figure 11-17 study report

Non-fatal stroke

A total of 27 first non-fatal strokes were confirmed with semaglutide versus 44 with placebo. The analysis of treatment difference showed a HR of 0.61 [0.38; 0.99]95% CI (p=0.0438). No effect of semaglutide dose level was apparent.

Figure 35 Kaplan Meier Plots of Time to First EAC-Confirmed Non-Fatal Stroke – FAS In–Trial SUSTAIN 6



Kaplan-Meier estimates: Analysis of time from randomisation to first EAC confirmed non-fatal stroke. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact or all-cause death of the subject, whichever comes first. Numbers below the graph are subjects at risk.
EAC: Event adjudication committee

Note: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first outcome. Subjects are censored at their planned end-of-trial visit, deaths or last direct subject-site contact, whichever comes first.
Abbreviations: EAC:event adjudication committee; sema: semaglutide
Source: Figure 11-18 study report

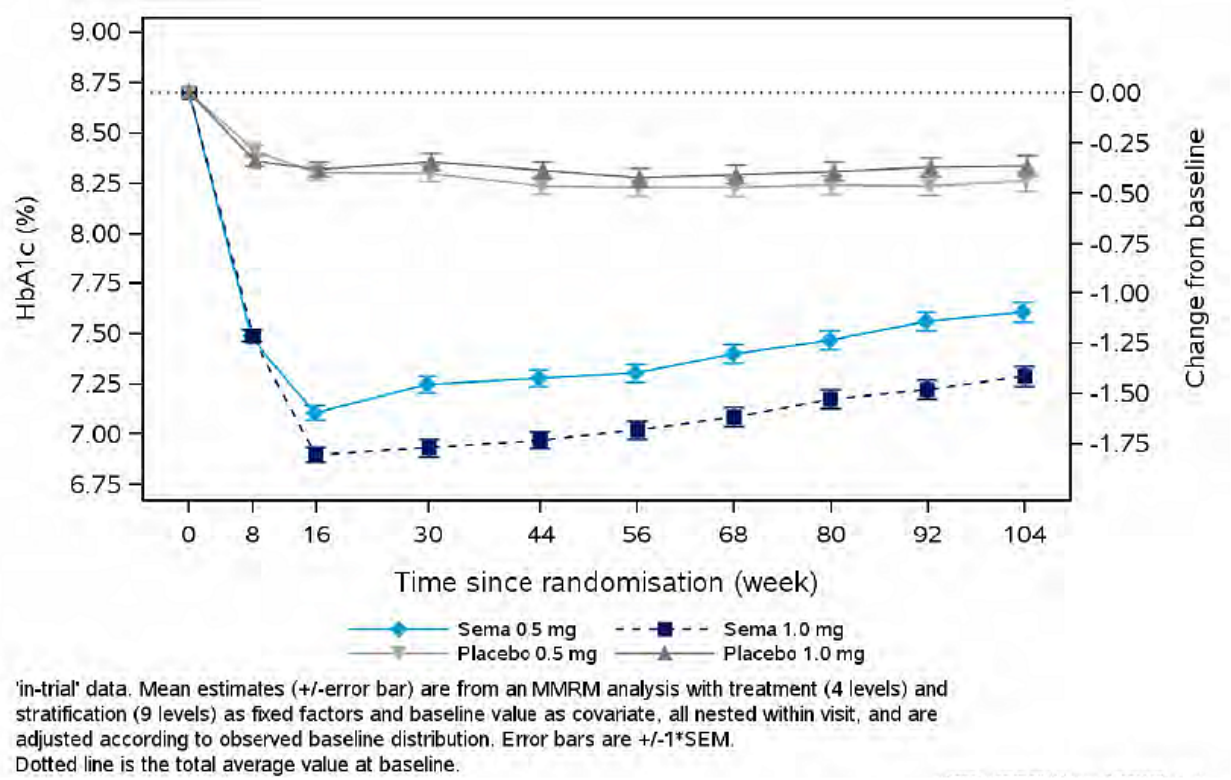
Change from baseline to week 104 in HbA1c

Although SUSTAIN 6 was a standard-of-care trial that aimed for optimal glycemic control for all patients, and investigators were thus encouraged to prescribe additional glucose-lowering medication in an attempt to reach glycemic control, the change in HbA1C was one of the many secondary outcomes.

For all four treatment groups, decreases in HbA1c were seen at week 104 with semaglutide demonstrating a larger decrease in HbA1c compared with placebo. From a mean baseline level of 8.70%, HbA1c levels had decreased at week 104 by 1.09 %-points and 1.41 %-points with semaglutide 0.5 mg and 1.0 mg, respectively, and by 0.44 %-point and 0.36 %-point, with placebo 0.5 mg and 1.0 mg, respectively. With semaglutide, the nadir in HbA1c occurred around week 16, with placebo HbA1c also reached a plateau after approximately 16 weeks.

With semaglutide, a small drift upwards in HbA1c was seen from week 16 and until week 104, while the decrease in HbA1c with placebo remained constant until week 104.

Figure 36 Mean HbA1c (%) by Treatment Week - FAS In-Trial – SUSTAIN 6



'in-trial' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
Dotted line is the total average value at baseline.

Source Table 12-1 study report

Although, with this trial design, the difference in HbA1c between treatment arms was set to be minimal, this trial is unusual in the sense that both semaglutide doses lead to statistically different reduction in HbA1c compared to the standard of care group. Notably, these differences are also clinically meaningful, and make the interpretation of the primary and secondary endpoints quite difficult. The evaluation of HbA1c change from baseline to last assessment for the in-trial, and on-treatment, observation periods supported the statistical conclusions, with larger estimated treatment differences with semaglutide when evaluating the on-treatment observation period.

Table 88 HbA1c - Statistical Analysis - MMRM – FAS In-Trial – SUSTAIN 6

	FAS	N	Estimate	SE	95% CI	p-value
HbA1c (%)						
Mean at visit 25 (week 104)						
Sema 0.5 mg	826	741	7.61	0.05		
Sema 1.0 mg	822	731	7.29	0.05		
Placebo 0.5 mg	824	724	8.26	0.05		
Placebo 1.0 mg	825	724	8.34	0.05		
Change from baseline at visit 25 (week 104)						
Sema 0.5 mg	826	741	-1.09	0.05		
Sema 1.0 mg	822	731	-1.41	0.05		
Placebo 0.5 mg	824	724	-0.44	0.05		
Placebo 1.0 mg	825	724	-0.36	0.05		
Treatment difference at visit 25 (week 104)						
Sema 0.5 mg - Placebo 0.5 mg			-0.66		[-0.80 ; -0.52]	<.0001
Sema 1.0 mg - Placebo 1.0 mg			-1.05		[-1.19 ; -0.91]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'in-trial' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Source: Table 12-1 study report

Additionally, a higher proportion of patients on either semaglutide dose achieved various HbA1c targets set by professional organizations, and a dose-response for semaglutide was observed.

Table 89 Patients Achieving HbA1c Response after 104 Weeks - FAS In-Trial – SUSTAIN 6

	FAS	N	R	Estimate	SE	95% CI	p-value
HbA1c <7.0% (ADA)							
Estimated odds at visit 25 (week 104)							
Sema 0.5 mg	826	826	319	0.58	0.04		
Sema 1.0 mg	822	822	403	0.95	0.07		
Placebo 0.5 mg	824	824	134	0.16	0.02		
Placebo 1.0 mg	825	825	126	0.15	0.02		
Estimated odds ratio at visit 25 (week 104)							
Sema 0.5 mg / Placebo 0.5 mg				3.63		[2.85 ; 4.63]	<.0001
Sema 1.0 mg / Placebo 1.0 mg				6.31		[4.93 ; 8.07]	<.0001
HbA1c ≤ 6.5% (AACE)							
Estimated odds at visit 25 (week 104)							
Sema 0.5 mg	826	826	191	0.26	0.02		
Sema 1.0 mg	822	822	277	0.47	0.04		
Placebo 0.5 mg	824	824	60	0.06	0.01		
Placebo 1.0 mg	825	825	63	0.07	0.01		
Estimated odds ratio at visit 25 (week 104)							
Sema 0.5 mg / Placebo 0.5 mg				4.10		[3.00 ; 5.62]	<.0001
Sema 1.0 mg / Placebo 1.0 mg				6.82		[5.05 ; 9.23]	<.0001

ADA: American Diabetes Association, AACE: American Association of Clinical Endocrinologists
N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval, SE: standard error. Analysis of 'in-trial' data. The binary endpoint is analysed using a logistic regression model with treatment (4 levels) and stratification (9 levels) as fixed factors and the baseline HbA1c value as covariate. Before analysis, missing data are imputed from a mixed model for repeated measures with treatment (4 levels) and stratification (9 levels) and baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.

Source: Table 12-2 study report

Requirement of additional glucose-lowering medications

As expected, at week 104, fewer patients with semaglutide 0.5 mg and 1.0 mg (21% and 19%) had addition of glucose-lowering medication during the trial compared with placebo 0.5 mg and 1.0 mg (42% and 39%) in an attempt to achieve glycemic control. The types of glucose-lowering mediations initiated during the trial are summarized below. With placebo, the type of glucose-lowering medication initiated was distributed evenly between insulin treatment (24.8% and 23.2% of patients with placebo 0.5 mg and 1.0 mg) and non-insulin glucose-lowering medication (24.2% and 23.9% of patients with placebo 0.5 mg and 1.0 mg). With semaglutide, the type of glucose-lowering medication initiated was distributed in favour of the non-insulin glucose-lowering medication (12.6% and 13.5% with semaglutide 0.5 mg and 1.0 mg) compared with insulin treatment (10.3% and 8.5% with semaglutide 0.5 mg and 1.0 mg).

Table 90 Additional Diabetes Medication During the Trial – FAS – SUSTAIN 6

	Sema 0.5 mg N	(%)	Sema 1.0 mg N	(%)	Placebo 0.5 mg N	(%)	Placebo 1.0 mg N	(%)
Number of subjects in FAS	826		822		824		825	
Glucose-lowering medication	172	(20.8)	160	(19.5)	345	(41.9)	325	(39.4)
Insulin treatment	85	(10.3)	70	(8.5)	204	(24.8)	191	(23.2)
Basal insulin	31	(3.8)	20	(2.4)	98	(11.9)	93	(11.3)
Basal+bolus insulin	60	(7.3)	50	(6.1)	123	(14.9)	118	(14.3)
Addition of bolus insulin	2	(0.2)	5	(0.6)	7	(0.8)	1	(0.1)
Non-insulin glucose-lowering medication	104	(12.6)	111	(13.5)	199	(24.2)	197	(23.9)
Alpha glucosidase inhibitors	1	(0.1)	4	(0.5)	8	(1.0)	11	(1.3)
Biguanides	30	(3.6)	21	(2.6)	46	(5.6)	29	(3.5)
Glucose-lowering combination therapy	4	(0.5)	0		4	(0.5)	2	(0.2)
DPP4-inhibitors	14	(1.7)	22	(2.7)	32	(3.9)	21	(2.5)
GLP-1 receptor agonists	8	(1.0)	15	(1.8)	7	(0.8)	9	(1.1)
Meglitinides	7	(0.8)	4	(0.5)	14	(1.7)	13	(1.6)
SGLT-2 inhibitors	21	(2.5)	23	(2.8)	40	(4.9)	53	(6.4)
Sulfonylureas	29	(3.5)	32	(3.9)	60	(7.3)	67	(8.1)
Thiazolidinediones	7	(0.8)	7	(0.9)	30	(3.6)	28	(3.4)

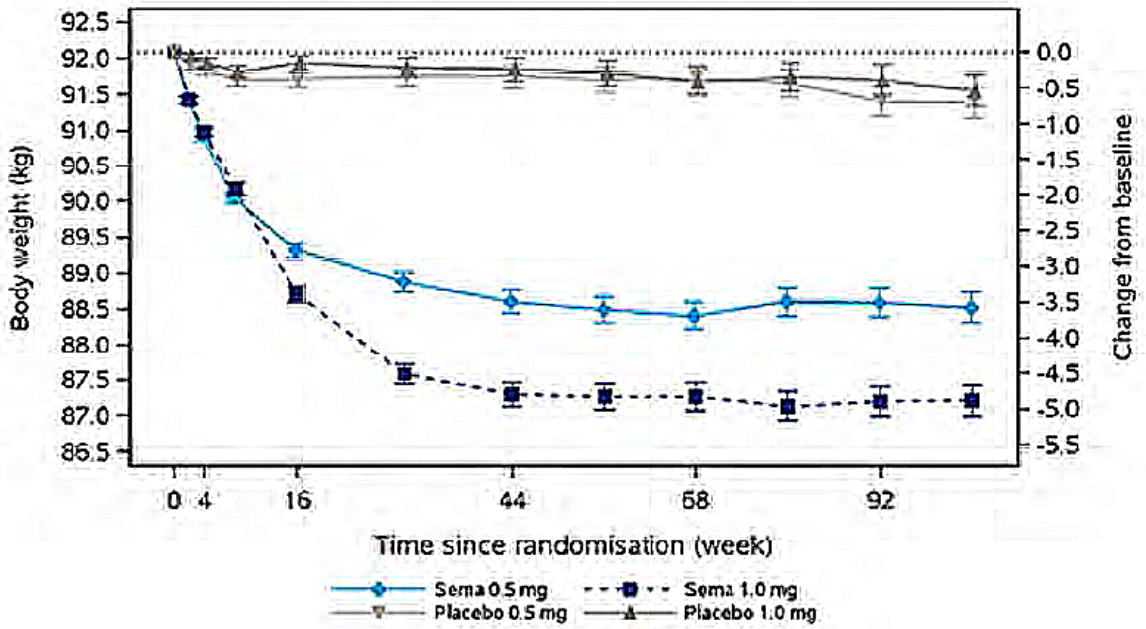
Notes: 'In-trial' data. Addition of glucose-lowering medication is defined as treatment for more than three consecutive weeks with a glucose lowering agent not used at randomisation.
Abbreviations: DPP-4: dipeptidyl peptidase-4, FAS: full analysis set, GLP-1: glucagon like-peptide 1, N: number of subjects in the summary statistic, SGLT-2: sodium-dependent glucose transporter two, %: percentage of subjects
Source: Table 10-18 study report

While overall more patients on placebo received additional anti-diabetic medications during the trial compared to patients on semaglutide (approximately 40% of patients on placebo vs approximately 20% of patients on semaglutide), the difference in glycemic control observed in the first 16 weeks after initiation of semaglutide persisted over the duration of the trial. This may be due still to lack of treatment optimization on the placebo arm. We do not know how well the insulin treatment was optimized, and insulin accounted for more than half of the anti-diabetic medications added during the trial. For the oral medications, dosing is not available, and the differences between placebo and semaglutide for any specific class of drugs are minor.

Body weight

A secondary confirmatory endpoint was change from baseline to week 104 in body weight (kg). Mean body weight at baseline was similar between treatment groups. With semaglutide, mean body weight started to decline from week 4 and reached a plateau after approximately one year of treatment (around week 44) and this reduction was maintained for the rest of the trial. Both semaglutide doses resulted in greater weight reduction at the 104 weeks cut-off compared to placebo, and a dose-response was apparent for semaglutide. Notably, this was in the context where insulin and sulfonylureas made up most of the anti-diabetic medications added during the trial as rescue for the placebo arm, and both these classes of medications are associated with weight gain.

Figure 37 Mean Body Weight (kg) by Treatment Week - FAS In-Trial – SUSTAIN 6



'in-trial' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
Dotted line is the total average value at baseline.

Source: Figure 12-8 study report

Table 91 Body Weight - Confirmatory Statistical Analysis - MMRM – FAS In-Trial – SUSTAIN 6

	FAS	N	Estimate	SE	95% CI	p-value
Body weight (kg)						
Mean at visit 25 (week 104)						
Sema 0.5 mg	826	742	88.53	0.21		
Sema 1.0 mg	822	736	87.21	0.22		
Placebo	1649	1448	91.48	0.15		
Change from baseline at visit 25 (week 104)						
Sema 0.5 mg	826	742	-3.57	0.21		
Sema 1.0 mg	822	736	-4.88	0.22		
Placebo	1649	1448	-0.62	0.15		
Treatment difference at visit 25 (week 104)						
Sema 0.5 mg - Placebo			-2.95		[-3.47 ; -2.44]	<.0001
Sema 1.0 mg - Placebo			-4.27		[-4.78 ; -3.75]	<.0001

N: Number of subjects contributing to analysis, SE: Standard error, CI: Confidence interval.
Observed 'in-trial' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. All visits were done in fasting state.

Source: Table 12-5 study report

Further, the applicant identified patients achieving weight loss of ≥5% or ≥10%. A weight loss response of ≥5% was reached for more patients with semaglutide 0.5 mg (36%) and 1.0 mg (47%) compared with placebo 0.5 mg (18%) and 1.0 mg (19%). A weight loss response of ≥10% was observed in a higher proportion pf patients on semaglutide 0.5 mg (13%) and 1.0 mg (20%) reached this criterion compared with placebo 0.5 mg (6%) and 1.0 mg (7%).

Table 92 Patients Achieving Weight Loss Response After 104 Weeks - FAS In-Trial - SUSTAIN 6

	FAS	N	R	Estimate	SE	95% CI	p-value
Body Weight Loss ≥ 10%							
Estimated odds at visit 25 (week 104)							
Sema 0.5 mg	826	825	109	0.15	0.02		
Sema 1.0 mg	822	821	168	0.26	0.02		
Placebo 0.5 mg	824	822	47	0.06	0.01		
Placebo 1.0 mg	825	823	54	0.07	0.01		
Estimated odds ratio at visit 25 (week 104)							
Sema 0.5 mg / Placebo 0.5 mg				2.53		[1.77 ; 3.61]	<.0001
Sema 1.0 mg / Placebo 1.0 mg				3.71		[2.68 ; 5.12]	<.0001
Body Weight Loss ≥ 5%							
Estimated odds at visit 25 (week 104)							
Sema 0.5 mg	826	825	297	0.56	0.04		
Sema 1.0 mg	822	821	383	0.88	0.06		
Placebo 0.5 mg	824	822	144	0.21	0.02		
Placebo 1.0 mg	825	823	154	0.23	0.02		
Estimated odds ratio at visit 25 (week 104)							
Sema 0.5 mg / Placebo 0.5 mg				2.68		[2.13 ; 3.37]	<.0001
Sema 1.0 mg / Placebo 1.0 mg				3.84		[3.07 ; 4.80]	<.0001

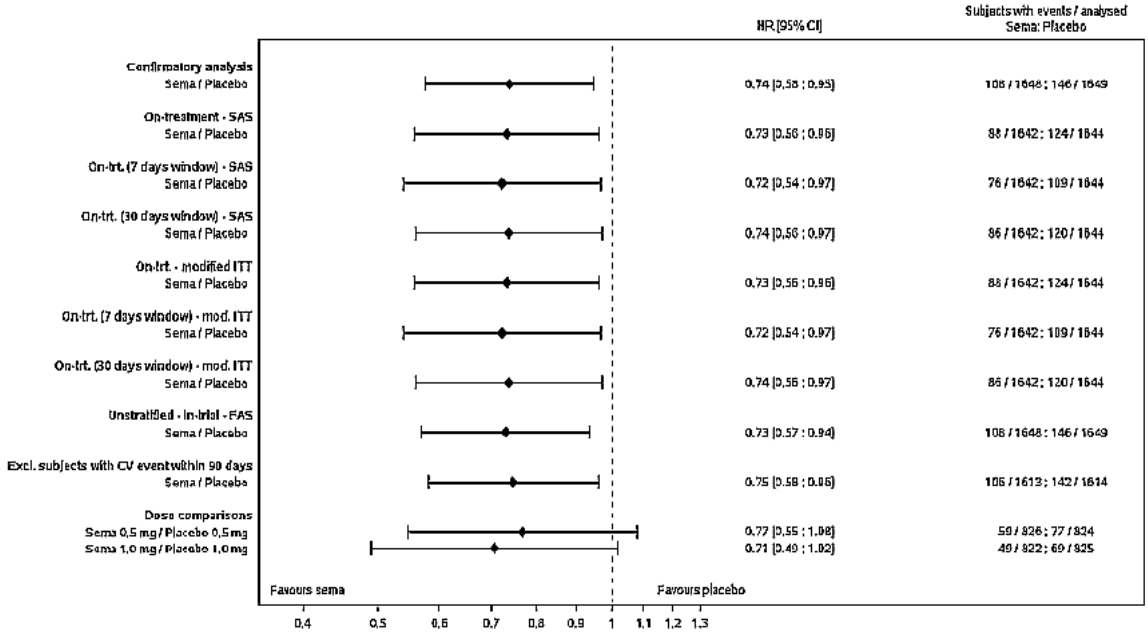
N: Number of subjects contributing to analysis, R: Number of subjects responding, CI: Confidence interval. Analysis of 'in-trial' data. The binary endpoint is analysed using a logistic regression model with treatment (4 levels) and stratification (9 levels) as fixed factors and the baseline weight value as covariate. Before analysis, missing data are imputed from a mixed model for repeated measures with treatment (4 levels) and stratification (9 levels) and baseline value, all nested within visit.
SE calculated on log-scale and back-transformed to original scale using the delta-method.
Source: Table 12-6 study report

All these findings are consistent with what is expected for the GLP-1 RA class of drugs.

Sensitivity and subgroup analyses of the primary endpoint

In order to assess the robustness of the primary analysis results, the applicant performed multiple sensitivity analyses as outlined in the figure below.

Figure 38 Forest Plot on Sensitivity Analyses of Time to First EAC-Confirmed MACE SUSTAIN 6



HR: Estimated hazard ratio CI: confidence interval, FAS: Full analysis set, SAS: Safety analysis set, ITT: Intention to treat, CV: Cardiovasvular, Excl: excluding.
Summary of results from analyses of time to first EAC confirmed MACE. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with treatment as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomisation procedure (in total 9 levels).

Notes: Summary of results from analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from a Cox proportional hazards model with treatment as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomisation process (9 levels in total).

Abbreviations: CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; Excl: excluding; FAS: full analysis set; HR: hazard ratio; ITT: intention-to-treat; mod: modified; On-trt: on-treatment observation period; SAS: safety analysis set; sema: semaglutide.

Source: Figure 11-4 study report

The results of the sensitivity analyses were consistent with the results from the primary analysis.

Subgroup analyses of the primary endpoint

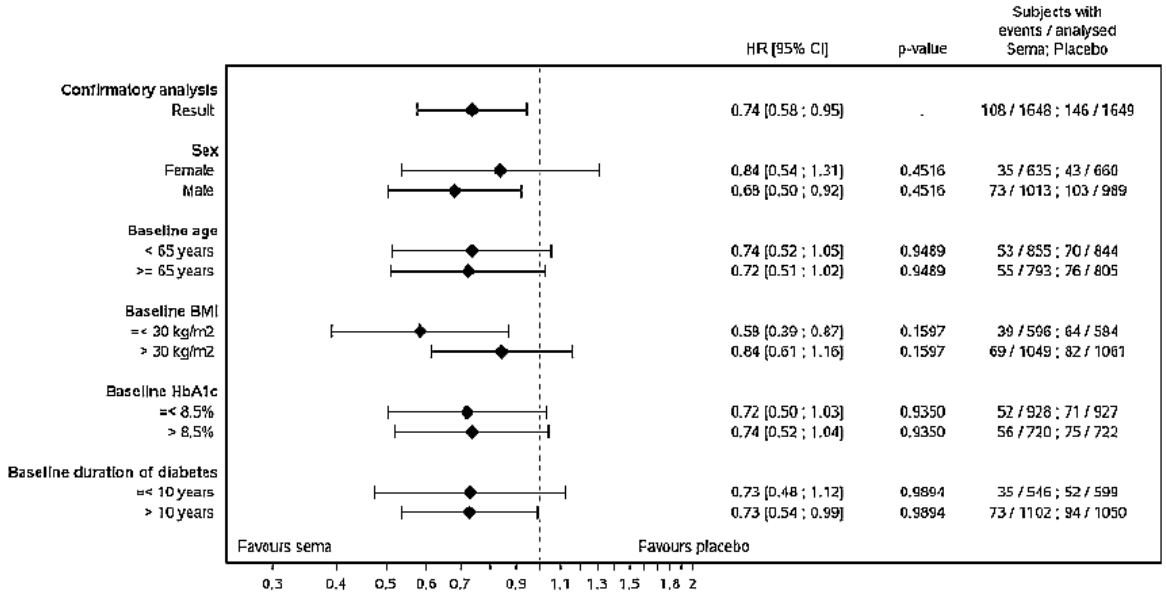
The consistency in the treatment effect for the primary endpoint was explored separately by the following pre-planned subgroups based on baseline information:

- Sex
- Age: <65 years or ≥65 years
- BMI: ≤30 kg/m2 or >30 kg/m2
- HbA1c: ≤8.5% or >8.5%
- Duration of diabetes: ≤10 years or >10 years
- Region defined as:
  o EU
  o United States

o Rest of the World

- Race defined as White, Black or African-American, Asian, or 'Other'
- Ethnicity defined as Hispanic or Latino (Yes or No)
- Chronic heart failure NYHA class II–III (Yes or No)
- Evidence of CV disease (clinical or subclinical) (stratification factor)
- Insulin treatment (none, basal insulin or pre-mixed insulin) (stratification factor)
- Severe renal impairment with GFR value <30 mL/min/1.73m2 per MDRD (Yes or No) (stratification factor)
- Severe or moderate renal impairment with GFR value <60 mL/min/1.73 m2 per MDRD (Yes or No)
- Severe renal impairment with GFR value <30 mL/min/1.73 m2 per CKD-Epi (Yes or No)
- Severe or moderate renal impairment with GFR value <60 mL/min/1.73m2 per CKD-Epi (Yes or No)

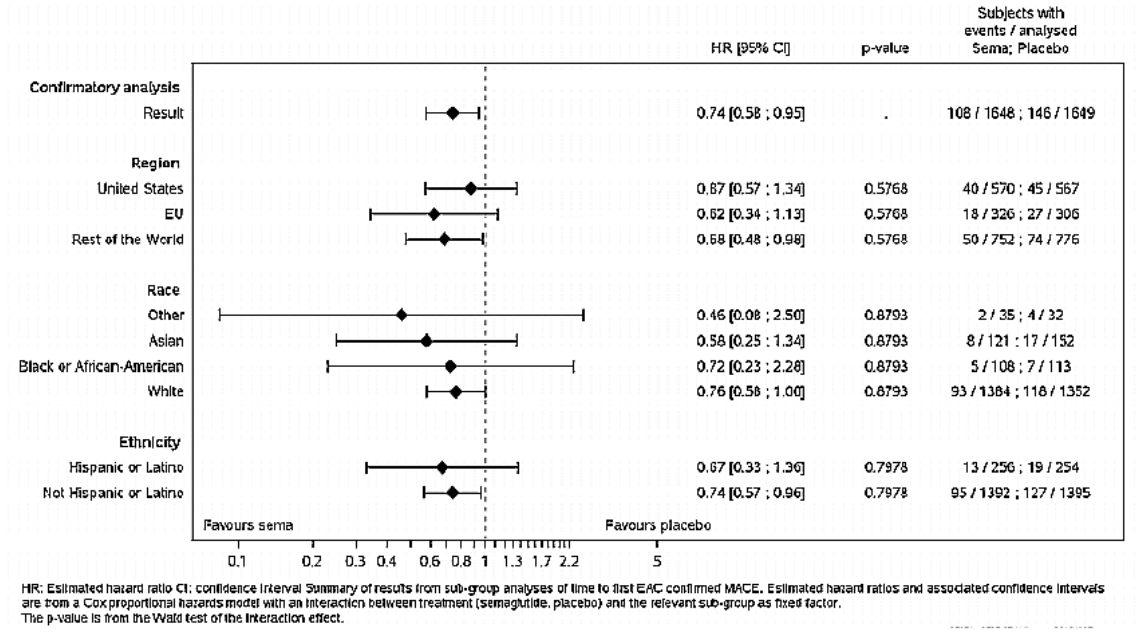
Figure 39 Forest Plot on Time to First EAC-Confirmed MACE, Statistical Subgroup Analyses for Sex, Age, BMI, HbA1c and Duration of Diabetes - FAS In-Trial- SUSTAIN 6



HR: Estimated hazard ratio CI: confidence interval Summary of results from sub-group analyses of time to first EAC confirmed MACE. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and the relevant sub-group as fixed factor.
The p-value is from the Wald test of the interaction effect.

Notes: Summary of results from subgroup analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment (semaglutide; placebo) and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction, i.e. for test of simplification of the model by omission of the interaction; the smaller the p-value, the stronger the evidence against such simplification. For each subgroup analysis, the p-value is repeated to avoid mistaken it for a p-value for test of treatment effect within a given subgroup level.
Abbreviations: BMI: body mass index; CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio; sema: semaglutide.
Source: Figure 11-5 study report

Figure 40 Forest Plot on Time to First EAC-Confirmed MACE, Statistical Subgroup Analyses for Region, Race and Ethnicity - FAS In-Trial – SUSTAIN 6

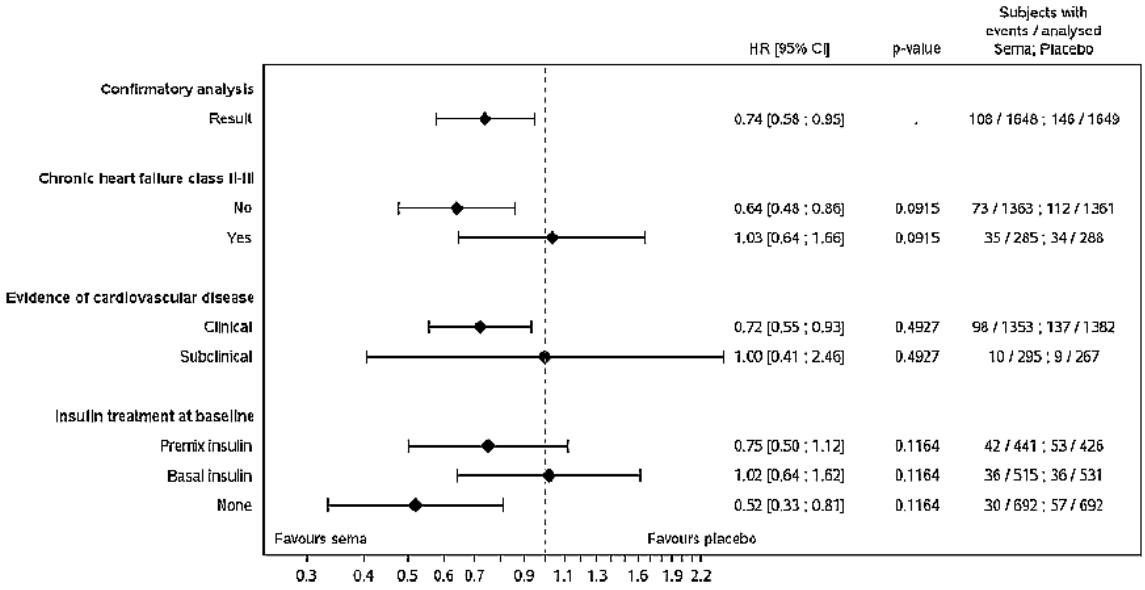


Notes: Summary of results from subgroup analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment (semaglutide; placebo) and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction, i.e. for test of simplification of the model by omission of the interaction; the smaller the p-value, the stronger the evidence against such simplification. For each subgroup analysis, the p-value is repeated to avoid mistaken it for a p-value for test of treatment effect within a given subgroup level.

Abbreviations: CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; EU: European Union; HR: hazard ratio; sema: semaglutide.

Source: Figure 11-6 study report

Figure 41 Forest Plot on Time to First EAC-Confirmed MACE, Statistical Subgroup Analyses for Chronic Heart Failure Class II-III, Evidence of Cardiovascular Disease and Insulin Treatment at Baseline - FAS In-Trial – SUSTAIN 6

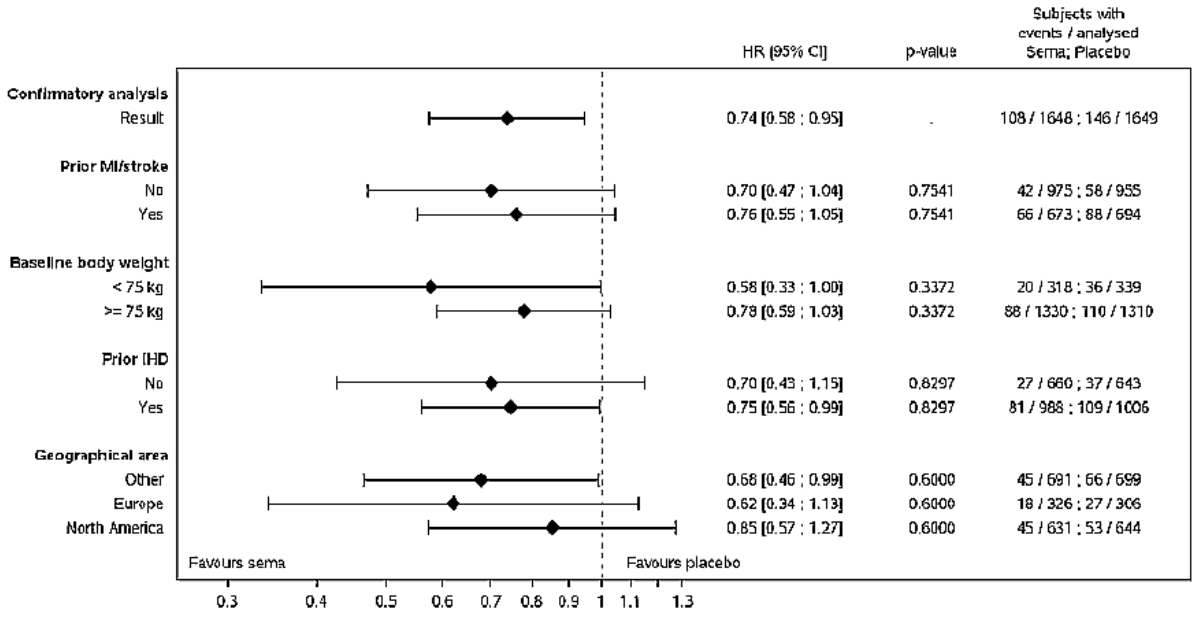


HR: Estimated hazard ratio CI: confidence interval Summary of results from sub-group analyses of time to first EAC confirmed MACE. Estimated hazard ratios and associated confidence interval's are from a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and the relevant sub-group as fixed factor.
The p-value is from the Wald test of the interaction effect.

Notes: Summary of results from subgroup analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment (semaglutide; placebo) and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction, i.e. for test of simplification of the model by omission of the interaction; the smaller the p-value, the stronger the evidence against such simplification. For each subgroup analysis, the p-value is repeated to avoid mistaken it for a p-value for test of treatment effect within a given subgroup level.
Abbreviations: CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio; sema: semaglutide.

Source: Figure 11-7 study report

Figure 42 Forest Plot on Time to First EAC-Confirmed MACE, Post Hoc Statistical Subgroup Analyses for Prior MI/Stroke, Baseline Body Weight, Prior Ischemic Heart Disease and Geographical Area - FAS In-Trial – SUSTAIN 6



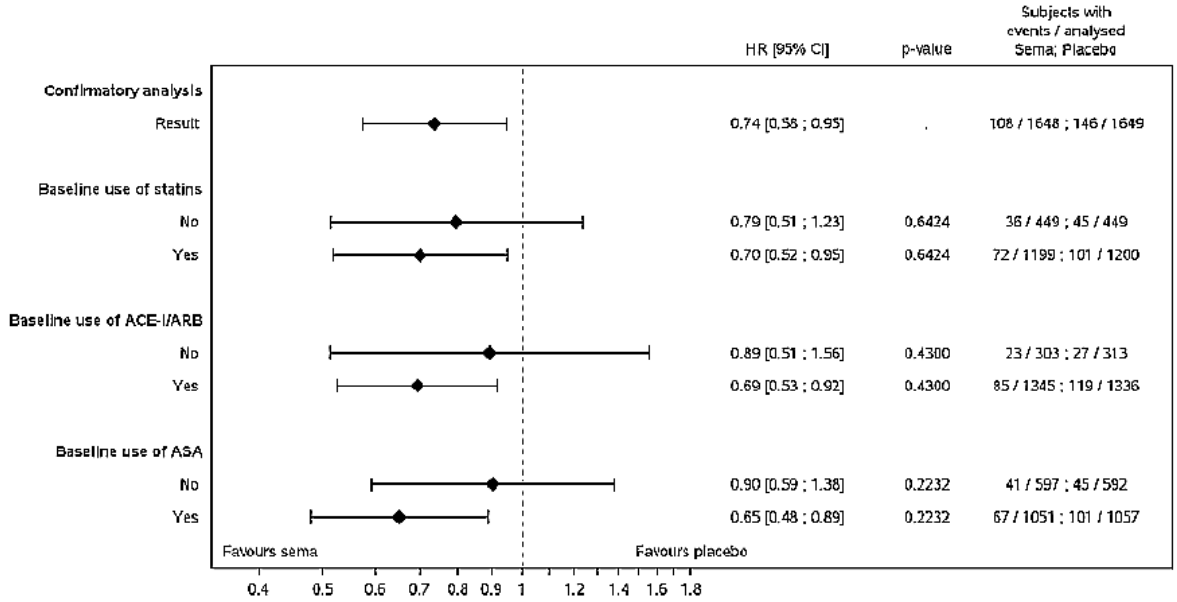
HR: Estimated hazard ratio CI: confidence interval Summary of results from post-hoc sub-group analyses of time to first EAC confirmed MACE. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and the relevant sub-group as fixed factor.
The p-value is from the Wald test of the interaction effect. IHD: Ischaemic heart disease

Notes: Summary of results from subgroup analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment (semaglutide; placebo and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction, i.e. for test of simplification of the model by omission of the interaction; the smaller the p-value, the stronger the evidence against such simplification. For each subgroup analysis, the p-value is repeated to avoid mistaken it for a p-value for test of treatment effect within a given subgroup level.

Abbreviations: CI: confidence interval; CKD-Epi: chronic kidney disease epidemiology collaboration; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio; IHD: ischamic heart disease; MDRD: modification of diet in renal disease; sema: semaglutide.

Source: Figure 11-8 study report

Figure 43 Forest Plot on Time to First EAC-Confirmed MACE, Post Hoc Statistical Subgroup Analyses for Baseline Use of Statins, Ace-Inhibitors/Angiotensin Receptor Blockers or Acetylsalicylic Acid - FAS In-Trial – SUSTAIN 6



HR: Estimated hazard ratio CI: confidence interval Summary of results from post-hoc sub-group analyses of time to first EAC confirmed MACE. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and the relevant sub-group as fixed factor.
The p-value is from the Wald test of the interaction effect. ACE-I: ACE inhibitors, ARB: Angiotensin receptor blockers, ASA: Acetylsalicylic acid

Notes: Summary of results from subgroup analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment (semaglutide; placebo) and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction, i.e. for test of simplification of the model by omission of the interaction; the smaller the p-value, the stronger the evidence against such simplification. For each subgroup analysis, the p-value is repeated to avoid mistaken it for a p-value for test of treatment effect within a given subgroup level.
Abbreviations: ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; ASA: acetylsalicylic acid; CI: confidence interval; CKD-Epi: chronic kidney disease epidemiology collaboration; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio; MDRD: modification of diet in renal disease; sema: semaglutide.
Source: Table 11-10 study report

These exploratory analyses did nto reveal any information that would affect my interpretation of the primary analysis.

<u>All MACE events analysis</u>

A total of 294 MACE (of which not all were first events) were confirmed by the EAC during the in-trial period, corresponding to a rate of 4.3 events per 100 PYO. The proportion of patients with events and the event rates were lower with semaglutide than with placebo; a total of 108 patients (6.6%) experienced EAC-confirmed MACE with semaglutide versus 146 (8.9%) with placebo, corresponding to incidence rates of 3.8 events per 100 PYO with semaglutide versus 4.9 events per 100 PYO with placebo.

Table 93 EAC-Confirmed MACE (All Events) – FAS In-Trial – SUSTAIN 6

	Semaglutide				Placebo				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1648				1649				3297			
PYO	3408.2				3401.1				6809.3			
MACE	108	(6.6)	129	3.8	146	(8.9)	165	4.9	254	(7.7)	294	4.3
Cardiovascular death	44	(2.7)	44	1.3	46	(2.8)	46	1.4	90	(2.7)	90	1.3
MI (non-fatal)	47	(2.9)	58	1.7	64	(3.9)	75	2.2	111	(3.4)	133	2.0
Stroke (non-fatal)	27	(1.6)	27	0.8	44	(2.7)	44	1.3	71	(2.2)	71	1.0

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: E: number of events; EAC: event adjudication committee; MACE: major adverse cardiovascular event; MI: myocardial infarction; N: number of subjects; PYO: patient years of observation; R: event rate per 100 patient years of observation (PYO); %: percentage of subjects

Source: Table 11-1 study report

A total of 11 EAC-confirmed MACE events had an onset date after the end of the in-trial observation period); 5 events with semaglutide and 6 events with placebo. The majority of these 11 patients (3 with placebo and 4 with semaglutide) completed the trial.

Table 94 EAC- Confirmed MACE Reported After End of In-Trial Observation Period – FAS – SUSTAIN 6

	Semaglutide		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	1648		1649		3297	
MACE	5	(0.3)	6	(0.4)	11	(0.3)
Cardiovascular death	2	(0.1)	4	(0.2)	6	(0.2)
MI (non-fatal)	2	(0.1)	2	(0.1)	4	(0.1)
Stroke (non-fatal)	1	(0.1)	0		1	(<0.1)

Note: Undetermined causes of deaths are classified as cardiovascular deaths.
Abbreviations: EAC: event adjudication committee; MACE: major adverse cardiovascular event; MI: myocardial infarction; N: number of subjects; PYO: patient years of observation; %: percentage of subjects

Table 11-2 study report

Dose/Dose Response

For the primary endpoint, primary analysis was based on the pooling of the semaglutide doses, and it would be difficult to assess whether any dose-response is apparent for the primary endpoint as the number of events would not be sufficient to draw a conclusion. However, for all endpoints pertaining to glycemic control and/or weight, a dose response is clearly observed for semaglutide.

Durability of Response

The semaglutide effect on glycemic control and weight appeared to be sustained for the duration of the study.

Persistence of Effect

The understanding of the persistence of effect is limited by the fact that the study was of limited duration, and it is not known whether the potential benefit on CV outcomes would persist after the discontinuation of the study drug.

Additional Analyses Conducted on the Individual Trial

See Biometrics review by Dr Ya-Hui Hsueh for analyses pertaining to SUSTAIN 6.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoint for SUSTAIN-6 is unique to this study, and was discussed in detail under the efficacy review for that study. I will not repeat the analysis for time to first MACE in this section. In this section I will focuse on the glycemic control findings from the efficacy trials, and SUSTAIN 6.

The primary endpoint for all other phase 3 studies pertained to glycemic control as evidenced by the change in HbA1c from baseline to the end of the trial. In addition to SUSTAIN 1-5, I will also refer to two phase 3 studies that were exclusively performed in Japan (as required by the Japanese regulatory authorities, trials 4091, and 4092), as supportive evidence.

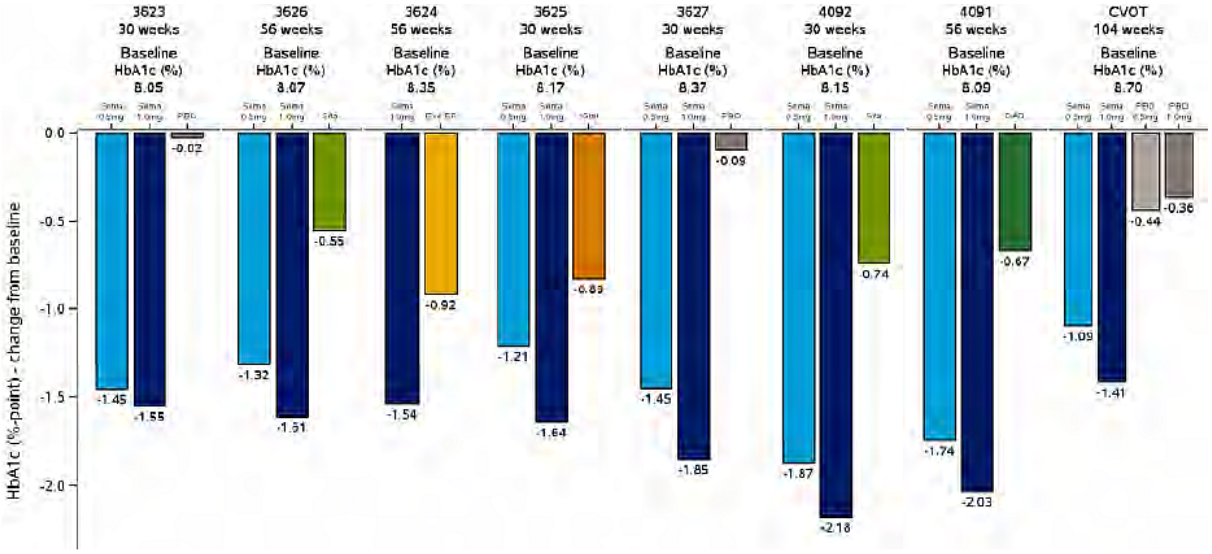
Change in HbA1c

Baseline levels of HbA1c ranged from 8.1% in trial 3623 to 8.7% in the CVOT. Semaglutide 0.5 mg and 1.0 mg consistently reduced HbA1c across drug naïve patients on semaglutide monotherapy, patients uncontrolled on OADs treated with semaglutide as add-on to 1−2 OADs and in patients with long-standing T2DM uncontrolled on basal insulin treated with semaglutide as add-on to basal insulin.

The reduction in HbA1c with semaglutide was most pronounced during the initial 5−6 months of treatment with the nadir being reached after approximately 16−30 weeks of treatment in all trials. The reduction in HbA1c was sustained during the entire treatment period of up to 104 weeks. The reduction in HbA1c by trial is presented in the Figure 44 below.

Across all eight phase 3 trials, both semaglutide 0.5 mg and 1.0 mg statistically significant reduced HbA1c from baseline to end-of-treatment vs the trial-specific comparators; placebo (as monotherapy or combination therapy with insulin), sitagliptin, exenatide ER, insulin glargine, and OADs.

Figure 44 Estimated Change from Baseline in HbA1c (%−Point) – Phase 3 Trials



Notes: Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline HbA_{1c} as covariate, all nested within visit, and adjusted according to observed baseline distribution. On-treatment without rescue medication data (key efficacy and Japanese trials) and in-trial data (CVOT).

Abbreviations: CVOT: cardiovascular outcomes trial; Exenatide ER: exenatide extended release; IGlar: insulin glargine; OAD: oral anti-glycaemic drug; PBO: placebo; Sita: sitagliptin.

Source: Figure 5-2 clinical overview

In all five key efficacy trials, statistical superiority of semaglutide 0.5 mg and 1.0 mg was confirmed.

Table 95 Statistical Testing of HbA1c (%–Point) Change from Baseline to End-of-Treatment

	Estimate	95% CI	p-value	Hypothesis	Conclusion
HbA1c (%-point)					
Trials with HbA_{1c} as the primary endpoint					
Trial 3623 vs Placebo (Mono)					
Treatment difference at visit 10 (week 30)					
Sema 0.5 mg - Placebo	-1.43	[-1.71 ; -1.15]	<.0001	Superiority	Confirmed
Sema 1.0 mg - Placebo	-1.53	[-1.81 ; -1.25]	<.0001	Superiority	Confirmed
Trial 3626 vs Sita (OADs)					
Treatment difference at visit 13 (week 56)					
Sema 0.5 mg - Sitagliptin	-0.77	[-0.92 ; -0.62]	<.0001	Superiority	Confirmed
Sema 1.0 mg - Sitagliptin	-1.06	[-1.21 ; -0.91]	<.0001	Superiority	Confirmed
Trial 3624 vs Exe ER (OADs)					
Treatment difference at visit 13 (week 56)					
Sema 1.0 mg - Exenatide ER	-0.62	[-0.80 ; -0.44]	<.0001	Superiority	Confirmed
Trial 3625 vs IGlar (OADs)					
Treatment difference at visit 16 (week 30)					
Sema 0.5 mg - IGlar	-0.38	[-0.52 ; -0.24]	<.0001	Superiority	Confirmed
Sema 1.0 mg - IGlar	-0.81	[-0.96 ; -0.67]	<.0001	Superiority	Confirmed
Trial 3627 vs Placebo (Insulin)					
Treatment difference at visit 16 (week 30)					
Sema 0.5 mg - Placebo	-1.35	[-1.61 ; -1.10]	<.0001	Superiority	Confirmed
Sema 1.0 mg - Placebo	-1.75	[-2.01 ; -1.50]	<.0001	Superiority	Confirmed
Trials with HbA_{1c} as a secondary endpoint					
Trial 4092 vs Sita (Mono), JP					
Treatment difference at visit 10 (week 30)					
Sema 0.5 mg - Sitagliptin	-1.13	[-1.32 ; -0.94]	<.0001	Significant	
Sema 1.0 mg - Sitagliptin	-1.44	[-1.63 ; -1.24]	<.0001	Significant	
Trial 4091 vs OAD (OAD), JP					
Treatment difference at visit 18 (week 56)					
Sema 0.5 mg - Additional OAD	-1.08	[-1.24 ; -0.91]	<.0001	Significant	
Sema 1.0 mg - Additional OAD	-1.37	[-1.53 ; -1.20]	<.0001	Significant	
Trial 3744 vs Placebo, CVOT					
Treatment difference at visit 25 (week 104)					
Sema 0.5 mg - Placebo 0.5 mg	-0.66	[-0.80 ; -0.52]	<.0001	Significant	
Sema 1.0 mg - Placebo 1.0 mg	-1.05	[-1.19 ; -0.91]	<.0001	Significant	

Abbreviations: CI: Confidence interval; Mono: monotherapy; Sitagliptin: Sitagliptin; OADs: oral antidiabetics; Exe ER: Exenatide Extended Release; IGlar: Insulin Glargine; JP: Japan; CVOT: cardiovascular outcomes trial

Source: Table 3-5 Summary of Clinical Efficacy T2DM

Reviewer Comment: Overall, the clinical development program is supportive of the glycemic lowering indication of semaglutide, on a variety of patients, both as monotherapy and on a background or oral antidiabetics and insulin. While the HbA1c lowering with semaglutide was statistically superior to the active comparators studied, it is unclear whether the therapy in the active comparator arm was optimized, particularly pertaining to the comparison with basal insulin.

7.1.2. **Secondary and Other Endpoints**

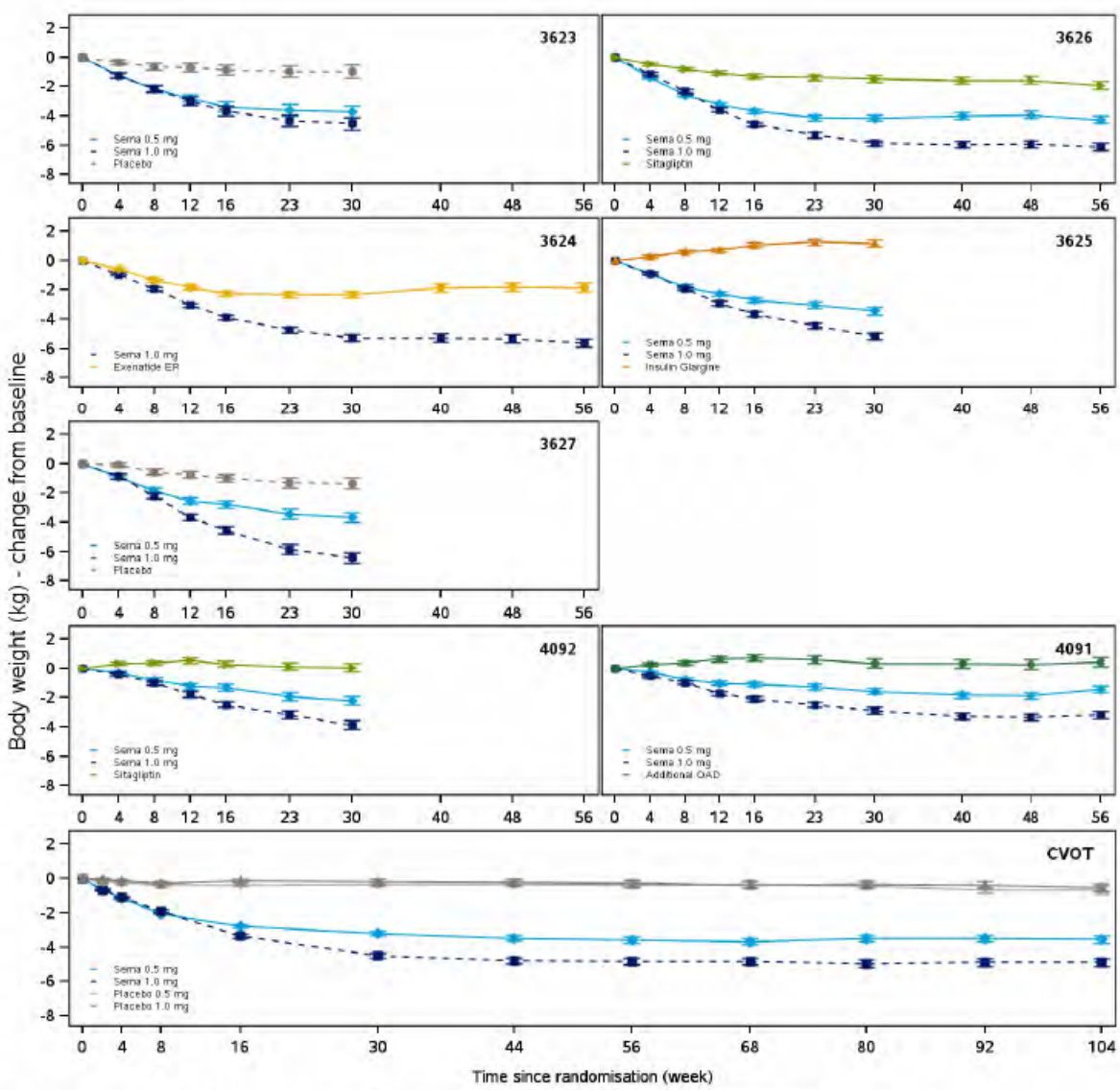
A summary of selected secondary endpoints is presented below.

Body Weight

All eight phase 3 trials investigated the efficacy of semaglutide on body weight. Change from baseline to end-of-treatment in body weight was the only secondary endpoint controlled for type 1 error in SUSTAIN 1-5.

For all eight phase 3 trials, treatment with semaglutide 0.5 mg or 1.0 mg resulted in marked, sustained improvements in body weight, reaching nadir after approximately 30 weeks. The reduction was maintained after long-term treatment of up to 104 weeks (in the CVOT). The effect appeared to be dose-dependent. In the key efficacy trials and the CVOT, semaglutide 1 mg treatment reduced the body weight by 4.5−6.4 kg whereas treatment with semaglutide 0.5 mg reduced body weight by 3.5−4.3 kg. The reduction in body weight was less for the Japanese trials, however, the starting weight of the patients was also lower in these two trials.

Figure 45 Body Weight (Kg) by Treatment Week – Mean Plot – Estimated – Phase 3 Trials



Exenatide ER: Exenatide Extended Release. OAD: Oral anti-diabetic drug. CVOT: Cardiovascular outcomes trial.
On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented.
Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline body weight as covariate, all nested within visit, and adjusted according to observed baseline distribution.

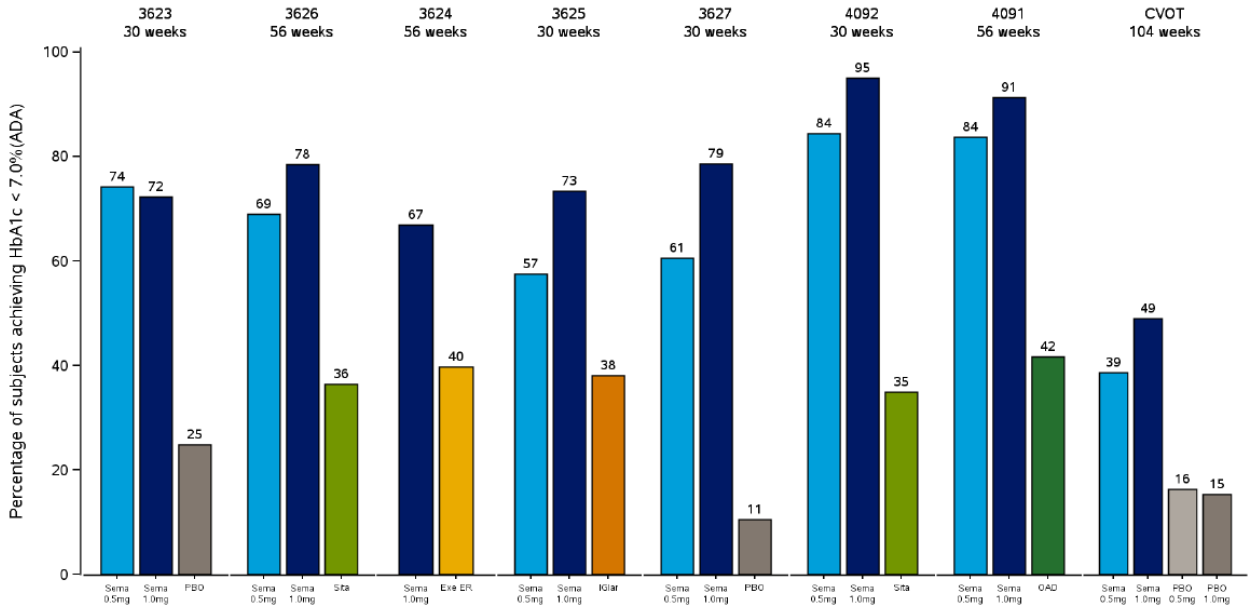
Source: Figure 3-17 Summary of Clinical Efficacy T2DM

In support of this, the proportion of patients achieving a weight loss of ≥5% or ≥10% was greater in both semaglutide arms vs all comparators for all trials. Again, a dose-response was observed.

<u>HbA1c targets</u>

The proportion of patients achieving the treatment targets defined by ADA and AACE of HbA1c <7% and HbA1c ≤6.5%, respectively, were evaluated at end-of-treatment in all trials. In line with the reduction observed in mean HbA1c with semaglutide, significantly greater proportions of patients with semaglutide than with comparators achieved pre-defined treatment targets of HbA1c <7% (ADA target), HbA1c ≤6.5% (AACE) and a composite clinically relevant measure of treatment success comprising HbA1c <7% without severe or BG-confirmed symptomatic hypoglycemia and no weight gain across all phase 3 trials.

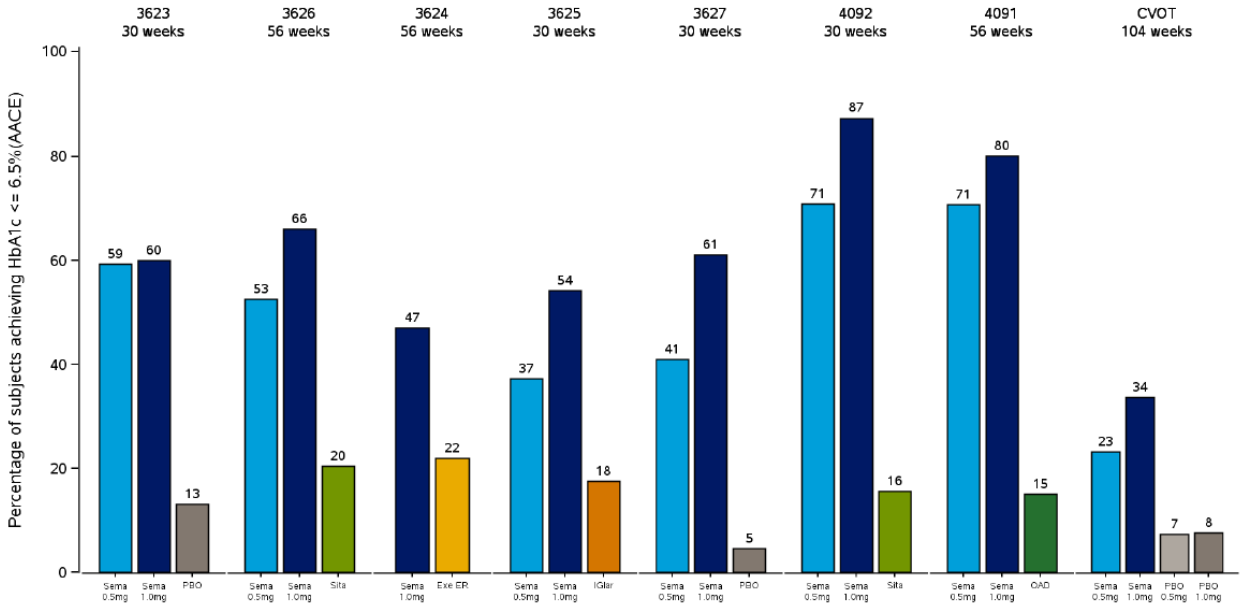
Figure 46 Proportion of Patients Reaching an HbA1c <7.0%



ADA: American Diabetes Association, CVOT: Cardiovascular outcomes trial, PBO: Placebo, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Missing data are imputed from the mixed model for repeated measurements for change from baseline with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline HbA1c as covariate, all nested within visit.

Source: Figure 3-5 Summary of Clinical Efficacy T2DM

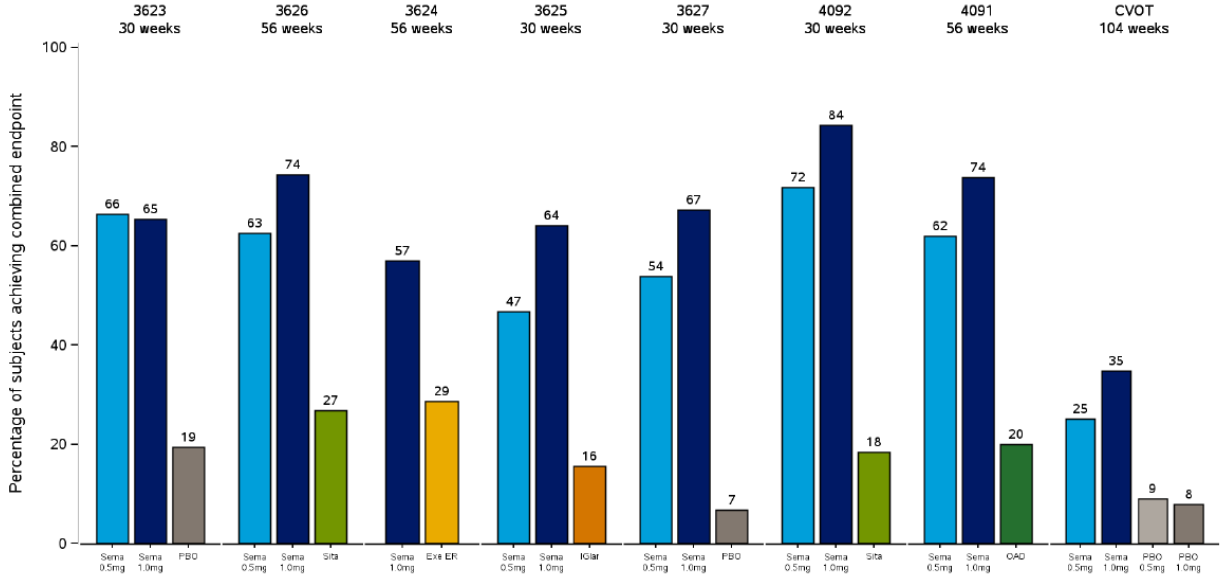
Figure 47 Proportion of Patients Reaching an HbA1c ≤6.5% (AACE)



AACE: American Association of Clinical Endocrinologists, CVOT: Cardiovascular outcomes trial, PBO: Placebo, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Missing data are imputed from the mixed model for repeated measurements for change from baseline with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline HbA1c as covariate, all nested within visit.

Source: Figure 3-6 Summary of Clinical Efficacy T2DM

Figure 48 Proportion of Patients Reaching an HbA1c <7.0% Without Severe or BG Confirmed Symptomatic Hypoglycemia and No Weight Gain



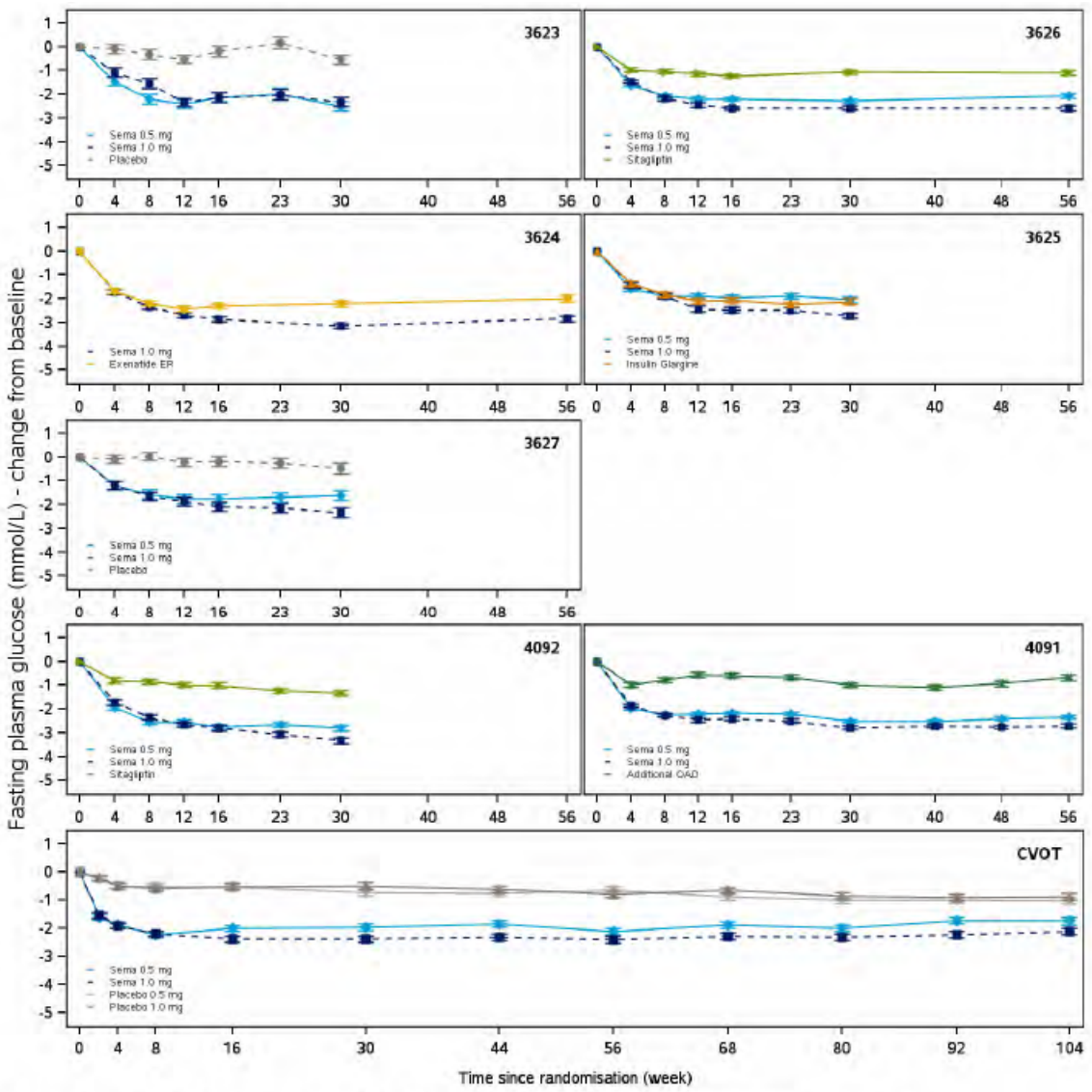
BG: Blood glucose, BG confirmed: BG < 3.1 mmol/L (56 mg/dL), CVOT: Cardiovascular outcomes trial, PBO: Placebo, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Missing data are imputed from the mixed model for repeated measurements for change from baseline with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline value (HbA1c or body weight) as covariate, all nested within

Source: Figure 3-7 Summary of Clinical Efficacy T2DM

Fasting Plasma Glucose

At baseline, observed levels of FPG were comparable across all trials. In general, FPG levels decreased progressively through week 12, after which the response stabilised or changed moderately (i.e. either a moderate decrease or a moderate increase) through the remaining treatment period. FPG reductions were significantly larger with both doses of semaglutide vs the trial-specific comparators in all trials except in trial 3625, where FPG reductions in patients treated with semaglutide 0.5 mg was similar with the comparator (insulin glargine). The FPG changes with semaglutide vs comparator are expected in light of HbA1c findings.

Figure 49 Fasting Plasma Glucose (mmol/L) by Treatment Week – Estimated Change from Baseline – Mean Plot – Phase 3 Trials



Exenatide ER: Exenatide Extended Release, OAD: Oral anti-diabetic drug, CVOT: Cardiovascular outcomes trial,
On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented.
Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline fasting plasma glucose as covariate, all nested within visit, and adjusted according to observed baseline distribution.

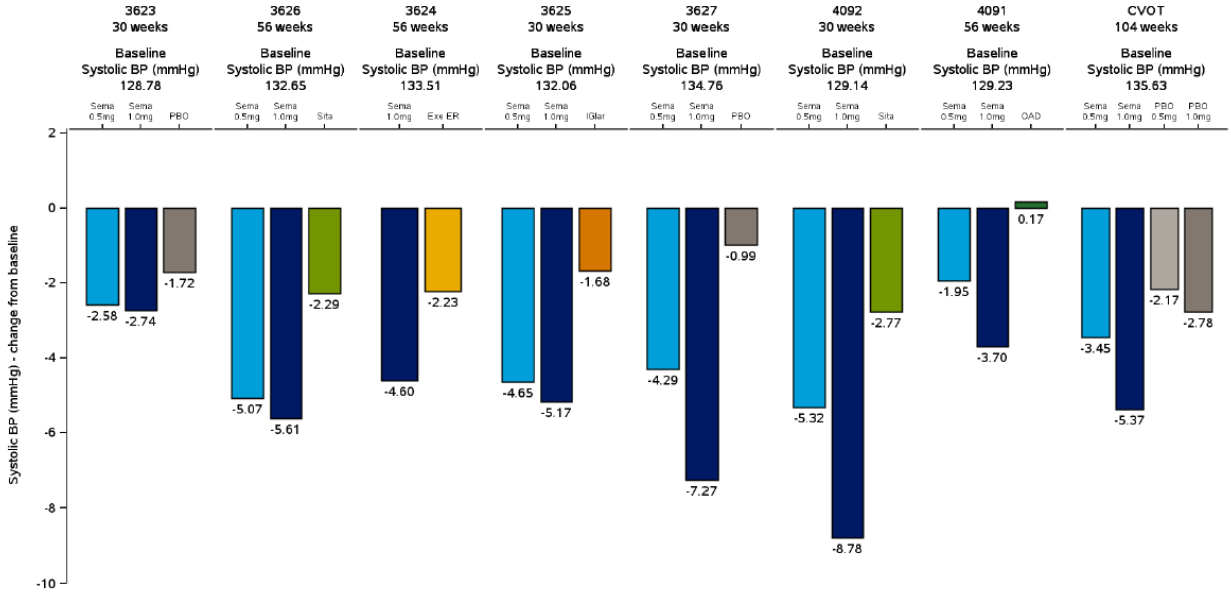
Source: Figure 3-8 Summary of Clinical Efficacy T2DM

Blood pressure

Mean change in systolic and diastolic blood pressure from baseline to end-of-treatment was investigated in all phase 3 trials. At baseline, systolic and diastolic blood pressure were comparable across treatment groups and within and across trials. Systolic blood pressure

decreased progressively during the first 23-30 weeks of semaglutide treatment, after which the levels stabilized through the remaining treatment period. Overall, systolic blood pressure decreased more with semaglutide 1 mg vs 0.5 mg vs comparators at end-of-treatment. Diastolic blood pressure also appeared to decrease over time, with no clear difference between semaglutide and comparators in the CVOT, however semaglutide appeared to lower it more than placebo in some of the phase 3 studies. In conclusion, if semaglutide has an effect on diastolic blood pressure, it appears to be a minor one.

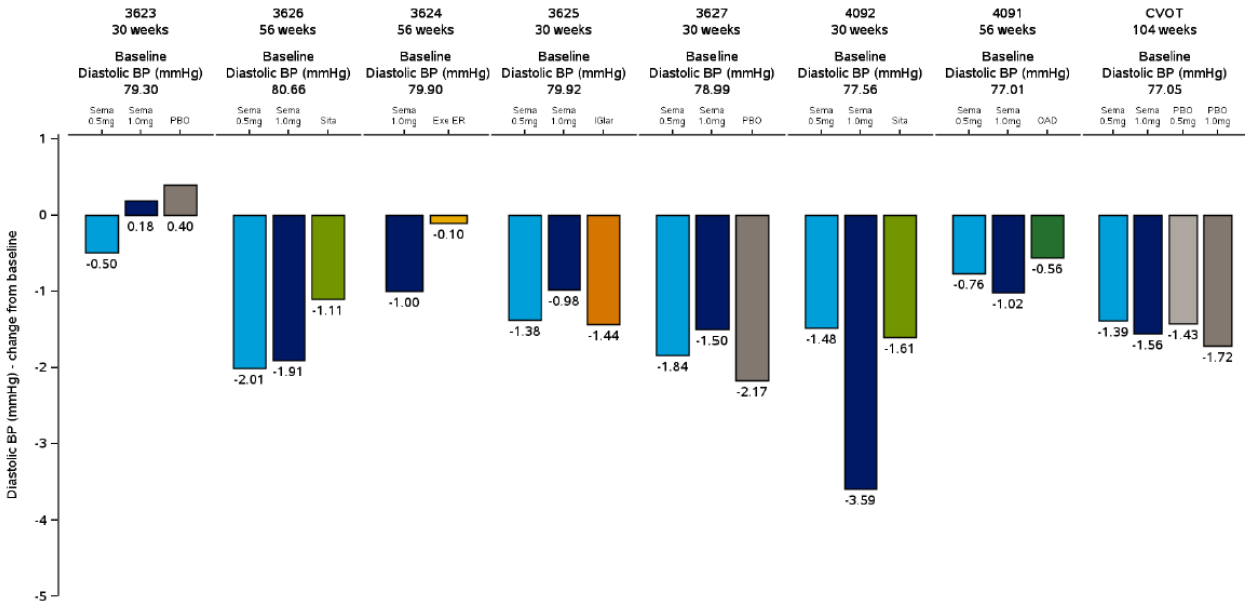
Figure 50 Systolic BP (mmHg) – Estimated Change from Baseline – Bar Plot – Phase 3 Trials



BP: Blood pressure, CVOT: Cardiovascular outcomes trial, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, BP: Blood pressure, PBO: Placebo, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline systolic BP as covariate, all nested within visit, and adjusted according to observed baseline distribution.

Source: Figure 6.4.8 ISE

Figure 51 Diastolic BP (mmHg) – Estimated Change from Baseline – Bar Plot – Phase 3 Trials



BP: Blood pressure, CVOT: Cardiovascular outcomes trial, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug. BP: Blood pressure, PBO: Placebo. On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline diastolic BP as covariate, all nested within visit, and adjusted according to observed baseline distribution.

Source: Figure 6.4.7 ISE

7.1.3. Subpopulations

As pooling the studies in the semaglutide program is not feasible due to their differences, please refer to the subgroup analyses for SUSTAIN 1-6 for details.

Generally, the efficacy response to semaglutide (0.5 mg and 1.0 mg) was consistent across sub-populations of major demographic factors (age, sex, race and ethnicity), relevant disease factors at baseline (duration of diabetes, body weight, BMI, and renal function), background diabetes treatment (metformin monotherapy, metformin + SU, other) and region (Africa, Asia+Australia, Europe, North America [US+Canada] and South America); hence, the estimated mean change from baseline and estimated treatment differences (ETD) between semaglutide and comparator were comparable across and within the different subgroups.

Refer to Biometrics review by Dr Jiwei He for the FDA's analysis of subgroups.

7.1.4. Dose and Dose-Response

A larger reduction in HbA1c from baseline to end-of-treatment was obtained with semaglutide

1 mg vs 0.5 mg in all trials, except in the multinational monotherapy trial 3623 vs Placebo (Mono). Given that trial 3623 was a monotherapy trial in a drug-naïve T2DM population, differences in degree of disease progression compared to that in other studies may explain the lack of dose-response. See Sections 7.1.1 and 7.1.2, as well as Section 6 for details.

Across the phase 3 trials, no differences in the HbA1c dose-response to semaglutide treatment were observed across subgroups relating to demography, region or disease characteristics, except for trial 3623 vs Placebo (Mono). Overall, this suggests that the treatment response to semaglutide 0.5 mg and 1.0 mg is similar across all subgroups with the high dose showing a larger reduction in HbA1c.

Similar results were observed for HbA1c targets and body weight, with the higher semaglutide dose having a stronger effect.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The change in HbA1c overtime for semaglutide for the five pivotal phase 3 trials, and the CVOT, is discussed in the individual trial sections. Overall, reduction in HbA1c occurred between 0-16 weeks for most trials, and remained relatively stable or increased slightly over time for treatment periods going beyond 30 weeks.

The decrease in weight with semaglutide also appeared relatively early and appeared to persist for the duration of the trials.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In general, semaglutide has been studied in a variety of diabetic patients, and on a variety of therapeutic backgrounds. The clinical program appears adequate for the NDA submission. The premarket assessment of cardiovascular risk was also performed in a 2 year cardiovascular outcomes trial. However, one consideration is that semaglutide has only been studied for up to 2 years, the duration of the longest trial in the program. In this context, events such as pancreatitis, gallbladder disease, malignancies, acute renal events, etc. could potentially be more common postmarketing, and with longer use of the drug. This would be in line with what was observed with other drugs in this class. So far, for the currently marketed GLP-1 RAs, the benefit-risk profile has not changed significantly in the post-marketing setting.

7.2.2. Other Relevant Benefits

Semaglutide is to be administered once weekly, via a subcutaneous injection. Of the currently marketed GLP-1 RAs, four (Bydureon, Trulicity, Tanzeum, and Bydureon BCise) are administered once weekly. Semaglutide would offer an additional option for the patients who prefer once weekly administration. With the available data, it is not clear how semaglutide compared to the other members of the GLP-1 RA class of drugs, as such comparison is not the purpose of an anti-diabetic development program. Semaglutide appears to offer robust glycemic control based on the data in the clinical development program, which is the mainstay of diabetes treatment. Additionally, the body weight lowering, which is a class effect, could also be regarded as advantageous in patients with T2DM and obesity, which constitute the great majority of patients with T2DM.

7.3. Integrated Assessment of Effectiveness

Semaglutide is a GLP-1 RA, evaluated for the treatment of T2DM. As presented in Section 2.2, GLP1 RAs are a class of medications commonly used in the treatment of T2DM. Semaglutide is similar to another GLP1 RA, liraglutide (also developed by Novo Nordisk), currently approved for treatment of T2DM (Victoza) and weight management (Saxenda).

