14 December 2017
EMA/CHMP/715701/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ozempic

International non-proprietary name: semaglutide

Procedure No. EMEA/H/C/004174/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ozempic
Applicant:	Novo Nordisk A/S Novo Allé 1 DK-2880 Bagsvaerd Denmark
Active substance:	semaglutide
International Non-proprietary Name/Common Name:	semaglutide
Pharmaco-therapeutic group (ATC Code):	blood glucose lowering drugs, excl. insulins, (A10BJ06)
Therapeutic indications:	Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.
Pharmaceutical form:	solution for injection
Strength:	1.34 mg/ml
Route of administration:	subcutaneous use
Packaging:	cartridge (glass) in pre-filled pen
Package size:	1 pre-filled pen + 6 needles

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List of abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
BNP	brain natriuretic peptide
bpm	beats per minute
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase-4
EAC	event adjudication committee
eGFR	estimated glomerular filtration rate
EOT	end of text
ESRD	end-stage renal disease
FAS	full analysis set
GCP	good clinical practise
GLP-1	glucagon-like peptide-1
GLP-1 R	glucagon-like peptide-1 receptor
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HDL	high density lipoprotein
HbA1c	glycosylated haemoglobin
HLGT	high level group term
HR	hazard ratio
hs-CRP	high-sensitive C-reactive protein
ICH	International Conference on Harmonisation
IL-6	interleucin-6
KM	Kaplan-Meier
LDL	low-density lipoprotein
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MDRD	modification of diet in renal disease
MI	myocardial infarction

MMRM	mixed model repeated measurement
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral antiglycaemic drug
PAI-1	plasminogen activator inhibitor-1
PBRER	periodic benefit risk evaluation report
PI	product information
PP	per protocol
PYE	patient year of exposure
PYO	patient year of observation
RMP	risk management plan
RR	rate ratio
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
s.c.	sub cutaneous
sema	semaglutide
SGLT-2	sodium-dependent glucose transporter two
SMQ	standardised MedDRA query
SOC	system organ class
SU	sulfonylurea
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2D	type 2 diabetes mellitus
TNF-alpha	tumour necrosis factor alpha
TZD	thiazolidinediones
UACR	urinary albumin-to-creatinine ratio
UAP	unstable angina pectoris
UKPDS	UK prospective Diabetes Study
ULN	upper limit normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 5 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Ozempic, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 February 2015.

The applicant applied for the following indications:

Glycaemic control
Ozempic is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Prevention of cardiovascular events
Ozempic is indicated to prevent cardiovascular events (see section 5.1) in adults with type 2 diabetes mellitus and high cardiovascular risk, as an adjunct to standard treatment of cardiovascular risk factors.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that semaglutide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0095/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0095/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance semaglutide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 October 2009, 24 June 2010, 22 July 2010, 15 November 2012 and 30 May 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Hanne Lomholt Larsen

- The application was received by the EMA on 5 December 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 July 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 6 October 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 25 October 2017.
- During the CHMP meeting on 9 November 2017, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 20 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 November 2017.
- During the meeting on 11-14 December 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ozempic on 14 December 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Type 2 Diabetes Mellitus (T2D) is a progressive chronic metabolic disease primarily characterised by abnormal glucose metabolism. Data support a heterogeneous pathogenesis that involves environmental, lifestyle, and genetic components leading to chronic hyperglycaemia caused by insulin resistance in the peripheral tissue, reduced insulin production in the pancreatic β-cells and increased hepatic glucose release.

Cardiovascular (CV) disease is the leading cause of death in patients with diabetes, and CV morbidity is more prevalent in patients with diabetes than those without. Diabetes, alongside smoking, obesity, hypercholesterolaemia and hypertension account for most of the risk for heart disease and stroke worldwide.

Requested therapeutic indications:

Glycaemic control
Ozempic is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on therapy
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Prevention of cardiovascular events
Ozempic is indicated to prevent cardiovascular events (see section 5.1) in adults with type 2 diabetes mellitus and high cardiovascular risk, as an adjunct to standard treatment of cardiovascular risk factors.

2.1.2. Epidemiology and risk factors

Close to 9% (415 million) of adults worldwide have diabetes with T2D accounting for ~90% of the diabetes cases. Glycaemic control is fundamental for the management of T2D to reduce the risk of T2D-related complications. While an increasing number of agents to treat diabetes exist, data collected from 2007−2010 demonstrate that close to 50% of all patients treated for their T2D do not achieve the recommended blood glucose target of an HbA1c <7% and are thus at increased risk of T2D-related complications.

The manifestations of CV disease often accompanying diabetes include ischaemic heart disease, stroke, peripheral artery disease, and congestive heart failure. Myocardial infarction is 2–4 times more frequent in men with diabetes, and 4−5 times more frequent in women with diabetes compared with those without diabetes. Improved CV outcomes in T2D can be achieved by addressing several risk factors including blood pressure, lipid levels and glucose control.

A well-known risk factor for hyperglycaemia, T2D and eventually risk of CV disease is obesity, an emerging epidemic in developing countries. A moderate weight loss of 5% improves glycaemic control and CV risk factors in patients with T2D, and thereby provides beneficial effects in T2D. Thus, anti-hyperglycaemic products that, in addition to lowering HbA1c, also reduce body weight provide additional clinical benefits to patients with T2D and on CV risk factors.

2.1.3. Biologic features

Glucagon-like peptide-1 (GLP-1) is both an incretin hormone secreted from the L-cells in the small intestine and a neuropeptide produced in the brain. The hormone stimulates insulin secretion and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner. Patients with T2D have a decreased response to endogenous incretins (GLP-1 and Glucose-dependent insulinotropic peptide (GIP)), but can respond to the blood glucose lowering effect of GLP-1 when administered at supraphysiological levels. Native GLP 1 and GLP-1 receptor agonists (GLP-1 RAs) also reduce body weight by lowering energy intake by inducing feelings of satiety and fullness and lowering feelings of hunger.

In addition to the pancreas and the hypothalamus, GLP-1 receptors are also expressed in the heart, the vasculature, cells of the immune system and the kidney and may thus mediate cardiovascular and microvascular effects. In humans, GLP-1 RAs lower systolic blood pressure and increase pulse rate and data from 2016 show improvements in cardiovascular outcomes following 3 years of treatment in a clinical trial. Altogether, these data suggest that targeting of the GLP-1 receptor with a GLP-1 RA can reduce CV risk.

GLP-1 and GLP-1 RAs thus target several aspects of the treatment of T2D, including glycaemic control, weight loss and possibly reduction of CV risk. Due to the short half-life of <1.5 minutes after i.v. administration, native GLP 1 is not suitable for therapeutic use. To realise the full therapeutic potential of GLP-1, the pharmacokinetic effect and hence the pharmacodynamic effect need to be protracted.

2.1.4. Available therapies and unmet medical need

There are several classes of medicinal products for the treatment of T2D. All products have been shown to reduce blood glucose level, and to improve HbA1c. Based on the extensive therapeutic experience (including possible CV benefits), metformin is currently recommended as first-line treatment for all patients with T2D, unless contraindications apply (most notably, GFR < 30 ml/min).

Recently, empagliflozin (SGLT2-inhibitor) and liraglutide (GLP-1 receptor agonist) have shown to be superior compared to placebo in reducing 3-point MACE in a CV outcome trial.

2.1.5. About the product

Semaglutide is a new GLP-1 RA and is structurally similar to liraglutide but modified to have a longer half-life, suitable for once weekly (OW) dosing. The extended half-life of the semaglutide molecule is primarily obtained by increased albumin binding, which is facilitated by a large fatty acid-derived chemical moiety attached to the lysine in position 26. The specific modifications in the GLP-1 molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone to increase stability against dipeptidyl peptidase 4 (DPP-4), and a change in position 34 from a lysine to an arginine to limit the options for acylation to the one remaining lysine in the sequence; 2) a large hydrophilic spacer between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group. The spacer and the fatty acid both contribute to increased albumin binding, which slows the degradation of semaglutide in plasma and results in decreased renal clearance prolonging the half-life of semaglutide to approximately 1 week making it suitable for OW s.c. administration.

The clinical development of semaglutide includes sixteen completed Phase 1 studies, one Phase 2 study and eight completed Phase 3 studies and one ongoing trial. Furthermore, a population pharmacokinetic and an exposure response analysis has been conducted, the Pop PK study used data from five Phase 3 studies (3623, 3626, 3624, 3744 and 4091). The dossier also includes nine *in vitro* studies using human samples or human cell material.

The studies were performed in line with the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus.

Initially the applicant also requested to include an indication: “Prevention of cardiovascular events” which was rejected by CHMP.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a clear colourless solution for injection containing 1.34 mg/ml of the active ingredient semaglutide. Semaglutide is a GLP-1 analogue substituted with a linker and a fatty acid side chain. Semaglutide is produced using recombinant DNA technology in Saccharomyces cerevisiae followed by chemical modifications.

The product is intended for subcutaneous injection.

Other ingredients are disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections

Semaglutide 1.34 mg/ml solution for injection will be marketed as a pre-filled multidose (0.25 mg, 0.5 mg and 1 mg) disposable pen-injector containing a 1.5 mL cartridge. One pack contains 1 pre-filled pen and 6 disposable NovoFine Plus needles.

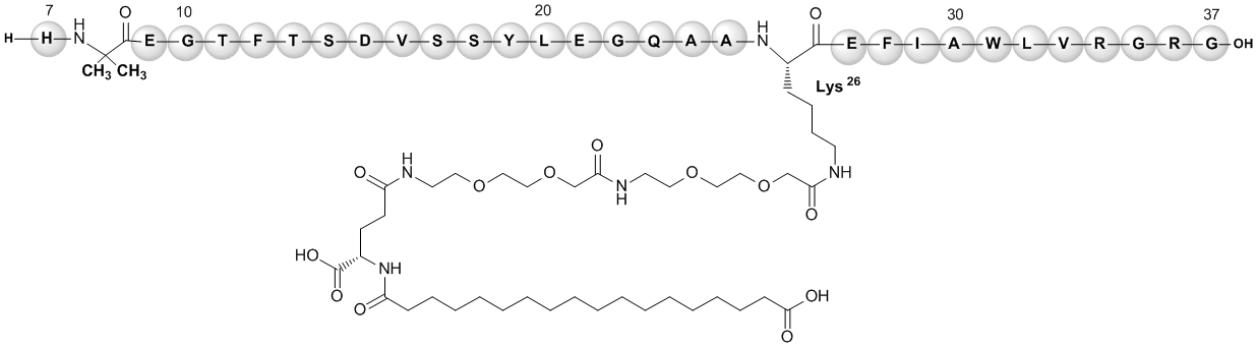
2.2.2. Active Substance

General Information

Semaglutide is a long acting analogue of human glucagon like-1 peptide i.e. an Aib^{8}, Arg^{34}-GLP-1(7-37) analogue substituted on the ε-amino group of the lysine residue in position 26 with an (S)-22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl side chain. The side chain consists of two 8-amino-3,6-dioxaoctanoic acid (ADO) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

The structural formula of semaglutide is given in Figure 1.

Figure 1 – Structural formula of semaglutide



Manufacture, characterisation and process controls

Manufacturing process

The manufacturing process for semaglutide active substance consists of a fermentation process in yeast cells, recovery and purification of semaglutide precursor. The semaglutide precursor is subjected to a synthetic modification process and purified. All steps have been described and explained.

The harvested culture broth from the fermentation process is split into several batches at delivery to recovery. The subsequent steps in recovery and purification (including modification) are all performed as batch processes, and unique batch numbers are assigned at designated steps.

In addition to the active substance itself three other intermediates are isolated and storage conditions and shelf life are defined.

Control of critical steps and intermediates

Critical operational parameters and critical in-process tests are defined for process steps. Critical in-process tests focus on microbial contamination and product purity (host cell proteins (HCP) and product related impurities).

A small set of critical operational parameters have been defined for the multistep process as has been supported by the evaluation studies in manufacturing process development. This limited selection and the fact that only these parameters have been fixed in the process description did raise questions on the criticality assignment. The issue was adequately addressed.

Process validation

The manufacturing process design consists of process characterisation and process justification. This is followed by process performance qualification (PPQ) on consecutive batches, confirming that the semaglutide manufacturing process is capable of consistently producing semaglutide active substance of the required quality in manufacturing scale.

To ensure that the semaglutide active substance manufacturing process remains in a state of control during commercial manufacture and that the validated state following PPQ is maintained, ongoing process verification (referred to as continued process verification) has been initiated.

Based on the totality of the experiments performed during process justification, ranges of both critical and non-critical operational parameters and the acceptance criteria for the critical in-process tests have been supported. Steps having one or more critical operational parameters have been defined as critical steps. The purity of the peptide before further chemical modification is specified. The results from the PPQ of the critical operational parameters, critical in-process tests, and the results of the semaglutide active substance specification tests were all consistent for the fermentation, recovery, and purification batches and all acceptance criteria were fulfilled. Based on these results it is concluded that the semaglutide manufacturing process consistently produces semaglutide active substance of reproducible quality in accordance with the predetermined specifications, the process is considered validated and ready for commercial production.

The evaluation of impurity reduction was carried out at manufacturing scale covering representative production batches from the PPQ.

- ***Control of materials***

The construction of the expression plasmid and the source and history of S cerevisiae strain ([Arg34]GLP-1-(9-37)) producing semaglutide precursor are described in detail. The cell bank system (master cell bank (MCB), working cell bank (WCB)) is explained and characterisation of MCB, WCB are reported. Stability results of MCB and WCB are available and the results comply with the specification acceptance criteria for the MCB and WCB.

No animal-derived substances are used in the production of semaglutide.

- ***Manufacturing process development***

Description and explanation of every change during product and process development is presented, batch analysis data and the use of the batch is indicated.

Comparability and stability data demonstrates that the process has been improved during development with respect to impurity levels and robustness of the manufacturing process. The changes made during development have not adversely affected the product with respect to quality, safety, or efficacy.

Characterisation

Structural characterisation and elucidation of the physico-chemical properties of semaglutide have been performed using active substance batches representative of the manufacturing process used for phase 3 clinical trials and intended for the commercial product. The results of the structural characterisation of semaglutide have confirmed the expected and theoretical structure.

The bioactivity of semaglutide is determined by a cell based bioactivity assay, which indirectly measures adenylate cyclase activation of the cloned human GLP-1 receptor. The bioactivity of isolated

semaglutide related impurities has been investigated by isolation of the semaglutide main peak and major semaglutide related impurities from semaglutide active substance, followed by testing for content and purity of each peak by reverse-phase high-performance liquid chromatography (RP-HPLC) and bioactivity. An evaluation of the correlation between the bioactivity and the content determined by RP-HPLC of semaglutide in active substance and finished product, including forced degraded samples, is provided. It is concluded that the RP-HPLC analytical procedure established for the determination of main peak content in the semaglutide active substance and finished product specifications offers a reliable measure of the bioactivity of semaglutide in both active substance and finished product.

Product-related impurities are structurally related to semaglutide. They are generated as by-products in fermentation by the host organism as well as in the recovery and purification process of semaglutide precursor, in the modification steps and in the purification process of semaglutide.

The major impurity peaks from semaglutide active substance have been isolated and the identity of the components present in each peak has been determined by high resolution liquid chromatography mass spectrometry (LC/MS).

It is noted that information given on control of product-related impurities solely relies on impurities as detected by either RP-HPLC or size-exclusion HPLC (SE-HPLC). It was confirmed that these techniques are able to detect all potential impurities.

Specification

The active substance specification includes control of identity, purity, bioactivity and other general tests.

Method descriptions and validation of test methods have been provided.

The analytical procedures are described and validation reports have been provided.

The analytical results for relevant semaglutide active substance batches are presented. The batches have been used for non-clinical studies, clinical trials (early phase 1 and 2 trials), clinical pharmacology and phase 3 trials, stability studies, reference material, process performance qualification, and setting of specifications. Data is presented as ranges obtained within the given campaign. All batch release data shown comply with the active substance specification for semaglutide, which was in force at the time for releasing the batches.

Justification of individual specification parameters and acceptance criteria is provided. A systematic and risk-based approach has been used to establish the control strategy of semaglutide active substance. The resulting control strategy for semaglutide active substance is a planned set of controls which are derived from accumulated product and process understanding and hereby ensures process performance and product quality.

- ***Reference standards***

A Novo Nordisk A/S reference material hierarchy has been established for semaglutide, consisting of a semaglutide primary reference material (PRM) and a semaglutide secondary reference material (SRM).

The content of the semaglutide PRM was assigned upon an analytical determination of nitrogen content, related to the theoretical content of nitrogen in semaglutide, and corrected for Sum of impurities by RP-HPLC. The semaglutide PRM serves as reference for identification and calibrator for

assignment of Content to semaglutide SRM, as well as to confirm bioactivity expressed as Specific bioactivity to semaglutide SRMs.

Semaglutide SRM is used for quality control of semaglutide active substance and finished product for identification and determination of Content, as well as to determine the biological activity expressed as Specific bioactivity of semaglutide active substance.

Stability

The semaglutide active substance, is stored frozen below or at 20°C.

All data for each test parameter from both supportive, primary, and PPQ studies, when stored at -20°C ± 5°C, are within the acceptance criteria and show no change over time. Furthermore, the batches have comparable trends. In addition, all data for each test parameter from both supportive, primary, and PPQ studies, when stored at accelerated condition at +5°C ± 3°C, show no change over time. The batches have comparable trends.

The proposed shelf-life of 60 months is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Semaglutide 1.34 mg/ml solution for injection is a clear and colourless solution filled into a 1.5 ml cartridge, assembled in a PDS290 pen-injector. Semaglutide finished product comprises the following ingredients: semaglutide (active substance), disodium phosphate, dehydrate (buffer agents), propylene glycol (tonicity agents), phenol (preservative), hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment), and water for injections (solvent) The primary packaging is a 1.5 mL cartridge. The 1.5 mL cartridge is assembled in a PDS290 pen-injector for semaglutide 1.34 mg/mL. Excipients are well known and approved for several EU licensed medicinal products.

Finished product understanding has been achieved based on prior knowledge of glucagon-like-peptide-1 (GLP-1) analogue products, formulation development studies, and risk assessment of the manufacturing process.

Different buffer systems and tonicity agents have been investigated; these did not improve product stability.

The formulation and filling process of semaglutide finished product manufactured for phase 1, phase 2 and phase 3 clinical trials is identical to the manufacturing process for the product to be marketed, with minor modifications. Analytical data for PPQ batches produced at the commercial scale do not indicate an impact (if any) on the product CQA following the introduction of these minor changes. In the section Process validation and/or evaluation, more detailed information is provided about the process development studies and justification for the intended commercial manufacturing process at commercial scale. All batches of semaglutide finished product used for phase 3 clinical trials have been manufactured in the same production plant facility in Denmark, which will also be used for manufacturing of the commercial finished product.

Although only a very high level overview is provided about the development studies in support of the chosen formulation, the formulation is considered to be justified in view of the available stability data and is supported by the product's safety and efficacy data.

Manufacture of the product and process controls

- ***Manufacturing***

Semaglutide 1.34 mg/mL solution for injection filled in a 1.5 mL cartridge is manufactured by Novo Nordisk A/S, Denmark.

Briefly, semaglutide active substance is dissolved in a solution containing all excipients and diluted with water for injections to obtain the desired weight. The pH is adjusted if needed by adding diluted sodium hydroxide or diluted hydrochloric acid. The final solution is sterile filtered into the stainless steel filling tank. Finally, the solution is filled aseptically into sterilized and depyrogenated 1.5 ml cartridges.

The inspected cartridges are assembled in the PDS290 pen-injector for semaglutide 1.34 mg/ml. After final assembly, the PDS290 pen-injector for semaglutide 1.34 mg/ml is labelled and packed in cartons before final release.

The critical steps together with limits and actions for critical in-process controls for semaglutide finished product are listed.

- ***Process validation***

Validation activities have been performed to confirm that the manufacturing process for semaglutide finished product is capable of consistently and reproducibly producing finished product of the required quality in commercial manufacturing scale. The process validation activities encompass: a) Process design, including process characterisation and process justification, b) Process performance qualification (PPQ), and c) Ongoing process verification.

The process justification program was designed based on a risk assessment of the semaglutide finished product manufacturing process summarising the experience from productions of clinical trial batches and development studies. The process justification was performed with scalable parameters (batch size independent) and non-scalable parameters (batch size dependent and/or equipment specific).

The process performance qualification programme (PPQ) was designed on the basis of the conclusions from the process justification. Three consecutive batches of semaglutide finished product have been manufactured in commercial scale. The study design for the process performance qualification of semaglutide finished product covers a) In-process controls, b) extensive sampling and c) additional sampling. Based on the results from the PPQ, it can be concluded that the manufacturing process for semaglutide finished product is in a validated state and suited commercial production.

Product specification

The specifications for semaglutide 1.34 mg/ml solution for injection in a 1.5 ml cartridge, assembled in a PDS290 pen-injector includes control of identity and other general tests.

Analytical procedures are described and validated according to relevant ICH guidelines or reference is made to compendial requirements (*Ph. Eur.*).

- ***Batch analyses***

An extensive overview of the batch analysis testing results of semaglutide finished product batches used during development is provided. Dose accuracy data for three batches of PDS290 pen-injector for semaglutide 1.34 mg/ml are presented as part of the container closure documentation.

- ***Characterisation of impurities***

A characterisation study was conducted to characterise the semaglutide related impurities generated during the manufacture and storage of semaglutide finished product. No new impurities of semaglutide were found to be generated during the manufacturing of semaglutide finished product.

- ***Justification of specifications***

The specification takes into consideration the consistency in the manufacturing process and the analytical procedure. After phase 3 and before submission, the acceptance criteria for impurities have been narrowed where justified. No release testing for bioactivity is proposed. According to the applicant, the bioactivity is indirectly controlled by the specification parameter Content of semaglutide, as a direct correlation has been demonstrated between the bioactivity of semaglutide finished product and Content of semaglutide (Content by RP-HPLC), independent of the degree of degradation of the semaglutide finished product. This approach has also been accepted for other GLP-1 analogues. A number of issues were raised on the justification of specifications and were adequately addressed. A systematic and risk-based approach has been used to establish the control strategy of semaglutide finished product.

Elemental impurities in semaglutide finished product have been assessed in alignment with ICH Q3D.

- ***Container closure system***

The container closure system for semaglutide 1.34 mg/mL solution for injection comprises the primary packaging and the PDS290 pen-injector for semaglutide 1.34 mg/mL. The PDS290 pen-injector is currently approved for delivery of several insulin and GLP-1 products in the EU.

The glass cartridge complies with the European Pharmacopoeia (Ph. Eur.) (type I glass).The PDS290 pen-injector for semaglutide 1.34 mg/ml can deliver doses of 0.25 mg, 0.5 mg or 1.0 mg.

The PDS290 pen-injector is intended to function with a standard needle thread or a needle with a bayonet coupling. The PDS290 pen-injector for semaglutide 1.34 mg/ml is the device part of a drug-device combination product according to the Council Directive 93/42/EEC concerning Medical Devices, Article 1 (3). Such products are regulated according to Directive 2001/83/EC relating to medicinal products for human use. The PDS290 pen-injector for semaglutide 1.34 mg/ml complies with ISO 11608-1 (Needle-based injection systems for medical use –Requirements and test methods – Part 1: Needle-based injection systems).

Stability of the product

The proposed shelf life for semaglutide is 36 months when stored in a refrigerator (2°C to 8°C) and kept away from the cooling element, protected from light.

The stability programme for G101semaglutide 1.34 mg/ml solution for injection (referred to as semaglutide finished product) was performed according to current ICH guidelines.

No changes in formulation and primary container closure system were introduced between production of the primary stability batches and process performance qualification (PPQ) batches.

Primary stability batches and PPQ batches were all produced in the same production facility.

All long term and accelerated stability studies were performed on semaglutide finished product in primary containers (1.5 mL cartridge). In order to perform the Dose accuracy test, the 1.5 mL cartridges were assembled in the PDS290 pen-injector. The primary container closure system used in the presented studies is identical to the one intended for market.

Collectively, the presented data support the proposed shelf life, i.e. 36 months when stored in a refrigerator (2°C to 8°C) and kept away from the cooling element, protected from light. After first use, the product should be stored below 30°C or in a refrigerator (2°C to 8°C). An in-use shelf-life for the pen, when stored below 30°C, of 6 weeks is accepted.

Adventitious agents

The semaglutide precursor peptide is produced from a yeast strain. Yeast is not a host for mammalian viruses. The cell line has been tested for microbial purity. As no further raw materials or excipients of human or animal origin are used for the manufacture of semaglutide, the finished product is evaluated to be safe with regards to TSE agents and there is no risk of contaminating the product with mammalian viruses.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

It is concluded that adequate information has been provided on process description, the justification of the process conditions which is supported by the manufacturing process validation.

Comprehensive information has been provided on development, characterisation and validation of the manufacturing process.

Adequate information on API starting materials has been provided

Several process intermediates are defined. The purity requirement for the peptide before conjugation has been adequately justified.

The characterisation demonstrates that the active substance is a single molecular entity with a high level of purity. Process-related impurities are adequately controlled at appropriate stages. The determination of the product-related impurities in process and at active substance release is exclusively performed with a RP-HPLC procedure while aggregation is only controlled with a SE procedure. An orthogonal approach was applied demonstrating that the main peak contains a compound having the same Mw and hydrophobicity and no compounds differing in Mw co-elute. Furthermore, the RP-HPLC methods provide good separation with closely related substances/impurities. The presented data support the selectivity of the RP-HPLC method towards impurities.

It has been assured that solvents and impurities from the chemical modification are well controlled.

Chromatographic procedures and system suitability criteria have been described to ensure that the methods consistently detect the impurities.

The applicant has developed a bioactivity assay, however chose to limit its use in routine testing to 1 out of 10 batches. This is considered acceptable since it concerns a molecule relatively well controlled by physical-chemical analysis and the RP-HPLC content method has shown a good correlation with bioactivity assay results.

The specification for bioactivity and RP-HPLC detectable impurities have been adjusted or appropriately justified.

The presented active substance stability studies support the storage condition and claimed storage period.

Finished product

The manufacturing process is considered to be appropriate. Detailed process description was provided in terms of ranges for process parameters for all process steps.

Process characterisation/justification studies and PPQ studies generally support the process ranges/limits and product intermediate holding times. Information was provided as regards the filter validation tests and aseptic validation for specific for the semaglutide finished product.

The cartridges are siliconised prior to depyrogenation. It is considered that sufficient information is provided to assure that the plungers and caps are acceptable in terms of microbial quality.

The proposed specifications / acceptance criteria have been justified based on knowledge obtained during the pharmaceutical development work as well as data obtained from production of clinical batches (phase 3, pilot scale) and batches used during late stage development (batch size, manufacturing scale).

The subsequent recalculations performed have resulted in adjustment of the specification limits, with due consideration for the safety and efficacy of the semaglutide finished product during the shelf life period as well as for the manufacturing capability. In principle, the proposed limits of related impurities detected in for semaglutide finished product are supported by the maximum levels detected in clinical trial. It is noted that a characterisation study has been conducted to characterise the semaglutide related impurities generated during the manufacture and storage of semaglutide finished product.

Dose accuracy test is performed by weighing and will be carried out as part of the release testing after assembly of semaglutide finished product in the PDS290 pen-injector for semaglutide 1.34 mg/ml.

The proposed shelf-life of 36 months at 5°C ± 3°C for the semaglutide finished product, semaglutide 1.34 mg/mL solution for injection is properly justified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Ozempic is considered to be in line with the quality of other approved recombinant DNA products. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Safety concerning adventitious agents has been sufficiently assured.

The overall quality of Ozempic is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends a point for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical safety programme was designed in accordance with ICH M3 (R2) and ICH S6 (R1).

2.3.2. Pharmacology

Semaglutide is a long-acting human glucagon-like peptide-1 (GLP-1) receptor agonist, which specifically activates the GLP-1 receptor (GLP-1R). Semaglutide is an Aib^{8}, Arg^{34}-GLP-1(7-37) analogue substituted with a side chain on the lysine residue in position 26. The side chain consists of two ADO (8-amino-3,6-dioxaoctanoic acid) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification. Semaglutide has a 94% structural homology to native GLP-1, a molecular weight of 4113,58 g/mol and is good soluble in an aqueous solution. Semaglutide is suitable for once-weekly administration in humans.

The pharmacological mechanism of GLP-1R agonists is well described in the literature, with blood glucose lowering and body fat loss mediated by lowered intake of calories. The primary pharmacological target tissues for GLP-1R agonists are the pancreas (beta-cells), the gastrointestinal system and the brain. The amino acid sequence of GLP-1 is preserved in mammals and only one receptor, the GLP-1R, has been identified. Rat and human GLP-1R have 90% homology and monkey and human 99%. The GLP-1R is a G-protein coupled receptor and the cellular action of GLP-1 is mediated through the G-protein and subsequent activation of adenylate cyclase leading to increased cAMP accumulation.

Baby hamster kidney (BHK) cell membranes, stably expressing the human GLP-1 receptor, were used to characterize the *in vitro* pharmacological receptor effect of semaglutide using binding and functional studies on the human GLP-1 receptor. The binding affinity of semaglutide to the GLP-1 receptor in the membrane preparation, was found to be influenced by albumin concentrations.

The results of the functional, receptor activating, studies, measuring cAMP production, showed that semaglutide is a GLP-1 receptor agonist with a potency of 0.15 nM, which is comparable to liraglutide and 8-fold less potent than GLP-1 itself.

In an *ex vivo* study using rat isolated perfused pancreas, semaglutide stimulated insulin secretion dose-dependently. Two pancreas preparations were studied with increasing concentration of semaglutide and the EC_{50} of insulin secretion was estimated to be ~14 nM.

The primary pharmacodynamic effect was evaluated in a number of animal models.

In normal male rats, the *in vivo* potency was estimated by dosing semaglutide subcutaneously (sc) followed by an i.v. glucose infusion 3 hrs later. Semaglutide stimulated plasma insulin secretion and lowered blood glucose at a dose of 123 μg/kg (~6 nM plasma exposure) and a trend towards stimulation was observed at 41 μg/kg.

In male diabetic db/db mice, upon single or repeated 4-week sc dosing, semaglutide lowered blood glucose dose-dependently and had a long duration of action. The ED_{50} for lowering of blood glucose (6 hours post dosing) was estimated to be 1.2 µg/kg for semaglutide, whereas it was about 20-fold higher for liraglutide indicating that semaglutide was more potent *in vivo* than liraglutide. The maximal effect on blood glucose lowering was comparable for semaglutide and liraglutide, and was obtained at 4 - 8 µg/kg for semaglutide in the 4-week study. The effect on body weight was maximal at a dose of 21 µg/kg.

The beta-cell-reduced Göttingen minipig is a model, in which the human conditions of impaired glucose tolerance are mimicked, and has more resemblance to humans than rodent models. This model was used for evaluation of duration of action of GLP-1R agonists. In a hyperglycaemic clamp study in beta-cell-reduced minipigs, semaglutide stimulated insulin secretion for up to 7 days after the last dose (8.2 µg/kg) was administered.