Semaglutide is administered via subcutaneous injection once weekly, as opposed to liraglutide which is administered daily. While this could potentially constitute an advantage for semaglutide, the once weekly administration is not novel for this medication class, as there are other members of the GLP1 RA class which are administered weekly.

Semaglutide phase 3 development program is comprised of 5 key efficacy trials, one CVOT of short duration (not an efficacy trial – outcomes trial to rule out excessive CV risk pre-marketing), and 2 Japanese trials. Of the key efficacy trials, two were open label as blinding would have been difficult due to the nature of the comparator (trial 3624 vs Exenatide ER, and trial 3625 vs insulin glargine). The remaining 3 key efficacy trials were double-blind as follows: two vs placebo – one as monotherapy in treatment-naïve patients (3623), and one on a background of basal insulin (3627), and one trial vs sitagliptin on a background of oral antidiabetics (OADs) (3626). The two Japanese trials were open label, one as monotherapy vs sitagliptin, and one vs OADs on a background of OADs.

In all the key efficacy trials, as well as the Japanese trials, semaglutide showed a dose-dependent reduction on HbA1c, sustained over the duration of the trials. This reduction was generally shown to be superior to placebo as monotherapy, and on a background of basal insulin. Semaglutide was also superior to sitagliptin on a background of OADs including metformin and SU. The applicant also argues that semaglutide was superior to insulin based on the results of the study 3625 (open label vs insulin glargine), it is not clear whether optimization of the insulin treatment was adequate.

In conclusion, regarding glycemic outcomes, the clinical program provides evidence that

semaglutide is efficacious in improving glycemic control in patients with T2DM both as monotherapy, and as add-on to OADs/basal insulin.

8. Review of Safety

8.1. Safety Review Approach

The primary focus of the safety evaluation is on the data from the 8 completed phase 3 trials, as these trials represent the intended target population as well as the majority of the overall exposure to semaglutide 0.5 mg and 1.0 mg.

Analysis sets

For the efficacy trials and the Japanese trials, both the full analysis set (FAS) and the safety analysis set (SAS) included all randomized subjects who had received at least one dose of randomized trial product, and contributed to the evaluation based on their randomized, or actual treatment, respectively.

For the CVOT, the FAS included all randomized subjects and contributed with data according to their randomized treatment. The SAS included all subjects exposed to at least one dose of trial product and contributed to the evaluation based on the trial product received for most the period when they were on treatment.

Observation periods

Safety assessments were based on two observation periods, depending on the type of event.

These are:

1. In-trial: the time-period from the date of randomization to either the end-of-trial follow-up visit or the date of withdrawal from trial, whichever comes first. Subjects contributed with data regardless of treatment adherence (e.g., premature treatment discontinuation or initiation of rescue medication).
2. On-treatment: the part of the in-trial observation period where subjects are considered exposed to trial product. The in-treatment period was different depending on the type of event as follows:
   - For AEs, adjudicated events, ECGs, hypoglycemic episodes and anti-semaglutide antibodies, the on-treatment observation period ends at the date of one of the following, whichever comes first:
     - Last dose plus 42 days (i.e. 35 days of follow-up due to the long half-life of semaglutide plus a visit window of 7 days)
     - Premature treatment discontinuation follow-up visit (only used for CVOT)

    - End-of-trial follow-up visit
    - Withdrawal from trial
- For laboratory assessments, physical examination and vital signs, the on-treatment observation period ends at the date of one of the following, whichever comes first:
    - Last dose plus a visit window of 7 days
    - End-of-trial follow-up visit
    - Withdrawal from trial
- For hypoglycemic episodes the on-treatment observation period ended at the date of initiation of rescue medication to avoid potential confounding by the rescue medication.

For the CVOT, data on the in-trial observation period is based on FAS, whereas data on the on-treatment observation period is based on SAS; FAS includes 11 subjects not exposed to trial product which are not included in SAS.

For the other phase 3 trials (excl. CVOT), including the trial pools and subsets, SAS is used for both observation periods.

The evaluation of cardiovascular and microvascular disorders, neoplasms and fatal events focuses primarily on the in-trial observation period due to a potential long latency and diagnostic lead time. For all other safety areas, the on-treatment period was used for analyses.

Applicant defined pools used for safety evaluation:

The phase 3 trials were designed to evaluate the efficacy and safety of semaglutide in a broad population of patients with T2DM covering the continuum of T2DM care, and included five multinational trials (trials 3623, 3624, 3625, 3626, 3627), two Japanese trials (trials 4091, 4092), and a cardiovascular outcome trial (trial 3744) referred to as the CVOT.

Data from the CVOT is always presented separately, since the CVOT differs on important parameters making it unsuitable for pooling with the other phase 3 trials. Key differences include a longer trial duration (104 treatment weeks), a trial population at high risk of CV events, and randomized treatment provided in addition to standard-of-care.

The evaluation of the semaglutide safety profile in the 7 other phase 3 trials, is primarily based on a broad pool of all seven trials to appropriately characterize the semaglutide safety profile and increase the likelihood of detecting potential treatment differences and signals for areas with low number of events. This trial pool is referred to as the phase 3 pool. The applicant submitted the data as semaglutide vs comparator, the comparator arm including placebo and different active comparators (exenatide ER 2.0 mg, sitagliptin, insulin glargine and different OADs).

In addition to the phase 3 pool, a phase 3 multinational pool comprising the 5 multinational

phase 3 trials, but excluding the two Japanese phase 3 trials was made after request from the FDA at the pre-NDA meeting.

A trial pool was also made comprising the two placebo-controlled trials: trial 3623 (monotherapy) and trial 3627 (add-on to insulin), referred to as the phase 3 placebo pool.

Due to the known and or potential GLP-1 RA class effect on gastrointestinal events, pulse rate, blood pressure and acute renal failure, the effect of semaglutide versus comparators was evaluated based on a pool of trials including only non-GLP-1 RA comparator products (trials 3623, 3625, 3626, 3627, 4091 and 4092), referred to as the phase 3 non-GLP-1 RA subset. Trial 3624 is referred to as GLP-1 RA trial.

Due to the potential incretin class effect on pancreatitis and gallstone disease, the effect of semaglutide was evaluated based on a pool of trials including only non-incretin comparator products (trials 3623, 3625, 3627, and 4091), referred to as the phase 3 non-incretin subset.

Table 96 Grouping and Pooling of Phase 3 Trials

Pools	Number of subjects in SAS S 0.5 / S 1 / comp	Trials and comparators 3623 Pbo	3624 Exe ER	3625 IGlar	3626 Sita	3627 Pbo	4091 OAD	4092 Sita
Placebo pool	260/261/262	X				X		
Phase 3 pool (excl CVOT)	1373/1777/1657	X	X	X	X	X	X	X
Phase 3 non-incretin subset	862/862/742	X		X		X	X	
Phase 3 incretin subset	512/915/915		X		X			X
Phase 3 non-GLP-1 RA subset	1373/1373/1252	X		X	X	X	X	X
Phase 3 GLP1 RA trial	---/404/405		X					

SAS= safety analysis set, S 0.5 = semaglutide 0.5 mg, S 1 = semaglutide 1 mg, comp = comparator, Pbo = placebo, Exe ER= exenatide ER, sita= sitagliptin, OAD= oral antidiabetics, IGlar= insulin glargine
Source: Modified from Table 2-1 Summary of Clinical Safety

For the safety review, I will mostly present the following pools:

- CVOT (3744)
- Phase 3 pool excluding CVOT (3623, 3624, 3625, 3626, 3627, 4091, and 4092), with the non-incretin, or non-GLP1 subset as appropriate
- Placebo pool (3623, 3627)

8.2. Review of the Safety Database

8.2.1. **Overall Exposure**

CVOT exposure

Exposure is defined as the time span between the date of the first trial product dose and the date of the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days (5 weeks plus the 7 days visit window) or end of the patient's in-trial period, whichever came first.

Out of a total of 3297 randomized patients, 3286 patients equally distributed across treatment groups were exposed to trial product.

Total patient-years exposure (PYE) (on treatment observation period) was slightly lower for the semaglutide (0.5 mg and 1.0 mg) groups than for the placebo groups in both FAS and SAS, consistent with slightly more patients discontinuing treatment prematurely in the beginning of the treatment period in the semaglutide treatment groups than in the placebo treatment group.

Table 97 Observation Periods CVOT

	Sema 0.5 mg	Sema 1.0 mg	Placebo
Number of subjects	826	822	1649
In-trial observation period (years) [a] - FAS			
N	826	822	1649
Mean (SD)	2.1 (0.3)	2.1 (0.3)	2.1 (0.3)
Min ; max	0.00 ; 2.89	0.00 ; 2.52	0.06 ; 2.74
Total	1708	1700	3401
On-treatment observation period (years) [b] - FAS			
N	824	818	1644
Mean (SD)	1.8 (0.6)	1.8 (0.7)	1.8 (0.6)
Min ; max	0.00 ; 2.34	0.00 ; 2.32	0.06 ; 2.32
Total	1491	1441	3035
On-treatment observation period (years) [b] - SAS			
N	823	819	1644
Mean (SD)	1.8 (0.6)	1.8 (0.7)	1.8 (0.6)
Min ; max	0.00 ; 2.34	0.00 ; 2.32	0.06 ; 2.32
Total	1488	1444	3035

Notes: (a): The in-trial observation period denotes the time period from the day of randomisation and until end-of-trial, defined for trial completers as the subject's planned end-of-trial visit or death, whichever comes first, and defined as the last direct subject-site contact for withdrawals and for subjects lost to follow-up. [b]: The 'on-treatment' observation period denotes the time period from the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first.
Abbreviations: FAS: full analysis set, N: number of subjects, SAS: safety analysis set, SD: standard deviation.
Source: Table 13-1 study report

The mean duration of exposure across the semaglutide (0.5 mg and 1.0 mg) and placebo

treatment groups was approximately 1.8 years. The proportion of patients exposed to trial product for at least 24 months was 76−79%.

Table 98 Exposure by Subgroup Variables – SAS On-Treatment – CVOT

	Sema 0.5		Sema 1		All sema		Placebo	
	N	PYE	N	PYE	N	PYE	N	PYE
Number of subjects	823		819		1642		1644	
Sex								
Male	494	882	513	916	1007	1798	987	1836
Female	329	606	306	528	635	1134	657	1199
Age (years)								
< 65	442	813	412	753	854	1567	843	1568
> 65	381	675	407	690	788	1366	801	1467
> 75	74	118	83	123	157	241	163	275
Race								
White	690	1249	688	1212	1378	2462	1347	2492
Black/Afr. Am	54	92	54	85	108	177	113	188
Asian	63	118	58	115	121	233	152	298
Other	16	29	19	32	35	61	32	57
CV History								
Yes	619	1103	633	1114	1252	2216	1258	2314
No	204	386	186	330	390	716	386	721

Abbreviations: Afr. Am: African-American; N: number of subjects; PYE: patient-years of exposure; sema: semaglutide
Source: Table 1-14 ISS

Phase 3 trials excl. CVOT

Total PYE (on-treatment observation period) was lower in the semaglutide 0.5 mg treatment group than in the semaglutide 1 mg and comparator treatment groups, as a treatment dose of 0.5 mg was not investigated in trial 3624.

Table 99 Phase 3 Pool Exposure by Study

	Sema 0.5		**Sema 1**		**All Sema**		**Comparator**	
	N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
Phase 3 pool (excl CVOT)	1373	1165	1777	1548	3150	2712	1357	1467
3623 vs Placebo (Mono)	128	80	130	82	258	162	129	81
3626 vs Sita (OADs)	409	435	409	431	818	866	407	453
3624 vs Exe ER (OADs)	---	---	404	414	404	414	405	408
3625 vs IGlar (OADs)	362	225	360	219	722	444	360	235
3627 vs Placebo (Insulin)	132	84	131	82	263	166	133	84
4092 vs Sita (Mono), JP	103	69	102	63	205	132	103	70
4091 vs OAD (OAD), JP	239	271	241	257	480	528	120	136

Abbreviations: JP: Japan; N: number of subjects; Mono: monotherapy; OAD: oral antidiabetic drug; PYE: patient-years of exposure; sema: semaglutide
Source: Table 1-7 Summary of clinical safety

The mean duration of exposure across the semaglutide (0.5 mg and 1.0 mg) and comparator

treatment groups was approximately 10 months. The proportion of patients exposed for 6 or more months was 91% for semaglutide 0.5 mg, 88% for semaglutide 1mg, and 91% for comparator. The exposure for 12 or more months was 42%, 49%, and 49% respectively.

Placebo pool

Exposure was similar between the semaglutide and placebo groups.

Table 100 Exposure – Placebo Pool

	Sema 0.5		Sema 1		All Sema		Comparator	
	N	**PYE**	**N**	**PYE**	**N**	**PYE**	**N**	**PYE**
Placebo pool	260	165	261	164	521	329	262	166
3623 vs Placebo (Mono)	128	80	130	82	258	162	129	81
3627 vs Placebo (Insulin)	132	84	131	82	263	166	133	84

Abbreviations: N: number of subjects; Mono: monotherapy; PYE: patient- years of exposure; sema: semaglutide
Source: Table 1-9 Summary of clinical safety

8.2.2. Relevant characteristics of the safety population:

The semaglutide program studied patients in various stages of T2DM, on a variety of background therapies, from drug naïve to patients on various OADs, and basal insulin.

Treatment completers were defined as subjects that did not discontinue treatment prematurely. For all trials, a subject was considered lost to follow-up if the subject did not complete the trial and did not withdraw consent.

For the CVOT, trial completers were defined as subjects that either attended the last follow-up visit or who died while considered active trial participants. Subjects for which vital status was not obtained were considered lost to follow-up for vital status.

For trials in the phase 3 pool, trial completers were defined as subjects that attended the last follow-up visit.

CVOT

Of the 4346 subjects screened, 3297 subjects were randomized, and 3286 subjects were exposed with similar number of subjects exposed across the treatment groups [semaglutide 0.5 mg 823 (99.6%), semaglutide 1 mg 819 (99.6%), placebo 1644 (99.7%)].

Table 101 Subject Disposition - CVOT

	Sema 0.5 mg		Sema 1 mg		Placebo	
	N	%	N	%	N	%
Randomized	826	100.0	822	100.0	1649	100.0
Exposed (safety analysis set)	823	99.6	819	99.6	1644	99.7
Treatment completers [a]	662	80.1	635	77.3	1339	81.2
Premature treatment discontinuers [b]	164	19.9	186	22.6	310	18.8
Gastrointestinal tolerability	47	5.7	77	9.4	18	1.1
Withdrawal of informed consent	1	0.1	1	0.1	2	0.1
Adverse event other than related to gastrointestinal tolerability	51	6.2	41	5.0	93	5.6
Introduction of disallowed medication	3	0.4	3	0.4	16	1.0
Suspicion of placebo (without introduction of disallowed medication)	3	0.4	3	0.4	25	1.5
Randomized in error	12	1.5	13	1.6	22	1.3
Resistance to injections	2	0.2			2	0.1
Trial fatigue	5	0.6	5	0.6	26	1.6
Other	40	4.8	43	5.2	106	6.4
Trial completers [c]	812	98.3	811	98.7	1609	97.6
Withdrawals in relation to or after treatment discontinuation [d]	2	0.2	5	0.6	8	0.5

Notes: [a]Subjects who were exposed, did not discontinue treatment prematurely, who did not withdraw from trial and who were not lost to follow-up before the last treatment visit. [b]Subjects who were not exposed, but had given a reason for premature treatment discontinuation are also included. [c]Subjects who died during the trial or who attended the end- of-trial follow-up visit. [d]All cases were withdrawal of informed consent
Abbreviations: N: number of subjects; %: percentages are based on randomized subjects; sema: semaglutide
Source: Table 1-10 Summary of Clinical Safety

Phase 3 pool excluding CVOT

Of the 6768 subjects screened, 4827 were randomized, and 4807 were exposed. Fewer subjects were exposed to semaglutide 0.5 mg (1373 subjects) than with semaglutide 1.0 mg (1777 subjects) and comparators (1657 subjects), reflecting the fact that one trial only tested the 1 mg semaglutide dose (3724). The proportion of patients completing treatment and/or trial was similar between treatment groups. GI AEs were more frequently the reason for premature discontinuation in the semaglutide arms vs comparator.

Table 102 Subject Disposition – Phase 3 excluding CVOT

	Sema 0.5 mg		**Sema 1 mg**		**Placebo**	
	N	**%**	**N**	**%**	**N**	**%**
Randomized	1375	100	1783	100	1669	100
Exposed	1373	99.9	1777	99.7	1657	99.3

Treatment completers [a]	1222	89.0	1498	84.3	1477	89.1
Without rescue medication	1176	85.7	1452	81.7	1296	78.2
With rescue medication	46	3.4	46	2.6	181	10.9
Premature treatment discontinuation						
Primary reason [b]	151	11.0	279	15.7	180	10.9
Pregnancy	1	0.1	1	0.1	3	0.2
Protocol violation	21	1.5	35	2.0	32	1.9
Violation of the inclusion and/or exclusion criteria	21	1.5	35	2.0	32	1.9
Intention of becoming pregnant	0	0.0	0	0.0	0	0.0
Adverse event	83	6.0	161	9.1	56	3.4
Gastro intestinal AEs	42	3.1	102	5.7	10	0.6
Pancreatitis	4	0.3	4	0.2	6	0.4
Other AEs	37	2.7	55	3.1	40	2.4
Other	46	3.4	81	4.6	89	5.4
Not applicable	0	0.0	1	0.1	0	0.0
Trial completers [c]	1304	94.8	1684	94.4	1559	93.4
Premature withdrawal from trial in relation to or after premature treatment discontinuation						
Primary	66	4.8	96	5.4	104	6.2
Withdrawal by subject	30	2.2	49	2.7	48	2.9
Lost to follow-up	12	0.9	16	0.9	26	1.6
Death	5	0.4	3	0.2	6	0.4
Missing follow-up information [d]	15	1.1	20	1.1	16	1.0
Other	4	0.3	8	0.4	8	0.5

Notes: For trial completers and withdrawals percentages are based on randomized subjects, a: Completion of treatment according to end-of-trial form; b: Includes only exposed subjects; c: Subjects with a follow-up visit, d: Subjects with no reason/date for withdrawal but without the follow-up visit.
Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)
Abbreviations: N: number of subjects; sema: semaglutide; %: for treatment completers and treatment non-completers percentages are based on exposed subjects. For trial completers and withdrawals percentages are based on randomized subjects.
Source: Table 1-11 Summary of Clinical Safety

Placebo pool

Of the 1186 subjects screened, 785 subjects were randomized, and 783 were exposed 260 and 261 in (semaglutide 0.5 mg and 1 mg, respectively, and 262 in placebo). The proportion of treatment completers was similar between the treatment groups (88.1% in semaglutide 0.5 mg, 88.7% in semaglutide 1 mg, and 89.7% in placebo). Trial completion rates were also similar between treatment groups, and no significant difference in the reasons for trial discontinuation were noted between the treatment arms, except for GI AEs, which were more frequent in the semaglutide arms.

Baseline characteristics for each phase 3 study are detailed in Section 6 of this review.

8.2.3. Adequacy of the safety database:

The phase 3 clinical program for semaglutide include 5 trials comparing semaglutide to placebo or active comparator drugs with treatment duration from 30 to 56 weeks. Additionally, a 2 year CVOT was completed and submitted with this application. The applicant also performed two studies in Japan, required by the Japanese authorities, which are somewhat redundant for the purpose of this NDA. Regardless, all these studies are included in the safety daytabase.

A total of 8,124 patients with T2DM were randomized in the completed phase 3 trials, including 3,297 patients in the CVOT. Total patient-years of exposure (PYE) (on-treatment observation period) was 10,147 of which the CVOT accounted for approximately 60%. The size of the safety database appears adequate for pre-marketing safety assessment.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

OSI audits dd not identify any issues regarding data integrity, and the submission is well organized.

8.3.2. Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a product, whether it had a causal relationship with the treatment, and it included clinically significant worsening of a concomitant illness.

A clinical laboratory adverse event was a clinical laboratory abnormality which was clinically significant, i.e., an abnormality that suggested a disease and/or organ toxicity and was of a severity that required active management (further investigations, more frequent follow up, change in dose of medication, etc.).

The following were not reported as AEs:

- Pre-existing conditions
- Pre-planned procedures (unless the condition worsened on treatment)
- Hypoglycemic episodes (they were to be reported on specific hypoglycemic episode forms), except for those fulfilling the definition of SAE (all trials), or the ADA definition of severe hypoglycemia (CVOT), which were to be reported as AEs.

A serious adverse event (SAE) was an experience that at any dose resulted in any of the following:

- Death

- A life-threatening experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening or require hospitalization may be considered an SAE when - based on appropriate medical judgment - they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE
- Suspicion of transmission of infectious agents via trial product was always to be considered an SAE

Additionally, medical events of special interest (MESI) were defined for the semaglutide program. A MESI was an AE that fulfilled one or more pre-defined MESI criteria (see Table 103 below).

Table 103 Medical Events of Special Interest

Event	Adjudication
Fatal events	X
Acute coronary syndrome (myocardial infarction, unstable angina requiring hospitalisation)	X
Cerebrovascular events (stroke, transient ischemic attack)	X
Coronary revascularisation procedure	X
Heart failure requiring hospital admission	X
Cardiac arrhythmia (e)	
Peripheral arterial revascularisation procedure	
Nephropathy (e)	X[e]
Diabetic retinopathy (e)	X[e]
Neoplasm, malignant and benign (excluding thyroid neoplasm)	X
Thyroid disease (a) (including thyroid neoplasm or resulting in thyroidectomy)	X[b]
Pancreatitis or clinical symptoms leading to suspicion of pancreatitis (c,d)	X
Acute gallstone disease (e)	
Acute renal failure (e)	
Episodes of severe hypoglycaemia (e)	
Immunogenicity events (allergic reactions, immune complex disease, and anti-semaglutide antibody formation) (d)	
Medication errors concerning trial products • Administration of wrong drug • Wrong route of administration, such as intramuscular instead of subcutaneous. • Administration of a high dose with the intention to cause harm (e.g., suicide attempt). • Administration of an accidental overdose, defined as a higher dose than 1.1 mg/week (±24 hours), as 1.1 mg is the highest dose the subject will be able to take in one injection	
Suspected transmission of an infectious agent via a trial product.	
AEs leading to treatment discontinuation (e)	

Notes:
a: all disorders of the thyroid gland irrespective of seriousness. Subjects scheduled for thyroidectomy (partial or total) for any reason during the trial, were asked to inform the investigator prior to their operation,
b: was only to be adjudicated in case of thyroid neoplasm or resulting in thyroidectomy;
c: Pancreatitis or acute, severe abdominal pain leading to a suspicion of pancreatitis irrespective of seriousness. Confirmed cases of pancreatitis were followed-up with investigations of other potential causes;
d: in some cases additional samples were to be collected.
e: CVOT only.
Source: Table 2-1 ISS

All AEs were to be recorded by the investigator on the standard AE form in the CRF. The investigator was to report the diagnosis, if available. If no diagnosis was available, the investigator was to record each sign and symptom as individual AEs using separate AE forms.

For each AE, the following parameters were recorded by the investigator in the CRF: description

of event, seriousness, onset date, resolved date, severity, relationship to trial product, action taken, outcome and whether the event was a MESI.

For SAEs, the safety information form (SIF) was to be completed in addition to the standard AE form. If several symptoms or diagnoses occurred as part of the same clinical picture, one SIF was to be used to describe all the SAEs.

MESIs, regardless of seriousness, were to be reported using both the AE form, the SIF and an event specific MESI follow-up form. For MESIs qualifying for event adjudication, an event specific source data collection form was also to be completed in the CRF. The source data collection form was a check list of clinical data to be provided from the site to the event adjudication committee (EAC).

All episodes of hypoglycemia were to be reported on specific hypoglycemic episode forms. Episodes of hypoglycemia fulfilling the criteria for an SAE were furthermore to be reported as an adverse event. In addition, in the CVOT, all episodes of severe hypoglycemia (ADA definition) were predefined as MESIs and were to be reported following the same procedure as other MESIs.

Coding of AEs

All serious and non-serious AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) using the current MedDRA version at the time of reporting. MedDRA version 18.0 was used for reporting of all phase 3 trials.

Non-serious AEs were coded by Novo Nordisk data management supervised by medically qualified staff. Serious AEs were coded by medically qualified staff at Global Safety, Novo Nordisk, who was also responsible for consistent coding of all AEs across the semaglutide clinical development program. All coding was done blinded.

Severity of AEs

The investigator was to classify the severity of each AE as:

- Mild: No or transient symptoms, no interference with the patient's daily activities
- Moderate: Marked symptoms, moderate interference with the patient's daily activities
- Severe: Considerable interference with the patient's daily activities, unacceptable

AE outcome (evaluated by investigator):

- Recovered/resolved: The patient had fully recovered, or by medical or surgical treatment the condition had returned to the level observed at the first trial-related activity after the patient signed the informed consent

- Recovering/resolving: The condition was improving and the patient was expected to recover from the event
- Recovered/resolved with sequelae: The patient had recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela met an SAE criterion, the AE was to be reported as an SAE
- Not recovered/not resolved: The condition of the patient had not improved and the symptoms were unchanged, or the outcome was not known at the time of reporting
- Fatal: This term was only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died were to be assessed as recovered/resolved, recovering/resolving, recovered/resolved with sequelae or not recovered/not resolved. An AE with fatal outcome was to be reported as an SAE
- Unknown: This term was only applicable if the patient was lost to follow-up

All SAEs and MESIs were to be followed until the outcome of the events was recovered, recovered with sequelae or fatal, and until all queries had been resolved.

For each AE reported during the semaglutide trials the action taken to trial product was to be recorded on the AE forms as:

- Product withdrawn temporarily
- Product withdrawn permanently
- Dose reduced
- Dose increased
- Dose not changed
- Unknown
- N/A

An external independent event adjudication committee (EAC) was established to perform ongoing blinded adjudication of selected AEs according to pre-defined diagnostic criteria. The types of events that were adjudicated in presented below.

Table 104 Adjudicated Events

Adjudicated events • **Categories within event**	**Adjudicator Specialty**
Fatal events • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	Cardiology/neurology[1]

Adjudicated events • **Categories within event**	**Adjudicator Specialty**
Acute coronary syndrome • Myocardial infarction (MI) – i.e., spontaneous MI, percutaneous coronary intervention related MI, coronary artery bypass graft surgery related MI, and silent MI[2] • Unstable angina requiring hospitalization	Cardiology
Cerebrovascular event • Stroke • Transient ischemic attack	Neurology
Coronary revascularization procedure	Cardiology
Heart failure requiring hospital admission	Cardiology
New or worsening nephropathy[3]	Nephrology
Diabetic retinopathy complications[3]	Ophthalmology
Neoplasms (excluding thyroid neoplasms) • Malignant neoplasm • *In situ* neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behavior	Oncology
Thyroid neoplasm or events resulting in thyroidectomy	Endocrinology and Oncology[4]
Pancreatitis or clinical symptoms leading to suspicion of pancreatitis • Acute pancreatitis • Chronic pancreatitis	Gastroenterology

[1] Fatal events were submitted to 2 Neurologist if related to a neurological event and to 2 Cardiologists for all other events; [2] Silent MI events (not reported by sites but identified via ECG screening) were submitted directly to full committee and reviewed by 3 Cardiologists including the Chair to achieve consensus adjudication; [3] only assessed in CVOT; [4]submitted to 1 endocrinologist and 1 oncologist
Source: Modified from Table 2-2 of the ISS

8.3.3. Routine Clinical Tests

Routine clinical tests performed during the semaglutide phase 3 trial are discussed in section 6 under the individual trials.

8.4. Safety Results

8.4.1. Deaths

CVOT

The cardiovascular outcomes study will be presented separately from the other phase 3 studies. For study 3744, vital status was available for 99.6% of patients (6 patients on

semaglutide, and 7 patients on placebo had unknown vital status). Deaths were adjudicated to attribute causality to a CV or non-CV cause of death, as the CV death was a component of the primary endpoint.

The applicant reported a total of 123 adverse events that resulted in death during the in-trial period, 62 with semaglutide, and 61 in placebo (3.8% of patients in each semaglutide arm, and 3.7% in the placebo arm). My analysis using JReview also yielded the same numbers. The distribution of events by treatment arm, and by body system organ class, are presented in the table below. All-cause mortality was not different between the treatment arms. There did not appear to be any dose-dependence regarding the total number of deaths between the two doses of semaglutide.

Table 105 All-Cause Death by SOC and Treatment Arm, CVOT

Primary System Organ Class	Placebo 0.5 mg N=749 N (%)	Placebo 1.0 mg N=739 N (%)	Sema 0.5 mg N=743 N (%)	Sema 1.0 mg N=737 N (%)
Patients with event	33(4.41%)	28 (3.79%)	31 (4.17%)	31 (4.21%)
Blood and lymphatic system disorders	0(0.00%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Cardiac disorders	12(1.60%)	15 (2.03%)	15 (2.02%)	13 (1.76%)
Gastrointestinal disorders	1(0.13%)	1 (0.14%)	1 (0.13%)	0 (0.00%)
General disorders and administration site conditions	5(0.67%)	3 (0.41%)	4 (0.54%)	3 (0.41%)
Hepatobiliary disorders	0(0.00%)	0 (0.00%)	1 (0.13%)	0 (0.00%)
Immune system disorders	1(0.13%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations	5(0.67%)	7 (0.95%)	4 (0.54%)	4 (0.54%)
Injury, poisoning and procedural complications	1(0.13%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Metabolism and nutrition disorders	1(0.13%)	1 (0.14%)	2 (0.27%)	1 (0.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5(0.67%)	1 (0.14%)	3 (0.40%)	7 (0.95%)
Nervous system disorders	4(0.53%)	3 (0.41%)	4 (0.54%)	3 (0.41%)
Renal and urinary disorders	3(0.40%)	2 (0.27%)	3 (0.40%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders	4(0.53%)	2 (0.27%)	3 (0.40%)	6 (0.81%)
Skin and subcutaneous tissue disorders	0(0.00%)	0 (0.00%)	1 (0.13%)	0 (0.00%)
Vascular disorders	3(0.40%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Primary System Organ Class	Placebo 0.5 mg N=749 N (%)	Placebo 1.0 mg N=739 N (%)	Sema 0.5 mg N=743 N (%)	Sema 1.0 mg N=737 N (%)
Patients with event	33(4.41%)	28 (3.79%)	31 (4.17%)	31 (4.21%)

Source: Reviewer generated using JReview (randomized population flag ADSL, planned treatment ADSL, SOC ADAE, and outcome = fatal ADAE)

Review of selected narratives for death events did not reveal any unexpected issues. CV death was discussed separately in section 6.7.

Phase 3 pool

There were 16 patients reported with a fatal outcome from this pool. All cases were sent to the EAC for adjudication to identify all potential cases of death. A total of 10 patients (0.3%) randomized to semaglutide died, and 6 patients (0.4%) randomized to comparator products died.

There were no significant differences within the individual trials as it can be seen in Table 106 below. The overall incidence of death was small, as expected in this patient population. There did not appear to be any dose-dependence between the semaglutide doses studied and fatal events.

Table 106 Deaths – Phase 3 Trials Excluding CVOT

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYO												
3623 vs Placebo (Mono)	128	85			130	87			129	85		
3626 vs Sita (OADs)	409	469			409	469			407	468		
3624 vs Exe ER (OADs)					404	460			405	458		
3625 vs IGlar (OADs)	362	238			360	238			360	239		
3627 vs Placebo (Insulin)	132	88			131	87			133	87		
4092 vs Sita (Mono), JP	103	70			102	68			103	70		
4091 vs OAD (OAD), JP	239	279			241	276			120	139		
All AEs with fatal outcome												
3623 vs Placebo (Mono)												
3626 vs Sita (OADs)	2	(0.5)	2	0.4	1	(0.2)	1	0.2	3	(0.7)	3	0.6
3624 vs Exe ER (OADs)					2	(0.5)	5	1.1				
3625 vs IGlar (OADs)	4	(1.1)	4	1.7					2	(0.6)	2	0.8
3627 vs Placebo (Insulin)												
4092 vs Sita (Mono), JP												
4091 vs OAD (OAD), JP	1	(0.4)	1	0.4					1	(0.8)	1	0.7

Note: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: E: number of events; Exe ER: exenatide extended release; IGlar: insulin glargine; JP: Japan; N: number of subjects from safety analysis set with at least one event; OAD: oral antidiabetic drug; PYO: patient-years of observation; R: events per 100 PYO; Sita: sitagliptin; %: percentage of subjects with at least one event.

Source: Table 2-14 ISS

Placebo pool

No deaths were reported in any of the two placebo-controlled trials (3623, and 3627).

8.4.2. **Serious Adverse Events**

CVOT

The proportion of patients reporting SAEs during the trial and the corresponding rate were lower with semaglutide (0.5 mg: 32.1% of patients, 1.0 mg: 29.2% of patients) than with placebo (34.9% of patients). A total of 72 patients had SAEs leading to discontinuation, with no major differences between the treatment groups.

Table 107 SAEs CVOT On Treatment

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
PYE	1488.3				1443.9				3034.8			
Events	264	(32.1)	599	40.2	240	(29.3)	481	33.3	574	(34.9)	1256	41.4
Severity												
Severe	134	(16.3)	247	16.6	115	(14.0)	216	15.0	310	(18.9)	556	18.3
Moderate	155	(18.8)	273	18.3	142	(17.3)	202	14.0	340	(20.7)	563	18.6
Mild	53	(6.4)	79	5.3	48	(5.9)	63	4.4	109	(6.6)	137	4.5
Relationship to trial product												
Probable	6	(0.7)	8	0.5	5	(0.6)	8	0.6	3	(0.2)	3	0.1
Possible	39	(4.7)	56	3.8	36	(4.4)	53	3.7	63	(3.8)	90	3.0
Unlikely	238	(28.9)	535	35.9	218	(26.6)	420	29.1	537	(32.7)	1162	38.3
Unknown	0				0				1	(0.1)	1	<0.1
Missing	0				0				0			
Outcome												
Recovered	219	(26.6)	475	31.9	201	(24.5)	383	26.5	489	(29.7)	991	32.7
Fatal	24	(2.9)	38	2.6	23	(2.8)	34	2.4	44	(2.7)	74	2.4
Recovering	13	(1.6)	14	0.9	10	(1.2)	10	0.7	18	(1.1)	26	0.9
Recovered with sequelae	15	(1.8)	17	1.1	18	(2.2)	18	1.2	44	(2.7)	52	1.7
Not recovered	46	(5.6)	55	3.7	28	(3.4)	36	2.5	88	(5.4)	113	3.7
Unknown	0				0				0			
Leading to premature treatment discontinuation	26	(3.2)	31	2.1	22	(2.7)	27	1.9	58	(3.5)	72	2.4
Action taken												
Dose not changed	220	(26.7)	468	31.4	205	(25.0)	352	24.4	473	(28.8)	937	30.9
Drug interrupted	19	(2.3)	30	2.0	15	(1.8)	26	1.8	43	(2.6)	100	3.3
Drug withdrawn	26	(3.2)	31	2.1	22	(2.7)	27	1.9	58	(3.5)	72	2.4
Dose reduced	0				0				0			
Dose increased	0				0				0			
Unknown	0				1	(0.1)	3	0.2	0			
Not applicable	42	(5.1)	70	4.7	37	(4.5)	73	5.1	82	(5.0)	147	4.8
Missing	0				0				0			

Notes: MedDRA version 18.0. The 'on-treatment' overview of adverse events comprises events with onset on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Exposure time is calculated as the duration of this time span.

Abbreviations: E: number of events; N: Number of subjects experiencing at least one event; PYE: Patient years of exposure; R: Event rate per 100 years of exposure; SAS: Safety analysis set; %: Percentage of subjects experiencing at least one event.

Source: Table 13-12 study report

Most of the SAEs reported were in the cardiac disorders SOC, which was expected considering that this study enrolled patients with high CV risk. The proportion of patients reporting SAEs within this SOC, and the corresponding rate were generally lower with semaglutide than placebo (in particular with semaglutide 1 mg). This was mostly due to fewer events with semaglutide in the cardiac disorders SOC.

Table 108 Serious Adverse Events by SOC and Preferred Term Reported by ≥1.0% of Patients in Any Arm – SAS On-Treatment - CVOT

System organ class Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Placebo N	(%)	E	R
N	823				819				1644			
PYE	1488.3				1443.9				3034.8			
All events (total)	264	(32.1)	599	40.2	240	(29.3)	481	33.3	574	(34.9)	1256	41.4
Cardiac disorders												
Angina unstable	10	(1.2)	11	0.7	11	(1.3)	14	1.0	39	(2.4)	42	1.4
Acute myocardial infarction	13	(1.6)	14	0.9	9	(1.1)	9	0.6	38	(2.3)	39	1.3
Coronary artery disease	11	(1.3)	11	0.7	9	(1.1)	9	0.6	5	(0.3)	6	0.2
Myocardial infarction	4	(0.5)	4	0.3	8	(1.0)	8	0.6	19	(1.2)	21	0.7
Angina pectoris	8	(1.0)	8	0.5	7	(0.9)	8	0.6	25	(1.5)	26	0.9
Atrial fibrillation	11	(1.3)	12	0.8	12	(1.5)	15	1.0	35	(2.1)	38	1.3
Cardiac failure congestive	14	(1.7)	17	1.1	10	(1.2)	13	0.9	29	(1.8)	35	1.2
Cardiac failure	10	(1.2)	11	0.7	8	(1.0)	8	0.6	7	(0.4)	7	0.2
Infections and infestations												
Pneumonia	15	(1.8)	15	1.0	11	(1.3)	11	0.8	30	(1.8)	33	1.1
Urinary tract infection	8	(1.0)	8	0.5	2	(0.2)	2	0.1	13	(0.8)	13	0.4
Surgical and medical procedures												
Coronary arterial stent insertion	10	(1.2)	11	0.7	7	(0.9)	8	0.6	30	(1.8)	33	1.1
Coronary revascularisation	11	(1.3)	12	0.8	7	(0.9)	7	0.5	24	(1.5)	27	0.9
Coronary artery bypass	8	(1.0)	8	0.5	4	(0.5)	4	0.3	21	(1.3)	21	0.7
Nervous system disorders												
Ischaemic stroke	8	(1.0)	8	0.5	6	(0.7)	7	0.5	18	(1.1)	18	0.6
Renal and urinary disorders												
Acute kidney injury	12	(1.5)	14	0.9	5	(0.6)	6	0.4	29	(1.8)	30	1.0
Chronic kidney disease	6	(0.7)	6	0.4	4	(0.5)	4	0.3	17	(1.0)	19	0.6
Injury, poisoning and procedural complications												
Fall	9	(1.1)	9	0.6	4	(0.5)	4	0.3	14	(0.9)	14	0.5
Musculoskeletal and connective tissue disorders												
Osteoarthritis	5	(0.6)	6	0.4	6	(0.7)	6	0.4	18	(1.1)	18	0.6

Notes: MedDRA version 18.0. The 'on-treatment' summary of adverse events comprises events with onset on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Exposure time is calculated as the duration of this time span. Table is sorted in descending order by class and/or term based on the total percentage of subjects experiencing at least one event.

Abbreviations: E: Number of events; N: Number of subjects experiencing at least one event; PYE: Patient years of exposure; R: Event rate per 100 PYE; SAS: Safety analysis set; %: Percentage of subjects experiencing at least one event.

Source: Table 13-13 study report

The proportion of patients reporting individual SAEs within the SOC GI disorders was <1%. For the SOC GI disorders, both the proportion of patients reporting SAEs and the corresponding rate were higher with semaglutide than placebo, and higher with semaglutide 0.5 mg than semaglutide 1 mg.

Phase 3 pool

The proportion of patients with SAEs, and the corresponding rate, was higher with semaglutide (0.5 mg and 1.0 mg) than with comparator products. No dose-response was evident for semaglutide. Most of the SAEs had reported outcomes of "recovered". The outcomes for the SAEs were similar with semaglutide (0.5 mg and 1.0 mg) and comparator products. Fatal SAEs

were discussed in section 8.4.1.

Table 109 SAEs- Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
SAEs	92	(6.6)	138	12.0	118	(6.7)	152	10.0	95	(5.8)	117	7.9
Severity												
Severe	44	(3.2)	60	5.2	61	(3.5)	73	4.9	39	(2.3)	43	2.9
Moderate	36	(2.6)	51	4.5	46	(2.6)	53	3.5	46	(2.8)	56	3.8
Mild	21	(1.5)	27	2.3	22	(1.2)	26	1.7	17	(1.0)	18	1.2
Outcome												
Recovered	76	(5.5)	113	9.9	106	(6.0)	132	8.7	70	(4.2)	85	5.7
Recovering	4	(0.3)	4	0.3	6	(0.3)	6	0.4	10	(0.6)	11	0.8
Recovered with sequelae	4	(0.3)	4	0.4	1	(<0.1)	1	<0.1	4	(0.2)	4	0.3
Not recovered	8	(0.6)	10	0.8	8	(0.4)	9	0.6	9	(0.6)	11	0.7
Fatal	7	(0.5)	7	0.6	3	(0.2)	3	0.2	6	(0.4)	6	0.4
Unknown					1	(<0.1)	1	<0.1				
Leading to premature discontinuation	16	(1.1)	18	1.5	13	(0.7)	13	0.8	8	(0.5)	9	0.6

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-16 ISS

A total of 37 patients had SAEs that led to premature treatment discontinuation. The proportions of patients with SAEs leading to premature treatment discontinuation and the rates of events were higher with semaglutide (0.5 mg and 1.0 mg) than with comparator products, although the overall number of events was small.

SAEs were reported evenly during the entire treatment period; both with semaglutide (0.5 mg and 1.0 mg) and comparator products.

The most frequently reported SAEs were within the following SOCs: infections and infestations, neoplasms, surgical and medical procedures, gastrointestinal disorders and cardiac disorders. SAEs within the SOC of gastrointestinal disorders were reported by a higher proportion of patients with semaglutide 0.5 mg (1.3%) than with semaglutide 1 mg (0.7%) and comparator products (0.5%,) driven by pancreatitis. Pancreatitis is discussed in section 8.4.5 of this review.

Table 110 SAEs (≥0.2% of patients) by System Organ Class and Preferred Term – SAS On-Treatment – Phase 3 Pool

System organ class Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
N	1373				1777				1657			
PYE	1165				1548				1467			
All events (total)	92	(6.6)	138	12.0	118	(6.7)	152	10.0	95	(5.8)	117	7.9
Infections and infestations												
Pneumonia	6	(0.4)	6	0.5	2	(0.1)	2	0.1	2	(0.1)	2	0.1
Sinusitis	2	(0.2)	2	0.2								
Surgical and medical procedures												
Coronary artery bypass					3	(0.2)	3	0.2	1	(<0.1)	1	<0.1
Coronary arterial stent insertion	2	(0.2)	2	0.2	2	(0.1)	2	0.1				
Gastrointestinal disorders												
Pancreatitis	2	(0.2)	2	0.2	3	(0.2)	3	0.2				
Pancreatitis acute	2	(0.2)	2	0.2								
Umbilical hernia	2	(0.2)	2	0.2	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Gastritis	2	(0.2)	2	0.2					1	(<0.1)	1	<0.1
Haemorrhoids	2	(0.2)	2	0.2								
Cardiac disorders												
Atrial fibrillation	3	(0.2)	3	0.3	1	(<0.1)	1	<0.1	4	(0.2)	4	0.3
Nervous system disorders												
Ischaemic stroke	2	(0.2)	2	0.2	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Hepatobiliary disorders												
Cholecystitis acute					4	(0.2)	4	0.3				
Cholelithiasis	2	(0.2)	2	0.2	2	(0.1)	2	0.1	2	(0.1)	2	0.1
Metabolism and nutrition disorders												
Hyponatraemia	2	(0.2)	2	0.2								
Investigations												
Weight decreased	2	(0.2)	2	0.2								
Eye disorders												
Cataract	2	(0.2)	2	0.2					1	(<0.1)	1	<0.1

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-17 ISS

Placebo pool

The proportion of patients with SAEs, rates of SAEs and types of SAEs reported in placebo-controlled trials were consistent with those reported in the phase 3 trial pool.

Table 111 SAEs – SAS On-Treatment – Placebo Pool

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(Adj%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
N and PYE (year)	260	174			261	164			262	166		
SAEs	15	(5.8)	20	12.2	19	(7.3)	25	15.3	14	(5.3)	17	10.3
Severity												
Severe	7	(2.7)	11	6.7	14	(5.4)	16	9.8	7	(2.7)	7	4.2
Moderate	7	(2.7)	8	4.9	7	(2.7)	7	4.3	6	(2.3)	8	4.8
Mild	1	(0.4)	1	0.6	1	(0.4)	2	1.2	2	(0.8)	2	1.2
Outcome												
Recovered	13	(5.0)	17	10.3	18	(6.9)	24	14.7	11	(4.2)	14	8.4
Recovering	1	(0.4)	1	0.6	1	(0.4)	1	0.6	2	(0.8)	2	1.2
Recovered with sequelae	1	(0.4)	1	0.6	0				0			
Not recovered	1	(0.4)	1	0.6	0				1	(0.4)	1	0.6
Fatal	0				0				0			
Unknown	0				0				0			
Leading to premature discontinuation	1	(0.4)	1	0.6	2	(0.8)	2	1.2	1	(0.4)	1	0.6

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Placebo pool: Trials included: 3623 and 3627

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-18 ISS

There appeared to be a higher proportion of patients with SAEs reported with semaglutide 1 mg compared to semaglutide 0.5 mg and placebo. However, the number of SAEs is small, and this finding could be due to chance.

Table 112 SAEs by SOC in the Placebo Pool, On-Treatment

Body System or Organ Class	Placebo N=262	Sema 0.5 mg N=260	Sema 1.0 mg N=261
Total patients with an SAE	14 (5.34%)	15 (5.77%)	19 (7.28%)
Blood and lymphatic system disorders	2 (0.76%)	0 (0.00%)	0 (0.00%)
Cardiac disorders	1 (0.38%)	2 (0.77%)	2 (0.77%)
Eye disorders	1 (0.38%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders	1 (0.38%)	1 (0.38%)	1 (0.38%)
General disorders and administration site conditions	1 (0.38%)	0 (0.00%)	1 (0.38%)
Hepatobiliary disorders	0 (0.00%)	1 (0.38%)	1 (0.38%)
Immune system disorders	0 (0.00%)	0 (0.00%)	1 (0.38%)
Infections and infestations	5 (1.91%)	3 (1.15%)	3 (1.15%)
Injury, poisoning and procedural complications	0 (0.00%)	1 (0.38%)	1 (0.38%)
Investigations	0 (0.00%)	2 (0.77%)	0 (0.00%)
Metabolism and nutrition disorders	1 (0.38%)	0 (0.00%)	1 (0.38%)

Body System or Organ Class	Placebo N=262	Sema 0.5 mg N=260	Sema 1.0 mg N=261
Musculoskeletal and connective tissue disorders	1 (0.38%)	0 (0.00%)	2 (0.77%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.00%)	1 (0.38%)	1 (0.38%)
Nervous system disorders	0 (0.00%)	2 (0.77%)	2 (0.77%)
Psychiatric disorders	1 (0.38%)	2 (0.77%)	0 (0.00%)
Renal and urinary disorders	0 (0.00%)	0 (0.00%)	1 (0.38%)
Reproductive system and breast disorders	0 (0.00%)	1 (0.38%)	0 (0.00%)
Surgical and medical procedures	1 (0.38%)	2 (0.77%)	6 (2.30%)
Vascular disorders	1 (0.38%)	0 (0.00%)	1 (0.38%)

Source: Reviewer generated using ADAE and ADSL for ISS

Reviewer's comment: In the phase 3 pool excluding the CVOT, slightly more SAEs were reported with semaglutide compared to placebo. However, this was not observed in the CVOT where the SAEs were balanced between the treatment groups. Even when observed, the differences between the treatment groups were small, and they will be explored further under the analysis of MESIs.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

CVOT

The proportions of patients with AEs leading to premature discontinuation and the corresponding rates were higher with semaglutide than with placebo.

A total of 130 SAEs led to premature treatment discontinuation of 106 patients. The proportions of patients with SAEs leading to premature discontinuation and corresponding rates were slightly lower with semaglutide than with placebo.

AEs in the SOC GI disorders and the PT decreased appetite (within the SOC metabolism and nutrition disorders) were the most frequent AEs leading to premature discontinuation. In general, the proportions of patients with AEs leading to premature discontinuation in SOC GI disorders were lower with semaglutide 0.5 mg than with semaglutide 1 mg, and lower with placebo than with both doses of semaglutide.

The most frequent SAEs leading to premature discontinuation were chronic kidney disease (4 events with semaglutide and 2 events with placebo), cerebrovascular accident (2 events with semaglutide and 4 events with placebo), MI (none with semaglutide and 4 events with placebo), coronary artery bypass (none with semaglutide and 4 events with placebo) and pancreatitis/pancreatitis acute (3 events with semaglutide and 5 events with placebo).

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Table 113 Adverse Events Leading to Premature Treatment Discontinuation – SAS On-Treatment – CVOT

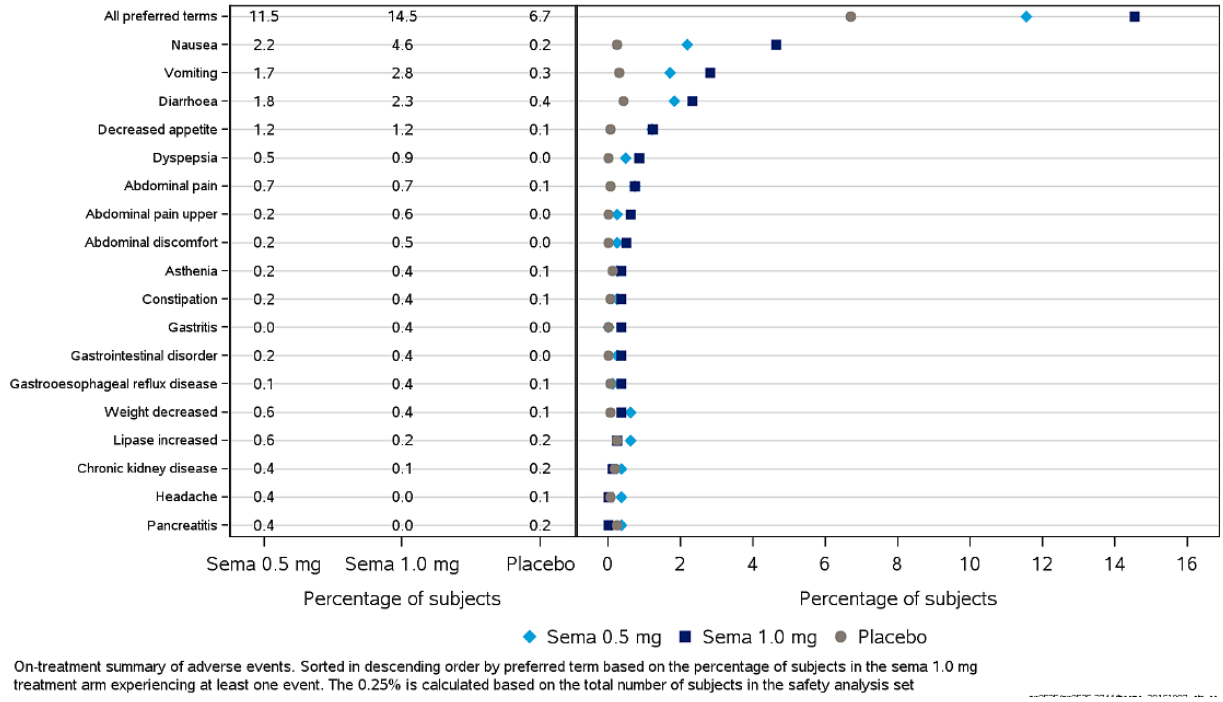
	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
PYE	1488.3				1443.9				3034.8			
Events	95	(11.5)	151	10.1	119	(14.5)	196	13.6	110	(6.7)	136	4.5
Serious												
Yes	26	(3.2)	31	2.1	22	(2.7)	27	1.9	58	(3.5)	72	2.4
No	70	(8.5)	120	8.1	100	(12.2)	169	11.7	53	(3.2)	64	2.1
Severity												
Severe	35	(4.3)	48	3.2	38	(4.6)	47	3.3	41	(2.5)	51	1.7
Moderate	49	(6.0)	73	4.9	57	(7.0)	87	6.0	46	(2.8)	52	1.7
Mild	22	(2.7)	30	2.0	39	(4.8)	62	4.3	29	(1.8)	33	1.1
Relationship to trial product												
Probable	42	(5.1)	79	5.3	50	(6.1)	88	6.1	22	(1.3)	27	0.9
Possible	29	(3.5)	39	2.6	45	(5.5)	67	4.6	29	(1.8)	32	1.1
Unlikely	29	(3.5)	33	2.2	32	(3.9)	41	2.8	62	(3.8)	77	2.5
Unknown	0				0				0			
Missing	0				0				0			
Outcome												
Recovered	73	(8.9)	124	8.3	101	(12.3)	169	11.7	75	(4.6)	97	3.2
Fatal	3	(0.4)	3	0.2	3	(0.4)	3	0.2	4	(0.2)	5	0.2
Recovering	3	(0.4)	3	0.2	2	(0.2)	2	0.1	2	(0.1)	2	0.1
Recovered with sequela	4	(0.5)	4	0.3	3	(0.4)	3	0.2	6	(0.4)	6	0.2
Not recovered	16	(1.9)	17	1.1	15	(1.8)	18	1.2	25	(1.5)	25	0.8
Unknown	0				1	(0.1)	1	0.1	1	(0.1)	1	0.1

Notes: MedDRA version 18.0. The 'on-treatment' overview of adverse events comprises events with onset on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Exposure time is calculated as the duration of this time span.

Abbreviations: E: number of events, N: Number of subjects experiencing at least one event; R: Event rate per 100 years of exposure; SAS: Safety analysis set; %: Percentage of subjects experiencing at least one event.

Source: Table 13-14 study report 3744

Figure 52 Adverse Events Leading to Premature Treatment Discontinuation - Most Frequent (≥0.25%) - SAS On-Treatment



Source: Figure 13-10 ISS

AE leading to premature treatment discontinuation occurred most frequently during the first 20 weeks of treatment with semaglutide, and the first 30 weeks of treatment with placebo. After 30 to 35 weeks on treatment, the frequency of AEs leading to premature treatment discontinuation was similar for all treatment groups.

Adverse events leading to temporary trial product discontinuation

Except in the case of suspicion of acute pancreatitis, temporary treatment discontinuation was not allowed in this trial. If a patient missed more than 3 consecutive doses or experienced repetitive instances of non-compliance (1 or more missed doses), this was to be documented as important PDs. The rates of AEs leading to study drug interrupted was higher with semaglutide (94 patients – 5.7%) vs placebo (73 patients – 4.4%). No dose-dependence was seen with semaglutide.

Adverse events leading to dose reduction

A total of 12 AEs (11 with semaglutide, 1 with placebo) in 7 patients (6 with semaglutide, 1 with

placebo) led to dose reduction. There was a higher number of AEs leading to dose reduction with semaglutide 0.5 mg (8 events in 3 patients) than with semaglutide 1 mg (3 events in 3 patients). None of the events were SAEs.

Phase 3 pool

The proportion of patients who discontinued treatment prematurely due to AEs was higher with semaglutide than with comparator products. A dose-response was apparent for semaglutide in this respect.

Table 114 Adverse Events Leading to Premature Treatment Discontinuation - SAS On-Treatment - Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	1373				1777				1657			
PYE	1165				1548				1467			
Events	84	(6.1)	131	11.6	156	(8.7)	241	15.6	51	(3.0)	83	5.5

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-19 ISS

This difference is mostly due to GI AEs (nausea, vomiting, diarrhea, etc.) leading to discontinuation in the semaglutide groups, and this was dose-dependent. Other AEs more frequently leading to premature treatment discontinuation with semaglutide than with placebo included decreased appetite, decreased weight and lipase increased

Table 115 Adverse Events (≥0.2% of Patients) Leading to Premature Treatment Discontinuation by System Organ Class and Preferred Term – SAS On Treatment – Phase 3 Pool

System organ class Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
N	1373				1777				1657			
PYE	1165				1548				1467			
All events (total)	84	(6.1)	131	11.6	156	(8.7)	241	15.6	51	(3.0)	83	5.5
Gastrointestinal disorders												
Nausea	21	(1.5)	21	1.9	45	(2.5)	48	3.1	9	(0.5)	9	0.6
Vomiting	7	(0.5)	7	0.6	28	(1.6)	28	1.9	2	(0.1)	2	0.1
Diarrhoea	14	(1.1)	14	1.3	27	(1.5)	29	1.9	1	(<0.1)	1	<0.1
Dyspepsia	3	(0.2)	3	0.3	10	(0.5)	10	0.6	0	(0.0)		
Abdominal pain	4	(0.3)	4	0.4	8	(0.5)	8	0.5	3	(0.2)	3	0.2
Abdominal discomfort	4	(0.3)	4	0.3	6	(0.4)	7	0.5	0	(0.0)		
Abdominal distension	3	(0.2)	3	0.3	5	(0.3)	5	0.3	0	(0.0)		
Constipation	4	(0.3)	4	0.3	4	(0.2)	4	0.3	3	(0.2)	3	0.2
Abdominal pain upper	2	(0.2)	2	0.2	4	(0.2)	4	0.3	2	(0.1)	2	0.1
Pancreatitis	1	(<0.1)	1	<0.1	3	(0.2)	3	0.2	1	(<0.1)	1	<0.1
Gastrointestinal disorder	4	(0.3)	4	0.4	2	(0.1)	3	0.2	1	(<0.1)	1	<0.1
Eructation	3	(0.2)	3	0.3	2	(0.1)	2	0.1	0	(0.0)		
Pancreatitis acute	3	(0.2)	3	0.3	0	(0.0)			1	(<0.1)	1	<0.1
Investigations												
Lipase increased	5	(0.4)	5	0.5	5	(0.3)	5	0.3	4	(0.2)	4	0.3
Weight decreased	3	(0.2)	3	0.3	5	(0.2)	5	0.3	0	(0.0)		
Amylase increased	3	(0.2)	3	0.3	4	(0.2)	4	0.3	3	(0.2)	3	0.2
Metabolism and nutrition disorders												
Decreased appetite	8	(0.6)	8	0.7	15	(0.8)	15	0.9	0	(0.0)		
Nervous system disorders												
Dizziness	2	(0.2)	2	0.2	4	(0.2)	4	0.3	2	(0.1)	2	0.1
Headache	1	(<0.1)	1	<0.1	3	(0.2)	3	0.2	2	(0.1)	2	0.1
General disorders and administration site conditions												
Fatigue	2	(0.2)	2	0.2	3	(0.2)	3	0.2	0	(0.0)		
Injection site nodule	0	(0.0)			0	(0.0)			5	(0.3)	5	0.3
Skin and subcutaneous tissue disorders												
Rash	2	(0.2)	2	0.2	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Urticaria	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	3	(0.2)	3	0.2
Infections and infestations												
Gastroenteritis	2	(0.2)	2	0.2	1	(<0.1)	1	<0.1	0	(0.0)		
Psychiatric disorders												
Insomnia	2	(0.2)	2	0.2	0	(0.0)			0	(0.0)		
Libido decreased	2	(0.2)	2	0.2	0	(0.0)			0	(0.0)		

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-20 ISS

The proportion of patients with AEs leading to temporary treatment discontinuation (drug interrupted) and the corresponding rates were higher with semaglutide (0.5 mg and 1.0 mg) than with comparators, mainly due to GI AEs.

Table 116 Most Frequent (≥0.2% of Patients) Adverse Events Leading to Temporary Treatment Discontinuation by System Organ Class and Preferred Term – SAS On-Treatment – Phase 3 Pool

System organ class Preferred term	Sema 0.5 mg N	(Adj.%)	E	Adj.R	Sema 1.0 mg N	(Adj.%)	E	Adj.R	Comparator N	(Adj.%)	E	Adj.R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
All events	28	(2.1)	50	4.4	59	(3.4)	83	5.5	31	(1.8)	48	3.2
Gastrointestinal disorders												
Diarrhoea	1	(<0.1)	1	<0.1	6	(0.3)	6	0.4	1	(<0.1)	1	<0.1
Constipation	0	(0.0)			4	(0.2)	4	0.3	0	(0.0)		
Abdominal pain	1	(<0.1)	1	<0.1	5	(0.3)	5	0.3	2	(0.1)	2	0.1
Nausea	6	(0.4)	6	0.5	5	(0.3)	5	0.3	3	(0.2)	3	0.2
Vomiting	4	(0.3)	5	0.4	2	(0.1)	2	0.1	0	(0.0)		
Investigations												
Lipase increased	3	(0.2)	3	0.2	11	(0.6)	11	0.7	6	(0.3)	6	0.4
Amylase increased	2	(0.1)	2	0.2	3	(0.2)	3	0.2	4	(0.2)	4	0.3
General disorders and administration site conditions												
Asthenia	1	(<0.1)	1	<0.1	3	(0.2)	3	0.2	0	(0.0)		

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-21 ISS

Adverse events leading to dose reduction

Fourteen patients had AEs leading to dose reduction. These were primarily GI AEs (12 with semaglutide and 2 with comparator). One event (hypoglycemic unconsciousness in the comparators group) was an SAE.

Table 117 Adverse Events Leading to Dose Reduction by System Organ Class and preferred Term – SAS On Treatment - Phase 3 Pool

System organ class Preferred term	Sema 0.5 mg N (Adj.%)	E	Adj.R	Sema 1.0 mg N (Adj.%)	E	Adj.R	Comparators N (%)	E	R
Number of subjects	1373			1777			1657		
PYE	1165			1548			1467		
All events	2 (0.2)	3	0.3	10 (0.6)	13	0.9	2 (0.1)	2	0.1
Gastrointestinal disorders	**2 (0.2)**	**3**	**0.3**	**8 (0.5)**	**10**	**0.7**	**1 (<0.1)**	**1**	**<0.1**
Nausea	1 (<0.1)	1	<0.1	5 (0.3)	5	0.3	0 (0.0)		
Vomiting	1 (<0.1)	1	<0.1	2 (0.1)	2	0.1	0 (0.0)		
Dyspepsia	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1	0 (0.0)		
Constipation	0 (0.0)			1 (<0.1)	1	<0.1	0 (0.0)		
Diarrhoea	0 (0.0)			1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
General disorders and administration	**0 (0.0)**			**1 (<0.1)**	**1**	**<0.1**	**0 (0.0)**		
Asthenia	0 (0.0)			1 (<0.1)	1	<0.1	0 (0.0)		
Infections and infestations	**0 (0.0)**			**1 (<0.1)**	**1**	**<0.1**	**0 (0.0)**		
Gastroenteritis viral	0 (0.0)			1 (<0.1)	1	<0.1	0 (0.0)		
Metabolism and nutrition disorders	**0 (0.0)**			**1 (<0.1)**	**1**	**<0.1**	**0 (0.0)**		
Decreased appetite	0 (0.0)			1 (<0.1)	1	<0.1	0 (0.0)		
Nervous system disorders	**0 (0.0)**			**0 (0.0)**			**1 (<0.1)**	**1**	**<0.1**
Hypoglycaemic unconsciousness	0 (0.0)			0 (0.0)			1 (<0.1)	1	<0.1

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: table 2-22 ISS

Placebo pool

AEs leading to premature treatment discontinuation

The proportion of patients who discontinued trial product prematurely due to AEs was higher with semaglutide than with placebo, however, no dose-response was observed for semaglutide. The most common AEs leading to premature treatment discontinuation with semaglutide were nausea (1.5%, corresponding to 27% of patients withdrawn due to AEs), vomiting (1.2%, corresponding to 21% of patients withdrawn due to AEs) and diarrhea (0.8%, corresponding to 14% of patients discontinued treatment prematurely due to AEs. Other AEs more frequently reported leading to premature treatment discontinuation with semaglutide than with placebo included gastric bypass (2 patients with semaglutide 1 mg) decreased weight (2 patients with semaglutide 0.5 mg) and dizziness (2 patients with semaglutide 0.5 mg).

Table 118 Adverse Events Leading to Premature Treatment Discontinuation - SAS On-Treatment - Placebo Pool

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	260				261				262			
PYE	165				164				166			
Events	14	(5.4)	24	14.6	15	(5.7)	23	14.0	4	(1.5)	6	3.6

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Placebo pool: Trials included: 3623 and 3627

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-23 ISS

AEs leading to temporary discontinuation

The proportion of patients with AEs or SAEs leading to temporary treatment discontinuation (drug interrupted) and the corresponding rates were higher with semaglutide (0.5 mg and 1.0 mg) than with comparator products. AEs more frequently reported leading to temporary treatment discontinuation with semaglutide than with placebo were nausea (2 patients with semaglutide 0.5 mg) and lipase increased (2 patients with semaglutide 1 mg). There were no SAEs leading to temporary treatment discontinuation in the semaglutide 1 mg group, compared to semaglutide 0.5 mg: 3 events; placebo: 1 event.

One non-serious AE (nausea with semaglutide 1 mg) led to a dose reduction in the placebo group.

Reviewer's comment: Semaglutide treatment appears to result in treatment discontinuation more frequently vs all comparators, and this is more common with the 1 mg dose of semaglutide vs the 0.5 mg. This difference between semaglutide and comparator, and the semaglutide doses, is mostly due to GI AEs, and it is expected with this class of drugs.

8.4.4. Significant Adverse Events

The following definitions were used by the applicant when assessing the severity of an AE:

- Mild - no or transient symptoms, no interference with the subject's daily activities.
- Moderate - marked symptoms, moderate interference with the subject's daily activities.
- Severe - considerable interference with the subject's daily activities; unacceptable.

Additionally, the applicant also analyzed the outcome of the AEs. Outcome categories and definitions are presented below:

- Recovered/resolved - The subject had fully recovered, or by medical or surgical treatment the condition had returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- Recovering/resolving - The condition was improving and the subject was expected to recover from the event. This term was only applicable if the subject had completed the trial or had died from another AE.
- Recovered/resolved with sequelae - The subject had recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela met an SAE criterion, the AE was to be reported as an SAE.
- Not recovered/not resolved - The condition of the subject had not improved and the symptoms were unchanged, or the outcome was not known.
- Fatal - This term was only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died were to be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome was to be reported as an SAE.
- Unknown - This term was only applicable if the subject was lost to follow-up.

CVOT

No significant difference was seen between the treatment arms in any severity category for AEs. Most AEs were listed as recovered in all treatment groups, with no significant differences.

Table 119 Adverse Events – SAS On-Treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N	823				819				1644			
PYE (year)	1488.3				1443.9				3034.8			
Adverse events	732	(88.9)	4981	334.7	722	(88.2)	5056	350.2	1453	(88.4)	9506	313.2
SAEs	264	(32.1)	599	40.2	240	(29.3)	481	33.3	574	(34.9)	1256	41.4
Severity												
Severe	185	(22.5)	359	24.1	185	(22.6)	332	23.0	366	(22.3)	729	24.0
Moderate	476	(57.8)	1522	102.3	476	(58.1)	1657	114.8	934	(56.8)	3073	101.3
Mild	646	(78.5)	3099	208.2	633	(77.3)	3067	212.4	1285	(78.2)	5699	187.8
Unknown	1	(0.1)	1	0.1	0				1	(0.1)	5	0.2
Outcome												
Recovered	683	(83.0)	3728	250.5	671	(81.9)	3832	265.4	1347	(81.9)	6895	227.2
Recovering	90	(10.9)	165	11.1	80	(9.8)	165	11.4	160	(9.7)	314	10.3
Recovered with sequelae	26	(3.2)	30	2.0	24	(2.9)	25	1.7	65	(4.0)	80	2.6
Not recovered	406	(49.3)	1008	67.7	401	(49.0)	994	68.8	814	(49.5)	2135	70.3
Fatal	24	(2.9)	38	2.6	23	(2.8)	34	2.4	44	(2.7)	74	2.4
Unknown	7	(0.9)	12	0.8	3	(0.4)	6	0.4	5	(0.3)	8	0.3
AEs leading to premature discontinuation	95	(11.5)	151	10.1	119	(14.5)	196	13.6	110	(6.7)	136	4.5

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-3 ISS

Phase 3 Pool

Similar to what was observed in the CVOT, no differences were seen between the treatment arms regarding the severity, or the outcome of the adverse events.

Table 120 Adverse Events – SAS On-Treatment – Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
Adverse events	1015	(73.4)	4292	370.7	1301	(72.7)	5724	370.0	1136	(68.7)	4220	284.4
SAEs	92	(6.6)	138	12.0	118	(6.7)	152	10.0	95	(5.8)	117	7.9
Severity												
Severe	79	(5.8)	127	11.3	104	(6.0)	148	9.9	75	(4.4)	107	7.1
Moderate	349	(26.0)	746	67.2	479	(27.5)	1154	76.7	445	(26.4)	1022	67.6
Mild	916	(65.9)	3419	292.2	1150	(63.9)	4422	283.4	999	(60.5)	3091	209.7
Outcome												
Recovered	940	(67.8)	3461	299.9	1204	(67.3)	4725	306.4	1018	(61.6)	3235	218.1
Recovering	92	(6.6)	121	10.3	97	(5.2)	119	7.4	83	(5.1)	103	7.0
Recovered with sequelae	6	(0.5)	7	0.6	10	(0.6)	13	0.9	9	(0.5)	14	0.9
Not recovered	386	(27.4)	695	59.0	495	(27.3)	859	54.8	473	(28.6)	859	57.7
Fatal	7	(0.5)	7	0.6	3	(0.2)	3	0.2	6	(0.4)	6	0.4
Unknown	1	(<0.1)	1	<0.1	5	(0.3)	5	0.3	3	(0.2)	3	0.2
AEs leading to premature discontinuation	84	(6.1)	131	11.6	156	(8.7)	241	15.6	51	(3.0)	83	5.5

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)
Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.
Source: Table 2-12 ISS

Reviewer comment: While no overall differences were observed between the treatment groups, I believe that this severity categorization is subjective, and does not add any important information to the analysis of adverse events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Common Adverse Events

CVOT

The proportion of patients with AEs was similar with semaglutide (semaglutide 0.5 mg: 88.9%; semaglutide 1.0 mg: 88.2%) and placebo (88.4%). Overall, there were no differences noted between semaglutide and placebo with regards to all AEs, SAEs, severity (as reported by the applicant), or outcome of the events (Table 121).

Table 121 Adverse Events – SAS On-Treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N	823				819				1644			
PYE (year)	1488.3				1443.9				3034.8			
Adverse events	732	(88.9)	4981	334.7	722	(88.2)	5056	350.2	1453	(88.4)	9506	313.2
SAEs	264	(32.1)	599	40.2	240	(29.3)	481	33.3	574	(34.9)	1256	41.4
Severity												
Severe	185	(22.5)	359	24.1	185	(22.6)	332	23.0	366	(22.3)	729	24.0
Moderate	476	(57.8)	1522	102.3	476	(58.1)	1657	114.8	934	(56.8)	3073	101.3
Mild	646	(78.5)	3099	208.2	633	(77.3)	3067	212.4	1285	(78.2)	5699	187.8
Unknown	1	(0.1)	1	0.1	0				1	(0.1)	5	0.2
Outcome												
Recovered	683	(83.0)	3728	250.5	671	(81.9)	3832	265.4	1347	(81.9)	6895	227.2
Recovering	90	(10.9)	165	11.1	80	(9.8)	165	11.4	160	(9.7)	314	10.3
Recovered with sequelae	26	(3.2)	30	2.0	24	(2.9)	25	1.7	65	(4.0)	80	2.6
Not recovered	406	(49.3)	1008	67.7	401	(49.0)	994	68.8	814	(49.5)	2135	70.3
Fatal	24	(2.9)	38	2.6	23	(2.8)	34	2.4	44	(2.7)	74	2.4
Unknown	7	(0.9)	12	0.8	3	(0.4)	6	0.4	5	(0.3)	8	0.3
AEs leading to premature discontinuation	95	(11.5)	151	10.1	119	(14.5)	196	13.6	110	(6.7)	136	4.5

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-3 ISS

Common AEs reported in ≥5% of patients are presented below, including the odds ratio semaglutide vs placebo, as reported by the applicant.

Table 122 Common Adverse Events >=5% by System Organ Class, High Level Group Term and Preferred Term - CVOT - In-Trial - FAS

System organ class High level group term Preferred term	Sema 0.5 mg (%)	 R	Sema 1.0 mg (%)	 R	All sema (%)	 R	Comparator (%)	 R	Sema 0.5 mg(a) OR [95%CI]	Sema 1.0 mg(b) OR [95%CI]
N and PYO (year)	826	1708	822	1700	1648	3408	1649	3401		
Gastrointestinal disorders										
Gastrointestinal signs and symptoms										
Nausea	(17.3)	13.6	(21.9)	16.8	(19.6)	15.2	(7.8)	5.1	2.47 [1.91;3.18]	3.30 [2.59;4.22]
Vomiting	(10.5)	7.5	(14.8)	10.2	(12.7)	8.8	(4.7)	2.8	2.40 [1.75;3.31]	3.56 [2.64;4.80]
Dyspepsia	(6.2)	4.0	(7.7)	5.2	(6.9)	4.6	(2.5)	1.3	2.58 [1.70;3.93]	3.26 [2.18;4.87]
Abdominal pain upper	(4.2)	2.2	(5.1)	3.1	(4.7)	2.6	(2.4)	1.6	1.83 [1.15;2.91]	2.22 [1.43;3.47]
Abdominal pain	(5.6)	3.3	(4.6)	2.7	(5.1)	3.0	(4.1)	2.3	1.37 [0.93;2.01]	1.13 [0.75;1.69]
Gastrointestinal motility and defaecation conditions										
Diarrhoea	(17.9)	16.3	(18.4)	14.8	(18.1)	15.6	(11.2)	8.1	1.73 [1.37;2.18]	1.78 [1.41;2.25]
Constipation	(5.7)	3.1	(9.7)	5.8	(7.7)	4.4	(4.5)	2.4	1.28 [0.88;1.87]	2.29 [1.65;3.19]
Infections and infestations										
Infections - pathogen unspecified										
Urinary tract infection	(10.3)	6.8	(8.8)	5.6	(9.5)	6.2	(8.6)	5.9	1.23 [0.92;1.63]	1.03 [0.76;1.38]
Nasopharyngitis	(8.0)	5.3	(7.3)	4.5	(7.6)	4.9	(8.7)	5.4	0.91 [0.67;1.23]	0.82 [0.60;1.13]
Upper respiratory tract infection	(6.4)	3.5	(6.2)	3.8	(6.3)	3.6	(7.9)	4.9	0.80 [0.58;1.12]	0.77 [0.55;1.08]
Bronchitis	(5.7)	3.2	(4.9)	2.6	(5.3)	2.9	(6.4)	3.6	0.89 [0.62;1.26]	0.75 [0.52;1.09]
Viral infectious disorders										
Influenza	(6.3)	3.6	(5.8)	3.4	(6.1)	3.5	(5.9)	3.6	1.06 [0.75;1.50]	0.98 [0.69;1.40]
Musculoskeletal and connective tissue disorders										
Musculoskeletal and connective tissue disorders NEC										
Back pain	(6.7)	3.2	(6.4)	3.6	(6.6)	3.4	(6.2)	3.4	1.08 [0.77;1.52]	1.05 [0.74;1.47]
Pain in extremity	(4.6)	2.6	(3.5)	1.8	(4.1)	2.2	(5.3)	2.8	0.86 [0.58;1.26]	0.65 [0.42;1.00]
Joint disorders										
Arthralgia	(5.0)	2.6	(4.3)	2.4	(4.6)	2.5	(7.1)	4.2	0.68 [0.47;0.99]	0.58 [0.40;0.86]
Osteoarthritis	(5.4)	2.9	(3.9)	2.1	(4.7)	2.5	(3.8)	2.1	1.47 [1.00;2.19]	1.04 [0.67;1.60]
Nervous system disorders										
Neurological disorders NEC										
Dizziness	(6.4)	3.3	(5.6)	3.2	(6.0)	3.3	(4.7)	3.0	1.38 [0.96;1.98]	1.19 [0.82;1.74]
Headaches										
Headache	(6.7)	4.6	(7.2)	5.3	(6.9)	4.9	(8.6)	6.6	0.76 [0.55;1.05]	0.83 [0.60;1.13]
Metabolism and nutrition disorders										
Appetite and general nutritional disorders										
Decreased appetite	(10.4)	5.7	(9.1)	5.2	(9.8)	5.4	(1.7)	0.9	6.73 [4.35;10.40]	5.81 [3.73;9.05]
Investigations										
Gastrointestinal investigations										
Lipase increased	(11.4)	7.1	(10.9)	7.3	(11.2)	7.2	(8.2)	4.7	1.44 [1.09;1.90]	1.38 [1.04;1.83]
Amylase increased	(3.8)	2.3	(5.8)	3.4	(4.8)	2.8	(3.4)	1.9	1.11 [0.71;1.73]	1.76 [1.19;2.62]
Eye disorders										
Retina, choroid and vitreous haemorrhages and vascular disorders										
Diabetic retinopathy	(6.1)	3.2	(7.1)	3.9	(6.6)	3.5	(5.0)	2.6	1.22 [0.85;1.74]	1.43 [1.01;2.03]
Anterior eye structural change, deposit and degeneration										
Cataract	(6.8)	3.5	(5.4)	2.9	(6.1)	3.2	(5.2)	2.7	1.32 [0.93;1.87]	1.03 [0.71;1.49]
Renal and urinary disorders										
Urinary tract signs and symptoms										
Microalbuminuria	(3.3)	1.8	(4.0)	2.1	(3.6)	1.9	(5.3)	2.8	0.60 [0.39;0.93]	0.74 [0.49;1.12]
General disorders and administration site conditions										
General system disorders NEC										
Fatigue	(2.9)	1.6	(5.1)	2.8	(4.0)	2.2	(2.5)	1.3	1.17 [0.70;1.96]	2.11 [1.36;3.27]
Respiratory, thoracic and mediastinal disorders										
Respiratory disorders NEC										
Cough	(4.4)	2.4	(3.9)	1.9	(4.1)	2.2	(5.2)	2.6	0.83 [0.56;1.23]	0.74 [0.49;1.11]
Blood and lymphatic system disorders										
Anaemias nonhaemolytic and marrow depression										
Anaemia	(5.6)	3.0	(4.5)	2.2	(5.0)	2.6	(5.8)	3.1	0.95 [0.66;1.37]	0.76 [0.52;1.12]

N: Number of subjects in the full analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, R: Event rate per 100 PYO, PYO: Patient years of observation is calculated as the duration of the in-trial period, trial (comparator): 3744 (placebo), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, In-trial is defined as the observation period from the date of randomisation to either the end-of-trial follow-up visit or the date of withdrawal from trial, whichever comes first, MedDRA version 18.0

Source: Table 7.3.90 ISS

GI AEs (including nausea, diarrhea, vomiting, constipation, dyspepsia, abdominal pain upper, and abdominal pain) were reported in a higher proportion of patients and at higher rates with semaglutide than with placebo. Lipase increased, amylase increased and diabetic retinopathy were reported in higher proportions of patients and at higher rates with semaglutide than with placebo. All these will be discussed in detail later in this review.

The applicant also reported selected PTs that were found to be reported more frequently with semaglutide vs placebo, not reported above as they did not make the cut-off of 5%, however they may be relevant for the AE profile of semaglutide. In this context, decreased appetite, weight decrease, dizziness, fatigue, asthenia, and disgeusia, were all reported more frequently with semaglutide vs placebo.

Reviewer comment: The common AEs reported with semaglutide (0.5 mg and 1.0 mg) were generally as expected for drugs in the GLP-1 RA class.

Phase 3 pool

Overall, the semaglutide AE profile was consistent across all phase 3 trials, and no significant imbalances were noted between semaglutide and comparator groups regarding all adverse events (Table 123).

Table 123 Adverse Events by Trial – SAS On-Treatment – Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
N and PYE (year)												
Ph 3a pool	1373	1165			1777	1548			1657	1467		
Multinational pool	1031	825			1434	1228			1434	1261		
Placebo pool	260	165			261	164			262	166		
3623 vs Placebo	128	80			130	82			129	81		
3626 vs Sita	409	435			409	431			407	453		
3624 vs Exe ER					404	414			405	408		
3625 vs IGlar	362	225			360	219			360	235		
3627 vs Placebo	132	84			131	82			133	84		
4092 vs Sita, JP	103	69			102	63			103	70		
4091 vs OAD, JP	239	271			241	257			120	136		
All Events												
Ph 3a pool	1015	(73.4)	4292	370.7	1301	(72.7)	5724	370.0	1136	(68.7)	4220	284.4
Multinational pool	732	(71.0)	3155	382.3	1016	(70.9)	4573	372.8	982	(68.5)	3765	299.3
Placebo pool	173	(66.5)	676	411.0	157	(60.2)	513	312.8	146	(55.7)	447	270.0
3623 vs Placebo	82	(64.1)	364	452.5	73	(56.2)	269	328.0	69	(53.5)	224	275.1
3626 vs Sita	306	(74.8)	1453	333.7	292	(71.4)	1358	315.2	292	(71.7)	1064	234.8
3624 vs Exe ER					303	(75.0)	1551	374.7	309	(76.3)	1511	370.4
3625 vs IGlar	253	(69.9)	1026	455.9	264	(73.3)	1151	525.2	235	(65.3)	743	316.7
3627 vs Placebo	91	(68.9)	312	370.5	84	(64.1)	244	298.0	77	(57.9)	223	265.2
4092 vs Sita, JP	77	(74.8)	228	331.8	73	(71.6)	197	312.6	68	(66.0)	186	267.4
4091 vs OAD, JP	206	(86.2)	909	335.5	212	(88.0)	954	371.5	86	(71.7)	269	197.9

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Placebo pool: Trials included: 3623 and 3627

Multinational pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin) and 3627 (placebo)

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-11 ISS

In the pool of phase 3 trials, the proportion of patients reporting any AE during the treatment period was approximately 70%. Over 60% of AEs were reported as 'mild', and the majority were reported by the applicant as recovered.

Table 124 Adverse Events – SAS On-Treatment – Phase 3 Pool

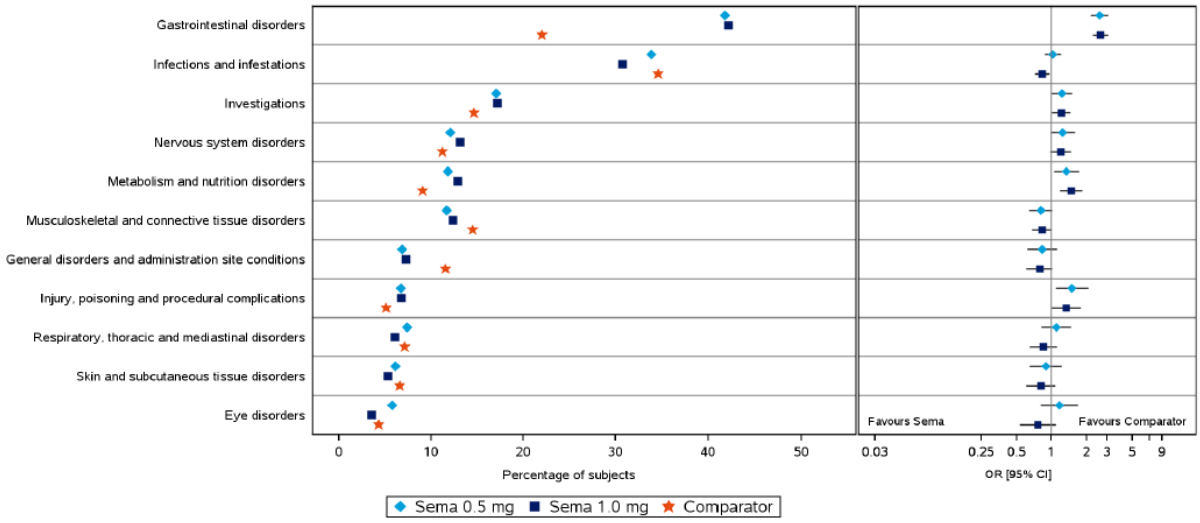
	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
Adverse events	1015	(73.4)	4292	370.7	1301	(72.7)	5724	370.0	1136	(68.7)	4220	284.4
SAEs	92	(6.6)	138	12.0	118	(6.7)	152	10.0	95	(5.8)	117	7.9
Severity												
Severe	79	(5.8)	127	11.3	104	(6.0)	148	9.9	75	(4.4)	107	7.1
Moderate	349	(26.0)	746	67.2	479	(27.5)	1154	76.7	445	(26.4)	1022	67.6
Mild	916	(65.9)	3419	292.2	1150	(63.9)	4422	283.4	999	(60.5)	3091	209.7
Outcome												
Recovered	940	(67.8)	3461	299.9	1204	(67.3)	4725	306.4	1018	(61.6)	3235	218.1
Recovering	92	(6.6)	121	10.3	97	(5.2)	119	7.4	83	(5.1)	103	7.0
Recovered with sequelae	6	(0.5)	7	0.6	10	(0.6)	13	0.9	9	(0.5)	14	0.9
Not recovered	386	(27.4)	695	59.0	495	(27.3)	859	54.8	473	(28.6)	859	57.7
Fatal	7	(0.5)	7	0.6	3	(0.2)	3	0.2	6	(0.4)	6	0.4
Unknown	1	(<0.1)	1	<0.1	5	(0.3)	5	0.3	3	(0.2)	3	0.2
AEs leading to premature discontinuation	84	(6.1)	131	11.6	156	(8.7)	241	15.6	51	(3.0)	83	5.5

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)
Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 12-2 ISS

A breakdown of common adverse events by system organ class is presented in Figure 53 below.

Figure 53 Adverse Events (≥5% of Patients) by System Organ Class – SAS On-Treatment – Phase 3 Trials excl. CVOT



OR: Odds ratio, CI:Confidence interval, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), For the pools the % is the Cochran-Mantel-Haenszel adjusted percentage, The OR and 95% CIs are Cochran-Mantel-Haenszel exact method stratified by trial, Sorted by highest frequency in the Sema 1.0 mg arm, if no events then Sema 0.5 mg.

Source: Figure 2–17 ISS

The proportion of patients with events within the SOCs of gastrointestinal disorders, investigations, nervous system disorders, metabolic and nutrition disorders and injury, poisoning and procedural complications were higher with semaglutide than with comparator products. I will discuss the most representative HLGT, HLT, or PT within each of these SOCs below.

Gastrointestinal disorders (GI) was the SOC where the highest proportion of patients reported AEs with semaglutide (0.5 mg and 1.0 mg). AEs within the SOC GI disorder (GI AEs) were reported by a significantly higher proportion of patients and higher rates with semaglutide than with comparator mainly due to a higher proportion of patients reporting nausea, vomiting, and diarrhea with semaglutide (0.5 mg and 1.0 mg) vs comparator. Gastrointestinal adverse events will be discussed in detail later in this review.

Infections and infestations included common events of urinary tract infection, nasopharyngitis, upper respiratory tract infection, influenza and bronchitis. There was no significant difference between semaglutide and placebo groups within this SOC.

AEs related to investigations were reported by a higher proportion of patients and corresponding rates with semaglutide (0.5 mg and 1.0 mg) than with comparator, primarily due to lipase increased and amylase increased. These will be discussed later in this review under pancreatitis adverse events.

Nervous system disorders were balanced between the treatment groups. The most commonly reported PTs in this SOC were headache (6.3% in semaglutide vs 5.5% in comparator), and dizziness (3.1% in semaglutide vs 1.7% in comparator). Both of these could potentially be the result of the dehydration that can occur with this class of drugs.

AEs within the SOC metabolism and nutrition disorders were reported by a higher proportion of patients with semaglutide 0.5 mg (11.8% of patients) and semaglutide 1 mg (12.9%) than with comparator 9.1% of patients). The difference is mainly due to the difference at the level of PT decreased appetite, which represents more than 50% of events in this SOC. Decreased appetite occurred in 6.9% of patients on semaglutide vs 2% in comparator. The other PTs that contributed significantly to this SOC belong in the HLT lipid metabolism disorders (2.7% in semaglutide vs 3.6% in placebo).

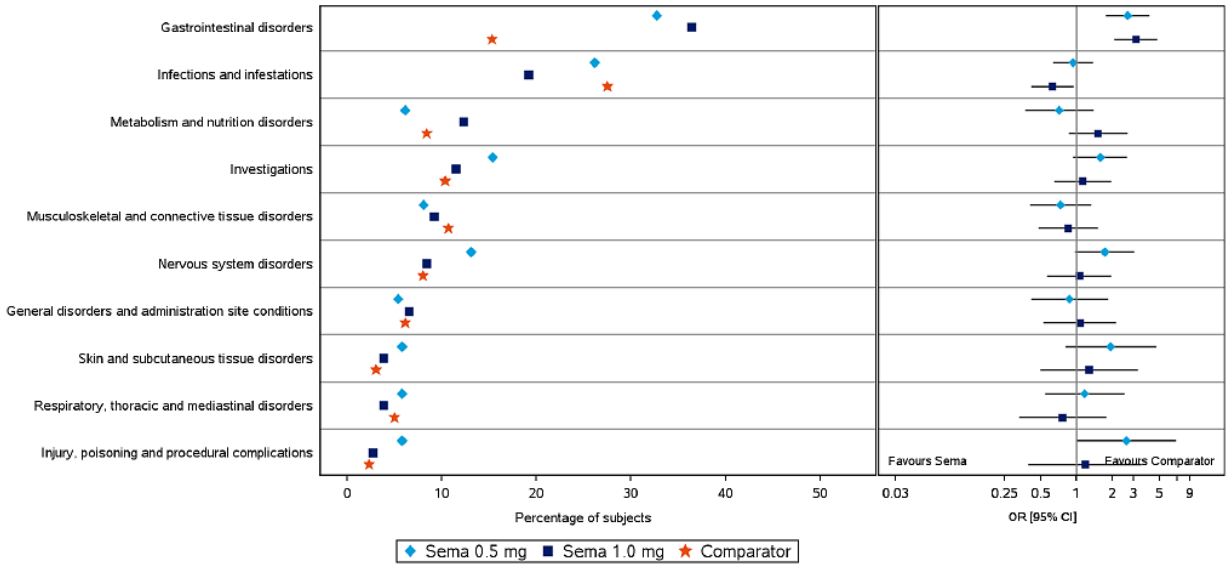
AEs of musculoskeletal and connective tissue disorder were reported in a lower proportion of patients and corresponding rates with semaglutide than with comparators. Back pain and joint pain (arthralgia) were reported at similar or lower proportion of patients with semaglutide than with comparator.

AEs related to injury, poisoning and procedural complications were reported in a higher proportion of patients and corresponding rates with semaglutide than with comparator, primarily due to injuries (HLGT, semaglutide 4.7%; comparator: 3.5%), procedural related injuries and complications (HLGT, semaglutide: 0.5%; comparator: 0.2%), medication errors (HLGT, semaglutide: 0.3%; comparator: 0.1%).

Placebo pool

AEs by SOC occurring in ≥5% of patients are presented below. The pattern is similar to that observed in the phase 3 pool.

Figure 54 System Organ Class for Most Frequent (≥5% of Patients) Adverse Events by Preferred Term – SAS On-Treatment – Placebo Pool



OR: Odds ratio, CI:Confidence interval, Placebo pool: trial (comparator): 3623 (placebo), 3627 (placebo). For the pools the % is the Cochran-Mantel-Haenszel adjusted percentage. The OR and 95% CIs are Cochran-Mantel-Haenszel exact method stratified by trial. Sorted by highest frequency in the Sema 1.0 mg arm, if no events then Sema 0.5 mg.

Source Figure 2-18 ISS

Reviewer comment: Overall the common AEs are consistent with our current knowledge of GLP1 RAs. Additionally, medication errors and procedural complications appear to be more common with semaglutide, however the overall numbers are small. Please see review by Dr (DMEPA) for details regarding medication errors.

Gastrointestinal Adverse Events

Gastrointestinal (GI) disorders, particularly nausea, vomiting and diarrhea, are the most common side effects of GLP-1 RAs. GI disorders were evaluated and summarized based on a MedDRA query for the System Organ Class 'Gastrointestinal disorders'.

CVOT

GI AEs were the most frequently reported AEs in this trial. The rates of GI AEs were also higher with semaglutide (both doses) vs placebo, and more so with semaglutide 1mg vs semaglutide 0.5 mg. The proportion of patients with GI AEs leading to premature treatment discontinuation was also higher with semaglutide than with placebo.

Table 125 Overview of GI AEs (MedDRA Search) – SAS On-Treatment – CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
PYE (year)	1488.3				1443.9				3034.8			
Events	415	(50.4)	1208	81.2	426	(52.0)	1370	94.9	564	(34.3)	1230	40.5
SAEs												
Yes	36	(4.4)	38	2.6	29	(3.5)	35	2.4	40	(2.4)	49	1.6
No	399	(48.5)	1170	78.6	422	(51.5)	1335	92.5	550	(33.5)	1181	38.9
Outcome												
Recovered	382	(46.4)	1068	71.8	404	(49.3)	1244	86.2	500	(30.4)	1016	33.5
Fatal	1	(0.1)	1	0.1	0				2	(0.1)	3	0.1
Recovering	16	(1.9)	22	1.5	11	(1.3)	22	1.5	21	(1.3)	31	1.0
Recovered with sequelae	3	(0.4)	3	0.2	4	(0.5)	4	0.3	4	(0.2)	4	0.1
Not recovered	78	(9.5)	111	7.5	71	(8.7)	100	6.9	125	(7.6)	174	5.7
Unknown	2	(0.2)	3	0.2	0				1	(0.1)	2	0.1
Leading to premature treatnt disontinion												
Yes	48	(5.8)	79	5.3	82	(10.0)	132	9.1	23	(1.4)	29	1.0
No	401	(48.7)	1129	75.9	391	(47.7)	1238	85.7	556	(33.8)	1201	39.6

Abbreviations: E: number of events, N: Number of subjects with at least one event, PYE: patient-years of exposure; R: events per 100 PYE, %: percentage of subjects with at least one event.

Source: Modified from Table 2-30 ISS

The majority of patients in all treatment groups who experienced GI AEs, reported their first event within the initial 3 to 4 months of treatment, as expected with the GLP-1 RA class.

The most frequently reported GI AEs (≥5% of the patients) were nausea, diarrhea, vomiting, constipation, dyspepsia, abdominal pain upper and abdominal pain, all of which were reported at a higher rate and by a larger proportion of patients with each of the semaglutide doses than with placebo. Other less common AEs (<5% of patients) reported more frequently with semaglutide (0.5 and 1.0 mg) vs placebo included abdominal discomfort, gastroesophageal reflux disease, flatulence, abdominal distension, gastritis and eructation. The most frequently reported PTs are presented below.

Table 126 GI AEs (≥1%) (MedDRA Search) by PT – SAS On-Treatment – CVOT

MedDRA Preferred Term	**Sema 0.5 N=823**	**Sema 1.0 N=819**	**Placebo N=1644**
	N (%)	**N (%)**	**N (%)**
Total patients with events	**426 (52.0)**	**415 (50.4)**	**564 (34.3)**
Events that were SAEs	**29 (3.5)**	**36 (4.4)**	**40 (2.4)**
Events leading to discontinuation	**81 (10)**	**48 (5.8)**	**23 (1.4)**
Nausea	142 (17.3)	178 (21.7)	127 (7.7)
Diarrhea	145 (17.6)	145 (17.7)	177 (10.8)
Vomiting	84 (10.2)	119 (14.5)	77 (4.7)

MedDRA Preferred Term	Sema 0.5 N=823	Sema 1.0 N=819	Placebo N=1644
	N (%)	N (%)	N (%)
Constipation	46 (5.6)	78 (9.5)	69 (4.2)
Dyspepsia	51 (6.2)	63 (7.7)	38 (2.3)
Abdominal pain upper	33 (4.0)	42 (5.1)	38 (2.3)
Abdominal discomfort	35 (4.3)	38 (4.6)	35 (2.1)
Gastroesophageal reflux disease	30 (3.7)	35 (4.3)	23 (1.4)
Abdominal pain	45 (5.5)	34 (4.2)	64 (3.9)
Flatulence	13 (1.6)	26 (3.2)	15 (0.9)
Abdominal distension	17 (2.1)	24 (2.9)	22 (1.3)
Gastritis	17 (2.1)	22 (2.7)	20 (1.2)
Eructation	10 (1.2)	19 (2.3)	0
Large intestine polyp	8 (0.9)	11 (1.3)	17 (1.0)
Hemorrhoids	9 (1.0)	10 (1.2)	14 (0.9)
Gastrointestinal disorder	6 (0.7)	9 (1.1)	4 (0.2)
Toothache	12 (1.5)	8 (0.9)	25 (1.5)
Diverticulum	9 (1.1)	5 (0.6)	15 (0.9)

Source: Reviewer generated using JReview, ADAE, ADSL datasets for trial 3744

SAEs within the GI SOC were reported by 4.4% of patients on semaglutide 0.5 mg (2.6 events per 100 PYE); 3.5% of patients on semaglutide 1 mg (2.4 events per 100 PYE); and 2.4% of patients on placebo (1.6 events per 100 PYE). The most common GI SAEs (>0.3%) were diarrhea, abdominal pain, gastrointestinal hemorrhage and gastroesophageal reflux disease with all semaglutide and gastrointestinal hemorrhage and pancreatitis with all placebo. Pancreatitis will be discussed separately in this review.

Phase 3 pool excluding CVOT

The discussion here will include additional subsets of this pool as, in one study, the comparator was from the GLP-1 RA class of drugs (exenatide ER), which are likely to have a similar AE profile.

The proportion of patients with GI AEs and the types of GI AEs observed with semaglutide (0.5 and 1.0 mg) were generally consistent for semaglutide across the phase 3 trials. Amongst the comparator products there was a higher frequency of GI AEs with exenatide ER than with the other comparators. Constipation was reported more frequently in the two Japanese trials 4091 and 4092, and particularly more so with semaglutide (0.5 and 1.0 mg) in these trials.

i. Phase 3, non-GLP-1 RA subset

This subset includes all trials in the phase 3 pool excluding CVOT, with the exception of trial 3624.

GI AEs were more common with semaglutide vs the non-GLP-1 RA comparators. The most frequently reported GI AEs, reported by ≥5% of patients with semaglutide 0.5 mg and 1.0 mg in the phase 3 non-GLP-1 RA trial subset, were nausea, diarrhea, vomiting, and constipation. GI AEs reported in >1% of patients in any treatment group are reported in Table 127 below.

Table 127 Gastrointestinal Adverse Events in Phase 3, Non-GLP-1 RA Subset Occurring in >1% in Any Treatment Arm

MedDRA Preferred Term	Sema 0.5 N=1373	Sema 1.0 N=1373	Comparator N=1252
	N (%)	N (%)	N (%)
Total patients with events	**580 (42.2)**	**586 (42.7)**	**231 (18.5)**
Events that were SAEs	**18 (1.3)**	**7 (0.5)**	**6 (0.5)**
Events leading to discontinuation	**53 (3.9)**	**82 (6)**	**4 (0.3)**
Nausea	231 (16.8)	264 (19.2)	60 (4.8)
Diarrhea	166 (12.1)	192 (14.0)	60 (4.8)
Vomiting	87 (6.3)	118 (8.6)	31 (2.5)
Constipation	102 (7.4)	90 (6.6)	23 (1.8)
Dyspepsia	56 (4.1)	65 (4.7)	17 (1.4)
Abdominal discomfort	48 (3.5)	41 (3.0)	8 (0.6)
Abdominal pain upper	37 (2.7)	37 (2.7)	19 (1.5)
Abdominal distension	32 (2.3)	41 (3.0)	7 (0.6)
Abdominal pain	37 (2.7)	28 (2.0)	13 (1.0)
Gastroesophageal reflux disease	22 (1.6)	42 (3.1)	7 (0.6)
Toothache	20 (1.5)	10 (0.7)	15 (1.2)
Gastritis	22 (1.6)	14 (1.0)	7 (0.6)
Dental caries	15 (1.1)	9 (0.7)	13 (1.0)
Eructation	17 (1.2)	16 (1.2)	2 (0.2)
Flatulence	7 (0.5)	19 (1.4)	5 (0.4)
Chronic gastritis	14 (1.0)	7 (0.5)	8 (0.6)

Source: Reviewer generated using ADAE and ADSL from the ISS

ii. Phase 3, GLP-1 RA comparator trial

Trial 3624 compared semaglutide 1 mg to exenatide ER. GI AEs were reported more frequently and at a higher rate with semaglutide 1 mg (41.8% and 133.1 events per 100 PYE) than with exenatide ER (33.3% and 83.6 events per 100 PYE). The most frequently reported GI AEs (≥5% of the patients) were nausea, diarrhea, vomiting, constipation and dyspepsia. Each of the most common AEs was reported at a higher rate and by a larger proportion of patients with semaglutide 1 mg than with exenatide ER.

Table 128 Gastrointestinal Adverse Events in Phase 3 GLP-1 RA Comparator Trial Occurring in >1% in Any Treatment Arm

MedDRA Preferred Term	Sema 1 mg N=404	Exenatide ER N=405
	N (%)	N (%)
Total patients with events	**169 (41.8)**	**135 (33.3)**
Events that were SAEs	**6 (1.5)**	**3 (0.7)**
Events leading to discontinuation	**23 (5.7)**	**11 (2.7)**
Nausea	90 (22.3)	48 (11.9)
Diarrhea	46 (11.4)	34 (8.4)
Vomiting	29 (7.2)	25 (6.2)
Dyspepsia	27 (6.7)	19 (4.7)
Constipation	26 (6.4)	21 (5.2)
Abdominal discomfort	18 (4.5)	14 (3.5)
Abdominal pain upper	16 (4.0)	15 (3.7)
Eructation	15 (3.7)	1 (0.3)
Abdominal pain	11 (2.7)	11 (2.7)
Abdominal distension	11 (2.7)	7 (1.7)
Gastroesophageal reflux disease	7 (1.7)	9 (2.2)
Gastritis	7 (1.7)	1 (0.3)
Flatulence	6 (1.5)	3 (0.7)
Hiatus hernia	5 (1.2)	2 (0.5)

Source: Reviewer generated using ADAE, ADSL ISS, on treatment summary flag

Placebo pool

In placebo-controlled trials (trials 3623 and 3627) GI AEs were reported more frequently and at a higher rate with semaglutide 0.5 mg and 1.0 mg vs placebo. The most frequently reported GI AEs (≥5% of the patients) were nausea, diarrhea, vomiting and constipation, all of which were reported at a higher rate and by a larger proportion of patients with each of the semaglutide doses than with placebo. In addition, less commonly reported GI AEs such as dyspepsia, abdominal discomfort, abdominal pain, eructation and gastroesophageal reflux disease were reported by a larger proportion of patients with semaglutide (0.5 mg and or 1.0 mg) vs placebo.

Table 129 Gastrointestinal Adverse Events in Placebo Pool Occurring in >1% in Any Treatment Arm

MedDRA Preferred Term	Sema 0.5 N=260	Sema 1.0 N=261	Placebo N=262
	N (%)	N (%)	N (%)
Total patients with events	**85 (32.7)**	**95 (36.4)**	**40 (15.3)**
Events that were SAEs	**1 (0.4)**	**1 (0.4)**	**1 (0.4)**
Events leading to discontinuation	**8 (4.6)**	**10 (6.1)**	**1 (0.7)**
Nausea	41 (15.8)	53 (20.3)	16 (6.1)

MedDRA Preferred Term	Sema 0.5 N=260	Sema 1.0 N=261	Placebo N=262
	N (%)	N (%)	N (%)
Diarrhea	22 (8.5)	23 (8.8)	5 (1.9)
Vomiting	13 (5.0)	24 (9.2)	6 (2.3)
Constipation	13 (5.0)	8 (3.1)	4 (1.5)
Dyspepsia	9 (3.5)	7 (2.7)	5 (1.9)
Abdominal discomfort	8 (3.1)	6 (2.3)	3 (1.2)
Abdominal pain	7 (2.7)	5 (1.9)	4 (1.5)
Abdominal pain upper	4 (1.5)	5 (1.9)	5 (1.9)
Eructation	7 (2.7)	3 (1.2)	0
Gastroesophageal reflux disease	5 (1.9)	4 (1.5)	0
Flatulence	1 (0.4)	4 (1.5)	2 (0.8)
Dry mouth	2 (0.8)	3 (1.2)	1 (0.4)
Toothache	1 (0.4)	2 (0.8)	3 (1.2)

Source: Reviewer generated using ADAE and ADSL from the ISS

Reviewer comment: As expected with this drug class, GIAEs were significantly more common with semaglutide vs all comparators. Surprisingly, even a head-to-head comparison to another member of the class (Exenatide ER) showed an imbalance in GI AEs not favoring semaglutide. This study is limited though, as it was a single, open-label study, which only included the higher semaglutide dose, not ideal for comparative safety assessments. A dose-dependence was seen regarding GI AEs, as expected since this class of medications usually requires slow titration to mitigate GI tolerability.

Hepatic Disorders

Patients with hepatic impairment or hepatic disorders were not excluded from the semaglutide phase 3 trials, with the exception of patients with end-stage liver disease who were excluded from the CVOT.

Hepatic disorders in the semaglutide program were evaluated by two external liver experts, blinded to treatment assignment, who were asked to judge the likelihood that the finding could be drug-related. The experts were asked to use a modified drug-induced liver injury network score as illustrated below.

Table 130 Modified Drug-Induced Liver Injury Network Score

Category	Numerical Scale	Summary
Probable	> 50% likely	Liver injury is compatible with the drug but the clinical picture may not be entirely typical. ***The "preponderance of the evidence" supports the link*** between the drug and the liver injury.
Possible	25 to 50% likely	Liver injury is possibly due to the drug, but the clinical picture may not be typical or convincing. Because there is less than "preponderance of evidence," ***attribution of the liver injury is weak*** but cannot be excluded.
Unlikely	<25% likely	Liver injury is not compatible with the drug. The bulk of the ***evidence is against an association*** between the drug and liver injury.

Source: Table 2-120 ISS

The applicant used the biochemical criteria from Hy's law[2] for identification of potential cases of drug-induced liver injury, as well as other indicators, such as liver aminotransferase elevations >3x, >5x, >10x, >20xULN. MedDRA search was also used for identification of liver adverse events.

Cases of concurrent elevations of ALT or AST >3xULN with TBL >2xULN

The applicant identified 12 patients in the entire program (including CVOT, and phase 1, 2, and 3 clinical trials) that fit the definition of Hy's law. Of these 12, 9 occurred in patients taking semaglutide, and 3 with comparators. One patient had concurrent elevations of ALT and AST >3xULN with TBL >2xULN prior to initiation of semaglutide treatment and one patient's elevated ALT and TBL measurements were not concurrent (8 months apart) (both on semaglutide 0.5 mg). The applicant also concluded, via review of the narratives, that the remaining 10 cases had alternate etiologies as an explanation for the changes in liver parameters. Narrative summaries for the 12 patients are presented below.

- Patient ID 104043, trial 3687 (phase 1). 23 year old healthy male volunteer who received two doses of semaglutide 0.5 mg approximately 6 weeks apart. 35 days after the second dose, he attended a scheduled follow-up visit and the liver enzymes were found to be elevated as follows: ALT: 97.2 U/L above normal range, AST was 45.7 U/L, total bilirubin: 34.30 umol/L above normal range direct bilirubin 4.7 umol/L above normal range, indirect bilirubin was 29.6 umol/l above normal range. Amylase was 102.5 U/L above normal range. Alkaline phosphatase was within normal range. Serum GGT was 19.9 U/L within normal range. The patient was not taking any concurrent medications. Laboratory testing repeated 8 days later showed worsening liver enzymes: ALT at 164.5 U/L, direct bilirubin7.6 umol/L , indirect bilirubin 34.9 umol/l ,

[2] Hy's law: elevated serum aminotransferases (AST or ALT) (>3xULN) and concomitant elevated bilirubin (>2xULN) with no evidence of biliary obstruction or impaired ability to conjugate bilirubin and no alternative etiology

and total bilirubin 42.50 umol/L. This date was reported as the onset date of this of biochemical Hy's law event. The patient was asymptomatic. On 20-JAN-2015, 49 days after the last dose of trial product, liver tests were performed again which showed a down trend in ALT and total bilirubin. The event was considered recovered on this date. Hepatitis serology (hep B and C) was negative at screening, was not repeated at the time of the event, and was again negative approximately 2 months post-event (LFTs also normalized by this point). Additionally, Novo Nordisk (NN) reported that the semaglutide levels at the time of the peak LFT values were undetectable. It was also reported patient was drinking on average 330ml alcohol per day with no changes over the course of the trial. Additionally, NN reported that he had a history of fluctuation LFTs seen in other NN trials in which he participated.

Reviewer comment: I do not fully agree with the applicant's assessment that this is likely not related to semaglutide treatment, although I agree that alcohol consumption could have contributed to the laboratory abnormality. I find it concerning that an event of Hy's law was seen in a healthy volunteer who only received two doses of semaglutide.

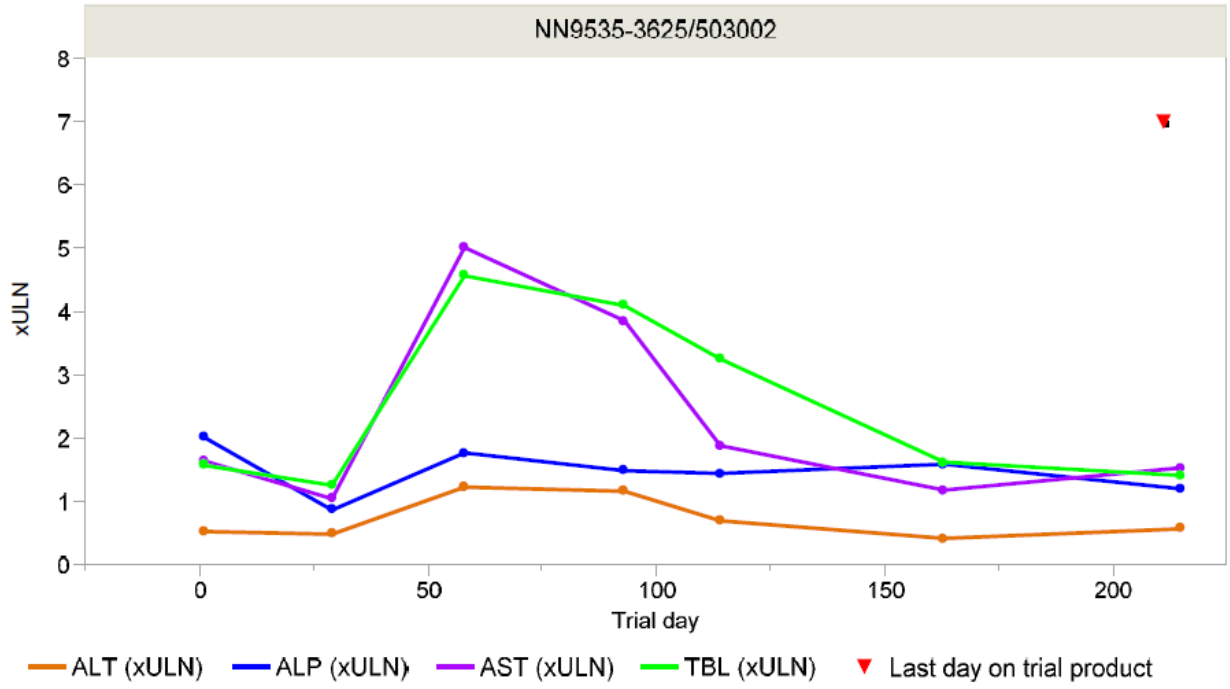
- Patient ID 401153: No narrative submitted. Healthy volunteer enrolled in phase 1 study with alcoholic hepatitis 8 days prior to initiating study treatment.

- Patient ID 452002 Phase 2 study 1821 (12 week comparison to liraglutide). 64 year old male patient with T2DM was reported with "chronic liver disease sclerogenic" based on CT evaluation, and gallstones, 116 days after the study treatment with semaglutide 0.4 mg ended. EGD revealed esophageal varices at that time, and liver laboratories were markedly abnormal as follows: bilirubin total 10.31 mg/dL; bilirubin direct 10.46 mg/dL; aspartate aminotransferase 1027 UI/L; alanine aminotransferase 603 UI/L; pancreatic amylase 166 U/L. The LFTs were reported as normalized 4 weeks later. Notably, the patient's LFTs were normal throughout the on-treatment period of the study. Based on this history this appears to be acute on chronic liver disease rather than DILI.

- Patient ID 451009 Trial 3625 (OL comparison to insulin glargine). 45 year old female with T2DM found with elevated LFTs and serology for acute hepatitis B positive during the study (semaglutide 0.5 mg). The temporal association with the start is not clear, however, it is not likely to be relevant in this case.

- Patient ID 503002 Trial 3625 (OL comparison to insulin glargine). 54 year old male randomized to semaglutide 1 mg. The applicant reported that the baseline levels of AST, alkaline phosphatase and total bilirubin were above ULN but stable. However, on trial day 58, LFTs increased in a pattern that met the biochemical definition of Hy's law. The study drug was not discontinued as a result of the laboratory abnormalities, and the event was reported as recovering on day 365. The patient was asymptomatic. He had a history of cholelithiasis but no other liver disease. Alcohol consumption prior to the

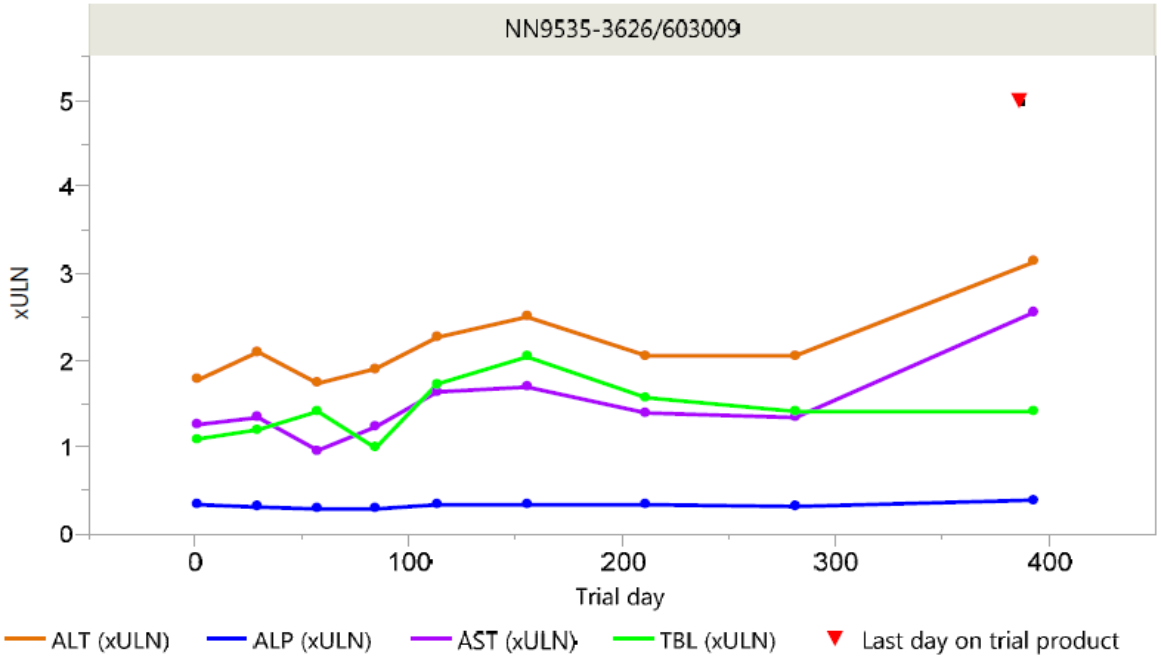
episode was reported as 2 units/day, however, per the narrative, the investigator suspected consumption higher than what the patient reported.



Liver parameters in normalised values (xULN) over time

Source: study report for trial 3625

- Patient ID 603009 Study 3626 comparison to sitagliptin on a background of metformin and/or TZD. 27 year old Asian male randomized to semaglutide 0.5 mg had both total bilirubin>2xULN and ALT activity levels >3xULN during the trial, however the elevations occurred at weeks 23 and 56, respectively. Since the elevations did not occur simultaneously, NN did not consider this as a biochemical Hy's law case. The patient did have a documented history of hepatic steatosis at trial entry, but denied alcohol consumption. Hepatitis panel was not performed. It is not clear what happened after the study was completed.

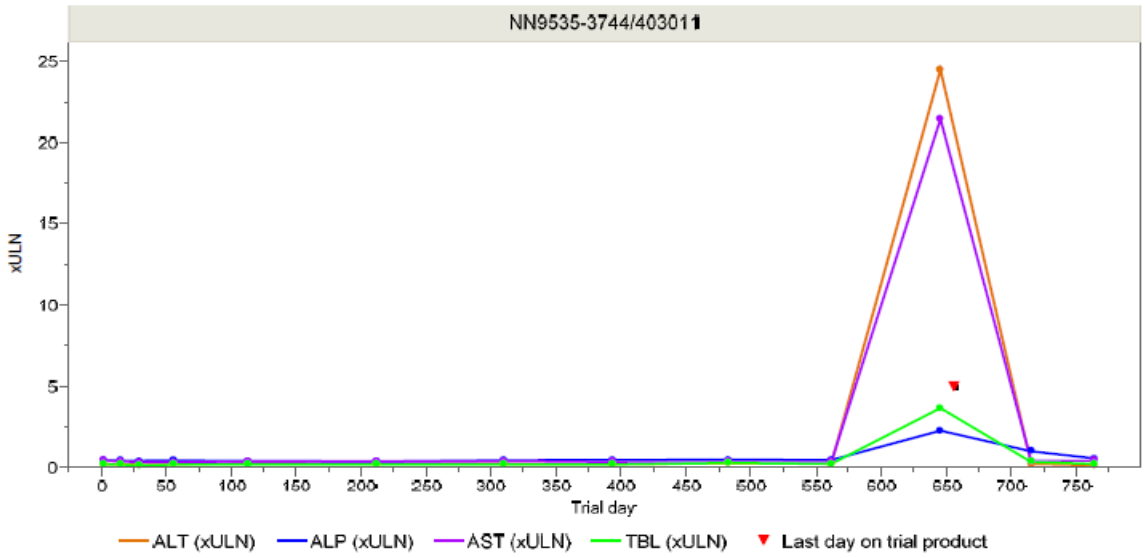


Liver parameters in normalised values (xULN) over time

Source: study report trial 3626

The following patients are from the CVOT. There were 3 patients on semaglutide, and 3 patients on placebo, who had laboratory abnormalities that met the biochemical definition of Hy's law in the CVOT.

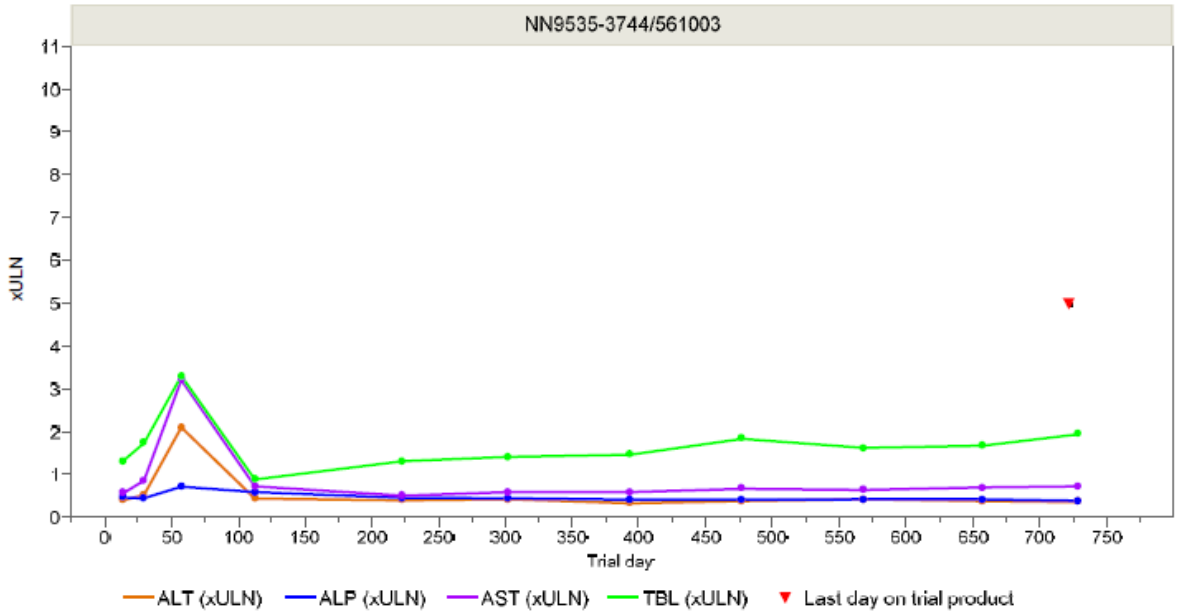
- Patient ID 403011: 66 year old female with normal baseline LFTs developed jaundice due to acute viral hepatitis (B) while receiving treatment with semaglutide 0.5 mg (trial day 645) The study drug was permanently withdrawn due to this adverse event.



Liver parameters (xULN) over time

Source: Study report – narratives

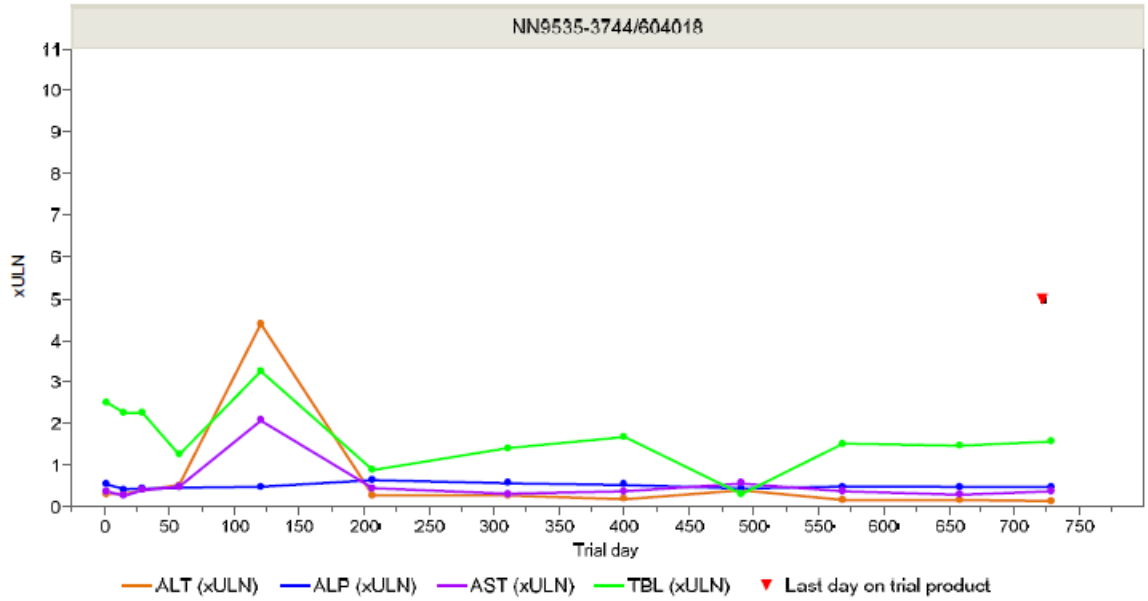
- Patient ID 561003: 68 year old male randomized to treatment with semaglutide 1 mg. Baseline laboratory parameters were missing at randomization, however, at the next on-treatment visit, ALT, AST, and ALP levels were below the ULN; TBL levels were slightly elevated about the ULN. On day 56, the patient developed biliary colic and was diagnosed with cholelithiasis based on an abdominal US. On day 57, the LFTs were elevated as follows: ALT (>2x ULN), AST (>3x ULN) and TBL (>2x ULN) had increased above the ULN, therefore meeting the definition of biochemical Hy's Law. The trial drug was not discontinued doe to the events listed above, however, an AE of "biliary cirrhosis" was documented on trial day 101.



Liver parameters (xULN) over time

Source: Study report – narratives

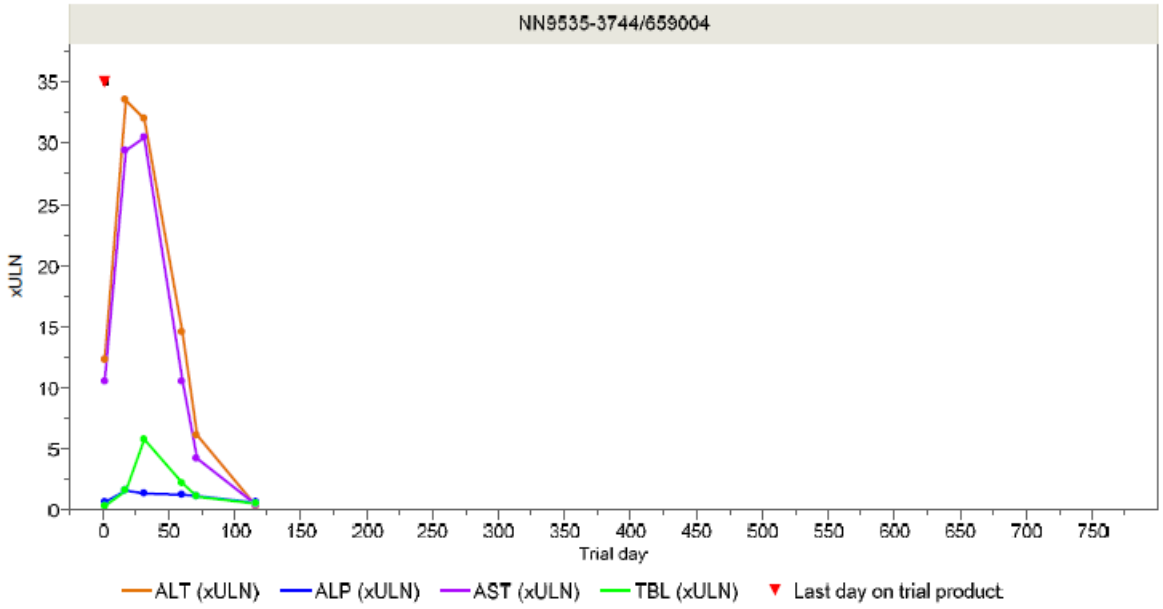
- Patient ID 604018 74 year old male with Gilbert Syndrome at study entry was randomized to treatment with semaglutide 1 mg. At randomization, ALT, AST and ALP levels were below the ULN; the baseline level of TBL was elevated >2x ULN. On trial day 120, ALT (>4x ULN) and AST (>2x ULN) levels had increased; TBL levels were 3x ULN, thus meeting the definition of biochemical Hy's Law. The patient was symptomatic with nausea. On trial day 128, he was reported with "cholelithiasis" based on an abdominal US. LFTs were reported as normalized by trial day 206. The study drug was not discontinued due to this AE.



Liver parameters (xULN) over time

Source: Study report – narratives

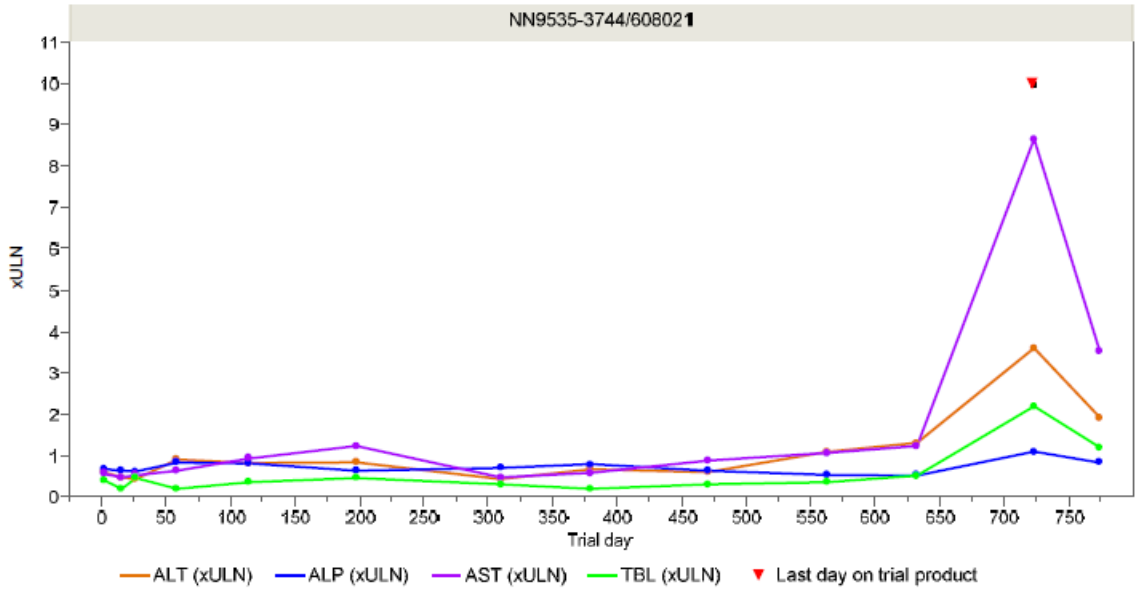
- Patient ID 659004 52 year old male randomized to placebo had markedly elevated ALT and AST at randomization (>10x ULN). On trial day 17, ALT and AST levels were further elevated (approximately >30x ULN); ALP and TBL levels were also elevated. On trial day 31, ALT and AST levels were >30x ULN and TBL levels had increased to >5x ULN, thus meting the definition of biochemical Hy's Law. The patient's hepatitis B core antibody, IGM, and Hepatitis B Surface Antigen were positive and hepatitis B was diagnosed. He only received study drug on trial day 1.



Liver parameters (xULN) over time

Source: Study report – narratives

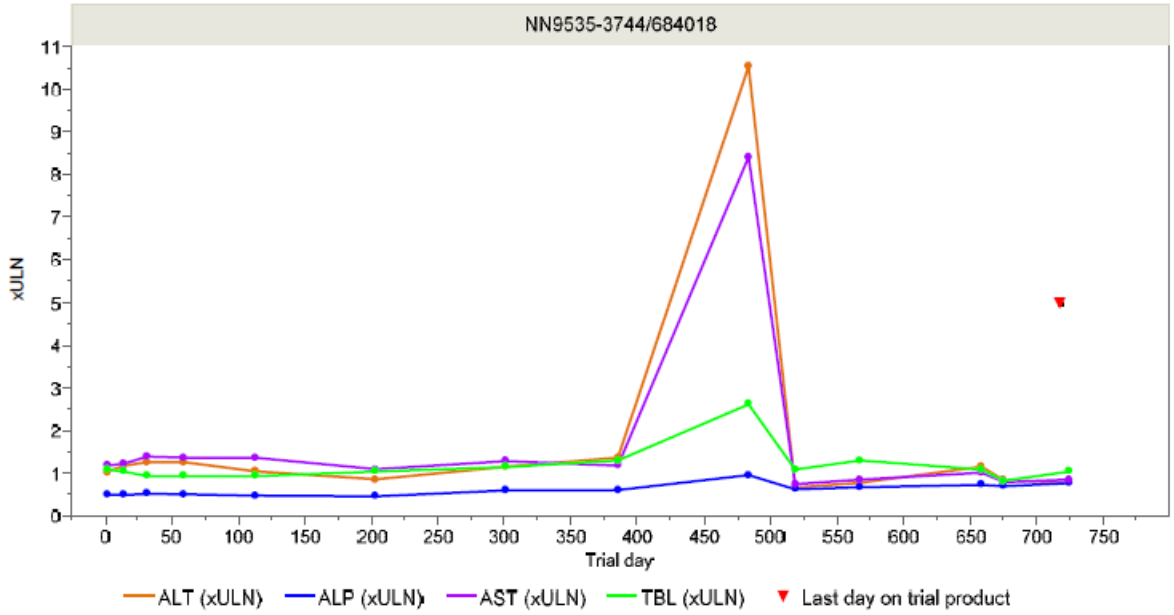
- Patient ID 608021 60 year old African American male randomized to placebo. LFTs were normal at randomization. On trial day 723, one day after the last dose of trial product, LFTs were found to be increased in a pattern that met the criteria for biochemical Hy's law. The patient admitted to being depressed and consuming large quantities of alcohol in the 3-4 weeks preceding the LFT abnormality. The LFTs were trending down at the follow up visit (study day 774).



Liver parameters (xULN) over time

Source: Study report – narratives

- Patient ID 684018 69 year old male randomized to placebo. At baseline, ALT, AST, and TB were slightly above ULN. On trial day 483, ALT was found to be increased to > 10x ULN, and TBL to >2x ULN, thus meeting the definition of biochemical Hy's Law. The patient was asymptomatic and the trial product was not discontinued at this time. It was reported that the patient had consumed alcohol the day prior to the laboratory tests being performed. The laboratory abnormalities normalized on trial day 518.



Liver parameters (xULN) over time

Source: Study report – narratives

The applicant's alternative etiologies for the 12 patients with laboratory evaluation that met the biochemical Hy's law definition are presented below.

Table 131 Overview of Patients with Concurrent Elevations of ALT/AST >3xULN and TBL >2xULN and Possible Alternative Etiologies – Semaglutide Clinical Development Program

CVOT			
NN9535-3744/403011[c]	Semaglutide 0.5 mg	645	Acute viral hepatitis.
NN9535-3744/561003	Semaglutide 1.0 mg	57	Gallstone disease
NN9535-3744/604018[c]	Semaglutide 1.0 mg	120	Gallstone disease
NN9535-3744/659004[c]	Placebo	31[d]	Acute viral hepatitis
NN9535-3744/608021	Placebo	723	Excessive alcohol consumption
NN9535-3744/684018[c]	Placebo	483	Alcohol consumption the day before samples were taken
Phase 3a pool			
NN9535-3625/451009[c]	Semaglutide 0.5 mg	56	Acute viral hepatitis
NN9535-3625/503002	Semaglutide 1.0 mg	58	Alcohol abuse and history of cholelithiasis
NN9535-3626/603009	Semaglutide 0.5 mg	155 TBL > 2xULN 393 ALT > 3xULN	TBL >2xULN occurred 8 months prior to the ALT >3xULN. History of hepatic steatosis and liver tests above ULN at randomisation.
Phase 2			
NN9535-1821/452002[c]	Semaglutide 0.4 mg	193	Chronic sclerogenic liver disease and gallstone disease, occurred 116 days after last treatment with trial product.
Phase 1			
NN9535-3651/401153[c]	Semaglutide 0.5 mg	-8 days	Alcoholic hepatitis in subject with severe hepatic impairment. Occurred prior to initiation of semaglutide treatment.
NN9535-3687/104043[c]	Semaglutide 0.5 mg	93	Occurred 44 days after 2nd and final single dose of drug. History of fluctuating liver enzymes measured in non-Novo Nordisk trials before and after this trial. Medwatch #453651

Notes: [a] The ALT/AST and TBL outliers were concurrent unless otherwise specified; [b] The brief alternative aetiologies are based on the categories provided in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009); [c] Narratives submitted for these subjects with the 'Response to FDA request' dated 03 September 2015. [d] This subject was prematurely discontinued on Trial Day 1 after one dose of trial product.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal.

Source: Table 2-123 ISS

Reviewer comment: While I generally agree that most of these cases likely have an alternative explanation for the LFT abnormalities, I was concerned with the one healthy volunteer, patient ID 104043, from trial 3687. However, the applicant stated that this patient has a history of fluctuating LFTs as observed during enrollment in various NN trials, and his daily alcohol

consumption could be higher than documented, which could explain LFT fluctuations. That and the lack of temporal association between drug administration and elevated LFTs are reassuring.

External liver expert evaluations - all phase 1, 2 and 3 trials including CVOT

The two liver experts were blinded to treatment asignment. A total of 43 cases were sent for evaluation of likelihood that the findings could be drug-related. The criteria leading to referral and number of cases for each criterion were:

- ALT>5xULN – 34 cases (4 of which also had TBL >2xULN)
- Cases of concurrent elevations of ALT and or AST >3xULN with TBL >2xULN – 12 cases, (4 of which also had ALT >5xULN)
- SAEs of potential concern were investigated and included 1 SAE of 'DILI'

Of the 34 patients that had ALT >5xULN, 4 patients had concurrent ALT>3xULN and TBL>2xULN (already discussed under Hy's law). Of the remaining 30 cases, 17 were judged to be unlikely related to the trial product (10 with semaglutide, and 7 with comparator). Eight cases with ALT > 5xULN were judged to be possibly related to the trial product (5 with semaglutide 0.5 mg, 1 with semaglutide 1 mg, 1 with exenatide ER and 1 with placebo). In all 8 cases patients were asymptomatic. The cases were generally evaluated as possibly related to trial product by the external experts as there may have been an alternative etiology, but this was not sufficiently substantiated. There was no apparent pattern in the timing of the ALT peaks: 1 peaked at week 8, 2 at week 16, 1 at week 23 and 4 at week 30.

The liver experts' assessment of the 34 patients with ALT>5XULN are summarized below.

Table 132 External Liver Expert Causality Assessment of ALT >5xULN Cases – CVOT, Phase 1, 2 and 3 Trials

Modified DILIN Score		
Subject ID	**Trial information**	**Treatment**
Unlikely		
NN9535-3625/749004	Phase 3a	IGlar
NN9535-3744/121011	Phase 3a	Placebo
NN9535-3744/447023	Phase 3a	Placebo
NN9535-3744/425003	Phase 3a	Placebo
NN9535-3744/667009	Phase 3a	Placebo
NN9924-3790/795004	Phase 2 Oral semaglutide dose-range finding trial	Placebo
NN9535-3626/605008	Phase 3a	Sitagliptin
NN9535-3623/601027	Phase 3a	Semaglutide 0.5 mg
NN9535-3625/702007	Phase 3a	Semaglutide 0.5 mg
NN9535-3625/638010	Phase 3a	Semaglutide 1.0 mg
NN9535-3625/701005	Phase 3a	Semaglutide 1.0 mg
NN9535-3744/172004	Phase 3a	Semaglutide 1.0 mg
NN9535-3744/165006	Phase 3a	Semaglutide 1.0 mg
NN9535-3744/260007	Phase 3a	Semaglutide 1.0 mg
NN9535-3744/323017	Phase 3a	Semaglutide 1.0 mg
NN9535-3744/443006	Phase 3a	Semaglutide 1.0 mg
NN9535-3744/525024	Phase 3a	Semaglutide 1.0 mg
Possible		
NN9535-3744/231005	Phase 3a	Placebo
NN9535-3624/725009	Phase 3a	Exenatide ER
NN9535-3623/202002	Phase 3a	Semaglutide 0.5 mg
NN9535-3627/324002	Phase 3a	Semaglutide 0.5 mg
NN9535-3651/401118	Phase 1 Hepatic impairment	Semaglutide 0.5 mg
NN9535-3626/588011	Phase 3a	Semaglutide 0.5 mg
NN9535-3623/602014	Phase 3a	Semaglutide 0.5 mg
NN9535-3744/466011	Phase 3a	Semaglutide 1.0 mg
Probable		
NN9535-3819/134	Phase 1 DDI - oral contraceptives	Semaglutide 1.0 mg
NN9535-3819/154	Phase 1 DDI - oral contraceptives	Semaglutide 1.0 mg
NN9535-3625/303006	Phase 3a	Semaglutide 1.0 mg
NN9535-3625/665007	Phase 3a	Semaglutide 1.0 mg
NN9535-3624/901006	Phase 3a	Semaglutide 1.0 mg

Notes: For the 4 cases with ALT >5xULN who also had concurrent TBL > 2xULN please see subject IDs: NN9535-3625/451009, NN9535-3744/403011, NN9535-3744/659004 and NN9535-3744/684018 in Table 2–123. Narratives for each of the above cases is provided in the list of narratives: Appendix 7.24.

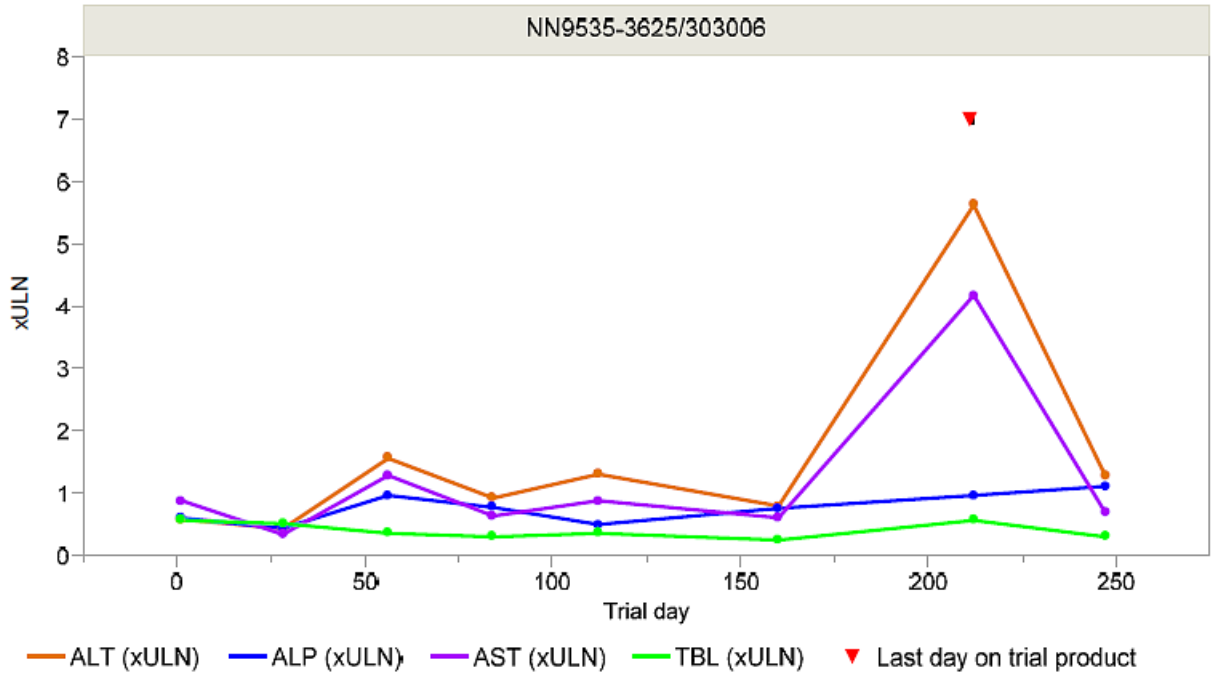
Abbreviations: DDI: drug-drug interaction; DILIN: Drug-Induced Liver Injury Network

Source: Table 2-124 ISS

Five cases with semaglutide 1 mg were judged probably related to trial product by the external experts: 2 patients in the DDI trial and 3 from the Phase 3 program. In all 5 patients, the ALT peaks returned to normal or near normal values within 2 months: 1 while temporarily

discontinuing treatment and 4 with peaks at the end-of-treatment visit that returned to normal after the end of treatment. Thus, it was difficult for the experts to assess whether the normalization of ALT was due to a drug de-challenge. There was no consistent pattern in the timing of the ALT >5xULN peaks. Narratives of the three patients from phase 3 trials are presented below.

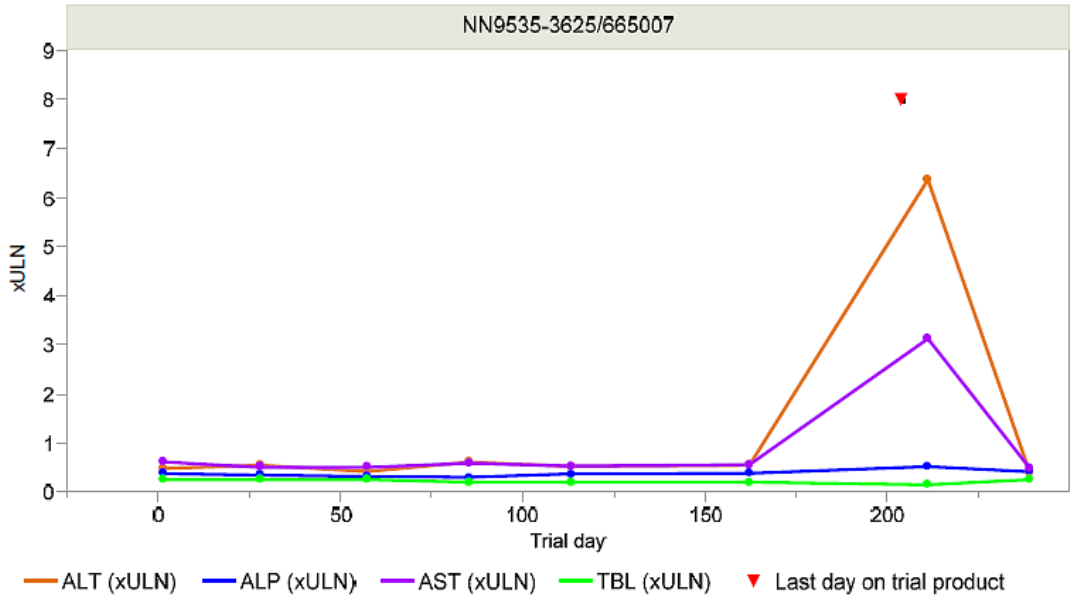
- Patient ID 303006 51 year old female randomized to semaglutide 1 mg, which she took for 211 days. LFT were normal at baseline, however were found to be elevated on study day 212. The patient was asymptomatic at the time. On trial day 247 the LFTs decreased but not normalized. The patient had a history of cholelithiasis at baseline, was also taking metformin, fenofibrate, and gliclazide at the time.



Liver parameters in normalised values (xULN) over time

Source: Study report – narratives

- Patient ID 665007: 47 year old female randomized to semaglutide 1 mg, which she received for 204 days. LFTs were normal at baseline. On trial day 211, ALT and AST s were elevated, however at repeat testing approximately one month later they were again normal.

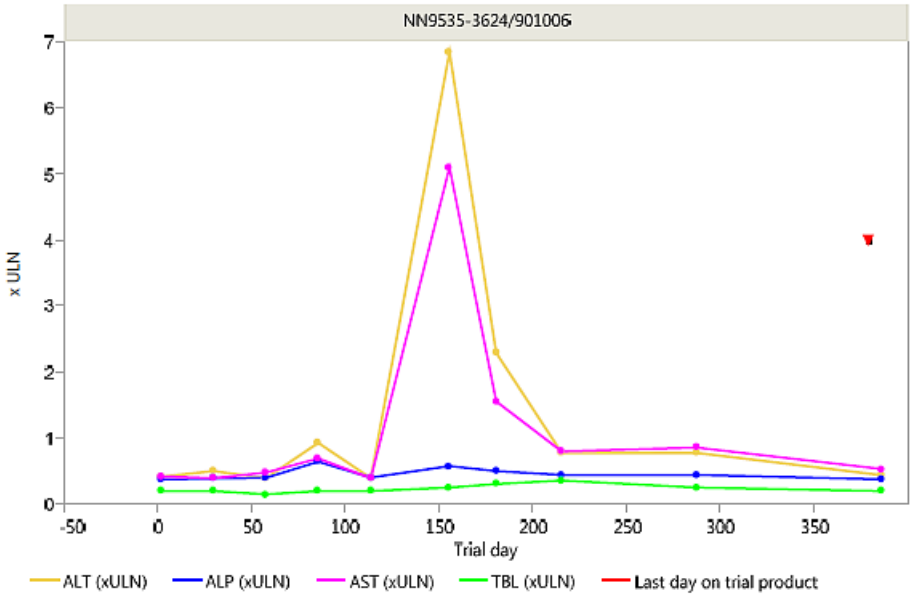


Liver parameters in normalised values (xULN) over time

Source: Study report – narratives

- Patient ID 901006: 49 year old female randomized to semaglutide 1 mg, with normal LFTs at baseline, was reported with elevated ALT and AST levels on trial day 155. At the same time she was diagnosed with hepatic steatosis, which was "confirmed" by abdominal ultrasound. The LFTs normalized by day 215. The patient had the last dose of study drug on study day 379, the treatment was not altered due to the abnormal LFTs. The patient was also taking metformin, benzafibrate, glimepiride, ethinylestradiol,

and drospirenone.



Liver parameters in normalised values (xULN) over time

Source: Study report – narratives

I could not find narratives for the other two patients, but review of the study report revealed the following:

- Patient ID 134 (Day 100: ALT; 92 U/L, AST; 49 U/L; lasted 18 days),
- Patient ID 154 (Day 100: ALT; 106 U/L, AST; 52 U/L; lasted 21 days),

Notably, these two patients were also taking oral contraceptives at the time, which could have led to LFT elevations.

Reviewer comment: In conclusion, the patients with events of ALT >5xULN categorized as possible, and probable related to the study drug by independent experts, most were on semaglutide. I reviewed the available data, and I am reassured by the lack of symptoms and spontaneous recovery in these patients.

MedDRA search for drug-related liver disorders.

CVOT

The overall proportion of patients with AEs captured by the MedDRA search for drug-related hepatic disorders and the corresponding rates were low and similar across treatment groups (semaglutide 0.5 mg: 5.2% and 4.6 events per 100 PYE; semaglutide 1 mg: 4.3% and 3.1 events

per 100 PYE; placebo: 4.9% and 3.4 events per 100 PYE). The treatment arms are generally balanced with regard to liver-related AEs.

Table 133 Hepatic Disorders Adverse Events - MedDRA Search - by System Organ Class, High Level Group Term and Preferred Term - CVOT - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	AComparator N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1644	3035		
All events	43	(5.2)	69	4.6	35	(4.3)	45	3.1	81	(4.9)	104	3.4
Hepatobiliary disorders	25	(3.0)	26	1.7	27	(3.3)	29	2.0	53	(3.2)	58	1.9
Hepatic and hepatobiliary disorders	25	(3.0)	26	1.7	27	(3.3)	29	2.0	53	(3.2)	58	1.9
Hepatic steatosis	15	(1.8)	15	1.0	19	(2.3)	20	1.4	40	(2.4)	40	1.3
Hepatic cyst	3	(0.4)	3	0.2	2	(0.2)	2	0.1	3	(0.2)	3	<0.1
Hepatic cirrhosis	1	(0.1)	1	<0.1	2	(0.2)	2	0.1	1	(<0.1)	1	<0.1
Hepatosplenomegaly	2	(0.2)	2	0.1	1	(0.1)	1	<0.1				
Liver disorder	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Biliary cirrhosis					1	(0.1)	1	<0.1				
Ischaemic hepatitis					1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Jaundice cholestatic					1	(0.1)	1	<0.1				
Autoimmune hepatitis	1	(0.1)	1	<0.1								
Hepatic function abnormal	1	(0.1)	1	<0.1								
Hepatomegaly	1	(0.1)	1	<0.1					4	(0.2)	4	0.1
Jaundice	1	(0.1)	1	<0.1								
Cholestasis									2	(0.1)	2	<0.1
Drug-induced liver injury									1	(<0.1)	1	<0.1
Hyperbilirubinaemia									1	(<0.1)	1	<0.1
Investigations	19	(2.3)	36	2.4	10	(1.2)	11	0.8	27	(1.6)	41	1.4
Hepatobiliary investigations	18	(2.2)	33	2.2	8	(1.0)	9	0.6	23	(1.4)	34	1.1
Alanine aminotransferase increased	9	(1.1)	11	0.7	3	(0.4)	4	0.3	9	(0.5)	10	0.3
Aspartate aminotransferase increased	10	(1.2)	11	0.7	1	(0.1)	1	<0.1	11	(0.7)	11	0.4
Blood bilirubin increased	5	(0.6)	6	0.4	1	(0.1)	1	<0.1	3	(0.2)	3	<0.1
Hepatic enzyme increased	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	6	(0.4)	6	0.2
Liver function test abnormal	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Transaminases increased	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Blood bilirubin abnormal	1	(0.1)	1	<0.1								
Ultrasound liver abnormal	1	(0.1)	1	<0.1								
Gamma-glutamyltransferase increased									1	(<0.1)	1	<0.1
Hepatic enzyme abnormal									1	(<0.1)	1	<0.1
Enzyme investigations NEC	3	(0.4)	3	0.2	1	(0.1)	1	<0.1	5	(0.3)	6	0.2
Blood alkaline phosphatase increased	2	(0.2)	2	0.1	1	(0.1)	1	<0.1	5	(0.3)	6	0.2
Blood alkaline phosphatase abnormal	1	(0.1)	1	<0.1								
Haematology investigations (incl blood groups)					1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
International normalised ratio increased					1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Modified from Table 7.11.423 ISS

In total, 17 SAEs captured by the MedDRA search for drug-related hepatic disorders were reported in 14 patients during the on-treatment period, with no apparent imbalance between the treatment groups.

Table 134 SAEs of Drug-Related Hepatic Disorders (MedDRA Search) by Preferred Term – SAS On-Treatment – CVOT

System organ class / Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
PYE (year)	823	1488		819	1444		1644		3035			
All events	4	(0.5)	4	0.3	4	(0.5)	4	0.3	6	(0.4)	9	0.3
Hepatobiliary disorders	1	(0.1)	1	<0.1	2	(0.2)	2	0.1	4	(0.2)	4	0.1
Ascites	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Hepatic cirrhosis					1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Ischaemic hepatitis					1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Liver function test abnormal					1	(0.1)	1	<0.1				
Jaundice	1	(0.1)	1	<0.1								
Hepatic cancer	1	(0.1)	1	<0.1								
Cholestasis									1	(<0.1)	1	<0.1
Hepatic congestion									1	(<0.1)	1	<0.1
Blood bilirubin increased									1	(<0.1)	1	<0.1
Transaminases increased									1	(<0.1)	1	<0.1
Blood alkaline phosphatase increased									1	(<0.1)	1	<0.1

N and

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-125 ISS

Twenty-eight additional AEs were observed in the in-trial observation period: these were distributed similarly between the semaglutide (both doses) and placebo groups. Four of these events were SAEs:

- One AE of hepatic failure was reported, in the semaglutide 0.5 mg group, in a 62 year old woman (patient ID NN9535-3744/638023) on day 482, 90 days after the site initially lost contact with the patient (last day of treatment was day 392). The event was co-reported with cardiac arrest, pneumonia, renal cyst and renal failure. Three days later the patient died due to myocardial infarction and cardiac arrest. The hepatic failure and renal failure SAEs had not recovered prior to the patient's death and were likely due to decreased blood flow post cardiac arrest.
- One ischemic hepatitis (in the semaglutide 0.5 mg group) was reported in a 61 year old female (patient ID NN9535-3744/563005) 515 days into the trial (approximately 3 months after premature treatment discontinuation due to pancreatitis, abdominal pain upper, vomiting and dyspepsia) and had fatal outcome.
- 2 SAEs in 2 patients on placebo (pneumobilia and hepatic cancer)

Phase 3 trials

The AE profile of drug-related hepatic disorders observed with semaglutide (0.5 mg and 1.0 mg) and comparator products was consistent across the phase 3 trials excluding the CVOT.

The overall proportion of patients with AEs of drug-related hepatic disorders and the corresponding rates were low and similar across treatment groups (semaglutide 0.5 mg: 3.8%

and 6.1 events per 100 PYE; semaglutide 1 mg: 2.5% and 3.4 events per 100 PYE; comparators: 3.4% and 5.0 events per 100 PYE).

There was no apparent imbalance across semaglutide doses or between semaglutide and comparators in the severity, seriousness, outcome or action to trial drug. Three (3) non-serious drug-related hepatic disorders led to premature treatment discontinuation: 2 with semaglutide 0.5 mg and one with comparator

Of note, 1 non-serious report of 'drug-induced liver injury' was reported in trial 4092 for a patient on semaglutide 0.5 mg (patient ID NN9535-4092/207024) at week 16. This patient had no signs, symptoms or AEs reported at the time of the event other than the elevated ALT (191 U/L) and AST (83 U/L). TBL was not elevated at any time and the AST and ALT levels returned to normal levels by the next visit.

Table 135 Hepatic Disorders Adverse Events - MedDRA Search - by System Organ Class, High Level Group Term and Preferred Term - Summary – Phase 3 Pool - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
All events	53	(3.8)	71	6.1	45	(2.5)	53	3.4	56	(3.4)	74	5.0
Hepatobiliary disorders	30	(2.2)	34	2.9	31	(1.7)	33	2.1	39	(2.4)	45	3.1
Hepatic and hepatobiliary disorders	30	(2.2)	34	2.9	31	(1.7)	33	2.1	39	(2.4)	45	3.1
Hepatic steatosis	16	(1.2)	17	1.5	19	(1.1)	19	1.3	32	(1.9)	33	2.3
Hepatic cyst	6	(0.4)	6	0.5	8	(0.4)	8	0.5	2	(0.1)	2	0.1
Hepatomegaly	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Hepatic cirrhosis					1	(<0.1)	1	<0.1	2	(0.1)	2	0.1
Hepatic pain					1	(<0.1)	1	<0.1				
Hepatosplenomegaly					1	(<0.1)	1	<0.1				
Hyperbilirubinaemia					1	(<0.1)	1	<0.1				
Portal hypertension					1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Drug-induced liver injury	2	(0.2)	2	0.2								
Non-alcoholic steatohepatitis	2	(0.2)	2	0.2								
Hepatic calcification	1	(<0.1)	1	<0.1					1	(<0.1)	1	<0.1
Hepatic function abnormal	1	(<0.1)	1	<0.1					4	(0.3)	4	0.3
Hepatitis acute	1	(<0.1)	1	<0.1								
Hepatitis toxic	1	(<0.1)	1	<0.1								
Jaundice	1	(<0.1)	1	<0.1								
Liver disorder	1	(<0.1)	1	<0.1					1	(<0.1)	1	<0.1
Investigations	25	(1.8)	37	3.2	13	(0.7)	16	1.0	18	(1.1)	27	1.8
Hepatobiliary investigations	24	(1.7)	35	3.0	12	(0.7)	14	0.9	15	(0.9)	24	1.6
Alanine aminotransferase increased	16	(1.1)	17	1.4	3	(0.2)	3	0.2	9	(0.5)	11	0.7
Aspartate aminotransferase increased	4	(0.3)	4	0.4	3	(0.2)	3	0.2	7	(0.4)	7	0.5
Hepatic enzyme increased	4	(0.3)	4	0.4	2	(0.1)	2	0.1	6	(0.4)	6	0.4
Liver function test abnormal	3	(0.2)	3	0.2	2	(0.1)	2	0.1				
Blood bilirubin increased	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1				
Gamma-glutamyltransferase increased	3	(0.2)	3	0.2	1	(<0.1)	1	<0.1				
Transaminases increased	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1				
Alanine aminotransferase abnormal	1	(<0.1)	1	<0.1								
Aspartate aminotransferase abnormal	1	(<0.1)	1	<0.1								
Enzyme investigations NEC	2	(0.2)	2	0.2	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Blood alkaline phosphatase increased	2	(0.2)	2	0.2	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					4	(0.2)	4	0.3	2	(0.1)	2	0.1
Hepatic and biliary neoplasms benign					3	(0.2)	3	0.2	1	(<0.1)	1	<0.1
Haemangioma of liver					2	(0.1)	2	0.1	1	(<0.1)	1	<0.1
Focal nodular hyperplasia					1	(<0.1)	1	<0.1				
Hepatobiliary neoplasms malignant and unspecified					1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Hepatocellular carcinoma					1	(<0.1)	1	<0.1				
Hepatic neoplasm									1	(<0.1)	1	<0.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Table 7.11.419 ISS

Table 136 SAEs of Drug-Related Hepatic Disorders (MedDRA SEARCh) by Preferred Term – SAS On-Treatment – Phase 3 Pool

Preferred term	Sema 0.5 mg N	(Adj.%)E	Adj. R	Sema 1.0 mg N	(Adj.%)E	R	Comparators N	(Adj.%) E	Adj.R
N and PYE (year)	1373	1165		1777	1548		1657	1467	
Drug-related hepatic disorder SAEs	1	(<0.1)	1 <0.1	2	(0.1)	2 0.1	1	(<0.1)	1 <0.1
Liver function test abnormal				1	(<0.1)	1 <0.1			
Hepatocellular carcinoma				1	(<0.1)	1 <0.1			
Drug-induced liver injury	1	(<0.1)	1 <0.1						
Hepatic function abnormal							1	(<0.1)	1 <0.1

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate, Table is sorted in descending order by system organ class based on the total number of subjects with at least one event when treated with Sema 1.0 mg, if missing then by semaglutide 0.5 mg. .