GLP-1 and its analogues are, among other effects, able to reduce food intake, which is an important aspect in the treatment of obesity and diabetes. The subchronic efficacy of semaglutide on body weight reduction was evaluated in diet-induced obese (DIO) aged female rats, which were given chocolate in addition to normal chow for 9 months. Subcutaneous doses of 1.2 and 4.1 µg/kg once-daily for 77 days led to a dose-dependent, significant decrease in body weight, primarily from fat. Furthermore, semaglutide dose dependently decreased overall food intake, which mainly consisted of chocolate. Leptin, total cholesterol and free fatty acids were significantly decreased after treatment with semaglutide while plasma glucose, HbA1c, insulin, glucagon and triglycerides were not changed.

The effects of semaglutide on hypothalamic appetite signals were evaluated in high fat diet obese (DIO) mice. Dosing of semaglutide for 18 days (0.15 mg/kg, s.c., daily) significantly lowered body weight. This was associated with increased mRNA expression of the satiety peptide cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus (ARC) in hypothalamus. Expression levels of the hunger peptides neuropeptide Y (NPY) and Agouti-related peptide (AGRP) in the ARC in hypothalamus were not different between semaglutide and vehicle but were lower than in the weight matched vehicle group.

The effect and duration of semaglutide on lowering of food intake were also studied in young, growing pigs. Steady state plasma levels of semaglutide were achieved by dosing every other day at 21 µg/kg. When steady state had been reached, dosing was stopped and daily food intake was assessed. Semaglutide decreased food intake in pigs for at least 2 days after cessation of dosing. The potency of semaglutide for decreasing food intake was in magnitude comparable to liraglutide in pigs, but with a longer duration of action.

The access and neuronal interaction of semaglutide in the rodent (SD rat, C57BL mice) brain was investigated using peripherally administered fluorescently labelled semaglutide. Semaglutide was shown to have access to discrete brain regions expressing the GLP-1R including some of the well-defined circumventricular organs. Fluorescently labelled semaglutide also gained access to brain regions protected by the blood brain barrier (BBB) such as NTS (nucleus tractus solitarus) in the brain stem and in hypothalamus, where it was present in CART positive neurons in the ARC. The fluorescent signal was lost in the GLP-1R Knock-Out (KO) mouse, suggesting dependence upon binding to the GLP-1 receptor. Electrophysiological measurements of mouse brain slices revealed that semaglutide

(100 nM) directly stimulated Pro-opiomelanocortin (POMC)/CART neurons and indirectly inhibited neural activity in neurons expressing NPY.

The effect of semaglutide on development of atherosclerosis was investigated in two hypercholesterolemic mouse models, the ApoE- and LDL-receptor KO mouse models, at sc doses of 4, 12 and 60 µg/kg administered once-daily for 13 or 17 weeks, respectively. These models are widely used to study plaque formation when on a western diet (WD) consisting of high fat and carbohydrate content and 0.2% cholesterol.

In the LDLr KO mouse model, semaglutide showed a significant, about two-third, reduction of aortic plaque area at all three dose levels tested. This effect was accompanied by a significantly reduced body weight gain and a reduction in plasma TG levels with the highest dose, while plasma cholesterol and cholesterol lipoprotein levels were not changed by semaglutide treatment.

In the ApoE KO mouse, semaglutide treatment showed a significant attenuation of aortic plaque area at all three dose levels tested after 13 week daily treatment. This effect was accompanied by a significantly reduced body weight gain with all doses.

In conclusion, the development of WD-induced aortic plaque lesion areas was attenuated by semaglutide in both KO models at all dose levels. The effect was partially independent of reduced body weight gain.

A broad profiling screening panel using 68 biochemical receptors, ion-channels and neurotransmitter transporters did not show a competitive interaction with semaglutide. Also, semaglutide, up to 10 µM, did not activate the glucagon receptor. No secondary pharmacology effects are expected from semaglutide.

In conclusion, the efficacy pharmacodynamic studies have been conducted *in vitro*, *ex vivo* as well as *in vivo* in normal, diabetic and obese rodent models and normal pigs and minipigs. The studies have shown that semaglutide has pharmacological properties consistent with a GLP-1R agonist showing increases of insulin secretion, plasma glucose lowering and weight lowering due to a reduction of food intake.

The safety pharmacology studies were designed to investigate the effect of semaglutide on major organ function (central nervous system, respiratory system and cardiovascular system). Exposure measurements in both the rat CNS study and in the cynomolgus monkey cardiovascular study exposure of treated animals confirmed exposure of treated animals could correlate effects to the exposure. Due to differences in dosing frequency between humans (once weekly) and animals (daily/biweekly), the mean maximal plasma concentration (C_{max}) at the maximum recommended human dose (MRHD) of 1 mg/week has been used for exposure comparison in the safety pharmacology section. A value of ~32 nM has been taken as the mean C_{max} in humans at MRHD.

The effect of semaglutide on the central nervous system was studied in the rat CNS (Irwin) study. In this study no significant gross behavioural or physiological changes were observed, during the 24 h post-dose period in rats receiving subcutaneous treatment with semaglutide. Abnormal gait (walking on toes), passivity, decreased touch response, increased urination, lethargy and piloerection were observed in animals administered 95 µg/kg semaglutide, which corresponds to 1.5-fold the maximal plasma (C_{max}) exposure at the maximum recommended human dose (MRHD). The observed effects are considered to be pharmacology related and likely due to the activity at GLP-1 receptors in the CNS. The No Observed Adverse Effect Level (NOAEL) was determined to be 22 µg/kg.

Semaglutide, given subcutaneously at doses up to 84 µg/kg, had no statistically significant effects on respiratory rate, tidal volume or minute volume up to 24 hours after dosing in male SD rats.

Treatment with semaglutide (>200-fold higher concentration than the mean maximal plasma concentration at the MRHD) produced no inhibition of hERG channel tail current recorded in HEK293 cells stably transfected with hERG cDNA, nor an effect on action potential parameters in isolated female rabbit Purkinje fibres. This indicates that semaglutide has a low potential for QT prolongation.

The acute effect of semaglutide on cardiovascular function was studied in male conscious unrestrained cynomolgus monkeys equipped with telemetry transmitters and dosed subcutaneously with ascending doses of semaglutide. No effects related to semaglutide were observed on arterial blood pressure (systolic, diastolic and mean) or the lead II ECG variables examined (RR, PR, QR, QTcF and QTcQ intervals or QRS duration). In conclusion, it was found that there were no clinically relevant findings in cynomolgus monkeys in single doses up to 470 µg/kg (about 14-fold above MRHD based on C_{max}).

In addition, in the repeat dose toxicology study at week 13, 26 and 52, the cardiac electrophysiology was monitored by ECG in male and female telemetered cynomolgus monkeys (10, 60 and 360 µg/kg twice-weekly sc). In this 52-week toxicity monkey study, a left-bundle-branch-block was observed in one female animal at high dose of 360 µg/kg (~27-fold above MRHD). The animal exhibited no clinical signs attributable to the ECG finding and histopathology revealed no correlating changes. Cardiac bundle-branch blocks are an occasional finding in monkeys and humans, and are in most cases a consequence of other underlying cardiac diseases. Although histopathology revealed no changes in the heart, the ECG finding was considered adverse. When heart rate was analysed as change from baseline, it was shown that there seems to be a transient increase in heart rate at week 26 which returns to baseline values at week 52 in males but remains elevated at week 52 in high dose females. This finding supports the increase in heart rate seen in patients in the clinical trials.

A renal function study was performed to evaluate the acute effects of semaglutide on the renal system in the rat. Semaglutide caused an acute transient increase in diuresis during the first 8 hours after dosing at the highest doses (23 and 89 µg/kg) and a decrease in the diuresis parameters thereafter. These observations are well known effects of GLP-1R agonists in the rat. Acute effects on diuresis have also been shown in humans with native GLP-1, but not following chronic administration of GLP-1R agonists. The NOAEL was determined to be 5 µg/kg.

Nonclinical pharmacodynamic drug interaction studies have not been conducted with semaglutide, which is agreed upon. GLP-1R agonists have been reported to delay gastric emptying but this was evaluated in clinical trials.

2.3.3. Pharmacokinetics

Analytical methods

The methods developed for analysis of semaglutide in plasma with LC-MS/MS (mouse, rat, monkey) and ELISA (mouse, rabbit, monkey) were sufficiently validated with satisfactory assay performance.

The LOCI assay was affected by interference from the plasma matrix and dilution linearity issues with a larger impact on low concentrations leading to underestimation of semaglutide exposures (rat, rabbit, monkey). For this reason, the plasma assay in rat and monkey was replaced by LC-MS/MS and ELISA. In the rabbit embryo-foetal development study (207360), measured concentration were below 200 nM, where Hook effect occurred and the values for dose-normalized average concentrations (Cavg) did not deviate from the other tests.

The methods developed for the detection anti-semaglutide antibodies (radioimmunoassay) and neutralizing antibodies (BHK cell based neutralising assay) measuring cAMP) in serum (mouse, rat, monkey) has been were sufficiently validated with satisfactory assay performance.

Single dose absorption and plasma pharmacokinetics

The pharmacokinetics were dose-proportional and there was no gender dependency. The absorption of Semaglutide from the subcutaneous injection site was rapid in mouse and rat, but slower in rabbit, monkey and minipig. The time to maximum concentration (tmax) was 2 to 3 hours in mouse and rat, and about 24 hours in rabbit, monkey and minipig. The bioavailability ranged from 86% (monkey) to 94% (minipig). In human, the bioavailability was equally high (89%), but the absorption was slower (tmax 60 h).

The mean dose-normalized concentration was similar in monkey and human, while it was lower in mouse, rabbit and rat due to faster clearance. The terminal half-life was estimated to be 8 h in the mouse, 11 hr in the rat, 28 h in the rabbit, 51 h in the monkey and 148 h in human.

The distribution volume was low (0.2 L/kg) following i.v. administration in the monkey, which corresponds approximately to the volume of extracellular water and indicates that a high fraction of semaglutide is circulating in plasma and extracellular fluid.

Comparison of single dose pharmacokinetics in monkey after subcutaneous and intravenous dosing indicated that elimination is not limited by the absorption rate from subcutis.

Toxicokinetics

The pharmacokinetics following repeated dosing of subcutaneous semaglutide showed a linear relationship between doses and exposures. No gender differences were noted. The dose normalised exposure was generally lower for mice, rats, rabbits and minipigs compared to monkeys and humans due to faster clearance. To ensure continued exposure, and to mimic the once-weekly exposure profile in humans, once-daily dosing was used in mice and rats, and twice-weekly dosing was used in monkeys. At these dose intervals, there was no apparent (i.e. < 2-fold) systemic accumulation

No difference in exposure was observed between pregnant and non-pregnant animals following repeated administration of semaglutide to rats, rabbits and monkeys. However, rabbits showed some accumulation in the embryofoetal development study, but the wide range (1.3 up to 13-fold) and the few data do not permit a clear conclusion.

Plasma protein binding

In-vitro binding studies showed that the plasma protein binding was high, >99%, and that albumin was the primary protein responsible for binding of semaglutide in plasma. The potential binding to other plasma proteins has not been studied. The fraction unbound was somewhat lower in plasma from mouse, rat and rabbit (0.07-0.28%) as compared to plasma from monkey (0.46%) and human (0.36%).

Distribution to red blood cells

As determined in rats, whole blood concentrations of semaglutide-related material were approximately half of the values in plasma, suggesting no preferential uptake into red cells.

Tissue distribution

Distribution studies in rats showed the highest presence of semaglutide-related material in blood and in highly perfused tissues.

After subcutaneous administration of [^{3}H]-Oct- or [^{3}H]-Tyr-labelled semaglutide, the tissue-to-blood ratios of semaglutide related material were generally below 1. The highest levels were associated with lung, tooth pulp, kidney (cortex and medulla), bladder, adrenal medulla and uterus. The high levels in the bile ducts, up to and including 3 days after dosing, suggests that biliary secretion may have played an important role in elimination by contributing to faecal excretion. In addition, the moderate levels of radioactivity present in the kidneys and bladder also suggest that urinary elimination occurred. The lowest concentrations were present in the central nervous system (brain and spinal cord) and white fat.

The distribution and concentrations of [^{3}H]-Oct-semaglutide related material in male pigmented rats were similar to that in male albino rats, suggesting that semaglutide related material does not bind to melanin or accumulate in pigmented tissues.

Metabolism

The *in-vitro* metabolism of radiolabelled semaglutide was studied in hepatocytes from rats, monkeys and humans. Limited metabolism was observed in all species, and no unique human metabolites were formed. It was shown that semaglutide is metabolised by proteolytic cleavage of the peptide backbone by neutral endopeptidase (neprilysin) and sequential beta-oxidation of the fatty acid side chain.

The *in-vivo* metabolism of semaglutide was investigated by chromatographic metabolite profiling of plasma, urine and faeces from rat, monkey and human following administration of radiolabelled semaglutide. The metabolite profiles from plasma were similar across species. The peptide backbone of semaglutide was metabolised by proteolytic degradation, and the fatty acid moiety was degraded by sequential beta-oxidation.

Semaglutide was the most abundant component in plasma across animal species, accounting for 69-93% of the total amount of semaglutide related material and 4 to 12 metabolites which constituted in total only a small part in relation to the amount unchanged semaglutide.

In human plasma, there were 6 metabolites, each contributing 0.4-7.7% to the total amount of semaglutide-related material, whereas the contribution of unchanged semaglutide was 83%. The largest metabolite (P3) contained at least three components (P3A, P3B and P3C). P3C was characterised as a semaglutide isomer. P3B was identified as a peptide metabolite from semaglutide, following proteolytic cleavage and the loss of the first 13 amino acids. Neprilysin was capable of forming the metabolite P3B *in vitro*. No further structural information could be provided P3A and P3C, due to the limited amounts in plasma. All human metabolites are also present in rats, and P3, P5 and P7 are also present in monkeys.

The two primary metabolites in human (U6 and U7) were identified as the free Lys26 amino acid bound to the ADO-linker with butyric (C4) or hexanoic (C6) di-acid side chains attached. These metabolites are products formed from full proteolytic cleavage of the peptide backbone with sequential removal of C2-units by beta-oxidation of the di-fatty acid side chain. The urine metabolite U22 was identified as semaglutide. Only limited amounts of unchanged semaglutide were observed in urine of animals (1%) and humans (3%).

The pharmacological activity of the metabolites has not been evaluated. These metabolites, such as P3B and P3C, may be pharmacologically active since they have structural similarities with semaglutide. The possible contribution of these metabolites to the pharmacological activity of the final product will be minor, because in plasma they are only a small part in relation to the amount of unchanged semaglutide (< 7.7%).

Excretion

Semaglutide was extensively metabolised prior to elimination. In human, unchanged semaglutide were observed in small amounts in human urine (3.1%), but was not detected in faeces. In rat and monkey, both urine and faeces were equally important as excretion routes of semaglutide and related material. The contribution of urinary excretion was 37% in rats and 30% in monkey, whereas the contribution of faecal excretion were 35% and 21% in these species, respectively. In human, the urinary excretion was the predominant route of excretion (53%), followed by faeces (18.6%).

In bile-cannulated rats, bile was primary route for excretion of semaglutide-related material into faeces (48%), of which approximately 14% was unchanged semaglutide. Other components in bile were metabolites, each accounting for less than 5% of the administered dose.

Placenta transfer

Semaglutide related material passed the placental barrier in rats and rabbits, but distributed to foetal tissue at levels lower than in dam plasma (<4%). This suggests limited distribution across placenta. Nevertheless, a single dose of semaglutide to pregnant rats at GD18, led to low, but measurable levels in foetuses at 24h post dose and effects on the foetus were observed.

Excretion into milk

Semaglutide and metabolites are excreted into rat milk. Mean concentrations were 3-12 times lower than in plasma up to 24 hours after a subcutaneous dose 0.3 mg/kg/day semaglutide. There are no data on the excretion of semaglutide in human milk. A risk to the newborns/infants cannot be excluded. Semaglutide should not be used during breastfeeding.

Pharmacokinetic drug interactions

The results of the *in-vitro* and *in-vivo* studies on the drug interaction potential of semaglutide have been evaluated in the clinical assessment report.

2.3.4. Toxicology

A single dose up to 12mg/kg (mouse) or 7.532 mg/kg (rat) was generally well tolerated. Observed major findings such as reduced body weight and food intake showed quick recovery and can be related to the pharmacological action of semaglutide.

Repeated dose studies in mice, rats and cynomolgus monkeys revealed mainly effects related to the pharmacological action of semaglutide. Reduction in food intake and body weight gain were dose limiting, as exceeding the maximum tolerated dose in monkeys led to dehydration consequently followed by euthanization. However, dose escalation improves tolerability.

Hypertrophy of Brunner's glands of the duodenum was observed in rats after 26 weeks of treatment. This effect is likely due to the high expression of GLP-1R on Brunner's glands. However, there was no progression to hyper- or neoplasia in the rodent carcinogenicity studies, and no similar observations in cynomolgus monkeys dosed for 52 weeks. Therefore, this observation is not considered a safety concern in humans. Thyroid C-cell hyperplasia was only observed in mice at all dose levels. This is an expected result also seen with other GLP-1 agonists and can be considered a class effect.

The 52-week monkey study revealed a chronic left bundle-branch-block in one high dose female. Although the abnormal ECG was confined to a single animal, the observation was considered adverse.

An increase in uterus fluid distension and luminal dilatation is seen in rats after 26 weeks of dosing. These findings are likely due to differences in the stage of the sexual cycle which could be treatment related, and likely secondary to reduction in body weight. Daily subcutaneous administration to Sprague-Dawley rats over a treatment period of 13 weeks with 0.48 mg/kg/day and 0.45 mg/kg/day semaglutide respectively, demonstrated generally similar observations between two formulations based on two different manufacturing processes and although there were a few minor differences, none was considered of any toxicological significance.

Semaglutide is not genotoxic *in vitro* or *in vivo*.

In carcinogenicity studies in mice and rats, thyroid C-cell adenomas and carcinomas were observed at all dose levels. This is an expected result also seen with other GLP-1 agonists and can be considered a class effect. No other tumours were found. Other non-neoplastic effects were secondary to the decreased body weight gain related to the pharmacological action of semaglutide. To determine whether the thyroid C-cell tumours are indeed caused by the same mechanism as is responsible for C-cell tumours observed after treatment with GLP-1 agonists, the applicant performed some mechanistic studies. The activation of the GLP-1R was tested *in vitro* on a thyroid C-cell tumour cell line and compared to GLP-1, exenatide and liraglutide. It was shown that the potency of semaglutide to activate the receptor was similar to liraglutide, and less potent than GLP-1 and exenatide.

Increased plasma calcitonin concentration is considered a marker for increased activation of GLP-1R on the thyroid C-cells. Upon chronic activation this leads to up-regulation of calcitonin synthesis and further to C-cell proliferation and tumour formation. Therefore, the applicant performed *in vivo* studies in mice and rats, which show that even after a single 1 mg/kg dose of semaglutide in mice, plasma calcitonin levels were increased 12 and 24 hours after injection. In rats however, an increase calcitonin level was not seen in females, and not very convincingly in males after 6 weeks of treatment. This could be due to the very short half-life of calcitonin in rats of 4 minutes, or a delayed effect which is still not apparent after 6 weeks. Further, an inconsistent effect on calcitonin levels in rats was also seen for liraglutide. Overall, the mechanism of formation of rodent thyroid C-cell tumours is well known and discussed in the public literature. There is no reason to suggest a different mechanism might be responsible for the C-cell tumours observed after treatment with semaglutide, and therefore the thyroid C-cell tumours are likely rodent specific. Since relevance for humans cannot be completely ruled out, thyroid C-cell tumours are listed in the RMP as potential risk.

In the main rat study which combined fertility and embryo-foetal development, there was no effect on male fertility. There was an increased number of females with irregular oestrus cycles, but this did not result in a reduced fertility index. From the mid-dose onward however, there was a reduced number of corpora lutea with reduced implantations and litter size at the high dose. As there was evidence of maternal toxicity at all doses, it is not clear whether these effects are related to treatment or secondary to reduced maternal body weight gain.

Semaglutide caused embryotoxicity in the rat. The observed effects included embryo-foetal mortality, growth retardation, and skeletal and visceral abnormalities. The effects were observed at dose levels of 0.03 mg/kg/day and above, with AUC exposures below the clinical exposure at the MRHD of 1 mg/week. The applicant describes a mechanism of action for the embryotoxic effects observed in the rat reproduction study, which involves the presence of GLP-1R on the yolk sac. Semaglutide binds to the receptors on the yolk sac, leading to inhibition of transport of nutrients across the membrane. This mechanism is likely rat specific, since rat embryos are dependent on the yolk sac for their nutrient supply which is e.g. less important in other species including humans and monkeys. Moreover, GLP-1R is not expressed on monkey yolk sacs.

It is agreed that the mechanism demonstrated is specific for rats, and could explain the malformations seen in the rat foetuses. Although undoubtedly this mechanism is responsible for most of the malformations observed, it cannot be excluded that other mechanisms that may not be rat specific are also involved. This is based on the fact that not only more and other malformations are present, but also foetal weight is much further reduced in embryos of dams treated up to GD17 as compared to GD13. This is after the period (GD12) in which embryos are solely dependent on the yolk sac for nutrition, but also rely on the developing chorioallantoic placenta. Although the additional skeletal abnormalities that occur between GD13 and GD17 could still be due to the impaired yolk sac, due to presence of the GLP-1R on the rat embryo from GD13.5 and presence of low levels of semaglutide in the foetus as measured on GD20, a direct effect of semaglutide on the foetus, of which the clinical relevance is unknown, cannot be excluded. It appears that a potential direct effect of semaglutide is only relevant in the later stages of pregnancy in rats, since the receptor is not present before GD13.5. Timing of receptor expression, if this is relevant for humans at all, is unknown, but a potential risk for humans is mitigated through the labelling in SmPC section 4.6, where it is stated that semaglutide should not be used during pregnancy and women of childbearing potential should use contraception to avoid unplanned pregnancies. Any further risk mitigation measures are not warranted.

A second embryo-foetal toxicity study was performed in rabbits. Once-daily SC administration of semaglutide to pregnant New Zealand White rabbits markedly reduced maternal body weight and food consumption. This coincided with increased post-implantation losses, incomplete ossification of foetal metacarpals/phalanges, and increased incidences of minor skeletal and visceral foetal abnormalities. The increased post-implantation losses and the foetal pathology findings were possibly secondary to the marked maternal effects, but a direct effect of semaglutide could not be excluded. On the other hand, marked maternal toxicity could also mask a direct effect on the embryo or foetus. Although exposure in the high dose group at GD19 was above the human exposure, it was below human exposure at GD6. The Applicant attributes the observations in the rabbit as described above, primarily to the maternal effects on body weight and food consumption. Delayed ossification observed without concomitant decreases in foetal body weight may warrant increased attention (Carney and Kimmel 2007). However, as the mid and high-dose dams showed lower body weight gains on GD 6-19, and higher than control body weight gains on GD 20-29, any decreased foetal body weights in the mid and high dose groups may have been recovered at termination of the study when the foetal examinations were performed.

Cynomolgus monkeys were used as a third species for embryo-toxicity testing of semaglutide, since monkeys do not rely on a yolk sac for nutrition. In all dose groups, the pregnant females had an initial loss of body weight, and a lower body weight gain as compared to control animals. There were 2 cases of abortion in all dose groups as compared to 1 in the control group. The incidence of 2 out of 16 (12.5%) is close to the incidence of pregnancy loss in cynomolgus monkey controls reported in literature of 11.5% up to GD75 (Jarvis et al, Birth Defects Research (Part B) 89:175–187 (2010)).

Further, two major malformations were reported in the study. In the mid-dose group a single foetus had a fused kidney, and in the high dose group there was one foetus with a misshapen brain. These effects have not previously been reported in historical controls from the same testing site. However, a relevance for humans is unlikely due to the lack of a mechanistic relation to semaglutide and lack of similar findings in other studies. Moreover, any potential risk is mitigated through the labelling in SmPC section 4.6.

There was no effect on postnatal development in offspring of cynomolgous monkeys treated with semaglutide until GD140. Initial maternal body weight losses likely led to an increased incidence of early pregnancy loss and reduced foetal weight in the mid and high dose. No other effects were observed.

A juvenile study was performed where rats from the age of 21 days were dosed for 11 weeks. Apart from general signs of toxicity, sexual maturation and fertility were investigated. Sexual maturation was delayed for both sexes, but this did not coincide effects on fertility or mating performance. No histopathological findings were noted, and therefore it is considered likely that the delay is due to the decreased body weight gain of the treated animals. No new findings were seen in these juvenile animals that were not seen in the adult animals. This study is of limited relevance in the current procedure, as the indication applied for is in adults only.

In a local toxicity study in pigs using the subcutaneous route of administration only mild effects related to the vehicle or injection procedure were seen. Further, in all pivotal toxicity studies the subcutaneous route of administration was applied, and therefore local toxicity is considered sufficiently investigated and no concerns for human safety were identified.

In clinical practise it is possible that the product will be administered by intravenous, intra-arterial or intramuscular routes by mistake. Therefore, possible adverse effects were investigated in rabbits using these routes of administration. No adverse effects were seen other than mild effects related to the vehicle or injection procedure.

2.3.5. Ecotoxicity / environmental risk assessment

The active substance is a peptide. Therefore, semaglutide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The Applicant has shown that semaglutide is effective in lowering blood glucose levels in diabetic animal models, as well as modulating satiety and giving rise to decreased food intake and have a body weight lowering effect. Furthermore, the duration of these effects are markedly longer than the once daily liraglutide. The Applicant has also shown that semaglutide has some effects on preventing atherosclerotic plaque formation in two knock-out mice models, and the positive effects of GLP-1R agonists in this aspect is further supported by literature. Standardised safety pharmacology studies did not reveal any cardiac safety signals following SC administration of semaglutide, however, in the 52 week toxicity study in cynomolgus monkey, one female animal in high dose group, developed left-bundle-branch-block, which might be related to treatment. When heart rate was analysed as change from baseline, it was shown that there seems to be a transient increase in heart rate at week 26 which returns to baseline values at week 52 in males but remains elevated at week 52 in high dose females. This finding supports the increase in heart rate seen in patients in the clinical trials.

Semaglutide showed linear relationship between dose and exposure without a gender dependency for all species used, where dose normalised exposure was slightly lower for rodents compared to minipigs and cynomolgus monkey and human. The T_{max} increased from 2 - 3 hours in the rodents to 24 hours in rabbit and cynomolgus monkey, and 60 hours in human. Half-life increased from 7.6 hours in the mouse, to 51 hours in cynomolgus monkey and 148 hours in human. The bioavailability following s.c. administration was 86%, 94% and 89% for cynomolgus monkey, minipig and human respectively. Plasma protein binding was found to be very high (>99%) in all species. Anti semaglutide antibody development was scarce in the nonclinical species.

The general toxicology studies showed findings expected from at GLP-1RA, with regards to single, repeat dose and carcinogenicity studies. However, with regards to the reproductive studies in rats and rabbits, both species were more sensitive than expected, where abnormalities gave rise to NOAELs resulting in lower than MHRD exposure levels. Additional studies were performed in the cynomolgus monkey, where a few observed abnormalities as well as early embryofoetal loss in high and mid dose levels also gave rise to NOAEL at the low dose level, and less than MHRD exposure levels. These changes were observed in concordance with body weight loss in the maternal animals. Mechanistic studies showing that GLP-1R in the yolk sack of rats were important in the energy uptake in early embryonic phase, and may in part be the explanation for the observed abnormalities and embryo loss in rats. No such GLP-1R was detected in cynomolgus monkey yolk sack, and the yolk sack does develop into a yolk sack placenta in primates as it does in the rat. However, despite the effort made to determine whether the observed reproductive effects were caused by rodent specific mechanisms, it is not possible to exclude that the observed effects may be related to treatment with semaglutide. This is reflected in the SmPC sections 4.6 and 5.3, and WOCP is advised to use effective contraception, and cease with semaglutide treatment prior to planned pregnancy as well as during pregnancy and lactation.

2.3.7. Conclusion on non-clinical aspects

The pharmacology, safety pharmacology, pharmacokinetics and toxicology programs are considered sufficient. There are no major objections from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

The clinical development of semaglutide includes sixteen completed Phase 1 studies, one Phase 2 study, eight completed Phase 3 studies, and one ongoing trial (Table 1). Furthermore a population

pharmacokinetic and an exposure response analysis has been conducted, the Pop PK study used data from five Phase 3 studies (3623, 3626, 3624, 3744 and 4091). The dossier also includes nine *in vitro* studies using human samples or human cell material. These studies are summarised in Table 2.

Table 1 Clinical studies semaglutide

Study	Population	Objectives of the study	Test product(s); Semaglutide dose	Number of subjects in full analysis set
Phase 1				
1820	healthy	First in human, dose escalation safety, PK and PD	0.625, 1.25, 2.5, 5, 10, 20, 40 and 80 µg/kg; single s.c dose	56 (M: 56, F: 0)
3679	healthy	Equivalence -product strength	1.0 mg/mL, 3.0 mg/mL and 10.0 mg/mL; single s.c. dose of 0.8 mg	44 (M: 44, F: 0)
3687	healthy	Equivalence -product strength / Bioavailability	1.0 mg/mL, 3.0 mg/mL and 10.0 mg/mL; single s.c. dose of 1.0 mg single i.v. dose of 0.25 mg	42 (M: 25, F: 17)
4010	healthy	Bioequivalence two manufacturing processes	Single s.c. 0.5 mg dose(1.34 mg/mL)	28 (M: 12, F: 16)
3633	healthy Japanese and Caucasian	Multiple dose-Caucasian/Japanese dose escalation trial	Multiple s.c. 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 1.2mg dose	84 (M: 84, F: 0)
3634	healthy Japanese and Caucasian	PK/PD-Caucasian / Japanese	1.34 mg/mL; 0.5 and 1.0 mg, multiple s.c. doses	44 (M: 44, F: 0)
3789	healthy	ADME	Labelled 0.5 mg, single s.c. dose	7 (M: 7, F: 0)
3616	healthy, mild, moderate, severe, ESRD	Renal impairment	0.5 mg and 10 µg/kg, single s.c. dose	0.5 mg: 56 (M: 34, F: 22); 10 µg/kg: 6 (M: 5, F: 1)
3651	healthy, mild, moderate, severe	Hepatic impairment	1.34 mg/mL; 0.5 mg, single s.c. dose	44 (M: 21, F: 23)
3817	healthy	DDI metformin and warfarin	1.34 mg/mL; 1.0 mg, multiple s.c. doses. Warfarin 5 mg; single 25 mg oral dose. Metformin 500 mg; twice daily, multiple oral dose	23 (M: 13, F: 10)
3818	healthy	DDI atorvastatin and digoxin	1.34 mg/mL; 1.0 mg, multiple s.c. doses. Atorvastatin 40 mg; single oral dose. Digoxin 0.25 mg; 0.5 mg single oral dose	31 (M: 15, F: 16)
3819	T2D	DDI oral contraceptives	1.0 mg, multiple s.c. doses; Microgynon (EE 0.03 mg/LNG 0.15 mg)	43 (M: 0, F: 43)
3652	healthy	QTc	1.34 mg/mL; 1.5 mg, multiple s.c. doses. Moxifloxacin 400 mg; single oral dose	166 (M: 99, F: 67)
3685	obese	Energy intake, appetite sensations, postprandial glucose and triglyceride metabolism, and gastric emptying	1.34 mg/mL; 1.0 mg, multiple s.c. doses	30 (M: 20, F: 10)
3635	T2D and healthy	Effects on β cell function	1.34 mg/mL; 1.0 mg, multiple s.c. doses	87 (M: 59, F: 28)
3684	T2D	Hypoglycaemia counter-regulation	1.34 mg/mL; 1.0 mg, multiple s.c. doses	37 (M: 25, F: 12)
Phase 2				
1821	T2D	Dose finding + effect gastric emptying (paracetamol)	(1.0 mg/mL and 10 mg/mL); 0.1, 0.2, 0.4, 0.8 and 1.6 mg once-weekly; s.c. doses	411 (M: 267, F: 144)

Study	Population	Objectives of the study	Test product(s); Semaglutide dose	Number of subjects in full analysis set
Phase 3				
3623	T2D drug-naïve	Efficacy and safety (vs placebo (SUSTAIN 1))	1.34 mg/mL or semaglutide-placebo solution; 0.5 and 1.0 mg once-weekly; s.c. doses	387 (M: 210, F: 177)
3626	T2D (on treatment with metformin and/or TZDs)	Efficacy and safety (vs sitagliptin (SUSTAIN 2))	1.34 mg/mL solution; 0.5 and 1.0 mg once weekly, s.c. doses. Sitagliptin, 100 mg once daily, oral doses	1225 (M: 620, F: 605)
3624	T2D (on treatment with 1-2 OADs)	Efficacy and safety (vs exenatide ER (SUSTAIN 3))	1.34 mg/mL solution; 1.0 mg once-weekly; s.c. doses. Exenatide ER; 2.0 mg once-weekly; s.c. doses	809 (M: 447, F: 362)
3625	T2D, (insulin-naïve, on treatment with metformin with or without SUs)	Efficacy and safety (vs insulin glargine (SUSTAIN 4))	1.34 mg/mL solution; 0.5 and 1.0 mg once-weekly; s.c. doses. Insulin glargine 100 IU/mL; initial dose of 10 IU, then treat-to-target once-daily; s.c. doses	1082 (M: 574, F: 508)
3627	T2D (on treatment with basal insulin with or without metformin)	Efficacy and safety (vs placebo (insulin)(SUSTAIN 5))	1.34 mg/mL or semaglutide-placebo solution; 0.5 and 1.0 mg once-weekly; s.c. doses	396 (M: 222, F: 174)
4092	T2D	Efficacy and safety (vs sitagliptin)	1.34 mg/mL solution; 0.5 and 1.0 mg once-weekly; s.c. doses. Sitagliptin, 100 mg once daily, oral doses	308 (M: 235, F: 73)
4091	T2D (on treatment with 1 OAD [SU, glinide, α-GI or TZD])	Efficacy and safety (vs OAD)	1.34 mg/mL solution; 0.5 and 1.0 mg once-weekly; s.c. administration. One OAD (SU, glinide, α-GI or TZD); dosing and administration as appropriate	600 (M: 429, F: 171)
3744	T2D (on treatment with 1-2 OADs or with insulin [basal, long-acting or premixed] with or without 1-2 OADs, or T2D drug-naïve)	Safety (vs placebo, CVOT (SUSTAIN 6))	1.34 mg/mL or semaglutide-placebo solution; 0.5 and 1.0 mg once-weekly; s.c. doses	3297 (M: 2002, F: 1295)

Table 2 *in vitro* studies using human biomaterial

Study	Objectives of the study
213363	[3H]Oct semaglutide: Metabolite profiling of human plasma
213363	[3H]Oct semaglutide: Metabolite profiling of human urine and faeces
214379	Metabolite identification in human plasma and urine
206642	Hepatocytes from: wistar rat, cynomolgus monkey and human
214064	[3H]Oct semaglutide: Metabolism in hepatocytes
215514	Metabolite Identification following incubations with NEP human
215048	CYP inhibition *in vitro* Human hepatocytes
214196	CYP induction *in vitro* Human hepatocytes
215026	Transporter inhibition *in vitro* Human hepatocytes

2.4.2. Pharmacokinetics

2.4.2.1. Methodology

Two different types of validated assays were used to measure total semaglutide plasma concentrations. In the early clinical development (studies 1820, 1821, 3633 and 3679), semaglutide in plasma was analysed using a luminescent oxygen channelling immunoassay (LOCI assay). Later in the clinical development, the assay was changed to LC-MS/MS assay as it was found that measurements with the LOCI assay were influenced by a matrix effect. Considerably higher and less variable semaglutide concentrations were measured with LC-MS/MS compared to LOCI method. For the analysis of semaglutide in urine an appropriately validated LC-MS/MS bioanalytical method has been used.

The multi-tiered approach has been used to assess the anti-semaglutide and neutralizing antibodies. In general, the assay validation was adequately performed. The employed four-tiered strategy including a screening, confirmatory, cross reactivity to endogenous glucagon-like peptide-1 (GLP-1) and neutralization assay is in agreement with the draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev. 1).

The plasma concentration-time data for semaglutide were analysed by non-compartmental methods and standard pharmacokinetic parameters have been calculated. Descriptive statistics of PK variables and power calculations have been provided for all PK/PD studies. In general, the pharmacokinetic endpoints were analysed and compared between treatments using linear normal models (ANCOVA) with the log-transformed endpoint as the dependent variable. Fixed and random factors were taken into account as independent variables. The software used to calculate and compare the pharmacokinetic parameters in the clinical trials was Kinetica or SAS release 9 or higher on a UNIX platform.

The applicant used a population pharmacokinetic model and several exposure-response analyses to investigate to what extent exposure of semaglutide is impacted by covariates, what the characteristics are of the exposure-response relationships for efficacy and safety and if the recommended dose is supported by these analyses. The influence of the covariates sex, age group, race, ethnicity, body weight, renal function, maintenance dose level and injection site have been evaluated in the population PK analysis. Exposure vs time since first dose and effects of antibody status on semaglutide exposure were evaluated graphically.

The population PK analysis was based on data from five phase 3a trials; 3623, 3626, 3624, 3744 and 4091. Maintenance doses of 0.5 and 1.0 mg semaglutide were investigated in all trials, except in trial 3624 where only the 1.0 mg dose was investigated. A one-compartment model with first-order absorption and elimination was used to describe the PK of semaglutide. k_a (fixed), CL/F and V/F were the parameters used in the structural model. The semaglutide absorption rate constant (k_a) was set to a value of 0.0286 h-1 obtained from a PK model based on full PK profiles from clinical pharmacology trials in normoglycaemic and T2D subjects (reported in responses to D120 questions). The assumption that k_a can be fixed without affecting the conclusions of the analysis, was verified by the applicant using a sensitivity analysis. The model was estimated on un-transformed concentration values and a proportional error model was used to describe the residual variability. Models were estimated using first order conditional estimation with interaction (FOCE+I).

The exposure–response analysis was conducted using four of the above trials (3623, 3626, 3624, and 4091) and thus excluding the cardiovascular outcome trial (3744). The exposure-response analysis was visualised by plotting the median semaglutide concentration (C_{avg}) versus the response by

presenting the mean and 95% CI of the response. Exposure estimates for the analysis were obtained from the full population PK model. The following PD parameters were plotted vs exposure as response measure: HbA1c change from baseline Responder analysis for HbA1c, Body weight change from baseline, pulse weight change from baseline, Calcitonin response, and Gastrointestinal adverse events (GIAEs).

2.4.2.2. Pharmacokinetics of semaglutide

The PK of semaglutide has been investigated in Japanese and Caucasian healthy subjects, in obese subjects and patients with T2 diabetes using single-dose studies, in repeat-dose studies; in subjects with renal and hepatic impairment and DDI studies with atorvastatin, digoxin, warfarin, metformin and oral contraceptives.

Semaglutide is a human GLP-1 analogue with a pharmacokinetic profile suitable for once weekly (OW) subcutaneous (s.c.) administration.

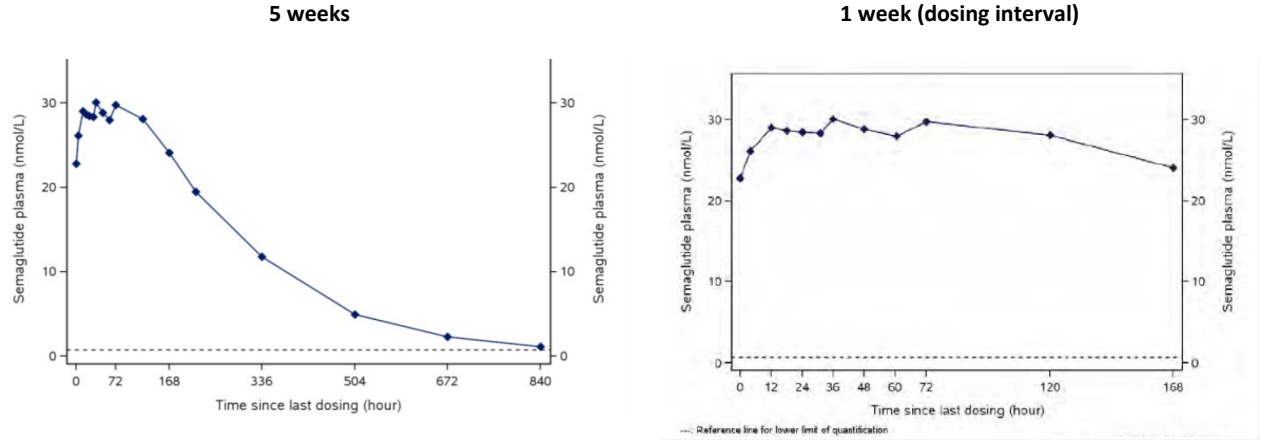
Compared to human native GLP-1, the semaglutide molecule has three minor but important modifications which make it suitable for once weekly use (Figure 1). These modifications mediate strong binding to albumin thereby reducing renal clearance and making semaglutide less susceptible to degradation by DPP-4. Furthermore, slow absorption from the subcutis also contributes to the prolonged exposure characteristics.

Absorption

In the submitted studies it is shown that absorption of semaglutide after subcutaneous injection is slow and Tmax is reached between 24-36 hours post dosing. The slow absorption from the subcutaneous compartment to the systemic circulation is clearly attributing to the prolonged exposure to semaglutide. The absolute bioavailability was estimated to be 89% after abdominal SC administration (study 3687). After a single dose of semaglutide S.C. the systemic concentrations were maintained at the same level for about 7 days. Steady state concentrations were achieved after 4-5 weeks. Fluctuation between $C_{max\ ss}$ and $C_{through}$ was small.

Figure 1 presents a typical concentration-time profile after a 1.0 mg dose of semaglutide administered at steady state in patients with T2D.

Figure 1 Semaglutide concentration versus time profile following administration of 1.0 mg semaglutide at steady state in patients with T2D – trial 3635



Note: horizontal line represent lower limit of quantification. Number of patients= 37.

The differences between injection sites using the thigh or abdomen has been evaluated in studies **3652** and **3684** using steady-state concentrations. This analysis showed similar steady state C_{max} concentrations for the two injection sites. Furthermore the applicant evaluated the differences between injection sites on the pharmacokinetics of semaglutide using population PK methods which show that injection site does not affect average exposure (Cavg). The Cavg of upper arm vs abdomen is 0.93 [0.90-0.96]90%CI and Cavg of thigh vs abdomen is 0.97 [0.93-1.00]90%CI. The number of subjects per injection site is: thigh (n=86), upper arm (n=71) and abdominal skin (n=1454).

Distribution

The apparent volume of distribution following s.c. administration of semaglutide was approximately 12-13 L (Studies 3635, 3684, 3819) and similar (when accounting for differences in BMI) between subjects with T2D and healthy subjects. This volume is small and close to the blood volume, indicating that a high fraction of semaglutide is circulating in the blood. The *in vitro* protein binding, mainly to albumin, was above 99% in human plasma. The unbound fraction was 0.19% and 0.36% in human samples of healthy volunteers (*in vitro* studies 208380 en 213228). The high protein binding prevents semaglutide from being rapidly eliminated from the circulation. Semaglutide passes the placental barrier, blood-brain barrier and is secreted in breast milk, see preclinical section.

Elimination

The cumulative recovery of total radioactivity was 75% of the administered dose; hereof 53.0% in urine, 18.6% in faeces and 3.2% in expired air. In urine unchanged semaglutide accounted for 3.1% of the administered dose (Study 3789). Mean CL/F was approximately 0.05 L/h in patients with T2D as compared to about 0.035 L/h in healthy subjects. This difference is largely attributable to differences in BMI. Mean t½ was approximately 155 hours (149 to 165 hours) in subjects with T2D and comparable to that in healthy volunteers. Semaglutide is metabolized by proteolytic degradation of the peptide backbone and beta-oxidation of the fatty acid side-chain. Semaglutide is extensively metabolised into many different metabolites. Its most abundant metabolites were P3 that was detected in plasma and U6 and U7 that were detected in urine (study 214379). Semaglutide is almost completely metabolised and degraded into peptides, amino acids and fatty acid fragments. All metabolites accounted for less than 10% of the total amount of semaglutide related material and are not expected to have any activity. One semaglutide isomer (P3C) has been identified and although it is considered likely that it has some activity it is not expected to be of clinical relevance as its concentration is low (<7.7%).

Because endogenous GLP-1 is metabolised by DPP-IV and NEP, these enzymes are expected to be involved in the metabolism of the structurally related semaglutide. This is confirmed for NEP, which was identified as one of the active metabolic enzymes (*in vitro* study 215514). The pharmacokinetics data do not indicate any influence of polymorphisms of NEP on the pharmacokinetics of semaglutide. The effects are therefore expected unlikely or minor. The applicant has demonstrated in vitro (data on file) that semaglutide was less sensitive to DPP-IV degradation than the endogenous GLP. Therefore DPP-IV degradation is not expected to be a major pathway and genetic polymorphisms of DPP-IV are expected to be negligible.

Dose proportionality

Dose proportionality of semaglutide has been investigated in study **3652**. Based on the results of this study it can be concluded that Semaglutide steady state exposure (AUC_{0-168h}, AUC_{0-48h} and C_{max}) increased approximately proportionally with semaglutide dose, at doses of 0.25 mg, 0.5 mg, 1.0 mg and 1.5 mg dose levels (estimated doubling constants of 2.01 [1.99; 2.04] 95% CI and 2.00 [1.97;

2.03]95% CI, respectively). The company also investigated dose proportionality in early study **1820**. The results of this study are in line with results of study 3652 but cannot be directly compared to other studies as the LOCI assay has been used.

Time dependency

Semaglutide steady state exposure is stable over time. Accumulation ratios of approximately 2 were calculated for Japanese subjects and approximately 2.3 for Caucasian subjects (study **3634**).

Variability

Within- and between subject variability in PK in healthy volunteers was low (within-subject variability: 5–10%, between-subject variability: 17-24%) at after single dose administration (study **4010**) and at state (study **3652**). For subjects with T2D, within- and between subject was evaluated in the population PK analysis and was estimated to be **13%** and **27%** respectively. According to the applicant, 75.8% of the variability was explained by the covariates, this conclusion is not supported (see Discussion on clinical pharmacology).

Different formulations

During the development programme the manufacturing process and the drug product strength varied. The semaglutide product used in all phase 3a trials and the majority of phase 1 and 2 trials is the same as the intended product to be marketed. The manufacturing process of semaglutide was changed between phase 2 and phase 3a, for which bioequivalence was appropriately demonstrated in trial **4010**.

The concentration of the to- be- marketed product is 1.34 mg/mL and this product has been used for the majority of the clinical trials, including the pivotal phase 3a trials. To bridge between all four strengths used in the clinical development programme, equivalence between the product strengths (1 mg/mL, 3 mg/mL and 10 mg/mL) were tested in studies **3679** and **3687**. The 1 mg/mL and 3 mg/mL formulations were bioequivalent with respect to AUC and C_{max}. Therefore is the data generated with 1 mg/mL and 3 mg/mL formulations also represent the to-be marketed 1.34 mg/mL formulation. Equivalence between the 10 mg/mL product strength versus 1 mg/mL and 3 mg/mL, respectively, was shown for overall exposure (AUC), but not for C_{max} and also t_{max} differed.

2.4.2.3. Pharmacokinetics in the target population

Steady state PK properties for semaglutide 1.0 mg in subjects with T2D were consistent across trials the mean AUC_{0-168h} was approximately 4700 nmol·h/L (mean range: 4602 to 4811 nmol·h/L) corresponding to an average concentration (AUC_{0-168h}/168h) of 28 nmol/L. Mean C_{max} was approximately 33 nmol/L (mean range: 32.2 to 33.8 nmol/L) and median t_{max} was 36 to 60 hours. The observed range (min–max) for t_{max} was broad as a result of the relatively flat plasma concentration profiles.

In the population PK study similar levels were observed. In patients with T2D, the mean steady state concentrations following s.c. administration of 0.5 mg and 1.0 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively.

In the target T2D population, estimated steady-state volume of distribution of semaglutide is about 12L compared to about 8L in healthy volunteers. Clearance in subjects with T2D is higher in the target population. Mean CL/F was approximately 0.05 L/h compared to about 0.035 L/h in healthy subjects.

Mean $t_{½}$ was around 155 hours (149 to 165 hours) in subjects with T2D and comparable to that in healthy volunteers.

2.4.2.4. Special Populations

Special population trials were performed in subjects with renal or hepatic impairment (studies **3616** and **3651**) and the influence of race has been evaluated in studies (**3633** and **3634**). In these studies the PK and PD of Japanese subjects has been characterised and compared with Caucasian subjects. The influence of other covariates (body weight, sex, age, race, etc.) has been evaluated using a population PK analysis approach as mentioned in 3.3.1.1.

The pharmacokinetics of semaglutide was comparable between subjects with a normal renal function and patients with various degrees of impaired renal function, categorised based on creatinine clearance estimated by the Cockcroft & Gault formula (mild, moderate, severe and end-stage renal disease). In patients with ESRD the exposure appeared to be lower, however after adjustment for differences in age, sex and body weight the exposure was comparable. Also, no major effect was observed in the population PK analysis.

The hepatic impairment study has shown that the total exposure of semaglutide and its c_{max} is comparable between subjects mild, moderate, and severe hepatic impairment (all with a diagnosis of cirrhosis and classified as Child-Pugh A,B, or C) to healthy matched controls. The fraction unbound of semaglutide was less than 0.5% for all subjects, but appeared to increase with increasing degree of hepatic impairment. As exposure and half-life were unchanged, hepatic impairment is not expected to change the efficacy.

The steady state PK properties of semaglutide 0.5 mg and 1.0 mg were comparable between healthy Japanese and Caucasian subjects.

The effect of body weight on the pharmacokinetics of semaglutide was investigated in the population PK analysis. The population PK analysis showed that exposure of semaglutide was inversely correlated to body weight (Figure 2 while none of the other covariates seemed to affect the semaglutide pharmacokinetics (Figure 3).

Figure 2 Semaglutide exposure versus body weight shown by sex.

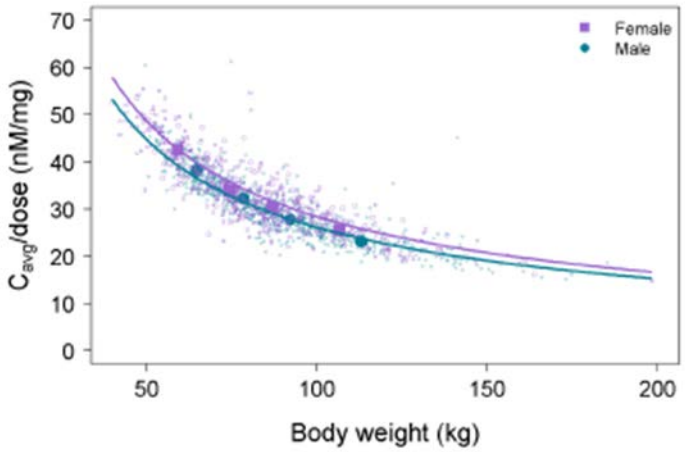
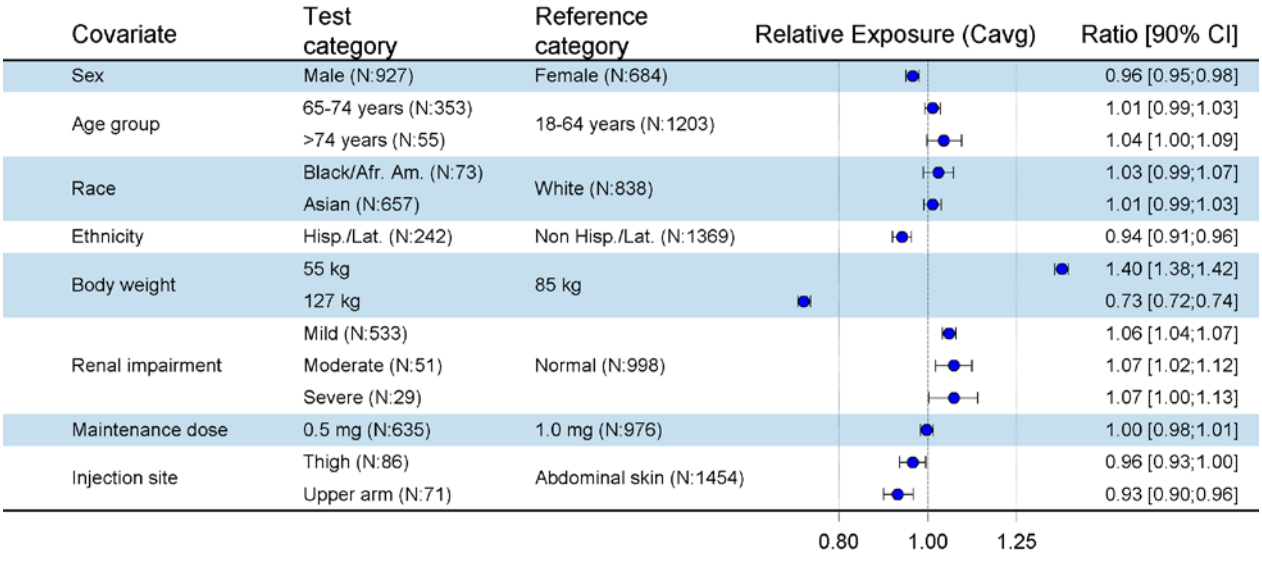


Figure 3 Effect of covariates on exposure.



2.4.2.5. Interactions

Little or no change in enzyme activity or on the mRNA levels of CYP1A2, CYP2B6, and CYP3A4/5 were observed. No direct or time/metabolism-dependent inhibition of semaglutide on the clinically relevant cytochrome P450 enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 was observed. These *in vitro* drug-drug interaction studies suggest that semaglutide has a very low potential to inhibit or induce CYP enzymes.

No inhibition was observed of the efflux P-gP and BCRP, nor of the uptake OAT1, OAT3 and OCT2 transporters. Partial inhibition of the OATP1B1 and OATP1B3 transporters was observed, with IC50 values of 3500 and 2950 nmol/L, respectively.

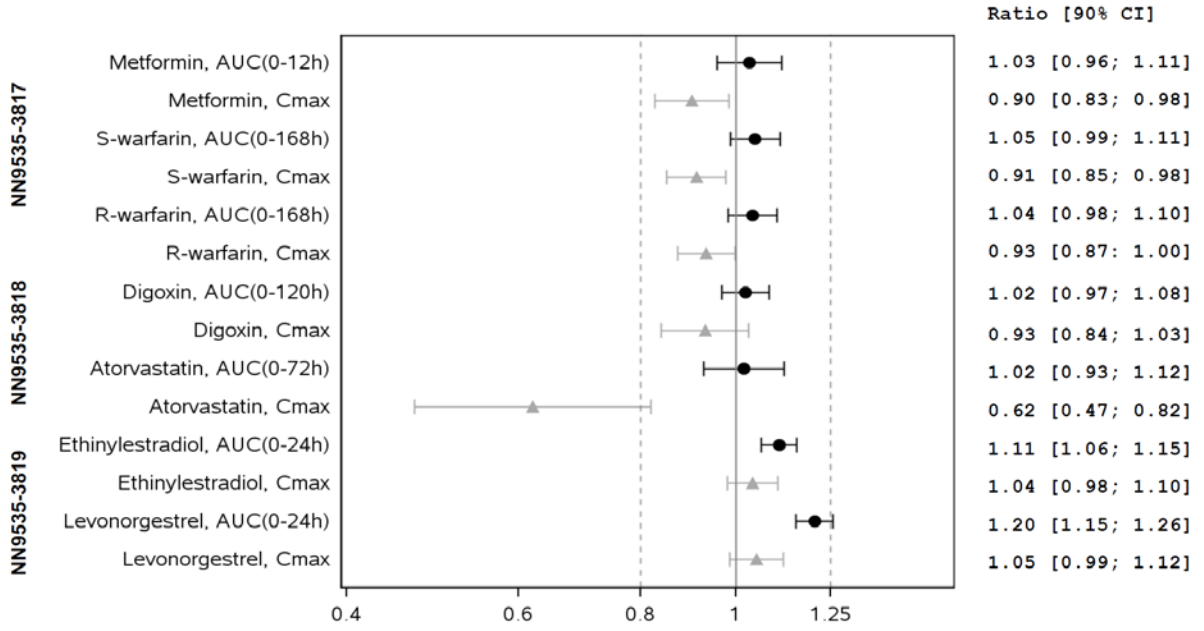
Furthermore, although semaglutide is strongly bound to plasma albumin the therapeutic plasma concentrations following semaglutide dosing is very low compared to that of albumin and it is considered unlikely that semaglutide will alter the protein binding of other drugs.

In study **1821** a delay in gastric emptying has been observed with semaglutide. The rates of gastric emptying have been assessed by paracetamol pharmacokinetics. The pharmacokinetics of paracetamol ($AUC_{0\text{-}60min}$ and C_{max}) was affected by concomitant use of Semaglutide at the 0.2-1.6mg dose levels and apparently this effect is dose dependent. The total paracetamol exposure $AUC_{0\text{-}240min}$ (within the 4-hour duration of the meal) was not affected (see Gastric emptying).

Three separate drug-drug interaction studies (3817, 3818, 3819) were performed to estimate the influence of delayed gastric emptying by semaglutide on metformin, warfarin, digoxin, atorvastatin and oral contraceptive combination therapy of ethinylestradiol and levonorgestrel. These drugs represent drugs that are commonly co-prescribed in patients with T2D and represent different properties with respect to solubility and permeability (different BCS classes) and therapeutic windows.

The results of these DDI studies are summarised in Figure 4. A lower C_{max} was observed for atorvastatin when co-administered with semaglutide but its overall exposure (AUC) has not been affected. The other investigated medication was not affected by concomitantly administered drugs. It was noted that the t_{max} was more variable and tended to be delayed for most medication.

Figure 4 Impact of semaglutide on the pharmacokinetics of co-administered oral medications - trials 3817, 3818, 3819



Note: Ratio is ETR (with/without semaglutide). Metformin, ethinylestradiol and levonorgestrel were assessed at steady state. Warfarin, digoxin and atorvastatin were assessed after a single dose. Pre-specified limit of 90% CI [0.8; 1.25].

INR was measured over a 168-hour period after a single dose of warfarin with and without semaglutide. An increase in INR indicates a prolonged blood clotting time. The average increase of clotting time after warfarin dosing during the two conditions were similar; the estimated treatment ratio (with/without semaglutide) for $iAUC_{INR,\ 0-168h}$ and INR_{max} were 1.05 $[0.87; 1.28]_{90\%\ CI}$ and 1.04 $[0.99; 1.10]_{90\%\ CI,}$ respectively.

2.4.3. Pharmacodynamics

To investigate the effect of semaglutide on PD properties related to glycaemic control and weight loss, a number of PD parameters were evaluated at steady state after 12 weeks in the clinical pharmacology programme.

Pharmacodynamic properties in relation to glucose metabolism

The primary mode of action responsible for the effects of the GLP-1 RAs on glycaemic control is increased insulin secretion and decreased glucagon secretion from the pancreatic islets during elevated glucose levels. Thus, several PD parameters assessing different aspect of islets function (mainly the β-cell) and responsiveness have been included as PD endpoints.

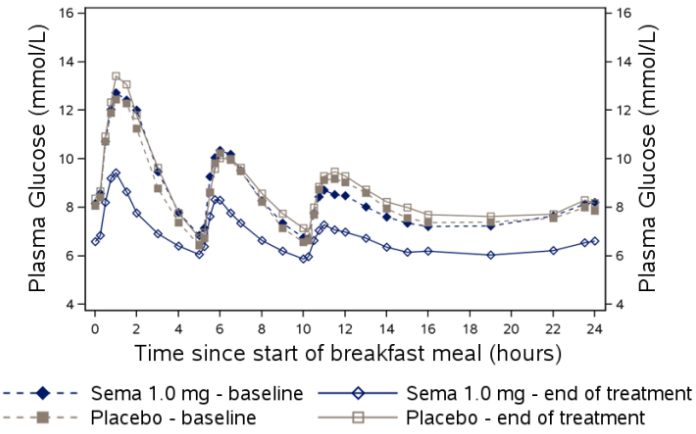
Fasting and postprandial plasma glucose responses

Semaglutide improves glycaemic control in patients with T2D by lowering fasting and postprandial glucose concentrations (Figure 5). The lowering of fasting plasma glucose (FPG) with semaglutide was evident already after the first dose for doses of 0.2 mg or higher (trial 1821).

Semaglutide lowered fasting glucose concentrations by 22% after 12 weeks of semaglutide treatment, the overall 24-hour glucose response (AUC_{0-24h}) by 22% and the absolute postprandial responses ($AUC_{0-5\ h}$ after each meal) by 20–29% compared with placebo assessed with three standardised meals (breakfast, lunch and protein-rich dinner) (trial 3635).

The mean postprandial increments in glucose were lowered by 0.6–1.1 mmol/L (11-20 mg/dL) with semaglutide compared with placebo. In addition, semaglutide lowered the 2-hour postprandial glucose concentration after the breakfast meal by 37% as compared to placebo; the decrease was 4.1 mmol/L (74 mg/dL) in semaglutide-treated patients. The reduced gastric emptying during the early postprandial phase contributed to a lower postprandial increase in glucose in patients treated with semaglutide as compared with placebo.

Figure 5 24-hour glucose profiles at baseline and steady state in patients with T2D - trial 3635



Note: Plasma glucose profiles after standardised meals at baseline and at steady state after 12 weeks of treatment with semaglutide 1.0 mg (N: 37) or placebo (N: 37).
Abbreviations: N: number of patients; sema: semaglutide; T2D: type 2 diabetes mellitus.