Abbreviations: Adj: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-126 ISS

Placebo-pool

Few events of drug-related hepatic disorders were reported in the two placebo-controlled trials. The proportion of patients and rate of events was similar with semaglutide 0.5 mg and with placebo, and lower with semaglutide 1 mg. Hepatic enzyme increased and hepatic steatosis were the most frequently reported AEs within this MedDRA search.

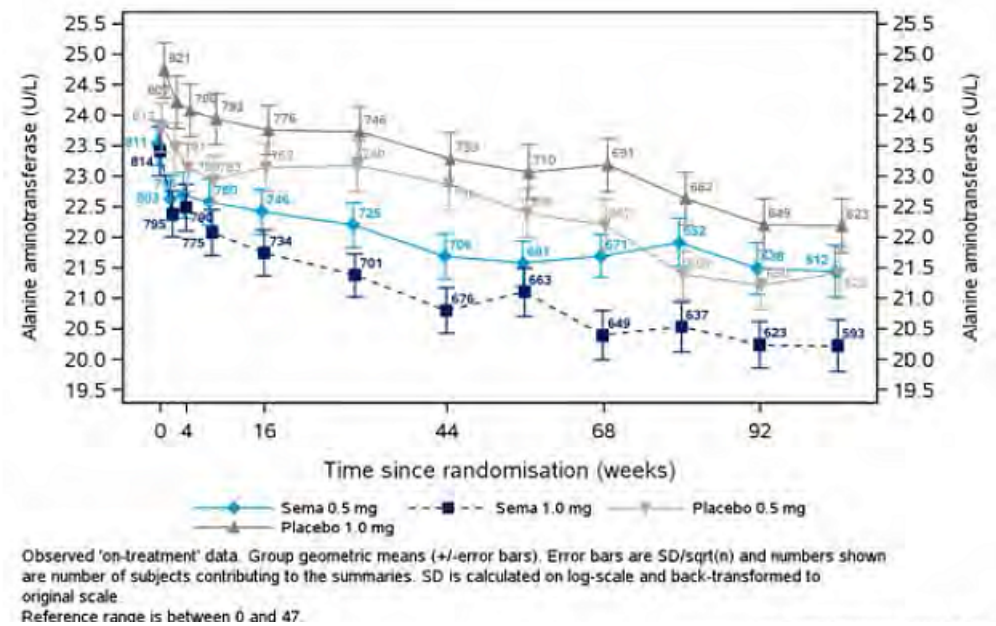
Liver function tests

Small mean and median decreases from baseline within the normal reference range were observed for each of the hepatic analytes (ALT, AST, ALP and TBL) after 4, 8, 16, 30 and 56 weeks of treatment in all treatment groups. The decrease in ALT and AST liver values was more pronounced with semaglutide 1 mg than semaglutide 0.5 mg and more so with semaglutide (both doses) than with all comparators.

The over-time trends for ALT and AST for each pool are presented below.

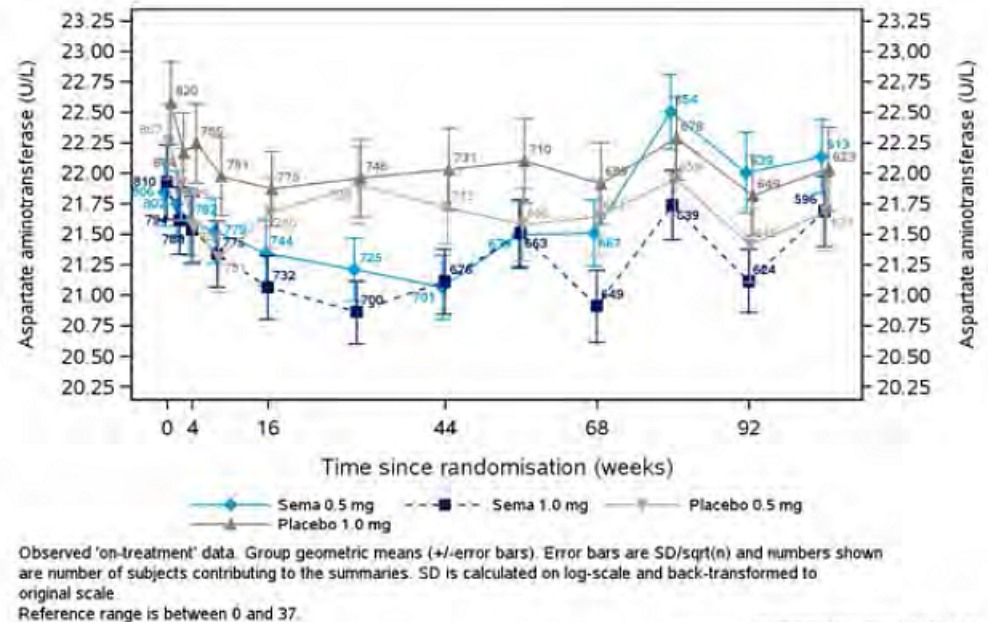
CVOT

Table 137 Alanine Aminotransferase (U/L) by Treatment Week - Geometric Mean–CVOT On-Treatment - Safety Analysis Set



Source: Figure15.3.5.28 study report 3744

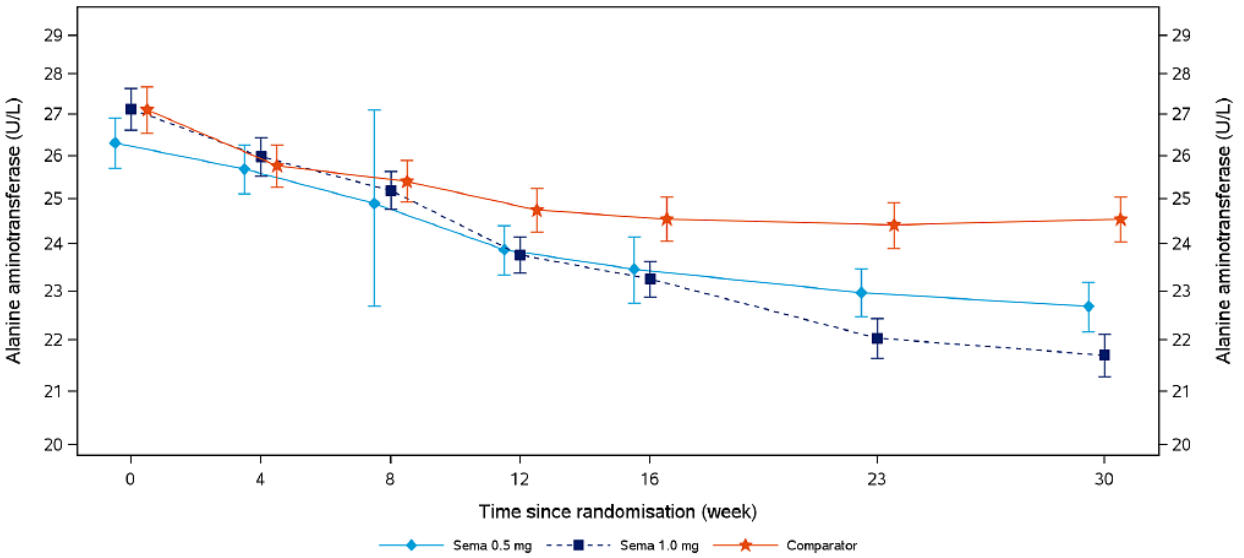
Table 138 Aspartate Aminotransferase (U/L) by Treatment Week - Geometric Mean– CVOT On-Treatment - Safety Analysis Set



Source: Figure 15.3.5.38 study report 3744

Phase 3 trials

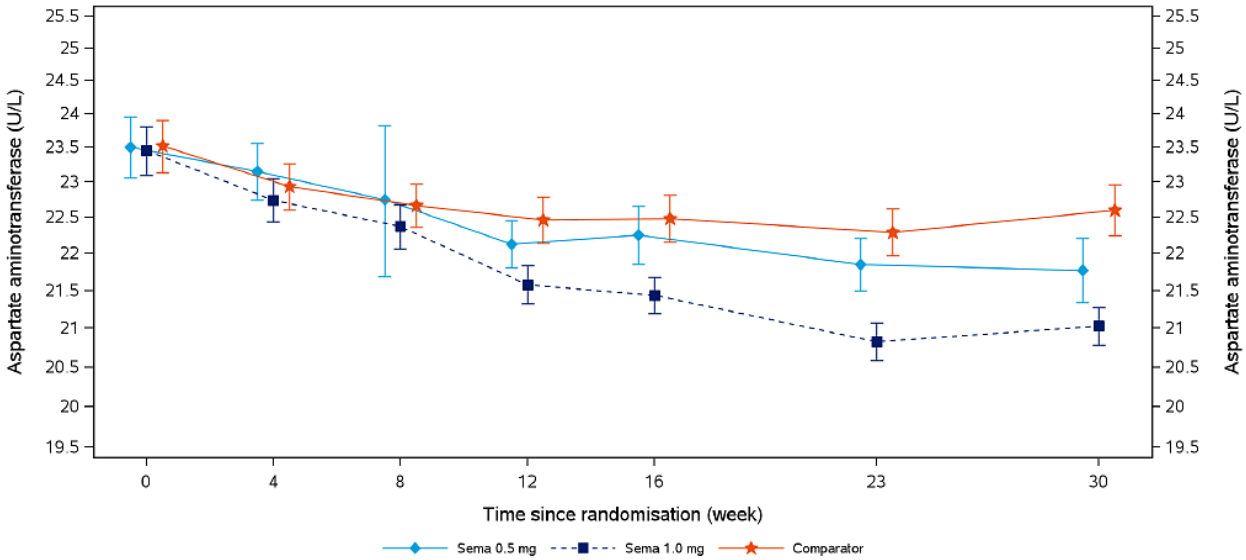
Table 139 Alanine Aminotransferase (U/L) by Treatment to Week 30 - Geometric Mean - Phase 3 Pool - On-Treatment



SAS, on-treatment observation period, observed data, Group geometric means (+/-error bars). Error bars are SD/sqrt(n), Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Source: Figure 7.16.47 ISS

Table 140 Aspartate Aminotransferase (U/L) by Treatment to Week 30 - Geometric Mean - Phase 3 pool - On-Treatment

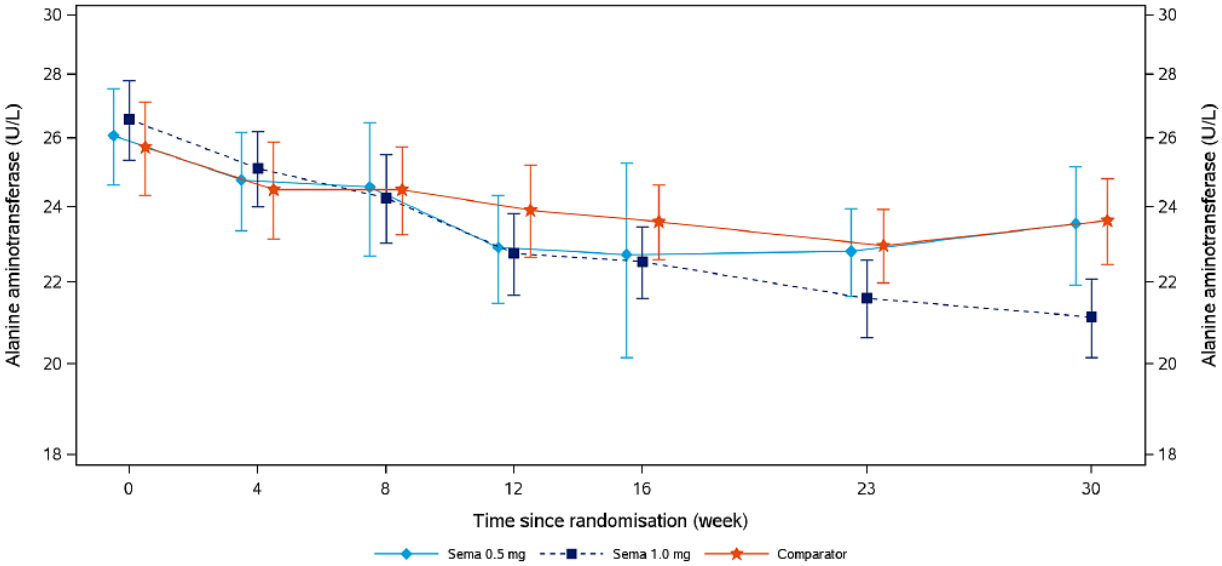


SAS, on-treatment observation period, observed data, Group geometric means (+/-error bars). Error bars are SD/sqrt(n), Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Source: Figure 7.16.62 ISS

Placebo pool

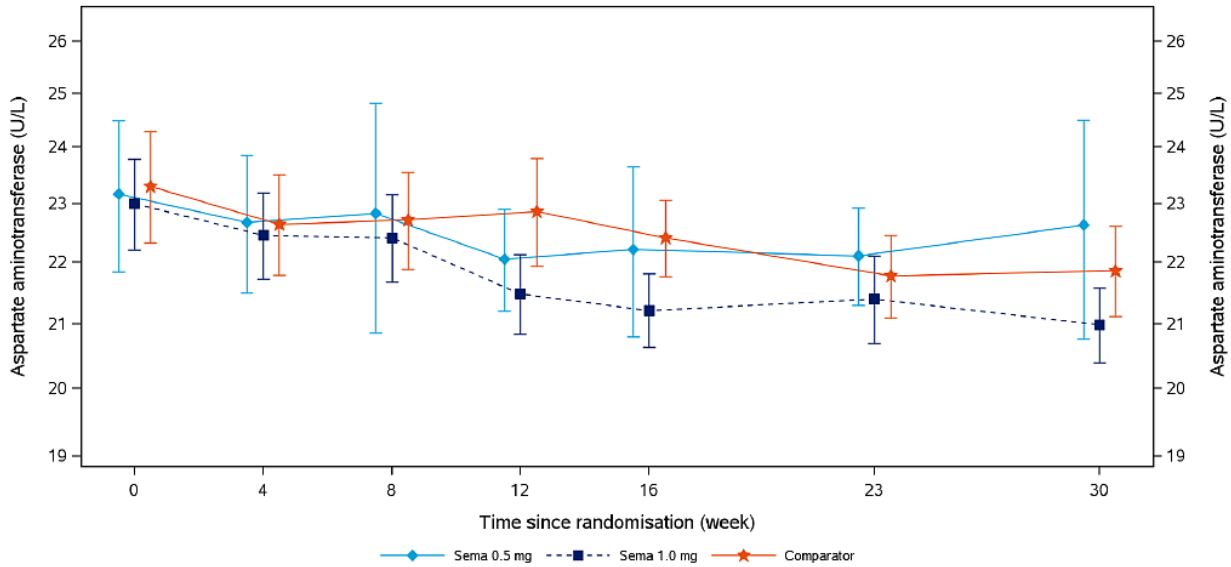
Table 141 Alanine Aminotransferase (U/L) by Treatment to Week 30 - Geometric Mean - Placebo Pool - On-Treatment



SAS, on-treatment observation period, observed data, Group geometric means (+/-error bars). Error bars are SD/sqrt(n), Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale, Placebo pool: trial (comparator): 3623 (placebo), 3627 (placebo).

Source: Figure 7.16.48 ISS

Table 142 Aspartate Aminotransferase (U/L) by Treatment to Week 30 - Geometric Mean - Placebo Pool - On-Treatment



SAS, on-treatment observation period, observed data, Group geometric means (+/-error bars). Error bars are SD/sqrt(n), Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale, Placebo pool: trial (comparator): 3623 (placebo), 3627 (placebo).

Source: Figure 7.16.63 ISS

Liver function outliers

The number of patients with increases in ALT or AST >3xULN was well-balanced between both semaglutide doses and between semaglutide and comparators in the CVOT and the phase 3 pool.

In the CVOT, the number of patients with increases in ALT or AST >5xULN was slightly lower with semaglutide 0.5 mg than with semaglutide 1 mg but the total numbers were similar between semaglutide and placebo groups. Conversely, in the phase 3 pool, there were more patients with elevated ALT or AST levels >5xULN and >10xULN on semaglutide (0.5 mg and 1.0 mg) vs comparators.

Alkaline phosphatase and bilirubin elevations were balanced between the treatment groups for both pools.

Table 143 Liver Tests – Categorical Summary of Extreme Post-Baseline Values – SAS – CVOT

	Sema 0.5 mg N	Sema 0.5 mg (%)	Sema 1.0 mg N	Sema 1.0 mg (%)	Placebo N	Placebo (%)
Number of subjects	826		822		1649	
ALT - Summary of maximum post-baseline value						
Normal	643	(78.13)	653	(79.73)	1293	(78.75)
High (>ULN)	180	(21.87)	166	(20.27)	349	(21.25)
>2x ULN	14	(1.70)	23	(2.81)	65	(3.96)
>3x ULN	4	(0.49)	10	(1.22)	22	(1.34)
>5x ULN	1	(0.12)	5	(0.61)	6	(0.37)
>10x ULN	1	(0.12)	1	(0.12)	3	(0.18)
AST - Summary of maximum post-baseline value						
Normal	634	(77.04)	649	(79.24)	1248	(76.00)
High (>ULN)	189	(22.96)	170	(20.76)	394	(24.00)
>2x ULN	24	(2.92)	24	(2.93)	73	(4.45)
>3x ULN	8	(0.97)	8	(0.98)	21	(1.28)
>5x ULN	2	(0.24)	4	(0.49)	7	(0.43)
>10x ULN	1	(0.12)	1	(0.12)	2	(0.12)
ALP - Summary of maximum post-baseline value						
Low	3	(0.36)	8	(0.98)	14	(0.85)
Normal	740	(89.91)	749	(91.45)	1439	(87.64)
High (>ULN)	80	(9.72)	62	(7.57)	189	(11.51)
>2x ULN	6	(0.73)	4	(0.49)	24	(1.46)
>3x ULN	1	(0.12)	3	(0.37)	7	(0.43)
>5x ULN						
>10x ULN						
TBL - Summary of maximum post-baseline value						
Normal	768	(93.32)	768	(93.77)	1540	(93.79)
High (>ULN)	55	(6.68)	51	(6.23)	102	(6.21)
>2x ULN	7	(0.85)	2	(0.24)	14	(0.85)
>3x ULN	2	(0.24)	2	(0.24)	2	(0.12)
>5x ULN	1	(0.12)			2	(0.12)
>10x ULN					1	(0.06)

Notes: For each subject, the maximum post-baseline values from all scheduled and un-scheduled visits are included in this summary; these values are then categorised. Each category comprises all values above the specified threshhold.
Abbreviations: ALT : alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; N: number of subjects; TBL: total bilirubin; ULN : upper limit of normal; %: percentage of subjects.

Source: Table 2-121 ISS

Table 144 Liver Tests – Categorical Summary of Extreme Post-Baseline Values – SAS – Phase 3 Pool

	Sema 0.5 mg N	Sema 0.5 mg (%)	Sema 1.0 mg N	Sema 1.0 mg (%)	All comparators N	All comparators (%)
Number of subjects	1373		1777		1657	
ALT - Summary of maximum post-baseline value						
Normal	1058	(77.5)	1368	(77.6)	1265	(76.8)
High (>ULN)	308	(22.5)	396	(22.4)	383	(23.2)
>2x ULN	55	(4.0)	48	(2.7)	64	(3.9)
>3x ULN	16	(1.2)	9	(0.5)	21	(1.3)
>5x ULN	7	(0.5)	4	(0.2)	2	(0.1)
>10x ULN	2	(0.1)				
AST - Summary of maximum post-baseline value						
Normal	1092	(79.9)	1429	(81.0)	1256	(76.2)
High (>ULN)	274	(20.1)	335	(19.0)	392	(23.8)
>2x ULN	46	(3.4)	42	(2.4)	67	(4.1)
>3x ULN	16	(1.2)	8	(0.5)	16	(1.0)
>5x ULN	7	(0.5)	4	(0.2)	2	(0.1)
>10x ULN	3	(0.2)				
ALP - Summary of maximum post-baseline value						
Low	19	(1.4)	24	(1.4)	14	(0.8)
Normal	1304	(95.5)	1688	(95.7)	1585	(96.2)
High (>ULN)	43	(3.1)	52	(2.9)	49	(3.0)
>2x ULN	4	(0.3)	4	(0.2)	3	(0.2)
>3x ULN	1	(0.1)	2	(0.1)	1	(0.1)
>5x ULN			1	(0.1)	1	(0.1)
>10x ULN						
TBL - Summary of maximum post-baseline value						
Normal	1253	(91.7)	1632	(92.5)	1531	(92.9)
High (>ULN)	113	(8.3)	132	(7.5)	117	(7.1)
>2x ULN	4	(0.3)	6	(0.3)	5	(0.3)
>3x ULN			1	(0.1)		
>5x ULN						

Notes: For each subject, the maximum post-baseline values from all scheduled and un-scheduled visits are included in this summary; these values are then categorised. Each category comprises all values above the specified threshhold.
Abbreviations: ALT : alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; N: number of subjects; TBL: total bilirubin; ULN : upper limit of normal; %: percentage of subjects.

Source: Table 2-122 ISS

No dose-response was seen with semaglutide in either pool.

Categorical shifts for the CVOT and the Phase 3 pool are presented below.

CVOT

Few patients experienced upward categorical shifts for ALT and AST in the CVOT, and no imbalance not favoring semaglutide was observed.

Table 145 Alanine Aminotransferase (U/L) Activity Levels at Week 104 (LOCF) - Shift Table– SAS, CVOT

		<2x ULN at baseline				≥2x ULN and ≤ 5x ULN at baseline			
		<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN		<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN	
	N	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
ALT (U/L) - Summary of observed and imputed 'on-treatment' data									
Visit 25 (week 104) (LOCF)									
Sema 0.5 mg	811	805 (99.63)	2 (0.25)	1 (0.12)		3 (100.0)			
Sema 1.0 mg	814	803 (99.50)	2 (0.25)	2 (0.25)		4 (80.00)	1 (20.00)		
Placebo 0.5 mg	813	800 (99.38)	4 (0.50)	1 (0.12)		6 (75.00)	2 (25.00)		
Placebo 1.0 mg	821	801 (99.38)	5 (0.62)			10 (76.92)	3 (23.08)		

Notes: Subjects with ALT >5xULN at baseline are in the unmodified EOT Table.

Abbreviations: ALT: alanine aminotransferase, N: number of subjects in the summary statistic, %: percentage of subjects in the given baseline category, ULN: upper limit of normal, LOCF: missing data imputed from last observation carried forward.

Source: Table 13-62 study report 3744

Table 146 Aspartate Aminotransferase (U/L) Activity Levels at Week 104 (LOCF) – Shift Table – SAS, CVOT

		<2x ULN at baseline				≥2x ULN and ≤ 5x ULN at baseline			
		<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN		<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN	
	N	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
AST (U/L) - Summary of observed and imputed 'on-treatment' data									
Visit 25 (week 104) (LOCF)									
Sema 0.5 mg	806	798 (99.63)	2 (0.25)	1 (0.12)		4 (80.00)	1 (20.00)		
Sema 1.0 mg	810	794 (99.50)	3 (0.38)	1 (0.13)		9 (90.00)	1 (10.00)		
Placebo 0.5 mg	807	787 (99.24)	5 (0.63)	1 (0.13)		12 (85.71)	2 (14.29)		
Placebo 1.0 mg	820	804 (99.75)	2 (0.25)			8 (61.54)	5 (38.46)		

Notes: Subjects with AST >5xULN at baseline are in the unmodified EOT Table.

Abbreviations: AST: aspartate aminotransferase, N: number of subjects in the summary statistic, %: percentage of subjects in the given baseline category, ULN: upper limit of normal range, LOCF: missing data imputed from last observation carried forward.

Source: Table 13-64 study report 3744

Phase 3 pool

In line with the CVOT, no imbalance was observed in upwards shifts for AST and ALT semaglutide vs comparator.

Table 147 Liver Function Tests - Shift Table - Phase 3 Pool - On-Treatment

		<2x ULN at baseline			>=2x ULN and <=5x ULN at baseline			>5x ULN at baseline		
		<2x ULN	>=2x ULN and <=5x ULN	>5x ULN	<2x ULN	>=2x ULN and <=5x ULN	>5x ULN	<2x ULN	>=2x ULN and <=5x ULN	>5x ULN
	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Alanine Aminotransferase Serum (U/L) - Summary of observed and imputed 'on-treatment' data										
Week 30 (LOCF)										
Sema 0.5 mg	1364	1326 (99.3)	8 (0.6)	1 (0.1)	19 (67.9)	8 (28.6)	1 (3.6)	1 (100.0)		
Sema 1.0 mg	1770	1732 (99.7)	3 (0.2)	2 (0.1)	29 (90.6)	3 (9.4)		1 (100.0)		
All sema	3134	3058 (99.5)	11 (0.4)	3 (0.1)	48 (80.0)	11 (18.3)	1 (1.7)	2 (100.0)		
Comparator	1647	1600 (99.2)	13 (0.8)		22 (66.7)	11 (33.3)				1 (100.0)
Week 56 (LOCF)										
Sema 0.5 mg	647	628 (98.9)	7 (1.1)		9 (75.0)	3 (25.0)				
Sema 1.0 mg	1050	1031 (99.5)	5 (0.5)		14 (100.0)					
All sema	1697	1659 (99.3)	12 (0.7)		23 (88.5)	3 (11.5)				
Comparator	926	896 (98.8)	11 (1.2)		12 (63.2)	7 (36.8)				
Aspartate aminotransferase (U/L) - Summary of observed and imputed 'on-treatment' data										
Week 30 (LOCF)										
Sema 0.5 mg	1363	1330 (99.4)	5 (0.4)	3 (0.2)	17 (70.8)	7 (29.2)			1 (100.0)	
Sema 1.0 mg	1768	1730 (99.7)	5 (0.3)		28 (87.5)	4 (12.5)		1 (100.0)		
All sema	3131	3060 (99.6)	10 (0.3)	3 (0.1)	45 (80.4)	11 (19.6)		1 (50.0)	1 (50.0)	
Comparator	1645	1603 (99.5)	8 (0.5)		20 (60.6)	13 (39.4)				1 (100.0)
Week 56 (LOCF)										
Sema 0.5 mg	646	627 (98.9)	6 (0.9)	1 (0.2)	10 (83.3)	2 (16.7)				
Sema 1.0 mg	1048	1026 (99.6)	4 (0.4)		17 (94.4)	1 (5.6)				
All sema	1694	1653 (99.3)	10 (0.6)	1 (0.1)	27 (90.0)	3 (10.0)				
Comparator	923	890 (98.6)	13 (1.4)		15 (75.0)	5 (25.0)				

N: Number of subjects in the safety analysis set, %: Percentage of subjects, ULN: Upper limit of normal, LOCF: Missing data imputed from last observation carried forward, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 7 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first

Source: Modified from Table 7.16.26 ISS

In conclusion, liver function was evaluated via expert evaluation, MedDRA search, and laboratory evaluation, including identifying patients with potential DILI. There was a higher incidence of ALT >5xULN cases that were judged by experts to be possibly or probably related to trial product with semaglutide than with comparators. These patients were generally asymptomatic, and the applicant stated that the causality was likely assigned due to the limited information regarding potential alternative etiologies. This is not entirely accurate, as some of these patients had a reasonable amount if information available. However, most of these patients were taking other medications that could have been responsible for the observed LFT changes. Out of the 12 patients identified with LFT abnormalities that met the Hy's law criteria, most were in the semaglutide treated group, but alternative etiologies are likely for 11 of these cases. The remaining case is somewhat confusing, however the timing of LFT elevations, fluctuating LFTs, and possible chronic alcohol consumption alleviate my concerns that this could be related to semaglutide. The upward shifts in AST and ALT were balanced between the treatment group, both for the CVOT, and for the pool.

Reviewer comment: Patients on semaglutide were more likely to have an event that fit the biochemical definition of Hy's law, as well as AST elevations >5XULN judged by independent experts as possibly or probably related to the study drug. However, alternative etiologies are present in all Hy's law patients. For the patients judged as possibly or probably associated to the drug, alternative etiologies are present in some of them (oral contraceptives), while in other cases alternative etiologies are not completely ruled out due to lack of available information. Assessment of liver AEs and outlier analyses for LFTs were generally reassuring. In conclusion,

based on the totality of data, there is no evidence to suggest at this time that semaglutide is associated with DILI.

Medication Errors

A MedDRA search was performed among all AEs reported in the phase 3 trials to capture all potential medication error events.

CVOT

Overall, medication errors captured by the MedDRA search were reported in approximately 2% of the patients in the CVOT; the proportion of patients with events and corresponding rate of events in the on-treatment observation period were similar between semaglutide and placebo. None of the medication error events were fatal. Eight medication error events were reported as SAEs and were reported for similar proportions of patients and corresponding rates for semaglutide and placebo.

The most frequently reported medication error AEs for both semaglutide and placebo treatments were within the SOC injury, poisoning and procedural complications and included the PTs accidental overdose, overdose, and inappropriate schedule of drug administration. Overdose was reported with a similar proportion of patients and rate of events with semaglutide and placebo.

Five episodes of hypoglycemia were co-reported within 7 days of a medication error AE (3 events with semaglutide and 2 events with placebo). One episode of severe hypoglycemia was reported for a patient in the semaglutide 0.5 mg group due to administration of wrong dose of concomitant insulin.

Phase 3 trials

Overall, numbers of medication error events captured by the MedDRA search were low and reported in 0.5% or less of the patients in the phase 3 pool. No relevant differences in the proportion of patients with events and corresponding rate of events in the on-treatment observation period were observed. None of the medication error events were SAEs.

The most frequently reported medication error AEs were accidental overdose (5 events for semaglutide 0.5 mg and 3 events for semaglutide 1 mg). No episodes of hypoglycaemia were co-reported within 7 days of a medication error AE.

Placebo pool

Of the placebo-controlled trials, medication error AEs were only reported in trial 3627; 2 events were reported in the semaglutide 0.5 mg group (PTs: accidental overdose and inappropriate schedule of drug administration).

Overall, medication error related events were infrequently reported in the semaglutide phase 3 program. The primary causes for the majority of medication errors were patient errors (e.g. misunderstandings regarding the dosing schedule) and medication error AEs were most frequently reported during the dose-escalation phase.

8.4.6. Laboratory Findings

Analyses of liver and kidney function tests, as well as calcitonin, and amylase/lipase are presented in section 8.4.5 of this review. This section will focus on the discussion of lipids. Other laboratory tests are not discussed as no clinically concerning changes were noted. There were no changes to mean hematology or chemistry parameters, no imbalance in the number of outliers between treatment groups, and no imbalance in the laboratory adverse events other than discussed in section 8.4.5.

Lipids

Fasting FFAs, total cholesterol, HDL, LDL, VLDL and triglycerides were measured in all phase 3 trials, the only exception being VLDL that was not measured in the CVOT. Changes in clinical laboratory values from baseline to end-of-treatment as well as changes over time were analyzed.

At baseline, levels of blood lipids were comparable across treatment groups and within trials.

A small decrease in LDL was seen with semaglutide treatment across all phase 3 trials. No change was seen with HDL in any treatment groups

Table 148 LDL (mg/dL) Mean Change from Baseline to Week 56 – Phase 3 Pool

	Sema 0.5	Sema 1	Comparator
Baseline mean (SD)	104.1 (34.3)	104.2 (34.6)	103.3 (36.5)
Mean change from baseline (SD)	-5.2 (24.8)	-6.0 (29.0)	-2.3 (30.1)

Source: Response to Information request dated 09/01/2017

Table 149 LDL (mg/dL) Mean Change from Baseline to Week 104 – CVOT

	Sema 0.5	Sema 1	Placebo 0.5	Placebo 1
Baseline mean (SD)	89.6 (39.1)	89.8 (34.5)	88.8 (38.2)	91.4 (38.1)
Mean change from baseline (SD)	-2.2 (31.7)	-1.9 (31.0)	1.7 (32.5)	0.2 (33.2)

Source: Response to Information request dated 09/01/2017

While it is unknown whether these changes are beneficial, it does not appear that semaglutide has a negative impact on lipids,

8.4.7. **Vital Signs**

Assessment of the effect of semaglutide on blood pressure is outlined in Section 6.7.2. In this section I will discuss the changes in heart rate.

Resting pulse rate (beats/min) was measured according to local clinical practice, with the patient sitting after having rested in a chair for 5 minutes. The change in pulse rate was analyzed in each of the phase 3 trials using the standard MMRM analysis method.
In addition to routine pulse rate measurements in the phase 3 trials, the effects of semaglutide on pulse rate, QT and PR interval have been assessed in a dedicated QTc trial (trial 3652). See review byfor details.

A MedDRA search was also performed among all AEs for 'pulse rate increase' including the PTs 'heart rate increased', 'palpitations', 'sinus tachycardia', 'tachycardia' and 'tachycardia paroxysmal'.

CVOT

Mean baseline pulse rate was 72.06 bpm. During treatment with semaglutide, the estimated mean pulse rate increased from initiation of treatment until week 16 followed by a decline that continued until one year of treatment. Thereafter the pulse rate remained stable at a higher than baseline level until the end of the 104-week treatment period.

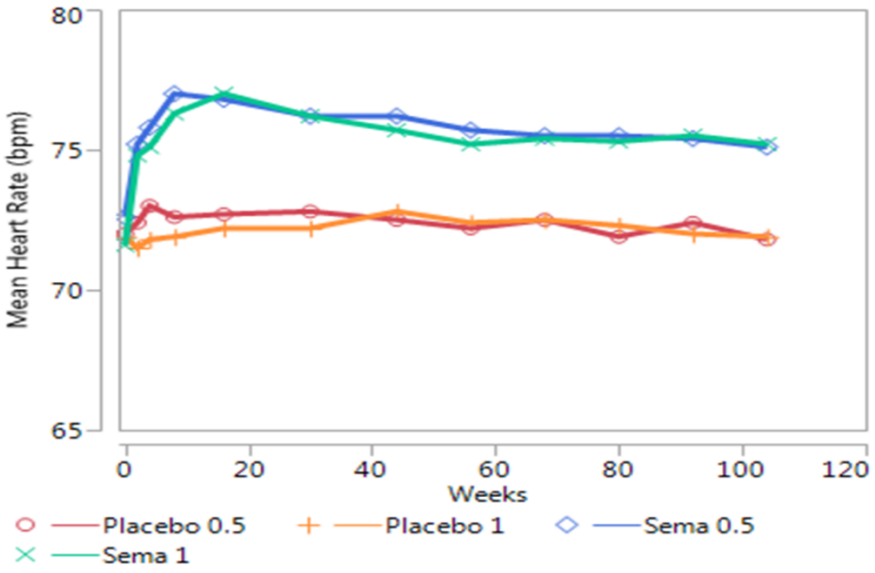
Table 150 Statistical Analysis of Pulse Rate (bpm) – SAS On-Treatment - CVOT

	SAS	N	Estimate	SE	95% CI	p-value
Mean at week 104 (year 2)						
Sema 0.5 mg	823	614	74.91	0.36		
Sema 1.0 mg	819	598	75.24	0.37		
Placebo 0.5 mg	819	628	72.16	0.36		
Placebo 1.0 mg	825	628	72.04	0.36		
Change from baseline at week 104 (year 2)						
Sema 0.5 mg	823	614	2.85	0.36		
Sema 1.0 mg	819	598	3.18	0.37		
Placebo 0.5 mg	819	628	0.10	0.36		
Placebo 1.0 mg	825	628	-0.02	0.36		
Treatment difference at week 104 (year 2)						
Sema 0.5 mg - Placebo 0.5 mg			2.75		[1.75 ; 3.75]	<.0001
Sema 1.0 mg - Placebo 1.0 mg			3.20		[2.20 ; 4.21]	<.0001

Note: The post-baseline responses are analysed using a mixed model for repeated measurements (MMRM) with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.
Abbreviations: CI: confidence interval; MMRM: mixed model for repeated measurements; N: number of subjects contributing to analysis: SE: standard error; sema: semaglutide.
Source: Table 2-67 ISS

The over time trends in heart rate are presented below.

Figure 55 Heart Rate Over Time by Treatment Arm - CVOT



Source: Reviewer generated using data from Response to Information request dated 09/01/2017

Consistent with the increase in mean pulse rate, categorical increases in resting pulse (in the categories >0, 5, 10, 15 or 20 beats/min) during treatment and at end-of-treatment were

generally observed in a higher proportion of patients with semaglutide than with placebo, but with no indication of a semaglutide dose-response.

MedDRA search

In the CVOT, the proportion of patients with pulse rate AEs tended to be slightly higher with semaglutide (0.5 mg: 1.8%; 1.0 mg: 1.5%) than with placebo (1.0%). Only one event was an SAE (tachycardia, patient ID 632014), 68 year old M receiving semaglutide 1 mg reported with tachycardia in the context of pulmonary embolism.

Table 151 Pulse Rate Adverse Events - MedDRA Search - by System Organ Class, High Level Group Term and Preferred Term CVOT - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1644	3035		
All events	15	(1.8)	17	1.1	12	(1.5)	13	0.9	17	(1.0)	19	0.6
Cardiac disorders	13	(1.6)	15	1.0	12	(1.5)	13	0.9	14	(0.9)	15	0.5
Cardiac arrhythmias	7	(0.9)	8	0.5	6	(0.7)	6	0.4	9	(0.5)	9	0.3
Tachycardia	4	(0.5)	5	0.3	5	(0.6)	5	0.3	5	(0.3)	5	0.2
Sinus tachycardia	3	(0.4)	3	0.2	1	(0.1)	1	<0.1	3	(0.2)	3	<0.1
Tachycardia paroxysmal									1	(<0.1)	1	<0.1
Cardiac disorder signs and symptoms	6	(0.7)	7	0.5	6	(0.7)	7	0.5	5	(0.3)	6	0.2
Palpitations	6	(0.7)	7	0.5	6	(0.7)	7	0.5	5	(0.3)	6	0.2
Investigations	2	(0.2)	2	0.1					4	(0.2)	4	0.1
Cardiac and vascular investigations (excl enzyme tests)	2	(0.2)	2	0.1					4	(0.2)	4	0.1
Heart rate increased	2	(0.2)	2	0.1					4	(0.2)	4	0.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Modified from Table 7.9.231 ISS

Phase 3 trials

Across the phase 3 trials excluding the CVOT, pulse rate was increased during treatment with semaglutide. The change in pulse rate was analyzed in each of the phase 3 trials using the standard MMRM analysis method. At end-of-treatment, the estimated mean pulse rate in the phase 3 trials had increased by 1 to 6 beats per minute with both semaglutide doses.

Table 152 Estimated Changes in Pulse Rate (bpm) - FAS On-Treatment - Individual Phase 3 Trials

Trial	Semaglutide 0.5 mg		Semaglutide 1.0 mg	
	Change[a] Estimate (SE)	Treatment difference[b] ETD (95% CI)	Change[a] Estimate (SE)	Treatment difference[b] ETD (95% CI)
3623 vs Placebo (Mono)	2.35 (0.77)	2.89 [0.74; 5.04]	2.43 (0.77)	2.97 [0.83; 5.12]
3626 vs Sita (OADs)	1.58 (0.42)	1.02 (-0.12; 2.17)	1.82 (0.42)	1.27 (0.11; 2.42)
3624 vs Exe ER (OADs)			2.11 (0.44)	1.03 [-0.19; 2.25]
3625 vs IGlar (OADs)	2.31 (0.47)	2.36 (1.07; 3.65)	3.14 (0.48)	3.19 (1.88; 4.50)
3627 vs Placebo (insulin)	0.83 (0.81)	1.63 (-0.62; 3.88)	3.95 (0.82)	4.74 (2.48; 7.01)
4092 vs Sita (Mono), JP	4.54 (0.79)	3.41 (1.22; 5.59]	6.08 (0.83)	4.94 [2.69; 7.19)
4091 vs OAD (OAD), JP	4.16 (0.56)	2.58 (0.70; 4.46)	4.94 (0.57)	3.36 (1.46; 5.26)

Notes: [a] Change from baseline to end-of-trial; [b] Treatment difference (sema-comparator) in change from baseline to end-of-trial. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.
Abbreviations: CI: confidence interval; Exe ER: exenatide extended release; ETD: estimated treatment difference; IGlar: insulin glargine; JP: Japan; mono: monotherapy; OAD: oral antidiabetic drug; SE: standard error; sita: sitagliptin.
Source: Table 2-70 ISS

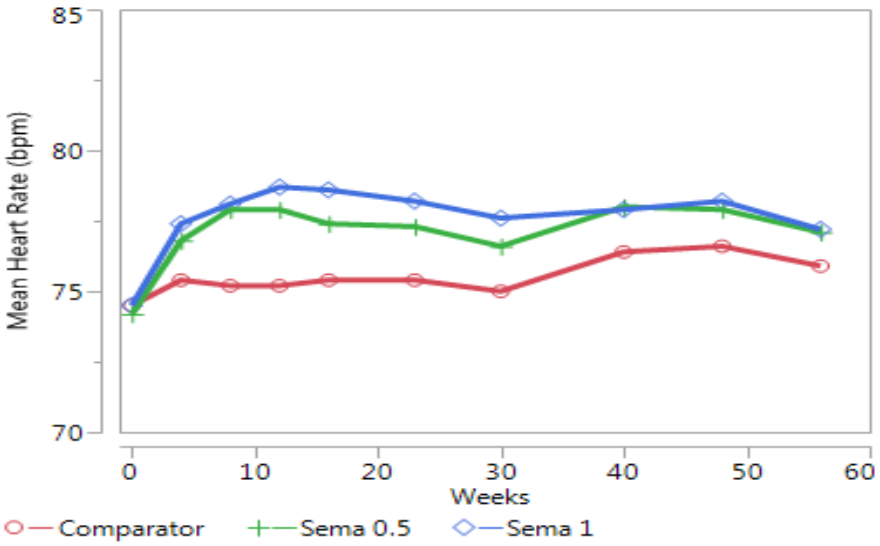
The pulse rate changes were consistent among non-GLP-1 RA comparators including placebo (trials 3623 and 3627), sitagliptin (trials 3626 and 4092), IGlar (trial 3627) and OADs (trial 4091). In trial 3624 semaglutide 1 mg vs exenatide ER

With semaglutide 1 mg and exenatide ER, the pulse rate increased from baseline until weeks 16 and 8, respectively. The pulse rate subsequently remained relatively stable in both treatment groups until week 48, where after it decreased but remained above baseline through week 56. The increase from baseline in pulse rate did not differ significantly between semaglutide 1 mg (2.11 beats/min) and exenatide ER (1.08 beats/min) with an estimated treatment difference of 1.03 beats/min [-0.19;2.25]95%CI.

There was a trend towards a semaglutide dose-response with respect to mean changes in pulse rate in the phase 3 trials excluding the CVOT. However, exposure-response analyses showed no exposure-response relationship for the change in pulse rate from baseline to end of treatment across the exposure range associated with 0.5 mg and 1.0 mg semaglutide.

The changes in heart rate over time are shown below.

Figure 56 Heart Rate Over Time by Treatment Arm – Phase 3 Pool



Source: Reviewer generated using data from Response to Information request dated 09/01/2017

Placebo pool

Heart rate changes with semaglutide in placebo-controlled trials were consistent with changes in the phase 3 pool (see trials 3623, and 3727 in Table 152 above).

Reviewer comment: Semaglutide treatment was associated with a slight increase in heart rate which was expected with this drug class. Despite some small differences in pulse rate AEs, the body of data does not support an increase in clinical events related to increase in heart rate.

8.4.8. Electrocardiograms (ECGs)

A routine ECG (12-lead) was obtained at baseline, end-of-treatment and at follow-up across the phase 3 trials, and ECGs were obtained at three additional visits during the treatment period of trial 3744 (CVOT).

All ECG recordings, including those from unscheduled visits, were evaluated by the investigator and rated as 'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant'. Any new findings or deterioration of previous findings observed during the trial were to be recorded as AEs/SAEs if they fulfilled the criteria for AEs/SAEs.

In addition to the investigator-performed evaluation of ECGs, central assessments were performed in all phase 3 trials by an external vendor (b) (4) where

an experienced reader assessed the ECGs for signs of ischemia, rhythm/conduction disorder or any other abnormalities. ECG abnormalities were categorized as (existing or new onset since baseline) infarction, ischemia, left bundle branch block, first degree AV block, second degree AV block, third degree AV block or other abnormalities.

CVOT

Central ECG reading

At baseline 11.8% of patients had signs of infarction, 3.1% had ischemia, 2.3% had left bundle branch block, 10.9% had first degree AV block, one patient had second degree AV block and none had third degree AV block.

No new AV-block abnormalities were identified by the scheduled ECG assessments. New onset abnormalities of infarction, ischemia and left bundle branch block identified during the treatment period were overall balanced between the treatment groups.

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Table 153 Central Reading of ECG Abnormalities – FAS In-Trial - CVOT

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo 0.5 mg N (%)	Placebo 1.0 mg N (%)
Number of subjects	826	822	824	825
Week 0 (baseline)				
Infarction	82 (10.0)	103 (12.6)	103 (12.5)	99 (12.1)
Ischemia	25 (3.1)	21 (2.6)	30 (3.7)	25 (3.1)
Left bundle branch block	22 (2.7)	13 (1.6)	20 (2.4)	22 (2.7)
First Degree AV Block	73 (8.9)	101 (12.3)	106 (12.9)	77 (9.4)
Second Degree AV Block		1 (0.1)		
Third degree AV Block				
Other abnormality	416 (50.8)	417 (50.9)	390 (47.5)	400 (48.8)
Week 56 (year 1)				
New onset Infarction	1 (0.1)	2 (0.3)	3 (0.4)	3 (0.4)
New onset Ischemia	3 (0.4)	2 (0.3)	5 (0.7)	2 (0.3)
New onset Left bundle branch block	3 (0.4)	2 (0.3)	1 (0.1)	2 (0.3)
New onset First Degree AV Block				
New onset Second Degree AV Block				
New onset Third degree AV Block				
New onset Other abnormality				
No abnormality	326 (42.5)	318 (41.8)	301 (39.8)	323 (42.9)
Week 104 (year 2)				
New onset Infarction		2 (0.3)	6 (0.8)	3 (0.4)
New onset Ischemia	5 (0.7)	3 (0.4)	5 (0.7)	1 (0.1)
New onset Left bundle branch block	1 (0.1)	6 (0.8)	1 (0.1)	2 (0.3)
New onset First Degree AV Block				
New onset Second Degree AV Block				
New onset Third degree AV Block				
New onset Other abnormality				
No abnormality	332 (45.7)	306 (42.4)	295 (41.1)	306 (43.0)
Week 109 (end-of-trial)				
New onset Infarction		1 (0.1)	3 (0.4)	5 (0.7)
New onset Ischemia	4 (0.6)	2 (0.3)	4 (0.6)	1 (0.1)
New onset Left bundle branch block	1 (0.1)	4 (0.6)	1 (0.1)	3 (0.4)
New onset First Degree AV Block				
New onset Second Degree AV Block				
New onset Third degree AV Block				
New onset Other abnormality				
No abnormality	340 (48.0)	318 (45.4)	289 (41.6)	314 (44.2)

Notes: New onset is evaluated in relation to baseline status. All available data are shown. For each visit the same subject may have multiple recordings for different parameters.
Abbreviations: N: number of subjects in the summary statistic; sema: semaglutide; %: percentage of subjects.
Source: Table 2-72 ISS

A total of 87 ECGs indicating new ischemia/infarction since last ECG reading were sent for adjudication by the EAC; of these 8 events were confirmed by the EAC

Abnormalities in ECG rhythm identified at baseline were similar across treatment groups 3.0% had atrial fibrillation and 9.2% of patients had other rhythm abnormalities. New onset rhythm abnormalities were identified during the trial period; events were well-balanced across semaglutide and placebo groups.

Table 154 Central Reading of ECG Rhythm Type– FAS In-Trial - CVOT

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo 0.5 mg N (%)	Placebo 1.0 mg N (%)
Number of subjects	826	822	824	825
Week 0 (baseline)				
Sinus	767 (93.9)	771 (94.0)	768 (93.9)	769 (94.1)
Atrial fibrillation	24 (2.9)	22 (2.7)	33 (4.0)	20 (2.4)
Other	71 (8.7)	83 (10.1)	64 (7.8)	82 (10.0)
Week 56 (year 1)				
New onset rhythm - Sinus	2 (0.3)	3 (0.4)		5 (0.7)
New onset rhythm - Atrial fibrillation	5 (0.7)	5 (0.7)	4 (0.5)	8 (1.1)
New onset rhythm - other	30 (3.9)	37 (4.9)	29 (3.8)	31 (4.1)
Week 104 (year 2)				
New onset rhythm - Sinus	3 (0.4)	2 (0.3)		5 (0.7)
New onset rhythm - Atrial fibrillation	3 (0.4)	9 (1.2)	7 (1.0)	7 (1.0)
New onset rhythm - other	42 (5.8)	50 (6.9)	43 (6.0)	47 (6.6)
Week 109 (end-of-trial)				
New onset rhythm - Sinus	4 (0.6)	2 (0.3)	1 (0.1)	3 (0.4)
New onset rhythm - Atrial fibrillation	3 (0.4)	7 (1.0)	8 (1.2)	7 (1.0)
New onset rhythm - other	49 (7.0)	48 (6.8)	52 (7.5)	48 (6.8)

Notes: New onset is evaluated in relation to baseline status. All available data are shown. For each visit the same subject may have multiple recordings for different parameters.
Abbreviations: N: number of subjects in the summary statistic; sema: semaglutide; %: percentage of subjects.
Source: Table 2-73 ISS

Investigator evaluation of ECGs

The majority (74.9%) of the measurements were 'normal' at baseline and week 30, with no apparent difference between semaglutide and placebo treatment groups of the CVOT. Shifts from normal to other categories are summarized below.

Table 155 Shifts from Baseline in ECG Investigator Assessments after 1 and 2 Years in Trial – FAS In-Trial – CVOT

		Normal at baseline				Abnormal at baseline	
		Abnormal		Abn. & clin.sign		Abn. & clin.sign	
	N	N	(%)	N	(%)	N	(%)
Week 56 (year 1)							
Sema 0.5 mg	763	58	(24.0)	1	(0.4)	11	(2.3)
Sema 1.0 mg	759	60	(28.7)	3	(1.4)	5	(1.0)
Placebo 0.5 mg	756	63	(27.5)	1	(0.4)	7	(1.4)
Placebo 1.0 mg	752	49	(21.8)	4	(1.8)	10	(2.0)
Week 104 (year 2)							
Sema 0.5 mg	723	58	(25.1)	3	(1.3)	7	(1.5)
Sema 1.0 mg	721	68	(33.8)			4	(0.8)
Placebo 0.5 mg	715	70	(32.1)	3	(1.4)	8	(1.7)
Placebo 1.0 mg	710	57	(26.9)	5	(2.4)	7	(1.5)

Notes: All available data are shown. For each visit the same subject may have multiple recordings for different parameters.
Abbreviations: Abn. & clin.sign: abnormal and clinically significant; N: number of subjects in the summary statistic; sema: semaglutide; %: percentage of subjects.
Source: Table 2-74 ISS

MedDRA searches related to ECG abnormalities (CVOT)

Overall, AEs related to ECG abnormalities were consistent with the outcome of the investigator evaluation and central reading of the ECGs.

Table 156 PR Interval Prolongation and AV-block (MedDRA Search) – SAS On-Treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N	823				819				1644			
PYE (year)	1488				1444				3035			
All events	6	(0.7)	6	0.4	6	(0.7)	6	0.4	17	(1.0)	17	0.6
Cardiac disorders												
Cardiac arrhythmias												
AV block first degree	4	(0.5)	4	0.3	4	(0.5)	4	0.3	8	(0.5)	8	0.3
AV block second degree					2	(0.2)	2	0.1	2	(0.1)	2	<0.1
AV block	1	(0.1)	1	<0.1					2	(0.1)	2	<0.1
AV block complete	1	(0.1)	1	<0.1					5	(0.3)	5	0.2

Abbreviations: AV: atrioventricular; N: number of subjects with at least one event; E: number of events; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.
Source: Table 2-75 ISS

In the CVOT, the proportion of patients with events identified by MedDRA search for cardiac arrhythmia were similar with semaglutide (0.5 mg: 9.7%; 1.0 mg: 9.8%) and placebo (10.3%). Approximately half of the AEs of cardiac arrhythmia were reported as SAEs. The applicant reported a total of 16 patients had events with fatal outcome; 7 (0.4%) patients with semaglutide and 9 patients (0.5%) with placebo).

Table 157 Arrhythmia Adverse Events - MedDRA Search - by High Level Group Term and Preferred Term CVOT - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1644	3035		
All events	80	(9.7)	96	6.5	80	(9.8)	108	7.5	169	(10.3)	221	7.3
Cardiac disorders	66	(8.0)	82	5.5	70	(8.5)	93	6.4	151	(9.2)	193	6.4
Cardiac arrhythmias	62	(7.5)	75	5.0	65	(7.9)	86	6.0	147	(8.9)	187	6.2
Atrial fibrillation	20	(2.4)	21	1.4	19	(2.3)	26	1.8	56	(3.4)	64	2.1
Ventricular tachycardia	1	(0.1)	1	<0.1	7	(0.9)	7	0.5	4	(0.2)	4	0.1
Bundle branch block right	6	(0.7)	6	0.4	6	(0.7)	6	0.4	7	(0.4)	7	0.2
Ventricular extrasystoles	6	(0.7)	7	0.5	6	(0.7)	6	0.4	10	(0.6)	10	0.3
Tachycardia	4	(0.5)	5	0.3	5	(0.6)	5	0.3	5	(0.3)	5	0.2
Supraventricular extrasystoles	1	(0.1)	1	<0.1	5	(0.6)	5	0.3	4	(0.2)	4	0.1
Atrioventricular block first degree	4	(0.5)	4	0.3	4	(0.5)	4	0.3	8	(0.5)	8	0.3
Bundle branch block left	4	(0.5)	4	0.3	4	(0.5)	4	0.3	8	(0.5)	9	0.3
Arrhythmia	2	(0.2)	3	0.2	3	(0.4)	3	0.2	10	(0.6)	10	0.3
Cardiac arrest	3	(0.4)	3	0.2	2	(0.2)	2	0.1	4	(0.2)	4	0.1
Bradycardia	2	(0.2)	3	0.2	2	(0.2)	2	0.1	12	(0.7)	12	0.4
Atrial flutter	1	(0.1)	1	<0.1	2	(0.2)	2	0.1	9	(0.5)	9	0.3
Sinus node dysfunction	1	(0.1)	1	<0.1	2	(0.2)	2	0.1	2	(0.1)	2	<0.1
Supraventricular tachycardia	1	(0.1)	1	<0.1	2	(0.2)	2	0.1	4	(0.2)	5	0.2
Atrioventricular block second degree					2	(0.2)	2	0.1	2	(0.1)	2	<0.1
Ventricular fibrillation					2	(0.2)	2	0.1	3	(0.2)	3	<0.1
Sinus tachycardia	3	(0.4)	3	0.2	1	(0.1)	1	<0.1	3	(0.2)	3	<0.1
Defect conduction intraventricular	2	(0.2)	2	0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Cardio-respiratory arrest	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1				
Cardiac flutter					1	(0.1)	1	<0.1				
Conduction disorder					1	(0.1)	1	<0.1				
Nodal rhythm					1	(0.1)	1	<0.1				
Sinus bradycardia	2	(0.2)	2	0.1					6	(0.4)	7	0.2
Atrioventricular block	1	(0.1)	1	<0.1					2	(0.1)	2	<0.1
Atrioventricular block complete	1	(0.1)	1	<0.1					5	(0.3)	5	0.2
Bundle branch block bilateral	1	(0.1)	1	<0.1								
Nodal arrhythmia	1	(0.1)	1	<0.1					1	(<0.1)	1	<0.1
Ventricular arrhythmia	1	(0.1)	1	<0.1					1	(<0.1)	1	<0.1
Ventricular tachyarrhythmia	1	(0.1)	1	<0.1					1	(<0.1)	1	<0.1
Atrial tachycardia									1	(<0.1)	1	<0.1
Extrasystoles									2	(0.1)	2	<0.1
Sinus arrhythmia									2	(0.1)	2	<0.1
Supraventricular tachyarrhythmia									1	(<0.1)	1	<0.1
Tachycardia paroxysmal									1	(<0.1)	1	<0.1
Ventricular asystole									1	(<0.1)	1	<0.1
Cardiac disorder signs and symptoms	6	(0.7)	7	0.5	6	(0.7)	7	0.5	5	(0.3)	6	0.2
Palpitations	6	(0.7)	7	0.5	6	(0.7)	7	0.5	5	(0.3)	6	0.2
Nervous system disorders	8	(1.0)	8	0.5	9	(1.1)	11	0.8	15	(0.9)	16	0.5
Neurological disorders NEC	8	(1.0)	8	0.5	9	(1.1)	11	0.8	15	(0.9)	16	0.5
Syncope	8	(1.0)	8	0.5	7	(0.9)	9	0.6	15	(0.9)	16	0.5
Loss of consciousness					2	(0.2)	2	0.1				
Investigations	4	(0.5)	4	0.3	4	(0.5)	4	0.3	10	(0.6)	11	0.4
Cardiac and vascular investigations (excl enzyme tests)	4	(0.5)	4	0.3	4	(0.5)	4	0.3	10	(0.6)	11	0.4
Electrocardiogram QT prolonged	1	(0.1)	1	<0.1	2	(0.2)	2	0.1	1	(<0.1)	1	<0.1
Electrocardiogram QRS complex prolonged					1	(0.1)	1	<0.1				
Heart rate irregular					1	(0.1)	1	<0.1				
Heart rate increased	2	(0.2)	2	0.1					4	(0.2)	4	0.1
Heart rate abnormal	1	(0.1)	1	<0.1								
Electrocardiogram abnormal									2	(0.1)	2	<0.1
Electrocardiogram change									4	(0.2)	4	0.1
General disorders and administration site conditions	2	(0.2)	2	0.1					1	(<0.1)	1	<0.1
Fatal outcomes	2	(0.2)	2	0.1					1	(<0.1)	1	<0.1
Sudden cardiac death	1	(0.1)	1	<0.1								
Sudden death	1	(0.1)	1	<0.1					1	(<0.1)	1	<0.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Table 7.9.343 ISS

My analysis of fatal arrhythmias revealed a higher number of patients compared to what the

applicant reported, however, there was not imbalance between the treatment groups. The results of my analysis are presented below.

Table 158 Fatal Arrhythmias by HLGT and PT – CVOT – in trial

High Level Group Term	Dictionary Derived Term	Placebo N=1649	Sema N=1648
Cardiac arrhythmias			
	Arrhythmia	0 (0.00%)	1 (0.06%)
	Atrioventricular block complete	1 (0.06%)	1 (0.06%)
	Atrioventricular block first degree	1 (0.06%)	0 (0.00%)
	Bradycardia	1 (0.06%)	0 (0.00%)
	Cardiac arrest	5 (0.30%)	6 (0.36%)
	Cardio-respiratory arrest	0 (0.00%)	2 (0.12%)
	Sinus bradycardia	0 (0.00%)	1 (0.06%)
	Ventricular asystole	1 (0.06%)	0 (0.00%)
	Ventricular fibrillation	2 (0.12%)	0 (0.00%)
	Ventricular tachycardia	1 (0.06%)	1 (0.06%)
Cardiac disorder signs and symptoms			
	Sudden cardiac death	0 (0.00%)	1 (0.06%)
	Sudden death	1 (0.06%)	1 (0.06%)
Total		11 (0.67%)	11(0.67%)

Source: Reviewer generated using ADSL and ADAE datasets

Phase 3 trials excluding CVOT

Investigator-identified ECG changes were not frequent, and not imbalanced between the treatment groups.

AEs related to PR interval prolongation and AV-block

The proportion of patients with AEs were similar with semaglutide (0.5 mg: 0.2%; 1.0 mg: 0.3%) and comparator products (0.3%).

Table 159 PR Interval Prolongation and AV-block (MedDRA Search) – SAS On-Treatment – Phase 3 Pool

	Sema 0.5 mg N (Adj%)	E	Adj.R	Sema 1.0 mg N (Adj%)	E	Adj.R	Placebo N (Adj%)	E	Adj.R
N	1373			1777			1657		
PYE (year)	1165			1548			1467		
All events	3 (0.2)	3	0.2	6 (0.3)	6	0.4	4 (0.3)	4	0.3
Cardiac disorders									
Cardiac arrhythmias									
AV block first degree	2 (0.2)	2	0.2	4 (0.2)	4	0.3	1(<0.1)	1	<0.1
AV block second degree	1(<0.1)	1	<0.1	1(<0.1)	1	<0.1	1(<0.1)	1	<0.1
AV block complete							2 (0.1)	2	0.2
Investigations									
Cardiac and vascular investigations									
ECG PR prolongation				1(<0.1)	1	<0.1			

Note: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Abbreviations: Adj: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event

Source: Table 7-26 ISS

Events identified in placebo-controlled trials comprised a single event of atrioventricular block first degree in a patient receiving semaglutide 0.5 mg.

Cardiac arrhythmias

In the phase 3 pool, the proportion of patients with cardiac arrhythmia events were similar with semaglutide (0.5 mg: 2.4%; 1.0 mg: 2.8%) and comparator products (2.3%). The majority of AEs of cardiac arrhythmia were reported as non-serious AEs.

Table 160 Arrhythmia Adverse Events - MedDRA Search - by System Organ Class, High Level Group Term and Preferred Term - Summary - Phase 3 Pool - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
All events	34	(2.4)	39	3.3	50	(2.8)	53	3.4	38	(2.3)	39	2.6
Cardiac disorders	26	(1.8)	30	2.5	46	(2.5)	48	3.1	31	(1.9)	32	2.2
Cardiac arrhythmias	21	(1.5)	24	2.1	38	(2.1)	40	2.6	25	(1.5)	26	1.8
Atrial fibrillation	6	(0.4)	6	0.5	7	(0.4)	7	0.5	7	(0.4)	7	0.5
Ventricular extrasystoles	2	(0.1)	2	0.2	6	(0.3)	6	0.4	1	(<0.1)	1	<0.1
Atrioventricular block first degree	2	(0.2)	2	0.2	4	(0.2)	4	0.3	1	(<0.1)	1	<0.1
Extrasystoles					4	(0.2)	4	0.3				
Tachycardia	4	(0.3)	5	0.5	3	(0.2)	3	0.2	2	(0.1)	2	0.1
Supraventricular extrasystoles	3	(0.2)	3	0.3	3	(0.1)	3	0.2				
Bundle branch block right	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1	5	(0.3)	6	0.4
Bundle branch block left					2	(0.1)	2	0.1	1	(<0.1)	1	<0.1
Bradycardia	2	(0.2)	2	0.2	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Atrioventricular block second degree	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Arrhythmia					1	(<0.1)	1	<0.1				
Bundle branch block					1	(<0.1)	2	0.1				
Cardio-respiratory arrest					1	(<0.1)	1	<0.1				
Defect conduction intraventricular					1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Sinus arrhythmia					1	(<0.1)	1	<0.1				
Sinus tachycardia					1	(<0.1)	1	<0.1				
Cardiac arrest	1	(<0.1)	1	<0.1								
Sinus node dysfunction	1	(<0.1)	1	<0.1								
Atrial flutter									1	(<0.1)	1	<0.1
Atrioventricular block complete									2	(0.1)	2	0.2
Bundle branch block bilateral									1	(<0.1)	1	<0.1
Sinus bradycardia									1	(<0.1)	1	<0.1
Cardiac disorder signs and symptoms	6	(0.4)	6	0.5	8	(0.4)	8	0.5	6	(0.3)	6	0.4
Palpitations	6	(0.4)	6	0.5	8	(0.4)	8	0.5	6	(0.3)	6	0.4
Nervous system disorders	5	(0.4)	5	0.4	3	(0.2)	3	0.2	4	(0.2)	4	0.3
Neurological disorders NEC	5	(0.4)	5	0.4	3	(0.2)	3	0.2	4	(0.2)	4	0.3
Syncope	2	(0.2)	2	0.2	3	(0.2)	3	0.2	4	(0.2)	4	0.3
Loss of consciousness	3	(0.2)	3	0.2								
Investigations	4	(0.3)	4	0.4	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Cardiac and vascular investigations (excl enzyme tests)	4	(0.3)	4	0.4	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Electrocardiogram PR prolongation					1	(<0.1)	1	<0.1				
Electrocardiogram change					1	(<0.1)	1	<0.1				
Heart rate increased	3	(0.2)	3	0.3					2	(0.1)	2	0.1
Electrocardiogram QT prolonged	1	(<0.1)	1	<0.1								
Electrocardiogram abnormal									1	(<0.1)	1	<0.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Modified from table 7.9.339 ISS

No effect of semaglutide dose level (0.5 mg and 1.0 mg) was identified.

Placebo pool

In placebo-controlled trials (trials 3623 and 3627) AEs of arrhythmia as identified byMedDRA search were few (6 events in 5 (1.0%) patients with semaglutide and 3 events in 3 (1.1%) patients with placebo), with no indications of an impact of semaglutide overall or by dose level.

8.4.9. QT

The effect of semaglutide on the QTc interval, PR interval, and pulse rate has been assessed at the 0.5 mg and 1.0 mg dose levels as well as at the supratherapeutic dose level of 1.5 mg in a dedicated QTc trial (trial 3652). This study was reviewed by Dr Janell Chen from Interdisciplinary Review Team for QT Studies Consultation, and the conclusion was that no significant QTc prolongation effect of semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) wasdetected in this Thorough QT (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. Please see review by Dr Chen for details.

8.4.10. Immunogenicity

See section 8.5 for evaluation of immunogenicity concerns. Additionally, please see Immunogenicity review by Dr Mohanraj Manageeswaran.

8.5. Analysis of Submission-Specific Safety Issues

Several medical events of special interest (MESIs) were pre-defined for the semaglutide clinical program, based on the known and potential risks of GLP-1 RAs. Discussion of the cardiovascular outcomes from SUSTAIN 6 can be found in section 6.6 of this review.
CV outcomes from the rest of the semaglutide clinical program, as well as other medical events of special interest.

Additionally, a new safety issue was identified in the CVOT. It appears that treatment with either dose of semaglutide increased the risk of diabetic retinopathy complications over the 2 year duration of the study, and this safety issue will also be discussed in this section of the review.

8.5.1. Cardiovascular Adverse Events

CV events were adjudicated in the semaglutide development program.

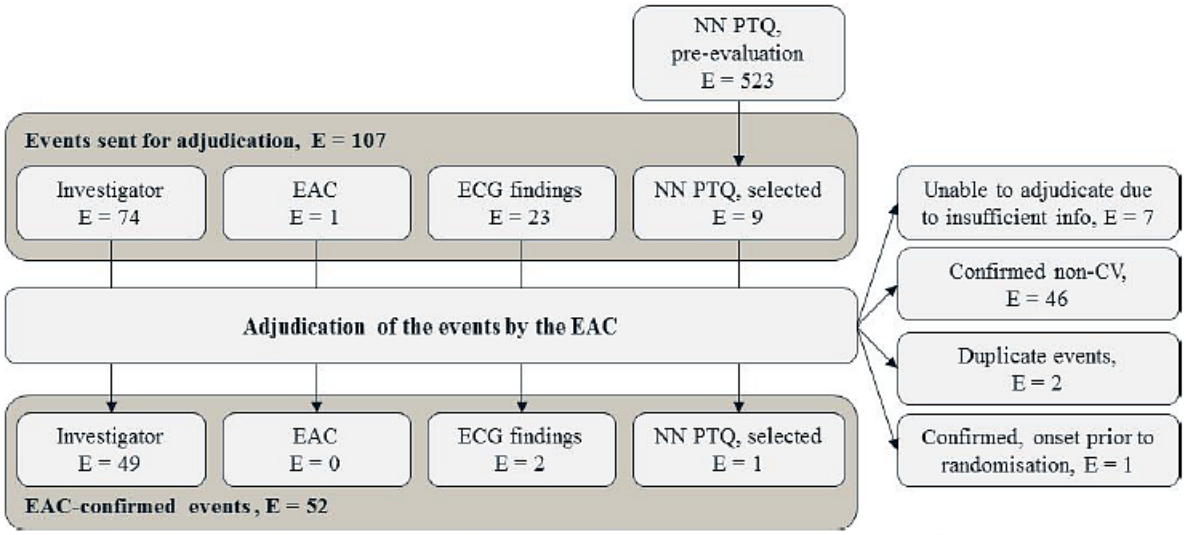
The cardiovascular safety of semaglutide was primarily evaluated in a dedicated CVOT (trial 3744 - SUSTAIN 6) in patients with T2DM at high risk of CV events. The primary endpoint in the CVOT was time from randomization to first occurrence of MACE, defined as CV death, non-fatal MI, or non-fatal stroke. The results of the primary endpoint are discussed in section 6.7 of this review and will not be repeated here.

Electrocardiogram, pulse rate, PR and QT interval are discussed in other sections of this review. The same applies to changes in blood pressure and lipids.

Phase 3 pool

An overview of the event adjudication process numbers is presented below.

Figure 57 Event Adjudication Process Flow for Cardiovascular Events – Phase 3 Pool



Note: Confirmed events with onset prior to randomisation are included in number of EAC-confirmed events.
Abbreviations: E: number of events; EAC: event adjudication committee; ECG: electrocardiogram; NN PTQ: Novo Nordisk preferred term query.

Source: Figure 2-26 ISS

A total of 52 CV events were confirmed by the EAC; 50 events had EAC-onset during the in-trial period; 1 event (transient ischemic attack) with semaglutide 1 mg had onset 2 days prior to randomization, and 1 event (coronary revascularization) with semaglutide 1 mg occurred after the in-trial period. The overall confirmation rate of CV events was 48.6%. While there were differences between the treatment arms for the confirmation rate for events identified by ECG, the number of events is small, and the differences are likely to be due to chance.

Table 161 EAC Confirmation Rates (%) of CV Events by Reporting Method – Phase 3 Pool

	Investigator		PTQ search		ECG		EAC		Total	
	E	Conf. rate	E	Conf. rate	E	Conf. rate	E	Conf. rate	E	Conf. rate
CV events -All	74	66.2%	9	11.1%	23	8.7%	1	0.0%	107	48.6%
Semaglutide	52	65.4%	6	0.0%	15	13.3%	0	0.0%	73	49.3%
Semaglutide 0.5 mg	18	72.2%	2	0.0%	6	33.3%	0	0.0%	26	57.7%
Semaglutide 1.0 mg	34	61.8%	4	0.0%	9	0.0%	0	0.0%	47	44.7%
Comparators	22	68.2%	3	33.3%	8	0.0%	1	0.0%	34	47.1%

Notes: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).
Abbreviations: Conf.: confirmation; EAC: event adjudication committee; CV: cardiovascular; PTQ: preferred term query.

Source: Table 2-38 ISS

A total of 7 CV events in 7 patients of the phase 3 pool (2 events with semaglutide 0.5 mg, 3 events with semaglutide 1 mg and 2 events with placebo) could not be adjudicated by the EAC due to insufficient information. Details are presented below.

Table 162 Patients with CV Events Where EAC was Unable To Adjudicate Due To Lack Of Information – Phase 3 Pool

Subject	Age/Sex/BMI	Event source	EAC category	Preferred term Reported term for the AE	Other confirmed CV events
Semaglutide 0.5 mg					
3625/613002	47/M/33.44	Inv.	CVE	Ischaemic stroke Basilar artery ischemic stroke	CV death on the same day
3627/363002	79/F/33.36	Inv.	CVE	Transient ischaemic attack Transient ischemic attack (probable)	No
Semaglutide 1.0 mg					
3624/776004	50/M/44.32	Inv.	CVE	Transient ischaemic attack Transient ischemic attack	No
3626/533017	59/F/45.54	PT search	Heart failure	Left ventricular dysfunction Left ventricular diastolic dysfunction	No
3626/921003	60/F/35.16	Inv.	CVE	Cerebrovascular accident Stroke	No
Comparator					
3626/540004	50/F/32.28	Inv.	CVE	Ischaemic stroke Ischemic stroke	No
4091/117002	64/M/26.33	Inv.	Heart failure	Cardiac failure Cardiac failure	No

Abbreviations: AE: adverse event; CVE: cerebrovascular event; EAC: event adjudication committee; F: female; Inv.: investigator; M: male; PT: preferred term.
Source: Table 2-39 ISS

EAC-confirmed events

A total of 50 CV events in 41 patients were confirmed by the EAC with onset during the in-trial period of the phase 3 trials, overall balanced between treatment groups.

Table 163 EAC-Confirmed Cardiovascular Events – SAS In-Trial – Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj%)	E	Adj.R	N	(Adj%)	E	Adj.R	N	(Adj%)	E	Adj.R
Number of subjects	1373				1777				1657			
PYO	1229				1685				1545			
Cardiovascular events	13	(1.0)	15	1.3	14	(0.8)	19	1.2	14	(0.8)	16	1.0
Cardiovascular death	5	(0.4)	5	0.4	1	(<0.1)	1	<0.1	4	(0.2)	4	0.2
Cardiovascular death	4	(0.3)	4	0.3	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Undetermined cause of death	1	(<0.1)	1	<0.1	0	(0.0)			3	(0.2)	3	0.2
Acute coronary syndrome	3	(0.2)	3	0.3	2	(0.1)	3	0.2	2	(0.1)	2	0.1
Acute MI	0	(0.0)			2	(0.1)	3	0.2	1	(<0.1)	1	<0.1
Silent MI	2	(0.2)	2	0.2	0	(0.0)			1	(<0.1)	1	<0.1
UAP req. hosp.	1	(<0.1)	1	<0.1	0	(0.0)			0	(0.0)		
Coronary revascularisation	3	(0.2)	3	0.3	7	(0.4)	8	0.5	4	(0.2)	4	0.2
Hosp. for heart failure	2	(0.1)	2	0.2	3	(0.2)	4	0.2	1	(<0.1)	1	<0.1
Cerebrovascular events	2	(0.2)	2	0.2	3	(0.2)	3	0.2	5	(0.3)	5	0.3
Stroke	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Transient ischaemic attack	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1

Notes: % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate. Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Abbreviations: Adj: adjusted; E: Number of events; EAC: (external) Event adjudication committee; Exe ER: exenatide extended release; IGlar: insulin glargine; N: Number of subjects with at least one event; NSTEMI: Non-ST-elevation myocardial infarction; OAD: oral antidiabetic drug; PYO: patient-years of observation; R: events per 100 years of PYO, Sita: sitagliptin; STEMI: ST-elevation myocardial infarction; %: percentage of subjects with at least one event.

Source: Table 2-40 ISS

Placebo pool

A total of 11 CV events in 9 patients were confirmed by the EAC with onset during the in-trial period of the placebo-controlled trials 3623 and 3627 combined. An additional confirmed event of transient ischemic attack with semaglutide 1 mg in trial 3627 had onset 2 days before randomization. Although, as seen below, the proportion of CV events was higher with semaglutide 0.5 mg vs semaglutide 1 mg, or placebo, the results are likely to be due to chance due to the small number of events.

Table 164 EAC-Confirmed Cardiovascular Events – SAS In-Trial – Placebo Pool

	Sema 0.5 mg N (Adj%)	E	Adj.R	Sema 1.0 mg N (Adj%)	E	Adj.R	Placebo N (Adj%)	E	Adj.R
Number of subjects	260			261			262		
Cardiovascular adverse events	5 (1.9)	6	3.4	2 (0.8)	3	1.7	2 (0.8)	2	1.2
Cardiovascular death	0 (0.0)			0 (0.0)			0 (0.0)		
Acute coronary syndrome	2 (0.8)	2	1.1	1 (0.4)	1	0.6	0 (0.0)		
Acute MI	0 (0.0)			1 (0.4)	1	0.6	0 (0.0)		
Silent MI	1 (0.4)	1	0.6	0 (0.0)			0 (0.0)		
UAP req. hosp.	1 (0.4)	1	0.6	0 (0.0)			0 (0.0)		
Coronary revascularisation	2 (0.8)	2	1.1	2 (0.8)	2	1.1	1 (0.4)	1	0.6
Hops. for heart failure	0 (0.0)			0 (0.0)			1 (0.4)	1	0.6
Cerebrovascular events	2 (0.8)	2	1.2	0 (0.0)			0 (0.0)		
Stroke	1 (0.4)	1	0.6	0 (0.0)			0 (0.0)		
Transient ischaemic attack	1 (0.4)	1	0.6	0 (0.0)			0 (0.0)		

Notes: Trials included: 3623 and 3627
Abbreviations: Adj: adjusted; E: number of events; MI: myocardial infarction; N: number of subjects from safety analysis set with at least one event; R: events per 100 PYO; UAP req. hosp.: unstable angina pectoris requiring hospitalisation; %: percentage of subjects with at least one event;
Source: Table 2-41 ISS

In conclusion, no imbalance was seen for adjudicated CV events in the phase 3 pool excluding CVOT, or the placebo pool. The small number of events precludes evaluation of individual components in these pools, and limits the interpretation of the analyses.