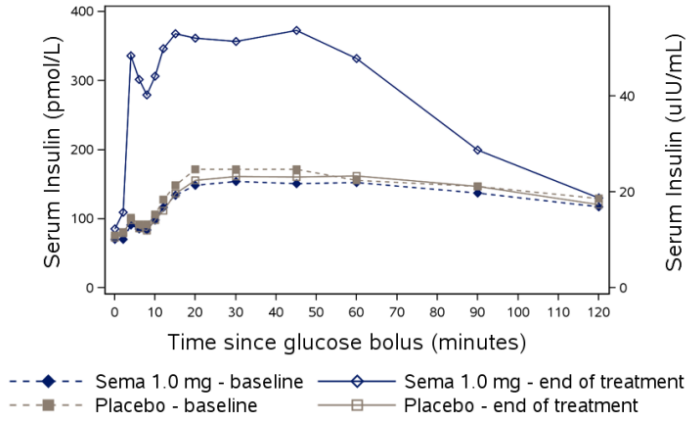
β-cell function and responsiveness

First and second phase insulin secretion

In patients with T2D, defects in insulin secretion occur at an early stage during development of the disease, and a decline in first phase insulin secretion is among the first observations. The influence of semaglutide on first and second phase insulin secretion was therefore investigated following an intravenous bolus of glucose (IVGTT) in patients with T2D (trial 3635).

First- and second-phase insulin concentration and insulin secretion rate increased approximate 3-fold and 2-fold with semaglutide as compared to placebo (Figure 6).

Figure 6 First phase (0-10 min) and second phase (10-120 min) insulin response in patients with T2D – trial 3635



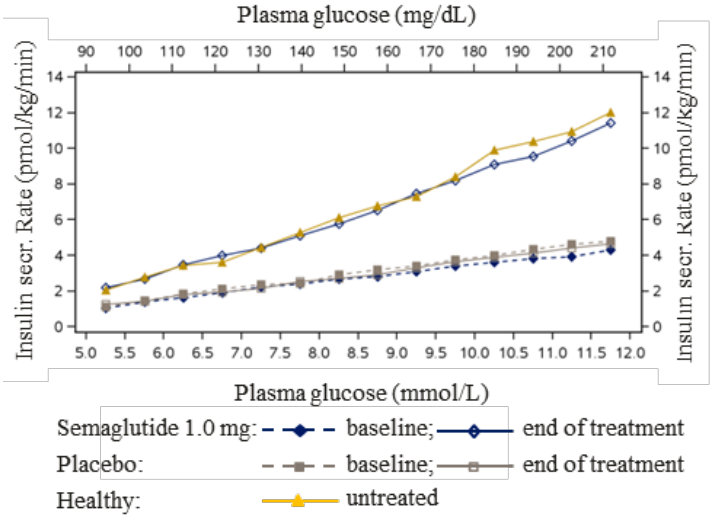
Note: IVGTT at baseline and at steady state after 12 weeks of treatment with semaglutide 1.0 mg (N: 37) or placebo (N:38).
Abbreviations: IVGTT: Intravenous glucose tolerance test; N: number of patients; sema: semaglutide; T2D: type 2 diabetes mellitus.

Glucose dependent insulin secretory response

Native GLP-1 is known to stimulate insulin secretion in a glucose-dependent manner, and this ability was investigated for semaglutide in a graded glucose infusion test during a gradual increase of glucose from normoglycaemia to hyperglycaemia in patients with T2D (trial 3635). Healthy untreated subjects were included as a comparator group.

The insulin concentration and insulin secretion rate (ISR) corresponding to the glucose increase from 5 to 12 mmol/L (90−216 mg/dL), was ~ 2.5 fold higher with semaglutide than with placebo in patients with T2D (Figure 7). With semaglutide, the insulin concentration and the ISR in patients with T2D was comparable to that of untreated healthy subjects. The increasingly larger insulin secretion with increasing glucose concentrations demonstrates that semaglutide improved the insulin secretory response to elevated glucose levels in a glucose-dependent manner.

Figure 7 Insulin secretion rate during graded glucose infusion test in patients with T2D and in healthy subjects – trial 3635



Maximum β-cell secretory capacity

An arginine stimulation test was performed to assess maximum β-cell secretory capacity on a basis of induced hyperglycaemic conditions. Semaglutide-treated patients had an approximate 4-fold larger increase in insulin secretion than placebo treated patients (trial 3635).

Fasting insulin and C-peptide levels

As expected of an incretin, fasting insulin and C-peptide increased 30% and 23%, respectively after 12 weeks treatment with semaglutide in patients with T2D, as compared with placebo (trial 3635).

HOMA-IR and HOMA-B

The data in the phase 3 trials show improvements in both HOMA-B and HOMA-IR. In the PD trial (3635), there was no apparent improvement in HOMA IR that may be explained by a generally better controlled diabetes (lower HbA1c, lower BMI) in line with the inclusion criteria of this PD trial and may thus have reduced the improvability of insulin resistance in these subjects.

Glucagon

T2D is associated with inappropriately high glucagon secretion both at fasting and at postprandial conditions, contributing to high hepatic glucose output. GLP-1 RAs induce glucose-dependent lowering of glucagon secretion, which in turn lowers the hepatic glucose output. The ability of semaglutide to decrease glucagon secretion was investigated in patients with T2D during various glucose metabolism tests. Semaglutide treatment resulted in relative reductions compared to placebo in fasting glucagon of 8-21%, postprandial glucagon response of 14-15% and mean 24-hour glucagon concentration of 12% (trials 3684 and 3635).

In the graded glucose infusion test, a glucose-dependent decrease in glucagon levels was observed with increasing glucose concentrations both with semaglutide and placebo, however, the glucagon

decrease was more pronounced with semaglutide, further supporting the glucose-dependent responses of both insulin and glucagon (trial 3635).

Counter-regulatory response to hypoglycaemia

During induced hypoglycaemia, semaglutide did not alter the counter regulatory responses of increased glucagon, and did not impair the plasma glucose dependent decrease in C-peptide concentrations in patients with T2D as compared to placebo (trial 3684).

There was a lower increase in concentrations of noradrenaline and cortisol for patients when treated with semaglutide compared with placebo. A decreased recognition of hypoglycaemia was also observed.

Gastric emptying

GLP-1 inhibits gastric emptying, causing a reduction in postprandial plasma glucose excursions. While decreased gastric emptying is an important physiological effect of native GLP-1, and short-acting GLP-1R agonists like exenatide and lixisenatide, decreased gastric emptying is less pronounced for long-acting GLP-1R agonist like liraglutide, dulaglutide, albiglutide and semaglutide. The effect of steady state semaglutide on gastric emptying was assessed after 12 weeks of treatment during standardised meal settings in subjects with obesity (trial 3685) and in patients with T2D (trial 1821).

Semaglutide reduced gastric emptying in subjects with obesity during the first hour after a meal (AUC of paracetamol reduced by 27%), and consistent reductions in early gastric emptying were seen in patients with T2D. The gastric emptying over the full postprandial period was not reduced, or slightly reduced for semaglutide doses of 0.2–1.6 mg (range for treatment ratios 0.87–0.96) when assessed in subjects with obesity and patients with T2D. The reduced gastric emptying during the early postprandial phase reduces the rate at which glucose appears in the circulation post-prandially, and may have contributed to the observed reductions in postprandial glucose. No effects of delayed gastric emptying on the PK properties of co-administered drugs were evident.

Pharmacodynamic properties in relation to weight loss

The GLP-1 receptor is expressed in the human brain in areas involved in satiety and appetite regulation, and changes in plasma GLP-1 concentrations increase the brain activity in these areas. GLP-1 has been shown to induce decreased hunger, increased satiety and a lower energy intake and thereby weight loss in humans. In animal studies, semaglutide is taken up in specific brain regions and increases key satiety and decreases key hunger signals. Using isolated brain tissue sections, semaglutide has been shown to activate satiety related neurons and inhibit hunger related neurons.

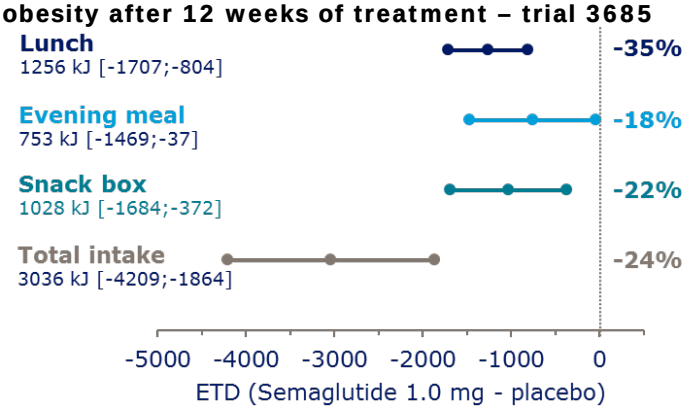
Body weight and composition

Change in body weight from baseline to end of treatment was assessed in all clinical pharmacology trials. A reduction in body weight with semaglutide was observed across trials and populations (T2D and obesity), with a mean weight loss of 4–5 kg in 12 weeks, compared with a neutral effect on body weight with placebo. The effect of semaglutide on body composition was investigated in subjects with obesity using air displacement plethysmography (trial 3685) showing that the body weight loss with semaglutide was predominantly from fat tissue with loss of fat mass being 3-fold larger than loss of lean mass.

Appetite, energy intake and energy expenditure

Semaglutide reduced appetite, improved control of eating, reduced food cravings and reduced preference for high fat foods, as compared to placebo in a dedicated trial (trial 3685) in subjects with obesity. This translated into a substantial lower energy intake with semaglutide. The energy intake of 3 consecutive *ad libitum* meals was 18-35% lower with semaglutide than with placebo (Figure 8). Across meals on the test day, this corresponds to a reduction in energy intake of more than 3000 kJ (appr. 700 kcal) with semaglutide, corresponding to 24% lower *ad libitum* energy intake as compared to placebo. Based on ratings of nausea and palatability, there were no indications of food aversion or nausea during the meals being responsible for this markedly reduced food and energy intake.

Figure 8 Effect of semaglutide on energy intake during *ad libitum* meals in subjects with obesity after 12 weeks of treatment – trial 3685



Note: Figure shows ETD and corresponding 95% CI.
Abbreviations: CI: confidence interval; ETD: estimated treatment difference.

Semaglutide reduced energy expenditure as assessed by resting metabolic rate (RMR) using indirect calorimetry/ventilated hood system by appr. 600 kJ per day. The underlying mechanism is not fully elucidated. A minor part of the difference could be explained by the observed difference in body lean mass between treatments. No effect of semaglutide on respiratory quotient (RQ) was shown, indicating no difference in oxidation of macronutrients following semaglutide treatment.

The semaglutide-induced weight loss due to the reduced energy intake was primarily mediated through less appetite, however, other mechanisms including improvements in the control of eating, fewer food cravings and a lower relative preference for fatty, energy-dense foods may also have contributed to the reduced energy intake.

Lipids

The effect of semaglutide on lipid metabolism was assessed prior to (fasting) and up to 8 hours postprandially during a standardised fat-rich breakfast meal in subjects with obesity (trial 3685). These results suggest an improvement in lipid metabolism.

Cardiac repolarisation by QT interval evaluation

The potential effects of semaglutide on QTc interval and cardiac repolarisation were tested in a dedicated thorough QTc trial, designed and conducted in accordance with recommendations in

guidelines including supra-therapeutic dose levels of semaglutide up to 1.5 mg at steady state as agreed with the FDA.

During the 48-hour post-dose ECG recording at steady state of the supratherapeutic 1.5 mg semaglutide/placebo dose level, 11 time-matched QTcI measurements (QT interval individually corrected for heart rate) were performed (Table 3).

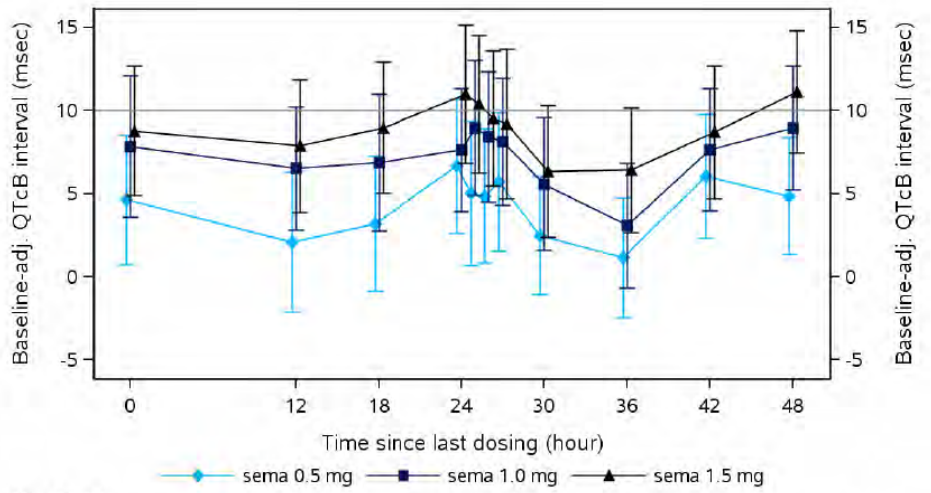
Table 3 QT interval individually corrected for heart rate

	Estimate	90% CI	p-value
Treatment difference, sema 1.5 mg - placebo			
0 hour	-3.16	[-6.62 ; 0.29]	<.0001
12 hours	-3.38	[-7.03 ; 0.26]	<.0001
18 hours	-5.15	[-8.84 ; -1.45]	<.0001
24 hours	-4.80	[-8.33 ; -1.28]	<.0001
25 hours	-4.26	[-7.75 ; -0.77]	<.0001
26 hours	-5.81	[-9.16 ; -2.45]	<.0001
27 hours	-5.29	[-8.75 ; -1.83]	<.0001
30 hours	-3.88	[-7.14 ; -0.63]	<.0001
36 hours	-5.89	[-9.50 ; -2.28]	<.0001
42 hours	-6.56	[-10.14 ; -2.98]	<.0001
48 hours	-5.13	[-8.27 ; -1.99]	<.0001

Note: The p-value is for the one-sided test of a mean difference greater than 10 msec.
Abbreviations: N: Number of subjects contributing to analysis, CI: Confidence interval

Evaluations were also made using QTcF, QTcB and QTcL corrections. No prolongation of QTcL and QTcF was observed at any of the three dose levels. For QTcB a prolongation was observed at all dose levels i.e. the upper limits of at least one of the 11 two-sided 90% CIs for the estimated mean treatment differences were above 10 ms (Figure 9). Bazett's correction may overcorrect the QT interval when the heart rate is elevated. Increased heart rate is a well-known class effect of GLP-1s as reproduced in this study (Figure 9) and hence QTcB is not appropriate for this analysis.

Figure 9 Baseline-adjusted QTcB interval analysis



Adj.: Adjusted
Means are from a linear mixed model for repeated measures, where all eleven time-matched sampling time points enter as dependent variables with treatment as fixed factor and baseline measurements as covariate. The treatment and covariate are nested within time points. An unstructured covariance matrix is applied.
Bars represent corresponding two-sided 90% CI.

Treatment with semaglutide was associated with an increase in heart rate and PR interval at all dose levels. The increase in pulse rate seemed dose dependant and varied over the day; the mean highest changes were:

- 0.5 mg: 8.48 bpm [6.87; 10.09]$_{90\% CI}$
- 1.0 mg: 9.66 bpm [8.04; 11.29]$_{90\% CI}$
- 1.5 mg: 11.10 bpm [9.58; 12.62]$_{90\% CI}$

The mean highest change in PR interval was apparently not dose dependant:

- 0.5 mg: 10.72 ms [6.25; 15.20]$_{90\% CI}$
- 1.0 mg: 9.22 ms [4.96; 13.47]$_{90\% CI}$
- 1.5 mg: 10.02 ms [6.15; 13.89]$_{90\% CI}$

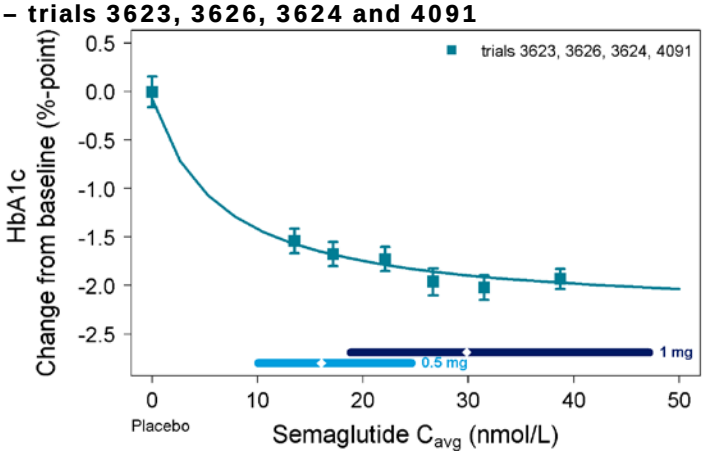
The effect of semaglutide on PR appears larger than with other GLP-1RAs. When assessed by office measurements, semaglutide seems to antagonize the beta-blocker-induced pulse rate reduction. As beta-blockers were not a randomised treatment in the CVOT, the implications hereof cannot be assessed. Extrapolation of the CV outcome results to subjects **without established CV disease** remains difficult. In these subjects the differences in office HR were larger than in the whole population.

Exposure-response analyses

Semaglutide 0.5 and 1.0 mg are the proposed maintenance doses for use in patients with T2D. The exposure-response analysis should be interpreted with caution, since no model evaluation for the development of the base population PK model and the exposure-response models has been provided by the applicant. The relationships were analysed using exposure-response models on data from four phase 3a trials (trials 3623, 3626, 3624 and 4091) using the average, model-derived semaglutide plasma concentration at maintenance dose level (C_{avg}) as the exposure variable (see 2.4.2.1.)

The change from baseline in HbA_{1c} was exposure-dependent. A consistent increase in effect was observed across the concentration range associated with 0.5 mg and 1.0 mg semaglutide (approximately 10–50 nmol/L) (Figure 10). Reductions in HbA_{1c} achieved with semaglutide in the lower end of the concentration range were substantial, and greater than those observed with placebo and comparators in the phase 3a clinical trials.

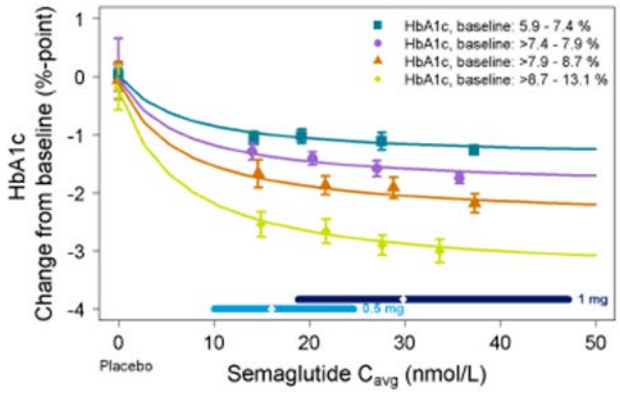
Figure 10 HbA1c change from baseline versus exposure of semaglutide in patients with T2D – trials 3623, 3626, 3624 and 4091



Notes: Data are mean HbA_{1c} values with 95% CI obtained after 30 weeks of treatment versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nM). Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges.

For exposures associated with semaglutide 0.5 and 1.0 mg, there was a clear exposure-response relationship with respect to change from baseline in HbA_{1c}, a relationship that was similar in males and females and across subgroups of body weight, age, race, ethnicity, diabetes duration and renal function. Thus, based on data from the population PK and exposure-response analyses, all patients should be dosed in accordance with the proposed dosing regimen for semaglutide. A small additional decrease of HbA1c was observed between when semaglutide 1.0 mg compared to 0.5 mg dose level. Both the 0.5 mg and 1.0 mg seem to reach the plateau of the Emax curve for HbA1c. In patients with a baseline HbA1c higher than 8.7% a clear additional effect of increasing dose to 1.0 mg can be observed.

Figure 11 HbA1c change from baseline after 30 weeks of treatment (mean and 95% CI in 6 quantiles + placebo) versus exposure of semaglutide for all subjects combined, stratified by baseline HbA1



The response versus semaglutide exposure shows that semaglutide effects level off at high concentrations, indicating that limited extra benefit would be achieved with semaglutide doses above 1.0 mg. The decrease in HbA_{1c} with exposure appeared larger with higher baseline HbA_{1c}. For patients with baseline HbA_{1c} in the lowest quantile (5.9–7.4%-points), the change in HbA_{1c} at high exposure was approximately 1%-points whereas at the highest baseline HbA_{1c} quantile (8.7–13.1%-points), the change was approximately 3%-points.

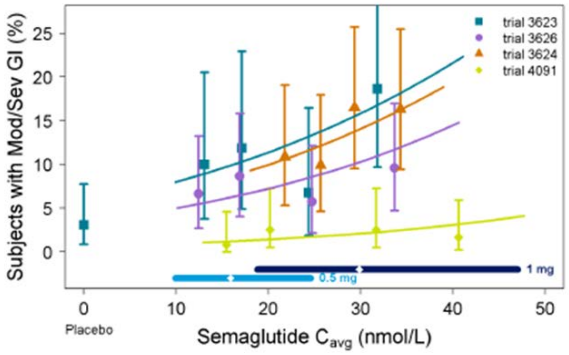
The proportion of patients reaching the ADA and AACE treatment targets of HbA_{1c} <7% and ≤6.5%, respectively, increased with increasing exposure. Overall, the glycaemic response as assessed by HbA_{1c} reduction and proportion of patients reaching HbA_{1c} targets increased with increasing semaglutide exposure within the concentration range obtained with 0.5 and 1.0 mg semaglutide. This also indicates that increasing the dose from 0.5 mg semaglutide to 1.0 mg semaglutide will provide improved glycaemic control.

Body weight loss increased with increasing exposure in a linear fashion in the investigated exposure range of approximately 10–50 nmol/L. The linear relationship between exposure and body weight change indicates that higher exposure may lead to larger weight loss (i.e., the effect did not reach a plateau).

The company also developed exposure response models to evaluate the safety of semaglutide. The exposure-response relationship for gastrointestinal adverse events (nausea, vomiting, diarrhoea and constipation) pulse rate and calcitonin concentration have been evaluated. A clear exposure response

relationship was observed for gastrointestinal adverse events. Pulse rate and calcitonin concentration showed no significant results.

Figure 12 Number of subjects with moderate or severe GIAEs per trial versus exposure at steady state.



The company evaluated the relationship between body weight and the safety and efficacy of semaglutide. The incidence of GI adverse effects (including nausea) was highest in the patient group with a body weight <70kg.However no difference between the semaglutide 0.5 and 1.0 mg dose level was observed. In other body weight categories an increased rate of GI AEs with semaglutide 1.0 mg versus semaglutide 0.5 mg was seen; the largest differences in rate of GI AEs between the two semaglutide dosing groups were not in the lowest body weight category (<70 kg) but in the second (70−90 kg) and third (90−110 kg) lowest body weight categories. The efficacy (HbA1c change from baseline response) appears to be similar across body weight subgroups with the same dose of semaglutide.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Methodology

During clinical development, it was discovered that the bioanalytical LOCI assay for the detection of semaglutide in plasma was influenced by a matrix effect. As a result of this the pharmacokinetic results the early studies 1820 1821, 3633 and 3679 in which the LOCI assay has been used, should be interpreted with caution and should not be directly compared to the results of the LC-MS/MS studies. As the essential studies 3634 (comparison PK/PD-Caucasian and Japanese subjects) and 3687 (Equivalence -product strength) were conducted to replace early studies (3633 and 3679), the differences between the analytical methods are no reason for concern.

The LC-MS/MS bioanalytical method is considered appropriately validated and suitable for the analysis of semaglutide. Also, the analytical methods that have been used in the interaction study with digoxin and the interaction study with the oral contraceptive LNG/EE comply with the bioanalytical guideline.

Appropriate pharmacokinetic parameters have been determined and standard statistical methods have been used in the submitted studies. The pharmacokinetic endpoints were analysed and compared between treatments using linear normal models (ANCOVA) with the log-transformed endpoint as the dependent variable. All statistical analyses were carried out using SAS (SAS Institute Inc. Cary, NC, USA). These statistical methods are acceptable.

The methods used in the development of the population PK model and exposure-response models have been described by the applicant. The analysis plan for the population PK and the different exposure-response models has been provided. However, no full model approach was used in the development of the model based on Phase III data. The results of the population PK and the exposure response analysis should therefore be interpreted with caution.

The structural population PK model was based on a one compartmental model including ka, CL/F and V/F, in which ka was fixed. The company fixed k_a due to the sparse sampling approach used in the phase III clinical trials. The k_a was fixed on a value based on early clinical pharmacology trials. Between-subject variability on k_a could only be determined using an additional model extension with a fixed variance for k_a. However, no details were presented by the company about the outcome of the model.

The applicant did not use a full modelling approach for the phase III data used in the development of the population PK model. The company adequately showed that including all pre-specified covariates did not significantly have any influence on the results of the population PK analysis. The included covariates (besides bodyweight) cannot explain between subject variability. Since the between-subject variability of semaglutide pharmacokinetics is relatively low in healthy volunteers and between subject variability on CL/F in the reduced model is relatively low in patients with T2D, the variability between patients is not expected to cause major differences in pharmacokinetics of semaglutide between patients.

The PD models used in the exposure-response analysis have been pre-specified. No details on the model development of these models has been provided by the applicant. Also, the modelling approach for the responder analysis for HbA1c and gastro-intestinal adverse events was not pre-specified. Therefore, the results of the PD models are interpreted with caution.

Pharmacokinetics of semaglutide

In general, the pharmacokinetics of semaglutide in patients with T2D are adequately characterised by the applicant during the clinical pharmacology programme. The maximum single dose tested in healthy subjects was 20 µg/kg body weight and the maximum tolerated single dose was 15 µg/kg body weight. The maximum multiple dose tested was 1.5 mg OW and in T2D patients, the maximum multiple dose tested was 1.6 mg OW.

The pharmacokinetic profile is suitable for once weekly subcutaneous administration due to the prolonged release characteristics (e.g. albumin binding, slow release from subcutis and reduced degradation by enzymes) of semaglutide.

The observed median t_{max} for semaglutide was 1–3 days (range 26–60 hours) and was similar across doses and populations. Based on the presented concentration time profiles be concluded that delayed absorption from the subcutis contributes to a prolonged half-life of semaglutide S.C. formulation. However, based on the fact that the mean t_{max} (38 hours) is relatively short compared to the MRT for s.c. semaglutide (230hours) it can be concluded that long t1/2 of semaglutide is driven mainly by systemic elimination (data from study 3687). This supports the claimed mechanisms of prolonged exposure.

Because endogenous GLP-1 is metabolised by DPP-IV and NEP, these enzymes are expected to be involved in the metabolism of the structurally related semaglutide. The company demonstrated that DPP-IV enzymes (and as such polymorphisms) have a minor role in the degradation of semaglutide. DPP-IV polymorphisms are therefore likely to be negligible. In vitro study 215514 shows that NEP is

one of the enzymes involved in semaglutide degradation. The company did not investigate the influence of genetic polymorphisms of NEP. However, the company discussed that no signs of influence of polymorphisms of NEP on the pharmacokinetics of semaglutide could be identified. Therefore, it is acceptable to conclude that polymorphisms are unlikely or the influence of these polymorphisms is minor.

Different formulations and injection sites

In study 3687 equivalence between the product strengths (1 mg/mL, 3 mg/mL and 10 mg/mL) were tested. The formulations were all bioequivalent with respect to total exposure (AUC) but a concentration dependent shift of the C_{max} and t_{max} has been observed, a faster absorption from the subcutaneous compartment was observed when a smaller volume with higher concentration was injected subcutaneously. These data suggest that the rate of absorption from the subcutaneous compartment is dependent on the concentration of the formulation.

The applicant evaluated the differences between injection sites in the population PK analysis using steady state data. Studies **3652** and **3684** demonstrated that injection site (abdomen or thigh) does not lead to any relevant differences in average steady state exposure of semaglutide. The conducted population PK analysis is suitable to compare steady state Cmax concentrations, however average exposure is considered more relevant than absorption rate or Cmax for a drug with limited fluctuation between minimum and maximum concentrations at steady state. Based on the totality of data can be concluded that steady state exposure is comparable between abdomen, upper arm and thigh injection.

Based on the presented data it can be concluded that all three injection sites, can be used interchangeably.

The population PK model does not describe semaglutide pharmacokinetics after a single dose accurately and therefore it cannot be excluded that the pharmacokinetics after the first dose of semaglutide are different between the injection sites due to a different ka. However, this is not expected to result in significant safety or efficacy results.

Pharmacokinetics in the target population

The pharmacokinetics of semaglutide has been studied in healthy volunteers, in T2D patients and in obese patients. The results are generally consistent across populations and across studies; though clearance and volume of distribution are significantly higher in T2D patients than in healthy volunteers. In the target T2D population, estimated steady-state volume of distribution of semaglutide is about 12L compared to about 8L in healthy volunteers. Clearance in subjects with T2D is higher in the target population. Mean CL/F was approximately 0.05 L/h compared to about 0.035 L/h in healthy subjects. It has been demonstrated that CL/F and Vz/F is dependent on body weight and, consequently, BMI. BMI inclusion criteria differed among the various clinical pharmacology studies, with a higher BMI allowed for studies in T2D patients. This difference largely drives the observed discrepancy of CL/F and Vz/F between healthy volunteers and T2D patients.

The population PK analysis was used to evaluate variability in subjects with T2D. However, since a lot of the included covariates had 1.00 in the 95% CI and the included covariates were likely to show collinearity. The applicant provided run results of a reduced model without including all covariates. This did not signifcantly change the population PK estimates and their inter-subject variabilities, therefore it can be concluded that the non-significant covariates are not relevant. Therefore, bodyweight is the only identified factor causing variability in pharmacokinetics.

Special populations

Various special populations have been evaluated by the applicant (e.g. renal/hepatic impairment, gender, race/ethnicity, age group, weight and subjects with the presence of anti-semaglutide antibodies). Gender, race/ethnicity, age groups and subjects with the presence of anti-semaglutide antibodies show no relevant effects on exposure of semaglutide. **Semaglutide was not studied in children.**

Since semaglutide is highly protein bound, pharmacokinetics could be influenced by renal function and albuminuria. The renal impairment study 3616 and the population PK analysis did not show a change in exposure of semaglutide for different degrees of renal impairment. However, urinary excretion of semaglutide could not be determined in the renal impairment study (3616) at the time, due to unavailability of a suitable assay. Urinary excretion was determined in two other studies (3789 and 3651). In study 3789 (AME trial) approximately 3% of semaglutide was estimated to be excreted. Study 3651 showed urinary concentrations below LOQ. This indicates low renal excretion of semaglutide, supporting the conclusion that semaglutide appears not to be dependent on degree of renal impairment. The company assessed if albuminuria could influence the pharmacokinetics of semaglutide. The company investigated the correlation between exposure (c_{avg}) versus baseline urinary albumin creatinin ratio (UACR) in data from phase IIIa studies. The semaglutide exposure was independent on the level of UACR. Further the LC-MS/MS assay used for the detection of semaglutide had a lower limit of quantitation of 1.94 nmol/L, while the C_{max} range was 7.4-9.8 nmol/L. The relatively high LLOQ may have consequences for the interpretation of the study results as low concentrations cannot be measured appropriately. However, in this study most subjects had samples with a concentration above LLOQ at 240 hours and a least the full dosing interval of 168 hours was covered. Therefore the results of the renal impairment study (3616) were considered to be reliable.

The study 3651 investigating the effect of hepatic impairment on the exposure of semaglutide, showed that the total exposure of semaglutide and its C_{max} is comparable between subjects mild, moderate, and severe hepatic impairment (all with a diagnosis of cirrhosis and classified as Child-Pugh A,B, or C) to healthy matched controls. An increase in the fraction unbound with increasing degree of hepatic impairment was observed. However, this increasing free fraction of semaglutide with increasing degree of hepatic impairment does not appear to affect the semaglutide exposure and half-life. As exposure was unchanged hepatic impairment is not expected to change the efficacy.

A clear effect of body weight on the pharmacokinetics of semaglutide was observed in the population PK analysis. This analysis showed that exposure of semaglutide was inversely correlated to body weight. Exposure increased by 40% in subjects weighing 55 kg and decreased by 27% in subjects weighing 127 kg as compared to a standard weight of 85 kg. From a PK point of view, body weight dosing would be in favour for semaglutide. This is further discussed in the pharmacodynamics section.

Interactions

In vitro studies suggest that semaglutide has a very low potential inhibit or induce CYP enzymes.

In clinical drug –drug interaction studies a delay in gastric emptying has been observed (Study 1821). Drug-drug interactions between semaglutide 1,0 mg and the following drugs from different BCS classes metformin, warfarin, digoxin, atorvastatin or oral contraceptive combination drug (ethinylestradiol and levonorgestrel) were evaluated. The atorvastatin C_{max} was substantially decreased by 38% (90% CI 18-53%) while AUC exposure of atorvastatin was unchanged. The reduced Cmax of atorvastatin, which may result from delayed gastric emptying caused by semaglutide, is unlikely to be of clinical relevance, as atorvastatin efficacy is related to AUC, which is unchanged, rather than Cmax.

The pharmacokinetics of other investigated medication was not affected by concomitantly administered drugs. It was noted that the tmax was more variable and tended to be delayed for most concomitant medication. The results demonstrate that delayed gastric emptying following semaglutide treatment is unlikely to result in clinically relevant DDIs with the investigated drugs, except perhaps for warfarin where in some subjects following a single dose a change in INR was seen The following sentence has therefore been included in the SmPC section 4.5: "However, upon initiation of semaglutide treatment in patients on warfarin and/or coumarin derivatives, frequent monitoring of INR is recommended."

In none of the DDI studies the concomitant drugs were administered for a sufficiently long time period to observe an effect on semaglutide exposure. However, no interaction with these drugs is expected based on the metabolic pathways and transporter properties of semaglutide.

The applicant did not conduct any interaction studies with drugs that may affect the bioavailability of semaglutide. Enzymes DPP-IV and NEP may play a role in the metabolism of semaglutide. The role of DPP-IV appears to be only minor in the degradation of semaglutide. Therefore, DPP-IV inhibitors are not expected to cause any relevant interactions. For NEP, semaglutide is metabolised by multiple metabolic pathways, including degradation by NEP. As degradation of semaglutide is not only based on NEP the impact of NEP interactions is expected to be limited. Nine subjects were co-treated with the NEP-inhibitor racecadotril (for diarrhoea) and safety data did not indicate elevated incidence of GI AEs. According to the applicant this would indicate that the exposure to semaglutide is not affected by the NEP inhibitor. Assessment of these safety data is difficult as the monitored adverse event is the same as the indication of racecadotril (diarrhoea) and PK data are absent. Despite of this, it is agreed that impact of NEP interactions is expected to be limited.

Pharmacodynamics

Semaglutide treatment, as compared with placebo, lowered fasting and postprandial blood glucose by improving multiple aspects of beta-cell function, including insulin secretion, and by reducing both fasting and postprandial glucagon concentrations, all in a glucose dependent manner. The data in the phase 3 trials show improvements in both HOMA-B and HOMA-IR. In the PD trial (3635), there was no apparent improvement in HOMA IR that may be explained by a generally better controlled diabetes (lower HbA1c, lower BMI) in line with the inclusion criteria of this PD trial and may thus have reduced the improvability of insulin resistance in these subjects. The mechanism of postprandial blood glucose lowering also involved a delay in gastric emptying.

Counter-regulation during hypoglycaemia was comparable with semaglutide treatment as compared with placebo. This was based on responses in concentrations of glucagon and C-peptide, and in glucose need during the clamp (AUC_{GIR}). A decreased recognition of hypoglycaemia was also observed. It is not clear if this should be considered favourable or not: on the one hand, it may represent subject's adaptation to normalised glucose levels, on the other hand, it could represent hypoglycaemia unawareness.

The body weight loss observed with semaglutide was primarily from fat tissue. The mechanism of body weight loss involved lowered appetite, both in the fasting and postprandial state, leading to lowered daily energy intake. Semaglutide improved control of eating, reduced food cravings and reduced the preference for high fat foods, as compared to placebo. However, semaglutide reduced energy expenditure as assessed by resting metabolic rate (RMR) using indirect calorimetry/ventilated hood system by appr. 600 kJ per day. The underlying mechanism is not clear.

As evidenced by the QTc trial, semaglutide does not prolong QTc values. However, the effect of semaglutide on pulse rate appears to be larger than with other GLP-1RAs. When assessed by office measurements, semaglutide seems to antagonize the beta-blocker-induced pulse rate reduction. As beta-blockers were not a randomised treatment in the CVOT, the implications hereof cannot be assessed. Extrapolation of the CV outcome results to subjects without established CV disease remains difficult. In these subjects the differences in office HR were larger than in the whole population. Consistent with the GLP-1 receptor agonist class effect, a small, persistent increase in resting pulse rate was observed with semaglutide in the clinical trial data available at the time of planning the thorough QT/QTc trial, trial 3652. QTcI, QTcL and QTcF changes were all below regulatory thresholds. For the observed data, a negative correlation between QTcB and RR interval was found; this association is demonstrated to materialize (albeit weakly) at a heart rate of 60. Consequently, overestimation may be an issue using QTcB in this study. Such association was not present for QTcI and RR intervals. Therefore QTcI (individual heart rate corrected QT interval) was pre-specified as the primary endpoint in this trial; avoiding correction methods for the primary objective that is known to be problematic for compounds with properties to elevate heart rate.

The exposure response model not provide support for the statements made in the report about a better glycaemic control with the 1.0 mg dose compared to the 0.5 mg dose. Both the 0.5 mg and 1.0 mg seem to reach the plateau of the E_{max} curve for HbA_{1c}. The number of GI events and time of GI events increases, whereas HbA_{1c} concentrations already seem to reach plateau at the E_{max} curve. This issue is further discussed in the Clinical Efficacy section.

The population PK analysis also showed a significant effect of body weight on the exposure of semaglutide. Patients with a relatively low body weight, and thus a higher exposure to semaglutide, appear to have a higher incidence of GI events and a lower chance that these adverse events subside over time due to tolerance. The applicant conducted an additional analysis to evaluate the relationship between body weight and the safety and efficacy of semaglutide. In this analysis no clear body weight related trend in the reporting of GI AEs and nausea has been observed across body weight categories and the efficacy (HbA1c change from baseline response) appears to be similar across body weight subgroups with the same dose of semaglutide. It can be concluded that both dose levels of semaglutide can be the safe and efficacious and should be based on individual needs.

2.4.5. Conclusions on clinical pharmacology

In general, the pharmacokinetics and pharmacodynamics of semaglutide have been sufficiently characterised.

2.5. Clinical efficacy

2.5.1. Dose selection, dose response studies

The selection of doses used in the phase 3a programme was determined by data from the phase 2 dose-finding trial (1821). Doses were selected based on pre-defined criteria: i) the lowest dose had to be at least 0.5 %-point better than placebo on HbA_{1c} change from baseline, ii) the increments between the two doses had to support a clinically meaningful separation on glycaemic control with a ΔHbA_{1c} ≥0.3 %-point when evaluating data from patients that completed the treatment, iii) both doses had to be well-tolerated.

The results and the model-estimated results predicted the 1.0 mg semaglutide dose had the greatest effect on HbA_{1c}. Based on these predicted responses both semaglutide 0.5 mg and 1.0 mg met the pre-specified criteria. However, the 0.4 mg already showed 0.61 %−point HbA1c reduction from baseline compared with placebo.

Mean values with 95% confidence intervals vs semaglutide dose (plus placebo at dose of 0 mg) for the completer population. The non-linear line represents the covariate-adjusted model-derived dose-response estimate for the completer population.

Although semaglutide 1.0 mg vs. 0.5 mg showed a larger effect on HbA1c and body weight, the estimated treatment differences were small (range: 0.10−0.43%−point HbA1c and 0.81−2.75 kg body weight). Also, additional reduction on CV risk was small (HR 0.77 vs. 0.71). In the clinical trials, significantly more patients with semaglutide 1.0 mg compared with 0.5 mg reached the treatment target of an HbA_{1c} <7%. The lowest dose response was observed in the global monotherapy trial 3623 where the difference between semaglutide doses did not reach statistical significance.

Gastrointestinal disorders were the most frequent adverse reactions with semaglutide 0.5 mg and 1.0 mg. In general, the proportion of patients experiencing an event - and the time with events - increased with semaglutide exposure. Dose-dependent increases in GI AEs were most notably with nausea and vomiting.

The proportion of patients with episodes of hypoglycaemia and the corresponding rates were generally similar for semaglutide 0.5 mg and 1.0 mg across the range of concomitant OADs and insulins. Dose-dependent increases in mean levels of pancreatic enzymes (lipase and amylase) were observed in the CVOT. A slightly higher increase in pulse rate was observed with semaglutide 1.0 mg than with 0.5 mg.

The company proposes that patients should be escalated to the semaglutide 0.5 mg maintenance dose, and if well-tolerated the dose can be increased to 1.0 mg to further improve efficacy based on the needs of the individual patient.

2.5.2. Main studies

The phase 3a trials evaluated the efficacy and safety of semaglutide in a broad T2D population. The programme evaluated mono- and combination therapy (primarily combinations with metformin, SU and/or insulin) with anti-hyperglycaemic therapies and compared semaglutide with diabetes drugs most commonly used at the time of initiating the phase 3a programme (Figure 13). Semaglutide was investigated at two dose levels (0.5 mg and 1.0 mg) in all phase 3a trials, except for trial 3624 (1.0 mg only vs exenatide ER).

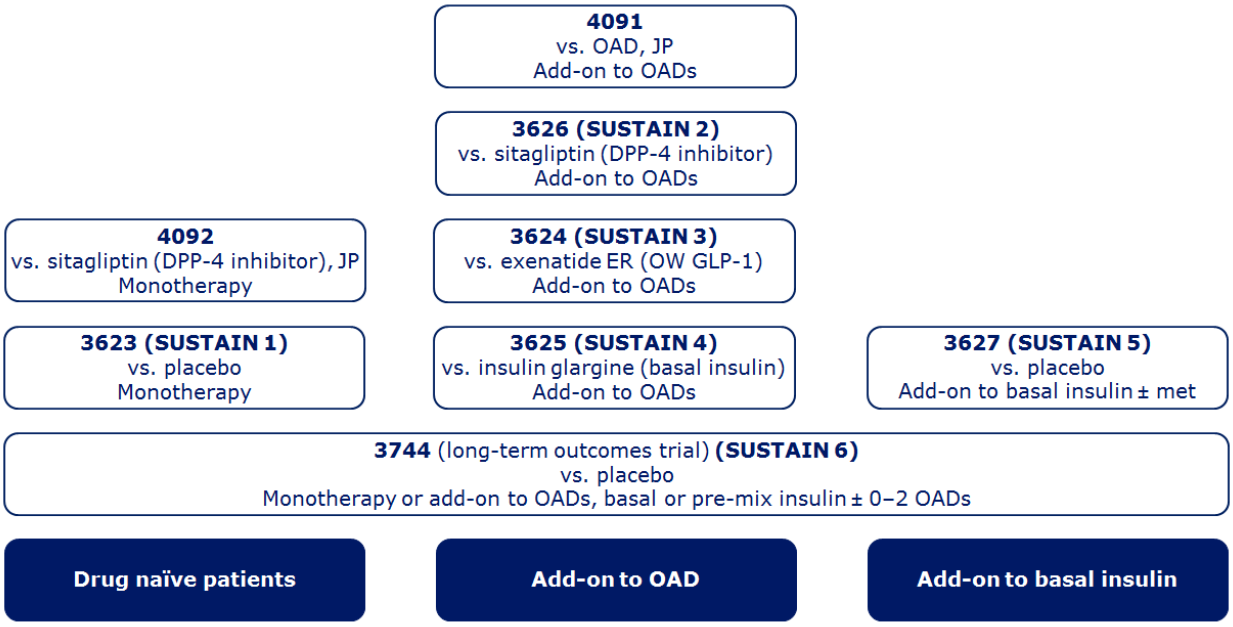
For five of the phase 3a trials, the primary objective was to evaluate the effect of semaglutide on glycaemic control (trials 3623, 3624, 3625, 3626 and 3627). Throughout this document, these five trials are referred to as the key efficacy trials. In addition, two phase 3a trials evaluated semaglutide for treatment of T2D in Japanese subjects (trials 4092 and 4091), referred to as the Japanese trials. While safety was the primary endpoint for the Japanese trials, they were designed and conducted in a similar manner to the key efficacy trials.

The last phase 3a trial was a 104−week cardiovascular outcomes trial (trial 3744) in a T2D population at high risk of CV events that investigated the effect of semaglutide on CV events as well as long-term safety and efficacy, and it is referred to as the CVOT.

All phase 3a trials were randomised, parallel group, multi-centre trials in which the therapeutic response to semaglutide was compared with that of placebo or an active comparator drug. There was

no washout or discontinuation of previous background medication prior to randomisation. The main design and trial procedures were very similar and aligned across all phase 3a trials (except the CVOT), but differed in the required diabetes background medication, comparators, and length of treatment periods. The duration of treatment in the phase 3a trials ranged from 30 to 104 weeks.

Figure 13 Combination therapy and comparators in the phase 3a trials.



Notes: Trial 3626 primarily included subjects (94%) receiving metformin as only background treatment. Trial 3624 primarily included subjects receiving 1-2 OADs as background medication (49% received metformin, and 45% received a combination of metformin and SU). Trial 3625 primarily included subjects receiving 1-2 OADs as background medication (48% received metformin and 51% received a combination of metformin and SU.

Dose-escalation regimen

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. Selection of dose-escalation regimen for the phase 3a programme was based on estimations from the phase 2 dose-finding trial (trial 1821) and tested by results from the clinical pharmacology trial 3819 prior to implementation in all phase 3a trials. Semaglutide 0.25 mg has not been investigated as a therapeutic dose.

Blinding

The phase 3a trials were blinded to the extent possible, based on the nature of the comparators to ensure the best possible basis for unbiased interpretation. Placebo-controlled trials (trials 3623, 3627 and 3744) were double-blinded, consistent with standard of research and regulatory guidance. Double-blinding was obtained within 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 sitagliptin (OADs) via a double-dummy treatment scheme. An open-label trial design was necessary for some trials. The insulin-comparator trial (trial 3625 vs insulin Glargin (as add-on to 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. Due to the complexity of preparing a placebo version of exenatide ER, the OW GLP-1

RA comparator trial (trial 3624) was conducted as an open-label trial. For both Japanese trials, an open-label trial design was used.

In and exclusion criteria

Phase 3a trials

The phase 3a trials included drug naïve subjects, subjects uncontrolled on OADs, subjects uncontrolled on basal insulin, and subjects with T2D at high risk for CV events.

Main exclusion criteria: known or suspected hypersensitivity to trial product(s), previous participation in this trial, female with potential pregnancy or breast-feeding, receipt of any investigational medicinal product within 90 days before screening, any chronic disorder or severe disease which may jeopardise subject's safety or compliance with the protocol, treatment with once-weekly glucagon-like peptide-1 (GLP-1) receptor agonists within 90 days prior to screening, treatment with any glucose lowering agent(s), other than stated in the inclusion criteria, in a period of 90 days prior to screening, experienced more than 3 episodes of severe hypoglycaemia within 6 months prior to screening, and/or hypoglycaemia unawareness, history of chronic or idiopathic acute pancreatitis, screening calcitonin value ≥ 50 ng/L (pg/mL), personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function (criteria differed per trial), acute coronary or cerebrovascular event within 90 days before randomisation, heart failure, New York Heart Association class IV, known proliferative retinopathy or maculopathy requiring acute treatment, diagnosis of malignant neoplasm in the previous 5 years.

CVOT

In the CVOT, enrolled subjects were men and women with T2D, age ≥50 years at screening and clinical evidence of CV disease or age ≥60 years at screening and subclinical evidence of CV disease, anti-diabetic drug naïve, or treated with one or two OADs, or treated with human Neutral Protamin Hagedorn (NPH) insulin or long-acting insulin analogue or pre-mixed insulin, both types of insulin either alone or in combination with one or two OADs, HbA1c ≥7.0% at screening.

Main exclusion criteria: Type 1 diabetes mellitus, use of glucagon-like peptide-1 (GLP-1) receptor agonist (exenatide, liraglutide, or other) or pramlintide within 90 days prior to screening, use of any dipeptidyl peptidase 4 (DPP-IV) inhibitor within 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, acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g. diabetes ketoacidosis) within 90 days prior to screening, history of chronic pancreatitis or idiopathic acute pancreatitis, acute coronary or cerebrovascular event within 90 days prior to randomisation, currently planned coronary, carotid or peripheral artery revascularisation, chronic heart failure New York Heart Association (NYHA) class IV, personal or family history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma, personal history of non-familial medullary thyroid carcinoma, calcitonin ≥50 ng/L at screening.

Statistical methods

Phase 3a trials

For the key efficacy trials, the primary endpoint was change in HbA1c from baseline to end-of-treatment at week 30 (trials 3623, 3625 and 3627) or week 56 (trials 3624 and 3626). The primary estimand was defined as the difference in change in HbA1c from baseline to end-of-treatment between semaglutide and comparator, assuming that all randomised subjects remained on trial product at end-of-treatment and had not initiated rescue medication.

The primary analysis method pre-specified in the protocols for HbA1c (primary endpoint) and body weight (confirmatory secondary endpoint) and other continuous secondary endpoints assessed over time was a mixed model for repeated measurements (MMRM), with treatment, country (for the key efficacy trials), and trial-specific stratification as fixed factors and baseline value as covariate, all nested within visits. An unstructured covariance matrix was assumed for measurements within the same subject. The analysis was based on the FAS using the on-treatment without rescue medication observation period. The outcomes from these subjects and from subjects with no data at the end-of-treatment visit were hereby assumed to be missing at random (MAR) in the analysis. Thus, this approach focuses on what these outcomes would have been, had they been measured, under the assumption that subjects had continued treatment without initiating rescue medication, in line with the primary estimand. The family-wise type 1 error rate was controlled in the strong sense (5%, two-sided) using a pre-specified hierarchical testing scheme.

Several sensitivity analyses were pre-specified in the protocols to evaluate the robustness of the conclusions drawn from the primary HbA1c analysis and the confirmatory secondary body weight analysis, and to investigate the impact of missing data and thus the validity of the MAR assumption of the MMRM. The sensitivity analyses included MMRM analysis based on all in trial data, complete case analysis, last observation carried forward analysis, comparator-based multiple imputation analysis and per-protocol analysis.

CVOT

The primary endpoint of the CVOT was defined as the time from randomisation to first MACE. To establish that semaglutide is not associated with an unacceptable excess cardiovascular risk, it was pre-specified in the statistical analysis that non-inferiority of semaglutide (pooled) vs placebo (pooled) was considered confirmed if the upper limit of the two-sided 95% confidence interval for the hazard ratio (HR) is below 1.8 for the primary MACE endpoint. The primary endpoint was analysed using a stratified Cox proportional hazards model with semaglutide and placebo treatment group as fixed factor. The model was stratified by all possible combinations of the 3 stratification factors used in the randomisation procedure. A number of sensitivity analyses were pre-specified for the primary MACE endpoint to evaluate the robustness of the primary analysis including analyses based on the on-treatment observation period and different ascertainment windows following last drug date (7, 30 and 42 days.

Table 4 Demographics and baseline characteristics across trials

Trial/ Characteristic	Key efficacy trials					Japanese trials		CVOT
	3623	3626	3624	3625	3627	4092	4091	3744
Sex (%, men/women)	54/ 46	51/ 49	55/ 45	53/ 47	56/ 44	76/ 24	71/ 29	61/ 39
Age (years) (min-max)	53.7 (18–88)	55.1 (23–83)	56.6 (20–83)	56.5 (22–82)	58.8 (19–86)	58.3 (22–83)	58.5 (26–83)	64.6 (50–89)
Race (%, White/ Black or Afr.Am/ Asian)	64/ 8/ 21	69/ 5/ 25	84/ 7/ 2	77/ 9/ 11	77.5/ 5/ 17	0/ 0/ 100	0/ 0/ 100	83/ 7/ 8
Ethnicity (%, Hisp or Lat/ not Hisp or Lat)	30/ 70	17/ 83	24/ 76	20/ 80	12/ 88	0/ 100	0/ 100	15.5/ 84.5
HbA_{1c} (%) (min-max)	8.05 (6.40-10.30)	8.07 (5.90-11.40)	8.35 (6.50–11.20)	8.17 (5.50-11.70)	8.37 (6.80-11.10)	8.15 (6.70-11.20)	8.09 (6.70–13.10)	8.70 (5.90–17.90)
Diabetes duration (years) (min-max)	4.18 (0.10-34.50)	6.58 (0.30-39.20)	9.21 (0.30-54.00)	8.57 (0.20-59.90)	13.32 (0.44-39.58)	7.97 (0.15-41.89)	8.85 (0.13–41.71)	13.90 (0.10–53.90)
Body weight (kg) (min-max)	91.93 (39.80-185.3)	89.48 (43.6-167.0	95.79 (49.90-198.3)	93.45 (43.00-187.8)	91.70 (47.50–165.6)	69.34 (39.10-129.4)	71.53 (39.50–142.0)	92.09 (40.7-216.8)
BMI (kg/m^2) (min-max)	32.93 (16.35–71.80)	32.46 (19.00-56.44)	33.76 (21.05-72.84)	33.01 (19.15-62.46)	32.18 (19.48-51.64)	25.43 (17.15-42.89)	26.41 (16.31–53.47)	32.80 (17.63–77.66)
Normal renal function, eGFR ≥90 mL/min/1.73 m^2 N (%))	247 (63.8)	803 (65.6)	518 (64.0)	652 (60.3)	201 (50.8)	202 (65.6)	412 (68.7)	990 (30)
Mild renal impairment, eGFR 60–<90 mL/min/1.73 m^2 (N (%))	121 (31.3)	418 (34.1)	290 (35.8)	378 (34.9)	160 (40.4)	106 (34.4)	176 (29.3)	1368 (41.5)
Moderate renal impairment, eGFR 30–<60 mL/min/1.73 m^2 (N (%))	19 (4.9)	3 (0.2)	NA	52 (4.8)	35 (8.8)	NA	12 (2.0)	832 (25.2)
Severe renal impairment, GFR 15–<30 mL/min/1.73 m^2 (N (%))	NA	NA	NA	NA	NA	NA	NA	95 (2.9)
End stage renal impairment eGFR <15 mL/min/1.73 m^2 (N (%))	NA	NA	NA	NA	NA	NA	NA	12 (0.4)

Abbreviations: CVOT: Cardiovascular outcomes trial; Afr.Am: African American; Hisp or Lat: Hispanic or Latino; BMI: Body mass index; eGFR: estimated glomerular filtration rate; N: Number of patients; NA: Not applicable.

Table 5 Cardiovascular history at screening for trial 3744 (CVOT)

Medical history	Semaglutide	Placebo	Total
Ischaemic heart disease, N (%)	988 (60.0)	1006 (61.0)	1994 (60.5)
Myocardial infarction, N (%)	530 (32.2)	542 (32.9)	1072 (32.5)
Heart failure, N (%)	381 (23.1)	396 (24.0)	777 (23.6)
Stroke (ischaemic and haemorrhagic), N (%)	230 (14)	261 (15.8)	491 (14.9)
Transient ischaemic attack, N (%)	98 (5.9)	94 (5.7)	192 (5.8)
Hypertension, N (%)	1543 (93.6)	1516 (91.9)	3059 (92.8)

Background treatment

The background treatments applied in the phase 3a programme reflect the treatment cascade in the T2D population; trials 3623 and 4092 evaluated semaglutide monotherapy in drug naïve patients; patients in trial 3626 vs Sita (as add-on to OADs) were mainly on a background treatment of metformin monotherapy, in trials 3624 vs Exe ER (as add-on to OADs) and 3625 vs IGlar (as add-on to OADs), close to half of patients were treated with metformin and the other half with metformin + SU at baseline. All patients in trial 3627 were on basal insulin therapy at baseline (Table 6). In trials 36224, 3625, 3626 and 3627, mean dose of background treatment was in general close to (or higher than) the highest recommended doses.

Table 6 Anti-glycaemic background treatment in individual phase 3a trials

Trial	N	No background treatment	Metformin monotherapy	Metformin + SU	SU monotherapy	Basal insulin +/- OADs	Other
Trial 3623	387	99.7%	0%	0%	0%	0%	0.3%
Trial 3626	1225	0.1%	94.2%	0.2%	0%	0%	5.6%
Trial 3624	809	0.1%	49.2%	45.1%	2.7%	0.1%	2.7%
Trial 3625	1082	0%	48.2%	51.4%	0.2%	0%	0.2%
Trial 3627	396	0%	0%	0%	0%	100%	0%
Trial 4092	308	100%	0%	0%	0%	0%	0%
Trial 4091	600	28.5%	0%	0%	28.3%	0%	43.2%
CVOT	3297	1.6%	11.8%	22.1%	3.7%	58.0%	2.8%

Notes: For the evaluation of efficacy in subgroups, the following treatment groups will be combined: SU monotherapy, Insulin monotherapy and combination therapy, and 'other'. N represents number of patients in FAS.
Abbreviations: FAS, full analysis set. N: number of patients; OADs: oral anti-glycaemic drugs; SU: sulfonylurea.
Cross-reference: /projstat/nn9535/nn9535-exploratory/sueot010.

Patients in the CVOT were treated with semaglutide as add-on to standard-of-care and could therefore be anti-glycaemic drug naïve, or treated with 1 or 2 OAD(s), or treated with basal insulin or pre-mixed insulin, alone or in combination with 1 or 2 OAD(s). Hence, in the CVOT, there was a mix of background treatments. Evaluation of the effect of semaglutide as add-on to SGLT-2inhibitors was not part of the phase 3a programme, as no SGLT-2 inhibitor products were marketed at the time of design

and initiation of the programme (only few patients in the CVOT had SGLT-2 inhibitors added as standard-of-care treatment).

Background medications were to be maintained at the stable, pre-trial dose and frequency during the treatment period in all trials except in the CVOT. Hence, other anti-glycaemic medications were administered and intensified in combination with semaglutide/placebo in the CVOT reflecting a real-world clinical situation. In the phase 3a trials (excl. CVOT), patients with unacceptable hyperglycaemia were to be offered treatment intensification (rescue medication) in addition to randomised treatment. Data from patients on rescue treatment were censored in the efficacy analyses but included in safety evaluations.

Comparators

Head-to-head trials with the most relevant active comparators (sitagliptin, exenatide ER and insulin glargine) available at the time of the programme planning were included in the phase 3a programme.

Patient disposition

The proportion of patients completing the pre-planned treatment periods in the individual trials were ranging from 79.4 to 93.2% (Table 7). The two Japanese trials had the highest proportion of patients completing the trial and treatment. All efforts were to be made to keep the patients on treatment. However, in case of a potential safety concern (including pregnancy and pancreatitis), unacceptable intolerability or at request of the patient, the trial product could be discontinued.

The primary reason for treatment discontinuation across trials were categorised as “adverse events” or “other reasons”. “Other reasons” included a variety of reasons not related to adverse events (AEs) or protocol deviations. The differences between semaglutide and placebo/comparators treatment groups were mainly due to a higher number of GI AEs leading to premature treatment discontinuation with semaglutide; see safety section for further details.

In the phase 3a trials, patients with unacceptable hyperglycaemia were to be offered treatment intensification (rescue medication) in addition to randomised treatment, at the discretion of the investigator in accordance with ADA/EASD guidance. In the CVOT, patients were on a background of standard-of-care, and thus no rescue criteria were defined. Among the treatment completers in phase 3a trials (excl. CVOT), the proportion of patients initiating rescue medication was generally lower with semaglutide (0.0−5.4%) than with comparators (1.4−20.2%).