Hospitalization for heart failure – EAC-confirmed

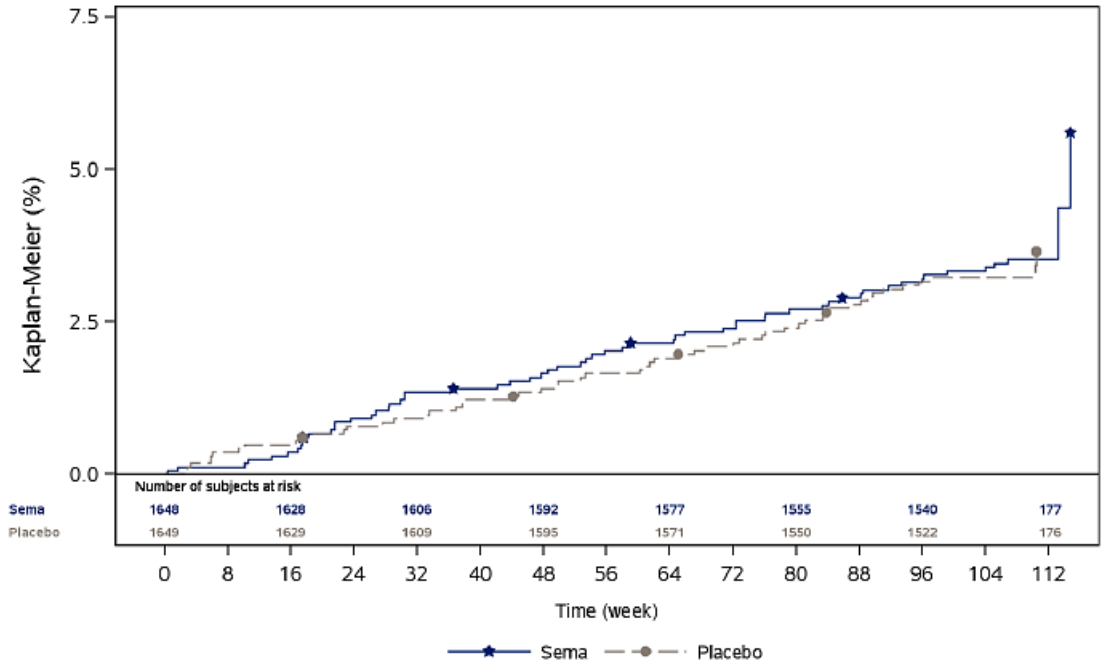
Heart failure requiring hospital admission was defined as a safety area of special interest in the semaglutide phase 3 trials. Heart failure requiring hospital admission was defined as a MESI, and it was adjudicated in all phase 3 trials. The applicant submitted the EAC charter, which included the definition for events of heart failure requiring hospitalization. While not presented here, I reviewed the definition used by the applicant and found it reasonable.

CVOT

First events

A total of 59 first events of hospitalization for heart failure were confirmed with semaglutide versus 54 with placebo for the FAS in-trial period of the CVOT. The analysis of treatment difference showed no difference, with a HR of 1.11 [0.77; 1.61] 95%CI; p=0.5735. The estimated cumulative risk of hospitalization for heart failure at week 104 was 3.4% with semaglutide and 3.2% with placebo. No effect of semaglutide dose level (0.5 mg and 1.0 mg) was apparent.

Figure 58 Kaplan Meier Plot of Time to First EAC-Confirmed Hospitalization for Heart Failure – FAS In–Trial - CVOT



Note: Numbers below the figure represents number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first outcome. Subjects are censored at their planned end-of-trial visit, deaths or last direct subject-site contact, whichever comes first.
Abbreviations: sema: semaglutide
Source: Figure 2-37 ISS

All events

In the CVOT, a total of 59 (3.6%) patients with semaglutide had 81 EAC-confirmed events of hospitalization for heart failure versus 54 patients (3.3%) with placebo having 71 events. The cause of death was judged as heart failure by the EAC in a total of 9 patients: 4 patients with semaglutide and 5 patients with placebo. No dose-dependence was apparent for semaglutide.

Table 165 EAC-Confirmed Hospitalization for Heart Failure – FAS In-Trial - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	826				822				1649			
PYO	1708.4				1699.8				3401.1			
Hosp. for heart failure	37	(4.5)	51	2.99	22	(2.7)	30	1.76	54	(3.3)	71	2.09
Cardiovascular death	21	(2.5)	21	1.2	23	(2.8)	23	1.4	46	(2.8)	46	1.4
Death due to heart failure	2	(0.2)	2	0.1	2	(0.2)	2	0.1	5	(0.3)	5	0.1

Abbreviations: hosp.: hospitalisation; N: number of subjects with at least one event; %: percentage of subjects with at least one event; E: number of events; PYO: patient-years of observation; R: events per 100 patient-years of observation.
Source: Table 2-61 ISS

While these results show a slight imbalance not favoring semaglutide, it is difficult to draw any conclusions given the overall small number of adjudicated events. Additionally, the imbalance was exclusively due to the 0.5 mg dose of semaglutide, whereas the 1 mg dose had a lower incidence of heart failure requiring hospitalization events compared to placebo. This makes it event more likely that the results are due to chance, as it is not obvious why the lower dose of semaglutide alone would have an increased risk.

Phase 3 trials excluding CVOT

In the phase 3 pool, the number of patients with EAC-confirmed events of heart failure requiring hospitalization was low (semaglutide: 5 patients with 6 events; comparator products: 1 patient with 1 event, and the proportions of patients with events were similar with semaglutide (0.5 mg: 0.1%; sema 1.0 mg: 0.2%) and comparator products (0.1%).

Placebo pool

A single event was identified in the placebo pool, in a patient receiving placebo.

Reviewer comment: While the number of events was small, the data does not appear to support an increased risk in heart failure events with semaglutide vs comparator, in any of the studied pools. This is in line with information known for other members of the GLP-1 RA class.

CV events MedDRA search

In addition to the evaluation of the cardiovascular safety of semaglutide based on adjudicated CV events, a predefined MedDRA search of the adverse events dataset (containing all reported events regardless of adjudication status) was performed to capture all CV events. This search included terms from the SMQs for 'Central nervous system disorders', 'Vasculitis', 'Ischemic heart disease', 'Cardiac arrhythmias', 'Cardiac failure', 'Cardiomyopathy', 'Embolic and thrombotic events', 'Shock', and 'Torsade de pointes/QT prolongation'.

CVOT

Overall, there was a trend towards fewer (both for AEs and SAEs) events with semaglutide (0.5 mg and 1.0 mg) compared with placebo. Events were reported in 32.4% of subjects treated with semaglutide 0.5 mg, 28.8% of subjects treated with semaglutide 1 mg, and 34.9% of subjects treated with placebo. No clear evidence of increased risk was seen for individual adverse event terms (by high level term or by preferred term).

Table 166 Overview of Cardiovascular Disorders (MedDRA Search) – FAS In-Trial - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	826				822				1649			
PYO	1708.4				1699.8				3401.1			
Events	268	(32.4)	562	32.9	237	(28.8)	500	29.4	576	(34.9)	1282	37.7
Serious												
Yes	160	(19.4)	317	18.6	134	(16.3)	265	15.6	359	(21.8)	680	20.0
No	169	(20.5)	245	14.3	164	(20.0)	235	13.8	376	(22.8)	602	17.7
Severity												
Severe	90	(10.9)	160	9.4	77	(9.4)	137	8.1	200	(12.1)	350	10.3
Moderate	131	(15.9)	214	12.5	123	(15.0)	194	11.4	316	(19.2)	515	15.1
Mild	143	(17.3)	188	11.0	125	(15.2)	169	9.9	292	(17.7)	417	12.3
Outcome												
Recovered	202	(24.5)	399	23.4	177	(21.5)	339	19.9	459	(27.8)	916	26.9
Fatal	24	(2.9)	29	1.7	17	(2.1)	21	1.2	46	(2.8)	60	1.8
Recovering	13	(1.6)	14	0.8	8	(1.0)	9	0.5	20	(1.2)	24	0.7
Recovered with sequelae	5	(0.6)	5	0.3	12	(1.5)	12	0.7	28	(1.7)	30	0.9
Not recovered	85	(10.3)	114	6.7	86	(10.5)	118	6.9	175	(10.6)	252	7.4
Unknown	1	(0.1)	1	0.1	1	(0.1)	1	0.1	0			
Action taken												
Dose not changed	202	(24.5)	364	21.3	179	(21.8)	326	19.2	457	(27.7)	897	26.4
Drug interrupted	12	(1.5)	12	0.7	7	(0.9)	11	0.6	32	(1.9)	58	1.7
Drug withdrawn	6	(0.7)	6	0.4	7	(0.9)	9	0.5	27	(1.6)	36	1.1
Dose reduced	0				0				0			
Dose increased	0				0				0			
Unknown	0				1	(0.1)	2	0.1	0			
Not applicable	78	(9.4)	174	10.2	76	(9.2)	145	8.5	145	(8.8)	280	8.2
Missing	4	(0.5)	6	0.4	4	(0.5)	7	0.4	10	(0.6)	11	0.3

Abbreviations: E: number of events; N: number of subjects with at least one event; R: events per 100 patient-years of observation; %: percentage of subjects with at least one event.
Source: Table 2-64 ISS

Cardiovascular AEs had onset throughout the entire observation period of the CVOT, with no clustering of events over time.

Atrial fibrillation was the most frequently reported type of CV AE in the CVOT, occurring in 3.0% and 3.5% of patients with semaglutide and placebo, respectively. The trends for proportion of patients with cardiovascular AEs as well as the types and rate of such events were consistent with the findings and conclusions based on EAC-confirmed events: there was a smaller

proportion of patients on semaglutide reported with MI, angina pectoris, unstable angina, and stroke, with semaglutide vs placebo.

AEs of congestive cardiac failure were reported for 2.3% of patients with semaglutide and for 2.5% of patients with placebo. AEs of cardiac failure were reported for 1.6% of patients with semaglutide and for 1.1% of patients with placebo. AEs of chronic cardiac failure were reported for 0.9% of patients with semaglutide and for 0.6% of patients with placebo.

Cardiovascular disorders (identified via MedDRA search) occurring in ≥1% of patients are summarized below by HLGT and PT.

Table 167 Adverse Events by High Level Term from the Cardiovascular Events MedDRA Search Occurring in ≥1% of Patients Treated with Semaglutide

High Level Term	Sema 0.5 N=826	Sema 1 N=822	Placebo N=1649
	N (%)	N (%)	N (%)
Any Event in Cardiovascular MedDRA Search	**268 (32.4)**	**237 (28.8)**	**576 (34.9)**
Ischemic coronary artery disorders	60 (7.3)	61 (7.4)	159 (9.6)
Arterial therapeutic procedures (excl aortic)	46 (5.6)	36 (4.4)	120 (7.3)
Heart failures NEC	6 (5.6)	32 (3.9)	75 (4.5)
Supraventricular arrhythmias	39 (4.7)	32 (3.9)	92 (5.6)
Breathing abnormalities	23 (2.8)	20 (2.4)	45 (2.7)
Ventricular arrhythmias and cardiac arrest	16 (1.9)	18 (2.2)	27 (1.6)
Renal failure and impairment	33 (4.0)	17 (2.1)	59 (3.6)
Cardiac conduction disorders	21 (2.5)	17 (2.1)	34 (2.1)
Coronary artery disorders NEC	22 (2.7)	16 (1.9)	32 (1.9)
Edema NEC	24 (2.9)	13 (1.6)	62 (3.8)
Central nervous system hemorrhages and cerebrovascular accidents	20 (2.4)	13 (1.6)	58 (3.5)

Source: Reviewer generated based on review of adae.xpt from trial 3744

Table 168 Adverse Events by Preferred Term from the Cardiovascular Events MedDRA Search Occurring in ≥1% of Patients Treated with Semaglutide

Preferred Term	Sema 0.5 N=826	Sema 1 N=822	Placebo N=1649
	N (%)	N (%)	N (%)
Any Event in Cardiovascular MedDRA Search	**268 (32.4)**	**237 (28.8)**	**576 (34.9)**
Atrial fibrillation	28 (3.4)	22 (2.7)	59 (3.6)
Dyspnea	21 (2.5)	20 (2.4)	45 (2.7)
Angina pectoris	23 (2.8)	18 (2.2)	53 (3.2)

Preferred Term	Sema 0.5 N=826	Sema 1 N=822	Placebo N=1649
	N (%)	N (%)	N (%)
Cardiac failure congestive	21 (2.5)	16 (1.9)	41 (2.5)
Angina unstable	13 (1.6)	16 (1.9)	45 (2.7)
Acute myocardial infarction	17 (2.1)	14 (1.7)	44 (2.7)
Acute kidney injury	24 (2.9)	12 (1.5)	49 (3.0)
Edema peripheral	20 (2.4)	12 (1.5)	59 (3.6)
Cardiac failure	14 (1.7)	12 (1.5)	19 (1.2)
Syncope	9 (1.1)	12 (1.5)	18 (1.1)
Chest pain	4 (0.5)	12 (1.5)	32 (1.9)
Myocardial infarction	5 (0.6)	11 (1.3)	25 (1.5)
Coronary arterial stent insertion	17 (2.1)	10 (1.2)	39 (2.4)
Coronary artery disease	14 (1.7)	10 (1.2)	17 (1.0)
Coronary revascularization	15 (1.8)	9 (1.1)	24 (1.5)
Peripheral arterial occlusive disease	5 (0.6)	9 (1.1)	17 (1.0)
Orthostatic hypotension	7 (0.8)	8 (1.0)	6 (0.4)
Transient ischemic attack	8 (1.0)	7 (0.9)	22 (1.3)
Peripheral swelling	12 (1.5)	6 (0.7)	23 (1.4)
Cardiac failure chronic	10 (1.2)	6 (0.7)	10 (0.6)
Coronary artery bypass	8 (1.0)	6 (0.7)	24 (1.5)
Ischemic stroke	8 (1.0)	6 (0.7)	21 (1.3)

Source: Reviewer generated based on review of adae.xpt from trial 3744

AEs related to valve disorders were reported in slightly higher proportion of patients and rates with semaglutide vs placebo in the CVOT (1.3% of patients in semaglutide 0.5 mg, 1.5% in semaglutide 1 mg, and 1% in placebo).

Phase 3 pool

The number of 'cardiovascular events' identified by MedDRA search with semaglutide (0.5 mg and 1.0 mg) and comparator products showed consistent trends across the phase 3 trials. The proportions of patients with CV events identified by MedDRA search were similar with semaglutide 0.5 mg: 8.0% vs comparators (8.1%), however a slighty higher proportion was seen with semaglutide 1 mg - 9.2%. Events of cardiac arrhythmias of ventricular extrasystoles, AV block first degree, supraventricular extrasystoles and tachycardia (PT) were reported at a slightly higher frequency with semaglutide relative to comparators. However, the overall rates of cardiac arrhythmias were similar with semaglutide and comparators (2.5 and 1.9 events per 100 PYO). Within other HLGTs, orthostatic hypotension was reported more frequently with semaglutide than with comparators (0.3 versus <0.1 events per 100 PYO). No imbalance was noted in CV SAEs, and no dose-dependence was apparent with semaglutide.

Placebo pool

The proportions of patients with CV events identified by MedDRA search were slightly lower with semaglutide (0.5 mg: 6.5%; 1.0 mg: 4.6%) vs comparators (7.6%). CV events were reported as SAEs in 1.9%, 1.5% and 1.1% of patients treated with semaglutide 0.5 mg, semaglutide 1 mg and placebo.

Reviewer comment: The MedDRA search for CV events in the CVOT and phase 3 pool yielded any findings that were generally consistent with the results of the adjudicated events analyses. As expected due to the relatively small number of events when the CVOT is excluded, the phase 3 pool excluding CVOT does not offer any meaningful information.

8.5.2. Diabetic Retinopathy

This section will mostly refer to the retinopathy findings in the CVOT, as the other studies in the phase 3 program were not specifically designed to look at retinopathy, and generally included a lower risk patient population.

CVOT

Patients with retinopathy were not excluded from the study. Retinal examinations, in the form of funduscopy or fundus photograph, were performed at baseline, year 1, and year 2.

Fundoscopy or fundus photography was performed by the investigator, a local ophthalmologist or an optometrist according to local practice. It was not recorded who performed the examination and dilation was not a requirement. Result of the fundoscopy/fundus photography was interpreted locally by the investigator and categorized as: 'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant'. Evaluation of visual acuity (VA) was not part of the baseline assessment and no other eye examinations were scheduled as part of the protocol, but patients could attend visits with their own ophthalmologist as needed/scheduled.

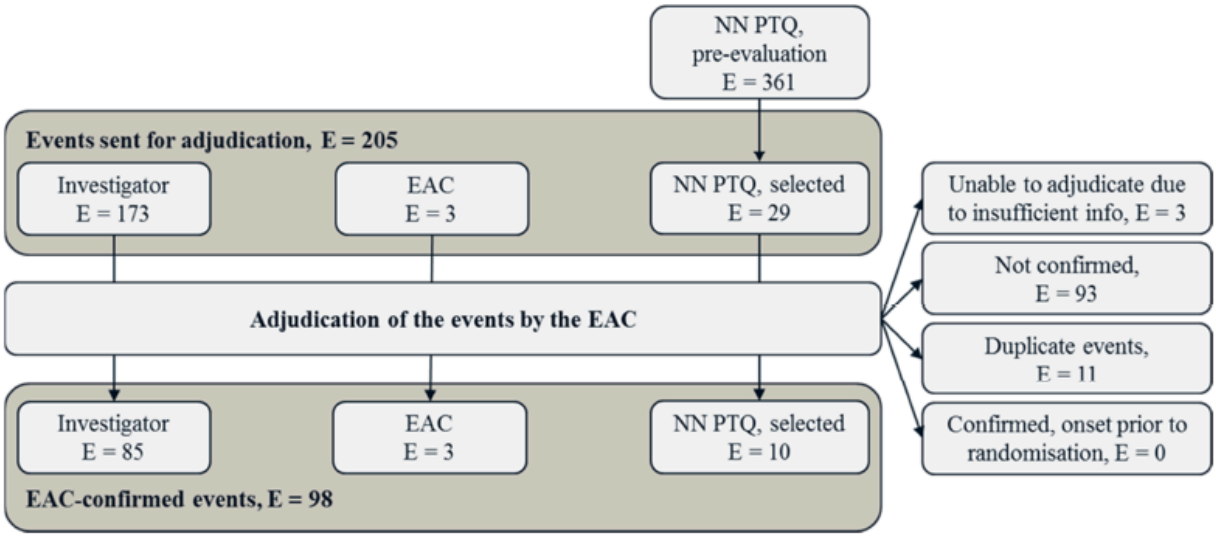
This is the only study where retinopathy events were adjudicated. Time to first EAC-confirmed event of diabetic retinopathy complications was a secondary endpoint. The events confirmed by adjudication had to fulfill at least one of the following criteria:

- Need for retinal photocoagulation
- Vitreous hemorrhage
- Need for treatment with intravitreal agents
- Onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible)

EAC-confirmed retinopathy events

The adjudication flow for diabetic retinopathy complications is presented below.

Figure 59 Adjudication Flow for Diabetic Retinopathy Complications – CVOT



Abbreviations: EAC: event adjudication committee; NN: Novo Nordisk; PTQ: preferred term query.

Source: Figure 2-50 ISS

The confirmation rate of events of diabetic retinopathy complications was 47.8%, similar between treatment groups.

Table169 Numbers of All Events of Diabetic Retinopathy Complications Adjudicated and EAC Confirmation Rates (%) by Reporting Method – CVOT

	Investigator		PTQ search		EAC		Total	
	E	Conf. rate	E	Conf. rate	E	Conf. rate	E	Conf. rate
All	173	49.1%	29	34.5%	3	100.0%	205	47.8%
Semaglutide	111	51.4%	17	29.4%	0		128	48.4%
Semaglutide 0.5 mg	48	50.0%	10	40.0%	0		58	52.8%
Semaglutide 1.0 mg	63	52.4%	7	14.3%	0		70	48.6%
Placebo	62	45.2%	12	41.7%	3	100.0%	77	46.8%

Note: The table shows the number of events. Each event could fulfil more than one criterion.
Abbreviations: Conf.: confirmation; E: number of events; EAC: event adjudication committee; PTQ: preferred term query.

Source: Table 2-78 ISS

A total of 98 events of diabetic retinopathy complications in 79 patients were confirmed by the EAC with onset during the in-trial period. Retinopathy complications occurred in a larger proportion of patients on semaglutide (3% - with no difference between the two semaglutide doses), compared to placebo (1.8%).

Table 170 All EAC-Confirmed Events of Diabetic Retinopathy Complications, Semaglutide Versus Placebo – FAS In-Trial – CVOT

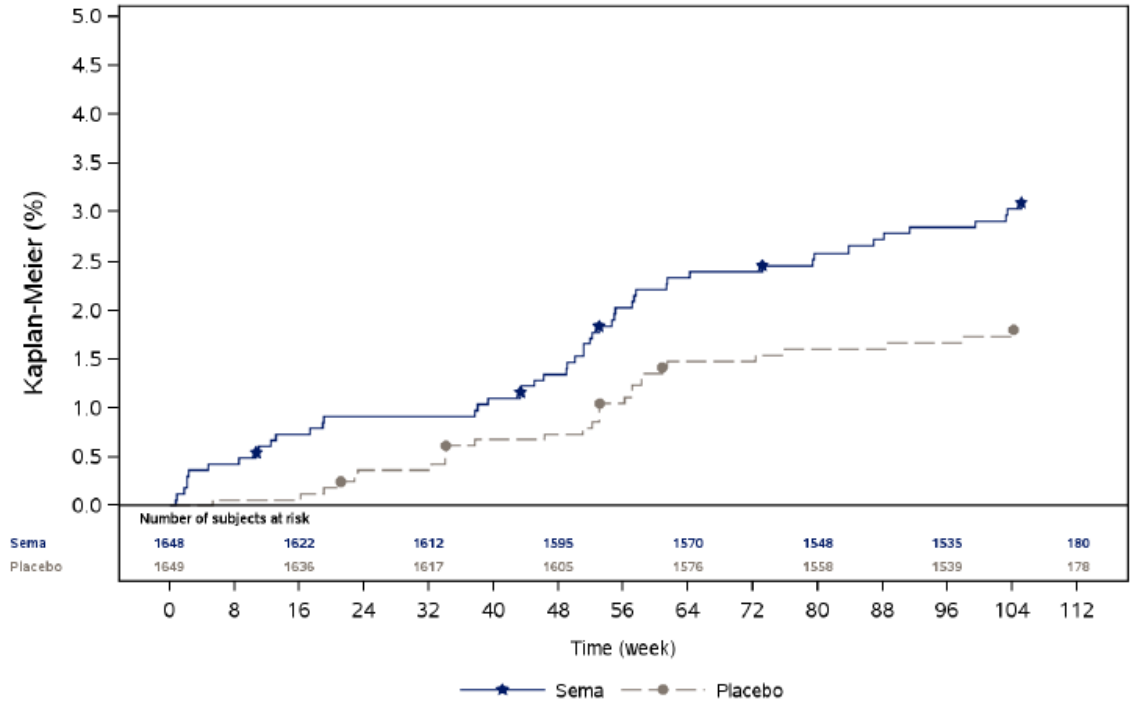
	Semaglutide				Placebo				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1648				1649				3297			
PYO	3408.2				3401.1				6809.3			
All events												
Diabetic retinopathy complications	50	(3.0)	62	1.8	29	(1.8)	36	1.1	79	(2.4)	98	1.4
Need for retinal photocoagulation	38	(2.3)	43	1.3	20	(1.2)	24	0.7	58	(1.8)	67	1.0
Need for treatment with intravitreal agents	16	(1.0)	18	0.5	13	(0.8)	14	0.4	29	(0.9)	32	0.5
Vitreous haemorrhage	16	(1.0)	19	0.6	7	(0.4)	8	0.2	23	(0.7)	27	0.4
Onset of diabetes-related blindness	5	(0.3)	5	0.2	1	(0.1)	1	0.03	6	(0.2)	6	0.1

Abbreviations: E: number of events; EAC: event adjudication committee; N: number of subjects; %: percentage of subjects with an event; PYO: patient-years of observation; R: events per 100 PYO.

Source: Table 2-79 ISS

It appears that the separation between the two treatment groups began very early over the course of the trial, starting at week 8. The difference persisted over the course of the trial. It is notable that HbA1c also decreased early and dramatically with both doses of semaglutide, which could potentially account for the worsening retinopathy with semaglutide. A rapid decrease in HbA1c can be associated with worsening retinopathy, but the expectation is that improved glycemic control will ultimately lead to a reduced risk of microvascular complications (including retinopathy) over time. This was the case in the DCCT, where an increase in progression of retinopathy with tight glycemic control was seen but which reversed after years 2-3 such that tight glycemic control yielded a reduction in retinopathy. The semaglutide CVOT was only two years in duration, and it is unclear what the long-term effect on retinopathy is.

Figure 60 Plot of Time To First EAC-Confirmed Events of Diabetic Retinopathy Complication – FAS In-Trial – CVOT



Note: Kaplan-Meier estimates: Analysis of time from randomisation to first EAC-confirmed event of diabetic retinopathy complications. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact or all-cause death of the subject, whichever comes first. Numbers below the figure are subjects at risk.
Abbreviations: EAC: event adjudication committee.
Source: Figure 2-51 ISS

The analysis of the treatment difference between semaglutide and placebo showed a HR of 1.76 [1.11; 2.78] 95%CI with a p-value of 0.0159 corresponding to an increased relative risk of 76% with semaglutide versus placebo.

A post-hoc analysis of the hazard ratios for semaglutide vs placebo for each category of retinopathy events is presented below. While only the need for retinal photocoagulation reached statistical significance, the small number of events in the remaining categories preclude any meaningful conclusions.

Table 171 Post Hoc Analyses of the Treatment Differences for Time to First EAC-Confirmed Events of the Individual Criteria for Diabetic Retinopathy Complications – FAS In-Trial – CVOT

Criterion	Subjects with events/analysed semaglutide;placebo	Hazard ratio	[95% CI]	p-value
Need for retinal photocoagulation	38/1648; 20/1649	1.91	[1.11; 3.28]	0.0193
Need for treatment with intravitreal agents	16/1648; 13/1649	1.23	[0.59; 2.56]	0.5793
Vitreus haemorrhage	16/1648; 7/1649	2.29	[0.94; 5.57]	0.0673
Onset of diabetes-related blindness	5/1648; 1/1649	5.01	[0.59; 42.88]	0.1413

Note: Onset of diabetes-related blindness was defined as Snellen visual acuity of 20/200 [6/60] or less or visual field of less based than 20 degrees, in the better eye with best correction possible.
Abbreviation: EAC: event adjudication committee.

Source: Table 2-84 ISS

More patients on semaglutide had events in more than one retinopathy event category during the trial. A total of 17 semaglutide treated subjects had more than one type of retinopathy event compared to 6 placebo subjects.

Table 172 Criteria Met for First EAC-Confirmed Events of Diabetic Retinopathy Complications – FAS In-Trial – CVOT

	semaglutide/placebo				
Criterion	Alone	+photocoag.	+intravitreal agents	+photocoag. +intravitreal agents	+photocoag. +vitreous haemorrhage
Need for retinal photocoagulation	22/14	NA	0/0	NA	NA
Need for treatment with intravitreal agents	6/7	4/0	NA	NA	0
Vitreal haemorrhage	4/1	6/2	2/1	1/3	NA
Onset of diabetes-related blindness	1/0	1/0	0/0	1/1	2/0

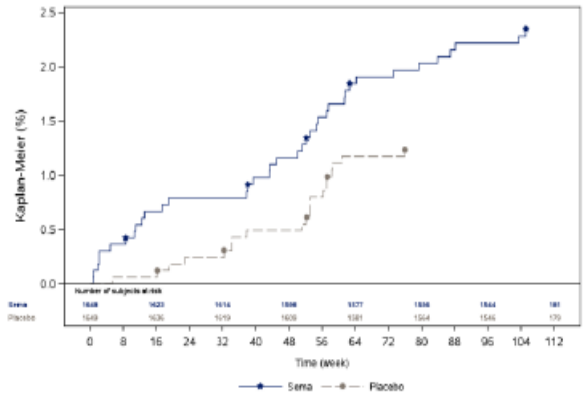
Note: The table summarises the criteria met for first EAC-confirmed retinopathy events. 'Onset of diabetes-related blindness' is defined as 'Snellen visual acuity of 20/200 (6/60) or less, or visual field of less than 20 degrees, in the better eye with best correction possible'.
Abbreviations: EAC: event adjudication committee; NA: not applicable

Source: Table 2-83 ISS

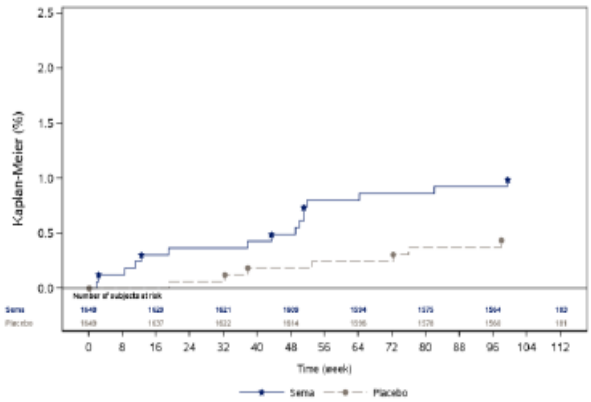
The Kaplan Meier curves for individual retinopathy categories are presented below. As was seen with the composite retinopathy endpoint, the individual components curves diverge from the beginning of the study.

Figure 61 Kaplan Meier Plots of Time To First EAC-Confirmed Event of Individual Criteria for Diabetic Retinopathy Complications – FAS In-Trial – CVOT

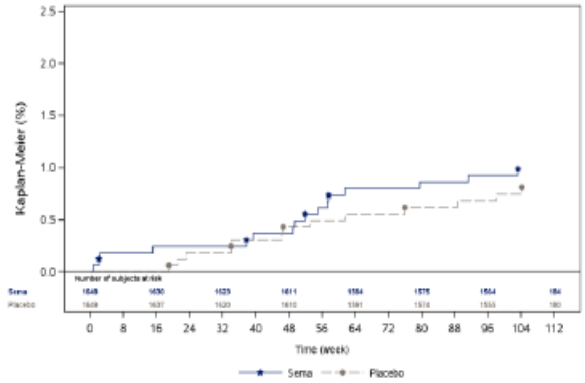
Time to first EAC-confirmed event of need for retinal photocoagulation



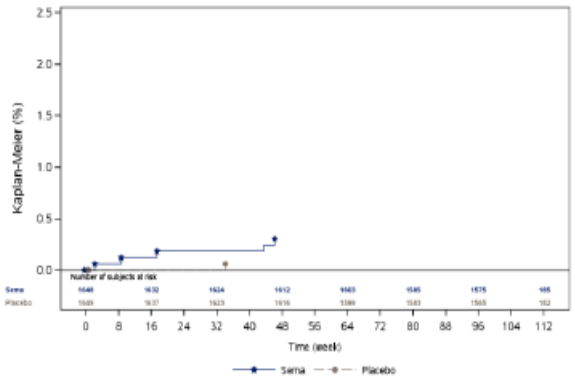
Time to first EAC-confirmed event of vitreous haemorrhage



Time to first EAC-confirmed event of need for treatment with intravitreal agent



Time to first EAC-confirmed event of diabetes-related blindness



Note: Kaplan-Meier estimates: Analysis of time from randomisation to first EAC-confirmed events of need for retinal photocoagulation, vitreous haemorrhage, need for treatment with intravitreal agent or onset of diabetes-related blindness. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact or all-cause death of the subject, whichever comes first. Numbers below the figure are subjects at risk.
Abbreviations: EAC:event adjudication committee.

Source: Figure 2-52 ISS

It appears that most of the EAC-confirmed retinopathy events were detected via routine eye examinations (i.e., exams conducted as part of study visits). I reviewed the narrative and adjudication packages for all the patients who experienced a vitreal hemorrhage, or diabetes-related blindness, and most these patients were detected, as expected, via clinical symptoms.

Table 173 Reasons for Eye Examination of First EAC-Confirmed Events Of Diabetic Retinopathy Complications – CVOT

Reason for eye examination	Semaglutide E (%)	Placebo E (%)
Routine[a]	30 (60.0)	17 (58.6)
Symptoms	12 (24.0)	5 (17.2)
Unknown	8 (16.0)	7 (24.2)
Total	50 (100.0)	29 (100.0)

a: The routine eye examinations were based on either the scheduled fundoscopy in the trial or the scheduled eye examination at the subjects's eye clinic.

Abbreviation: EAC: event adjudication committee.

Source: Table 2-82 ISS

Diabetic retinopathy complications were not evaluated based on a standardized retinopathy scale, and therefore the significance of the events in the applicant analyses is unclear. My evaluation of the adjudication packages and narratives evaluated for the patients with blindness and vitreal hemorrhage revealed that the information available is very limited and difficult to interpret, and very few retinal photographs were available to allow retinopathy scoring. For example, for the 6 patients that were positively adjudicated as diabetes –related blindness, it is unclear to what extent cataracts could have contributed to blindness, rather than blindness due to retinopathy (patient characteristics presented in **Table 174** below). Additionally, one patient in the semaglutide 0.5 mg arm experienced reading comprehension issues due to CVA that was categorized as diabetic blindness. All 5 patients on semaglutide had history of PDR at baseline, while the patient on placebo did not have diabetic retinopathy at baseline. Details regarding the 6 patients with EAC-confirmed blindness are presented below.

Table 174 Patient Characteristics – Blindness - CVOT

Patient ID/age/sex/ country	Diabetes duration	Baseline DR/treatment	Onset day	Other information
Semaglutide 0.5 mg				
144007/M/57/Australia	13.5	PDR/macular edema/laser therapy & intravitreal agents	15	Reading comprehension issues in the context of CVA
681004/M/62/US	20.5	PDR	121	Surgery for tractional detachment of retina
663010/M/67/US	20.5	PDR/laser therapy & intravitreal agents	304	Non-resolving vitreous hemorrhage and tractional retinal detachment involving the macula, underwent pars plana vitrectomy with membrane stripping and panretinal laser

Patient ID/age/sex/ country	Diabetes duration	Baseline DR/treatment	Onset day	Other information
604015/F/71/US	43.3	PDR/laser therapy & intravitreal agents	323	Complicated history and little known about the event as the patient died of septicemia
Semaglutide 1 mg				
524008/M/70/UK/sema 1	13.2	PDR/laser therapy & intravitreal agents	60	History of recurrent vitreous hemorrhage
Placebo				
649001/F/52/US	25.2	No retinopathy	239	Cataracts Macular edema at baseline

Source: Modified from Table 2-85, review of narratives and adjudication packages

Of the 5 semaglutide-treated patients, vision improved 18 months after the event for 2 patients, vision worsened for 1 patient and no information was available for the remaining 2 patients. For the placebo-treated patient, vision remained the same 16 days after the event.

In addition to the issues pertaining to the cause of blindness, the FDA Ophthalmology consultant, Dr Wiley Chambers, also noted that only 2 of the patients actually met the EAC definition of blindness in both eyes. Please see Dr Chambers' review for details.

The severity of vitreal hemorrhage was not captured in the trial, and review of the narratives and adjudication packages did not yield any additional information. Therefore, the clinical significance of the events reported is not clear.

The other two adjudication categories, need for photocoagulation, and need for treatment with intra-vitreal agents, are not standardized, and their interpretation is confounded by multiple factors, including the availability of treatments, economic considerations, etc. Additionally, Dr Chambers noted that actual administration of treatment was captured, rather than need.

The applicant performed multiple post-hoc analyses looking at baseline characteristics of the patients who developed retinopathy events during the trial vs the ones who did not. Baseline characteristics of the two populations are presented below.

Compared to the overall population, the patients who had EAC-confirmed events of diabetic retinopathy complications during the trial were characterized by a longer diabetes duration (17.53 years), a higher baseline HbA1c (9.37%), more patients on insulins at baseline (75.9%), and more patients with a history of diabetic retinopathy (83.5%). This si consistent with general risk factors for diabetic retinopathy. Only 14 adjudicated retinopathy events did not occur in patients with a history of diabetic retinopathy at baseline (8 events with semaglutide, and 5 with placebo).

Table 175 Baseline Characteristics of All Patients and Patients with EAC-Confirmed Events Of Diabetic Retinopathy Complications – FAS In-Trial – CVOT

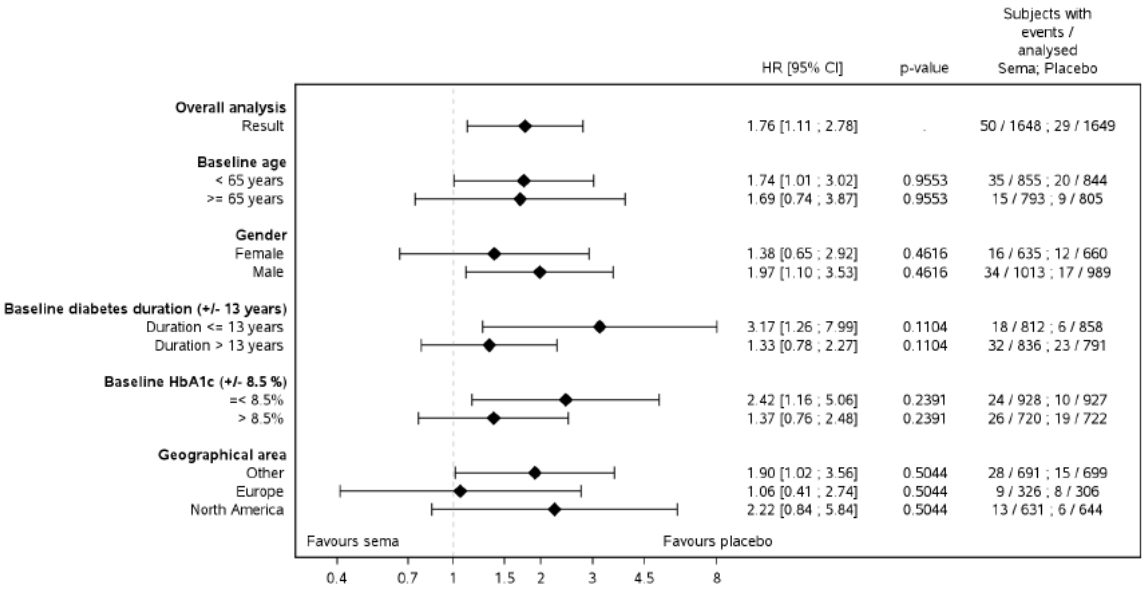
Baseline characteristics	Subjects with EAC-confirmed events of diabetic retinopathy complications in-trial			Entire CVOT population
	Semaglutide (N =50)	Placebo (N=29)	All subjects (N=79)	All subjects (N=3297)
Age (years), Mean (SD)	63.0 (5.6)	61.8 (7.0)	62.6 (6.1)	64.6 (7.4)
Sex				
Male, N (%)	34 (68.0)	17 (58.6)	51 (64.6)	2002 (60.7)
Female, N (%)	16 (32.0)	12 (41.4)	28 (35.4)	1295 (39.3)
Diabetes duration (years), Mean (SD)	17.08 (9.15)	18.29 (6.89)	17.53 (8.37)	13.89 (8.11)
HbA_{1c} (%), Mean (SD)	9.18 (1.95)	9.71 (1.83)	9.37 (1.91)	8.70 (1.46)
Insulin treatment, N (%)	38 (76.0)	22 (75.9)	60 (75.9)	1913 (58.0)
Basal insulins, N (%)	14 (28.0)	12 (41.4)	26 (32.9)	1046 (31.7)
Premix insulins, N (%)	24 (48.0)	10 (34.5)	34 (43.0)	867 (26.3)
History of diabetic retinopathy, N (%)				
Yes	42 (84.0)	24 (82.8)	66 (83.5)	969 (29.4)
Proliferative	14 (28.0)	9 (31.0)	23 (29.1)	202 (6.1)
Macular oedema	3 (6.0)	1 (3.4)	4 (5.1)	31 (0.9)
Laser therapy/intravitreal agents	10 (20.0)	4 (13.8)	14 (17.7)	112 (3.4)
Surgery	2 (4.0)	2 (6.9)	3 (3.8)	24 (0.7)
Non-proliferative	26 (52.0)	13 (44.8)	39 (49.4)	750 (22.7)
Macular oedema	7 (14.0)	4 (13.8)	11 (13.9)	64 (1.9)
Laser therapy/intravitreal agents	10 (20.0)	5 (17.2)	15 (19.0)	100 (3.0)
Surgery	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.3)
Unknown	2 (4.0)	2 (6.9)	4 (5.1)	17 (0.5)
Macular oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Laser therapy/intravitreal agents	1 (2.0)	0 (0.0)	1 (1.3)	4 (0.1)
No	5 (10.0)	4 (13.8)	9 (11.4)	2112 (64.1)
Unknown	3 (6.0)	1 (3.4)	4 (5.1)	216 (6.6)
Hypertension[a]	48 (96.0)	25 (86.2)	73 (92.4)	3042 (92.3)

a: Includes both hypertension and essential hypertension. **Abbreviations:** EAC: event adjudication committee; HbA_{1c}: glycated haemoglobin; N: number of subjects; %: percentage of subjects; SD: standard deviation.

Source: Table 2-86 ISS

To better understand the source of the increase in the relative risk for retinopathy events with semaglutide, the applicant performed multiple post-hoc subgroup analyses.

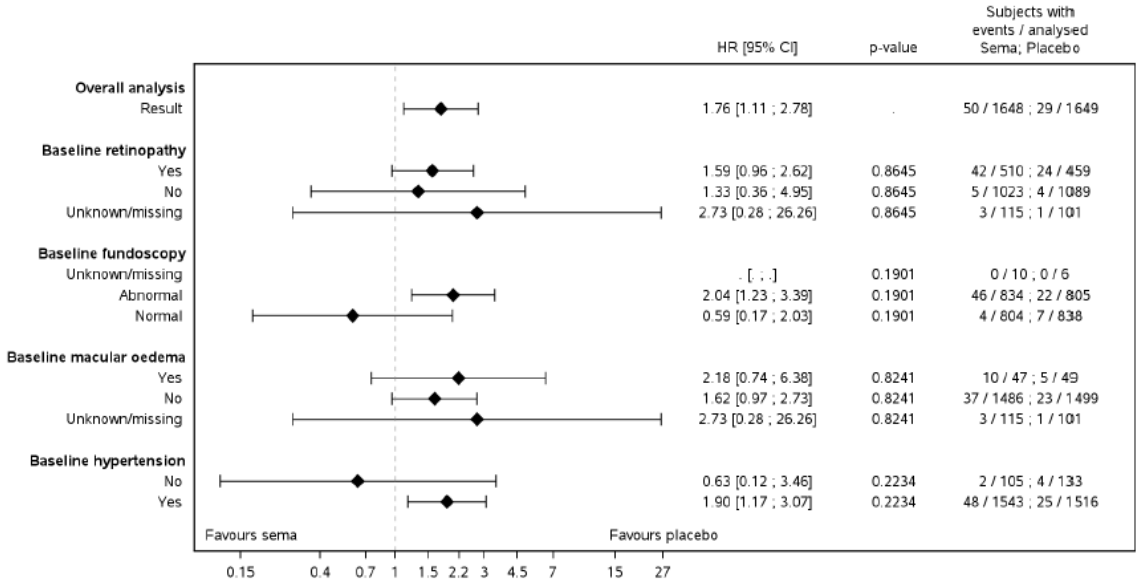
Figure 62 Forest Plot on Time To First EAC-Confirmed Event of Diabetic Retinopathy Complications – Post Hoc Statistical Subgroup Analyses for Duration of Diabetes, HbA1c, Age, Sex and Geographical Area – FAS In-Trial – CVOT



Note: Summary of results from subgroup analyses of time to first EAC-confirmed event of diabetic retinopathy complications. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and the relevant subgroup as fixed factor. The p-value is from the Wald test of the interaction effect.
Abbreviations: CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.
Source: Figure 2-53 ISS

Figure 63 Forest Plot on Time To First EAC-Confirmed Event Of Diabetic Retinopathy Complications – Post Hoc Statistical Subgroup Analyses for Baseline Diabetic Retinopathy,

Baseline Fundoscopy, Baseline Macular Edema and Baseline Hypertension - FAS In-Trial – CVOT



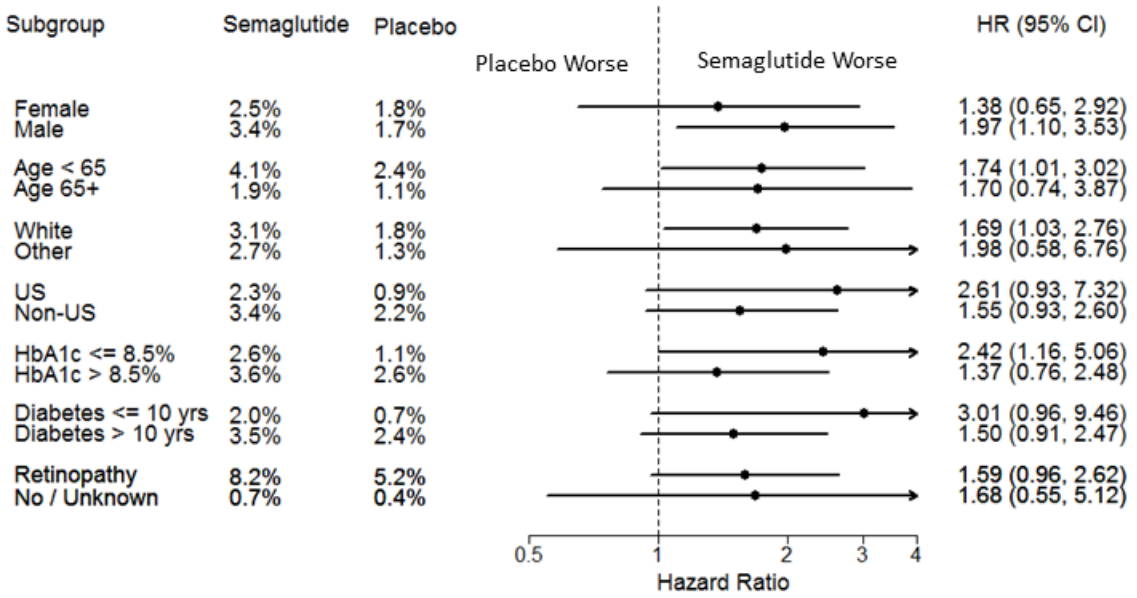
Note: Summary of results from subgroup analyses of time to first EAC-confirmed event of diabetic retinopathy complications. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and the relevant subgroup as fixed factor. The p-value is from the Wald test of the interaction effect.

Abbreviations: CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.

Source: Figure 2-54 ISS

The FDA's subgroup analysis (Biometrics review by Dr Hsueh) is presented below. No meaningful interactions between subgroups and treatment were noted.

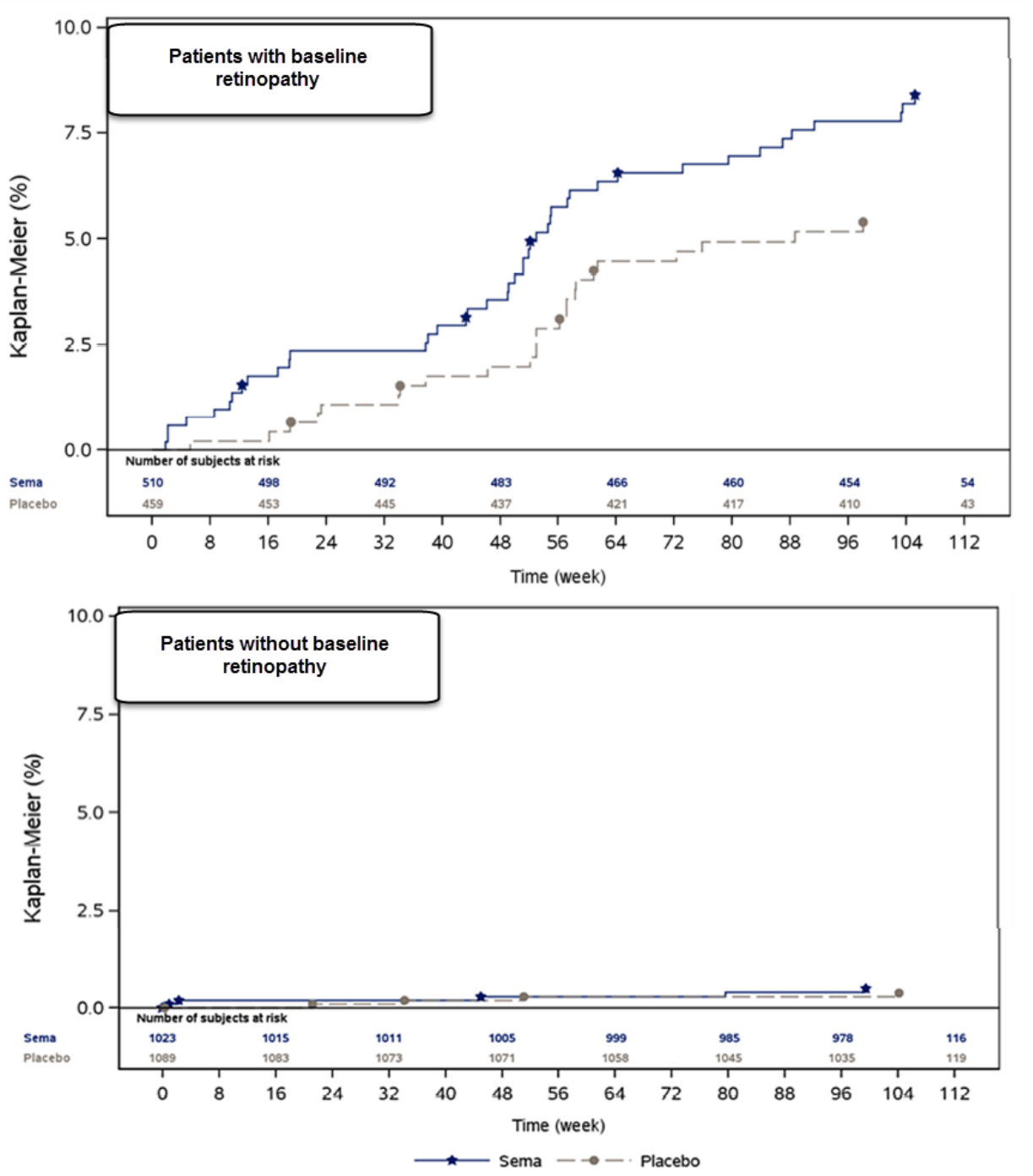
Figure 64 Forest Plot of Hazard Ratio for Diabetic Retinopathy Complications by Baseline Subgroups



Source: Created by the statistical reviewer

The Kaplan Meier curves for EAC-confirmed retinopathy events for patients with and without diabetic retinopathy at baseline are presented in the figures below. The absolute risk of developing diabetic retinopathy in the subgroup of patients without baseline diabetic retinopathy is overall low, while it is significanctly increased in patients with baseline diabetic retinopathy.

Figure 65 Kaplan Meier Plots Of Time To First EAC-Confirmed Retinopathy Event by Baseline Retinopathy



Source: Figures 2-55 and 2-56 ISS

It is possible that the rapid improvement in glycemic control with semaglutide contributed to the observed increase in the retinopathy risk. This was seen in the DCCT where intensive glycemic control lead to an initial worsening in retinopathy, followed by long term benefit for all microvascular diabetes complications. The applicant analyzed the HbA1c changes over time in patients with and without an EAC-confirmed retinopathy event. The applicant concluded that, in both placebo and semaglutide groups, the patients without retinopathy events experienced a smaller decrease in HbA1c at any timepoint during the trial.

Table 176 Baseline HbA1c and Change from Baseline in HbA1c at Weeks 8, 16 and 104 in Patients With and Without EAC-Confirmed Events of Diabetic Retinopathy Complications – FAS In-Trial – CVOT

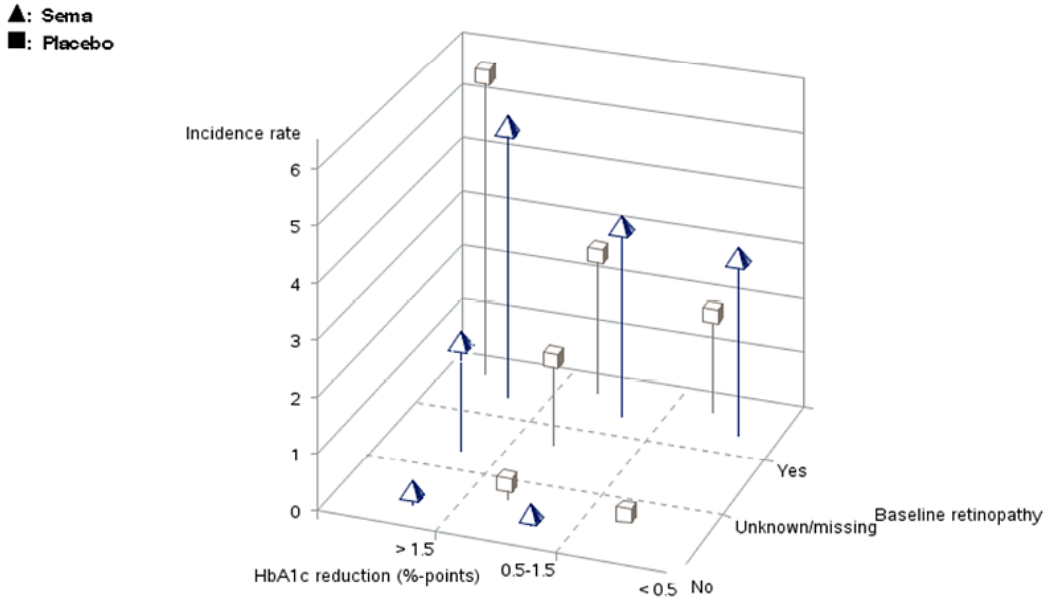
	Sema 0.5 mg	Sema 1.0 mg	Placebo 0.5 mg	Placebo 1.0 mg
Number of subjects				
Retinopathy	25	25	14	15
No retinopathy	801	797	810	810
Week 0 - baseline HbA_{1c}				
Mean (SD)-retinopathy	9.38 (1.96)	8.98 (1.95)	10.04 (1.80)	9.40 (1.86)
Mean (SD)-no retinopathy	8.65 (1.37)	8.72 (1.50)	8.68 (1.48)	8.69 (1.44)
Week 8 - change from baseline in HbA_{1c}				
Mean (SD)-retinopathy	-1.33 (1.30)	-1.66 (1.10)	-0.53 (1.62)	-0.75 (1.13)
Mean (SD)-no retinopathy	-1.21 (0.92)	-1.22 (0.97)	-0.29 (0.93)	-0.34 (1.04)
Week 16 - change from baseline in HbA_{1c}				
Mean (SD)-retinoathy	-1.87 (1.69)	-2.47 (1.94)	-0.88 (1.89)	-1.27 (1.74)
Mean (SD)-no retinopathy	-1.59 (1.20)	-1.82 (1.37)	-0.38 (1.17)	-0.36 (1.25)
Week 104/end-of-trial - change from baseline in HbA_{1c}				
Mean (SD)-retinopathy	-1.40 (1.72)	-1.81 (2.28)	-1.12 (2.24)	-0.66 (1.64)
Mean (SD)-no retinopathy	-1.06 (1.52)	-1.43 (1.68)	-0.40 (1.55)	-0.36 (1.58)

Abbreviations: EAC: event adjudication committee; N: number of subjects; %: percentage of subjects; SD: standard deviation.

Source: Table 2-87 ISS

The applicant further conducted a post-hoc mediator analysis to evaluate whether the mechanism underlying the effects of semaglutide on retinopathy could be attributed to the initial rapid decline in blood glucose. For this analysis, the applicant used the HbA1c at week 16, which is reasonable considering the HbA1c trends over time observed in this study (most of the glucose lowering effect occurred by this time in the study). The result of the applicant's analysis is presented in the figure below.

Figure 66 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 HbA_{1c} (%-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.

Source: Figure 2-58 ISS

The table corresponding to the figure is presented below.

Table 177 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

Treatment	Baseline retinopathy	HbA1c reduction	Number of subjects with event	Number of subjects	Incidence rate per 100 PYR
Sema	No	< 0.5 %-points	0	131	0.00
Sema	Unknown/missing	< 0.5 %-points	0	9	0.00
Sema	Yes	< 0.5 %-points	4	61	3.26
Sema	No	0.5-1.5 %-points	2	399	0.24
Sema	Unknown/missing	0.5-1.5 %-points	0	31	0.00
Sema	Yes	0.5-1.5 %-points	15	213	3.51
Sema	No	> 1.5 %-points	3	493	0.29
Sema	Unknown/missing	> 1.5 %-points	3	75	2.00
Sema	Yes	> 1.5 %-points	23	236	5.02
Placebo	No	< 0.5 %-points	2	658	0.15
Placebo	Unknown/missing	< 0.5 %-points	0	57	0.00
Placebo	Yes	< 0.5 %-points	9	245	1.80
Placebo	No	0.5-1.5 %-points	2	291	0.33
Placebo	Unknown/missing	0.5-1.5 %-points	1	31	1.60
Placebo	Yes	0.5-1.5 %-points	7	138	2.59
Placebo	No	> 1.5 %-points	0	140	0.00
Placebo	Unknown/missing	> 1.5 %-points	0	13	0.00
Placebo	Yes	> 1.5 %-points	8	76	5.58

Source: Table 15.2.863 study report

Based on the above analysis, the applicant concluded that the incidence rates of first EAC-confirmed event of diabetic retinopathy complications for different subgroups of patients increased with increasing HbA1c reduction, and were highest in the patients with diabetic retinopathy at baseline. The HR semaglutide vs placebo controlled for the effect of change in HbA1c at week 16 was 1.22 (0.71; 2.09).

While the sponsor analysis is interesting, it is not clear that this analysis shows conclusively that HbA1c reduction is the driver behind the retinopathy findings in SUSTAIN 6. This may be because many of the subgroups had none or too few patients to make a conclusive argument. However, although difficult to demonstrate with the available data, the applicant's hypothesis that the retinopathy worsening is mediated via the improved glycemic control is quite reasonable in the context of the currently available literature.

Please see Ophtalmology consult by Dr Wiley Chambers, and Biometrics review by Dr Catherine Hsueh for details regarding their opinion on the retinopathy findings, and the post-hoc analyses, respectively.

MedDRA search

Additionally, a MedDRA search was performed by the applicant for diabetic retinopathy.

The results of the MedDRA search for events suggestive of diabetic retinopathy revealed, again, an imbalance not favoring semaglutide. The most frequently reported preferred term was "diabetic retinopathy". However, the information available for these patients is minimal, and it

is not clear whether these are new cases, or how severe they are (the applicant's evaluation of severity is subjective, not based on retinopathy scoring). None of the events was fatal, but a large proportion in each treatment group is listed as not recovered.

Regardless, all analyses appear to support the idea that semaglutide, at least initially, may be associated with a worsening risk of diabetic retinopathy compared to standard of care.

Table 178 AEs of Diabetic Retinopathy (MedDRA Search) by System Organ Class, High Level Group Term and Preferred Term – FAS In-Trial – CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	826				822				1649			
PYO	1708				1700				3401			
All events	74	(9.0)	86	5.0	82	(10.0)	99	5.8	125	(7.6)	145	4.3
Eye disorders												
Retina, choroid and vitreous haemorrhages and vascular disorders												
Diabetic retinopathy	50	(6.1)	54	3.2	58	(7.1)	66	3.9	83	(5.0)	88	2.6
Retinopathy	8	(1.0)	8	0.5	8	(1.0)	8	0.5	13	(0.8)	13	0.4
Vitreous haemorrhage	4	(0.5)	4	0.2	7	(0.9)	7	0.4	3	(0.2)	3	<0.1
Retinal haemorrhage	2	(0.2)	2	0.1	4	(0.5)	4	0.2	6	(0.4)	6	0.2
Retinal neovascularisation					1	(0.1)	1	<0.1				
Retinopathy proliferative					1	(0.1)	1	<0.1	2	(0.1)	2	<0.1
Retinal exudates	1	(0.1)	1	<0.1					2	(0.1)	2	<0.1
Ocular infections, irritations and inflammations												
Macular oedema	3	(0.4)	3	0.2	6	(0.7)	7	0.4	8	(0.5)	8	0.2
Cystoid macular oedema	2	(0.2)	2	0.1	1	(0.1)	1	<0.1	2	(0.1)	2	<0.1
Diabetic retinal oedema	1	(0.1)	1	<0.1					4	(0.2)	4	0.1
Ocular structural change, deposit and degeneration NEC												
Vitreous detachment	2	(0.2)	2	0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Papilloedema					1	(0.1)	1	<0.1				
Retinal detachment	3	(0.4)	4	0.2					6	(0.4)	6	0.2
Maculopathy	2	(0.2)	2	0.1					4	(0.2)	4	0.1
Vitreous opacities	1	(0.1)	1	<0.1								
Vision disorders												
Visual acuity reduced	2	(0.2)	2	0.1	2	(0.2)	2	0.1	6	(0.4)	6	0.2

Note: Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm.

Abbreviations: Adj: adjusted; E: number of events; N: number of subjects with at least one event; %: percentage of subjects with at least one event; PYO: patient-years of observation; R: event per 100 PYO.

Source: Table 2-89 ISS

Phase 3 pool

The retinopathy events in the phase 3 pool were not adjudicated. The following exclusion criterion was instituted in all trials: "Known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator". However, this did not preclude patients with diabetic retinopathy from being included in the trials, although the proportion was overall low (only about 8% of patients were listed as having diabetic retinopathy at baseline).

There were no standardized retinal exams other than at baseline in most of these studies, with the exception of the two studies performed exclusively in Japan, where funduscopy was also performed at the end of treatment.

Since the duration of the 7 phase 3 trials differed; 4 of the 7 trials had a duration of 30 weeks and 3 of the 7 trials had a duration of 56 weeks, the results are best presented by study. A small number of retinopathy events were identified by the applicant via MedDRA search, and the results are presented below.

Table 179 Incidence of MedDRA Identified Retinopathy Events by Phase 3 Study

	Sema 0.5 mg			Sema 1.0 mg			Comparators		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
3623 vs Placebo (Mono)							1 (0.8)	1	1.2
3626 vs Sita (OADs)	5 (1.2)	5	1.1	1 (0.2)	2	0.4	10 (2.5)	10	2.1
3624 vs Exe ER (OADs)				4 (1.0)	8	1.7	4 (1.0)	4	0.9
3625 vs IGlar (OADs)	3 (0.8)	3	1.3				5 (1.4)	5	2.1
3627 vs Placebo (Insulin)	4 (3.0)	5	5.7	1 (0.8)	1	1.1			
4092 vs Sita (Mono), JP	4 (3.9)	4	5.7	4 (3.9)	4	5.9	4 (3.9)	4	5.7
4091 vs OAD (OAD), JP	16 (6.7)	18	6.5	20 (8.3)	21	7.6	7 (5.8)	7	5.0

Abbreviations: Adj: adjusted; E: number of events; N: number of subjects with at least one event; PYO: patient-years of observation; %: percentage of subjects with at least one event; R: events per 100 PYO.

Source: Table 2-91 ISS

None of the events was reported as an SAE. An imbalance not favoring semaglutide was observed in a few studies, however this was probably countered by a lower risk in other phase 3 studies. Given the patient population and the methods of ascertainment of such events in these trials, it would not be wise to draw any conclusions regarding the semaglutide effect on the risk of retinopathy based on this pool.

Placebo pool

As seen in **Table 179** above, a total of 6 events of diabetic retinopathy were reported in 5 patients treated with semaglutide (4 patients on 0.5 mg semaglutide and 1 patients on 1.0 mg semaglutide) with no evidence of an effect of the semaglutide dose, and 1 event of diabetic retinopathy in 1 patient treated with placebo. Given the small number of events, the data is inconclusive.

Reviewer comment: The interpretation of the retinopathy data is limited by the fact that there was no retinopathy scoring using an adequate retinopathy scale (i.e., ETDRS [Early Treatment Diabetic Retinopathy Study]). As defined by the applicant, the outcomes of need for retinal photocoagulation or treatment with intravitreal agents are not adequate, as various factors such as cost, reimbursement, medical alternatives and a variety of individual interests can

influence the "need" or "actual" retinal photocoagulation treatment. Diabetes-related blindness as defined by the applicant is also confusing as it is not clear that the adjudicated blindness in the semaglutide program is actually a consequence of diabetic retinopathy. Vitreal hemorrhage would be a reasonable endpoint, however, the duration of the event was not adequately captured, and the number of events is small. Despite these limitations, a trend towards worsening nephropathy with semaglutide was observed compared to placebo, based on the adjudicated data from the CVOT. It is possible that the worsening in retinopathy is seen in response to a rapid improvement in glycemic control with semaglutide, which was seen in all phase 3 trials, including the CVOT. The most well-known of the studies to demonstrate this was the Diabetic Control and Complications Trial (DCCT). The DCCT study demonstrated that rapid decreases in HbA1c resulted in initial increased risk of retinopathy, followed by benefit in the long run with aggressive glycemic lowering. While the DCCT demonstrated this finding in patients with Type 1 diabetes, Dr Wiley Chambers, the FDA ophthalmology consultant is of the opinion that this applies for both Type 1 and Type 2 diabetics [Literature examples include by are not limited to Arch Ophthalmol. 2006; 124: 38-45. and Diabetes Research and Clinical Practice. 2014; 103 (3): e37-39.] As expected, patients with retinopathy at baseline appear to be at higher risk for this type of event. In studies of patients with T2DM, such as UKPDS, and ACCORD Eye study, better glycemic control did result in improvement in diabetic retinopathy outcomes in the long run, however it is not clear whethes an initial worsening in DR was seen with better glycemic control in either of these studies as the earliest follow up was 3 years for UKPDS, and 4 years for ACCORD. However, in the case of semaglutide, we have no evidence that glycemic lowering will lead to improvement in retinopathy in the long run, as the longest trial in the program was only of 2 years duration. It is likely that a longer study looking specifically at retinopathy may be needed to elucidate this issue.

8.5.3. **Diabetic Nephropathy**

CVOT

New or worsening nephropathy was a MESI and adjudicated in the CVOT. The new or worsening nephropathy composite was defined as:

- new onset of persistent macroalbuminuria, or
- persistent doubling of serum creatinine level and creatinine clearance per MDRD ≤45 mL/min/1.73m2, or
- the need for continuous renal replacement therapy (in the absence of an acute reversible cause) or
- death due to renal disease

Macroalbuminuria was defined either as a 24-hour urine collection above 300 mg or as an elevated concentration in a spot sample above 300 mg/L. To confirm persistent

macroalbuminuria or persistent doubling of serum creatinine, a confirmatory measurement was to be performed within 12 weeks.

The nephropathy events sent for adjudication by the investigators were based both on their identification of AEs and on their evaluation of laboratory results (from samples taken at scheduled visits). In addition, elevated laboratory values could trigger separate laboratory reports for adjudication: elevated laboratory values were identified through an automated screening of all available laboratory values (independent of the evaluation made by the investigators). In the automated screening, elevated values for creatinine and urinary albumin-to-creatinine ratio were defined relative to the lowest available value for each patient.

A total of 174 events of nephropathy were confirmed by the EAC with onset during the in-trial period. There appeared to be a higher percentage of patients with applicant-defined new or worsening nephropathy in the placebo group compared to semaglutide, however, this difference was entirely due to a difference in the persistent macroalbuminuria category. There was no difference in the initiation of continuous renal-replacement therapy, and there was a slightly higher proportion of patients in the semaglutide group that experienced doubling of serum creatinine and creatinine clearance compared to placebo.

The applicant did not report any deaths due to renal disease, but specified that one patient in the semaglutide 0.5 mg arm died due to complications from peritoneal dialysis (lactic acidosis due to sepsis), however, this event was not confirmed by the EAC as nephropathy event.

Table180 EAC-Confirmed New or Worsening Nephropathy, Semaglutide Versus Placebo-FAS In-Trial, CVOT

	Sema total				Placebo total			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1648				1649			
PYO	3408.2				3401.1			
All events								
New or worsening nephropathy	62	(3.8)	68	2.00	100	(6.1)	106	3.12
Persistent macroalbuminuria	44	(2.7)	46	1.35	81	(4.9)	82	2.41
Persistent doubling of serum creatinine level and creatinine clearancea	18	(1.1)	19	0.56	14	(0.8)	15	0.44
Continuous renal-replacement therpy	11	(0.7)	11	0.32	12	(0.7)	12	0.35

Note: a per MDRD<45 mL/min/1.73m^2. Number of events for each component of the composite microvascular outcome represents the total number of diagnostic criteria met in the adjudication. An event with more diagnostic criteria met thus contributes with more than 1 to the number of events."
Abbreviations: E: number of events; EAC: event adjudication committee; FAS: full analysis set; MDRD: modification of diet in renal disease; N: number of subjects; PYO: patient years of observation; R: event rate per 100 patient years of observation (PYO); sema: semaglutide; %: proportion of subjects with event.

Source: Table 13-50 study report CVOT

In conclusion, fewer cases of new, persistent macroalbuminuria were seen with semaglutide compared to placebo. The other components of the pre-defined nephropathy endpoint

occurred in small numbers and they were balanced between the treatment arms. Renal AEs and changes in eGFR will be discussed later in this review.

Reviewer comment: Macroalbuminuria in patients with type 2 diabetes is typically associated with a progressive reduction in glomerular filtration rate (GFR). However, despite a difference in persistent macroalbuminuria favoring semaglutide, no difference in eGFR trends was seen over time between the treatment arms.

This, in addition to other factors that affect the amount of albumin in the urine (such as glycemic control, blood pressure, etc), render the macroalbuminuria findings in SUSTAIN 6 inconclusive. Notably, the glycemic control was significantly different between the semaglutide arms and placebo, more in the range of an efficacy study rather than what was observed previously in similarly designed studied. This is important as it makes us question whether the diabetes treatment in the placebo (standard of care) arm was appropriately optimized, and further questions the significance of the nephropathy findings, whether they can be attributed to the drug or just better glycemic control with the drug compared to placebo.

Nephropathy- MedDRA search

Additionally, MedDRA search performed by the applicant to identify all events potentially related to new or worsening nephropathy in the semaglutide phase 3 program.

The pre-specified MedDRA search is presented in Section 13.2.

CVOT

The proportion of patients with events was lower with semaglutide compared to placebo (8.7% of patients in the semaglutide 0.5 mg, 6.5% in the semaglutide 1 mg, and 9.9% in placebo), with no dose-dependence observed. SAEs were reported in 1.2% of patients in semaglutide 0.5 mg, 1.1% in the semaglutide 1 mg, and 1.5% in placebo).

Table 181 Nephropathy Adverse Events - MedDRA Search - by System Organ Class, High Level Group Term and Preferred Term - CVOT - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N (%)	E	R	Sema 1.0 mg N (%)	E	R	All sema N (%)	E	R	Comparator N (%)	E	R
N and PYE (year)	823 1488			819 1444			1642 2932			1644 3035		
All events	72 (8.7)	83	5.6	53 (6.5)	57	3.9	125 (7.6)	140	4.8	163 (9.9)	197	6.5
Renal and urinary disorders	51 (6.2)	56	3.8	38 (4.6)	39	2.7	89 (5.4)	95	3.2	128 (7.8)	145	4.8
Renal disorders (excl nephropathies)	29 (3.5)	30	2.0	18 (2.2)	18	1.2	47 (2.9)	48	1.6	60 (3.6)	68	2.2
Chronic kidney disease	14 (1.7)	14	0.9	8 (1.0)	8	0.6	22 (1.3)	22	0.8	43 (2.6)	49	1.6
Renal impairment	10 (1.2)	10	0.7	6 (0.7)	6	0.4	16 (1.0)	16	0.5	9 (0.5)	9	0.3
Renal failure	5 (0.6)	5	0.3	4 (0.5)	4	0.3	9 (0.5)	9	0.3	7 (0.4)	8	0.3
Azotaemia	1 (0.1)	1	<0.1				1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Anuria										1 (<0.1)	1	<0.1
Nephropathies	10 (1.2)	10	0.7	13 (1.6)	13	0.9	23 (1.4)	23	0.8	41 (2.5)	42	1.4
Diabetic nephropathy	5 (0.6)	5	0.3	7 (0.9)	7	0.5	12 (0.7)	12	0.4	19 (1.2)	19	0.6
Nephropathy	5 (0.6)	5	0.3	6 (0.7)	6	0.4	11 (0.7)	11	0.4	23 (1.4)	23	0.8
Urinary tract signs and symptoms	16 (1.9)	16	1.1	8 (1.0)	8	0.6	24 (1.5)	24	0.8	33 (2.0)	35	1.2
Proteinuria	14 (1.7)	14	0.9	8 (1.0)	8	0.6	22 (1.3)	22	0.8	31 (1.9)	32	1.1
Albuminuria	2 (0.2)	2	0.1				2 (0.1)	2	<0.1	2 (0.1)	3	<0.1
Investigations	22 (2.7)	25	1.7	16 (2.0)	17	1.2	38 (2.3)	42	1.4	45 (2.7)	51	1.7
Renal and urinary tract investigations and urinalyses	22 (2.7)	25	1.7	16 (2.0)	17	1.2	38 (2.3)	42	1.4	45 (2.7)	51	1.7
Blood creatinine increased	21 (2.6)	23	1.5	12 (1.5)	13	0.9	33 (2.0)	36	1.2	38 (2.3)	41	1.4
Urine albumin/creatinine ratio increased	1 (0.1)	1	<0.1	2 (0.2)	2	0.1	3 (0.2)	3	0.1	8 (0.5)	8	0.3
Glomerular filtration rate decreased				1 (0.1)	1	<0.1	1 (<0.1)	1	<0.1	2 (0.1)	2	<0.1
Urine albumin/creatinine ratio abnormal				1 (0.1)	1	<0.1	1 (<0.1)	1	<0.1			
Protein urine present	1 (0.1)	1	<0.1				1 (<0.1)	1	<0.1			
Blood and lymphatic system disorders	1 (0.1)	1	<0.1	1 (0.1)	1	<0.1	2 (0.1)	2	<0.1			
Anaemias nonhaemolytic and marrow depression	1 (0.1)	1	<0.1	1 (0.1)	1	<0.1	2 (0.1)	2	<0.1			
Nephrogenic anaemia	1 (0.1)	1	<0.1	1 (0.1)	1	<0.1	2 (0.1)	2	<0.1			
Endocrine disorders	1 (0.1)	1	<0.1				1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Parathyroid gland disorders	1 (0.1)	1	<0.1				1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Hyperparathyroidism secondary	1 (0.1)	1	<0.1				1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Table 7.10.25 ISS

Data from the in-trial observation period were consistent with data from the on-treatment period.

Phase 3 pool

Nephropathy events were identified based on investigator-reported AEs, and the events were not adjudicated. Events were reported in 1.3% of patients on semaglutide 0.5 mg, 1.7% of patients on semaglutide 1 mg, and 1.5% of patients on placebo. The SAEs were rare, one in each semaglutide group, and none in placebo.

Table 182 Nephropathy Adverse Events - MedDRA SEARCh - by System Organ Class, High Level Group Term and Preferred Term - Phase 3 Pool - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	All sema N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			3150	2712			1657	1467		
All events	18	(1.3)	21	1.9	29	(1.7)	30	2.0	47	(1.6)	51	2.0	25	(1.5)	26	1.8
Investigations	7	(0.5)	9	0.8	15	(0.8)	16	1.0	22	(0.7)	25	0.9	15	(0.9)	15	1.0
Renal and urinary tract investigations and urinalyses	7	(0.5)	9	0.8	15	(0.8)	16	1.0	22	(0.7)	25	0.9	15	(0.9)	15	1.0
Blood creatinine increased	4	(0.3)	4	0.4	10	(0.6)	10	0.6	14	(0.5)	14	0.5	5	(0.3)	5	0.3
Urine albumin/creatinine ratio increased	1	(<0.1)	1	<0.1	3	(0.2)	3	0.2	4	(0.1)	4	0.1	5	(0.3)	5	0.3
Glomerular filtration rate decreased	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1	3	(0.1)	3	0.1				
Blood creatinine abnormal	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	2	(<0.1)	2	<0.1				
Glomerular filtration rate abnormal	1	(<0.1)	1	<0.1					1	(<0.1)	1	<0.1				
Urine albumin/creatinine ratio abnormal	1	(<0.1)	1	<0.1					1	(<0.1)	1	<0.1				
Protein urine present													5	(0.3)	5	0.4
Renal and urinary disorders	12	(0.9)	12	1.1	14	(0.8)	14	0.9	26	(0.9)	26	1.0	11	(0.7)	11	0.7
Nephropathies	4	(0.3)	4	0.4	6	(0.3)	6	0.4	10	(0.3)	10	0.4	5	(0.3)	5	0.4
Diabetic nephropathy	4	(0.3)	4	0.4	5	(0.3)	5	0.3	9	(0.3)	9	0.4	4	(0.3)	4	0.3
Nephropathy					1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Renal disorders (excl nephropathies)	3	(0.2)	3	0.3	5	(0.3)	5	0.3	8	(0.3)	8	0.4	5	(0.3)	5	0.3
Renal failure	2	(0.2)	2	0.2	3	(0.2)	3	0.2	5	(0.2)	5	0.2	1	(<0.1)	1	<0.1
Renal impairment	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1	3	(0.1)	3	0.1	3	(0.2)	3	0.2
Chronic kidney disease													1	(<0.1)	1	<0.1
Urinary tract signs and symptoms	5	(0.4)	5	0.4	3	(0.2)	3	0.2	8	(0.2)	8	0.3	1	(<0.1)	1	<0.1
Proteinuria	3	(0.2)	3	0.3	3	(0.2)	3	0.2	6	(0.2)	6	0.2	1	(<0.1)	1	<0.1
Albuminuria	2	(0.1)	2	0.2					2	(<0.1)	2	<0.1				

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Table 7.10.21 ISS

Placebo pool

Nephropathy events identified by MedDRA search for the placebo-controlled trials 3623 and 3627 comprise 7 events in 7 (1.3%) patients with semaglutide and 7 events in 6 (2.3%) patients with placebo.

Table 183 Nephropathy Adverse Events - MedDRA Search - by System Organ Class, High Level Group Term and Preferred Term – Placebo Pool - On-Treatment

System organ class High level group term Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	All sema N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	260	165			261	164			521	329			262	166		
All events	1	(0.4)	1	0.6	6	(2.3)	6	3.7	7	(1.3)	7	2.1	6	(2.3)	7	4.2
Investigations					4	(1.5)	4	2.4	4	(0.8)	4	1.2	4	(1.5)	4	2.4
Renal and urinary tract investigations and urinalyses					4	(1.5)	4	2.4	4	(0.8)	4	1.2	4	(1.5)	4	2.4
Blood creatinine increased					3	(1.2)	3	1.8	3	(0.6)	3	0.9	1	(0.4)	1	0.6
Urine albumin/creatinine ratio increased					1	(0.4)	1	0.6	1	(0.2)	1	0.3	1	(0.4)	1	0.6
Protein urine present													2	(0.8)	2	1.2
Renal and urinary disorders	1	(0.4)	1	0.6	2	(0.8)	2	1.2	3	(0.6)	3	0.9	3	(1.1)	3	1.8
Nephropathies					1	(0.4)	1	0.6	1	(0.2)	1	0.3				
Diabetic nephropathy					1	(0.4)	1	0.6	1	(0.2)	1	0.3				
Urinary tract signs and symptoms					1	(0.4)	1	0.6	1	(0.2)	1	0.3	1	(0.4)	1	0.6
Proteinuria					1	(0.4)	1	0.6	1	(0.2)	1	0.3	1	(0.4)	1	0.6
Renal disorders (excl nephropathies)	1	(0.4)	1	0.6					1	(0.2)	1	0.3	2	(0.8)	2	1.2
Renal failure	1	(0.4)	1	0.6					1	(0.2)	1	0.3	1	(0.4)	1	0.6
Chronic kidney disease													1	(0.4)	1	0.6

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Placebo pool: trial (comparator): 3623 (placebo), 3627 (placebo), Table is sorted by system organ class, high level group term and preferred term based on highest frequency in the Sema 1.0 mg arm, if no events then by the Sema 0.5 mg arm, For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Table 7.10.23 ISS

8.5.4. **Acute renal Failure**

In patients with T2DM, AEs of acute renal failure have been associated with some GLP-1 RAs, including liraglutide. The majority of such events occurred in patients with pre-existing risk factors such as renal impairment, advanced age and concomitant use of diuretics, and were reported in association with gastrointestinal symptoms such as nausea, vomiting and diarrhea leading to dehydration. Acute renal failure was pre-defined as a safety area of interest for the semaglutide program.

The potential effect of semaglutide on renal function is evaluated based on data from the CVOT and on the data from the phase 3 trials excluding the CVOT. AEs of acute renal failure as well as reports of significant kidney-related laboratory abnormalities were identified by a narrow and a broad MedDRA search.

Acute renal failure – narrow MedDRA search

CVOT

Events were balanced between treatment groups. the three most common were AEs of acute kidney injury, renal impairment and renal failure, the frequency and rates of which were low and comparable across the groups.

Table 184 Acute Renal Failure (Narrow MedDRA Search) by Preferred Term - SAS On-Treatment - CVOT

System organ class Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Placebo N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1644	3035		
All events	33	(4.0)	35	2.4	19	(2.3)	21	1.5	58	(3.5)	63	2.1
Renal and urinary disorders	33	(4.0)	35	2.4	19	(2.3)	21	1.5	58	(3.5)	63	2.1
Acute kidney injury	16	(1.9)	18	1.2	10	(1.2)	11	0.8	41	(2.5)	43	1.4
Renal impairment	10	(1.2)	10	0.7	6	(0.7)	6	0.4	9	(0.5)	9	0.3
Renal failure	5	(0.6)	5	0.3	4	(0.5)	4	0.3	7	(0.4)	8	0.3
Acute prerenal failure	1	(0.1)	1	<0.1					1	(<0.1)	1	<0.1
Azotaemia	1	(0.1)	1	<0.1					1	(<0.1)	1	<0.1
Anuria									1	(<0.1)	1	<0.1

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.
Source: Table 2-99 ISS

In the 'in-trial' observation period, 32 AEs were identified by the narrow MedDRA search in addition to those belonging to the 'on-treatment' period, however the event distribution between the treatment arms is similar to the on-treatment analysis.

Almost half of the events were SAEs, balanced between semaglutide and placebo.

Table 185 Acute Renal Failure Adverse Events (Narrow MedDRA Search) – SAS On-Treatment – CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
PYE	1488.3				1443.9				3034.8			
Events	33	(4.0)	35	2.4	19	(2.3)	21	1.5	58	(3.5)	63	2.1
Serious adverse events												
Yes	17	(2.1)	19	1.3	8	(1.0)	9	0.6	33	(2.0)	35	1.2
No	16	(1.9)	16	1.1	11	(1.3)	12	0.8	26	(1.6)	28	0.9
Outcome												
Recovered	25	(3.0)	26	1.7	14	(1.7)	15	1.0	45	(2.7)	48	1.6
Fatal	2	(0.2)	2	0.1	0				3	(0.2)	3	0.1
Recovering	1	(0.1)	1	0.1	1	(0.1)	1	0.1	2	(0.1)	2	0.1
Recovered with sequelae	0				0				2	(0.1)	2	0.1
Not recovered	6	(0.7)	6	0.4	5	(0.6)	5	0.3	8	(0.5)	8	0.3
Unknown	0				0				0			
Leading to premature treatment discontinuation												
Yes	2	(0.2)	2	0.1	0				2	(0.1)	2	0.1
No	31	(3.8)	33	2.2	19	(2.3)	21	1.5	57	(3.5)	61	2.0
Action taken												
Dose not changed	24	(2.9)	26	1.7	16	(2.0)	16	1.1	42	(2.6)	44	1.4
Drug interrupted	3	(0.4)	3	0.2	1	(0.1)	1	0.1	4	(0.2)	4	0.1
Drug withdrawn	2	(0.2)	2	0.1	0				2	(0.1)	2	0.1
Dose reduced	0				0				0			
Dose increased	0				0				0			
Unknown	0				0				0			
Not applicable	4	(0.5)	4	0.3	4	(0.5)	4	0.3	12	(0.7)	13	0.4
Missing	0				0				0			

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-100 ISS

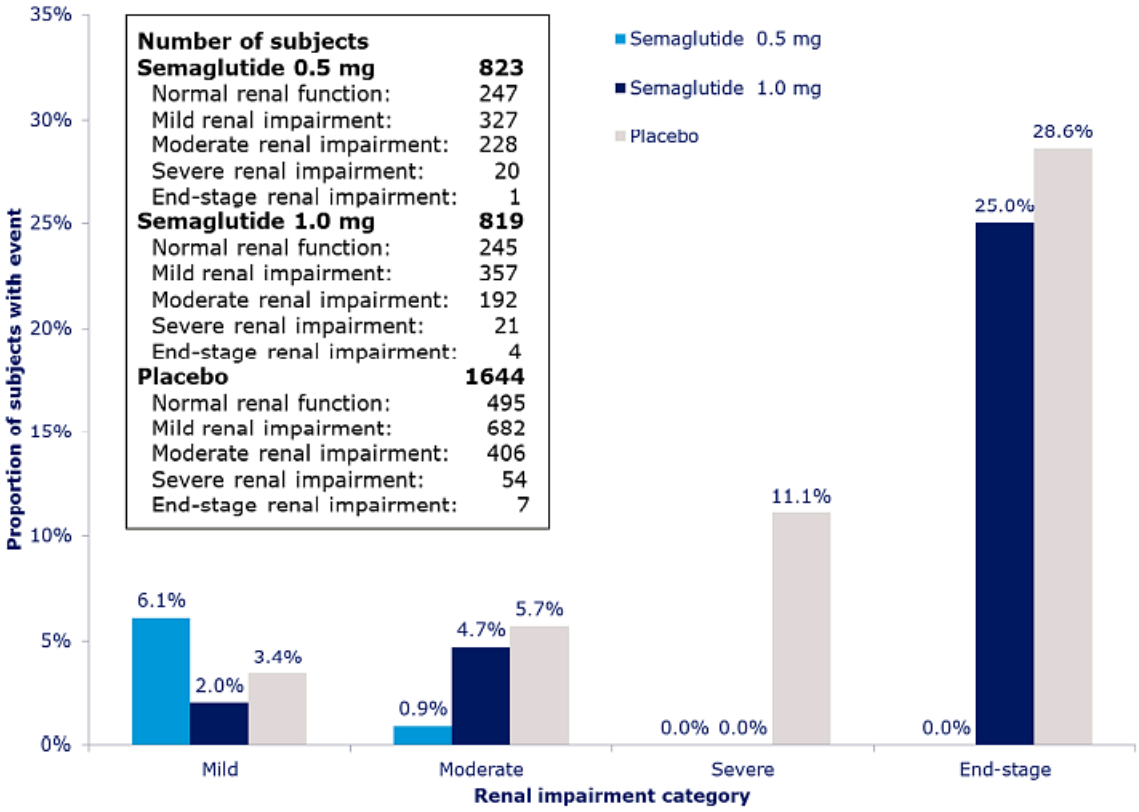
The most commonly reported SAE was acute kidney injury (1.5%, 0.6% and 1.8% of the patients with semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively).

The majority (52 of 63) of the SAEs had recovered or were recovering at the end of treatment. Five SAEs had a fatal outcome (all due to SAEs of acute kidney injury and all treatment-emergent); 2 with semaglutide 0.5 mg and 3 with placebo. The 2 patients with semaglutide died in connection with sepsis and multi-organ failure; the cause of death for the 3 patients with placebo was congestive heart failure, cardiogenic shock, and sepsis, respectively.

Two additional SAEs with a fatal outcome belonged to the 'in-trial' observation period; 1 SAE of anuria (semaglutide 0.5 mg) and 1 SAE of acute kidney injury (placebo).

While a higher proportion of patients with renal dysfunction at baseline developed acute renal AEs, the risk did not appear to be increased with semaglutide vs placebo.

Figure 67 Proportion of Patients with AEs Related to Acute Renal Failure (Narrow MedDRA Search) by Renal Impairment Category at Baseline – SAS On-Treatment – CVOT



N = total number of subjects. Proportion of subjects with events are relative to the number of subjects in each renal impairment category
Source: Figure 2-62 ISS

Phase 3 trials excl. CVOT and placebo pool

Across the phase 3 trials (excl. the CVOT), the number of AEs identified by the acute renal failure MedDRA search (narrow) was low with semaglutide 0.5 mg, semaglutide 1 mg and comparators. As seen in **Table 186** below, no specific trends can be observed.

Table 186 Acute Renal Failure - Adverse Events - Narrow - MedDRA Search - Phase 3 trials and Pools - On-Treatment

	Sema 0.5 mg				Sema 1.0 mg				All sema				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYE (year)																
Ph 3a pool	1373	1165			1777	1548			3150	2712			1657	1467		
Placebo pool	260	165			261	164			521	329			262	166		
3623 vs Placebo (Mono)	128	80			130	82			258	162			129	81		
3626 vs Sita (OADs)	409	435			409	431			818	866			407	453		
3624 vs Exe ER (OADs)					404	414			404	414			405	408		
3625 vs IGlar (OADs)	362	225			360	219			722	444			360	235		
3627 vs Placebo (Insulin)	132	84			131	82			263	166			133	84		
4092 vs Sita (Mono), JP	103	69			102	63			205	132			103	70		
4091 vs OAD (OAD), JP	239	271			241	257			480	528			120	136		
All Events																
Ph 3a pool	3	(0.2)	3	0.3	9	(0.5)	9	0.6	12	(0.5)	12	0.6	5	(0.3)	5	0.3
Placebo pool	1	(0.4)	1	0.6	1	(0.4)	1	0.6	2	(0.4)	2	0.6	2	(0.8)	2	1.2
3626 vs Sita (OADs)	1	(0.2)	1	0.2					1	(0.1)	1	0.1	2	(0.5)	2	0.4
3624 vs Exe ER (OADs)					5	(1.2)	5	1.2	5	(1.2)	5	1.2	1	(0.2)	1	0.2
3625 vs IGlar (OADs)	1	(0.3)	1	0.4	3	(0.8)	3	1.4	4	(0.6)	4	0.9				
3627 vs Placebo (Insulin)	1	(0.8)	1	1.2	1	(0.8)	1	1.2	2	(0.8)	2	1.2	2	(1.5)	2	2.4
Serious																
Yes																
Ph 3a pool	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1	3	(<0.1)	3	0.1				
3626 vs Sita (OADs)	1	(0.2)	1	0.2					1	(0.1)	1	0.1				
3625 vs IGlar (OADs)					2	(0.6)	2	0.9	2	(0.3)	2	0.5				
No																
Ph 3a pool	2	(0.2)	2	0.2	7	(0.4)	7	0.5	9	(0.4)	9	0.5	5	(0.3)	5	0.3
Placebo pool	1	(0.4)	1	0.6	1	(0.4)	1	0.6	2	(0.4)	2	0.6	2	(0.8)	2	1.2
3626 vs Sita (OADs)													2	(0.5)	2	0.4
3624 vs Exe ER (OADs)					5	(1.2)	5	1.2	5	(1.2)	5	1.2	1	(0.2)	1	0.2
3625 vs IGlar (OADs)	1	(0.3)	1	0.4	1	(0.3)	1	0.5	2	(0.3)	2	0.5				
3627 vs Placebo (Insulin)	1	(0.8)	1	1.2	1	(0.8)	1	1.2	2	(0.8)	2	1.2	2	(1.5)	2	2.4

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), Placebo pool: trial (comparator): 3623 (placebo), 3627 (placebo), Multinational pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin) and 3627 (placebo), For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent, MedDRA version 18.0

Source: Table 7.6.138 ISS

The narrow MedDRA search identified 3 SAEs of acute renal failure (SAEs of renal failure with semaglutide 0.5 mg and semaglutide 1 mg, and a SAE of acute renal failure with semaglutide 1 mg; none with comparators). All 3 SAEs were secondary to dehydration due to GI AEs or insufficient fluid intake. None of the SAEs had a fatal outcome. The broad MedDRA search did not identify any additional SAEs.

There was no apparent clustering in the onset of the AEs.

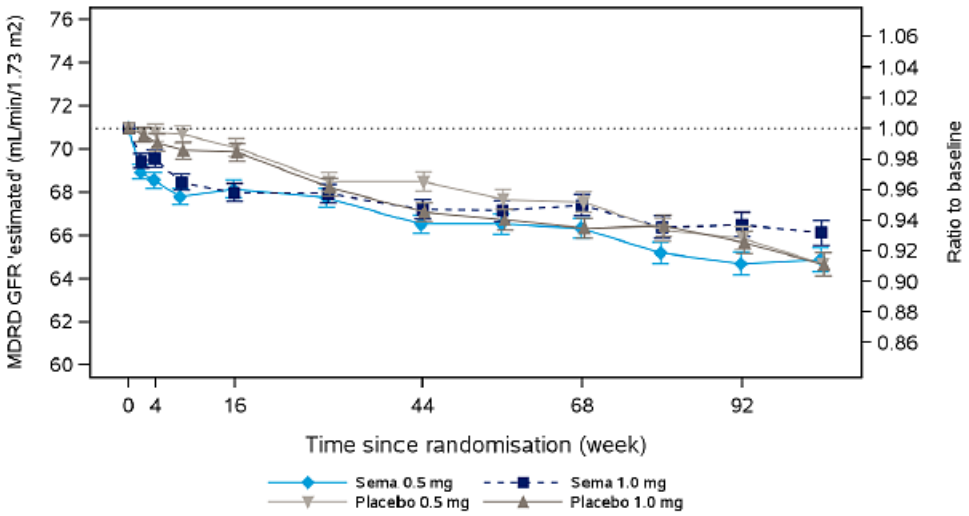
Renal function tests

CVOT

eGFR

In all groups, the mean eGFR decreased and remained below the baseline throughout the trial

Figure 68 eGFR by Treatment Week (Geometric Mean) – SAS On-Treatment – CVOT



'On-treatment' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM calculated on log-scale and back-transformed to original scale.
Dotted line is the total average value at baseline.

Source: Figure 2-63 ISS

Table 187 Post-Baseline Decrease in eGFR by Baseline Renal Function

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo 0.5 mg N (%)	Placebo 1.0 mg N (%)
MDRD GFR 'estimated' (mL/min/1.73 m2) - Summary of minimum post-baseline value				
Increase to max 10% decrease	178 (21.63)	187 (22.83)	231 (28.17)	201 (24.45)
Normal	52 (21.14)	40 (16.26)	71 (29.10)	66 (26.19)
Mild	77 (23.48)	89 (25.07)	101 (30.15)	89 (25.72)
Moderate	46 (20.18)	54 (27.98)	50 (23.36)	40 (20.94)
Severe	3 (14.29)	4 (16.00)	9 (33.33)	6 (18.18)
From 10% to 25% decrease	378 (45.93)	399 (48.72)	368 (44.88)	377 (45.86)
Normal	126 (51.22)	143 (58.13)	120 (49.18)	134 (53.17)
Mild	146 (44.51)	176 (49.58)	157 (46.87)	152 (43.93)
Moderate	101 (44.30)	72 (37.31)	89 (41.59)	81 (42.41)
Severe	5 (23.81)	8 (32.00)	2 (7.41)	10 (30.30)
From 25% to 50% decrease	225 (27.34)	216 (26.37)	188 (22.93)	212 (25.79)
Normal	62 (25.20)	59 (23.98)	48 (19.67)	44 (17.46)
Mild	87 (26.52)	83 (23.38)	65 (19.40)	97 (28.03)
Moderate	69 (30.26)	63 (32.64)	64 (29.91)	63 (32.98)
Severe	7 (33.33)	11 (44.00)	11 (40.74)	8 (24.24)
More than 50% decrease	42 (5.10)	17 (2.08)	33 (4.02)	32 (3.89)
Normal	6 (2.44)	4 (1.63)	5 (2.05)	8 (3.17)
Mild	18 (5.49)	7 (1.97)	12 (3.58)	8 (2.31)
Moderate	12 (5.26)	4 (2.07)	11 (5.14)	7 (3.66)
Severe	6 (28.57)	2 (8.00)	5 (18.52)	9 (27.27)

N: Number of subjects in the summary statistic, %: Percentage of subjects, The minimum and maximum values from all scheduled and un-scheduled post-baseline visits are used; these values are then categorised according to laboratory range values.

Source: Table 15.3.5.61 study report 3744

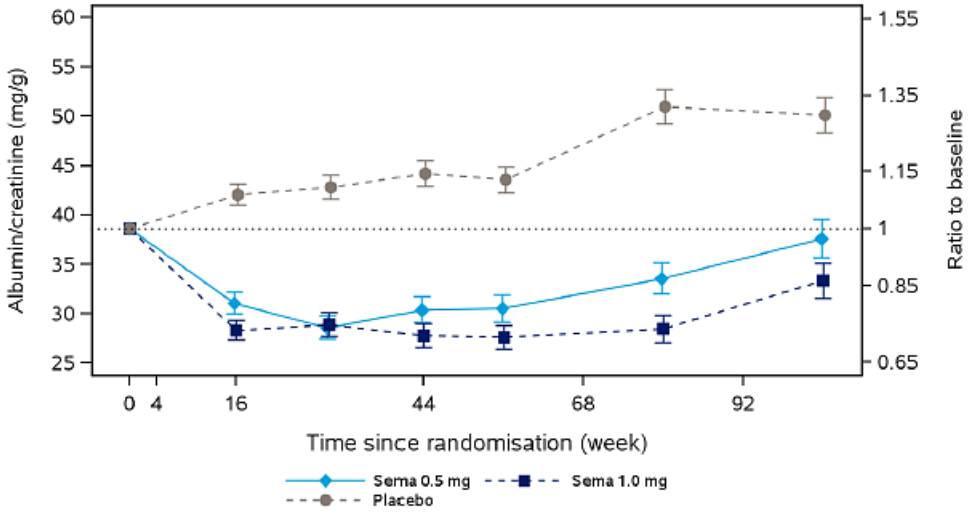
Urine albumin-to-creatinine ratio (UACR)

The interpretation of this data is limited by the missing data; of the total number of patients randomized to semaglutide and placebo, respectively, 82.8% and 81.0% had UACR data available at baseline compared with 67.5% and 68.9% at week 104.

At baseline, the mean UACR was similar across groups, and a decrease was observed at week 16 with both semaglutide doses, however at the end of the study, patients on semaglutide 0.5 mg were back to baseline levels for UACR, while patients on semaglutide 1 mg were still slightly below baseline values. By contrast, the patients on placebo had a gradual increase in UACR over the duration of the trial.

The UACR over time is presented below.

Figure 69 Estimated UACR (mg/g) by Treatment Week (Geometric Mean) – SAS On-Treatment – CVOT



'On-treatment' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment group (4 levels) and stratification (9 levels) as fixed factors and baseline amylase as a covariate, all nested within visit, and are adjusted according to observed baseline distribution. From this model, the mean for pooled placebo was derived.
Error bars are +/-1*SEM calculated on log-scale and back-transformed to original scale.
Dotted line is the total average value at baseline.

Source: Figure 2-64 ISS

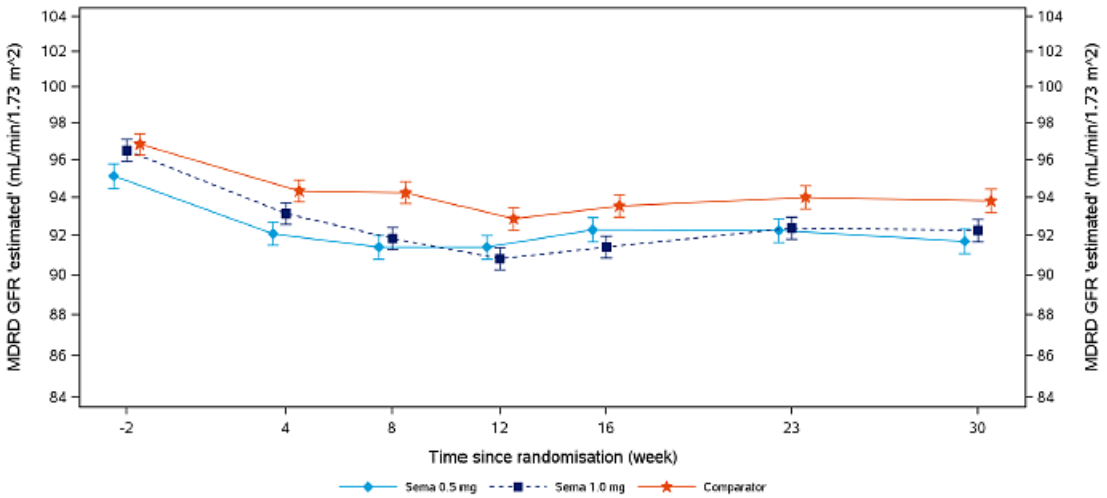
Reviewer's comment: While a slight benefit is apparent with semaglutide vs placebo based on the data presented above, I believe that the interpretation of the data is confounded by the profound differences in glycemic control between semaglutide groups and placebo in this trial, despite the treat to target design.

<u>Phase 3 trials excluding CVOT</u>

eGFR

From comparable baseline levels across the groups, the mean eGFR decreased initially and then remained stable below the baseline through week 30 with semaglutide 0.5 and 1.0 mg and with comparators. Overall, no major differences were seen semaglutide vs comparator.

Figure 70 eGFR (mL/min/1.73 m2) by Treatment Week (Geometric Mean) – SAS On-Treatment - Phase 3 Pool



SAS. on-treatment observation period. observed data. Group geometric means (+/-error bars). Error bars are SD/sqrt(n). Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale. Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin). MDRD: modification of diet in renal disease. eGFR: estimated glomerular filtration rate.

Source: Figure 2-65 ISS

UACR

In the phase 3 trials excluding the CVOT, the UACR was assessed at baseline and at end-of-trial. The mean UACR was similar at both assessments across the groups.

The summary of minimum port-baseline values for eGFR and UACR are presented in **Table 188** below by treatment group. Most patients had decreased in eGFR over time between 10-25% of baseline (the lowest eGFR), with no significant differences between treatment groups. Over 70% of patients in each treatment group had a maximum value for UACR that was in the normal range.

Table 188 Renal Laboratory Parameters - Categorical Summary of Extreme Post-Baseline Values - Phase 3 Pool

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Comparators N (%)
Number of subjects	1373	1777	1657
eGFR (mL/min/1.73 m^2) - Summary of minimum post-baseline value			
Increase to max 10% decrease	552 (40.4)	617 (35.0)	664 (40.3)
From 10% decrease to 25% decrease	687 (50.3)	894 (50.7)	789 (47.9)
From 25% decrease to 50% decrease	122 (8.9)	231 (13.1)	180 (10.9)
More than 50% decrease	5 (0.4)	19 (1.1)	14 (0.9)
UACR (mg/g) - Summary of maximum post-baseline value			
<30 mg/g	659 (73.7)	911 (76.9)	793 (70.0)
>=30 mg/g and <=300 mg/g	201 (22.5)	235 (19.8)	281 (24.8)
>300 mg/g	34 (3.8)	39 (3.3)	59 (5.2)

Notes: For each subject, the extreme post-baseline value from all scheduled and un-scheduled visits are included in the summary.

Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)

Abbreviations: eGFR: estimated glomerular filtration rate, N: number of subjects in the summary statistic, UACR: urinary albumin-to-creatinine ratio, ULN: upper limit of the normal, %: percentage of subjects

Source: Table 2-102 ISS

Based on data from the CVOT and the phase 3 pool, no dose-response relationship was apparent for semaglutide with regards to the frequency, severity, seriousness and rate of premature treatment discontinuation for AEs identified by the acute renal failure MedDRA search (narrow). Additionally, the eGFR decrease with semaglutide did not appear to be dose-dependent.

In conclusion, overall, the totality of the data do not suggest any kidney-related adverse effects with semaglutide treatment. However, AKI is a an adverse event with the GLP-1 RA class of drugs, currently labelled in the Warnings and Precautions sections of the product information for the other members of the class. Despite the lack of data for semaglutide, I recommend that the prescribing information is in line with other members of the class. The GI adverse events with semaglutide (and other members of the class) can lead to dehydration and AKI, and this may not be seen in a small development program.

8.5.5. Pancreatitis

Pancreatitis was identified as a MESI, as the use of incretin-based drugs has been associated with development of pancreatitis, although this association is still under discussion.

Patients with history of acute or chronic pancreatitis were excluded from the semaglutide clinical program. Additionally, the study drug was discontinued is there was suspicion of acute pancreatitis during the trial, and it could be reinitiated if pancreatitis was ruled out.

Events suspected of pancreatitis were evaluated by the EAC.

The process was as follows: all suspected cases of pancreatitis either investigator-reported or identified via a PTQ were sent for adjudication. The applicant also performed ongoing searches on blinded database for reported AEs of elevated pancreatic enzymes with concomitant reporting of pre-defined gastrointestinal signs and symptoms occurring within 30 days of the elevated enzyme event.

The diagnosis of pancreatitis was confirmed is at least two of the following criteria were fulfilled:

- Characteristic abdominal pain
- Lipase and/or amylase >3xULN
- Characteristic imaging (US, CT, MRI)

Confirmed pancreatitis events were further characterized as acute or chronic. Chronic pancreatitis was defined by characteristic imaging findings with abnormal pancreatic function tests or characteristic histological findings. For the events of acute pancreatitis, the EAC was asked to further classify the severity based on the revised Atlanta criteria. Two additional categories (unable to distinguish between moderately severe and severe pancreatitis, and unable to assess severity) were added in case not enough data was available, but the applicant reported that no events were classified in these additional categories.

Table 189 Classification of Acute Pancreatitis

Pancreatitis	Subclassification[a]	Characteristic symptoms
Acute	Mild	No organ failure, local or systemic complications; resolves in the first week
	Moderate	Transient organ failure (<48 h) and/or local or systemic complications without persistent organ failure
	Severe	Persistent organ failure (>48 h, single/multiple organs)

[a]The revised Atlanta classification of acute pancreatitis[102]

Source: Table 2-103 ISS

Additionally, a MedDRA based strategy was employed to identify all pancreatitis events reported during the trial, as well as monitoring of amylase and lipase throughout the clinical trials.

Monitoring of lipase and amylase levels

Amylase and lipase levels were monitored in all phase 3 clinical trials.

Lipase and amylase were analyzed based on mean levels over time and change from baseline, as well as on data from individual patients with either outlier levels or categorical shifts (>ULN, >2xULN, >3×ULN, >5xULN and >10×ULN) of lipase/amylase are presented. In addition to the laboratory assessments, a MedDRA search (elevated lipase and/or amylase) was performed among all AEs for all trials.

The events of pancreatitis and abnormalities in amylase and/or lipase will be discussed below in the CVOT, phase 3 pool excluding CVOT, and placebo pool.

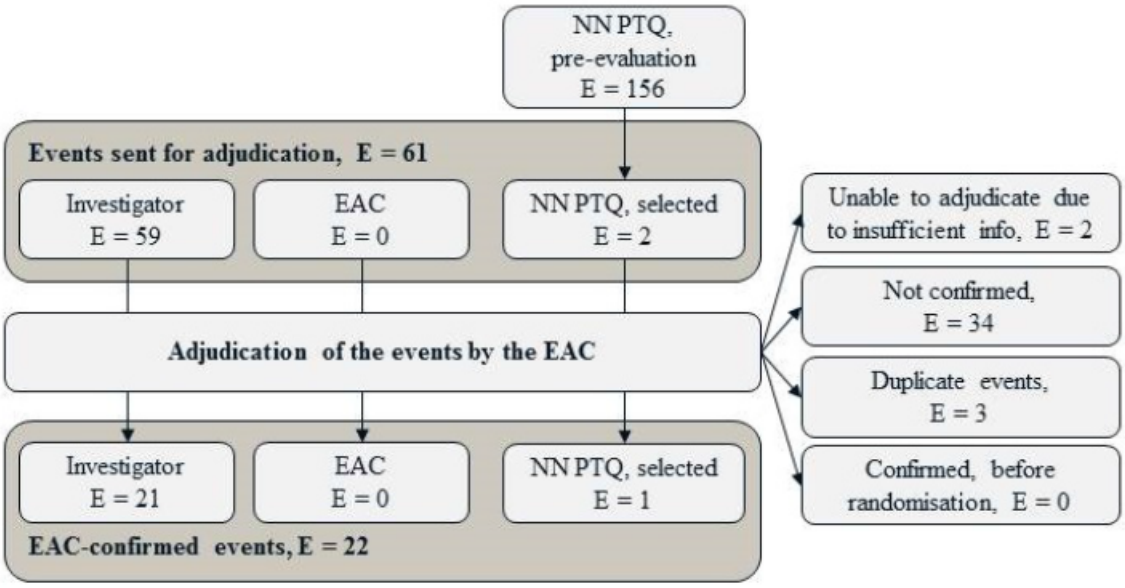
CVOT

EAC confirmed pancreatitis

A total of 22 events of pancreatitis were confirmed by the EAC in the CVOT. Of the 22 confirmed events, 18 occurred during the on-treatment observation period, and additional 3 events during the in-trial observation period. The last event occurred after the in-trial observation period.

The EAC was unable to adjudicate 2 investigator-reported events due to insufficient information, 1 with semaglutide 0.5 mg. and 1 with placebo.

Figure 71 Adjudication Process Flow for Pancreatitis - CVOT



Notes: Diagram presents all events reported from randomisation to data base lock. One (1) event pre-evaluated as pancreatitis, but only adjudicated as a pancreatic neoplasm is not included in this diagramme; see Section 2.11.5 for EAC-confirmed pancreas neoplasms.

Abbreviations: E: number of events; EAC: (external) event adjudication committee; NN PTQ: Novo Nordisk preferred term query.

Source: Figure 2-66 ISS

There were 34 non-confirmed events, mainly reported as elevated pancreatic enzymes, suspicion of pancreatitis, or abdominal pain. The overall confirmation rate for events sent for adjudication was lower for the semaglutide arms (30%) compared to placebo (43%).

Of the 18 patients with on-treatment EAC-confirmed pancreatitis, 8 were on semaglutide, and 10 on placebo, balanced between the treatment groups.

Table 190 EAC-Confirmed Pancreatitis – SAS On-Treatment – CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
Pancreatitis	5	(0.6)	5	0.34	3	(0.4)	3	0.21	10	(0.6)	10	0.33
Acute pancreatitis	5	(0.6)	5	0.34	3	(0.4)	3	0.21	10	(0.6)	10	0.33
Mild acute	5	(0.6)	5	0.34	3	(0.4)	3	0.21	10	(0.6)	10	0.33
Moderately severe	0				0				0			
Severe	0				0				0			
Chronic pancreatitis	0				0				0			

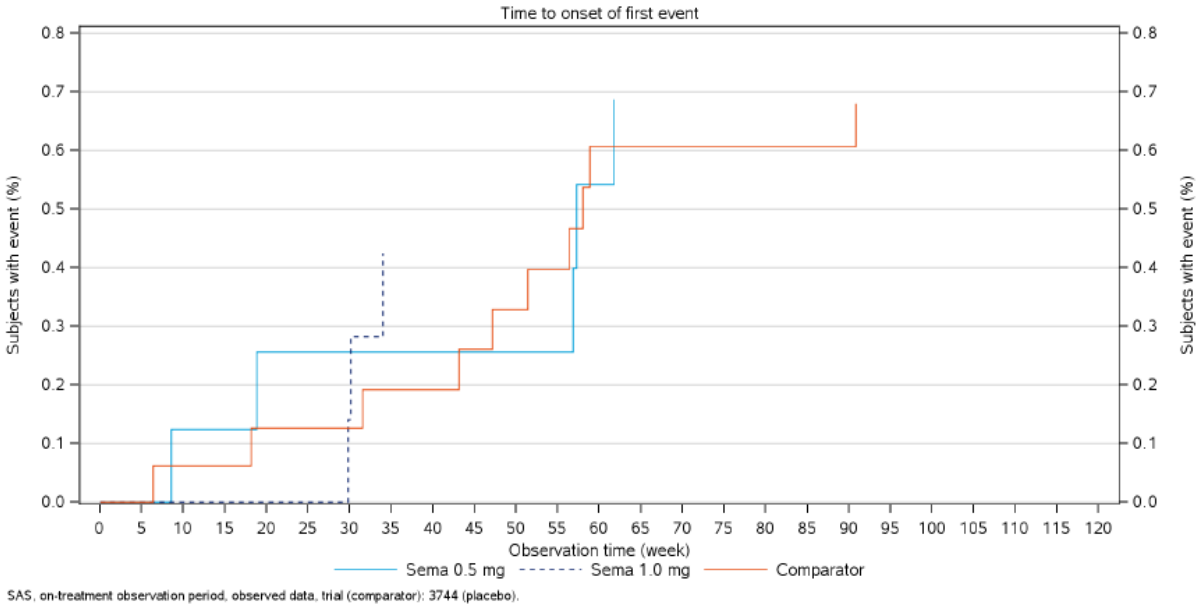
Abbreviations: E: number of events; EAC: (external) event adjudication committee; N: number of subjects with at least one event; %: percentage of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE.

Source: Table 2-105 ISS

The in-trial analysis revealed additional 3 EAC-confirmed patients, one in placebo, and 2 in the semaglutide 0.5 mg group. Even adding these events, semaglutide and placebo groups remain balanced regarding EAC-confirmed pancreatitis.

EAC confirmed pancreatitis events occurred throughout the trial, and there was no evidence of any significant difference between semaglutide and placebo treated patients. The onset ranged between trial days 60–432 days (semaglutide 0.5 mg), 210–238 days (semaglutide 1 mg), and 45–637 days (placebo). No patient had more than one EAC-confirmed event of pancreatitis.

Figure 72 Time to First Pancreatitis Event - CVOT



Source: Figure 2-67 ISS

In addition to the events identified during the trial, 1 non-CV death confirmed by the EAC as pancreatic death and severe acute pancreatitis occurred after the in-trial observation period. After having received semaglutide 1 mg, the patient discontinued treatment on treatment day 21 because of gastrointestinal side effects, but completed the trial. On day 854, the patient developed severe acute pancreatitis, sepsis, and multi-organ failure, and died 2 days after event onset.

MedDRA search

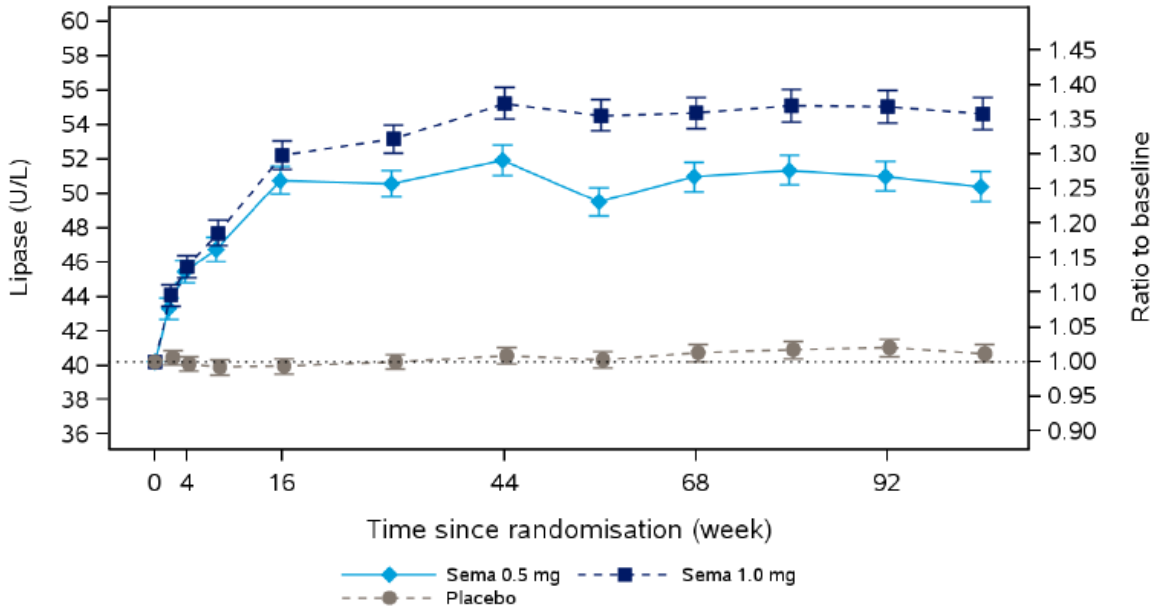
The MedDRA search identified 22 AEs in 21 patients (semaglutide 0.5 mg: 8 events; semaglutide 1 mg: 3 events; placebo: 11 events). All the 21 events were sent for adjudication, and 13 were confirmed by the EAC (semaglutide 0.5 mg: 4 patients; semaglutide 1 mg: 1 patient; placebo: 8 patients). Again, a higher proportion of patients in the placebo group were confirmed by the EAC compared to either semaglutide group.

Pancreatic enzymes

Lipase

Estimated mean lipase levels increased significantly from baseline to end-of-treatment (week 104) with both semaglutide doses compared to placebo, where no change in lipase levels over time was apparent.

Figure 73 Estimated Lipase (U/L) by Treatment Week (Geometric Mean) – SAS On-Treatment – CVOT



'On-treatment' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment group (4 levels) and stratification (9 levels) as fixed factors and baseline amylase as a covariate, all nested within visit, and are adjusted according to observed baseline distribution. From this model, the mean for pooled placebo was derived.
Error bars are +/-1*SEM calculated on log-scale and back-transformed to original scale.
Dotted line is the total average value at baseline.

Abbreviations: MMRM: mixed model for repeated measurements; SEM: standard error of the mean.
Source: Figure 2-68 ISS

Additionally, a larger proportion of patients on semaglutide had a maximum lipase value >3XULN, >5XULN, or >10XULN compared to placebo, at any scheduled or non-scheduled post-baseline assessment. The shifts in lipase levels by treatment arm are presented below.

Table 191 Lipase (U/L) at Week 104 – Shift Table – SAS On-Treatment

		<2x ULN at baseline			≥2x ULN and ≤ 5x ULN at baseline			>5x ULN at baseline		
		<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN	<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN	<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN
	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Lipase (U/L) - Summary of observed and imputed 'on-treatment' data										
Visit 25 (week 104) (MMRM)										
Sema 0.5 mg	805	745 (96.50)	26 (3.37)	1 (0.13)	17 (65.38)	5 (19.23)	4 (15.38)	6 (85.71)	1 (14.29)	
Sema 1.0 mg	810	747 (95.04)	35 (4.45)	4 (0.51)	14 (63.64)	7 (31.82)	1 (4.55)		2 (100.0)	
Placebo 0.5 mg	804	763 (97.82)	14 (1.79)	3 (0.38)	17 (85.00)	3 (15.00)		2 (50.00)	2 (50.00)	
Placebo 1.0 mg	819	773 (98.35)	9 (1.15)	4 (0.51)	17 (56.67)	10 (33.33)	3 (10.00)	3 (100.0)		

Notes: Missing data imputed from a mixed model for repeated measures with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

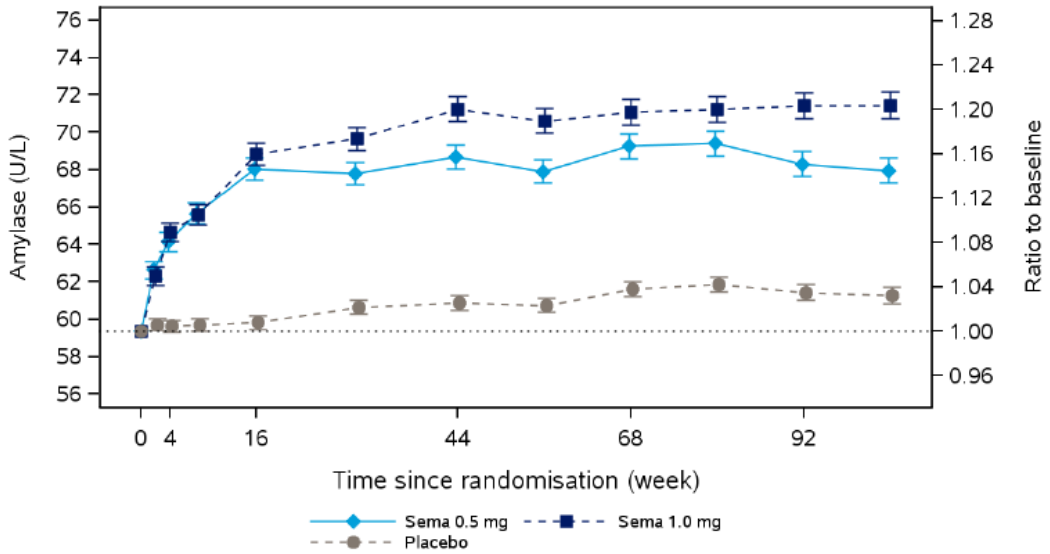
Abbreviations: MMRM: mixed model for repeated measures; N: Number of subjects in the summary statistic; %: Percentage of subjects in the given baseline category; ULN: Upper limit of normal.

Source: Table 13-55 study report 3477

Amylase

Estimated mean amylase activity levels increased significantly from baseline to end-of-treatment (week 104) with both semaglutide doses compared to placebo

Figure 74 Estimated Amylase (U/L) by Treatment Week (Geometric Mean) – SAS On-Treatment – CVOT



'On-treatment' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment group (4 levels) and stratification (9 levels) as fixed factors and baseline amylase as a covariate, all nested within visit, and are adjusted according to observed baseline distribution. From this model, the mean for pooled placebo was derived.
Error bars are +/-1*SEM calculated on log-scale and back-transformed to original scale.
Dotted line is the total average value at baseline.

Abbreviations: MMRM: mixed model for repeated measurements; SEM: standard error of the mean.

Source: Figure 2-69 ISS

A greater proportion of patients on either semaglutide dose had a maximum amylase value >3XULN compared to placebo. The shifts at week 104 are presented below.

Table 192 Amylase (U/L) at Week 104 – Shift Table – SAS On-Treatment

		<2x ULN at baseline			≥2x ULN and ≤ 5x ULN at baseline			>5x ULN at baseline		
		<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN	<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN	<2x ULN	≥2x ULN and ≤ 5x ULN	>5x ULN
	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Amylase (U/L) - Summary of observed and imputed 'on-treatment' data										
Visit 25 (week 104) (MMRM)										
Sema 0.5 mg	813	799 (99.50)	4 (0.50)		9 (90.00)	1 (10.00)				
Sema 1.0 mg	814	799 (99.01)	8 (0.99)		3 (42.86)	4 (57.14)				
Placebo 0.5 mg	813	802 (99.63)	3 (0.37)		6 (75.00)	2 (25.00)				
Placebo 1.0 mg	821	815 (99.76)	2 (0.24)		1 (33.33)	1 (33.33)	1 (33.33)		1 (100.0)	

Notes: Missing data imputed from a mixed model for repeated measures with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Abbreviations: MMRM: mixed model for repeated measures; N: Number of subjects in the summary statistic; %: Percentage of subjects in the given baseline category; ULN: Upper limit of normal.

Source: Table 13-57 study report 3744

The applicant's MedDRA search for elevated amylase and lipase used the following preferred terms: lipase increased, lipase abnormal, lipase, hyperamylasemia, amylase increased, amylase abnormal, amylase.

Of the 317 patients with AEs of elevated lipase and/or amylase (MedDRA), 15 had events sent for adjudication, and of these patients, 7 had EAC-confirmed pancreatitis during the on-treatment period (semaglutide 0.5 mg: 1 patient; semaglutide 1 mg: 2 patients; placebo: 4 patients).

Two SAEs of amylase increased and lipase increased (PTs) were reported simultaneously in 1 patient (patient ID 323017) with semaglutide 1 mg (the patient recovered). The event was sent for adjudication, but not confirmed as pancreatitis by the EAC – unclear why. No SAEs were reported with semaglutide 0.5 mg or placebo.

Table 193 MedDRA Search Elevated Amylase/Lipase - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
Observation time (year)	1488.3				1443.9				3034.8			
Events	92	(11.2)	143	9.6	92	(11.2)	171	11.8	133	(8.1)	206	6.8
Serious	0				1	(0.1)	2	0.1	0			
Severity												
Severe	4	(0.5)	5	0.3	2	(0.2)	2	0.1	3	(0.2)	3	0.1
Moderate	28	(3.4)	41	2.8	27	(3.3)	48	3.3	32	(1.9)	46	1.5
Mild	71	(8.6)	97	6.5	78	(9.5)	121	8.4	107	(6.5)	157	5.2
Relationship to trial product												
Probable	19	(2.3)	29	1.9	31	(3.8)	58	4.0	24	(1.5)	38	1.3
Possible	58	(7.0)	89	6.0	48	(5.9)	82	5.7	82	(5.0)	119	3.9
Unlikely	21	(2.6)	25	1.7	23	(2.8)	31	2.1	37	(2.3)	49	1.6
Outcome												
Recovered	78	(9.5)	112	7.5	77	(9.4)	137	9.5	117	(7.1)	172	5.7
Fatal	0				0				0			
Recovering	6	(0.7)	9	0.6	9	(1.1)	12	0.8	5	(0.3)	5	0.2
Recovered with sequelae	0				0				0			
Not recovered	20	(2.4)	22	1.5	18	(2.2)	22	1.5	22	(1.3)	29	1.0
Leading to premature treatment discontinuation												
Yes	5	(0.6)	6	0.4	2	(0.2)	2	0.1	5	(0.3)	8	0.3
No	88	(10.7)	137	9.2	91	(11.1)	169	11.7	128	(7.8)	198	6.5

Notes: MedDRA version 18.0. The 'on-treatment' overview of adverse events comprises events with onset on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Exposure time is calculated as the duration of this time span.

Abbreviations: E: number of events, N: Number of subjects experiencing at least one event, %: percentage of subjects experiencing at least one event; R: event rate per 100 years of exposure.

Source: Table 13-58 report body 3744

Additional 64 AEs (semaglutide 0.5 mg: 25 events; semaglutide 1 mg: 13 events; placebo: 26 events) in 31 patients were captured during the in-trial observation period. None of these events were SAEs.

Phase 3 pool excluding CVOT

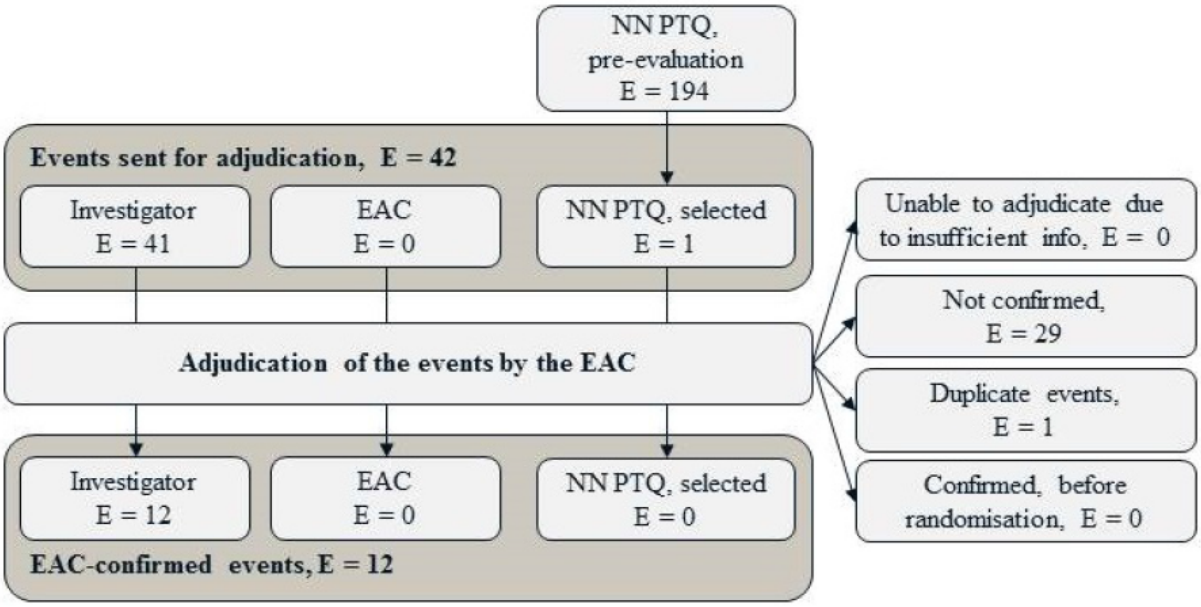
Due to uncertainty of the risk of pancreatitis with antidiabetic drugs that act via the incretin pathway, the discussion here will consider a subset that exclude drugs that act via the incretin pathway and also consider subset with comparators that act via the incretin pathway.

EAC confirmed pancreatitis

A total of 12 events of pancreatitis were confirmed by the EAC in the phase 3 pool. Of the 12 confirmed events, 11 occurred during the on-treatment observation period, and 1 additional event of chronic pancreatitis with semaglutide 0.5 mg was confirmed in the in-trial period. The 29 non-confirmed events were mainly reported as elevated pancreatic enzymes or suspicion of

pancreatitis. More of the non-confirmed events with semaglutide (0.5 mg and 1.0 mg) than with comparators were reported using terms related to elevated pancreatic enzymes.

Figure 75 Event Adjudication Process Flow for Pancreatitis – Phase 3 Pool



Notes: Diagram presents all events from randomisation to data cut-off date.
Abbreviations: E: number of events; EAC: event adjudication committee; NN PTQ: Novo Nordisk pre-defined preferred term query.
Source: Figure 2-70 ISS

Table 194 Number of Adjudicated Events of Pancreatitis and EAC Confirmation Rates (%) by Reporting Method – Phase 3 Pool

	Investigator		PTQ search		EAC		Total	
	E	Conf. rate	E	Conf. rate	E	Conf. rate	E	Conf. rate
All	41	29.3%	1	0.0%	0		42	28.6%
Semaglutide	26	34.6%	0		0		26	34.6%
Semaglutide 0.5 mg	11	54.5%	0		0		11	54.5%
Semaglutide 1.0 mg	15	20.0%	0		0		15	20.0%
Comparators	15	20.0%	1	0.0%	0		16	18.8%

Notes: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).
Abbreviations: Conf.: confirmation; E: number of events; EAC: (external) event adjudication committee; PTQ: preferred term query.
Source: Table 2-109 ISS

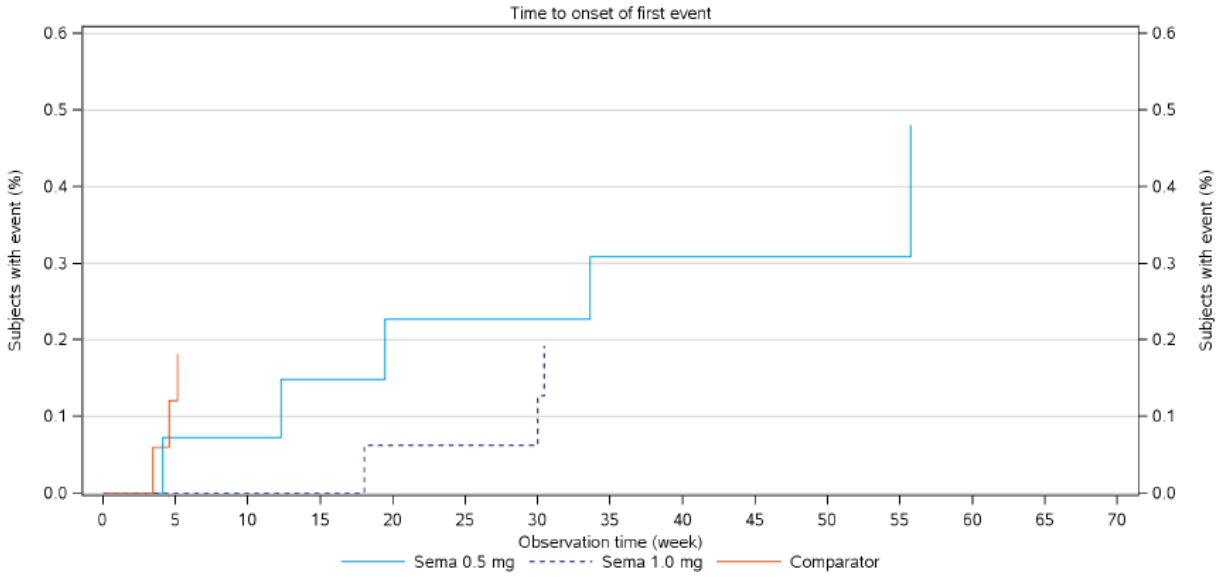
The event rate for EAC-confirmed pancreatitis was similar with semaglutide 1 mg and comparators (3 events each), but higher with semaglutide 0.5 mg (5 events) compared to

semaglutide 1 mg or comparators. All comparator events occurred in trial 3624 with exenatide ER and no events were confirmed by the EAC for patients receiving sitagliptin or non-incretin comparators.

The applicant categorized most events of EAC-confirmed pancreatitis as mild acute pancreatitis. Only one event in the semaglutide 0.5 mg group was categorized as severe pancreatitis. The case of severe pancreatitis was a 42 year old obese male from Ukraine who developed necrotizing pancreatitis on trial day 226 (patient no 588011/study 3626). This led to treatment discontinuation. The patient did not have any history of gallstones or pancreatitis, but the applicant suspects that this attack was brought by dietary non-compliance. The patient recovered after surgery and intensive treatment. Notably, in the comparator group, of the 3 patients, one lacked imaging and the other two had imaging (one CT and one US) that did not show evidence of pancreatitis. At the same time, of the cases of EAC-confirmed pancreatitis with semaglutide, 2/5 patients on semaglutide 0.5 mg, and 1/3 patients on semaglutide 1 mg, had imaging positive for acute pancreatitis.

There was no apparent temporal clustering of the events with semaglutide, the event onset ranging between trial days 29–390 (semaglutide 0.5 mg: 29–390 days; semaglutide 1 mg: 126–213 days).

Figure 76 Time to First Event of EAC-Confirmed Pancreatitis – SAS On-Treatment – Phase 3 Pool



SAS, on-treatment observation period, observed data. Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Source: Figure 2-71 ISS

Pancreatitis MedDRA search

A total of 20 AEs in 18 patients were captured in the phase 3 pool (semaglutide 0.5 mg: 7 events; semaglutide 1 mg: 6 events; comparators: 7 events).

There were no events identified in the non-incretin comparators. However, in the non-incretin subset, there were 3 AEs identified in the semaglutide arms (one event with semaglutide 1mg, and 2 events with semaglutide 0.5 mg). The two events in the semaglutide 0.5 mg lead to treatment discontinuation.

In the phase 3 pool incretin subset, the proportion of patients experiencing AEs and the rate of events were similar between semaglutide (0.5 mg and 1.0 mg) and the pooled incretin comparators sitagliptin and exenatide ER (semaglutide 0.5 mg: 5 events; semaglutide 1 mg: 5 events; comparators: 7 events). While 7 events reported with semaglutide were SAEs (4 events with seamglutide 0.5 mg, and 3 events with semaglutide 1 mg), none of the events reported with the comparator incretins were SAEs.

A total of 9 AEs led to premature treatment discontinuation (semaglutide 0.5 mg: 2 events; semaglutide 1 mg: 4 events; comparators: 3 events). Of the 15 patients with events, 14 had events sent for adjudication, and of these patients, 6 had EAC-confirmed pancreatitis during the on-treatment period (semaglutide 0.5 mg: 3 patients; semaglutide 1 mg: 2 patients; comparators: 1 patient).

Pancreatic enzymes

Lipase

Lipase levels increased with semaglutide treatment in the phase 3 pool excluding the CVOT. In the non-incretin subset, this increase was not matched by an increase in lipase values in the comparator. In the incretin subset, both semaglutide and exenatide ER lead to increases in lipase levels compared to baseline, with no significant difference between the arms. However, an increase in lipase levels over time was seen in the semaglutide group when compared to sitagliptin treated patients.

Table 195 Estimated Changes in Lipase Levels – SAS On-Treatment – Individual Phase 3 Trials

Trial	Semaglutide 0.5 mg		Semaglutide 1.0 mg	
	Ratio[a] Estimate (SE)	Treatment ratio[b] ETR[95% CI]	Ratio[a] Estimate (SE)	Treatment ratio[b] ETR [95% CI]
3623 vs Placebo (Mono)	1.18 (0.04)	1.25 [1.13 ; 1.39]	1.22 (0.04)	1.29 [1.16 ; 1.43]
3626 vs Sita (OADs)	1.22 (0.02)	1.07 [1.01 ; 1.13]	1.30 (0.03)	1.14 [1.08 ; 1.21]
3624 vs Exe ER (OADs)	NA		1.29 (0.03)	0.98 [0.92 ; 1.05]
3625 vs IGlar (OADs)	1.24 (0.03)	1.29 [1.21 ; 1.37]	1.26 (0.03)	1.30 [1.22 ; 1.39]
3627 vs Placebo (insulin)	1.28 (0.05)	1.35 [1.21 ; 1.51]	1.21 (0.05)	1.28 [1.14 ; 1.43]
4092 vs Sita (Mono), JP	1.27 (0.04)	1.21 [1.12 ; 1.32]	1.34 (0.04)	1.28 [1.17 ; 1.39]
4091 vs OAD (OAD), JP	1.32 (0.03)	1.27 [1.18 ; 1.35]	1.39 (0.03)	1.33 [1.25 ; 1.43]

Notes: [a] Ratio to baseline at end-of-treatment; [b] Treatment ratio (semaglutide/comparator) to baseline from end-of-treatment. 'On-treatment' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and log-transformed baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Abbreviations: CI: confidence interval; ETR: estimated treatment ratio; Exe: exenatide ER; IGlar: insulin glargine; JP: Japan; NA: not applicable; OAD: oral antidiabetic drugs; SE: standard error; Sita: sitagliptin.

Source: Table 2-112 ISS

In the placebo pool, mean lipase levels increased over the course of the trial in the semaglutide group compared to placebo where no change in lipase levels was observed.

Table 196 Estimated Changes in Lipase Levels – SAS On-Treatment – Individual Phase 3 Trials

Trial	Semaglutide 0.5 mg		Semaglutide 1.0 mg	
	Ratio[a] Estimate (SE)	Treatment ratio[b] ETR[95% CI]	Ratio[a] Estimate (SE)	Treatment ratio[b] ETR [95% CI]
3623 vs Placebo (Mono)	1.18 (0.04)	1.25 [1.13 ; 1.39]	1.22 (0.04)	1.29 [1.16 ; 1.43]
3626 vs Sita (OADs)	1.22 (0.02)	1.07 [1.01 ; 1.13]	1.30 (0.03)	1.14 [1.08 ; 1.21]
3624 vs Exe ER (OADs)	NA		1.29 (0.03)	0.98 [0.92 ; 1.05]
3625 vs IGlar (OADs)	1.24 (0.03)	1.29 [1.21 ; 1.37]	1.26 (0.03)	1.30 [1.22 ; 1.39]
3627 vs Placebo (insulin)	1.28 (0.05)	1.35 [1.21 ; 1.51]	1.21 (0.05)	1.28 [1.14 ; 1.43]
4092 vs Sita (Mono), JP	1.27 (0.04)	1.21 [1.12 ; 1.32]	1.34 (0.04)	1.28 [1.17 ; 1.39]
4091 vs OAD (OAD), JP	1.32 (0.03)	1.27 [1.18 ; 1.35]	1.39 (0.03)	1.33 [1.25 ; 1.43]

Notes: [a] Ratio to baseline at end-of-treatment; [b] Treatment ratio (semaglutide/comparator) to baseline from end-of-treatment. 'On-treatment' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and log-transformed baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Abbreviations: CI: confidence interval; ETR: estimated treatment ratio; Exe: exenatide ER; IGlar: insulin glargine; JP: Japan; NA: not applicable; OAD: oral antidiabetic drugs; SE: standard error; Sita: sitagliptin.

Source: Table 2-112 ISS

In the phase 3 pool non-incretin subset, lipase levels increased by week 30 with semaglutide (0.5 mg and 1.0 mg), but not with comparators. A larger proportion of patients in this subset on semaglutide had a maximum lipase value >3XULN during the course of the trial, or had an upwards categorical shift from baseline at week 30.

In the incretin pool, lipase levels increased in the semaglutide arms compared to sitagliptin, but no significant difference was seen between semaglutide 1 mg and exenatide ER in study 3624.

There was no difference between the treatment and comparator regarding the proportion of patients with maximum lipase level >3XULN, or the upward categorical shifts from baseline to week 30.

Amylase

A similar trend was observed for amylase.

Table 197 Estimated Changes in Amylase Activity – SAS On-Treatment – Individual Phase 3 Trials

Trial	Semaglutide 0.5 mg		Semaglutide 1.0 mg	
	Ratio[a] Estimate (SE)	Treatment ratio[b] ETR [95% CI]	Ratio[a] Estimate (SE)	Treatment ratio[b] ETR [95% CI]
3623 vs Placebo (Mono)	1.11 (0.02)	1.11 [1.06 ; 1.17]	1.16 (0.02)	1.16 [1.10 ; 1.22]
3626 vs Sita (OADs)	1.15 (0.01)	1.05 [1.02 ; 1.09]	1.19 (0.01)	1.09 [1.05 ; 1.13]
3624 vs Exe ER (OADs)	NA		1.19 (0.02)	1.04 [1.00 ; 1.08]
3625 vs IGlar (OADs)	1.14 (0.02)	1.06 [1.02 ; 1.11]	1.17 (0.02)	1.09 [1.05 ; 1.13]
3627 vs Placebo (insulin)	1.10 (0.02)	1.15 [1.08 ; 1.22]	1.13 (0.03)	1.18 [1.11 ; 1.26]
4092 vs Sita (Mono), JP	1.16 (0.03)	1.10 [1.04 ; 1.17]	1.17 (0.03)	1.12 [1.05 ; 1.19]
4091 vs OAD (OAD), JP	1.18 (0.02)	1.12 [1.07 ; 1.17]	1.21 (0.02)	1.14 [1.09 ; 1.20]

Notes: [a] Ratio to baseline at end-of-treatment; [b] Treatment ratio (semaglutide/comparator) to baseline from end-of-treatment. 'On-treatment' data. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment and country as fixed factors and log-transformed baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution.

Abbreviations: CI: confidence interval; ETR: estimated treatment ratio; Exe: exenatide ER; IGlar: insulin glargine; JP: Japan; NA: not applicable; OAD: oral antidiabetic drugs; SE: standard error; Sita: sitagliptin.

Source: Table 2-114 ISS

EAC-confirmed pancreatitis in patients with lipase and/or amylase >3XULN.

Of the 422 patients with maximum post-baseline lipase value >3xULN at any scheduled or unscheduled visit, 27 had events sent for adjudication, and of these patients, 6 had EAC-confirmed pancreatitis during the on-treatment period (semaglutide 0.5 mg: 2 patients; semaglutide 1 mg: 2 patients; comparators [exenatide ER]: 2 patients). Of the 33 patients with maximum post-baseline amylase value >3xULN at any scheduled or unscheduled visit, 1 patient had an event sent for adjudication, but not confirmed by the EAC-confirmed during the on-treatment period.

In addition to the pancreatic enzymes reported by the central lab, there were 4 patients with reports of amylase and/or lipase elevations >3XULN coming from local laboratories. The one patient that had EAC-confirmed pancreatitis also had laboratory abnormalities confirmed by the central lab.

Elevated lipase and/or amylases by MedDRA search

In the non-incretin subgroup, there were 170 reports of elevated or abnormal pancreatic enzymes PTs in the pooled semaglutide group (9.7%), and 31 (4.1%) in the comparator group. None of these events were SAEs. This difference was observed at study level as well.

194 patients had PT reported as elevated amylase and/or elevated lipase. Out of these, 7 patients were sent for adjudication, 2 patients had an EAC-confirmed event, both in the semaglutide 0.5 mg group.

A total of 10 events in 6 patients led to premature discontinuation.

In the incretin subset, events were reported in 135 patients in the pooled semaglutide greoup (9.9%), and 89 patients in the comparator group (9.7%). None of the AEs reported were serious. There were 224 patients with PTs of elevated amylase and/or lipase, 13 sent for adjudication. Of these, only 4 patients had an EAC-confirmed event of pancreatitis, one in semaglutide 1 mg and 3 in the comparator.

Placebo pool

There were no events of EAC-confirmed pancreatitis in the placebo pool.

MedDRA search: one event was reported with semaglutide 0.5 mg, non-serious, however, it led to treatment discontinuation. This event was sent for adjudication, but not confirmed by the EAC.

In the placebo pool, lipase levels increased by week 30 with semaglutide (0.5 mg and 1.0 mg), but not with placebo. In the placebo pool, a greater proportion of patients with semaglutide (0.5 mg and 1.0 mg) than placebo had a maximum lipase value >3xULN at any scheduled or unscheduled post-baseline visit or had experienced upward categorical shifts from baseline at week 30. The same trend was observed for amylase.

PTs reflecting elevated amylase and/or lipase occurred more frequently in the semaglutide group (38 patients – 7.3%) than in the comparator (10 patients – 3.8%). Of these 48 patients, 2 were sent for adjudication, and neither was confirmed. None of these events were SAEs.

In conclusion, there appears to be an increase incidence of pancreatitis and elevated pancreatic enzymes with semaglutide vs non-incretin comparator, regardless of the method used for analysis of the events. The incidence of pancreatitis events was not significantly different when the comparator was an incretin drug, and similar increases in pancreatic enzymes were observed with semaglutide and exenatide ER, but no significant increase was seen with sitagliptin. There did not appear to be a dose response with semaglutide pertaining to the EAC-confirmed pancreatitis events, however the increases in pancreatic enzymes did appear to occur in a dose dependent manner in the CVOT but not in the pool excluding the CVOT. My

conclusion is that, overall, the data does not suggest a dose –dependence for pancreatitis in the semaglutide group.

Reviewer comment: The body of data suggests that, despite an increase in amylase/lipase with semaglutide, this did not result in an increase of acute pancreatitis events. The adjudication of pancreatitis events is generally a good way to identify and confirm such events. However, it is notable that the adjudication rate was lower for semaglutide groups compared to placebo. For this reason, I reviewed all available narratives for the 34 patients with events not confirmed by the EAC (most narrative are available). I did not find any patients on semaglutide that I would have adjudicated differently than the EAC, most were cases of asymptomatic amylase/lipase elevations, and a few chronic pancreatitis. One patient on placebo, ID 667010, 72 year old male with abdominal pain and elevated pancreatic enzymes that resolved when the patient was placed on a liquid diet, might have had pancreatitis although not confirmed by the EAC. This does not alter my original conclusions.

8.5.6. **Gallbladder-related Disorders**

A general link between incretin-based therapies (and specifically GLP-1 receptor agonists) and gallbladder-related AEs (cholelithiasis and cholecystitis) has been suggested, as gallbladder emptying appears to be slower with this class of drugs.

A higher rate of gallbladder-related AEs (especially cholelithiasis and cholecystitis) was noted in the liraglutide program for the weight management indication (3 mg, marketed as Saxenda), but not in the T2DM program (1.2 and 1.8 mg, marketed as Victoza).

The applicant reported no abnormal gallbladder necropsy or histological findings in repeated dose toxicity studies with semaglutide in mice and monkeys up to 13-weeks and 52-weeks in duration, respectively. In the 2-year carcinogenicity study in mice, increased incidences of distension and abnormal content of the gallbladder (pale or dark, sometimes including particles) were observed, with no obvious dose-response. These non-adverse observations were considered secondary to low food consumption. There were no associated histopathological changes or any signs of compromised bile efflux.

The applicant performed a pre-defined MedDRA search (acute gallstone disease, including gallbladder and bile duct related disorders) was performed among all reported AEs to identify and summarize all events potentially related to gallbladder-related disorders. This included the following SMQs: Biliary tract disorders, Biliary system related investigations, signs and

symptoms, Gallbladder related disorders, Gallstone related disorders, and Infectious biliary disorders.

CVOT

The applicant identified 142 gallbladder-related AEs via the MedDRA search outlined above, 43 of which were SAEs. Considering all events, there does not appear to be any difference between the treatment arms. When focusing on events of cholecystitis only, there was no significant difference between patients treated with either dose of semaglutide or placebo. There was a slightly higher proportion of patients with cholelithiasis in both semaglutide arms compared to placebo (2.3% in semaglutide 1 mg, 2.1% in the semaglutide 0.5 mg, and 1.6% in placebo). 10 of the patients with cholelithiasis were reported as SAEs, and 9/10 led to cholecystectomy (3 with semaglutide 0.5 mg, 2 with semaglutide 1 mg and 4 with placebo). Additionally, there was a higher proportion of patients who were reported with the PT blood bilirubin increased with semaglutide 1 mg compared to semaglutide 0.5 mg and placebo.

Table 198 Gallbladder-Related Adverse Events - Pre-Defined MedDRA Search - by System Organ Class and Preferred Term– SAS On-Treatment

System organ class Preferred term	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	823				819				1644			
Observation time (year)	1488.3				1443.9				3034.8			
All events	29	(3.5)	39	2.6	26	(3.2)	31	2.2	56	(3.4)	72	2.4
Hepatobiliary disorders	**25**	**(3.0)**	**28**	**1.9**	**25**	**(3.1)**	**29**	**2.0**	**49**	**(3.0)**	**62**	**2.0**
Cholelithiasis	19	(2.3)	19	1.3	17	(2.1)	17	1.2	27	(1.6)	27	0.9
Cholecystitis acute	4	(0.5)	4	0.3	0				8	(0.5)	8	0.3
Cholecystitis chronic	0				1	(0.1)	1	0.1	8	(0.5)	8	0.3
Biliary colic	1	(0.1)	1	0.1	3	(0.4)	3	0.2	3	(0.2)	3	0.1
Cholecystitis	0				1	(0.1)	1	0.1	5	(0.3)	5	0.2
Bile duct stone	0				2	(0.2)	2	0.1	3	(0.2)	3	0.1
Biliary tract disorder	0				2	(0.2)	2	0.1	0			
Cholangitis	1	(0.1)	1	0.1	0				1	(0.1)	1	<0.1
Cholestasis	0				0				2	(0.1)	2	0.1
Biliary cirrhosis	0				1	(0.1)	1	0.1	0			
Biliary dilatation	0				0				1	(0.1)	1	<0.1
Cholelithiasis obstructive	1	(0.1)	1	0.1	0				0			
Gallbladder cholesterolosis	0				0				1	(0.1)	1	<0.1
Gallbladder necrosis	0				0				1	(0.1)	1	<0.1
Gallbladder pain	0				1	(0.1)	1	0.1	0			
Hydrocholecystis	1	(0.1)	1	0.1	0				0			
Hyperbilirubinaemia	0				0				1	(0.1)	1	<0.1
Jaundice	1	(0.1)	1	0.1	0				0			
Jaundice cholestatic	0				1	(0.1)	1	0.1	0			
Sphincter of Oddi dysfunction	0				0				1	(0.1)	1	<0.1
Investigations	**7**	**(0.9)**	**10**	**0.7**	**2**	**(0.2)**	**2**	**0.1**	**7**	**(0.4)**	**9**	**0.3**
Blood bilirubin increased	5	(0.6)	6	0.4	1	(0.1)	1	0.1	3	(0.2)	3	0.1
Blood alkaline phosphatase increased	2	(0.2)	2	0.1	1	(0.1)	1	0.1	5	(0.3)	6	0.2
Blood alkaline phosphatase abnormal	1	(0.1)	1	0.1	0				0			
Blood bilirubin abnormal	1	(0.1)	1	0.1	0				0			
Gastrointestinal disorders	**1**	**(0.1)**	**1**	**0.1**	**0**				**1**	**(0.1)**	**1**	**<0.1**
Abnormal faeces	0				0				1	(0.1)	1	<0.1
Faeces pale	1	(0.1)	1	0.1	0				0			

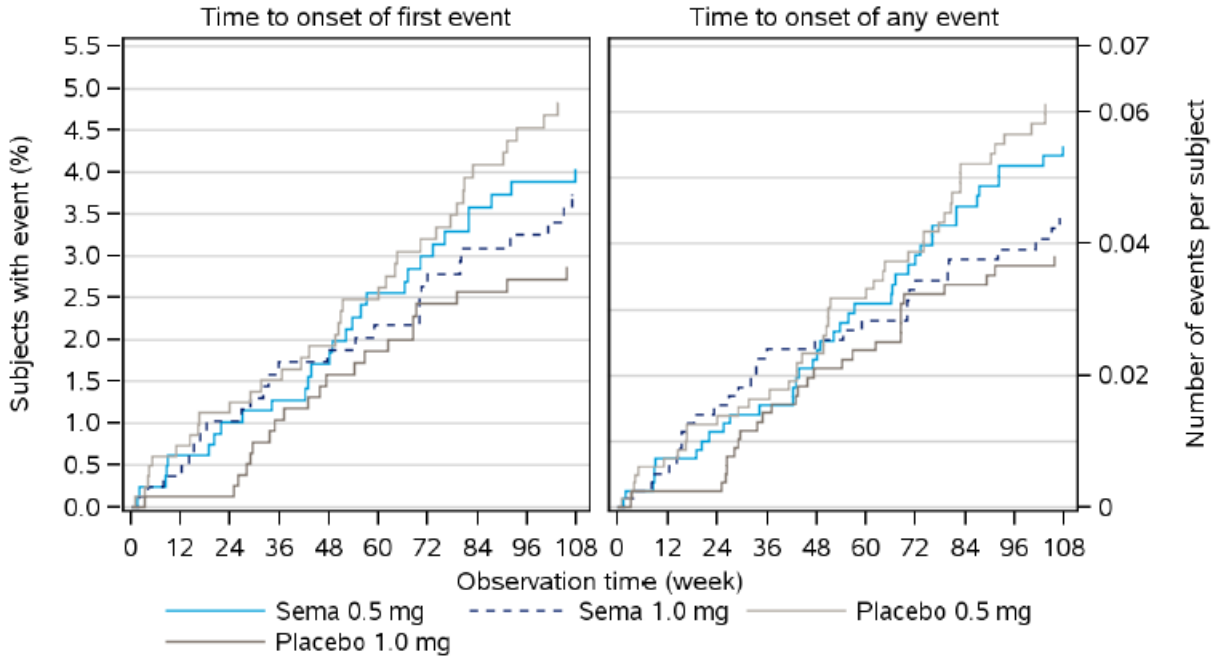
Notes: PYE is calculated from the time of first drug date to the follow-up visit or first drug date of second treatment in cross-over trials. The on-treatment summary of adverse events includes treatment-emergent events with onset on or after the day of first randomised dose and until the follow-up visit scheduled 5 weeks after end-of-treatment (inclusive). Observation time is calculated from randomisation to the scheduled end-of-treatment follow-up visit. The table is sorted in descending order by system organ class based on the percentage of subjects experiencing at least one event when treated with semaglutide 1.0 mg. MedDRA version 18.0.

Abbreviations: N: number of subjects experiencing at least one event, %: percentage of subjects experiencing at least one event, E: number of events, PYE: patient-years of exposure, R: events per 100 PYE

Source: Table 13-59 study report

None of the events was fatal, and the semaglutide treatment did not appear to influence the timing of the gallbladder related events.

Figure 77 Proportion of Patients with Gallbladder-Related Adverse Events (MedDRA Search) and Mean Number of Events per Patient Over Time – SAS On-Treatment - CVOT



Subjects are considered on treatment while having an event if the event has onset date on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Left panel: Kaplan-Meier estimator. Right panel: mean cumulative function estimator.

Source: Figure 2-72 ISS

Gallbladder SAEs were balanced between treatment groups. The most common SAEs were cholecystitis acute, cholelithiasis and cholecystitis; these were reported infrequently and with no clear imbalance between treatment groups

Table 199 Gallbladder SAEs – SAS On-Treatment

System organ class Preferred term	Sema				Placebo				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1642				1644				3286			
Observation time (year)	2932.2				3034.8				5967.0			
Events	15	(0.9)	17	0.6	20	(1.2)	26	0.9	35	(1.1)	43	0.7
Hepatobiliary disorders	15	(0.9)	17	0.6	19	(1.2)	24	0.8	34	(1.0)	41	0.7
Cholecystitis acute	3	(0.2)	3	0.1	8	(0.5)	8	0.3	11	(0.3)	11	0.2
Cholelithiasis	6	(0.4)	6	0.2	4	(0.2)	4	0.1	10	(0.3)	10	0.2
Cholecystitis	1	(0.1)	1	<0.1	5	(0.3)	5	0.2	6	(0.2)	6	0.1
Bile duct stone	2	(0.1)	2	0.1	3	(0.2)	3	0.1	5	(0.2)	5	0.1
Biliary colic	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	2	(0.1)	2	<0.1
Cholangitis	1	(0.1)	1	<0.1	0				1	(<0.1)	1	<0.1
Cholecystitis chronic	0				1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Cholelithiasis obstructive	1	(0.1)	1	<0.1	0				1	(<0.1)	1	<0.1
Cholestasis	0				1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Gallbladder necrosis	0				1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Hydrocholecystis	1	(0.1)	1	<0.1	0				1	(<0.1)	1	<0.1
Jaundice	1	(0.1)	1	<0.1	0				1	(<0.1)	1	<0.1
Investigations	0				1	(0.1)	2	0.1	1	(<0.1)	2	<0.1
Blood alkaline phosphatase increased	0				1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Blood bilirubin increased	0				1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1

Source: Table 15.3.1.208 study report AE

Four events (all SAEs) led to premature treatment discontinuation, 3 with semaglutide 0.5 mg (jaundice, cholelithiasis and hydrocholecystitis) and 1 with placebo (bile duct stone). While this is a noticeable imbalance, the numbers are exceedingly small and no conclusion can be drawn from these data.

The applicant reported that 10 additional AEs, reported by 8 patients, were captured during the in-trial period: 3 with semaglutide 0.5 mg (no SAEs), and 7 with placebo (2 were SAEs).

It is not clear, based on the data from the CVOT, that there is an association between semaglutide use and gallbladder events.

Phase 3 pool

In the entire phase 3 pool, the overall proportion of patients with gallbladder-related AEs and the corresponding rates were greater with semaglutide than with pooled comparators.

This difference was primarily driven by the proportion of patients with AEs of cholelithiasis with semaglutide, most pronounced in the semaglutide 1 mg group (0.7% of patients in the semaglutide 0.5 mg group, 1.1% in the semaglutide 1 mg group, vs 0.5% of patients on pooled comparator group). As expected, this difference is mostly due to the difference observed in the trials with non-incretin comparators. In the non-incretin subset, there was one event reported in the comparator group (0.1%), 13 events with semaglutide 0.5 mg (1.5%), and 9 events with semaglutide 1 mg (0.9%).

The gallbladder-related SAEs comprised cholecystitis acute (4 with semaglutide 1 mg), cholecystitis (2 with semaglutide 1 mg) and cholelithiasis (2 with each semaglutide dose and 2 in the comparator group). There were no gallbladder AEs that were fatal, or leading to treatment discontinuation, in this pool.