Table 7 Patient dispositions for the phase 3a trials

Trial / Patients	Key efficacy trials					Japanese trials		CVOT
	Trial 3623	**Trial 3626**	**Trial 3624**	**Trial 3625**	**Trial 3627**	**Trial 4092**	**Trial 4091**	**Trial 3744**
	Total Sema 0.5 /1.0 mg / PBO	Total Sema 0.5 mg / 1.0 mg / Sita	Total Sema 1.0 mg / Exe ER	Total Sema 0.5 mg / 1.0 mg / IGlar	Total Sema 0.5 mg / 1.0 mg / PBO	Total Sema 0.5 mg / 1.0 mg / Sita	Total Sema 0.5 mg / 1.0 mg / OAD	Total Sema 0.5/1.0 mg PBO 0.5/1.0 mg
FAS	387 128/130/129	1225 409/409/407	809 404/405	1082 362/360/360	396 132/131/133	308 103/102/103	600 239/241/120	3297 826/822/ 824/825
Premature treatment discontinuation (%)	12.1 13.3/12.3/10.9	11.9 13.0/14.9/7.9	20.6 20.3/21.0	12.0 13.5/15.3/7.2	10.9 10.6/12.2/9.8	6.8 2.9/14.7/2.9	9.3 6.3/14.1/5.8	20.0 19.9/22.6/ 18.3/19.3
- *GI AEs*	1.6 2.3/2.3/0.0	4.2 4.6/7.6/0.2	3.3 4.5/2.2	2.5 2.8/4.7/0.0	1.8 1.5/3.8/0.0	3.6 1.0/9.8/0.0	4.2 2.9/7.5/0.0	4.3 5.7/9.4/1.2/1.0
- *Other AEs*	3.1 3.9/3.1/2.3	2.9 3.4/2.4/2.7	5.0 5.2/4.9	2.2 2.5/2.8/1.4	2.6 3.1/3.8/0.8	1.6 1.9/1.0/1.9	3.2 2.9/3.3/3.3	5.6 6.2/5.0/4.6/6.7
- *Protocol violation (in- or exclusion criteria)*	1.8 3.1/1.5/0.8	1.1 1.0/1.0/1.5	4.4 3.7/5.2	2.5 3.3/3.6/0.6	0.8 0.8/0.0/1.5	0.3 0.0/1.0/0.0	0.0 0.0/0.0/0.0	NA[b]
- *Other reasons*	5.7 3.9/5.4/7.8	3.8 3.9/3.9/3.4	7.6 6.7/8.4	4.8 5.0/4.2/5.3	5.9 5.3/4.6/7.5	1.3 0.0/2.9/1.0	2.0 0.4/3.3/2.5	10.0 8.0/8.3/12.4/11.6
Withdrawals (%)	6.7 7.0/5.4/7.8	5.4 5.6/5.1/5.6	8.5 7.9/9.1	5.8 6.6/5.2/5.5	3.8 3.0/3.0/5.3	1.6 0.0/2.9/1.9	3.5 2.5/4.1/4.1	0.5 0.2/0.6/ 0.5/0.5
Completed treatment with rescue medication (%)	9.6 4.7/3.8/20.2	9.1 5.4/2.2/19.7	7.5 5.4/9.6	2.6 3.9/2.5/1.4	5.8 2.3/0.8/14.3	1.9 1.0/0.0/4.9	1.2 0.0/0.0/5.8	NA
Completed treatment without rescue medication (%)	78.3 82.0/83.8/69.0	79.0 81.7/82.9/72.5	71.8 74.3/ 69.4	85.4 82.6/82.2/91.4	83.3 87.1/87.0/75.9	91.2 96.1/85.3/92.2	89.5 93.7/85.9/88.3	NA
Completed treatment (%)	87.9 86.7/87.7/89.1	88.1 87.0/85.1/92.1	79.4 79.7/79.0	88.0 86.5/84.7/92.8	89.1 89.4/87.8/90.2	93.2 97.1/85.3/97.1	90.7 93.7/85.9/94.2	80.0 80.1/77.3/ 81.7/80.7
Completed trial (%)	92.5 92.2/94.6/90.7	94.5 94.4/94.6/94.4	91.4 92.1/90.7	93.7 92.5/94.5/94.0	95.7 96.2/96.2/94.7	98.4 100/97.1/98.1	96.3 97.5/95.9/95.0	98.0 98.3/98.7/ 97.6/97.6

Abbreviations: N: number of patients; PBO: placebo; sema: semaglutide; Sita: Sitagliptin; Exe ER: Exenatide Extended Release; IGlar: Insulin glargine; NA: Not applicable.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8 Trial NN9535-3623

Title: SUSTAIN 1: Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve subjects with type 2 diabetes			
Study identifier	Protocol number: NN9535-3623; EudraCT number: 2013-000632-94 Study identifier: NCT02054897. See Trial 3623 report body (M 5.3.5.1)		
Design	This was a randomised, double-blind, parallel-group, placebo-controlled, multinational, multicentre, four-armed trial to evaluate the efficacy and safety of once-weekly semaglutide as monotherapy in adult subjects with type 2 diabetes (T2D). Male and female subjects diagnosed with T2D and treated with diet and exercise for at least 30 days before screening were included in the trial. Following a 2-week screening period, eligible subjects were randomised 2:2:1:1 to treatment with either semaglutide 0.5 mg, semaglutide 1.0 mg, semaglutide placebo 0.5 mg or semaglutide placebo 1.0 mg (hereafter referred to as placebo) once weekly for 30 weeks. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently was not to be changed. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued and in such cases treatment should not be re-initiated, except in cases where suspicion of acute pancreatitis was ruled out. Subjects had a final follow-up visit 5 weeks after the last treatment visit. The placebo groups were pooled in the analysis.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	30 week 2 week Not applicable	
Hypothesis	**Primary objective:** To demonstrate superiority of once-weekly dosing of two dose levels of semaglutide versus placebo on glycaemic control after 30 weeks of treatment in drug-naïve subjects with T2D. **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.		
Treatments groups	Semaglutide 0.5 mg	129 subjects were randomised to the semaglutide 0.5 mg group.	
	Semaglutide 1.0 mg	130 subjects were randomised to the semaglutide 1.0 mg group.	
	Placebo	129 subjects were randomised to the placebo group.	
Endpoints and definitions	Primary endpoint	Change from baseline in glycosylated haemoglobin (HbA_{1c}) at 30 weeks	The primary endpoint was analysed using a standard mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment and country were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit. Superiority was confirmed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%.
	Confirmatory secondary	Change from baseline in body	Superiority was tested using a MMRM similar to the model used for analysis of the primary endpoint but

	endpoint	weight at 30 weeks	with body weight at baseline as covariate.
	Supportive secondary endpoints	Change from baseline in fasting plasma glucose (FPG) at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with the associated baseline value as covariate.
		Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), HbA_{1c} ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline HbA_{1c} and as covariate. For the composite endpoint, both HbA_{1c} and body weight were included as covariates. Missing continuous response data at 30 weeks were imputed from the MMRM used for the primary analysis of HbA_{1c}.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
Database lock	22 June 2015		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or placebo and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.			
Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Placebo**
	Number of subjects (FAS)	128	130	129
HbA_{1c} (%)	Change in HbA_{1c} at 30 weeks, % points	-1.45	-1.55	-0.02
	ETD (95% CI) vs placebo	-1.43 (-1.71, -1.15)	-1.53 (-1.81, -1.25)	-
	HbA_{1c} ≤6.5%, % subjects	59	60	13
	EOR (95% CI) vs placebo	15.99 (7.82, 32.68)	18.34 (8.96, 37.54)	-
	HbA_{1c} <7.0%, % subjects	74	72	25
	EOR (95% CI) vs placebo	16.92 (8.44, 33.89)	15.70 (8.00, 30.83)	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	66	65	19
	EOR (95% CI) vs placebo	12.69 (6.57, 24.52)	12.45 (6.46, 23.99)	-

Body weight (kg)	Change in body weight at 30 weeks ETD (95% CI) vs placebo	-3.73 -2.75 (-3.92, -1.58)	-4.53 -3.56 (-4.74, -2.38)	-0.98 -
	Weight loss ≥5%, % subjects EOR (95% CI) vs placebo	37 7.88 (3.65, 17.04)	45 12.01 (5.53, 26.07)	7 -
	Weight loss ≥10%, % subjects EOR (95% CI) vs placebo	8 3.60 (1.09, 11.95)	13 6.23 (1.98, 19.61)	2 -
FPG (mmol/L)	Change in FPG at 30 weeks ETD (95% CI) vs placebo	-2.51 -1.96 (-2.49, -1.43)	-2.34 -1.79 (-2.31, -1.26)	-0.55 -
BP (mmHg)	Change in diastolic BP at 30 weeks ETD (95% CI) vs placebo	-0.50 -0.89 (-2.81, 1.02)	0.18 -0.21 (-2.12, 1.69)	0.40 -
	Change in systolic BP at 30 weeks ETD (95% CI) vs placebo	-2.58 -0.86 (-4.15, 2.43)	-2.74 -1.03 (-4.29, 2.24)	-1.72 -

Table 9 Trial NN9535-3626

Title: SUSTAIN 2: Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin and/or thiazolidinedione in subjects with type 2 diabetes		
Study identifier	Protocol number: NN9535-3626; EudraCT number: 2012-004827-19 Study identifier: NCT01930188. See Trial 3626 report body (M 5.3.5.1)	
Design	This was a 56-week randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre, 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 subjects with type 2 diabetes (T2D) who had not achieved adequate glycaemic control on metformin, thiazolidinedione (TZD) or a combination of metformin/TZD. Male and female subjects diagnosed with T2D were included in the trial. Following a 2-week screening period, eligible subjects were randomised 2:2:1:1 to one of four treatment groups: semaglutide 0.5 mg once-weekly + sitagliptin placebo once-daily; semaglutide 1.0 mg once-weekly + sitagliptin placebo once-daily; sitagliptin 100 mg once-daily + semaglutide placebo 1.0 mg once-weekly; sitagliptin 100 mg once-daily + semaglutide placebo 0.5 mg once-weekly. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently was not to be changed. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued; in such cases treatment was not to be re-initiated. Treatment continued for 56 weeks. Subjects had a final follow-up visit 5 weeks after the last treatment visit.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	56 week 2 week Not applicable
Hypothesis	**Primary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic 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	
Treatments groups	Semaglutide 0.5 mg	410 subjects were randomised to the semaglutide 0.5 mg group.
	Semaglutide 1.0 mg	410 subjects were randomised to the semaglutide 1.0 mg group.
	Sitagliptin	411 subjects were randomised to the Sitagliptin group.

Endpoints and definitions	Primary endpoint	Change from baseline in glycosylated haemoglobin (HbA_{1c}) at 56 weeks	The primary endpoint was analysed using a mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment and country were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit. Non-inferiority and superiority were concluded if the upper limit of the two-sided 95% CI for the estimated difference in HbA_{1c} at week 56 between semaglutide and sitagliptin were less than 0.3% and 0%, respectively.
	Confirmatory secondary endpoint	Change from baseline in body weight at 56 weeks	Superiority was tested using a MMRM similar to the model used for analysis of the primary endpoint but with body weight at baseline as covariate.
	Supportive secondary endpoints	Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), HbA_{1c} ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline HbA_{1c} and as covariate. For the composite endpoint, both HbA_{1c} and body weight were included as covariates. Missing continuous response data at 56 weeks were imputed from the MMRM used for the primary analysis of HbA_{1c}.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 56 weeks	Analysed using the same type of model as described for the primary endpoint but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 56 weeks	Analysed using the same type of model as described for the primary endpoint but with the associated baseline value as covariate.
		Change from baseline in Diabetes Treatment Satisfaction Questionnaire ($DTSQ_s$) components at 56 weeks	The post-baseline responses are analysed using an ANCOVA model with treatment and country as fixed factors and baseline value as covariate.
Database lock	24 November 2015		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or sitagliptin and had any post-randomisation data. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.			
Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Sitagliptin**
	Number of subjects (FAS)	409	409	407
HbA_{1c} (%)	Change in HbA_{1c} at 56 weeks, % points	-1.32	-1.61	-0.55
	ETD (95% CI) vs sitagliptin	-0.77 (-0.92, -0.62)	-1.06 (-1.21, -0.91)	-
	HbA_{1c} ≤6.5%, % subjects	53	66	20
	EOR (95% CI) vs sitagliptin	4.39 (3.15, 6.12)	8.99 (6.36, 12.72)	-
	HbA_{1c} <7%, % subjects	69	78	36
	EOR (95% CI) vs sitagliptin	4.16 (3.02, 5.74)	7.92 (5.59, 11.22)	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	63	74	27
	EOR (95% CI) vs sitagliptin	4.84 (3.51, 6.68)	9.52 (6.75, 13.43)	-
Body weight (kg)	Change in body weight at 56 weeks	-4.28	-6.13	-1.93
	ETD (95% CI) vs sitagliptin	-2.35 (-3.06, -1.63)	-4.20 (-4.91, -3.49)	-
	Weight loss ≥5%, % subjects	46	62	18
	EOR (95% CI) vs sitagliptin	3.76 (2.72, 5.19)	7.47 (5.38, 10.37)	-
	Weight loss ≥10%, % subjects	13	24	3
	EOR (95% CI) vs sitagliptin	4.09 (2.26, 7.40)	8.85 (5.01, 15.61)	-
FPG (mmol/L)	Change in FPG at 56 weeks	-2.07	-2.59	-1.10
	ETD (95% CI) vs sitagliptin	-0.97 (-1.26, -0.69)	-1.49 (-1.77, -1.21)	-
BP (mmHg)	Change in diastolic BP at 56 weeks	-2.01	-1.91	-1.11
	ETD (95% CI) vs sitagliptin	-0.90 (-2.10, 0.30)	-0.80 (-2.00, 0.40)	-
	Change in systolic BP at 56 weeks	-5.07	-5.61	-2.29
	ETD (95% CI) vs sitagliptin	-2.78 (-4.59, 0.97)	-3.32 (-5.13, -1.52)	-
$DTSQ_s$	Change in 'Treatment satisfaction' at 56 weeks: ETD (95% CI) vs sitagliptin	0.83 (0.18, 1.48)	1.46 (0.81, 2.11)	-

Table 10 Trial NN9535-3624

Title: SUSTAIN 3: Efficacy and safety of semaglutide once-weekly versus exenatide ER 2.0 mg once-weekly as add-on to 1-2 oral antidiabetic drugs in subjects with type 2 diabetes.	
Study identifier	Protocol number: NN9535-3624; EudraCT number: 2012-004826-92 Study identifier: NCT01885208. See Trial 3624 report body (M 5.3.5.1)
Design	This was a 56-week randomised, open-label, active-controlled, parallel-group, multi-national, multicentre, two-armed, efficacy and safety trial that compared once-weekly semaglutide 1.0 mg against once-weekly exenatide ER 2.0 mg. Male and female subjects

	diagnosed with type 2 diabetes (T2D) were included in the trial. Following a 2-week screening period, eligible subjects were randomised 1:1 to treatment with once-weekly subcutaneous injections with either semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 1.0 mg maintenance dose, which subsequently was not to be changed. Subjects randomised to treatment with exenatide ER were to be treated with the 2.0 mg throughout the entire trial. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued; in such cases treatment was not to be re-initiated. Subjects had a final follow-up visit 5 weeks after the last treatment visit.		
	Duration of main phase:	56 week	
	Duration of Run-in phase:	2 week	
	Duration of Extension phase:	Not applicable	
Hypothesis	**Primary objective:** To compare the effect of semaglutide 1.0 mg once-weekly versus exenatide ER 2.0 mg once-weekly on glycaemic control after 56 weeks of treatment. **Secondary objective:** To compare the effect of semaglutide 1.0 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		
Treatments groups	Semaglutide 1.0 mg	406 subjects were randomised to the semaglutide 1.0 mg group.	
	Exenatide ER	407 subjects were randomised to the exenatide ER group.	
Endpoints and definitions	Primary endpoint	Change from baseline in glycosylated haemoglobin (HbA_{1c}) at 56 weeks	The primary endpoint was analysed using a mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment and country were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit. Non-inferiority and superiority were concluded if the upper limit of the two-sided 95%CI for the estimated difference in HbA_{1c} at week 56 between semaglutide 1.0 mg and exenatide ER 2.0 mg were less than 0.3% and 0%, respectively.
	Confirmatory secondary endpoint	Change from baseline in body weight at 56 weeks	Superiority was tested using a MMRM similar to the model used for analysis of the primary endpoint but with body weight at baseline as covariate.
	Supportive secondary endpoints	Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), HbA_{1c} ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline HbA_{1c} and as covariate. For the composite endpoint, both HbA_{1c} and body weight were included as covariates. Missing continuous response data at 56 weeks were imputed from the MMRM used for the primary analysis of HbA_{1c}.

		hypoglycaemia and no weight gain	
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 56 weeks	Analysed using the same type of model as described for the primary endpoint but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 56 weeks	Analysed using the same type of model as described for the primary endpoint but with the associated baseline value as covariate.
		Change from baseline in Diabetes Treatment Satisfaction Questionnaire ($DTSQ_s$) components at 56 weeks	The post-baseline responses are analysed using an ANCOVA model with treatment and country as fixed factors and baseline value as covariate. Mean estimates are adjusted according to observed baseline distribution
Database lock	15 January 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or exenatide ER and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.		
Results		**Treatment group**	
		Semaglutide 1.0 mg	**Exenatide ER**
	Number of subjects (FAS)	404	405
HbA_{1c} (%)	Change in HbA_{1c} at 56 weeks, % points ETD (95% CI) vs exenatide ER	-1.54 -0.62 (-0.80, -0.44)	-0.92 -
	HbA_{1c} ≤6.5%, % subjects EOR (95% CI) vs exenatide ER	47 3.73 (2.66, 5.23)	22 -
	HbA_{1c} <7%, % subjects EOR (95% CI) vs exenatide ER	67 3.88 (2.80, 5.38)	40 -
	HbA_{1c} <7.0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain EOR (95% CI) vs exenatide ER	57 4.03 (2.90, 5.59)	29 -
Body weight (kg)	Change in body weight at 56 weeks ETD (95% CI) vs exenatide ER	-5.63 3.78 (-4.58, -2.98)	-1.85 -
	Weight loss ≥5%, % subjects EOR (95% CI) vs placebo	52 5.12 (3.68, 7.11)	17 -
	Weight loss ≥10%, % subjects	21	4

	EOR (95% CI) vs placebo	5.39 (3.20, 9.07)	-
FPG (mmol/L)	Change in FPG at 56 weeks	-2.84	-2.00
	ETD (95% CI) vs exenatide ER	-0.84 (-1.21, -0.47)	-
BP (mmHg)	Change in diastolic BP at 56 weeks	-1.00	-0.10
	ETD (95% CI) vs exenatide ER	-0.90 (-2.16, 0.36)	-
	Change in systolic BP at 56 weeks	-4.60	-2.23
	ETD (95% CI) vs exenatide ER	-2.37 (-4.29, -0.45)	-
$DTSQ_s$	Change in'Treatment satisfaction' at 56 weeks	4.98	3.96
	ETD (95% CI) vs exenatide ER	1.02 (0.28, 1.76)	-

Table 11 Trial NN9535-3625

Title: SUSTAIN 4: Efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonylurea in insulin-naïve subjects with type 2 diabetes			
Study identifier	Protocol number: NN9535-3625; EudraCT number: 2013-004392-12 Study identifier: NCT02128932. See Trial 3625 report body (M 5.3.5.1)		
Design	This was a 30-week randomised, open-label, active-controlled, parallel-group, multicentre, multinational, three-armed trial comparing two doses of semaglutide (0.5 mg and 1.0 mg) once-weekly versus insulin glargine once-daily. Male and female subjects diagnosed with type 2 diabetes (T2D) were included in the trial. Following a 2-week screening period, eligible subjects were randomised 1:1:1 to treatment with either once-weekly subcutaneous injections of either semaglutide 0.5 mg or semaglutide 1.0 mg or insulin glargine once daily for 30 weeks. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently was not to be changed. Subjects on insulin glargine started on 10 IU subcutaneous injected once daily at the same time every day. The insulin dose was to be titrated by the investigator based on the lowest value of the subject's fasting 1 point profile self-measured plasma glucose (SMPG) levels 3 days prior to both visits and phone contacts. Insulin glargine could be titrated between visits at the investigator's discretion. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued; in such cases treatment was not to be re-initiated. Subjects had a final follow-up visit 5 weeks after the last treatment visit.		
	Duration of main phase:	30 week	
	Duration of Run-in phase:	2 week	
	Duration of Extension phase:	Not applicable	
Hypothesis	**Primary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily on glycaemic control after 30 weeks of treatment in insulin-naïve subjects 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 and tolerability		
Treatments groups	Semaglutide 0.5 mg	362 subjects were randomised to the semaglutide 0.5 mg group.	
	Semaglutide 1.0 mg	362 subjects were randomised to the semaglutide 1.0 mg group.	
	Insulin glargine	365 subjects were randomised to the insulin glargine group.	
Endpoints and definitions	Primary endpoint	Change from baseline in glycosylated haemoglobin (HbA_{1c})	The primary endpoint was analysed using a mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c}

		at 30 weeks	measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment, country and pre-trial oral antidiabetic drug (OAD) were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit. Non-inferiority and superiority were concluded if the upper limit of the two-sided 95%CI for the estimated difference in HbA_{1c} at week 30 between semaglutide and insulin glargine were less than 0.3% and 0%, respectively.
	Confirmatory secondary endpoint	Change from baseline in body weight at 30 weeks	Superiority was tested using a MMRM similar to the model used for analysis of the primary endpoint but with body weight at baseline as covariate.
	Supportive secondary endpoints	Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), HbA_{1c} ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline HbA_{1c} and as covariate. For the composite endpoint, both HbA_{1c} and body weight were included as covariates. Missing continuous response data at 30 weeks were imputed from the MMRM used for the primary analysis of HbA_{1c}.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with the associated baseline value as covariate.
		Change from baseline in SF-36v2 at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with the associated baseline value as covariate.
		Change from baseline Diabetes Treatment Satisfaction Questionnaire ($DTSQ_s$) components at 30 weeks	The post-baseline responses are analysed using an ANCOVA model with treatment, country and stratum as fixed factors and baseline value as covariate.

Database lock	23 October 2015			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or insulin glargine and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.			
Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Insulin glargine**
	Number of subjects (FAS)	362	360	360
HbA_{1c} (%)	Change in HbA_{1c} at 30 weeks, % points	-1.21	-1.64	-0.83
	ETD (95% CI) vs insulin glargine	-0.38 (-0.52, -0.24)	-0.81 (-0.96, -0.67)	-
	HbA_{1c} ≤6.5%, % subjects	37.3	54.2	17.5
	EOR (95% CI) vs insulin glargine	3.02 (2.11, 4.33)	6.86 (4.76, 9.89)	-
	HbA_{1c} <7%, % subjects	57.5	73.3	38.1
	EOR (95% CI) vs insulin glargine	2.39 (1.73, 3.28)	5.78 (4.08, 8.19)	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	46.7	64.2	15.6
	EOR (95% CI) vs insulin glargine	5.39 (3.72, 7.81)	12.88 (8.73, 19.02)	-
Body weight (kg)	Change in body weight at 30 weeks	-3.47	-5.17	1.15
	ETD (95% CI) vs insulin glargine	-4.62 (-5.27, -3.96)	-6.33 (-6.99, -5.67)	-
	Weight loss ≥5%, % subjects	37.0	50.8	4.7
	EOR (95% CI) vs insulin glargine	13.37 (7.71, 23.20)	23.94 (13.80,41.50)	-
	Weight loss ≥10%, % subjects	7.7	15.8	1.7
	EOR (95% CI) vs insulin glargine	6.35 (2.42, 16.69)	14.51 (5.70, 36.92)	-
FPG (mmol/L)	Change in FPG at 30 weeks	-2.04	-2.73	-2.12
	ETD (95% CI) vs insulin glargine	0.08 (-0.24, 0.40)	-0.61 (-0.93, -0.29)	-
BP (mmHg)	Change in diastolic BP at 30 weeks	-1.38	-0.98	-1.44
	ETD (95% CI) vs insulin glargine	0.06 (-1.12, 1.24)	0.45 (-0.74, 1.64)	-
	Change in systolic BP at 30 weeks	-4.65	-5.17	-1.68
	ETD (95% CI) vs insulin glargine	-2.97 (-4.92, -1.03)	-3.50 (-5.46, -1.54)	-
SF-36v2	Change in 'General Health' at 30 weeks: ETD (95% CI) vs insulin glargine	0.33 (-0.70, 1.35)	1.15 (0.12, 2.18)	-
	Change in 'Role Emotional' at 30 weeks: ETD (95% CI) vs insulin glargine	0.83 (-0.63, 2.29)	1.67 (0.20, 3.14)	-
$DTSQ_s$	Change in 'Treatment satisfaction' at 30 weeks: ETD (95% CI) vs insulin glargine	0.87 (0.11, 1.63)	1.38 (0.60, 2.15)	-

Table 12 Trial NN9535-3627

Title: SUSTAIN 5: Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin

alone or basal insulin in combination with metformin in subjects with type 2 diabetes.			
Study identifier	Protocol number: NN9535-3627; EudraCT number: 2013-004502-26 Study identifier: NCT02305381. See Trial 3627 report body (M 5.3.5.1)		
Design	This was a multinational, multi-centre, randomised, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of once-weekly semaglutide as add-on to basal insulin in adult subjects with type 2 diabetes (T2D). Male and female subjects diagnosed with T2D inadequately controlled with basal insulin alone or in combination with metformin were included in the trial. Following a 2-week screening period, eligible subjects were randomised in a 2:2:1:1 manner to receive either semaglutide 0.5 mg, semaglutide 1.0 mg, semaglutide placebo 0.5 mg or semaglutide placebo 1.0 mg (hereafter referred to as placebo) once weekly for 30 weeks as add-on to the pre-trial background medication. The randomisation was stratified according to glycosylated haemoglobin (HbA_{1c}) level at screening (≤8.0% or >8.0%) and use of metformin (yes or no). After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently was not to be changed. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued; in such cases treatment was not to be re-initiated. Subjects had a final follow-up visit 5 weeks after the last treatment visit. The placebo groups were pooled in the analysis.		
	Duration of main phase:	30 week	
	Duration of Run-in phase:	2 week	
	Duration of Extension phase:	Not applicable	
Hypothesis	**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 glycaemic control in subjects with T2D on basal insulin. **Secondary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide (0.5 mg and 1.0 mg) versus placebo in subjects with T2D on basal insulin with regards to: - Inducing and maintaining weight loss - Other parameters of efficacy, safety, tolerability and patient reported outcomes		
Treatments groups	Semaglutide 0.5 mg	132 subjects were randomised to the semaglutide 0.5 mg group.	
	Semaglutide 1.0 mg	132 subjects were randomised to the semaglutide 1.0 mg group.	
	Placebo	133 subjects were randomised to the placebo group.	
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} at 30 weeks	The primary endpoint was analysed using a mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment, country, and the stratification variable (HbA_{1c} at screening and use of metformin) were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit. Superiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in HbA_{1c} at week 30 between semaglutide and placebo was less than 0%.
	Confirmatory secondary	Change from baseline in body weight at	Superiority was tested using a MMRM similar to the model used for analysis of the primary

	endpoint	30 weeks	endpoint but with body weight at baseline as covariate.
	Supportive secondary endpoints	Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), HbA_{1c} ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline HbA_{1c} and as covariate. For the composite endpoint, both HbA1c and body weight were included as covariates. Missing continuous response data at 30 weeks were imputed from the MMRM used for the primary analysis of HbA_{1c}.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 30 weeks	Analysed using the same type of model as described for the primary endpoint but with the associated baseline value as covariate.
		Change from baseline in Insulin dose at 30 weeks	Analysed using an analysis of covariance (ANCOVA) model with treatment, country, and stratification variable (HbA_{1c} 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 insulin dose as covariate.
		Change from baseline Diabetes Treatment Satisfaction Questionnaire ($DTSQ_s$) components at 30 weeks	The post-baseline responses are analysed using an ANCOVA model with treatment and country as fixed factors and baseline value as covariate.
Database lock	21 January 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or sitagliptin and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.			
Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Placebo**
	Number of subjects (FAS)	132	131	133
HbA_{1c} (%)	Change in HbA_{1c} at 30 weeks, % points	-1.45	-1.85	-0.09

	ETD (95% CI) vs placebo	-1.35 (-1.61, -1.10)	-1.75 (-2.01, -1.50)	-
	HbA_{1c} ≤6.5%, % subjects	41	61	5
	EOR (95% CI) vs placebo	15.61 (6.47, 37.64)	35.84 (14.72, 87.27)	-
	HbA_{1c} <7%, % subjects	61	79	11
	EOR (95% CI) vs placebo	14.68 (7.43, 29.02)	34.28 (16.59, 70.83)	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	54	67	7
	EOR (95% CI) vs placebo	17.90 (8.26, 38.78)	29.93 (13.65, 65.61)	-
Body weight (kg)	Change in body weight at 30 weeks	-3.67	-6.42	-1.36
	ETD (95% CI) vs placebo	-2.31 (-3.33, -1.29)	-5.06 (-6.08, -4.04)	-
	Weight loss ≥5%, % subjects	42	66	11
	EOR (95% CI) vs placebo	5.91 (3.08, 11.31)	16.59 (8.52, 32.30)	-
	Weight loss ≥10%, % subjects	9	26	3
	EOR (95% CI) vs placebo	3.18 (1.05, 9.63)	12.80 (4.51, 36.33)	-
FPG (mmol/L)	Change in FPG at 30 weeks	-1.62	-2.35	-0.47
	ETD (95% CI) vs placebo	-1.14 (-1.75, -0.54)	-1.88 (-2.48, -1.28)	-
BP (mmHg)	Change in diastolic BP at 30 weeks	-1.84	-1.50	-2.17
	ETD (95% CI) vs placebo	0.33 (-1.80, 2.45)	0.66 (-1.47, 2.80)	-
	Change in systolic BP at 30 weeks	-4.29	-7.27	-0.99
	ETD (95% CI) vs placebo	-3.31 (-6.92, 0.31)	-6.29 (-9.91, -2.66)	-
Insulin dose	Change in Insulin dose at 30 weeks (ratio)	0.90	0.85	0.96
	Treatment ratio(95% CI) vs placebo	0.94 (0.90, 0.98)	0.88 (0.84, 0.92)	-
$DTSQ_s$	Change in 'Treatment satisfaction' at 30 weeks: ETD (95% CI) vs placebo	1.48 (0.14, 2.82)	2.22 (0.87, 3.56)	-

Table 13 Trial NN9535-4092

Title: Safety and efficacy of semaglutide once weekly versus sitagliptin once daily, both as monotherapy in Japanese subjects with type 2 diabetes	
Study identifier	Protocol number: NN9535-4092; EudraCT number: Not applicable Study identifier: NCT02254291. See Trial 4092 report body (M 5.3.5.1)
Design	This was a randomised, open-label, parallel-group, active-controlled, single country, multicentre trial to evaluate the safety and efficacy of once-weekly dosing of semaglutide as monotherapy compared to sitagliptin once daily as monotherapy in Japanese subjects with type 2 diabetes (T2D). Male or female subjects ≥20 years old diagnosed with T2D and being treated with oral antidiabetic (OAD) monotherapy in addition to diet and exercise therapy or diet and exercise therapy alone, were included in the trial. Following an 8-week wash-out period for subjects who, at trial entry, were being treated with OAD monotherapy or a 2-week screening period for subjects who, at trial entry, were being treated with diet and exercise therapy subjects attended a randomisation visit. Eligible subjects were randomised 1:1:1 to treatment with either semaglutide 0.5 mg, semaglutide 1.0 mg (both once weekly) or sitagliptin (once daily) for 30 weeks. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently

	was not to be changed. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued; in such cases treatment was not to be re-initiated. Subjects had a final follow-up visit 5 weeks after the last treatment visit.		
	Duration of main phase:	30 week	
	Duration of Run-in phase:	2 week (or 8 week wash out)	
	Duration of Extension phase:	Not applicable	
Hypothesis	**Primary objective:** To compare the safety of once-weekly dosing of semaglutide (0.5 and 1.0 mg) versus sitagliptin (100 mg) once daily, both as monotherapy during 30 weeks of treatment in Japanese subjects with type 2 diabetes. **Secondary objective:** To compare the efficacy of once-weekly dosing of semaglutide (0.5 and 1.0 mg) versus sitagliptin (100 mg) once daily, both as monotherapy after 30 weeks of treatment on: - Glycaemic control - Inducing and maintaining weight loss - Other parameters of efficacy		
Treatments groups	Semaglutide 0.5 mg	103 subjects were randomised to the semaglutide 0.5 mg group.	
	Semaglutide 1.0 mg	102 subjects were randomised to the semaglutide 1.0 mg group.	
	Sitagliptin	103 subjects were randomised to the Sitagliptin group.	
Endpoints and definitions	Supportive secondary efficacy endpoints	Change from baseline in glycosylated haemoglobin (HbA_{1c}) at 30 weeks	Analysed using a mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment and pre-trial treatment at screening were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit.
		Change from baseline in body weight at 30 weeks	Analysed using a MMRM similar to the model used for analysis of change in HbA_{1c} but with body weight at baseline as covariate.
		Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and pre-trial treatment at screening as fixed factors and baseline HbA_{1c} as covariate. Missing response data at 30 weeks were imputed from the MMRM used for the analysis of HbA_{1c}. For the composite endpoint, both HbA_{1c} and body weight were included as covariates.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 30	Analysed using the same type of model as described for the change in HbA_{1c} endpoint but with FPG at baseline as covariate.

		weeks	
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 30 weeks	Analysed using the same type of model as described for the change in HbA_{1c} endpoint but with the associated baseline value as covariate.
Database lock	12 February 2016		
Results and Analysis			
Analysis description	**Secondary Analysis**		
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or sitagliptin and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.		

Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Sitagliptin**
	Number of subjects (FAS)	103	102	103
HbA_{1c} (%)	Change in HbA_{1c} at 30 weeks, % points	-1.87	-2.18	-0.74
	ETD (95% CI) vs sitagliptin	-1.13 (-1.32, -0.94)	-1.44 (-1.63, -1.24)	-
	HbA_{1c} ≤6.5%, % subjects	71	87	16
	EOR (95% CI) vs sitagliptin	18.70 (8.73, 40.04)	45.19 (19.36, 105.47)	-
	HbA_{1c} <7%, % subjects	84	95	35
	EOR (95% CI) vs sitagliptin	16.53 (7.39, 36.99)	43.66 (15.67, 121.62)	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	72	84	18
	EOR (95% CI) vs sitagliptin	14.78 (7.15, 30.58)	28.43 (12.93, 62.54)	-
Body weight (kg)	Change in body weight at 30 weeks	-2.21	-3.87	0.02
	ETD (95% CI) vs sitagliptin	-2.22 (-3.02, -1.42)	-3.88 (-4.70, -3.07)	-
	Weight loss ≥5%, % subjects	29	57	7
	EOR (95% CI) vs sitagliptin	5.28 (2.23, 12.53)	19.35 (8.17, 45.83)	
	Weight loss ≥10%, % subjects	7	19	0
FPG (mmol/L)	Change in FPG at 30 weeks	-2.81	-3.33	-1.34
	ETD (95% CI) vs sitagliptin	-1.47 (-1.78, -1.16)	-1.99 (-2.30, -1.67)	-
BP (mmHg)	Change in diastolic BP at 30 weeks	-1.48	-3.59	-1.61
	ETD (95% CI) vs sitagliptin	0.12 (-1.97, 2.21)	-1.99 (-4.13, 0.16)	-
	Change in systolic BP at 30 weeks	-5.32	-8.78	-2.77
	ETD (95% CI) vs sitagliptin	-2.54 (-5.64, 0.55)	-6.01 (-9.16, -2.85)	-

Table 14 Trial NN9535-4091

Title: Safety and efficacy of semaglutide once weekly in monotherapy or in combination with one oral antidiabetic drug (OAD) in Japanese subjects with type 2 diabetes who are insufficiently controlled on diet/exercise therapy or OAD monotherapy.	
Study identifier	Protocol number: NN9535-4091; EudraCT number: Not applicable

	Study identifier: NCT02207374. See Trial 4091 report body (M 5.3.5.1)		
Design	This was a 56-week, randomised, open-label, active-controlled, parallel-group, multi-centre, single-country trial to evaluate the safety and efficacy of once-weekly semaglutide in monotherapy or in combination with one OAD in Japanese subjects with type 2 diabetes (T2D). Male or female subjects ≥20 years old diagnosed with T2D and being treated with OAD monotherapy in addition to diet and exercise therapy or diet and exercise therapy alone, were included in the trial. Following a 2-week screening period, eligible subjects were randomised 2:2:1 to treatment with either semaglutide 0.5 mg, semaglutide 1.0 mg (both once weekly) or one additional OAD for 56 weeks. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently was not to be changed. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued; in such cases treatment was not to be re-initiated. The type and dosage of the additional OAD was to be selected by the investigator according to the approved Japanese labelling including drug combinations and contraindications. One choice of DPP-4 inhibitor, sulphonylurea (SU), glinide, biguanide, alpha-glucosidase inhibitors (α-GI) or thioazolidinediones (TZD) would be selected as the additional OAD. For the subjects treated with OAD monotherapy as pre-trial treatment, the type and dosage of the additional OAD with a different mechanism of action from the pre-trial OAD was to be chosen. The dose of the additional OAD would be optimised within approved Japanese labelling until week 8; thereafter the dose had to remain unchanged unless rescue medication was needed. The type of the additional OAD was not to be changed during the trial. Subjects had a final follow-up visit 5 weeks after the last treatment visit.		
	Duration of main phase:	56 week	
	Duration of Run-in phase:	2 week	
	Duration of Extension phase:	Not applicable	
Hypothesis	**Primary objective:** To compare the safety of once-weekly dosing of semaglutide (0.5 and 1.0 mg) in monotherapy or in combination with one OAD (either of SU, glinide, α-GI or TZD) versus OAD therapy during 56 weeks of treatment in Japanese subjects with T2D who are insufficiently controlled on diet/exercise therapy or OAD monotherapy (either of SU, glinide, α-GI or TZD). **Secondary objective:** To compare the efficacy of once-weekly dosing of semaglutide (0.5 and 1.0 mg) in monotherapy or in combination with one OAD (either of SU, glinide, α-GI or TZD) versus OAD therapy after 56 weeks of treatment on: - Glycaemic control - Inducing and maintaining weight loss - Other parameters of efficacy		
Treatments groups	Semaglutide 0.5 mg	239 subjects were randomised to the semaglutide 0.5 mg group.	
	Semaglutide 1.0 mg	241 subjects were randomised to the semaglutide 1.0 mg group.	
	Additional OAD	121 subjects were randomised to the additional OAD group.	
Endpoints and definitions	Supportive secondary efficacy endpoints	Change from baseline in glycosylated haemoglobin (HbA_{1c}) at 56 weeks	Analysed using a mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment, pre-trial treatment at screening and interaction between treatment and pre-trial treatment at screening were included as fixed

			factors and baseline HbA_{1c} as fixed covariate, all nested within visit.
		Change from baseline in body weight at 56 weeks	Analysed using a MMRM similar to the model used for analysis of change in HbA_{1c} but with body weight at baseline as covariate.
		Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and pre-trial treatment as fixed factors and baseline HbA_{1c} as covariate. Missing response data at 56 weeks were imputed from the MMRM used for the analysis of HbA_{1c}. For the composite endpoint, both HbA_{1c} and body weight were included as covariates.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 56 weeks	Analysed using the same type of model as described for the change in HbA_{1c} endpoint but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 56 weeks	Analysed using the same type of model as described for the change in HbA_{1c} endpoint but with the associated baseline value as covariate.
Database lock	18 April 2016		

Results and Analysis

Analysis description	**Secondary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects who had received at least one dose of randomised semaglutide or additional OAD and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was 'On-treatment without rescue medication'.			
Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Additional OAD**
	Number of subjects (FAS)	239	241	120
HbA_{1c} (%)	Change in HbA_{1c} at 56 weeks, % points	-1.74	-2.03	-0.67
	ETD (95% CI) vs additional OAD	-1.08 (-1.24, -0.91)	-1.37 (-1.53, -1.20)	-
	HbA_{1c} ≤6.5%, % subjects	71	80	15
	EOR (95% CI) vs additional OAD	17.76 (9.64, 32.72)	35.76 (18.66, 68.50)	-

	HbA_{1c} <7%, % subjects	84	91	42
	EOR (95% CI) vs additional OAD	9.42 (5.39, 16.46)	23.06 (11.99, 44.36)	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	62	74	20
	EOR (95% CI) vs additional OAD	7.63 (4.40, 13.25)	15.79 (8.84, 28.21)	-
Body weight (kg)	Change in body weight at 56 weeks	-1.43	-3.18	0.41
	ETD (95% CI) vs additional OAD	-1.84 (-2.67, -1.01)	-3.59 (-4.43, -2.75)	-
	Weight loss ≥5%, % subjects	26	46	6
	EOR (95% CI) vs additional OAD	5.61 (2.51, 12.51)	14.83 (6.69, 32.85)	-
	Weight loss ≥10%, % subjects	8	17	1
	EOR (95% CI) vs additional OAD	7.41 (1.42, 38.73)	17.69 (3.48, 89.99)	-
FPG (mmol/L)	Change in FPG at 56 weeks	-2.35	-2.72	-0.69
	ETD (95% CI) vs additional OAD	-1.66 (-1.94, -1.38)	-2.03 (-2.32, -1.75)	-
BP (mmHg)	Change in diastolic BP at 56 weeks	-0.76	-1.02	-0.56
	ETD (95% CI) vs additional OAD	-0.20 (-1.88, 1.48)	-0.46 (-2.16, 1.23)	-
	Change in systolic BP at 56 weeks	-1.95	-3.70	0.17
	ETD (95% CI) vs additional OAD	-2.12 (-4.81, 0.57)	-3.87 (-6.59, -1.15)	-

Table 15 Trial NN9535-3744

Title: SUSTAIN 6- Long Term Outcomes: A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.		
Study identifier	Protocol number: NN9535-3744; EudraCT number: 2012-002839-28 Study identifier: NCT01720446. See Trial 3744 report body (M 5.3.5.1)	
Design	This trial was a long-term, multi-centre, multi-national, randomised, double-blind, parallel-group, controlled trial performed to establish the cardiovascular (CV) safety and long term outcomes of semaglutide compared to placebo, when added to standard-of-care, in men and women with type 2 diabetes (T2D) at high risk of CV events. Following a 2 week screening period, eligible subjects were randomised 1:1:1:1 to either semaglutide 0.5 mg, semaglutide 1.0 mg or volume-matched placebo once-weekly, a treatment period of 104 weeks and a post-treatment follow-up period of 5 weeks. After randomisation, subjects randomised to semaglutide treatment followed a fixed dose-escalation regimen to reach the 0.5 mg or 1.0 mg maintenance dose, which subsequently was not to be changed. The trial duration was partly event-driven and was to be terminated when the projected number of subjects with 3-component event adjudication committee (EAC) confirmed major adverse cardiovascular event (MACE) was at least 122, and at the earliest 104 weeks after the last subject had been randomised. 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 subject was treated for 104 weeks with a post-treatment follow-up period of 5 weeks, resulting in a planned trial duration of 109 weeks per subject. Randomisation was stratified to ensure even distribution within strata according to the following 3 stratification variables: evidence of CV disease at baseline (clinical or subclinical), insulin treatment at baseline (none, basal insulin or pre-mixed insulin), renal impairment with globular filtration rate value <30 mL/min/1.73 m^2 at baseline (presence or absence). By trial design, subjects with severe renal impairment always fall into the "clinical evidence of CV disease" stratum. This resulted in a total of 9 strata.	
	Duration of main phase:	104 week

	Duration of Run-in phase:	2 week	
	Duration of Extension phase:	Not applicable	
Hypothesis	**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 T2D. This is done by demonstrating that the upper limit of the two-sided 95% CI of the hazard ratio for semaglutide versus placebo is less than 1.8 when comparing time to first occurrence of a MACE. **Secondary objective:** To assess the long-term safety and efficacy of semaglutide 0.5 mg and 1.0 mg once weekly compared to placebo, both added on to standard-of-care, in adults with T2D at high risk of cardiovascular events.		
Treatments groups	Semaglutide 0.5 mg	826 subjects were randomised to the semaglutide 0.5 mg group.	
	Semaglutide 1.0 mg	822 subjects were randomised to the semaglutide 1.0 mg group.	
	Placebo	1649 subjects were randomised to the placebo group.	
Endpoints and definitions	Primary endpoint	Time from randomisation to first occurrence of a MACE, defined as CV death, non-fatal myocardial infarction, or non-fatal stroke.	Analysed using a stratified Cox proportional hazards model with treatment group (pooled semaglutide, pooled placebo) as fixed factor. The model was stratified by all possible combinations of the 3 stratification factors used in the randomisation procedure (in total 9 levels). From this model the hazard ratio (HR; semaglutide/placebo) together with the 2-sided 95% CI were estimated. MACEs occurring after a subject's first EAC-confirmed MACE did not contribute to the Cox analysis. The analysis was considered confirmatory.
	Confirmatory secondary efficacy endpoints	Change from baseline in body weight at 104 weeks	Analysed using a mixed model for repeated measurement (MMRM); all post-baseline measurements obtained at scheduled visits were included as dependent variables. Treatment group (3 levels: semaglutide 0.5 mg, semaglutide 1.0 mg, pooled placebo) and stratification (9 levels) were included as fixed factors and baseline value as covariate, all nested within visit. Superiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in change in body weight between semaglutide and placebo was less than 0 kg.
		Change from baseline in glycosylated haemoglobin (HbA_{1c}) at 30 weeks for subjects on premix insulin at baseline and subjects on SU monotherapy at baseline	Analysed using a MMRM similar to the model used for analysis of change in body weight but with HbA_{1c} at baseline as covariate. The model included interaction between treatment group and the relevant subgroup (2 levels for SU monotherapy subgroup analysis, 3 levels for insulin subgroup analysis). An unstructured covariance matrix was assumed for measurements within the same subject. Superiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in HbA_{1c} at week 30 between semaglutide and placebo was less than 0%.
	Supportive	Change from baseline in	Analysed using a MMRM. The model included

	secondary efficacy endpoints	HbA_{1c} at 104 weeks	treatment group (4 levels: semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg, placebo 1.0 mg) and stratification (9 levels) as fixed factors and the corresponding baseline value as a covariate, all nested within visit. An unstructured covariance matrix was assumed for measurements within the same subject.
		Requirement of additional glucose-lowering medication at 104 weeks	Analysed using a logistic regression model with treatment (4 levels: semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg and placebo 1.0 mg) and stratification (9 levels) as fixed factors and baseline HbA_{1c} as a covariate.
		Percent subjects achieving HbA_{1c} <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol), HbA_{1c} <7% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia and no weight gain	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and stratification as fixed factors and baseline HbA_{1c} as covariate. For the composite endpoint, both HbA_{1c} and body weight were included as covariates.
		Percent subjects achieving weight loss ≥5%, weight loss ≥10%	Analysed using a logistic regression model presenting odds ratio and 95% CI. The model included treatment and stratification as fixed factors and baseline body weight as covariate.
		Change from baseline in fasting plasma glucose (FPG) (mmol/L) at 104 weeks	Analysed using the same type of model as described for the change in HbA_{1c} endpoint at 104 weeks but with FPG at baseline as covariate.
		Change from baseline in systolic and diastolic blood pressure (BP) (mmHg) at 104 weeks	Analysed using the same type of model as described for the change in HbA_{1c} endpoint at 104 weeks but with the associated baseline value as covariate.
Database lock	22 June 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and description	Analyses of efficacy endpoints were based on the full analysis set (FAS). The FAS included all randomised subjects and contributed to the evaluation based on their randomised treatment. The primary observation period for examination of efficacy endpoints was the 'In-trial'.			
Results		**Treatment group**		
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Placebo**
	Number of subjects (FAS)	826	822	1649
EAC-confirmed MACE	First MACE; subjects with events (%)	108 (6.6)		146 (8.9)
	HR (95% CI) vs placebo	0.74 (0.58, 0.95)		-
	Non-fatal MI; subjects with events (%)	47 (2.9)		64 (3.9)

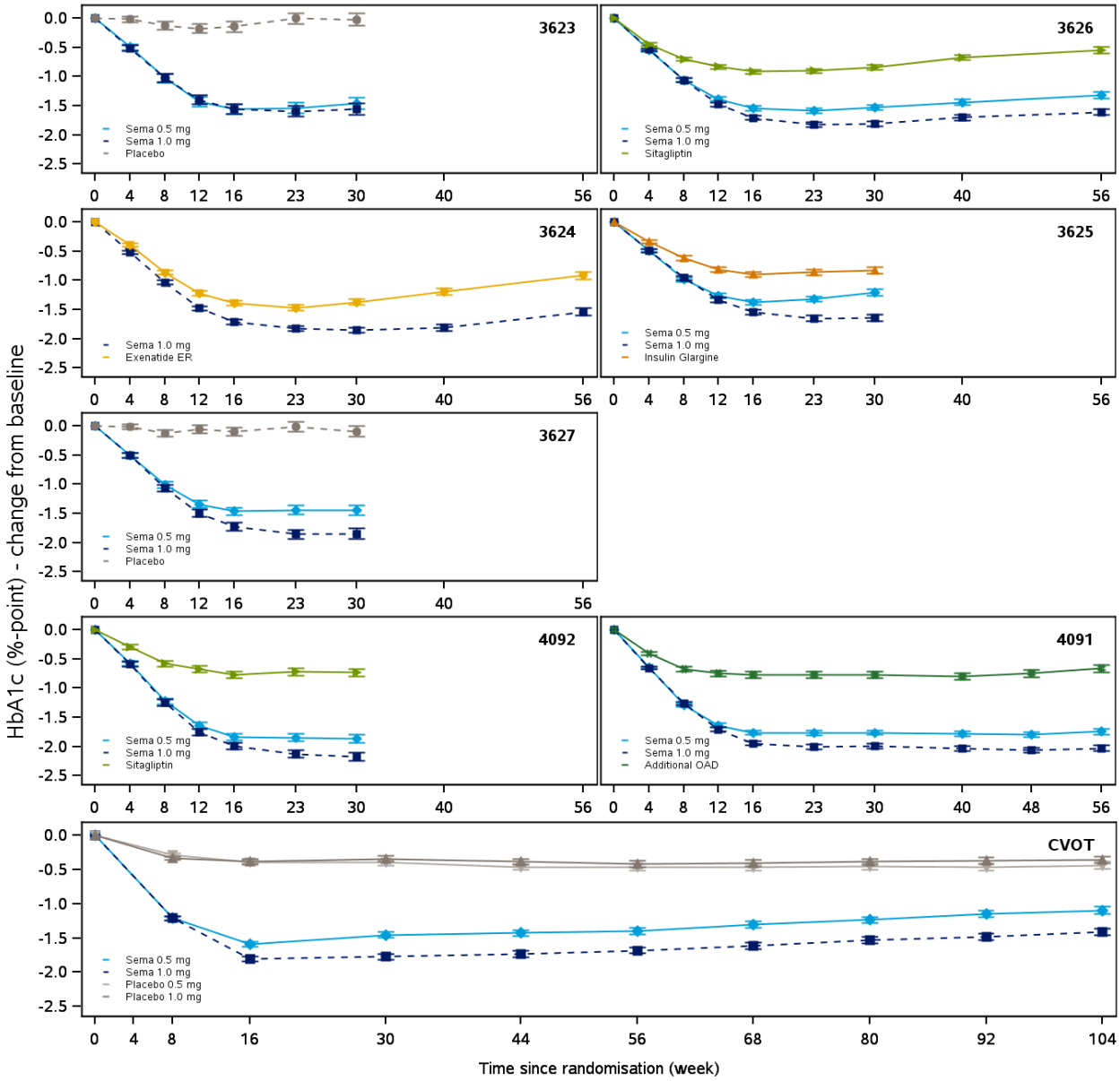
	HR (95% CI) vs placebo	0.74 (0.51, 1.08)		-	
	Non-fatal Stroke; subjects with events (%)	27 (1.6)		44 (2.7)	
	HR (95% CI) vs placebo	0.61 (0.38, 0.99)		-	
	CV Death; subjects with events (%)	44 (2.7)		46 (2.8)	
	HR (95% CI) vs placebo	0.98 (0.65, 1.48)		-	
Body weight (kg)	Change in body weight at 104 weeks	-3.57	-4.88	-0.62	
	ETD (95% CI) vs placebo	-2.95 (-3.47, -2.44)	-4.27 (-4.78, -3.75)		
HbA_{1c} (%)	Change in HbA_{1c} at 30 weeks by baseline use of premix insulin, % points	-1.27	-1.78	-0.41	
	ETD (95% CI) vs placebo	-0.86 (-1.06, -0.66)	-1.37 (-1.57, -1.17)	-	
	Change in HbA_{1c} at 30 weeks by baseline use of SU monotherapy, % points	-1.60	-1.50	0.13	
	ETD (95% CI) vs placebo	-1.74 (-2.28, -1.19)	-1.64 (-2.16, -1.12)	-	
		Semaglutide 0.5 mg	**Semaglutide 1.0 mg**	**Placebo 0.5 mg**	**Placebo 1.0 mg**
	Number of subjects (FAS)	826	822	824	825
HbA_{1c} (%)	Change in HbA_{1c} at 104 weeks, % points	-1.09	-1.41	-0.44	-0.36
	ETD (95% CI) vs placebo	-0.66 (-0.80, -0.52)	-1.05 (-1.19, -0.91)	-	-
	HbA_{1c} ≤6.5%, % subjects	23	34	7	8
	EOR (95% CI) vs placebo	4.10 (3.00, 5.62)	6.82 (5.05, 9.23)	-	-
	HbA_{1c} <7%, % subjects	39	49	16	15
	EOR (95% CI) vs placebo	3.63 (2.85, 4.63)	6.31 (4.93, 8.07)	-	-
	HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain, % subjects	25	35	9	8
	EOR (95% CI) vs placebo	3.72 (2.77, 5.00)	7.15 (5.29, 9.65)	-	-
Body weight (kg)	Weight loss ≥5%, % subjects	36	47	18	19
	EOR (95% CI) vs placebo	2.68 (2.13, 3.37)	3.84 (3.07, 4.80)	-	-
	Weight loss ≥10%, % subjects	13	20	6	7
	EOR (95% CI) vs placebo	2.53 (1.77, 3.61)	3.71 (2.68, 5.12)	-	-
Glucose lowering medication	Addition of glucose-lowering medication at 30 weeks, % subjects	21	19	42	39
	EOR (95% CI) vs placebo	0.33 (0.27, 0.42)	0.35 (0.27, 0.44)	-	-
FPG (mmol/L)	Change in FPG at 104 weeks	-1.75	-2.11	-1.02	-0.88
	ETD (95% CI) vs placebo	-0.72 (-1.06, -0.38)	-1.22 (-1.56, -0.88)	-	-
BP (mmHg)	Change in diastolic BP at 104 weeks	-1.37	-1.57	-1.42	-1.71
	ETD (95% CI) vs placebo	0.04 (-0.83, 0.92)	0.14 (-0.74 ; 1.03)	-	-
	Change in systolic BP at 104 weeks	-3.44	-5.37	-2.17	-2.78
	ETD (95% CI) vs placebo	-1.27 (-2.77, 0.23)	-2.59 (-4.09, -1.08)	-	-

Analysis performed across trials (pooled analyses AND meta-analysis)

HbA1c

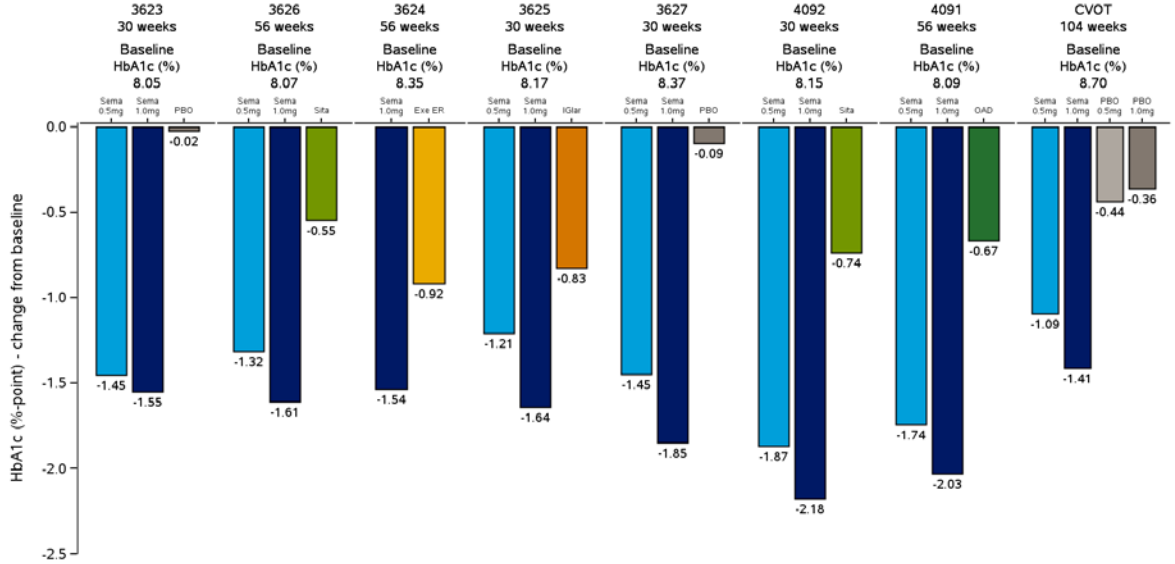
For all eight phase 3a trials, treatment with semaglutide 0.5 mg or 1.0 mg resulted in marked, sustained improvements in glycaemic control, as shown by a reduction in HbA_{1c}, beginning after 4 weeks of treatment and reaching nadir after 16−30 weeks. The reduction was maintained after long-term treatment of up to 104 weeks (in the CVOT) (Figure 14). The effect appeared to be dose-dependent. The estimated mean plots for HbA_{1c} change from baseline are presented in Figure 14. The estimated change from baseline in HbA_{1c} at end-of-treatment is shown in Figure 16, for HbA_{1c} levels at end-of-treatment. Both doses of semaglutide resulted in significantly larger reductions in HbA_{1c} than comparators: placebo, sitagliptin, exenatide ER and insulin glargine, and improvements in glycaemic control with semaglutide were seen for all treatment regimens investigated: monotherapy and combination therapy with metformin +/- other OADs or insulin +/- metformin.

Figure 14 HbA_{1c} (%-point) by treatment week – mean plot – estimated – phase 3a 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 HbA1c as covariate, all nested within visit, and adjusted according to observed baseline distribution.

Figure 15 HbA_{1c} (%–point) – estimated change from baseline to end of treatment – statistical analyses – bar plot – phase 3a trials

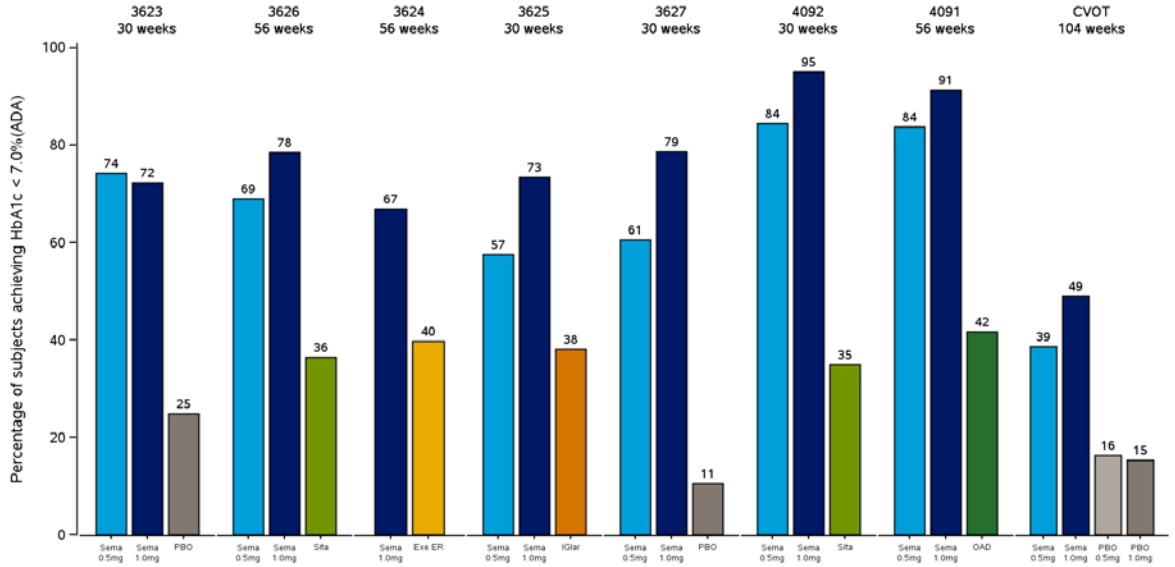


PBO: Placebo, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, CVOT: Cardiovascular outcomes trial, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country (key efficacy trials) as fixed factors and baseline HbA1c as covariate, all nested within visit, and adjusted according to observed baseline distribution.

HbA_{1c} treatment targets

For all trials, significantly more subjects with semaglutide reached the three HbA_{1c} treatment target <7% vs comparator (Figure 16).

Figure 16 Proportion of subjects reaching an HbA_{1c} <7.0 %



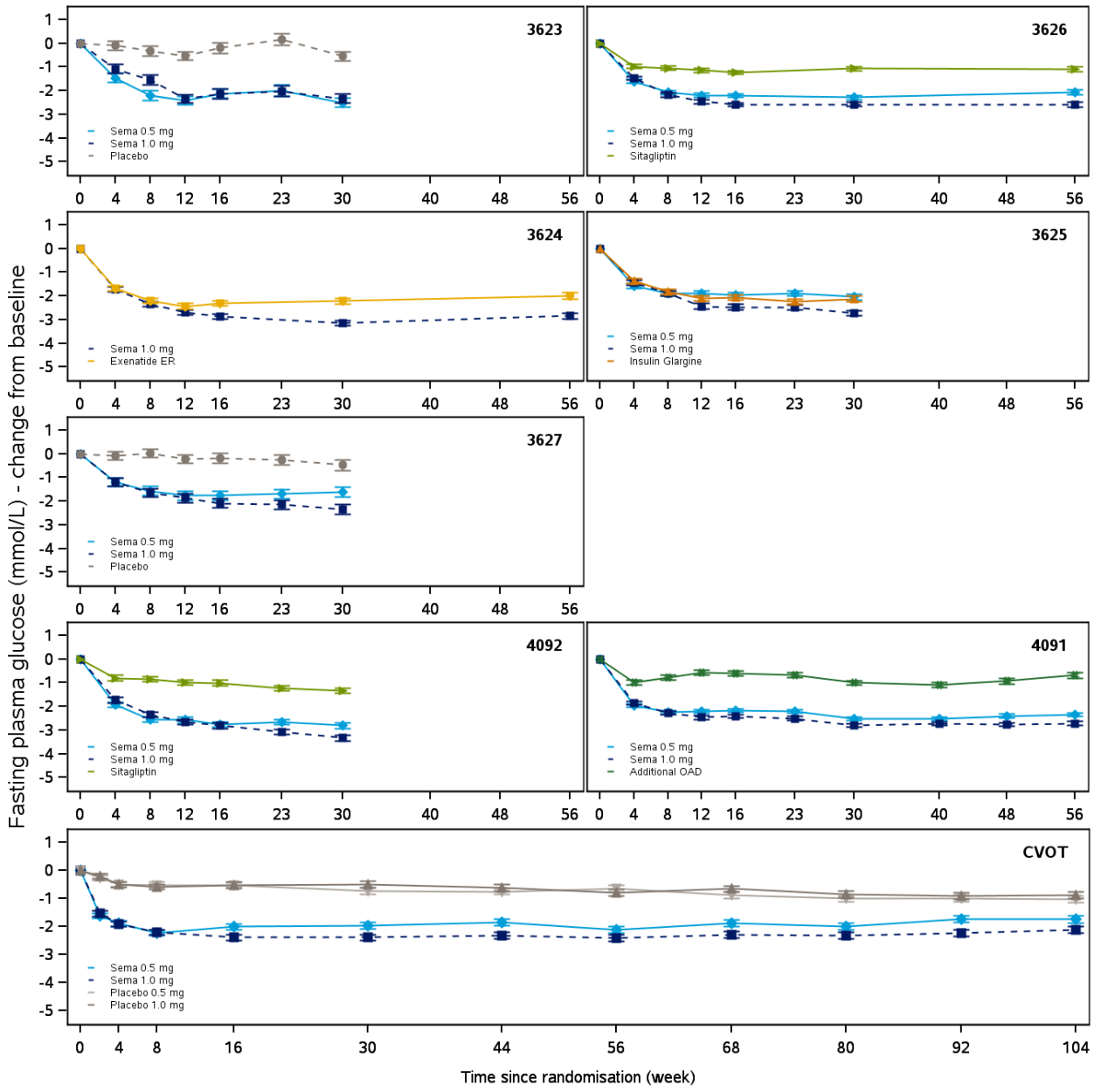
ADA: American Diabetes Association, CVOT: Cardiovascular outcomes trial, PBO: Placebo, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are 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.