Table 200 Gallbladder-Related Adverse Events (MedDRA search) by System Organ Class, High Level Group Term and Preferred Term - SAS On-Treatment - Phase 3 Pool

System organ class High level group term Preferred term	Sema 0.5 mg N	(Adj.%)	E	R	Sema 1.0 mg N	(Adj.%)	E	R	Comparator N	(Adj.%)	E	R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
All events	18	(1.3)	19	1.6	30	(1.7)	32	2.1	14	(0.8)	15	1.0
Hepatobiliary disorders	15	(1.1)	16	1.4	27	(1.5)	28	1.9	12	(0.7)	12	0.8
Gallbladder disorders	14	(1.0)	15	1.3	24	(1.4)	25	1.7	12	(0.7)	12	0.8
Cholelithiasis	10	(0.7)	10	0.8	19	(1.1)	19	1.2	8	(0.5)	8	0.5
Cholecystitis acute					4	(0.2)	4	0.3				
Cholecystitis					2	(0.1)	2	0.1				
Gallbladder disorder	2	(0.2)	2	0.2								
Cholecystitis chronic	1	(<0.1)	1	<0.1					4	(0.2)	4	0.3
Gallbladder pain	1	(<0.1)	1	<0.1								
Porcelain gallbladder	1	(<0.1)	1	<0.1								
Bile duct disorders					2	(0.1)	2	0.1				
Biliary colic					2	(0.1)	2	0.1				
Hepatic and hepatobiliary disorders	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1				
Hyperbilirubinaemia					1	(<0.1)	1	<0.1				
Jaundice	1	(<0.1)	1	<0.1								
Investigations	3	(0.2)	3	0.3	3	(0.2)	4	0.3	3	(0.2)	3	0.2
Enzyme investigations NEC	2	(0.2)	2	0.2	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Blood alkaline phosphatase increased	2	(0.2)	2	0.2	2	(0.1)	2	0.1	3	(0.2)	3	0.2
Hepatobiliary investigations	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1				
Blood bilirubin increased	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1				

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)
Abbreviations: Adj: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.
Source: Table 2-118 ISS

The applicant looked at the potential relationship between gallbladder events and weight loss, and reported no clear association.

Placebo pool

There were no gallbladder-related events in the patients who received placebo, while 8 AEs were reported in the patients who received semaglutide (6 with semaglutide 0.5 mg, and 2 with semaglutide 1 mg). Two of the 8 events were SAEs (cholelithiasis and cholecystitis acute with semaglutide 0.5 mg and 1.0 mg, respectively.

Reviewer coment: There was overall no consistency regarding dose-response for semaglutide. While cholelithiasis was more frequently seen with semaglutide compared to placebo/comparator, cholecystitis was not. This may be because of the relatively short duration of the studies, and it is possible that an increased incidence of cholecystitis will be observed in the postmarketing setting, should semaglutide be approved. This is within what is expected with this drug class.

8.5.7. **Neoplasms**

In general, GLP-1 receptor agonists have not been associated with an increased risk of neoplasms in humans. Non-clinical data for semaglutide did not suggest any mutagenicity or genotoxicity. Thyroid C-cell neoplasia has been seen in the mouse and rat semaglutide carcinogenicity studies, preceded by an increase in serum calcitonin. This is in line with what was observed with other long acting GLP-1 receptor agonists, however, no clinical implications of this finding has been detected so far despite increased surveillance for approved long acting GLP-1 receptor agonists (including post-approval REMS.

A series of animal studies have suggested a potential association between incretin-based therapy and both pancreatic exocrine (pancreatic ductal adenocarcinomas) and pancreatic islet cell (glucagonomas) neoplasms. After an extensive review of all available nonclinical and clinical trial data, FDA and EMA published a joint commentary stating that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer were inconsistent with the then available data. Nonetheless, assessment of pancreatic neoplasms in clinical trials with incretin-based therapies remains an area of special interest.

Thyroid C-cell and pancreatic cancers are specific focus areas for GLP-1 RAs, and breast cancer and benign colon adenomas were also included for semaglutide as areas of interest due to higher frequencies with liraglutide than with placebo in the Saxenda weight management clinical development program.

Patients with a diagnosis of malignant neoplasm in the previous 5 years prior to enrolment in the trials (except basal cell skin cancer or squamous cell skin cancer) as well as patients with screening calcitonin value ≥ 50 ng/L (pg/mL) or known personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 were excluded from the phase 3 trials in the semaglutide development programme. No screening for neoplasms were conducted at baseline, nor were specific information on neoplasms collected at baseline.

Neoplasms were to be reported as a MESI in the phase 3 trials and they were adjudicated (confirmation of the diagnosis yes/no). The EAC was not required to provide a reason for rejection of an event as a neoplasm. EAC-confirmed neoplasms were classified by the EAC with regards to malignancy status (classification of confirmed neoplasms into 'malignant', 'pre-malignant/carcinoma in situ/borderline', benign and 'unclassified'), staging (for malignant neoplasm), and tissue of origin/organ class. For all confirmed neoplasms, the EAC was also to confirm the onset date or provide an alternative date. Thyroid neoplasms and thyroidectomies were adjudicated separately.

Table 201 Classification of Neoplasms by the External Event Adjudication Committee

Event	Definitions, classifications and criteria	
Neoplasms, including thyroid neoplasms (if adjudicated as 'Neoplasm')	**Definitions:** - Neoplasm was defined as an abnormal growth of tissue **Classification:** Neoplasms were classified according to - tissue of origin/organ system - stage - malignancy status	**Stage:** - Stage 0: *in situ* - Stage I: localised - Stage II: locally advanced - Stage III: advanced - Stage IV: metastatic - Undetermined **Malignancy status:** - malignant - pre-malignant/carcinoma *in situ*/borderline - benign - unclassified
Thyroid neoplasms (if adjudicated as 'Thyroid Disorder requiring thyroidectomy')	**Definition** Neoplasms of the thyroid were defined as described above; medullary carcinoma of the thyroid was defined as a distinct thyroid carcinoma, originating in the calcitonin producing parafollicular C-cells of the thyroid gland. **Classification:** Thyroid neoplasms were classified according to: - type (C-cell hyperplasia, medullary microcarcinoma (carcinoma in situ), medullary carcinoma, other (please specify)) - stage (only if medullary microcarcinoma or medullary carcinoma) - malignancy status (all thyroid neoplasms)	**Stage:** - Stage 0: *in situ* - Stage I: localised - Stage II: locally advanced - Stage III: advanced - Stage IV: metastatic - Undetermined **Malignancy status:** - malignant - pre-malignant/carcinoma *in situ*/borderline - benign - unclassified

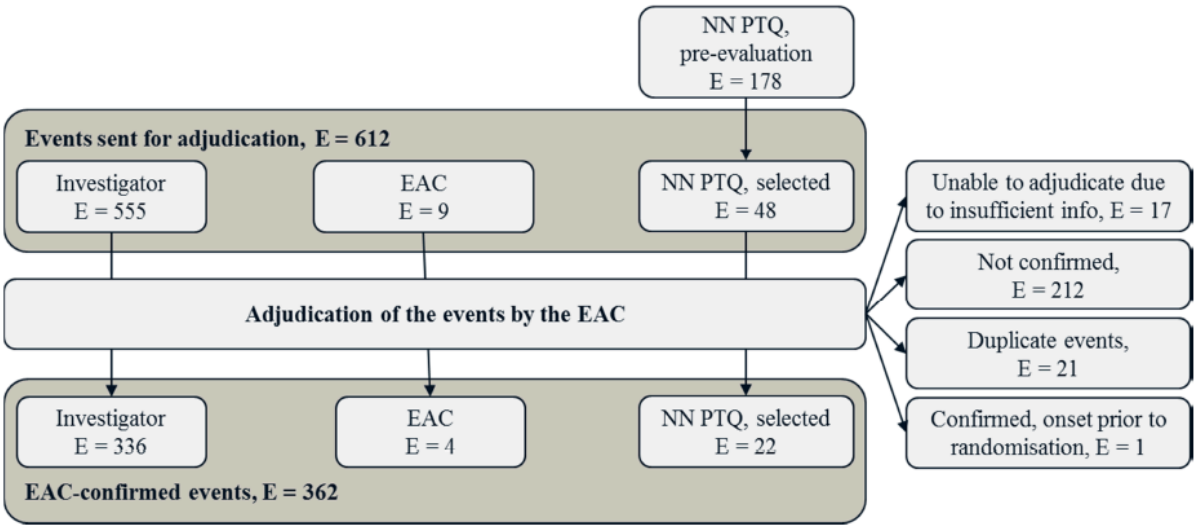
Source: Table 2-127 ISS

Additionally, neoplasms were identified via a pre-defined MedDRA search. In addition, a pre-defined SMQ was performed to identify AEs of 'malignant tumors' and NNMQs on ' pancreatic carcinoma' and 'blood calcitonin' were performed.

CVOT – EAC confirmed neoplasms

A total of 612 events were sent for adjudication (excluding thyroid), and 362 were confirmed. Additionally, the EAC confirmed 4 thyroid neoplasms. Overall, the confirmation rate for neoplasms was higher with semaglutide compared to placebo (62.9% with pooled semaglutide vs 55.1% with placebo).

Figure 78 Event Adjudication Process Flow for Neoplasms (Excluding Thyroid) - CVOT



Note: Confirmed events with onset prior to randomisation are included in number of EAC-confirmed events.
Abbreviations: E: number of events; EAC: event adjudication committee; NN PTQ: Novo Nordisk preferred term query.

Source: Figure 2-80 ISS

Of the confirmed neoplasms, 152 were confirmed as malignant neoplasms (in 136 patients). There were generally more confirmed malignant neoplasms in the semaglutide 1 mg arm compared to placebo, however, there were more events in placebo compared to semaglutide 0.5 mg. The higher proportion of patients with malignancy in the semaglutide 1 mg group was driven by skin, breast, and lung cancer. Pancreatic cancer was only identified in one patient on semaglutide 1 mg, none in semaglutide 0.5 mg, and 4 patients in placebo.

Considering the small number of events for each individual type of cancer, I do not think that any conclusions can be drawn from this analysis.

Table 202 EAC-Confirmed Malignant Neoplasms by Tissue or Organ of Origin as Assessed by the EAC - FAS In-Trial - CVOT

	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	826				822				1649			
Number of women	331				304				660			
Number of men	495				518				989			
Malignant	26	(3.1)	28	1.64	40	(4.9)	52	3.06	70	(4.2)	72	2.12
Skin	9	(1.1)	10	0.59	15	(1.8)	24	1.41	17	(1.0)	18	0.53
Male reproductive (b, e)	4	(0.8)	4	0.39	3	(0.6)	3	0.28	9	(0.9)	9	0.44
Lung/bronchus	1	(0.1)	1	0.06	7	(0.9)	8	0.47	6	(0.4)	6	0.18
Colorectal	1	(0.1)	1	0.06	3	(0.4)	3	0.18	8	(0.5)	8	0.24
Other	2	(0.2)	2	0.12	3	(0.4)	3	0.18	6	(0.4)	6	0.18
Breast (f)	1	(0.3)	1	0.15	4	(1.3)	4	0.64	3	(0.5)	3	0.22
Lymphomas (c)	1	(0.1)	1	0.06	1	(0.1)	1	0.06	4	(0.2)	4	0.12
Blood (d)					2	(0.2)	2	0.12	3	(0.2)	3	0.09
Pancreatic					1	(0.1)	1	0.06	4	(0.2)	4	0.12
Female reproductive (a, f)	1	(0.3)	1	0.15	1	(0.3)	1	0.16	2	(0.3)	2	0.15
Renal/adrenal	1	(0.1)	1	0.06					3	(0.2)	3	0.09
Gastric/intestinal	3	(0.4)	3	0.18								
Liver	1	(0.1)	1	0.06					2	(0.1)	2	0.06
Thyroid neoplasm					1	(0.1)	1	0.06	2	(0.1)	2	0.06
Other					1	(0.1)	1	0.06	2	(0.1)	2	0.06
C-cell hyperplasia												
Medullary carcinoma												
Medullary microcarcinoma												
Brain/CNS	1	(0.1)	1	0.06					1	(0.1)	1	0.03
Laryngeal	1	(0.1)	1	0.06					1	(0.1)	1	0.03
Bladder					1	(0.1)	1	0.06				

Note: [a] vaginal, cervical, ovarian; [b] penile, prostate, testicular; [c] non Hodgkin, Hodgkin; [d] leukaemias; anaemias; myelomas; [e] proportion of subjects with events and rates based on men only; [f] proportion of subjects with events and rates based on women only.
Abbreviations: E: number of events; EAC: (external) event adjudication committee; N: number of subjects with at least one event; R: events per 100 observation years; sema: semaglutide; %: proportion of subjects with at least one event.

Source: Table 2-130 ISS

Lung cancer

There were 14 events of lung cancer in the CVOT: one in the semaglutide 0.5 mg group, 7 in the semaglutide 1 mg group, and 6 in the pooled placebo group. Each case is briefly described below:

Placebo

- 525018 68 year old male randomized to placebo diagnosed with metastatic bronchial carcinoma approximately 23 months after the treatment started. He is reported as having a 40 year history of smoking (60 pack years), stopped 10 years prior. No action was taken with the study drug, and the event was ongoing at the end of the study.

- 653029 72 year old male randomized to placebo diagnosed with lung adenocarcinoma 4 1/2months after the start of the study treatment. No action was reported with the study treatment. The patient was a previous smoker with an average of 10 cigarettes per day for approximately 41 years, and had a history of COPD.

- Patient ID 640010 71 year old female randomized to placebo, diagnosed with non-small cell lung cancer approximately 9 months after the start of the study drug. The study drug was not discontinued, and the event was ongoing at the end of the study. The patient was a former smoker, quit 14 years prior to the diagnosis, and had a history of COPD.

- Patient ID 425003: 73 year old white male randomized to placebo was diagnosed with small cell lung cancer and hyponatremia on trial day 684, the study drug was not discontinued due to the event, and the event was considered ongoing at the end of the trial. The patient had been a smoker since 1970, average 40 cigarettes/day.

- Patient ID 680016 71 year old male randomized to placebo, diagnosed with small-cell lung cancer 11 months after the initiation of study treatment. He reported a history of smoking 1pack/day for 25 years. The study drug was discontinued an dthe event was ongoing at that time.

- Patient ID 485016 71 year old male randomized to placebo, diagnosed with squamous cell cancer of the lung approximately 20 months after the initiation of treatment. The patient is a previous smoker (Average of 20 cigarettes per day, for approximately 46 years of smoking). No action was taken with the study drug and the event was ongoing.

Semaglutide 0.5 mg

- Patient ID 283013 (listed as IC in the dataset, but confirmed in the adjudication package) 62 year old male diagnosed with lung cancer 23 months after the initiation of the study drug. No action was taken with the study drug, and the event was ongoing at the end of the trial. The patient was a former smoker , 3 packs/day for more than 30 years, quit 5 years prior to the diagnosis.

Semaglutide 1 mg

- Patient ID 424002 74 year old male diagnosed with malignant mesothelioma 2 years and 4 months after randomization (following multiple episodes of pneumonia while on treatment: first on treatment episode documented 4 months after the initiation of study drug). He was a former smoker, 35 cigarettes/day for 48 years, discontinued 15 years prior to the diagnosis. More importantly, the patient was occupationally exposed to asbestos for about 10 years. The patient died 5 months after the diagnosis.

- Patient ID 444009 65 year old male randomized to semaglutide 1 mg was reported with lung adenocarcinoma stage IV approximately 19 months after the initiation of the study drug. Smoking history was reported for 40+ years, approximately 40 cigarettes/day. The trial drug was discontinued due to the event, and the patient died approximately 4 months after the diagnosis.

- Patient ID 462011 77 year old male randomized to semaglutide 1 mg was diagnosed with small-cell lung cancer approximately 13 months after study drug initiation, and died less than a month later. The patient was a smoker, 30 cigarettes/day for30 years.

- Patient ID 466009 66 year old male randomized to semaglutide 1 mg was diagnosed with lung adenocarcinoma almost 2 years after the initiation of the study drug. The patient was a current smoker with an average of 20 cigarettes per day for approximately 20 years. He underwent surgery and the event was reported as recovering at the end of the study. No action was taken with the study drug as a result of this event.

- Patient ID 483009 70 year old male patient reported with "pulmonary blastoma" approximately 15 months after the initiation of the study drug. The patient was a former smoker 30 cigarettes/day for40 years, discontinued 18 years prior to the event. He had lobectomy and the event was listed as recovered with sequelae at the end of the study. The study drug was permanently discontinued because of the event.

- Patient ID 604037 70 year old female randomized to semaglutide 1 mg, was diagnosed with mucinous adenocarcinoma in situ right lung approximately 1 year and 8 months after the initiation of the study drug. The patient was no longer on treatment at that time, as the treatment was permanently discontinued 9 weeks after initiation. The patient reported a 40 year smoking history, 30 cigarettes/day, and had a history of COPD.

- Patient ID 638024 63 year old male diagnosed with stage IV lung cancer (mediastinal adenopathy, CNS metastases, and bone metastases requiring hip replacement) approximately 9 months after the initiation of study drug. The patient was reported to be a current smoker, also with a history of alcohol abuse, and with a family history of cancer (unspecified). In retrospect, the patient noticed weight loss for 1 to 1.5 years prior to the diagnosis. The patient died 11 months after the diagnosis. No action was reported with the study drug.

- Patient ID 659017 60 year old female randomized to semaglutide 1 mg, diagnosed with small cell lung cancer 4.5 months after the initiation of the study drug. The patient presented with cough within 2 months of initiation of the study drug, and the study drug was only administered for 9 weeks. Therefore, at the time of the diagnosis, the patient was already off study drug. The patient was a previous smoker 10 cigarettes/day for 41 years. The patient died from this event approximately 7 months after the diagnosis.

It does not appear that any of the cases was likely to be related to the study drug as all patients had significant history of smoking as a confounder.

<u>Breast cancer</u>

In the CVOT, there were 8 events of breast cancer, one in the semaglutide 0.5 mg group (0.3%), 4 in the semaglutide 1 mg group (1.3%), and 3 in the placebo (0.5%). All these cancers occurred in women, and the percentages listed are reported using the number of women in each treatment group as the denominator. I was able to reproduce the applicant's results using JReview. Each case is briefly described below:

- Patient ID 258019: 62 year old post-menopausal female randomized to placebo, was diagnosed with stage III breats adenocarcinoma approximately 3 months after the initiation of the study drug. She had a history of fibrocystic breast disease and intraductal papilloma prior to randomization. She did not receive HRT, did not have genetic predisposition towards cancers, and denied excessive alcohol consumption. The study drug was discontinued permanently because of this event.

- Patient ID 604019: 72 year old female randomized to placebo, was diagnosed with invasive mammary carcinoma of the left breast (stage II/III) approximately 22 months after the initiation of the study drug (routine mammogram). Notably, she was not on the study drug at the time of the event, as it was discontinued about 10 months prior to the event (due to an adverse event of idiopathic thrombocytopenic purpura). She was post-menopausal since age 55 (no HRT), reported menarche at age 9, and did not have genetic predisposition for cancers.

- Patient ID 502004: 73 year old female randomized to semaglutide 0.5 mg, was diagnosed with breast cancer approximately 5 months after the initiation of the study drug (patient identified a breast nodule). The patient was postmenopausal (unknown if she received HRT), and there was no family history of cancers. The study drug was not discontinued due to this event.

- Patient ID 638014: 71 year old female randomized to semaglutide 1 mg, was diagnosed with ER and PR positive breast cancer approximately 21 months after the initiation of the study drug. The patient had a personal history of lung cancer (smoker), and a family history of cancer (mother and father with lung cancer, and brother with CLL). Genetic testing was not performed. The patient denied history of HRT.

- Patient ID 502008: 64 year old female randomized to semaglutide 1 mg, was diagnosed with right ER and PR positive breast carcinoma in situ 11 months after the initiation of the study drug. She was post-menopausal and denied HRT treatment. The only potentially significant family history is listed as "colonic and vesicle tumors" in her father. The patient denied excessive alcohol consumption. No action was taken with the study drug.

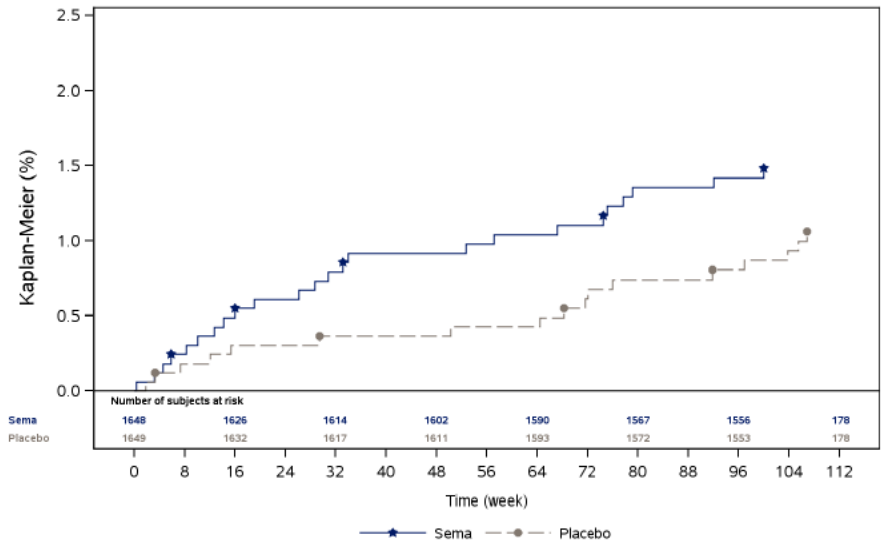
- Patient ID 521001: 70 year old post-menopausal female randomized to semaglutide 1 mg, was diagnosed with invasive ductal carcinoma approximately 16 months after the initiation of the study drug. Notably, at the time of the event, the patient was not on the study drug as it was discontinued 5 months after initiation. Reproductive history and treatments were not known for this patient. Family history was also not available.

- Patient ID 617005: 64 year old female randomized to semaglutide 1 mg, was diagnosed with stage IIIc T2N3, ER/PR positive, HER2 negative right breast ductal carcinoma with no lymphovascular involvement approximately 7 weeks after the initiation of the study drug. Family history did not mention any cancers, the patient herself did not have history of cancers, and she was post-menopausal at the time of the event (no HRT).

Skin cancer

There were 41 confirmed malignant skin neoplasms in the CVOT, 9 (1.1%) in the semaglutide 0.5 mg, 15 (1.8%) in the semaglutide 1 mg, and 17 (1%) in the placebo group. Most of the skin malignancies were basal cell carcinomas, with only one case of malignant melanoma in the semaglutide 0.5 mg arm. Most of the cancers were identified in countries with more sun exposure, with a large proportion of patients with EAC-confirmed events being from Australia. It appears that the separation between the semaglutide arms and placebo occurs early in the course of the study, which makes it unlikely that this finding is attributable to the study drug.

Figure 79 Time to First EAC Confirmed Malignant Skin Neoplasm - Kaplan-Meier Plot –CVOT



Notes: Kaplan-Meier estimates. Analyses of time from randomisation to first EAC confirmed malignant skin neoplasm. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact or all-cause death of the subject, whichever comes first. Numbers below the graph are subjects at risk.
Abbreviations: EAC: (external) event adjudication committee; sema: semaglutide.

Source: Figure 2-95 ISS

Table 203 EAC-Confirmed Events of Skin Cancer by Preferred Term - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	826				822				1649			
PYO	1708.4				1699.8				3401.1			
Malignant	9	(1.1)	10	0.59	15	(1.8)	24	1.41	17	(1.0)	18	0.53
Basal cell carcinoma	6		6		10		17		13		14	
Malignant melanoma	1		1									
Squamous cell carcinoma of skin	1		2		2		2					
Squamous cell carcinoma					4		5					
Bowen's disease									1		1	
Neoplasm skin	1		1									
Hyperkeratosis									1		1	
Keratoacanthoma									1		1	
No term									1		1	

Source: Table 13-88 study report CVOT

Phase 3 pool

There were only a few EAC-confirmed malignancies in this pool, 11 events (0.8%) in semaglutide 0.5 mg treatment group, 16 (0.9%) in the semaglutide 1 mg arm group, and 9 (0.5%) in placebo.

Table 204 EAC-Confirmed Malignancies in Phase 3 Pool

Neoplasm organ system of origin	Sema 0.5 N (%)	Sema 1 N (%)	Comparator N (%)
Number of subjects	1373	1777	1657
Number of women	590	765	715
Number of men	783	1012	942
Any malignancy[1]	11 (0.8)	16 (0.9)	9 (0.5)
Breast[2]	2 (0.3)	2 (0.3)	1 (0.1)
Male reproductive (penile, prostate, testicular)[3]	0	2 (0.2)	0
Colorectal	0	1 (0.1)	0
Female reproductive (vaginal, cervical, ovarian)[2]	0	1 (0.1)	1 (0.1)
Gastric/intestinal	0	1 (0.1)	1 (0.1)
Liver	0	1 (0.1)	0
Skin	3 (0.2)	1 (0.1)	1 (0.1)
Pancreatic	2 (0.1)	0	2 (0.1)
Lung/bronchus	1 (0.1)	0	0
Lymphomas (Non-Hodgkin, Hodgkin)	1 (0.1)	0	1 (0.1)
Naso-pharyngeal	1 (0.1)	0	0
Renal/adrenal	1 (0.1)	0	0
Other	0	4 (0.2)	2 (0.1)

Neoplasm organ system of origin	Sema 0.5 N (%)	Sema 1 N (%)	Comparator N (%)

[1] includes 3 thyroid neoplasms in semaglutide 1 mg that are not included in the individual malignancies shown in this table; [2] incidence based on number of women; [3] incidence based on number of men
Source: Modified from Table 1-15 of the SCS and Table 2-136 of the ISS

Pancreatic cancer

Pancreatic cancer was balanced between treatment groups, reported in 2 patients in the semaglutide 0.5 mg group, and in 2 patients in the comparator pool.

Lung cancer
There were only two reports of lung cancer in the pool excluding the CVOT, one in the semaglutide 1 mg arm (study 3626), and one in the semaglutide 0.5 mg arm (study 4091). Both patients were current smokers.

Breast cancer

Five patients were reported with events of breast cancer in the phase 3 pool, 2 in each of the semaglutide groups (0.3%), and one in comparator (Exenatide ER 0.1%).

Skin cancer

Only 5 patients had EAC-confirmed events of skin cancer in this pool, 3 in the semaglutide 0.5 mg arm (0.2%), and one in each semaglutide 1 mg and placebo arms (<0.1%). Considering the short duration of the studies included in this pool, the small number of events is not surprising, and it is very likely that the events observed were due to chance.

Placebo pool

There were few EAC-confirmed malignancy events in the placebo pool. No events were identified in the placebo arm vs. 5 events identified in the semaglutide arm (3 skin malignancies, 1 breast, and 1 male reproductive).

Lung cancer

No events of lung cancer were reported in the placebo pool.

Breast cancer

One event of breast cancer was reported from study 3623, in the semaglutide 0.5 mg group.

Skin cancers

There were 3 events of EAC confirmed skin cancers in the placebo pool, 2 in the semaglutide 0.5 mg group (0.8%), and one in the semaglutide 1 mg group (0.4%). No events were reported in the placebo group. While this shows an increase in the incidence of skin malignancies with semaglutide vs placebo, I believe that this finding is due to chance as the number of events is small, and I cannot think of a plausible mechanism by which semaglutide can cause skin cancer in such a short time.

Reviewer's comment: While an imbalance not favoring placebo was seen for lung, breast, and skin cancers, the numbers are too small to be conclusive. Additionally, confounding factors are present in most cases. Pancreatic cancer was rare, and no imbalance not favoring semaglutide was observed.

8.5.8. **Thyroid neoplasms**

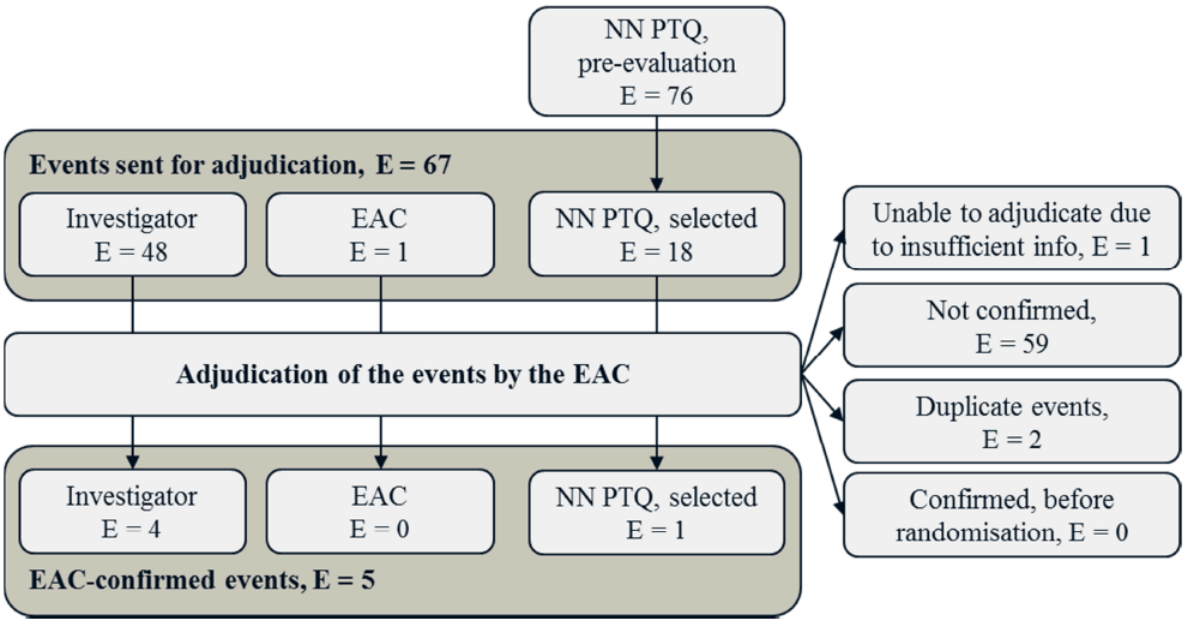
In this section I will present thyroid neoplasms, including MTC, as well as changes in serum calcitonin as a biomarker for increased c-cell mass and activation.

All suspected cases of thyroid disease requiring thyroidectomy and thyroid neoplasms were prospectively adjudicated. The events were evaluated with regards to whether the event was a thyroid neoplasm, the malignancy status and whether the event was a medullary thyroid carcinoma.

EAC-confirmed events

CVOT
A total of 67 events were sent for adjudication, and only 5 were confirmed by the EAC (4 thyroid neoplasms, and one thyroidectomy). The confirmation rate for semaglutide was 6.9% overall (0% for semaglutide 0.5 mg, and 14.3% for semaglutide 1 mg), and for placebo 7.9%. There were no c-cell hyperplasia or MTC events. The 4 events of thyroid neoplasm were evenly distributed between the treatment groups (2 with semaglutide, and 2 with placebo).

Figure 80 Event Adjudication Process Flow for Thyroid Neoplasms and Events Leading to Thyroidectomy – CVOT



Note: Confirmed events with onset prior to randomisation are included in number of EAC-confirmed events.
Abbreviations: E: number of events; EAC: event adjudication committee; NN PTQ: Novo Nordisk pre-defined preferred term query.
Source: Figure 2-93 ISS

Table 205 EAC-Confirmed Thyroid Neoplasms (Excluding Thyroidectomy) – FAS/SAS In-Trial – CVOT

	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Placebo N	(%)	E	R
CVOT												
Number of subjects	826				822				1649			
PYO	1708.4				1699.8				3401.1			
Malignant	0	(0.0)	0	0.0	1	(0.1)	1	0.06	2	(0.1)	2	0.06
Medullary carcinoma	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Medullary microcarcinoma	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
C-cell hyperplasia	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Other	0	(0.0)	0	0.0	1	(0.1)	1	0.06	2	(0.1)	2	0.06
Pre-malignant	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Benign	0	(0.0)	0	0.0	1	(0.1)	1	0.06	0	(0.0)	0	0.0
Other	0	(0.0)	0	0.0	1	(0.1)	1	0.06	0	(0.0)	0	0.0

Source: Adapted from table 2-144 ISS

The two events of thyroid neoplasia with semaglutide were as follows:

- Patient no 227015, 71 year old female randomized to semaglutide 1 mg, was reported with metastatic thyroid papillary cancer on study day 661. The study drug was discontinued due to this event, and the event led to the patient's demise 5 months later.
- Patient no 683041, 75 year old female randomized to semaglutide 1 mg, reported with benign goiter on study day 624. The study drug had already been discontinued on day 71 due to GI events.
- Patient no 506005, 56 year old male randomized to placebo, reported with micro-papillary thyroid cancer detected during evaluation of worsening goiter (study day 716).
- Patient no 604025 85 year old male randomized to placebo, reported with papillary thyroid cancer on study day 12.

Review of the narratives did not raise any concerns. It is unlikely in my opinion that any of these events is related to the study drug.

Phase 3 pool excluding CVOT

A total of 29 events were sent for adjudication and 8 of these events were confirmed by the EAC. Six events were confirmed thyroid neoplasms (although one occurred prior to randomization), and 2 were events of thyroidectomy. Of the 5 neoplasms that occurred after randomization, four were in the semaglutide 1 mg group (3 malignant , and one benign), and one in the comparator group (benign). One of the 3 malignancies was a case of c-cell hyperplasia in the semaglutide 1 mg group (phase 3 excluding CVOT pool). Patient no 741002 was randomized to semaglutide 1 mg in the study 3624, was reported with c-cell hyperplasia on study day 6 (thyroid nodule present at randomization). The thyroid nodule was reported as follicular thyroid cancer and the multifocal c-cell hyperplasia was found in the surgical specimen. The other two malignancies were events of papillary thyroid cancer that occurred on study day 111, and 363, respectively.

Table 206 EAC-Confirmed Thyroid Neoplasms (Excluding Thyroidectomy) – FAS/SAS In-Trial - Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				All comparators			
	N	(Adj%)	E	Adj.R	N	(Adj%)	E	Adj.R	N	(Adj%)	E	Adj.R
Phase 3a pool												
Number of subjects	1373				1777				1657			
PYO	1229				1685				1545			
Malignant	0	(0.0)	0	0.0	3	(0.2)	3	0.2	0	(0.0)	0	0.0
Medullary carcinoma	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Medullary microcarcinoma	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
C-cell hyperplasia	0	(0.0)	0	0.0	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Other	0	(0.0)	0	0.0	2	(0.1)	2	0.1	0	(0.0)	0	0.0
Pre-malignant	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Benign	0	(0.0)	0	0.0	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1
Other	0	(0.0)	0	0.0	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1

Source: Adapted from table 2-144 ISS

Placebo pool

There were no confirmed events of thyroid neoplasm or thyroidectomy in the placebo pool.

Calcitonin – CVOT and phase 3 pool

Across the CVOT and phase 3 trials a small proportion of patients had post-baseline events of calcitonin ≥20 ng/L both with semaglutide, placebo and pooled comparators. Looking at the maximum calcitonin value, in the CVOT, a slightly higher proportion of patients on semaglutide had an event of high calcitonin over the course of the trial. It is notable though that, in the CVOT, only 2 patients had events of calcitonin above 100 ng/L during the trial, both on semaglutide 0.5 mg (none of them had clinical events). In the phase 3 pool, there was a slightly larger proportion of patients on comparator that were reported with high calcitonin over the course of the trial (7.6% vs 6.9%). There were no patients with calcitonin above 100 ng/L.

Overall these small differences were not reflected in any clinical outcomes, and it is unlikely that they are significant.

Table 207 Calcitonin - Categorical Summary of Maximum Post-Baseline Values, Incidental Increases and Persistent Increases – CVOT

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)
Number of subjects	826	822	1649
Maximum post-baseline values			
Normal	666 (82.12)	687 (84.61)	1380 (85.40)
High (> ULN)	145 (17.88)	125 (15.39)	236 (14.60)
>20 ng/L	31 (3.82)	20 (2.46)	53 (3.28)
>50 ng/L	3 (0.37)	4 (0.49)	2 (0.12)
>100 ng/L	2 (0.25)		
Incidental increase			
Females			
N	329 (40.0)	306 (37.4)	657 (40.0)
From < UNR to ≥ UNR	18 (5.5)	5 (1.6)	25 (3.8)
From < UNR to ≥ 1.5×UNR	7 (2.1)	1 (0.3)	6 (0.9)
From < UNR to ≥ 20 ng/L	2 (0.6)	0 (0.0)	1 (0.2)
From < UNR to ≥ 50 ng/L	1 (0.3)	0 (0.0)	0 (0.0)
From < 20 ng/L to ≥ 20 ng/L	2 (0.6)	2 (0.7)	1 (0.2)
From < 50 ng/L to ≥ 50 ng/L	1 (0.3)	1 (0.3)	0 (0.0)
Males			
N	494 (60.0)	513 (62.6)	987 (60.0)
From < UNR to ≥ UNR	63 (12.8)	61 (11.9)	85 (8.6)
From < UNR to ≥ 1.5×UNR	12 (2.4)	13 (2.5)	21 (2.1)
From < UNR to ≥ 20 ng/L	2 (0.4)	0 (0.0)	3 (0.3)
From < UNR to ≥ 50 ng/L	0 (0.0)	0 (0.0)	0 (0.0)
From < 20 ng/L to ≥ 20 ng/L	24 (4.9)	13 (2.5)	40 (4.1)
From < 50 ng/L to ≥ 50 ng/L	2 (0.4)	3 (0.6)	2 (0.2)
Persistent increase			
Females			
N	329 (40.0)	306 (37.4)	657 (40.0)
From < UNR to ≥ UNR	7 (2.1)	1 (0.3)	9 (1.4)
From < UNR to ≥ 1.5×UNR	2 (0.6)	0 (0.0)	1 (0.2)
From < UNR to ≥ 20 ng/L	0 (0.0)	0 (0.0)	1 (0.0)
From < UNR to ≥ 50 ng/L	0 (0.0)	0 (0.0)	0 (0.0)
From < 20 ng/L to ≥ 20 ng/L	0 (0.0)	1 (0.3)	0 (0.0)
From < 50 ng/L to ≥ 50 ng/L	0 (0.0)	0 (0.0)	0 (0.0)
Males			
N	494 (60.0)	513 (62.6)	987 (60.0)
From < UNR to ≥ UNR	30 (6.1)	31 (6.0)	42 (4.3)
From < UNR to ≥ 1.5×UNR	4 (0.8)	2 (0.4)	5 (0.5)
From < UNR to ≥ 20 ng/L	0 (0.0)	0 (0.0)	3 (0.3)
From < UNR to ≥ 50 ng/L	0 (0.0)	0 (0.0)	0 (0.0)
From < 20 ng/L to ≥ 20 ng/L	13 (2.6)	8 (1.6)	25 (2.5)
From < 50 ng/L to ≥ 50 ng/L	1 (0.2)	1 (0.2)	0 (0.0)

Notes: Incidental increase: at least one scheduled post-baseline calcitonin measurement is above or equal to upper limit of normal range. Persistent increase: at least 2 consecutive scheduled post-baseline calcitonin measurements are above or equal to upper limit of normal range. ULN females: 5.0 ng/L; ULN males: 8.4 ng/L.

Abbreviations: N: number of subjects with event; ULN: upper limit of normal; UNR: upper normal range; %: percentage of subjects with event.

Source: Table 2-145 ISS

Table 208 Calcitonin - Categorical Summary of Maximum Post-Baseline Values, Incidental Increases and Persistent Increases – Phase 3 Pool

	Sema 0.5 mg N	(%)	Sema 1.0 mg N	(%)	All comparators N	(%)
Number of subjects	1373		1777		1657	
Maximum post-baseline values						
High (> ULN)	94	(6.9)	121	(6.9)	124	(7.6)
>20 ng/L	13	(1.0)	18	(1.0)	17	(1.0)
>50 ng/L			2	(0.1)	1	(0.1)
>100 ng/L						
<20 ng/L	1341	(99.0)	1729	(99.0)	1609	(99.0)
20-50 ng/L	13	(1.0)	16	(0.9)	16	(1.0)
>50 ng/L			2	(0.1)	1	(0.1)
Incidental increase						
Females						
N	590	(43.0)	765	(43.1)	715	(43.2)
From < UNR to ≥ UNR	10	(1.7)	16	(2.1)	8	(1.1)
From < UNR to ≥ 1.5×UNR	2	(0.3)	5	(0.7)	4	(0.6)
From < UNR to ≥ 20 ng/L	0	(0.0)	3	(0.4)	0	(0.0)
From < UNR to ≥ 50 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
From < 20 ng/L to ≥ 20 ng/L	2	(0.3)	3	(0.4)	0	(0.0)
From < 50 ng/L to ≥ 50 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
Males						
N	783	(57.0)	1012	(56.9)	942	(56.8)
From < UNR to ≥ UNR	30	(3.8)	33	(3.3)	44	(4.7)
From < UNR to ≥ 1.5×UNR	8	(1.0)	4	(0.4)	6	(0.6)
From < UNR to ≥ 20 ng/L	1	(0.1)	1	(0.1)	0	(0.0)
From < UNR to ≥ 50 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
From < 20 ng/L to ≥ 20 ng/L	3	(0.4)	5	(0.5)	7	(0.7)
From < 50 ng/L to ≥ 50 ng/L	0	(0.0)	2	(0.2)	1	(0.1)
Persistent increase						
Females						
N	590	(43.0)	765	(43.1)	715	(43.2)
From < UNR to ≥ UNR	5	(0.8)	4	(0.5)	1	(0.1)
From < UNR to ≥ 1.5×UNR	0	(0.0)	2	(0.3)	0	(0.0)
From < UNR to ≥ 20 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
From < UNR to ≥ 50 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
From < 20 ng/L to ≥ 20 ng/L	1	(0.2)	0	(0.0)	0	(0.0)
From < 50 ng/L to ≥ 50 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
Males						
N	783	(57.0)	1012	(56.9)	942	(56.8)
From < UNR to ≥ UNR	7	(0.9)	13	(1.3)	13	(1.4)
From < UNR to ≥ 1.5×UNR	1	(0.1)	1	(0.1)	1	(0.1)
From < UNR to ≥ 20 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
From < UNR to ≥ 50 ng/L	0	(0.0)	0	(0.0)	0	(0.0)
From < 20 ng/L to ≥ 20 ng/L	2	(0.3)	1	(0.1)	0	(0.0)
From < 50 ng/L to ≥ 50 ng/L	0	(0.0)	0	(0.0)	1	(0.1)

Notes: Incidental increase: at least one scheduled post-baseline calcitonin measurement is above or equal to upper limit of normal range. Persistent increase: at least 2 consecutive scheduled post-baseline calcitonin measurements are above or equal to upper limit of normal range. ULN females: 5.0 ng/L; ULN males: 8.4 ng/L. Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Abbreviations: N: number of subjects with event; ULN: upper limit of normal; UNR: upper normal range; %: percentage of subjects with event.

Source: Table 2-146 ISS

No effect of semaglutide dose was identified looking at post-baseline calcitonin levels.

The applicant also performed a MedDRA search to identify increased calcitonin events, and this analysis is discussed below.

Table 209 Adverse Events of Calcitonin Increased On-Treatment – CVOT and Phase 3 Pool

	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	Placebo N	(%)	E	R
CVOT												
Number of subjects	823				819				1644			
PYE	1488				1444				3035			
Investigations												
Endocrine investigations												
Blood calcitonin increased	4	(0.5)	4	0.3	7	(0.9)	7	0.5	13	(0.8)	13	0.4
Metabolism and nutrition disorders												
Bone, calcium, magnesium and phosphorus metabolism disorders												
Hypercalcitoninaemia									1	(<0.1)	1	<0.1

	Sema 0.5 mg N	(Adj%)	E	Adj.R	Sema 1.0 mg N	(Adj%)	E	Adj.R	All comparators N	(Adj%)	E	Adj.R
Phase 3a pool												
Number of subjects	1373				1777				1657			
PYE	1165				1548				1467			
Investigations												
Endocrine investigations												
Blood calcitonin increased	4	(0.3)	4	0.3	11	(0.6)	11	0.7	3	(0.2)	3	0.2
Metabolism and nutrition disorders												
Bone, calcium, magnesium and phosphorus metabolism disorders												
Hypercalcitoninaemia	1	(<0.1)	1	<0.1								

Notes: For the phase 3a pool, % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate. Phase 3a pool: Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).
Abbreviations: Adj.: adjusted; E: number of events; EAC: (external) event adjudication committee; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYO; sema: semaglutide; %: percentage of subjects with at least one event.
Source: Table 2-147 ISS

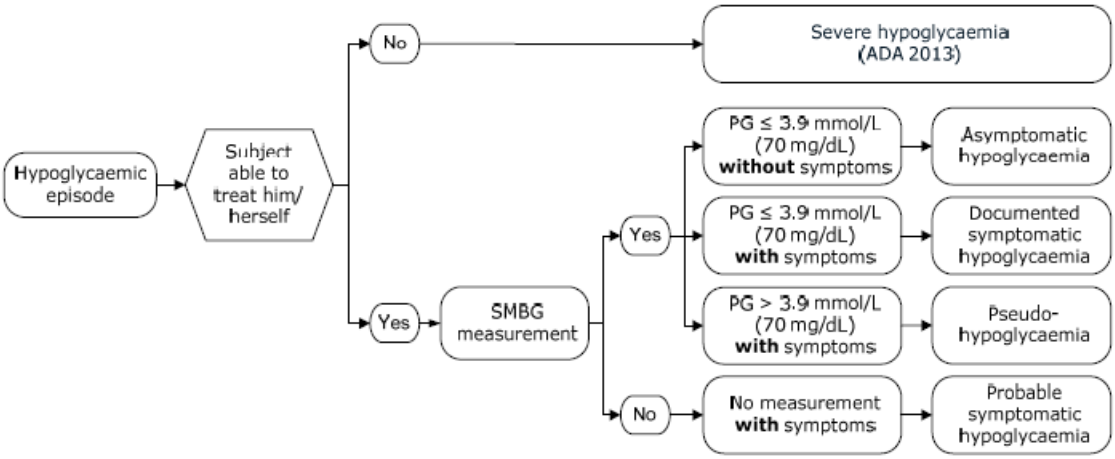
Reviewer comment: Despite the theoretical concern for medullary thyroid carcinoma, no cases of MTC were identified in the semaglutide program. This is not unusual as this is a very rare type of cancer, and longer follow-up may be needed. No other thyroid disorders were associated with the use of semaglutide. Small changes in calcitonin were not reflected in any clinical outcomes.

8.5.9. **Hypoglycemia**

In the phase 3 trials (including the CVOT), patients were to measure and record plasma glucose when a hypoglycemic episode was suspected and in connection with self-measured plasma glucose values, as according to the trial protocols. All plasma glucose values equal to or below 70 mg/dL, or higher than 70 mg/dL in conjunction with symptoms of hypoglycemia, were to be recorded by the patient in their diary. In addition, all FPG values (measured by the central laboratory) that met the criteria of biochemical hypoglycemia by the Novo Nordisk and ADA criteria were to be reported as an episode of hypoglycemia.

In addition to the ADA hypoglycemia classification presented below, the applicant included severe symptomatic hypoglycemia as documented glucose below 56 mg/dL with symptoms in the Novo Nordisk classification of hypoglycemia. I do not agree with the inclusion of such episodes as blood glucose meters are not very accurate when glucose is low, and this category could include episodes that would not even qualify as hypoglycemia. I feel that looking at the severe hypoglycemia by the ADA definition is the most specific way to evaluate hypoglycemic events. The applicant also defined nocturnal hypoglycemia as hypoglycemia episodes having time of onset between 1 and 5:59 AM.

Figure 81 ADA Classification of Hypoglycemia



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Source: Figure 2-98 ISS

All episodes of hypoglycemia were reported on hypoglycemia forms. In the CVOT, all episodes of severe hypoglycemia were to be reported as AEs. Data presented for the phase 3 trials (except the CVOT), only include hypoglycemic episodes reported until initiation of rescue medication to avoid the confounding bias of the rescue medication (see further below).

The applicant analyzed the hypoglycemia events based on the on-treatment observation period. Hypoglycemic episodes were defined as treatment emergent if the onset of the

episode occurred on or after the first day of trial product administration, and no later than the 5-week follow-up visit.

Because the trials design were designed differently regarding the background antidiabetic medications, and adjustment of background therapies, these aspects will have to be considered in the hypoglycemia analyses.

CVOT

The number of severe hypoglycemia was small overall, which is expected in a clinical program in patients with T2DM. Most of the events occurred in patients with sulfonylureas and/or insulin as background therapies. While there were some small differences between treatment arms, I do not think that, overall, semaglutide was associated with an increase incidence of severe hypoglycemia compared to standard of care.

Table 210 Episodes of ADA Severe Hypoglycemia by Baseline Background Medication –On-Treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Add on to SUs and 'standard of care'												
N and PYE (year)	230	420.1			219	399.1			434	808.2		
Subjects with episodes	3	(1.3)	3	0.7	3	(1.4)	3	0.8	2	(0.5)	4	0.5
Add on to insulin and 'standard of care'												
N and PYE (year)	358	653.3			345	599.6			678	1248.1		
Subjects with episodes	8	(2.2)	8	1.2	3	(0.9)	7	1.2	14	(2.1)	23	1.8
Add on to SU + insulin and 'standard of care'												
N and PYE (year)	117	210.7			131	238.2			276	514.0		
Subjects with episodes	2	(1.7)	3	1.4	3	(2.3)	3	1.3	9	(3.3)	12	2.3
Add on to other OADs (not SU or insulin) and 'standard of care'												
N and PYE (year)	118	204.2			124	207.0			256	464.5		
Subjects with episodes	1	(0.8)	1	0.5	0	(0.0)			1	(0.4)	1	0.2

Notes: The on-treatment summary of hypoglycaemic episodes comprises treatment-emergent events with onset on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose date, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Besides SU and/or insulin, subjects can also receive other types of antidiabetic background medication.

Abbreviations: ADA: American Diabetes Association; BG: Blood glucose; Blood glucose confirmed: BG < 3.1 mmol/L (56 mg/dL); E: number of events; N: number of subjects with at least one event; %: percentage of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; SU: Sulphonylurea.

Source: Table 2-157 ISS

The applicant also analyzed hypoglycemia events based on the Novo Nordisk definition outlined above. It does appear that there was an increased incidence of such events with both semaglutide arms compared to placebo in the subset of patients on sulfonylurea, or sulfonylurea and insulin, at baseline. This was not true for the patients on insulin at baseline.

Table 211 Episodes of Severe or Blood Glucose Confirmed Symptomatic Hypoglycemia by Baseline Background Medication –on-treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Add on to SUs and 'standard of care'												
N and PYE (year)	230	420.1			219	399.1			434	808.2		
Subjects with episodes	32	(13.9)	58	13.8	34	(15.5)	93	23.3	49	(11.3)	145	17.9
Add on to insulin and 'standard of care'												
N and PYE (year)	358	653.3			345	599.6			678	1248.1		
Subjects with episodes	104	(29.1)	396	60.6	102	(29.6)	365	60.9	210	(31.0)	826	66.2
Add on to SU + insulin and 'standard of care'												
N and PYE (year)	117	210.7			131	238.2			276	514.0		
Subjects with episodes	38	(32.5)	141	66.9	36	(27.5)	125	52.5	63	(22.8)	233	45.3
Add on to other OADs (not SU or insulin) and 'standard of care'												
N and PYE (year)	118	204.2			124	207.0			256	464.5		
Subjects with episodes	9	(7.6)	18	8.8	2	(1.6)	3	1.4	11	(4.3)	32	6.9

Notes: The on-treatment summary of hypoglycaemic episodes comprises treatment-emergent events with onset on or after the day of first dose and until the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose date, date of last dose plus 42 days or end of the subject's in-trial period, whichever comes first. Besides SU and/or insulin, subjects can also receive other types of antidiabetic background medication.

Abbreviations: ADA: American Diabetes Association; BG: Blood glucose; Blood glucose confirmed: BG < 3.1 mmol/L (56 mg/dL); E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; SU: Sulphonylurea; %: percentage of subjects with at least one event.

Source: Table 2-156 ISS

My analysis using JReview and the Hypoglycemic episode analysis dataset, selecting for severe hypoglycemia episodes on treatment, revealed 14 patients in the semaglutide 0.5mg (1.69%), 11 in the semaglutide 1 mg (1.34%), and 29 in placebo (1.76%). Hypoglycemia SAEs occurred in a similar proportion of patients on placebo (15 patients), and semaglutive (17 patients). Looking at hypoglycemic coma, and hypoglycemic unconsciousness SAEs, I identified 5 patients in placebo, and 8 patients in the semaglutide pool, which suggests that a higher proportion of patients on semaglutide experienced this type of event. Additionally, I reviewed the narratives for all SAEs of coma, confusional state, dizziness, epilepsy, presyncope, seizure, and syncope, and none of these events could be attributable to hypoglycemia.

The same analysis looking at the combination of severe and documented symptomatic hypoglycemia (as defined by the applicant) showed the following: 191 patients on semaglutide 0.5 mg (23.12%) experienced an event, compared to 178 patients on semaglutide 1 mg (21.65%), and 349 (21.2%) patients on placebo. Most of these patients had multiple episodes of documented hypoglycemia throughout the course of the trial, although most of these episodes did not fit the definition(s) used for these analyses.

While these numbers differ slightly from the applicant's analysis, they do not change my conclusions. Notably, no dose response was seen for the two semaglutide doses.

<u>Phase 3 pool excluding CVOT</u>

A total of 203 Novo Nordisk-defined hypoglycemic events were reported in the phase 3 pool, 20 of which were reported as severe hypoglycemia. There were no significant differences between the treatment groups in the pool.

Table 212 Novo Nordisk-defined Hypoglycemia – Phase 3 pool Excluding CVOT

NN classification of Hypoglycemia	Sema 0.5 N=1373	Sema 1.0 N=1777	Comparator N=1657
	N (%)	N (%)	N (%)
Patients with Event N (%)	**38 (2.8)**	**77 (4.3)**	**88 (5.3)**
Severe hypoglycemia	3 (0.2)	9 (0.5)	8 (0.5)
Symptomatic plasma glucose <56 mg/dL confirmed hypoglycemia	36 (2.6)	70 (3.9)	82 (4.9)

Source: Reviewer generated using ADSL, hypoglycemia dataset from the ISS

However, because background therapy and study design may impact the incidence of hypoglycemia, findings by individual study are presented **Table 213**. Most of the hypoglycemia events occurred on a background that included SU and/or insulin.

Table 213 Novo Nordisk-Defined Hypoglycemia Phase 3 Pool by Study and Background Medication – On-Treatment Without Rescue

Study Identifier	Comparator	Background Medication	Novo-Nordisk defined hypoglycemia		
			Comparator	Sema 0.5 mg	Sema 1.0 mg
3624	**Exenatide ER**	**Total**	**27 (6.67%) N 405**	**-**	**29 (7.18%) N 404**
		Metformin + SU	26 (6.42%)	-	21 (5.20%)
		Metformin mono	1 (0.25%)	-	5 (1.24%)
		SU mono	0	-	1 (0.06%)
		Other	0	-	1 (0.25%)
3625	**Insulin glargine**	**Total**	**38 (10.56%) N 360**	**15 (4.14%) N 362**	**19 (5.28%) N 360**
		Metformin + SU	34 (9.44%)	14 (3.87%)	16 (4.44%)
		Metformin mono	4 (1.11%)	1 (0.28%)	3 (0.83%)
3626	**Sitagliptin**	**Total**	**5 (1.23%) N 407**	**7 (1.71%) N 409**	**2 (0.49%) N 409**
		Metformin mono	4 (0.98%)	7 (1.71%)	2 (0.49%)
		Other	1 (0.25%)	0	0

Study Identifier	Comparator	Background Medication	Novo-Nordisk defined hypoglycemia		
			Comparator	**Sema 0.5 mg**	**Sema 1.0 mg**
3627	**Placebo**	**Total**	**7 (5.26%) N 133**	**11 (8.33%) N 132**	**14 (10.69%) N 131**
		Insulin +/- metformin	7 (5.26%)	11 (8.33%)	14 (10.69%)
4091	**OADs**	**Total**	**2 (1.67%) N 120**	**3 (1.26%) N 239**	**6 (2.49%) N 241**
		SU mono	2 (1.67%)	2 (0.84%)	6 (2.49%)
		Other	0	1 (0.42%)	0
4092	**Sitagliptin**	**Total (monotherapy)**	**0 N 103**	**0 N 102**	**1 (0.98%) N 102**

Source: Reviewer generated using JReview, hypoglycemia dataset ISS

SAEs of hypoglycemia occurred in 2 patients on comparator (one on glargine and one on sitagliptin), one in semaglutide 0.5 mg (background of metformin and SU), and 3 patients on semaglutide 1 mg (one on background of metformin and SU, two on insulin).

Episodes of severe or BG confirmed symptomatic hypoglycemic episodes by baseline background medication, as presented by the applicant, are shown below. As expected, the majority of events come from add-on to SU and add-on to insulin trials. A higher proportion of patients on comparator experienced a hypoglycemic event that fit the NN definition compared to either semaglutide arm in the patients on a background of SU. For most of the events in this subgroup, exenatide ER or insulin glargine were used as comparator.

Data for the patients on a background of insulin comes from the trial 3627 where background was insulin with or without metformin. In this study there was a slightly higher proportion of patients on semaglutide who experienced a hypoglycemic event vs comparator (insulin with or without metformin).

Due to the small number of events overall, it is difficult to assess the significance of these findings.

Table 214 Episodes of Severe or Blood Glucose Confirmed Symptomatic Hypoglycemia by Baseline Background Medication –On-Treatment - Phase 3 Trials

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Monotherapy												
N and PYE (year)	299	226			300	215			237	157		
Subjects with episodes	0	(0.0)			1	(0.4)	1	0.7	0	(0.0)		
Add-on to SUs												
N and PYE (year)	255	196			436	377			435	380		
Subjects with episodes	16	(6.5)	33	18.2	45	(10.4)	77	20.8	62	(14.0)	108	27.4
Add-on to insulin												
N and PYE (year)	132	84			131	82			133	84		
Subjects with episodes	11	(8.3)	17	20.2	14	(10.7)	25	30.5	7	(5.3)	12	14.2
Add-on to other OADs (not SU or insulin)												
N and PYE (year)	687	659			910	874			851	845		
Subjects with episodes	9	(1.3)	9	1.4	11	(1.2)	12	1.4	10	(1.1)	13	1.5

Notes: The subgroups are based on the baseline medication. Table only contains data from the on-treatment period without rescue medication. % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Comparators: Subjects in each baseline background medication subgroup may have been in different studies and, therefore, received different comparators.

Abbreviations: BG: blood glucose, BG confirmed: BG < 3.1 mmol/L (56 mg/dL), E: number of events, N: number of subjects in the safety analysis set with at least one episode during the treatment period without rescue medication, OAD: Oral antidiabetic drug, PYE: patient-years of exposure, R: events per 100 PYE, SU: Sulfonylurea, %: percentage of subjects with at least one event.

Source: Table 2-158 ISS

SAEs of hypoglycemia occurred in 2 patients on comparator (one on glargine and one on sitagliptin), one in semaglutide 0.5 mg (background of metformin and SU), and 3 patients on semaglutide 1 mg (one on background of metformin and SU, two on insulin).

Placebo pool

There were no events of severe hypoglycemia in study 3623, and the events in study 3627 are presented in the table above. There were 35 events of Novo Nordisk-defined hypoglycemia as presented below.

Table 215 Novo Nordisk-defined Hypoglycemia – Placebo Pool

NN classification of Hypoglycemia	**Sema 0.5 N=260**	**Sema 1.0 N=261**	**Placebo N=262**
	N (%)	**N (%)**	**N (%)**
Patients with Event N (%)	**12 (4.6)**	**14 (5.4)**	**9 (3.4)**
Severe hypoglycemia	1 (0.4)	2 (0.8%)	1 (0.4)

Symptomatic plasma glucose <56 mg/dL confirmed hypoglycemia	11 (4.2)	12 (4.6)	9 (3.4)

Source: Reviewer generated using ADSL, hypoglycemia dataset from the ISS

The small number of events precludes any meaningful conclusions regarding the incidence of severe hypoglycemia with semaglutide compared to placebo in this pool

In summary, severe hypoglycemia, as expected, was rare. In the CVOT, patients on semaglutide had an increased risk of severe and confirmed symptomatic hypoglycemia on a background of SU, and SU plus insulin compared to standard of care. Hypoglycemic coma and hypoglycemic unconsciousness were reported in slightly more patients on semaglutide (8) vs placebo (5). Severe and confirmed symptomatic hypoglycemia were even more rare in the rest of the phase 3 program, and semaglutide appeared to increase the risk of hypoglycemia when added to insulin. No dose-response was seen for hypoglycemia. Overall, there appears that semaglutide has a low inherent risk of hypoglycemia, but it may increase the incidence of hypoglycemia when used together with insulin secretagogues and/or insulin.

8.5.10. **Immunogenicity**

Immunogenicity reactions were considered a safety area of interest because semaglutide is a protein-based product. In the phase 3 trials, antibody formation was assessed regularly throughout the trial period.

Upon suspicion of severe immediate hypersensitivity, a sample for assessment of anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies was to be collected after a suitable washout period (minimum 5 weeks). In these cases, it was recommended to confirm if an event was an allergic reaction by measuring tryptase at the time of the reaction and again at the same time as the IgE antibody sample was obtained.

Additionally, MedDRA searches were performed among all AEs reported in the phase 3 trials to capture and summarize events potentially related to antibodies, allergic reaction events, immune complex disease and injection site reaction events.

Anti-semaglutide antibodies

The proportion of patients that tested positive for anti-semaglutide antibodies was 1.9% in CVOT, 1.0% in the phase 3 pool and 2.2% in the pool of placebo-controlled trials.

Allergic reactions – MedDRA search

CVOT

There was no difference between the proportion of patients on semaglutide vs placebo who experienced an allergic event (5.5% of patients in each semaglutide arm, and 6% in placebo). However, a higher proportion of patients on semaglutide 0.5 mg experienced an allergic reaction SAE (5 patients, 0.6%), compared to semaglutide 1 mg (2 patients, 0.2%), and placebo (2 patients, 0.1%). Only a small proportion of AEs lead to premature treatment discontinuation (0.4% in semaglutide 0.5 mg, 0.1% in semaglutide 1 mg, and 0.5% in placebo).

One event was fatal, in the placebo treatment group (PT: anaphylactic shock).

- Patient no 562005 was a 72 year old female who developed anaphylactic shock and septicemia the day the study drug was started, and died 3 days later. It appears that the patient was hospitalized for digitalis toxicity and sepsis, and the treatment with digibind or the antibiotics were the possible cause for the anaphylactic shock.
-

The only other event of anaphylactic shock in the study was reported in the semaglutide 0.5 mg arm and was not fatal.

- Patient no 302012, 81 year old female, was reported with anaphylactic shock on trial day 770. The event was attributed to treatment with cefazolin which was administered before a pacemaker insertion.

Table 216 Allergic reactions (MedDRA search) – SAS on-treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
PYE (year)	1488				1444				3035			
Events	45	(5.5)	50	3.4	45	(5.5)	48	3.3	98	(6.0)	123	4.1
Serious												
Yes	5	(0.6)	5	0.3	2	(0.2)	2	0.1	2	(0.1)	2	<0.1
No	40	(4.9)	45	3.0	43	(5.3)	46	3.2	96	(5.8)	121	4.0
Severity												
Severe	5	(0.6)	5	0.3	0				3	(0.2)	3	<0.1
Moderate	14	(1.7)	14	0.9	16	(2.0)	16	1.1	23	(1.4)	26	0.9
Mild	26	(3.2)	31	2.1	30	(3.7)	32	2.2	75	(4.6)	94	3.1
Leading to premature treatment discontinuation												
Yes	3	(0.4)	3	0.2	1	(0.1)	<1	0.1	8	(0.5)	8	0.3
No	43	(5.2)	47	3.2	45	(5.5)	47	3.3	91	(5.5)	115	3.8

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.

Source: Table 2-160 ISS

My analysis using JReview and the adverse event dataset found a few more allergic reactions SAEs, and the results are presented in the table below, by preferred term and treatment arm. SAEs occurred more frequently with semaglutide vs placebo, however the overall number of events was small. No SAE lead to treatment discontinuation, however there were a few non-

serious events that lead to discontinuation (8 with placebo - 0.5%, and 4 with semaglutide – 0.2%).

Table 217 Allergic Reactions SAEs – FAS - CVOT

MedDRA Preferred Term	Sema 0.5 N=826	Sema 1 N=822	Placebo N=1649
	N (%)	N (%)	N (%)
Total patients with SAEs	**7 (0.9)**	**2 (0.2)**	**2 (0.1)**
Anaphylactic shock	1 (0.1)	0	1 (<0.1)
Angioedema	0	1 (0.1)	0
Bronchospasm	1 (0.1)	0	0
Circulatory collapse	1 (0.1)	0	0
Drug hypersensitivity	1 (0.1)	0	1 (<0.1)
Hypersensitivity	1 (0.1)	0	0
Skin necrosis	1 (0.1)	1 (0.1)	0
Stevens-Johnson syndrome	1 (0.1)	0	0

Source: Reviewer generated using adverse events dataset for study 3744

Angioedema:

- Patient ID 621008 65 year old female, trial day 771, presented to the ER with tongue swelling and palmar pruritis that occurred 15 minutes after ingesting generic OTC antacid.

Bronchospasm:

- Patient ID 563005 61 year old female who had a complicated clinical course s/p gastric sleeve surgery. She developed renal failure, arrhythmias, pneumoperitoneum, and died during the hospitalization. The bronchospasm was not allergic.

Circulatory collapse:

- Patient ID 441007 78 year old female reported with circulatory collapse that was due to dehydration (preceded by vomiting and diarrhea).

Drug hypersensitivity:

- Patient ID 444019 58 year old male randomized to placebo with allergic reaction to drug administered in the context of anesthesia (surgery for umbilical hernia).
- Patient ID 633014: 67 year old male randomized to semaglutide 0.5 mg developed allergic reaction to azithromycin (treated for bronchitis).

Hypersensitivity:

- Patient ID 673016 51 year old female randomized to semaglutide 0.5 mg presented to the ER with rash and pruritis while eating a snack of walnuts. The event recovered and there was no change to the trial medication.

Skin necrosis

- Patient ID 122025 53 year old male randomized to semaglutide 0.5 mg reported with necrotic ulcer on the side of the foot, no allergic reaction. This was in the context of peripheral vascular disease.
- Patient ID 327001 62 year old male randomized to semaglutide 1 mg reported with lower extremity necrotic ulcer in the context of PVD.

Stevens-Johnson syndrome:

- Patient ID 526026 69 year old female randomized to semaglutide 0.5 mg, reported with SAE Stevens Johnson syndrome approximately 5 months after the initiation of the study treatment. This happened in the context of the patient being administered Trimetoprim for a UTI. The clinical manifestations were as follows: sore mouth including lips and chin, tongue ulcers, creamy yellowish discharge from palate, blisters on cheeks, rash on abdomen and dysphagia, but no swelling or fever. The study drug was not discontinued due to this event.

The time to onset of first allergic event was similar between semaglutide and placebo, with more events in both treatment groups reported in the first 12 weeks of treatment.

None of the patients that tested positive for semaglutide antibodies post-baseline was reported with any allergic-related adverse event.

Phase 3 pool

The proportion of patients with an allergic event was similar between the treatment groups. All the SAEs though occurred in the semaglutide arm (4 patients - 5 events).

The proportion of patients with an allergic event was similar between the treatment groups. All the SAEs though occurred in the semaglutide arm (4 patients - 5 events).

Table 218 Allergic Reactions (MedDRA Search) – SAS On-Treatment – Phase 3 Pool

MedDRA Preferred term	Sema 0.5 N=1373	Sema 1 N=1777	Comparator N=1657
	N (%)	N (%)	N (%)
Total with events	59 (4.3)	70 (3.9)	57 (3.4)
Events that were SAEs	2 (0.2)	2 (0.1)	0
Events leading to treatment discontinuation	2 (0.2)	5 (0.3)	9 (0.5)
Allergic bronchitis	0	0	2 (0.1)
Allergic pharyngitis	0	0	1 (<0.1)
Angioedema	0	3 (0.2)	1 (<0.1)
Bronchospasm	1 (0.1)	0	0
Circulatory collapse	0	2 (0.1)	1 (<0.1

MedDRA Preferred term	Sema 0.5 N=1373	Sema 1 N=1777	Comparator N=1657
	N (%)	N (%)	N (%)
Conjunctivitis allergic	6 (0.4)	1 (<0.1)	2 (0.1)
Dermatitis	3 (0.2)	5 (0.3)	4 (0.2)
Dermatitis allergic	2 (0.2)	1 (<0.1)	0
Dermatitis atopic	2 (0.2)	0	0
Dermatitis contact	2 (0.2)	4 (0.2)	3 (0.2)
Dermatitis infected	2 (0.2)	0	0
Dermatitis psoriasiform	1 (0.1)	0	0
Drug eruption	2 (0.2)	0	3 (0.2)
Drug hypersensitivity	2 (0.2)	2 (0.1)	0
Eczema	6 (0.4)	14 (0.8)	9 (0.5)
Eczema nummular	1 (0.1)	0	1 (<0.1)
Eye allergy	0	1 (<0.1)	0
Eye swelling	0	1 (<0.1)	0
Eyelid oedema	2 (0.2)	2 (0.1)	2 (0.1)
Hypersensitivity	1 (0.1)	1 (<0.1)	2 (0.1)
Injection site hypersensitivity	0	0	1 (<0.1)
Injection site rash	1 (0.1)	1 (<0.1)	1 (<0.1)
Laryngeal oedema	0	1 (<0.1)	0
Lip swelling	0	1 (<0.1)	0
Multiple allergies	0	1 (<0.1)	0
Oedema mouth	0	0	1 (<0.1)
Palatal oedema	0	1 (<0.1)	0
Periorbital oedema	0	1 (<0.1)	0
Pharyngeal oedema	1 (0.1)	0	0
Rash	11 (0.8)	10 (0.6)	14 (0.8)
Rash erythematous	1 (0.1)	3 (0.2)	0
Rash generalized	0	0	2 (0.1)
Rash maculo-papular	1 (0.1)	1 (<0.1)	0
Rash pruritic	1 (0.1)	0	0
Rash pustular	0	0	1 (<0.1)
Rhinitis allergic	10 (0.7)	4 (0.2)	5 (0.3)
Swelling face	1 (0.1)	1 (<0.1)	0
Swollen tongue	1 (0.1)	2 (0.1)	0
Toxic skin eruption	0	1 (<0.1)	0

MedDRA Preferred term	Sema 0.5 N=1373	Sema 1 N=1777	Comparator N=1657
	N (%)	N (%)	N (%)
Urticaria	4 (0.3)	10 (0.6)	6 (0.4)

Source: Reviewer generated using ADSL, ADAE from the ISS

The four patients with events compatible with a drug-induced allergic reaction (allergic reaction SAEs) are briefly described in **Table 219**. Only three of the events were true allergic reactions, one was likely cellulitis. For the three allergic reactions, two appear to have been caused by and ACE-I, and one by amoxicillin. The study drug was not discontinued in any of the 4 cases, all events resolved. No AEs of anaphylactic reaction or anaphylactic shock were reported, and no AE was fatal.

Table 219 Allergic Reactions SAEs Phase 3 Pool

Patient ID	Age/sex	Study treatment	Time after initiation of study drug	Symptoms	Alternative etiology
472015	54/F	Sema 1	10 months	Swelling of uvula	The patient was also taking enalapril, and the reaction was attributed to enalapril, which was replaced with losartan
110003	55/F	Sema 1	1 month	Swelling of face, left eye and throat, hoarseness and allergic eczema of extremities	Treatment with amoxicillin for acute parotitis
584012	37/F	Sema 0.5	9 months	Fever and redness and swelling of the right leg	Likely cellulitis
702001	62/M	Sema 0.5	8 months	Swelling of the tongue, throat, and shortness of breath	Ramipril for hypertension, and the patient underwent allergy testing which recommended discontinuation of Ramipril (unclear whether allergy to Ramipril was tested specifically, or the recommendation was based on known information regarding ACE-I).

Source: Reviewer generated from review of narratives

No AEs of anaphylactic reactions or anaphylactic shock were reported, and no AE was fatal.

Placebo pool

A total of 20 events of allergic reactions were reported in the two placebo-controlled trials. A higher proportion of patients reported allergic reactions in the semaglutide 0.5 mg and semaglutide 1 mg treatment groups than in the placebo group (7 events with semaglutide 0.5 mg, 10 events with semaglutide 1 mg and 3 events with placebo).

Table 220 Allergic Reactions MedDRA Search – Placebo pool – On-Treatment

MedDRA Preferred term	Sema 0.5 N=260	Sema 1 N=261	Placebo N=262
	N (%)	N (%)	N (%)
Total with events	**7 (2.7%)**	**10 (3.8)**	**3 (1.2)**
Events that were SAEs	**0**	**1 (0.4)**	**0**
Events leading to treatment discontinuation	**1 (0.4)**	**1 (0.4)**	**0**
Bronchospasm	1 (0.4)	0	0
Dermatitis	0	1 (0.4)	1 (0.4)
Dermatitis contact	0	11 (0.4)	0
Drug hypersensitivity	0	1 (0.4)	0
Eczema	0 (	1 (0.4)	0
Hypersensitivity	1 (0.4)	0	0
Lip swelling	0	1 (0.4)	0
Rash	4 (1.5)	0	1 (0.4)
Rhinitis allergic	0	3 (1.2)	1 (0.4)
Swollen tongue	0	1 (0.4)	0
Urticaria	1 (0.4)	2 (0.8)	0

Source: Reviewer generated using ADSL, ADAE from the ISS

There was one SAE and 2 AEs leading to premature treatment discontinuation reported with semaglutide and none with placebo.

Overall there did not appear to be any dose response for semaglutide as it pertains to allergic reactions.

Immune complex disease

The applicant used this search to identify additional potential immunogenicity concerns with semaglutide (i.e., events that might result from antigen-antibody complexes). However, the

MedDRA query used for this search, which is a standard MedDRA query, is not specific in identifying events that are truly immunogenicity related as it pertains to the drug review.

CVOT

Overall, potential immune complex diseases captured by the MedDRA search were reported in approximately 4% of the patients; the proportion of patients with events and corresponding rate of events in the on-treatment observation period were slightly lower in the semaglutide 0.5 mg and semaglutide 1 mg treatment groups compared to the placebo treatment group.

Table 221 Immune Complex Disease (MedDRA Search) – SAS On-Treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	823				819				1644			
PYE (year)	1488				1444				3035			
Events	31	(3.8)	31	2.1	24	(2.9)	26	1.8	80	(4.9)	88	2.9
Serious												
Yes	5	(0.6)	5	0.3	4	(0.5)	4	0.3	10	(0.6)	12	0.4
No	26	(3.2)	26	1.7	20	(2.4)	22	1.5	70	(4.3)	76	2.5
Severity												
Severe	2	(0.2)	2	0.1	2	(0.2)	2	0.1	3	(0.2)	4	0.1
Moderate	13	(1.6)	13	0.9	13	(1.6)	15	1.0	27	(1.6)	29	1.0
Mild	16	(1.9)	16	1.1	9	(1.1)	9	0.6	50	(3.0)	54	1.8
Unknown									1	(<0.1)	1	(<0.1)
Leading to premature treatment discontinuation												
Yes	0				1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
No	31	(3.8)	31	2.1	23	(2.8)	25	1.7	79	(4.7)	87	2.9

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; %: percentage of subjects with at least one event.
Source: Table 2-162 ISS

The most frequently reported AEs related to immune complex diseases were proteinuria, arthritis and pleural effusion; the proportion of patients with events and the corresponding rates were similar between semaglutide and placebo treatment groups, except for proteinuria which was lower in the semaglutide 1 mg treatment group compared to the semaglutide 0.5 mg and placebo treatment groups.

A small proportion of events were SAEs, with no significant differences between treatment groups. Only 2 AEs led to premature treatment discontinuation, 1 event reported in the semaglutide 1 mg treatment group and 1 event in the placebo treatment group.

Table 222 Immune Complex SAEs, On-Treatment – CVOT

MedDRA Preferred Term	Sema 0.5 N=826	Sema 1 N=822	Placebo N=1649
	N (%)	N (%)	N (%)

Total patients with events	**5 (0.6)**	**4 (0.5)**	**10 (0.6)**
Arthritis	0	1 (0.1)	3 (0.2)
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.1)	0	0
Epilepsy	1 (0.1)	1 (0.1)	0
Mouth ulceration	1 (0.1)	0	0
Pericardial effusion	1 (0.1)	0	0
Pleural effusion	0	1 (0.1)	2 (0.1)
Pleurisy	0	0	1 (<0.1)
Proteinuria	0	1 (0.1)	0
Seizure	0	0	3 (0.2)
Temporal arteritis	1 (0.1)	0	0
Thrombocytopenia	0	0	1 (<0.1)
Vasculitis	0	0	1 (<0.1)

Source: Reviewer generated ADAE ADSL

Phase 3 pool

Potential immune complex diseases captured by the MedDRA search were reported in approximately 1% of the patients, with no differences between the treatment groups.

Only one was reported as an SAE – pericarditis reported in a patient on semaglutide 1 mg – and no AE was fatal.

Table 223 Immune Complex Disease (MedDRA Search) - SAS On-Treatment - Phase 3 Pool

MedDRA Preferred term	**Sema 0.5 N=1373**	**Sema 1 N=1777**	**Comparator N=1657**
	N (%)	**N (%)**	**N (%)**
Total with events	**14 (1.0)**	**15 (0.8)**	**17 (1.0)**
Events that were SAEs	**0**	**1 (<0.1)**	**0**
Events leading to treatment discontinuation	**0**	**1 (<0.1)**	**0**
Arthritis	3 (0.2)	2 (0.1)	4 (0.2)
Generalised tonic-clonic seizure	0	1 (<0.1)	0
Leukopenia	1 (0.1)	0	2 (0.1)
Mouth ulceration	1 (0.1)	2 (0.1)	0
Pericardial effusion	0	0	1 (<0.1)
Pericarditis	0	1 (<0.1)	0
Platelet count decreased	1 (0.1)	2 (0.1)	1 (<0.1)
Pleural effusion	1 (0.1)	1 (<0.1)	0
Protein urine present	0	0	5 (0.3)
Proteinuria	3 (0.2)	3 (0.2)	1 (<0.1)
Seizure	1 (0.1)	0	1 (<0.1)

MedDRA Preferred term	Sema 0.5 N=1373	Sema 1 N=1777	Comparator N=1657
	N (%)	N (%)	N (%)
Thrombocytopenia	0	1 (<0.1)	3 (0.2)
White blood cell count decreased	3 (0.2)	2 (0.1)	0

Source: Reviewer generated using ADSL, ADAE from the ISS

Placebo pool

A total of 12 events were reported using the immune complex disease query, 4 (1.54%) on semaglutide 0.5 mg, 3 (1.15%) on semaglutide 1 mg, and 5 in comparator (1.91%).

Table 224 Immune Complex Diseases MedDRA Search – Placebo pool – On-Treatment

MedDRA Preferred term	Sema 0.5 N=260	Sema 1 N=261	Placebo N=262
	N (%)	N (%)	N (%)
Total with events	**4 (1.5)**	**3 (1.2)**	**5 (1.9)**
Events that were SAEs	**0**	**1 (0.4)**	**0**
Events leading to treatment discontinuation	**0**	**0**	**0**
Arthritis	2 (0.8)	0	0
Leukopenia	1 (0.4)	0	1 (0.4)
Pericarditis	0	1 (0.4)	0
Platelet count decreased	0	0	1 (0.4)
Protein urine present	0	0	2 (0.8)
Proteinuria	0	1 (0.4)	1 (0.4)
Seizure	1 (0.4)	0	0
Thrombocytopenia	0	1 (0.4)	0

Source: Reviewer generated using ADSL, ADAE from the ISS

Injection site reactions – MedDRA search

CVOT

Overall, injection site reactions captured by the MedDRA search were reported by approximately1% of the patients; the proportion of patients with events and corresponding rate of events in the on-treatment observation period were similar across the semaglutide 0.5 mg, semaglutide 1 mg and placebo treatment groups. No SAEs, or events leading to discontinuation were reported.

Table 225 Injection Site Reactions (MedDRA Search) –On-Treatment - CVOT

MedDRA Preferred Term	Sema 0.5 N=826	Sema 1 N=822	Placebo N=1649
	N (%)	N (%)	N (%)
Total patients with events	**6 (0.7)**	**9 (1.1)**	**20 (1.2)**
Injection site atrophy	0	0	1 (<0.1)
Injection site bruising	1 (0.1)	4 (0.5)	10 (0.6)
Injection site discoloration	1 (0.1)	0	0
Injection site discomfort	0	1 (0.1)	0
Injection site hematoma	1 (0.1)	1 (0.1)	0
Injection site hemorrhage	1 (0.1)	1 (0.1)	2 (0.1)
Injection site induration	1 (0.1)	0	0
Injection site mass	0	1 (0.1)	1 (<0.1)
Injection site nodule	0	0	1 (<0.1)
Injection site pain	1 (0.1)	1 (0.1)	2 (0.1)
Injection site reaction	1 (0.1)	1 (0.1)	1 (<0.1)
Injection site warmth	0	0	1 (<0.1)
Vessel puncture site bruise	0	0	1 (<0.1)

Source: Reviewer generated ADAE ADSL

The events appeared to be reported more frequently in the first 12 weeks of treatment. All injection site reaction AEs were reported within the general disorders and administration site conditions SOC and included the PTs injection site bruising, injection site hemorrhage, injection site pain and injection site hematoma; the proportion of patients and rate of events of these PTs were low and similar between the semaglutide and placebo treatment groups. None of these events was reported in patients with positive anti-semaglutide antibodies.

Phase 3 pool

Twenty six events were reported in 17 patients on semaglutide (8 on semaglutide 0.5 mg – 0.6%, and 9 on semaglutide 1 mg – 0.5%), vs 138 events in 99 patients on comparator (5.8%). Of the events reported with comparator, 128 events in 89 patients were reported with exenatide ER in study 3624. No SAEs were reported. Excluding study 3624, events were reported in 8 patients on semaglutide 0.5 mg (0.6%), 4 patients on semaglutide 1 mg (0.3%), vs 10 patients in the comparator group (0.8%). None of the patients reported with injection-site reaction tested positive for anti-semaglutide antiobodies.

Placebo pool

Four events were reported in one patient on semaglutide 0.5 mg (0.4%), vs 2 events in 2 patients on comparator (0.8%).

In conclusion, injection site reactions did not appear to occur more frequently with semaglutide injections, and the data, as submitted, do not raise any concerns regarding semaglutide-related immunogenicity.

Overall, the low immunogenicity of semaglutide is consistent with other GLP-1 analogues derived from the human amino acid sequence. No AEs related with anti-semaglutide antibodies were reported.

8.6. 4 Month Safety Update

A 4 month safety update (4 MSU) was submitted by the applicant on March 30, 2017. The data submitted was from blinded ongoing clinical trials, between the NDA submission cut-off date (April 18, 2016) and December 6, 2016. There have been no new nonclinical studies since the cut-off date (April 18, 2016) for the original NDA submission.

The applicant submitted data on deaths, SAEs, and pregnancies for the period covered in the 4 MSU. As agreed at the pre-NDA meeting, SAEs from the three ongoing trials investigating semaglutide daily treatment for T2DM, weight management, and chronic management of NASH were also included.

Throughout this 120-day safety update the trials are referred by:

- Completed semaglutideT2DM trials:
  – all completed trials, investigating semaglutide s.c. OW in T2DM
  – trial NN9924-3790, investigating oral semaglutide OD in T2DM (included semaglutide s.c. OW as comparator)
- Ongoing semaglutideT2DM trials:
  – trial NN9535-4216, investigating semaglutide s.c. OW vs dulaglutide in T2DM
  – trial NN9535-4215, investigating semaglutide s.c. OD versus semaglutide s.c. OW in T2DM
- Supportive ongoing semaglutide trials:
  – trial NN9535-4191, investigating dose finding of semaglutide s.c. OD in T2D
  – trial NN9536-4153, investigating dose finding of semaglutide s.c. OD in weight management
  – trial NN9931-4296, investigating dose finding of semaglutide s.c. OD in chronic management of NASH

Table 226 Overview of Ongoing Semaglutide T2DM Trials and supportive ongoing semaglutide Trials included in the 120-Day Safety Update

Trial ID	Clinical development phase/ intended indication	Number of subjects randomised	Treatment period (weeks)	FPFV	LPFV	LPLV
Ongoing semaglutide once-weekly T2D s.c. trials						
NN9535-4216	Phase 3a/T2D	1201	40	Jan 06, 2016	Jun 22, 2016	May 24, 2017[a]
NN9535-4215[b]	Phase 1/T2D	114	12	Sep 23, 2015	Dec 15, 2015	Apr 14, 2016
Supportive ongoing semaglutide s.c. trials						
NN9535-4191	Phase 2/T2D	706	26	Sep 21, 2015	Feb 12, 2016	Oct 13, 2016
NN9536-4153	Phase 2/weight management	957	52	Oct 01, 2015	Feb 11, 2016	Apr 12, 2017[a]
NN9931-4296	Phase 2/chronic management of NASH	372[a]	72	Nov 30, 2016	Nov 22, 2017[a]	Jul 11, 2019[a]

Notes: [a]planned date or number, [b]trial contained semaglutide s.c. once-weekly and semaglutide s.c. once-daily treatment arms.

Abbreviations: FPFV: first patient first visit; LPFV: last patient first visit; LPLV: last patient last visit; s.c.: subcutaneous; NASH: non-alcoholic steatohepatitis; T2D: type 2 diabetes mellitus.

Source: Table 1-1 4 MSU

Deaths

No deaths were reported from the completed semaglutide T2DM trials.

Ongoing semaglutide T2DM trials

A total of (b) (4) patients had fatal AEs in trial NN9935-4216 during the safety update period. The AEs with fatal outcome are presented below.

Table 227 Adverse Events with Fatal Outcome – Trial NN9535-4216

Trial ID	Subject ID (hyperlink)	Case no.	SOC	Preferred term
NN9535-4216	[redacted] (b) (4)			

Source: Table 2-1 4 MSU

[redacted] (b) (4)

The short exposure time for development of these neoplasms makes a causal relationship to treatment unlikely.

Supportive ongoing semaglutide trials

[redacted] (b) (4) in trial NN9536-4153 (weight management) in the 120-day safety update cut-off period (the patient was diagnosed with [redacted] (b) (4)

Deaths reported up until the original NDA submission cut-off date

In the period up until the original NDA submission cut-off date (April 18, 2016), [redacted] (b) (4) in the supportive ongoing semaglutide s.c. trials.

Other SAEs

Completed semaglutide T2DM trials

The 2 events were reported in 2 subjects treated with placebo in trial 3744 (cardiovascular outcomes trial); 1 event of cardiac failure and 1 event of paresis. Both events were reported after the subjects had completed the trial.

Ongoing semaglutide T2DM trials

A total of (b) (4) SAEs were reported in (b) (4) subjects in trial NN9535-4216, and no SAEs were reported in trial 4215. The (b) (4) SAEs were distributed across several SOCs; the SOCs with the highest occurrence of SAEs were (b) (4)

Table 228 Serious Adverse Events by System Organ Class – Trial NN9535-4216

System organ class	NN9535-4216 (T2D) N	E
(b) (4)		

Notes: Data are extracted from the safety database (Argus). System organ classes are sorted by descending total number of subjects with at least one event.
Abbreviations: E: number of events; N: number of subjects with at least one event; T2D: type 2 diabetes.

Source: Table 2-3 4MSU

Supportive ongoing semaglutide trials

A total of (b) (4) SAEs were reported in (b) (4) subjects from supportive ongoing semaglutide trials in the 120-day safety update cut-off period; (b) (4) SAEs were reported in (b) (4) subjects participating in trial NN9535-4191 (T2DM) and a total of (b) (4) SAEs were reported for (b) (4) subjects in trial NN9536-

4153 (weight management). No SAEs were reported in trial NN9931-4296 (NASH) in the 120-day safety update cut-off period.

The (b) (4) SAEs were distributed across several SOCs; the SOCs with the highest occurrence of SAEs were (b) (4)

Table 229 Serious Adverse Events by System Organ Class – Trials NN9535-4191 and NN9536-4153

System organ class	NN9535-4191 (T2D) N	NN9535-4191 (T2D) E	NN9536-4153 (obese without diabetes) N	NN9536-4153 (obese without diabetes) E
(b) (4)				

Notes: Data are extracted from the safety database (Argus). System organ classes are sorted by descending total number of subjects with at least one event.
Abbreviations: E: number of events; N: number of subjects with at least one event.
Source: Table 2-5 4MSU

Review of the reported PTs in both ongoing and supportive trials revealed the following:

(b) (4)

Serious adverse events up until the original NDA submission cut-off date (not included in the ISS)

In the period up until the original NDA submission cut-off date, (b) (4) SAEs were reported in the semaglutide s.c. OD trials; (b) (4) SAEs were reported in (b) (4) subjects participating in trial NN9535-4191 (T2DM) and a total of (b) (4) SAEs were reported in (b) (4) subjects in trial NN9536-4153 (weight management). Of these, most PTs were reported only once, with the exception of (b) (4)

Overall, my review of preferred terms and selected SAE narratives did not reveal any information that impacts my evaluation of risk-benefit with semaglutide.

Pregnancies

A total of 12 pregnancies have been reported across trials included in this 120-day safety update; 8 pregnancies from completed semaglutide trials (included in the ISS of the original NDA) and 4 pregnancies from supportive ongoing semaglutide trials. No pregnancies from ongoing semaglutide T2DM trials have been reported at the 120-day safety cut-off date.

Per the applicant, there are no new updates on the 8 pregnancies that were included in the ISS. Of the other 4 pregnancies, 2 were mentioned in the ISS as they were reported befor the cut-off date. The applicant submitted updates on these 2 pregnancies as follows:

- (b) (4)
-

The remaining 2 pregnancies, one reported in trial 4191, and one in 4153, were reported after the ISS cut-off date, and both pregnancies are still ongoing.

In conclusion, the additional information on pregnancies reported in this safety update does not change the pregnancy safety profile reported in the ISS of the original NDA: there is currently insufficient clinical experience to support the use of semaglutide in pregnant or lactating woman.

8.7. Safety Analyses by Demographic Subgroups

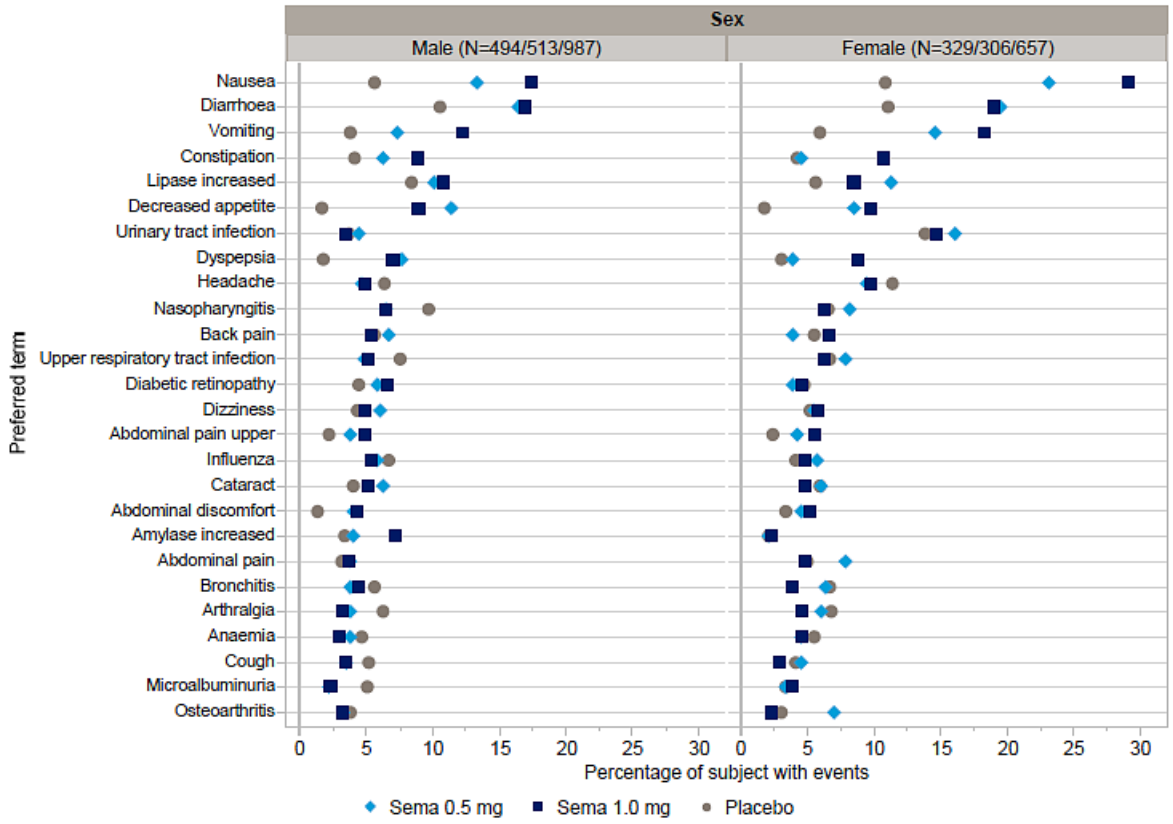
The potential impact of various factors (demographic parameters) on the safety profile of semaglutide (0.5 mg and 1.0 mg) was investigated based on the CVOT and pooled data from the other phase 3 trials. These factors included sex, baseline age, race, ethnicity, baseline CV history, baseline renal function (eGFR), geographic region, and antidiabetic background medication.

8.7.1. Sex

CVOT

Overall, both male and female patients experienced AEs in comparable proportions and at higher rates with semaglutide (0.5 mg and 1.0 mg) than placebo, with no significant differences between genders. Common adverse events by sex are presented in Figure 82 below.

Figure 82 Common (PTs in ≥5% of Patients) Adverse Events by Sex –On-Treatment – CVOT

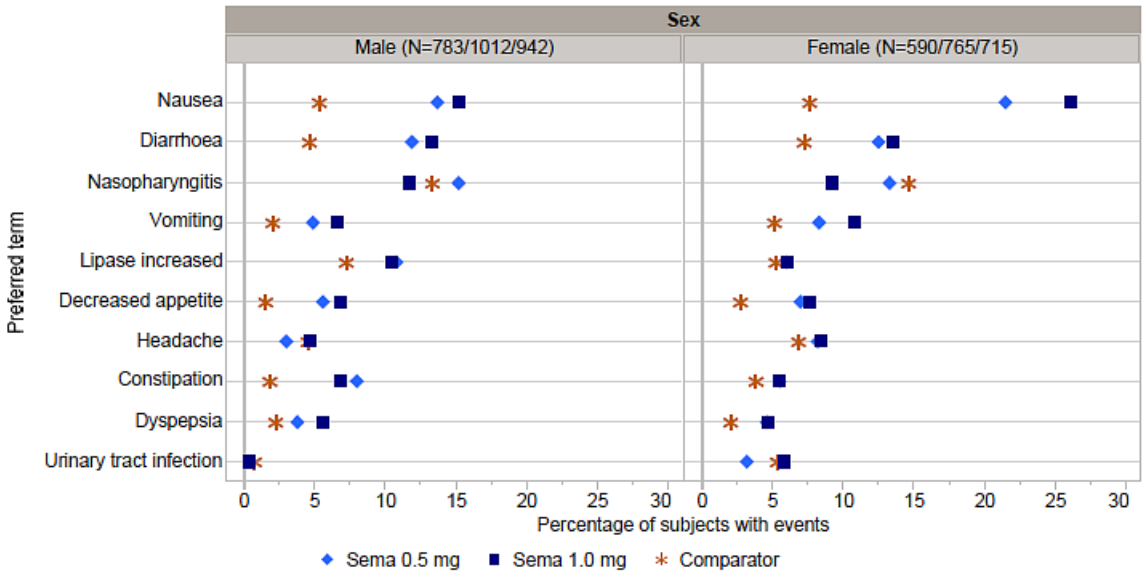


Source: Figure 5-1 ISS

Phase 3 pool

Overall, AEs were reported at a higher rate with semaglutide than comparators in both male and female patients, and the treatment differences were comparable in both subgroups. SAEs were reported by a slightly greater proportion of patients and at a higher rate with semaglutide than comparators among male patients, whereas there was no treatment difference among female patients.

Figure 83 Common (PTs in ≥5% of Patients) Adverse Events by Sex –On-Treatment – Phase 3 Pool



Notes: The percentages are Cochran-Mantel-Haenszel-adjusted. Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Source: Figure 5-2 ISS

Placebo pool

No differences were observed in the placebo pool.

8.7.2. Age

CVOT

The overall rates of AEs increased by age both with semaglutide and placebo, and AEs were reported at higher rates with semaglutide than placebo in all age subgroups. No particular trends were observed for SAEs in any age group.

Table 230 Adverse Events by Age (Years) - CVOT - On-Treatment

	Sema 0.5 mg				Sema 1.0 mg				All sema				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1642	2932			1644	3035		
< 65	442	813			412	753			854	1567			843	1568		
>= 65	381	675			407	690			788	1366			801	1467		
>= 75	74	118			83	123			157	241			163	275		
All Events	732	(88.9)	4981	334.7	722	(88.2)	5056	350.2	1454	(88.6)	10037	342.3	1453	(88.4)	9506	313.2
< 65	387	(87.6)	2555	314.2	358	(86.9)	2485	329.8	745	(87.2)	5040	321.7	733	(87.0)	4770	304.2
>= 65	345	(90.6)	2426	359.3	364	(89.4)	2571	372.4	709	(90.0)	4997	365.9	720	(89.9)	4736	322.8
>= 75	68	(91.9)	462	391.6	76	(91.6)	534	433.9	144	(91.7)	996	413.2	141	(86.5)	955	346.9
Serious																
Yes	264	(32.1)	599	40.2	240	(29.3)	481	33.3	504	(30.7)	1080	36.8	574	(34.9)	1256	41.4
< 65	122	(27.6)	264	32.5	117	(28.4)	223	29.6	239	(28.0)	487	31.1	274	(32.5)	587	37.4
>= 65	142	(37.3)	335	49.6	123	(30.2)	258	37.4	265	(33.6)	593	43.4	300	(37.5)	669	45.6
>= 75	30	(40.5)	69	58.5	30	(36.1)	61	49.6	60	(38.2)	130	53.9	62	(38.0)	133	48.3
No	718	(87.2)	4382	294.4	707	(86.3)	4575	316.9	1425	(86.8)	8957	305.5	1406	(85.5)	8250	271.8
< 65	379	(85.7)	2291	281.7	346	(84.0)	2262	300.2	725	(84.9)	4553	290.6	708	(84.0)	4183	266.8
>= 65	339	(89.0)	2091	309.7	361	(88.7)	2313	335.0	700	(88.8)	4404	322.5	698	(87.1)	4067	277.2
>= 75	65	(87.8)	393	333.1	75	(90.4)	473	384.3	140	(89.2)	866	359.3	133	(81.6)	822	298.6

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.32 ISS

Phase 3 pool

Overall, AEs were reported more frequently and at higher rates with semaglutide than comparators, all age subgroups showing comparable treatment differences. While generally a higher proportion of patients on semaglutide experienced an SAE vs comparator, it appears that for patients age 65-75, this trend was reversed. It is not clear that this is meaningful, rather than just chance as the number of events was not large.

Table 231 Adverse Events by Age (Years) - Phase 3 Pool - On-Treatment

	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	All sema N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			3150	2712			1657	1467		
< 65	1034	887			1372	1207			2406	2093			1248	1105		
>= 65	339	278			405	341			744	619			409	362		
>= 75	45	33			57	45			102	78			54	45		
All Events	1015	(73.4)	4292	360.6	1301	(72.7)	5724	359.4	2316	(73.2)	10016	360.7	1136	(68.7)	4220	275.8
< 65	758	(72.7)	3224	367.1	997	(72.3)	4357	361.6	1755	(72.8)	7581	363.6	840	(67.5)	3072	276.1
>= 65	257	(75.3)	1068	379.9	304	(74.2)	1367	401.8	561	(74.7)	2435	396.6	296	(72.5)	1148	309.1
>= 75	35	(76.5)	154	440.9	44	(77.2)	211	458.1	79	(76.6)	365	466.1	37	(69.2)	146	308.6
Serious																
Yes	92	(6.6)	138	11.7	118	(6.7)	152	9.7	210	(7.0)	290	10.8	95	(5.8)	117	7.7
< 65	66	(6.3)	103	11.8	90	(6.6)	113	9.5	156	(7.0)	216	11.0	60	(4.8)	76	6.8
>= 65	26	(7.6)	35	12.5	28	(7.1)	39	11.9	54	(6.8)	74	11.1	35	(8.5)	41	11.2
>= 75	5	(11.6)	9	28.0	4	(6.7)	7	14.6	9	(7.2)	16	16.1	4	(6.8)	5	9.9
No	997	(72.1)	4154	348.9	1281	(71.5)	5572	349.7	2278	(71.9)	9726	349.9	1120	(67.7)	4103	268.0
< 65	746	(71.6)	3121	355.2	982	(71.2)	4244	352.1	1728	(71.5)	7365	352.6	830	(66.6)	2996	269.2
>= 65	251	(73.5)	1033	367.4	299	(72.8)	1328	389.9	550	(73.2)	2361	385.5	290	(71.1)	1107	297.9
>= 75	34	(73.9)	145	412.9	44	(77.2)	204	443.6	78	(75.6)	349	450.0	36	(67.8)	141	298.7

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.31 ISS

Additionally, the applicant noted that while events of decreased appetite (PT) were reported more with semaglutide than comparators across all age subgroups, the treatment difference was the most pronounced among patients of ≥75 years.

Overall, no major age-dependent variation in treatment differences was observed.

8.7.3. **Race**

The trial population was divided into subgroups by race as follows:

- White
- Asian (Asian, Native Hawaiian, Pacific Islander)
- Black/African-American
- Other (American Indian, Alaska Native, unknown)

As most patients were white for the key efficacy trials and the CVOT, the data on other racial subgroups should be interpreted with caution.

CVOT

Overall, AEs were reported at higher rates with semaglutide than placebo in all race subgroups except other. SAEs were reported less frequently with semaglutide than placebo in all race subgroups except Asian, in which SAEs were reported more frequently with semaglutide than placebo.

Table 232 Adverse Events by Race - CVOT - On-Treatment

	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	All sema N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1642	2932			1644	3035		
White	690	1249			688	1212			1378	2462			1347	2492		
Black/Afr. Am	54	92			54	85			108	177			113	188		
Asian	63	118			58	115			121	233			152	298		
Other	16	29			19	32			35	61			32	57		
All Events	732	(88.9)	4981	334.7	722	(88.2)	5056	350.2	1454	(88.6)	10037	342.3	1453	(88.4)	9506	313.2
White	613	(88.8)	4356	348.6	617	(89.7)	4329	357.1	1230	(89.3)	8685	352.8	1196	(88.8)	8103	325.1
Black/Afr. Am	49	(90.7)	275	299.0	49	(90.7)	336	396.5	98	(90.7)	611	345.7	101	(89.4)	548	291.0
Asian	55	(87.3)	275	233.2	40	(69.0)	268	233.5	95	(78.5)	543	233.4	127	(83.6)	605	203.3
Other	15	(93.8)	75	258.6	16	(84.2)	123	382.0	31	(88.6)	198	323.5	29	(90.6)	250	440.0
Serious																
Yes	264	(32.1)	599	40.2	240	(29.3)	481	33.3	504	(30.7)	1080	36.8	574	(34.9)	1256	41.4
White	222	(32.2)	511	40.9	198	(28.8)	379	31.3	420	(30.5)	890	36.2	478	(35.5)	1047	42.0
Black/Afr. Am	17	(31.5)	38	41.3	17	(31.5)	43	50.7	34	(31.5)	81	45.8	42	(37.2)	90	47.8
Asian	20	(31.7)	43	36.5	20	(34.5)	47	41.0	40	(33.1)	90	38.7	43	(28.3)	100	33.6
Other	5	(31.3)	7	24.1	5	(26.3)	12	37.3	10	(28.6)	19	31.0	11	(34.4)	19	33.4
No	718	(87.2)	4382	294.4	707	(86.3)	4575	316.9	1425	(86.8)	8957	305.5	1406	(85.5)	8250	271.8
White	602	(87.2)	3845	307.7	604	(87.8)	3950	325.9	1206	(87.5)	7795	316.7	1160	(86.1)	7056	283.1
Black/Afr. Am	48	(88.9)	237	257.7	47	(87.0)	293	345.7	95	(88.0)	530	299.9	94	(83.2)	458	243.2
Asian	54	(85.7)	232	196.8	40	(69.0)	221	192.6	94	(77.7)	453	194.7	123	(80.9)	505	169.7
Other	14	(87.5)	68	234.4	16	(84.2)	111	344.7	30	(85.7)	179	292.4	29	(90.6)	231	406.6

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.152 ISS

The applicant noted that AEs of decreased appetite (PT) were reported at higher rates and by larger proportions of patients with semaglutide than placebo in all race groups; the treatment difference was most pronounced among Asian patients. Additionally, eye disorders were reported more with semaglutide vs placebo in Asian patients (PTs diabetic retinopathy and cataract).

Phase 3 pool

Overall, rates for AEs and SAEs were higher with semaglutide than comparators across the race subgroups, all subgroups displaying comparable treatment differences.

Table 233 Adverse Events by Race – Phase 3 Pool - On-Treatment

	Sema 0.5 mg				Sema 1.0 mg				All sema				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			3150	2712			1657	1467		
White	749	596			1085	944			1834	1540			1074	950		
Black/Afr. Am	65	46			106	83			171	129			97	74		
Asian	535	505			537	474			1072	979			425	388		
Other	19	15			22	20			41	35			31	28		
Unclassified	5	3			27	26			32	30			30	27		
All Events	1015	(73.4)	4292	370.7	1301	(72.7)	5724	370.0	2316	(73.2)	10016	370.8	1136	(68.7)	4220	284.4
White	529	(70.6)	2434	408.8	764	(70.5)	3519	372.7	1293	(71.1)	5953	384.5	733	(68.2)	2974	313.8
Black/Afr. Am	38	(59.4)	113	254.7	70	(66.4)	255	317.5	108	(64.4)	368	306.3	66	(67.4)	220	288.9
Asian	431	(79.7)	1687	333.2	426	(78.1)	1716	361.1	857	(79.0)	3403	346.7	291	(69.1)	835	213.2
Other	14	(74.5)	44	288.4	17	(76.2)	142	731.7	31	(76.0)	186	533.6	24	(77.3)	101	354.6
Unclassified	3	(60.0)	14	420.5	24	(89.1)	92	350.4	27	(85.1)	106	336.5	22	(74.1)	90	327.1
Serious																
Yes	92	(6.6)	138	12.0	118	(6.7)	152	10.0	210	(7.0)	290	11.1	95	(5.8)	117	7.9
White	54	(7.2)	82	13.8	82	(7.6)	110	11.7	136	(7.8)	192	12.6	75	(7.0)	94	9.9
Black/Afr. Am	2	(3.1)	5	11.4	9	(8.1)	11	11.9	11	(7.1)	16	11.8	3	(3.0)	3	4.0
Asian	33	(5.9)	43	8.4	22	(4.0)	25	5.3	55	(5.0)	68	7.0	14	(3.7)	17	4.9
Other	2	(10.7)	7	48.0	3	(12.7)	4	19.4	5	(10.4)	11	26.1	1	(3.1)	1	3.5
Unclassified	1	(20.0)	1	30.0	2	(7.6)	2	7.8	3	(7.6)	3	7.8	2	(6.3)	2	7.0
No	997	(72.1)	4154	358.6	1281	(71.5)	5572	360.0	2278	(71.9)	9726	359.7	1120	(67.7)	4103	276.4
White	517	(69.0)	2352	395.1	750	(69.2)	3409	361.0	1267	(69.5)	5761	371.9	721	(67.1)	2880	303.9
Black/Afr. Am	38	(59.4)	108	243.3	66	(63.3)	244	305.6	104	(62.5)	352	294.4	66	(67.4)	217	284.8
Asian	425	(78.6)	1644	324.8	425	(77.9)	1691	355.8	850	(78.4)	3335	339.7	288	(68.3)	818	208.4
Other	14	(74.5)	37	240.5	17	(76.2)	138	712.3	31	(76.0)	175	507.4	24	(77.3)	100	351.2
Unclassified	3	(60.0)	13	390.5	23	(85.4)	90	342.6	26	(81.5)	103	328.7	21	(70.6)	88	320.1

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.151 ISS

The following trends were noted by the applicant:

- GI AEs were reported at higher rates and by greater proportions of patients with semaglutide than placebo in all race groups; the treatment difference was most pronounced among Asian patients and mainly driven by AEs of nausea, diarrhoea, vomiting and constipation (PTs).
- Decreased appetite PT was more common with semaglutide vs comparator, and the difference was more pronounced in Asian patients
- Eye disorders were reported more with semaglutide vs placebo in Asian patients (PTs dry eye, cataract and asthenopia).

In conclusion, the treatment difference for GI AEs, and AEs of decreased appetite (PT) with semaglutide compared to comparators was most pronounced in the Asian subgroup in both the CVOT and the phase 3 pool. A similar trend was present in the SOC eye disorders, but the differences were partly driven by different PTs in the CVOT and the phase 3 pool.

8.7.4. Ethnicity

The trial population was divided into subgroups by ethnicity as follows:

- Not Hispanic/Latino
- Hispanic/Latino

CVOT

Overall, AEs and SAEs were reported by similar proportions of patients in the Hispanic/Latino and non-Hispanic/Latino patients with semaglutide and placebo. While the AE rate was slightly higher with semaglutide than placebo among the non-Hispanic/Latino patients, there was no treatment difference among Hispanic/Latino patients.

Table 234 Adverse Events by Ethnicity - CVOT - On-Treatment

	Sema 0.5 mg				Sema 1.0 mg				All sema				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1642	2932			1644	3035		
Hispanic/Latino	132	250			122	229			254	479			252	469		
Not Hispanic/Latino	691	1238			697	1215			1388	2453			1392	2566		
All Events	732	(88.9)	4981	334.7	722	(88.2)	5056	350.2	1454	(88.6)	10037	342.3	1453	(88.4)	9506	313.2
Hispanic/Latino	123	(93.2)	645	257.5	108	(88.5)	626	273.3	231	(90.9)	1271	265.1	229	(90.9)	1234	263.2
Not Hispanic/Latino	609	(88.1)	4336	350.3	614	(88.1)	4430	364.7	1223	(88.1)	8766	357.4	1224	(87.9)	8272	322.4
Serious																
Yes	264	(32.1)	599	40.2	240	(29.3)	481	33.3	504	(30.7)	1080	36.8	574	(34.9)	1256	41.4
Hispanic/Latino	24	(18.2)	49	19.6	30	(24.6)	55	24.0	54	(21.3)	104	21.7	66	(26.2)	104	22.2
Not Hispanic/Latino	240	(34.7)	550	44.4	210	(30.1)	426	35.1	450	(32.4)	976	39.8	508	(36.5)	1152	44.9
No	718	(87.2)	4382	294.4	707	(86.3)	4575	316.9	1425	(86.8)	8957	305.5	1406	(85.5)	8250	271.8
Hispanic/Latino	121	(91.7)	596	238.0	108	(88.5)	571	249.3	229	(90.2)	1167	243.4	221	(87.7)	1130	241.0

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3744 (placebo), On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.182 ISS

AEs of decreased appetite (PT) were reported at higher rates and by greater proportions of patients with semaglutide than placebo in both subgroups; the treatment difference was more pronounced among the non-Hispanic/Latino patients.

Phase 3 pool

The overall AE rates and proportions of patients experiencing AEs and SAEs were lower among the Hispanic/Latino compared to non-Hispanic/Latino patients

Table 235 Adverse Events by Ethnicity – Phase 3 Pool - On-Treatment

	Sema 0.5 mg N	(%)	E	R	Sema 1.0 mg N	(%)	E	R	All sema N	(%)	E	R	Comparator N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			3150	2712			1657	1467		
Hispanic/Latino	179	141			289	245			468	386			312	270		
Not Hispanic/Latino	1194	1024			1488	1303			2682	2326			1344	1196		
Unclassified													1	1		
All Events	1015	(73.4)	4292	370.7	1301	(72.7)	5724	370.0	2316	(73.2)	10016	370.8	1136	(68.7)	4220	284.4
Hispanic/Latino	123	(68.1)	554	393.6	179	(62.7)	757	312.1	302	(63.1)	1311	322.2	208	(66.7)	689	254.6
Not Hispanic/Latino	892	(74.2)	3738	366.6	1122	(74.8)	4967	382.0	2014	(75.2)	8705	379.8	927	(69.1)	3523	290.7
Unclassified	0	(0.0)			0	(0.0)			0	(0.0)			1	(100.0)	8	1155
Serious																
Yes	92	(6.6)	138	12.0	118	(6.7)	152	10.0	210	(7.0)	290	11.1	95	(5.8)	117	7.9
Hispanic/Latino	9	(5.0)	20	14.0	15	(5.4)	16	6.7	24	(5.2)	36	8.6	17	(5.4)	18	6.6
Not Hispanic/Latino	83	(6.9)	118	11.7	103	(7.0)	136	10.6	186	(7.3)	254	11.6	78	(5.9)	99	8.2
Unclassified	0	(0.0)			0	(0.0)			0	(0.0)			0	(0.0)		
No	997	(72.1)	4154	358.6	1281	(71.5)	5572	360.0	2278	(71.9)	9726	359.7	1120	(67.7)	4103	276.4
Hispanic/Latino	122	(67.6)	534	379.5	177	(62.0)	741	305.5	299	(62.5)	1275	313.7	205	(65.7)	671	247.9
Not Hispanic/Latino	875	(72.7)	3620	354.9	1104	(73.6)	4831	371.4	1979	(73.7)	8451	368.3	914	(68.1)	3424	282.5
Unclassified	0	(0.0)			0	(0.0)			0	(0.0)			1	(100.0)	8	1155

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), For the pools and subsets the % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.181 ISS

AEs of decreased appetite (PT) were reported at higher rates and by greater proportions of patients with semaglutide than comparators in the non-Hispanic/Latino subgroup, whereas there was no substantial treatment difference in the Hispanic/Latino subgroup.

In conclusion, the treatment difference in decreased appetite was more pronounced in the non-Hispanic/Latino subgroup than in the Hispanic/Latino subgroup.

8.7.5. Baseline CV history

CVOT

The overall AE and SAE rates were higher among patients with CV history at baseline than among patients without CV history. The AE rates were higher with semaglutide than placebo in both subgroups, whereas SAEs were more commonly reported with placebo than semaglutide.

Phase 3 pool

The overall rates and proportions of patients with AEs were higher in the subgroup with baseline CV history than without CV history, and higher with semaglutide than comparators in both subgroups. A similar pattern was observed in SAEs, with a more pronounced treatment difference among patients with CV history.

In conclusion, although minor differences were observed between the subgroups by baseline CV history, the overall safety profile of semaglutide was similar in these subgroups.

8.7.6. Baseline renal function

The trial population was divided to subgroups by baseline renal function (based on estimated eGFRclearance according to the MDRD equation) as follows:

- Normal renal function [≥90 mL/min per 1.73 m2]
- Mild renal impairment [60−89 mL/min per 1.73 m2]
- Moderate renal impairment [30−59 mL/min per 1.73 m2]
- Severe renal impairment [15−29 mL/min per 1.73 m2]
- End-stage renal disease [<15 mL/min per 1.73 m2]

CVOT

As expected, the overall AE and SAE rates increased by the degree of renal impairment at baseline both with semaglutide and placebo.

AE rates were higher with semaglutide than placebo in patients with normal or mildly impaired renal function, and comparable in both treatment groups among patients with moderately or severely impaired renal function. SAEs were reported at lower rates and by smaller proportions of patients with semaglutide than placebo across the baseline renal function subgroups.

Phase 3 pool excluding CVOT

Baseline renal function was unclassified for 2 patients in the phase 3 pool. Notably, patients with severe renal impairment or end-stage renal disease were excluded from all trials in the phase 3 pool. As the number of patients with moderate renal impairment was relatively low (semaglutide 0.5 mg: 35 patients; semaglutide 1 mg: 48 patients; comparators: 38 patients), the data for this subgroup are to be interpreted with caution.

Overall, all subgroups reported AEs more frequently with semaglutide than comparators, and the AE rates increased by worsening baseline renal impairment with both treatments. A similar pattern was observed for SAEs.

In conclusion, although minor differences were observed, the overall safety profile of semaglutide was not substantially affected by baseline renal function.

8.7.7. Geographic region

The trial population was divided to subgroups by region as follows:

- Europe
- North America (United States, Canada)
- South America
- Asia/Australia
- Africa

CVOT

As the number of patients in the African subgroup was low (semaglutide 0.5 mg: 16 patients; semaglutide 1 mg: 20 patients; placebo: 58 patients), these data are to be interpreted with caution.

The overall AE rates were higher with semaglutide than placebo in all regional subgroups except South America, in which no treatment difference was observed; the overall reporting rate was highest in North America. Patients in Europe and North America reported fewer SAEs with semaglutide than placebo, while there was no treatment difference in the South American or Asian/Australian subgroups.

The applicant reported the following trends:

- AEs of constipation (PT) were reported at higher rates and by larger proportions of patients with semaglutide than placebo in the Asian/Australian subgroup, while there was little or no treatment difference in the other regional subgroups.
- AEs of decreased appetite (PT) were reported at higher rates and by larger proportions of patients with semaglutide than placebo across all subgroups; the treatment difference was most pronounced among the European and the Asian/Australian regional subgroups.
- Eye disorders were reported more with semaglutide than placebo in the Asian/Australian regional subgroup, while there were no marked treatment differences in the other regional subgroups (PTs of diabetic retinopathy and cataract).

Phase 3 pool excluding CVOT

As the total number of patients from Africa was low (semaglutide 0.5 mg: 46 patients; semaglutide 1 mg: 52 patients; comparators: 46 patients), the data of this subgroup are to be interpreted with caution.

The overall AE rates were higher with semaglutide than comparators across the regional subgroups, all subgroups displaying comparable treatment differences; the overall AE rate was highest in North America. SAEs were more frequent with semaglutide vs comparator in all subgroups.

The following trends were reported by the applicant:

- For GI AEs, treatment difference was more pronounced in the subgroups South America and Asia/Australia. The difference was partly driven by AEs of nausea and, for Asia/Australia, also vomiting and constipation (PTs).
- For PT of weight decrease, the treatment difference was most pronounced in Asia/Australia.
- Decreased appetite PT had the greatest treatment difference in the Asia/Australia subgroup
- For eye disorders, the semaglutide-associated treatment difference was most pronounced in Asia/Australia and mainly driven by AEs of dry eye, cataract and asthenopia (PTs).

In conclusion, while the treatment difference for specific PTs was more pronounced in specific subgroups, the differences were small and do not necessarily impact the overall safety profile of semaglutide.

8.7.8. Antidiabetic background medication

The trial population was divided into subgroups by antidiabetic background medication as follows:

- Metformin (monotherapy)
- Metformin and SU
- Other OADs (also combined with insulin)
- None

For safety in subgroups by premix insulin and SU monotherapy in the CVOT please see section 6.7.

Phase 3 excluding the CVOT

The overall AEs rates were higher with semaglutide than comparators in all subgroups receiving different antidiabetic background medications, and all subgroups displayed comparable treatment differences. A similar pattern was observed for SAEs.

Table 236 Adverse Events by Background Medication - Phase 3 Pool - On-Treatment

	Sema 0.5 mg				Sema 1.0 mg				All sema				Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYE (year)	1373	1165			1777	1548			3150	2712			1657	1467		
Metformin + SU	186	117			353	288			539	405			387	330		
Metformin mono	559	518			775	731			1334	1249			745	727		
None	297	224			300	215			597	439			237	157		
Other	331	306			349	314			680	620			288	252		
All Events	1015	(73.4)	4292	370.7	1301	(72.7)	5724	370.0	2316	(73.2)	10016	370.8	1136	(68.7)	4220	284.4
Metformin + SU	125	(67.2)	440	376.3	264	(74.9)	1311	455.7	389	(73.6)	1751	443.2	279	(71.9)	1044	315.8
Metformin mono	413	(73.9)	1927	371.6	559	(72.1)	2572	354.0	972	(72.7)	4499	353.5	525	(70.5)	2159	299.9
None	221	(70.2)	858	397.9	205	(64.0)	736	326.0	426	(67.2)	1594	363.3	142	(61.0)	421	264.7
Other	256	(76.7)	1067	351.1	273	(77.2)	1105	351.6	529	(77.0)	2172	351.1	190	(66.6)	596	234.0
Serious																
Yes	92	(6.6)	138	12.0	118	(6.7)	152	10.0	210	(7.0)	290	11.1	95	(5.8)	117	7.9
Metformin + SU	10	(5.4)	15	12.8	20	(5.7)	30	10.4	30	(6.0)	45	10.9	24	(6.2)	29	8.8
Metformin mono	41	(7.3)	70	13.5	63	(8.1)	79	10.7	104	(8.2)	149	12.2	45	(6.0)	56	7.7
None	19	(5.8)	23	11.2	13	(4.0)	15	6.8	32	(4.9)	38	9.0	8	(4.0)	11	8.8
Other	22	(6.6)	30	9.8	22	(6.4)	28	9.2	44	(6.5)	58	9.6	18	(6.2)	21	8.0
No	997	(72.1)	4154	358.6	1281	(71.5)	5572	360.0	2278	(71.9)	9726	359.7	1120	(67.7)	4103	276.4
Metformin + SU	124	(66.7)	425	363.4	262	(74.3)	1281	445.3	386	(72.9)	1706	432.3	275	(70.9)	1015	307.0
Metformin mono	405	(72.5)	1857	358.1	547	(70.6)	2493	343.3	952	(71.0)	4350	341.2	518	(69.6)	2103	292.3
None	215	(68.5)	835	386.7	202	(62.8)	721	319.2	417	(65.7)	1556	354.3	142	(61.0)	410	255.9
Other	253	(75.8)	1037	341.3	270	(76.2)	1077	342.3	523	(76.1)	2114	341.5	185	(64.9)	575	226.0

N: Number of subjects in the safety analysis set experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 PYE, PYE: Patient years of exposure is calculated as the duration of the on-treatment period, trial (comparator): 3624 (exenatide ER), Sema 1.0 mg represents the All sema arm shown in other outputs, On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first, The events are considered treatment-emergent

Source: Table 7.18.361 ISS

The applicant concludes that, although minor differences were observed between the subgroups, the overall safety profile of semaglutide was not substantially affected by different antidiabetic background medications.

While, based on the information presented in the table, the applicant's conclusions may be correct, I do not think that this type of pooling and the subgroups chosen are the best ways to look at, for example, the risk of hypoglycemia. However, hypoglycemia is discussed separately in section 8.4.4.

8.8. Specific Safety Studies/Clinical Trials

Trial 3744 is a CVOT of short duration which was conducted to rule out unacceptable increase in CV risk with semaglutide pre-marketing. The results of the study are reviewed in detail in section 6.7 of this review.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

As noted in the Pharmacology and Toxicology review, the administration of semaglutide once

daily by subcutaneous injection to mice and rats for two years resulted in an increased incidence of thyroid C-cell adenoma and combined C-cell adenoma and carcinomas in all treated groups. Thyroid neoplasms occurred at the clinical exposure in rats, and at slightly higher than the clinical exposure in mice (2X and 5X in female and males, respectively). The incidence of C-cell carcinomas was statistically significant increased in male rats at ≥0.01 mg/kg/day (0.4X the clinical exposure). A numerical increase in C-cell carcinoma was noted in mice. Proliferative C-cell changes in rodents are a known class effect of long-acting GLP-1R agonists and have been reported in rodent carcinogenicity studies with liraglutide, exenatide, lixisenatide, and dulaglutide. Based on the mechanistic data available for semaglutide and other GLP-1R agonists, the absence of GLP-1Rs on normal monkey or human thyroid C-cells, and the absence of changes in calcitonin levels or proliferative lesions in chronic monkey studies, the applicant believes that the human relevance of rodent C-cell tumors is low. However, it is currently unclear whether a lack of calcitonin secretion in non-human primates and humans is a valid indicator that a mitogenic signal is not being initiated in these non-rodent species. Therefore, the human relevance of C-cell tumors is unknown. Please see Pharmacology and Toxicology review by Dr Federica Basso for details.

8.9.2. Human Reproduction and Pregnancy

Eight pregnancies were reported across the trials included in this summary (4 in patients exposed to semaglutide, 4 in patients exposed to comparator). Two (2) additional pregnancies were reported in trials investigating semaglutide in other development programs where treatment is still blinded (outcome: 1 spontaneous abortion in 1st trimester and 1 not yet delivered).

Of the 8 pregnancies:

- 4 patients were treated with semaglutide (outcome: 4 healthy children).
- 4 patients were treated with comparators (outcome: 2 healthy children and 2 elective abortions).

Table 237 Pregnancies Reported in the Semaglutide Development Program and the NN9924-3790 Trial

Treatment	Subject ID	Age/Gender/ Country/BMI	Exposure to foetus (approximate weeks + day)[a]	Pregnancy outcome
Semaglutide				
Semaglutide 0.5 mg	NN9535-3627/327002	28/ F/ US/ 45.1	8+6	Healthy child
Semaglutide 1.0 mg	NN9535-3625/694001	29/ F/ US/ 43.1	5+0	Healthy child
Semaglutide 1.0 mg	NN9535-4091/139010	34/ F/ JP/ 28.8	6+6	Healthy child
Oral semaglutide 40 mg S	NN9924-3790/774006	29/ F/ US/ 35.1	7+2	Healthy child
Comparators				
Placebo	NN9535-3623/803009	33/ F/ ZA/ 40.4	9+0	Healthy child
Exenatide ER	NN9535-3624/450005	37/ F/ RS/ 44.7	5+1	Elective abortion
Insulin Glargine	NN9535-3625/705003	35/ F/ US/ 42.2	3+4	Healthy child
Placebo/moxifloxacin	NN9535-3652/104047	37/ F/ DE/ 22.7	No information	Elective abortion

Note: [a]Due to the long half-life of semaglutide, 5 weeks were added to the gestational exposure time for subjects treated with semaglutide.
Abbreviations: BMI: body mass index; F: female.

Source: Table 5-1 ISS

No congenital abnormalities were reported in the babies born of women who had been exposed to semaglutide.

In the CVOT, a MedDRA search identified 5 AEs related to fertility in the CVOT; 3 AEs in patients treated with semaglutide and 2 AEs in patients on placebo. The AEs (PTs: hypogonadism, hypogonadism male and hematospermia) were all reported in adult male patients.

In the phase 3 pool, 1 AE reported for a male patient treated with comparator was captured by the MedDRA search for events related to fertility (hypogonadism).

No AEs related to lactation were identified by the MedDRA search in the CVOT and phase 3 pool including the placebo-controlled trials.

These limited data did not suggest an effect of semaglutide exposure during early pregnancy on embryo-fetal development. However, the potential risk during pregnancy and lactation is still unknown.

8.9.3. Pediatrics and Assessment of Effects on Growth

Not applicable. There is no data on semaglutide in pediatric patients.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Limited data are available regarding overdoses of semaglutide. Expected adverse events in connection with an overdose of semaglutide are GI AEs and hypoglycemia (especially if combined with SU and insulin).

In the CVOT, events related to overdose were captured via a MedDRA search. A small percentage of patients reported such events in either treatment arm. The only SAEs were reported in the placebo group (2SAEs).

Table 238 Overdose (MedDRA Search) – SAS On-Treatment - CVOT

	Sema 0.5 mg				Sema 1.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
N and PYE (year)	823	1488			819	1444			1644	3035		
All Events	3	(0.4)	3	0.2	8	(1.0)	9	0.6	21	(1.3)	26	0.9
Serious												
Yes	0				0				2	(0.1)	2	<0.1
No	3	(0.4)	3	0.2	8	(1.0)	9	0.6	19	(1.2)	24	0.8
Severity												
Severe	0				0				2	(0.1)	2	<0.1
Moderate	1	(0.1)	1	<0.1	1	(0.1)	1	<0.1	1	(<0.1)	1	<0.1
Mild	2	(0.2)	2	0.1	7	(0.9)	8	0.6	18	(1.1)	23	0.8
Leading to premature discontinuation												
Yes	0				0				0			
No	3	(0.4)	3	0.2	8	(1.0)	9	0.6	21	(1.3)	26	0.9

Abbreviations: E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; Sema: semaglutide; %: percentage of subjects with at least one event.
Source: Table 5-2 ISS

In the phase 3 pool excluding the CVOT, a MedDRA search was again performed, and identified a total of 11 events (10 with semaglutide and 1 with placebo), and none of them was an SAE. However, the number of events is very small and one needs to be cautious when interpreting the results, especially since an opposite trend was observed in the CVOT above.

Table 239 Overdose (MedDRA Search) - SAS On-Treatment - Phase 3 Pool

	Sema 0.5 mg				Sema 1.0 mg				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
N and PYE (year)	1373	1165			1777	1548			1657	1467		
All Events	6	(0.5)	6	0.5	4	(0.2)	4	0.3	1	(<0.1)	1	<0.1
Serious												
Yes	0				0				0			
No	6	(0.5)	6	0.5	4	(0.2)	4	0.3	1	(<0.1)	1	<0.1
Severity												
Severe	0				0				0			
Moderate	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	0			
Mild	5	(0.4)	5	0.5	3	(0.2)	3	0.2	1	(<0.1)	1	<0.1
Leading to premature discontinuation												
Yes	0				0				0			
No	6	(0.5)	6	0.5	4	(0.2)	4	0.3	1	(<0.1)	1	<0.1

Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate. Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; Sema: semaglutide; %: percentage of subjects with at least one event.

Source: Table 5-3 ISS

In the placebo-controlled trials, 1 overdose AE was reported in trial 3627; in the semaglutide 0.5 mg group (PTs: accidental overdose).

In conclusion, while a few overdose cases have been observed with both semaglutide and comparators in the semaglutide clinical program, it is not clear whether the overdose potential of semaglutide is more, or less, vs comparators, due to the small number of events.

Safety in the Postmarket Setting

8.9.5. Safety Concerns Identified Through Postmarket Experience

Not applicable. There is no postmarketing experience with semaglutide.

8.9.6. Expectations on Safety in the Postmarket Setting

Semaglutide is intended to be prescribed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Ina ddition to the safety concerns with the GLP-1 RA class of drugs, a new safety concern was identified in the semaglutide program, an increased risk of worsening diabetic retinopathy complications. As discussed in other section of this review, this is likely to be due to the rapid improvement in glucose control as observed in previous studies with insulin. While restricting the target population was not recommended by our Ophthalmology consultant and Advisory Committee memebers, this safety signal will be reflected in the prescribing information (Warnings and Precautions section).

8.9.7. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by the other review disciplines that would affect regulatory decision-making, product labeling, or postmarketing requirements (PMRs).

8.10. Integrated Assessment of Safety

The safety of semaglutide has been studied in over 4000 semaglutide-treated patients, including patients across the T2DM spectrum, from drug-naïve to patients using a variety of background antidiabetics, including metformin, SU, and insulin. The 2-year CVOT provided safety data in patients with high CV risk and other diabetes comorbidities. Overall, the semaglutide safety profile was consistent across the phase 3 studies, and with the known safety profile for GLP1 RAs.

A number of medical events of special interest were pre-defined and captured across all phase 3 trials (based on the information already known with other GLP1 RAs), and some of these events were adjudicated.

Semaglutide treatment appears to result in treatment discontinuation more frequently vs all comparators. This is mostly due to GI AEs.

As expected with the drug class, GI AEs (nausea, vomiting, diarrhea), reduced appetite and weight decrease and hypoglycemia (when combined with insulin or SU) as adverse drug reactions frequently reported with semaglutide. While the GI AEs could lead to dehydration and renal impairment, no increase in acute renal events was apparent in the development program. However, this is an issue that will require monitoring in post-marketing setting.

The data do not suggest an increased risk for major adverse cardiovascular events with semaglutide. Certain CV events (MI, stroke) were less frequent with semaglutide, per the primary analysis of the CVOT and supported by the MedDRA search. Additionally, the data does not appear to support an increased risk in heart failure events with semaglutide vs comparator.

The patients on semaglutide experienced less applicant-defined nephropathy vs placebo, however this was mostly due to a difference in the risk of macroalbuminuria wits semaglutide. Other factors that affect the amount of albumin in the urine (such as glycemic control, blood pressure, etc), render the macroalbumin findings in SUSTAIN 6 inconclusive. Acute renal events were not seen more commonly with semaglutide vs comparator. The eGFR decreased over time with both semaglutide, and comparator.

As for other GLP-1 RAs, MTC was assessed to be an important potential risk for semaglutide, based on nonclinical data and due to the potential serious clinical consequences and impact on the individual patient as well as on public health. No MTC cases were reported in the clinical development program.

While cholelithiasis was more frequently seen with semaglutide compared to placebo/comparator, cholecystitis was not. This may be because of the relatively short duration of the studies, and it is possible that an increased incidence of cholecystitis will be observed with longer use.

Pancreatitis and pancreatic cancer were balanced between the treatment groups, however pancreatic enzymes increased with semaglutide over time. Semaglutide was associated with an increase in other neoplasms, such as lung, breast, and skin cancers, however, most patients had confounding factors and the number of events was small.

Liver function evaluation showed a higher incidence of ALT >5xULN cases that were judged by experts to be possibly or probably related to trial product with semaglutide vs comparators. These patients were generally asymptomatic, and most of them were taking other medications that could have been responsible for the observed LFT changes, however no clear alternate etiology was present (possibly because of the relatively limited data available). Out of the 12 patients identified with LFT abnormalities that met the Hy's law criteria, most (9) were in the semaglutide treated group, but alternative etiologies are likely for all of these cases. LFT outlier analyses and liver AEs did not suggest a liver safety signal for semaglutide.

Severe hypoglycemia, as expected, was rare. In the CVOT, patients on semaglutide had an increased risk of severe and confirmed symptomatic hypoglycemia on a background of SU, and SU plus insulin compared to standard of care. Hypoglycemic coma and hypoglycemic unconsciousness were reported in slightly more patients on semaglutide (8) vs placebo (5). .

Severe and confirmed symptomatic hypoglycemia were even more rare in the rest of the phase 3 program, and semaglutide appeared to increase the risk of hypoglycemia when added to insulin. No dose-response was seen for hypoglycemia.

Semaglutide treatment was associated with a slight increase in pulse rate which was expected with this drug class. Despite some small differences in pulse rate AEs, the body of data does not support an increase in clinical events related to increase in heart rate.

There were no indications of an immunogenic response against semaglutide as witnessed by low frequencies of anti-semaglutide antibodies (1−2%), with no neutralizing antibodies as well as no IgE's. Furthermore, allergic reactions (4−6%) and injection site reactions (~1%) were generally infrequent.

However, semaglutide appears to increase the risk of diabetic retinopathy based on the adjudicated retinpathy events in the CVOT. While the interpretation of this outcome is difficult since the retinopathy events were not using an adequate retinopathy scale, the HR of 1.76 not favoring semaglutide is unsettling. Events of diabetic retinopathy complications occurred in patients with pre-existing diabetic retinopathy (83.5% of those with events), long duration of diabetes (mean of 17.53 years), high baseline HbA1c (mean of 9.37%) and in patients treated with insulins at baseline (75.9% of those with events). The treatment difference appeared early and continued throughout the trial. It is possible that the worsening in retinopathy is seen in response to a rapid improvement in glycemic control with semaglutide, and that, over time, glycemic control with semaglutide will lower the retinopathy risk. This mechanism has been suggested by Dr Chambers, the FDA ophthalmology consultant. To verify that, it may be that a longer study looking specifically at retinopathy will be needed to elucidate this issue.

The safety profile was generally consistent across sub-groups of sex, age, race, ethnicity, CV history, renal function, region, anti-glycemic background medication.

9. Advisory Committee Meeting and Other External Consultations

On October 18, 2017, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss the overall findings in EMPA-REG, and to specifically address the following questions:

Question 1 (Discussion)

Semaglutide is proposed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Discuss the efficacy of semaglutide with respect to glycemic control.

Question 2 (Discussion)

Semaglutide once weekly injection has been studied in seven phase 3 studies and a two-year cardiovascular outcomes trial (SUSTAIN 6). Excluding issues related to diabetic retinopathy and CV risk, discuss any safety concerns you have related to semaglutide.

Question 3 (Discussion)

In SUSTAIN 6, a pre-specified secondary safety endpoint was time from randomization to the first occurrence of either a need for retinal photocoagulation, need for treatment with intravitreal agent, vitreous hemorrhage, or diabetes related blindness. The results for this composite endpoints showed an increased risk with semaglutide [HR: 1.76 (95% CI: 1.11, 2.78)]

a. Discuss the strengths and limitations of this assessment (e.g., endpoint definitions, methods of ascertainment, adjudication, trial design, and any other considerations relevant to interpretation of the results).
b. One hypothesis regarding this finding is that rapid and large reductions in HbA1c can be expected to increase the short-term risk of diabetic retinopathy complications. Discuss the extent to which you are convinced that a reduction in blood glucose is the mediator of the observed increase in diabetic retinopathy complications in SUSTAIN 6.
c. Improving glycemic control should be expected to reduce the risk of retinopathy over the long-term. Discuss whether the increase in diabetic retinopathy complications in the two-year controlled trial affects your assessment of the clinical benefits expected from long-term use of semaglutide for glycemic control.
d. In SUSTAIN 6, the increase in absolute risk of diabetic retinopathy complications was greater among those with diabetic retinopathy at baseline (8.2% semaglutide, 5.2% placebo) compared to those without diabetic retinopathy at baseline (0.7% semaglutide, 0.4% placebo), although the relative risk increases were similar. Patients with diabetic retinopathy are often among those most in need of improved glycemic control. Discuss whether you would have any concerns about the use of semaglutide among patients with diabetic retinopathy.
e. Comment on your level of concern related to the observed increased risk in diabetic retinopathy complications in SUSTAIN 6.

Question 4 (Discussion)

In SUSTAIN 6, a total of 254 first MACE occurred during a median 2-year follow-up. The estimated hazard ratio of MACE and the components of MACE for semaglutide vs. placebo are

shown:

	Semaglutide N=1648 PY=3408.2	**Placebo** N=1649 PY=3401.1	**Hazard Ratio (95% CI)**
MACE	**108 [3.2]**	**146 [4.3]**	**0.74 (0.58, 0.95)**
Cardiovascular death	44	46	0.98 (0.65, 1.48)
Non-fatal MI	47	64	0.74 (0.51, 1.08)
Non-fatal Stroke	27	44	0.61 (0.38, 0.99)
MI (fatal+nonfatal)	54	67	0.81 (0.57, 1.16)
Stroke (fatal+nonfatal)	30	46	0.65 (0.41, 1.03)

a. Discuss these results and comment whether these data are adequate to characterize the CV safety of semaglutide.

Question 5 (Voting)

Do the available efficacy and safety data support approval of semaglutide 0.5 mg and 1 mg administered subcutaneously once weekly, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus?

a. If yes, please explain your rationale and comment whether any additional studies should be required after approval.
b. If no, please describe what further studies you believe the applicant must conduct to establish favorable benefit/risk to support approval.

Committee discussion

Question 1: The committee members agreed that semaglutide was efficacious for improving glycemic control.

Question 2: The committee members agreed that the gastrointestinal events were common, which is expected with the GLP-1 RA class, and that this may have contributed to the weight loss seen with semaglutide. There were not concerns regarding renal adverse events. There were some concerns expressed regardiong the risk for certain malignancies and it was suggested that longer surveillance is needed for evaluation of such adverse events. From a CV perspective, the committee members felt that the decrease in SBP was favorable, and possibly correlating with a decreased risk for stroke. The committee did not express any concerns regarding other aspects of CV safety, despite the observed increase in HR with semaglutide.

Question 3

a. The committee members concluded that the assessment of retinopathy complications

was not done well in SUSTAIN 6, and, in addition, the limited duration of the study is an issue. There was no consensus whether the poor assessment in this case would be more likely to bias the results towards the null. There was also lack of consensus whether a study targeted to look at diabetic retinopathy complications may be needed.

b. The committee members were somewhat undecided in interpreting the post-hoc analysis, and concluded that while the hypothesis is plausible, it is not proven. In this context, while it was agreed that the change in HbA1c was likely a mediator for the diabetes retinopathy complications, it may not be "the' mediator, as even patients with small HbA1c decrese in the first 16 weeks had increased risk of diabetic retinopathy complications. One of the committee members noted that, unlike the DCCT, the KM curves for retinopathy complications do not appear to trend towards coming together with time.
c. The committee agreed that longer term observation may be needed to confirm that glycemic control with semaglutide improves, in the long run, diabetic retinopathy complications, as it is not known based on the current data. It was also noted that DCCT, and UKPDS, are older trials, and that diabetic retinopathy treatment has improved significantly since then, which reassured some committee members. The potential for a follow up study was discussed. The patient representative on the committee expressed confusion with the way the benefit-risk will be presented to the patients.
d. While the absolute risk for patients with baseline retinopathy is higher, the non-ophthalmologists in the committee felt comforted by the assurance from the ophthalmologist members that such complications can be treated. The ophthalmologists on the committee recommended that patients have a retinal exam by an ophthalmologist at the start of the treatment with semaglutide., and that more frequent follow up may be needed for patients with diabetic retinopathy at baseline.
e. One committee member brought up that there were 21 excess diabetic retinopathy events in SUSTAIN 6, vs 38 less MACE events, and therefore felt that the risk was not excessive. The other members of the panel expressed a moderate level of concern, and suggested that there is a need for adequately labelling the diabetic retinopathy complications to better inform prescribers and patients, although details regarding what would constitute adequate labelling were not provided. There was some reassurance that the most impactful diabetic retinopathy complication, blindness, was very rare. Most members of the committee found the DCCT data reassuring in suggesting that better glycemic control with semaglutide may positively impact diabetic retnopathy long-term, but agreed that we do nto know that for sure, and that we may never have an answer to this question.

Question 4

The committee members strongly felt that semaglutide was safe from a CV standpoint, and some of the members felt that the data suggest superiority, although not this not a prespecified statistical test. The committee members expressed a desire for the study to have been longer,

with better representation of minorities. There was consensus that the results were driven by morbidity, and not mortality.

Voting questions posed to EMDAC and discussion:

Question 5: 16 members voted Yes, and one abstained.

The reasons for voted yes were similar between the committee members, such as impressive HbA1c lowering, weight loss, expected AE profile for the class, and no concerns regarding CV safety. The diabetic retinopathy complications were a modest concern, but most committee members felt that the benefits outweighed this risk, and that the risk was manageable. Labelling this risk in a manner similar to what was done wioth insulin products was also suggested, and, while most members thought that it would be nice to have a follow-up retinopathy study, none felt that this should be either a pre- or post-approval requirement. Only one of the members who voted yes felt that the FDA should require a post-marketing retinopathy study. One committee member suggested a potential black box labelling for retinopathy. Some committee members encouraged the applicant to perform a longer CVOT to demonstrate superiority regarding MACE, and that maybe retinopathy could also be assessed in such a study. The abstaining member felt that there should be a retinopathy follow up study, although not necessarily requied by the FDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling is not yet finalized at the time of this review. I will discuss my opinion regarding some information from the prescribing information below.

Indication

The applicant submitted the following indication for semaglutide:

- OZEMPIC is a glucagon-like peptide (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Reviewer Comment: I agree with the proposed indication

Dosage and administration:

- Start at 0.25 mg subcutaneously once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After 4 weeks dose can be increased to 1 mg once

weekly for additional glycemic control.

Reviewer Comment: The dosing and titration strategy proposed by the applicant are supported by the clinical program.

Black box warning

As for other long acting GLP-1RAs, the applicant proposed a black box warning for thyroid c-cell tumors.

Reviewer Comment: I agree with the applicant's approach.

Contraindications

- OZEMPIC is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
- OZEMPIC is contraindicated in patients with hypersensitivity to OZEMPIC or any of the product components

Reviewer Comment: The contraindications appear reasonable and in line with other members of the class.

Warnings and precautions

- Thyroid C-cell Tumors: See Boxed Warning
- Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. (b) (4)
- Diabetic Retinopathy Complications: (b) (4) Patients with a history of diabetic retinopathy should be monitored (b) (4)
- Never share an OZEMPIC pen between patients, even if the needle is changed
- Hypoglycemia: When OZEMPIC is used with an insulin secretagogue (b) (4) or insulin, consider lowering the dose of the (b) (4) or insulin to reduce the risk of hypoglycemia
- (b) (4) Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions
- Hypersensitivity Reactions: Discontinue OZEMPIC if suspected. (b) (4)

Reviewer Comment: The warning and precautions appear generally adequate, and consistent with labeling for other GLP-1 RAs. However, the language proposed by the sponsor has been modified to reflect the current knowledge with seaglutide.

Section 14
The applicant proposes to include SUSTAIN 1-6. For SUSTAIN 1-5 (efficacy trials) the applicant is proposing tables including the primary HbA1c analysis, patients achieving HbA1c<7, FPG change at the end of trial, and body weight changes at the end of trial. Additionally, for SUSTAIN 2, and 3, the applicant is proposing to present the graph of HbA1c trend over time.

Reviewer comment: While the parameters included in the table are generally reasonable, the A1c trend over time, especially for active control trials, is not appropriate for inclusion in the label.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was deemed to be necessary for semaglutide. Please see review by Dr Till Olickal from Division of Risk Management for details.

12. Postmarketing Requirements and Commitments

I am recommending the following PMRs:

1) Conduct a 26-week, randomized, double-blind, placebo-controlled parallel group study of the safety and efficacy of Ozempic (semaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 26-week open-label, controlled extension. Background therapy will consist of either metformin, insulin, or metformin plus insulin.

2) Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Ozempic (semaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Ozempic (semaglutide).

Additionally, the following PMCs were recommended by the Office of Biotechnology Products :

- Develop and validate a sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies and its cross-neutralizing effect on native GLP-1.

- Conduct a study to assess the incidence of neutralizing antibodies to semaglutide and GLP-1 in subjects treated with semaglutide using the assays developed under PMC #3. The samples may be derived from pre-existing clinical studies. Sample selection criteria will be submitted to and reviewed by the Agency prior to initiation of sample analysis.

13. Appendices

13.1. References

1. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.
2. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N Engl J Med 2000;342:381-9.
3. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-53.
4. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631-42.

5. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.
6. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854-65.
7. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology. 2014 Dec;121(12):2443-51
8. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013 May; 36(5): 1384-1395.

13.2. MedDRA Queries used for the safety analyses

MedDRA version 18.0 – list of terms within safety focus areas

HLGT: higher level group term, HLT: higher level term, NEC: not elsewhere classified, NNMQ: Novo Nordisk MedDRA queries, PT: preferred term, SMQ: standard MedDRA queries, SOC: system organ class

Gastrointestinal adverse events
SOC 'gastrointestinal disorders'

Cardiovascular disorders
NNMQ 'Cardiovascular disorders' including:
SMQ Central nervous system vascular disorders
SMQ Vasculitis
SMQ Ischaemic heart disease
SMQ Cardiac arrhythmias
SMQ Cardiac failure
SMQ Cardiomyopathy
SMQ Embolic and thrombotic events
SMQ Shock
SMQ Torsade de pointes/QT prolongation

Thyroid disorders
NNMQ 'Thyroid disorders' + PT ‘blood calcitonin’ including:
SMQ Hyperthyroidism
SMQ Hypothyroidism
HLGT Thyroid gland disorders (including both primary and secondary linked PTs)

Single PT: Blood calcitonin abnormal
Single PT: Blood calcitonin increased
Single PT: Ectopic calcitonin production
Single PT: Hypercalcitoninaemia
Single PT: Blood calcitonin

Acute renal failure - broad
SMQ Acute renal failure all terms

Acute renal failure - narrow
SMQ Acute renal failure narrow terms only

Pancreatitis
NNMQ 'Pancreatitis' narrow terms only including:
SMQ Acute pancreatitis (narrow scope)
HLT Acute and chronic pancreatitis (including primary and secondary terms)

Acute gallstone disease
NNMQ 'Gallbladder related disorders'
SMQ: Biliary tract disorders
SMQ: Biliary system related investigations, signs and symptoms
SMQ: Gallbladder related disorders
SMQ: Gallstone related disorders
SMQ: Infectious biliary disorders

Allergic reactions
NNMQ 'Allergic reactions' but including only narrow terms:
SMQ Anaphylactic reaction (narrow scope)
SMQ Angioedema (narrow scope)
SMQ Severe cutaneous adverse reactions (narrow scope)
SMQ Anaphylactic/anaphylactoid shock conditions (narrow scope)
SMQ Hypersensitivity (narrow scope)

Immune complex disease
NNMQ 'Immune complex disease' including
SMQ for Systemic lupus erythematous (broad and narrow terms)
SMQ Vasculitis (broad and narrow terms)
SMQ Guillain-Barre syndrome (narrow terms only)

Antibody

NNMQ Antibody non-product specific including:
Single PT: Antibody test
Single PT: Antibody test abnormal
Single PT: Antibody test positive Single PT: Autoantibody positive
Single PT: Autoantibody test
Single PT: Drug specific antibody present
Single PT: Inhibiting antibodies
Single PT: Neutralising antibodies
Single PT: Neutralising antibodies positive
Single PT: Non-neutralising antibodies positive

Injection site reactions
NNMQ 'Injection site reactions' including:
HLT Administration site reactions
HLT Application and instillation site reactions
HLT Infusion site reactions
HLT Injection site reactions

Medication error
NNMQ 'Medication errors' including:
HLGT Medication errors
HLGT Device issues
HLGT Product Quality Issue
HLT Complications associated with device NEC
HLT Overdoses NEC
HLT Underdoses NEC
Single PT: Contraindicated drug administered
Single PT: Drug administered to patient of inappropriate age

Overdose
NNMQ 'Overdose' including:
HLT 'Overdoses NEC'
Single PT: ‘Accidental overdose’
Single PT: ‘Completed suicide’
Single PT: ‘Suicide attempt’

Neoplasms
NNMQ 'neoplasm’ including:
SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) (primary and secondary terms)
SMQ Biliary neoplasms

SMQ Breast neoplasms, malignant and unspecified
SMQ Liver neoplasms, benign (incl cysts and polyps)
SMQ Liver neoplasms, malignant and unspecified
SMQ Malignant or unspecified tumours
SMQ Ovarian neoplasms, malignant and unspecified
SMQ Oropharyngeal neoplasms
SMQ Premalignant disorders
SMQ Prostate neoplasms, malignant and unspecified
SMQ Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), broad and narrow
SMQ Haematopoietic leukopenia (SMQ), broad and narrow terms
SMQ Haematopoietic thrombocytopenia (SMQ), narrow terms only
SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ), narrow terms only
SMQ Hepatitis, non-infectious (SMQ), broad and narrow terms
SMQ Severe cutaneous adverse reactions (SMQ), narrow terms only
SMQ Interstitial lung disease (SMQ) narrow terms only
SMQ Neuroleptic malignant syndrome (SMQ), narrow terms only
SMQ Pseudomembranous colitis (SMQ), narrow terms only
SMQ Retroperitoneal fibrosis (SMQ), narrow terms only
SMQ Acute Pancreatitis, narrow (A) terms only
SOC Congenital, familial and genetic disorders (SOC), (primary and secondary routed PTs)
HLT Acute and chronic pancreatitis (primary and secondary routed PTs)
HLT Angioedemas (primary and secondary routed PTs)
HLT Glomerulonephritis and nephrotic syndrome (primary and secondary routed PTs)
HLT Nephritis NEC (primary and secondary routed PTs)
single PT: disseminated intravascular coagulation
single PT: Multi-organ failure
SMQ Skin neoplasms, malignant and unspecified SMQ Tumour markers
SMQ Uterine and fallopian tube neoplasms, malignant and unspecified

Diabetic retinopathy
Search including the following PTs from the SOC 'Eye disorders:
Single PT: Amaurosis
Single PT: Cystoid macular oedema
Single PT: Diabetic blindness
Single PT: Diabetic eye disease
Single PT: Diabetic glaucoma
Single PT: Diabetic retinal oedema

Malignant neoplasms
SMQ Malignant tumours

Pancreatic carcinoma
NNMQ Pancreatic cancer
All PTs within the HLT pancreatic neoplasms which are also within the SMQ malignant tumours

Lipase and amylase
NNMQ 'Elevated lipase and/or amylase' including:
Single PT: Hyperlipasaemia
Single PT: Lipase increased
Single PT: Lipase abnormal
Single PT: Lipase
Single PT: Hyperamylasaemia
Single PT: Amylase increased
Single PT: Amylase abnormal
Single PT: Amylase

Diabetic Nephropathy
Search including the following:
HLT Renal failure complications
Single PT: Albuminuria
Single PT: Protein urine present
Single PT: Proteinuria
Single PT: Blood creatinine abnormal
Single PT: Creatinine renal clearance abnormal
Single PT: Creatinine renal clearance increased
Single PT: Glomerular filtration rate abnormal
Single PT: Glomerular filtration rate decreased
Single PT: Hypercreatininaemia
Single PT: Urine albumin/creatinine ratio increased
Single PT: Urine albumin/creatinine ratio abnormal
Single PT: Urine protein/creatinine ratio abnormal
Single PT: Urine protein/creatinine ratio increased
Single PT: Diabetic nephropathy
Single PT: Nephropathy
Single PT: Renal impairment
Single PT: Renal failure
Single PT: Chronic kidney disease
Single PT: Biopsy kidney abnormal
Single PT: Oliguria

Single PT: Diabetic end stage renal disease
Single PT: Anuria
Single PT: Continuous haemodiafiltration
Single PT: Dialysis
Single PT: Haemodialysis
Single PT: Haemofiltration
Single PT: Peritoneal dialysis
Single PT: Intradialytic parenteral nutrition
Single PT: Dialysis efficacy test

Hepatic disorders
SMQ Drug related hepatic disorders - comprehensive search

Pulse rate increase
Search including the following:
Single PT: Heart rate increased
Single PT: Palpitations
Single PT: Sinus tachycardia
Single PT: Tachycardia
Single PT: Tachycardia paroxysmal

Hypotension
Search including the following: Single PT: Blood pressure decreased
Single PT: Blood pressure diastolic decreased
Single PT: Blood pressure orthostatic decreased
Single PT: Blood pressure systolic decreased
Single PT: Blood pressure systolic inspiratory decreased
Single PT: Diastolic hypotension
Single PT: Hypotension
Single PT: Mean arterial pressure decreased
Single PT: Orthostatic hypotension
Single PT: Procedural hypotension

Arrhythmia
SMQ Cardiac arrhythmias

PR Interval prolongation and AV-block
Search including the following:
Single PT: Atrioventricular block
Single PT: Atrioventricular block complete
Single PT: Atrioventricular block first degree
Single PT: Atrioventricular block second degree

Single PT: Atrioventricular dissociation
Single PT: Electrocardiogram PQ interval
Single PT: Electrocardiogram PQ interval prolonged
Single PT: Electrocardiogram PR interval
Single PT: Electrocardiogram PR prolongation
Single PT: Lenegre's disease

Peripheral arterial revascularisation
NNMQ 'Peripheral Artery Vascular Procedure Semaglutide'
Single PT: Peripheral artery angioplasty
Single PT: Peripheral artery stent insertion
Single PT: Peripheral artery bypass
Single PT: Peripheral endarterectomy
Single PT: Peripheral revascularisation
Single PT: Arterial stent insertion
Single PT: Arterial therapeutic procedure
Single PT: Endarterectomy
Single PT: Thromboembolectomy
Single PT: Thrombectomy
Single PT: Vascular operation
Single PT: Vascular stent insertion
Single PT: Arterectomy
Single PT: Arterectomy with graft replacement
Single PT: Arterial bypass operation
Single PT: Arterial graft

Abuse/Misuse
NNMQ 'AbuseMisuse'
SMQ Drug abuse and dependence (SMQ)narrow terms selected narrow terms from
SMQ Suicide/self-injury:
Single PT: Complete suicide
Single PT: Intentional self-injury
Single PT: Poisoning deliberate
Single PT: Suicide attempt

Anaphylactic Reactions Grouped Terms
Search including the following:
Single PT: Anaphylactic reaction
Single PT: Anaphylactic shock

Increased Lipase Grouped Terms
Search including the following:

Single PT: Lipase increased
Single PT: Lipase abnormal
Single PT: Hyperlipasaemia
Single PT: Lipase

Increased Amylase Grouped Terms
Search including the following:
Single PT: Amylase increased
Single PT: Amylase abnormal
Single PT: Hyperamylasaemia
Single PT: Amylase

13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): 3623

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 424		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 3624

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 695		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 3625

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 999		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 (although one investigator became sponsor employee before the NDA submission)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 3626

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 440		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 3627

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 486		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 10		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 3744

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1285		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 8		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 29		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 29 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREEA O LUNGU
11/27/2017

WILLIAM H CHONG
11/27/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 209637 **Applicant: Novo Nordisk** **Stamp Date: December 5, 2016**

Drug Name: semaglutide **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:NN9535-1821, NN9924-3790 Study Title: Sample Size: Arms: Location in submission:	x			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? (see Comment for summary of clinical studies)	x			The applicant submitted 8 phase 3 studies (3623, 3627, 3626, 3624, 3625, 3744 – multinational studies, and 4091, 4091 in Japan). The

	Content Parameter	Yes	No	NA	Comment
					studies evaluate a wide range of patients with diabetes, from drug-naïve, background of metformin and/or TZD, metformin with or without SU, other OADs, basal insulin, etc. Study 3744 is a cardiovascular outcomes study.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			Yes, QT study results submitted.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			MedDRA 18
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments:

(b) (4)

2. We have concerns with regard to the reported increased incidence of retinopathy with semaglutide in your development program. This data will be reviewed carefully and it may be given special consideration in our risk-benefit assessment for semaglutide.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREEA O LUNGU
11/16/2017

WILLIAM H CHONG
11/16/2017
delayed submission of filing review.