Fasting plasma glucose

Mean change in FPG levels from baseline to end-of-treatment was investigated in all phase 3a trials.

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 (Figure 17).

Figure 17 Fasting plasma glucose (mmol/L) by treatment week – estimated change from baseline – mean plot – phase 3a trials

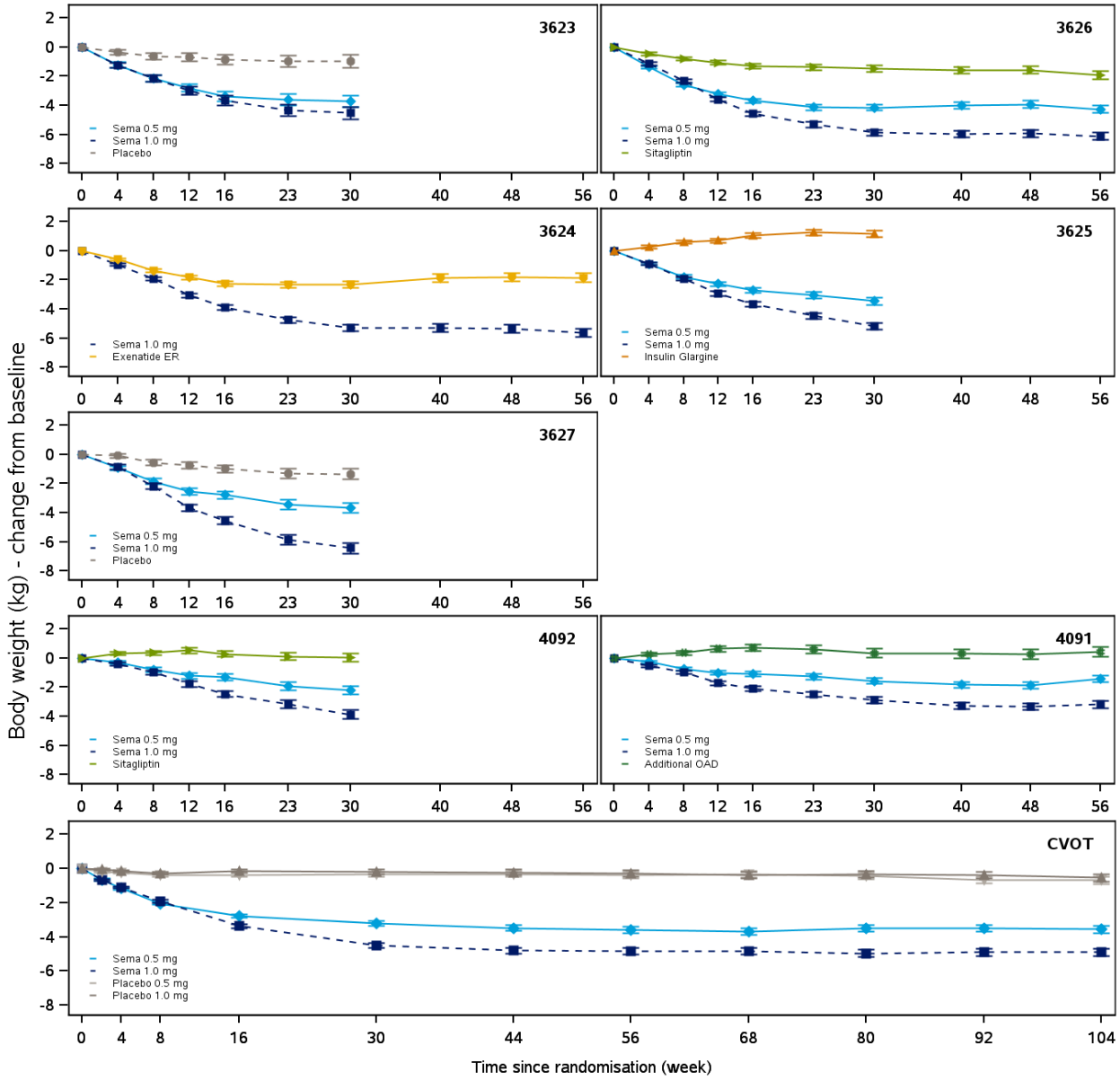


Exenatide ER: Exenatide Extended Release, OAD: Oral anti-diabetic drug, CVOT: Cardiovascular outcomes trial, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Estimates are from the mixed model for repeated measurements with treatment, 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.

Body weight

For all eight phase 3a 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) (Figure 18). The effect appeared to be dose-dependent (Figure 18 .

Figure 18 Body weight (kg) by treatment week – mean plot – estimated – phase 3a trials

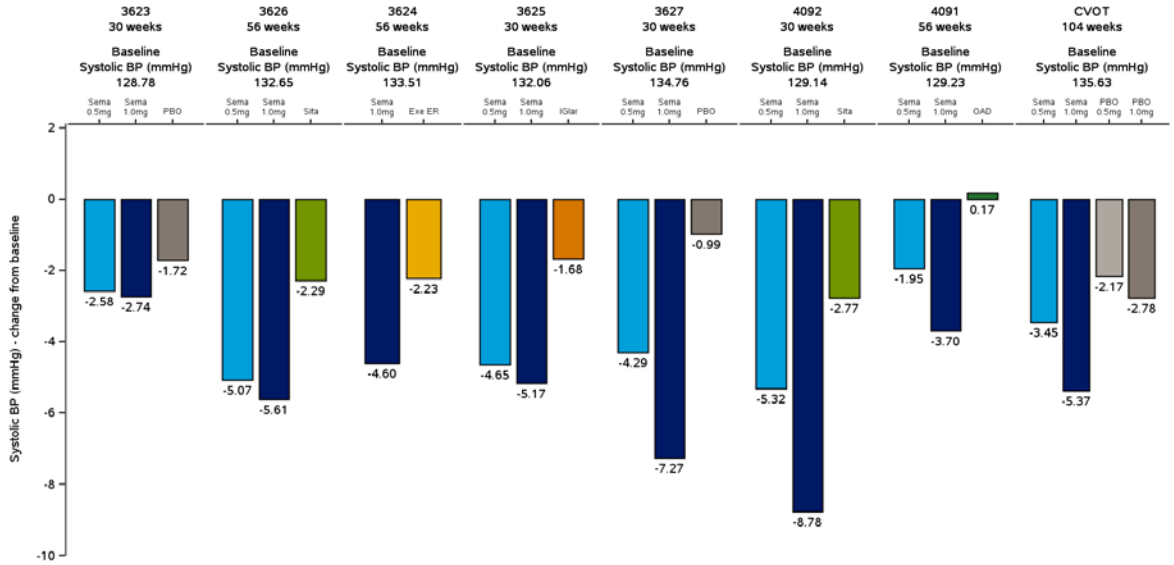


Exenatide ER: Exenatide Extended Release, OAD: Oral anti-diabetic drug, CVOT: Cardiovascular outcomes trial, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) are presented. Estimates are from the mixed model for repeated measurements with treatment, 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.

Blood pressure

In general, systolic blood pressure decreased progressively during the first 23-30 weeks of semaglutide treatment, after which the levels stabilised through the remaining treatment period. Overall, systolic blood pressure decreased more with semaglutide 1.0 mg vs 0.5 mg vs comparators at end-of-treatment (Figure 19). In general, diastolic blood pressure also appeared to decrease over time (Figure 19). Overall, apparent reductions in diastolic blood pressure were seen with semaglutide but also with the comparators at end-of-treatment.

Figure 19 Systolic blood pressure (mmHg) - estimated change from baseline – bar plot – phase 3a trials

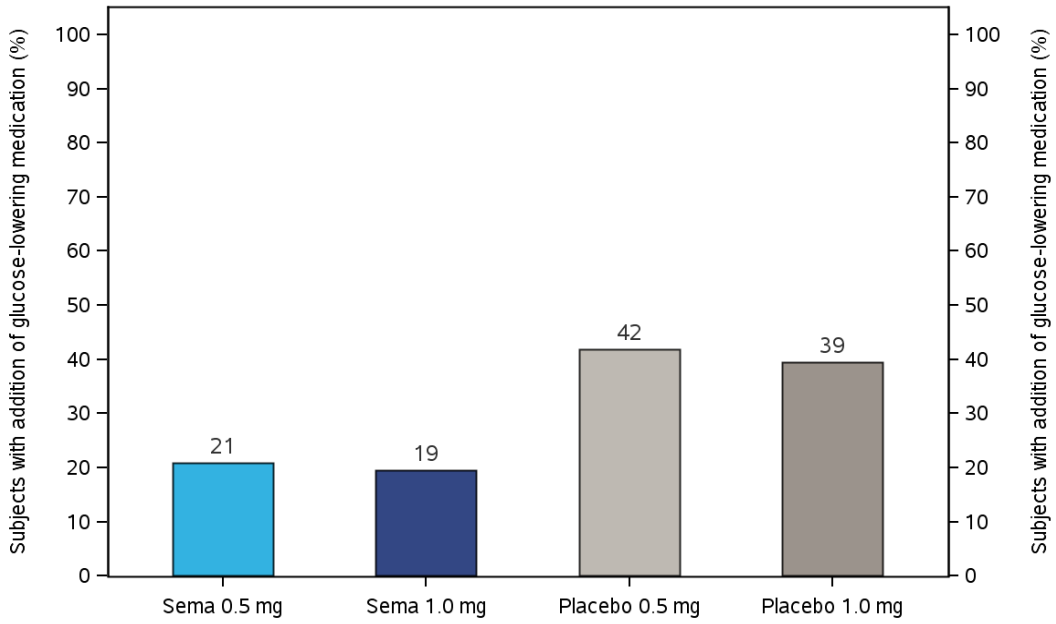


BP: Blood pressure, CVOT: Cardiovascular outcomes trial, Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, BP: Blood pressure, PBO: Placebo, On-treatment without rescue medication data (key efficacy + Japanese trials) and in-trial data (CVOT) 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.

Intensification of anti-glycaemic therapy

In the CVOT, glucose-lowering medications (except treatments affecting the incretin pathway such as other GLP-1 RAs, DPP-4 inhibitors or pramlintide) were to be added to the anti-glycaemic regimen during the entire course of the trial to achieve and maintain optimal glycaemic control according to local standards. The long-term effect of semaglutide on HbA_{1c} was demonstrated by analyses of initiation of glucose-lowering medication during the CVOT showing that half as many patients treated with semaglutide (0.5 mg: 21%; 1.0 mg: 19 %) than with placebo (0.5 mg: 42%; 1.0 mg: 39%) required additional glucose-lowering medication (Figure 20). The findings from the CVOT are supported by data from the phase 3a trials. Less patients completed treatment with added rescue medication in the semaglutide group (0.0–5.4%) than in the placebo group (14.3–20.2%) or active comparator group (1.4–19.7%).

Figure 20 Proportion of subjects with addition of glucose-lowering medication



Observed 'in-trial' data. Addition of glucose-lowering medication is defined as the addition of a new type of anti-diabetic medication compared to baseline background treatment that is taken for at least 21 consecutive days.

Patient-reported outcomes

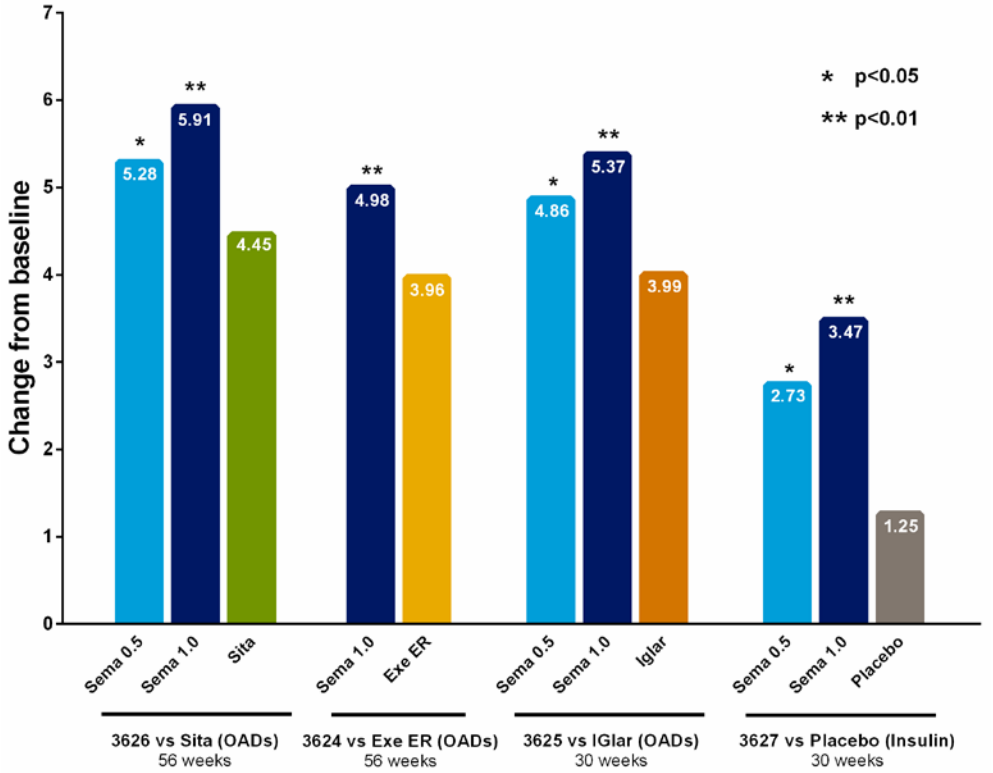
For trials 3624, 3625, 3626 and 3627, diabetes treatment satisfaction questionnaire (DTSQ) and short form (36) health survey (SF-36) scores were investigated at end-of-treatment. For the CVOT, only SF-36 scores were investigated, also at end-of-treatment. Of note, trial 3626 vs Sita (as add-on to OADs) had a double dummy design, subjects were thus treated both with an injection and with an oral formulation, and this could affect the results of the comparison of the two treatments. For trial 3624 vs Exe ER (as add-on to OADs), the device used for exenatide injection was not the same as the current marketed product, and this could affect the relevance of the results to the currently marketed product.

Diabetes Treatment Satisfaction Questionnaire (DTSQ)

At baseline, the three main DTSQ components; treatment satisfaction, perception of hyperglycaemia and perception of hypoglycaemia were similar across treatment groups both within and across trials, albeit treatment satisfaction was slightly higher at baseline in trial 3627 vs Placebo (Insulin) for all three treatment groups.

For all trials investigating DTSQ, both doses of semaglutide significantly improved the summary score of treatment satisfaction (Figure 21) and significantly lowered the perceived frequency of hyperglycaemia compared to placebo and active comparators; sitagliptin, exenatide ER and insulin glargine. There was no difference in the perceived frequency of hypoglycaemia with semaglutide vs comparators.

Figure 21 Diabetes Treatment Satisfaction Questionnaire - Treatment satisfaction summary score – estimated change from baseline – bar plot - trials 3626, 3624, 3625 and 3627



Note: Sita: Sitagliptin, Exe ER: Exenatide Extended Release, IGlar: Insulin Glargine, OAD: Oral anti-diabetic drug, On-treatment without rescue medication data are presented. Estimated change from baseline data are shown. Estimates are from the mixed model for repeated measurements with treatment, trial-specific stratification, and country as fixed factors and baseline Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores as covariate, all nested within visit, and adjusted according to observed baseline distribution.

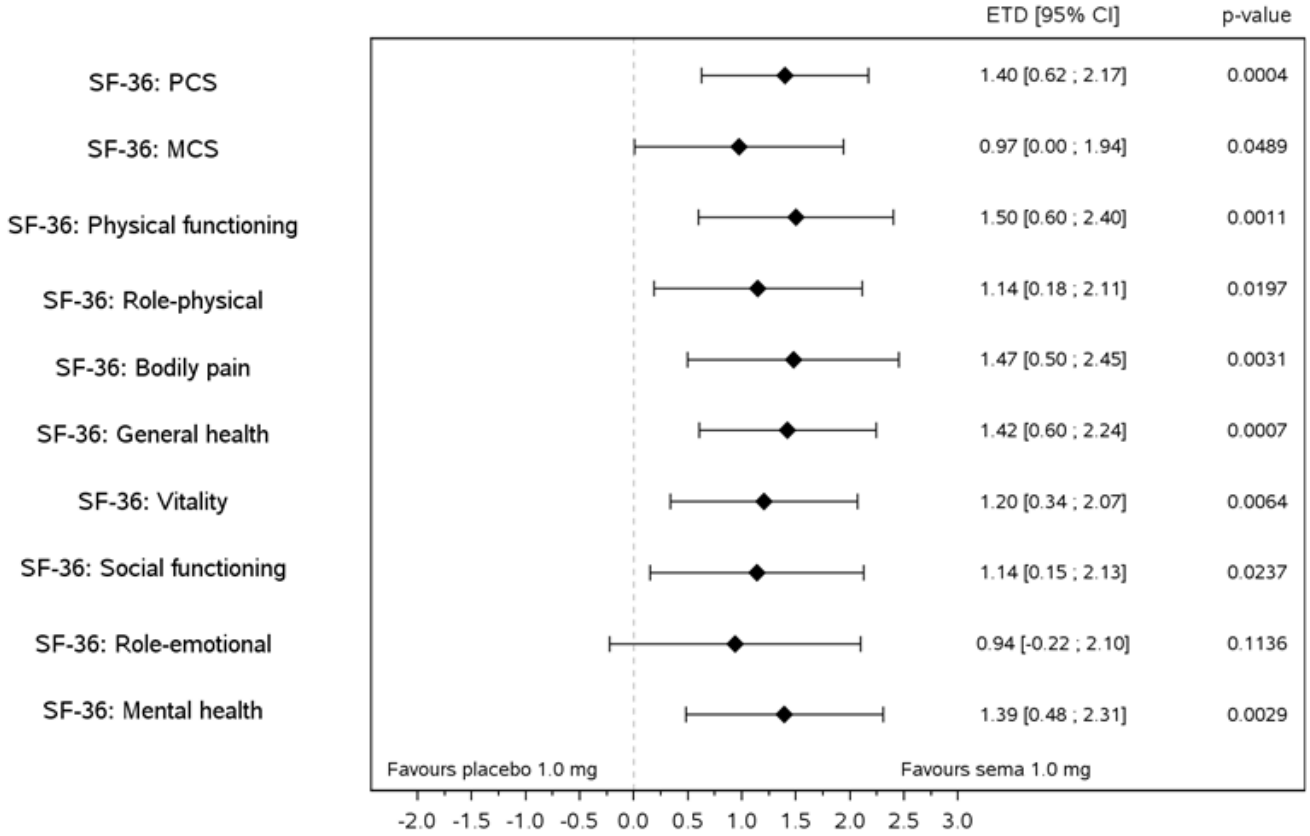
When patients were able to distinguish between treatments (trial 3625), once-weekly semaglutide (0.5 and 1.0 mg) improved treatment satisfaction to a greater extent than once-daily insulin glargine (semaglutide 1.0 mg vs insulin glargine). In addition, once-weekly semaglutide injections were evaluated to be more convenient and flexible than the once-daily insulin glargine regimen.

SF-36

Semaglutide (0.5 and 1.0 mg) provided significantly greater improvements in general health status, as assessed by the Short Form health survey (SF-36 version 2), than placebo in the CVOT in addition to standard-of-care.

Greater improvements with semaglutide 1.0 mg were demonstrated versus placebo across all components including both mental component summary (MCS) and physical component summary (PCS) scores (Figure 22).

Figure 22 Estimated treatment differences in SF-36 summary and subscores after 2-years of treatment (semaglutide 1.0 mg vs placebo 1.0 mg) – FAS in-trial – CVOT



Note: Summary of estimated treatment differences and associated confidence intervals from statistical analyses of SF-36 outcome at week 104. Responses are analysed using an MMRM with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit.
Abbreviations: CI: confidence interval; CVOT: cardiovascular outcomes trial; ETD: estimated treatment difference; MCS: mental component summary; PCS: physical component summary; FAS: full analysis set.

Cardiovascular risk

Cardiovascular outcomes in the CVOT

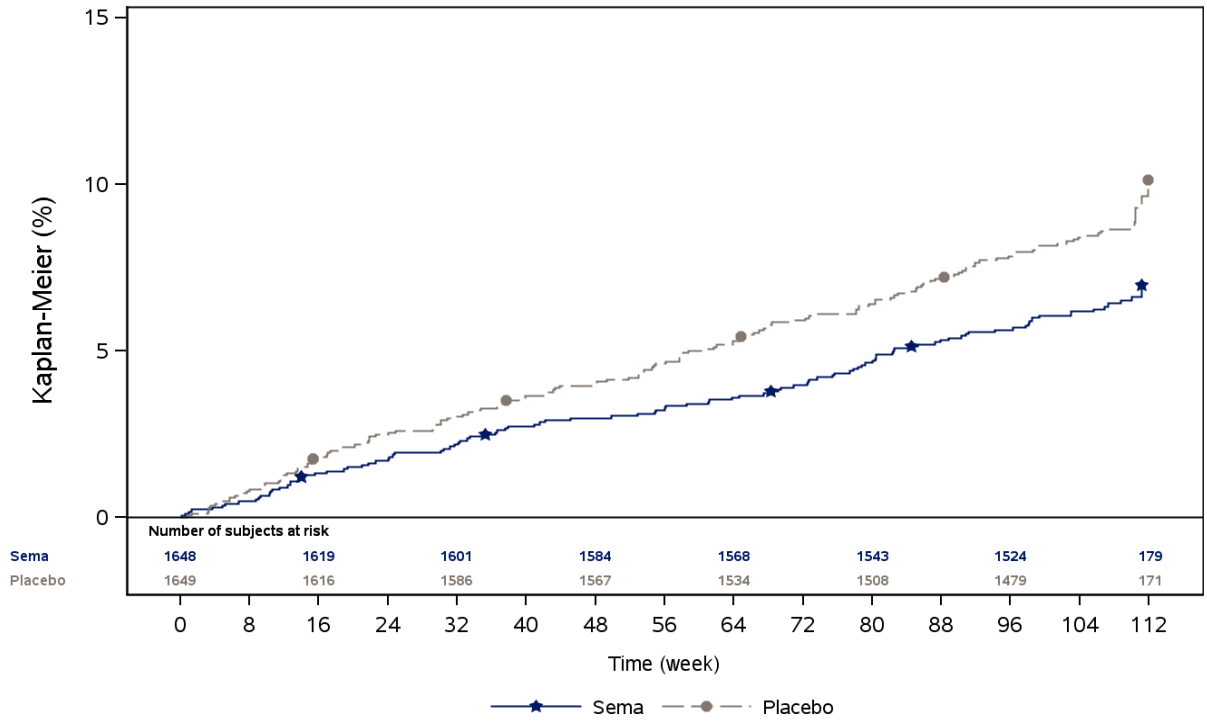
The primary endpoint in trial 3744 was the time from randomisation to the first occurrence of a 3-composite MACE (defined as non-fatal myocardial infarction, non-fatal stroke or cardiovascular death). The primary endpoint was pre-defined as a safety endpoint.

For the primary endpoint of time to first EAC-confirmed MACE, the primary pre-specified hypothesis that semaglutide would be non-inferior to placebo was confirmed, with the upper bound of the 95% CI being below 1.8 with associated p-value <0.0001. Semaglutide-treated subjects had a significantly lower risk of the primary MACE outcome than those receiving placebo (HR: 0.74 [0.58; 0.95]95%CI, p=0.0167) corresponding to a 26% relative risk reduction (Figure 23).

The CVOT was not intended to conclusively demonstrate cardiovascular safety nor benefits in favour of semaglutide. Thus, a non-inferiority hypothesis with a margin of 1.3 followed by a test for superiority was not part of the pre-specified statistical testing strategy in the protocol. Nevertheless, evidence for cardiovascular risk reduction emerged from the trial. Events had onset throughout the entire observation period, with no clustering of events over time, assessed from time of randomisation. The

semaglutide and placebo curves separated around week 16 and the lines continued to separate throughout the trial, suggestive of a constant treatment effect, as seen from the Kaplan-Meier plot for time to first MACE (Figure 23).

Figure 23 Plot of time to first EAC-confirmed MACE, semaglutide vs placebo – CVOT



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

The Kaplan-Meier estimate of the cumulative risk of MACE at week 104 was 6.2% with semaglutide and 8.4% with placebo, corresponding to an absolute risk reduction of 2.2%, meaning that 45 subjects would need to be treated with semaglutide to prevent one subject experiencing MACE during the 104-week treatment period.

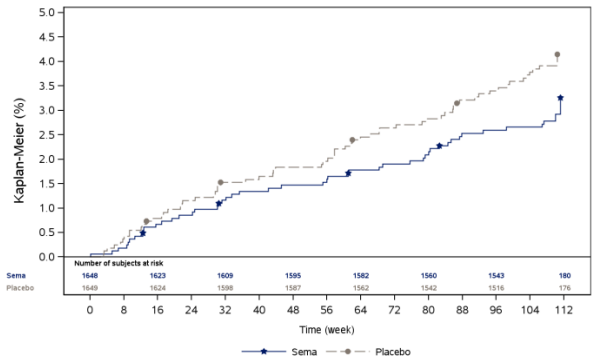
Clinically relevant risk reductions were observed for both doses of semaglutide compared with their individual placebo groups with an apparent larger risk reduction with semaglutide 1.0 mg (HR: 0.71 [0.49 ; 1.02]$_{95\%CI}$) compared with semaglutide 0.5 mg (HR: 0.77 [0.55 ; 1.08]$_{95\%CI}$). Importantly, the analyses within the semaglutide dose groups were independent of each other, as each semaglutide dose was compared with its volume-matched placebo group.

Post-hoc, the p-value was calculated for superiority on the primary MACE endpoint without a statistical penalty for multiple testing.

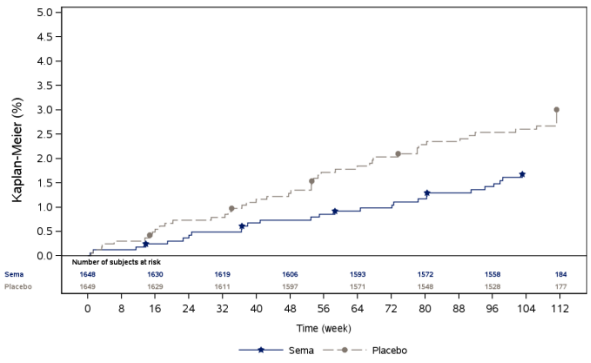
For the 3-component MACE, the individual components of events of non-fatal MI and non-fatal stroke appeared lower with semaglutide compared with placebo, while occurrence of events of CV death appeared similar with semaglutide and placebo (Figure 24).

Figure 24 Kaplan Meier plot of time to first EAC-confirmed non-fatal MI, non-fatal stroke or CV death – CVOT

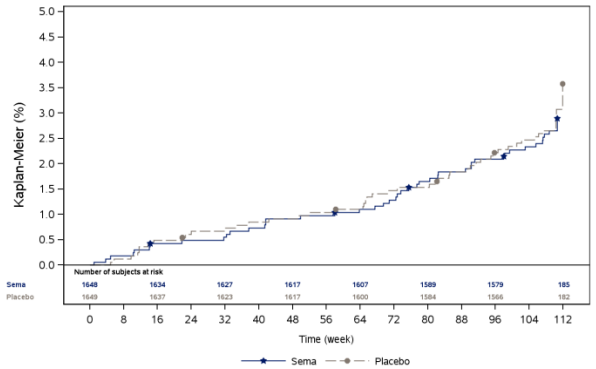
Non-fatal MI



Non-fatal stroke



CV death

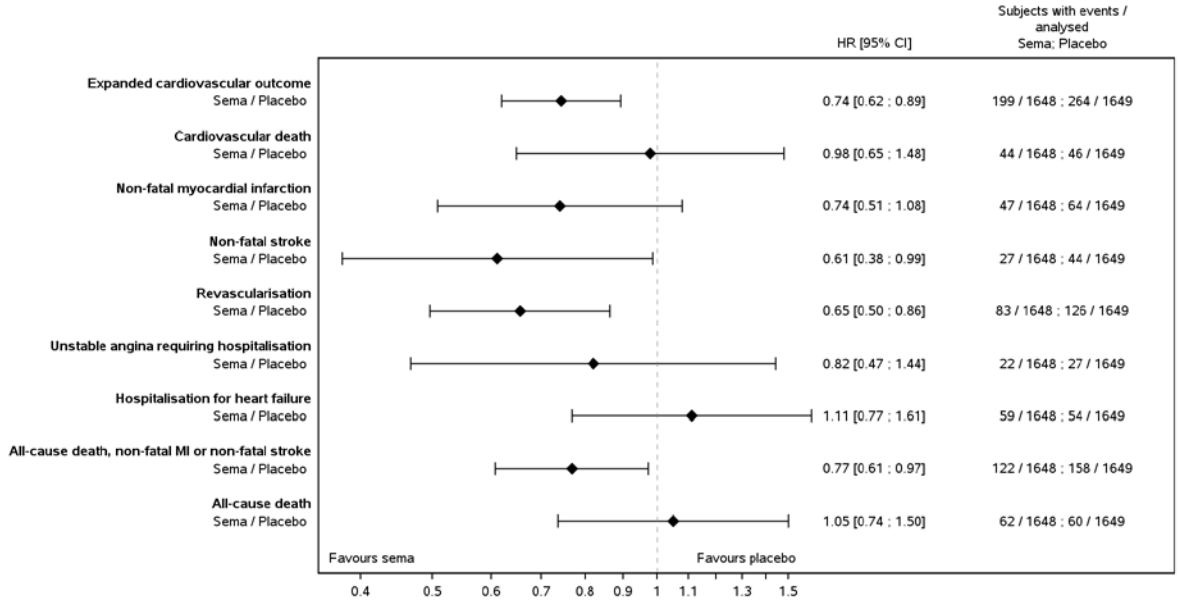


Note: Numbers below the figure represent number of subjects at risk. Kaplan-Meier estimates: Analysis of time from randomisation to first outcome. Subjects are censored at their planned end-of-trial visit, death (for CV death: non-CV death) or last direct subject-site contact, whichever comes first.
Abbreviations: EAC:event adjudication committee

As a broader definition of MACE may be more sensitive to detect CV effects, a secondary endpoint in the CVOT addressed the time from randomisation to first occurrence of an expanded composite CV outcome, defined as MACE, revascularisation (coronary and peripheral), unstable angina requiring hospitalisation, or hospitalisation for heart failure.

The proportion of subjects that experienced an expanded MACE was lower with semaglutide (199 subjects, 12.1%) than with placebo (264 subjects, 16.0%). The hazard ratio for the expanded composite CV outcome (0.74 [0.62 ; 0.89]95% CI) was identical to that of the 3-component MACE. The individual components; events of non-fatal MI, non-fatal stroke, revascularisation, and unstable angina requiring hospitalisation all contributed to the favourable treatment effect of semaglutide with hazard ratios below 1. However, Hospitalisation for heart failure and all cause of death had a hazard ratio above 1 (Figure 25).

Figure 25 Forest plot on time to first expanded CV composite outcomes and individual components, semaglutide versus placebo – CVOT



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).

Cardiovascular outcomes in phase 3a trials excluding the CVOT

The number of subjects with MACEs across the seven phase 3a trials were similar across the treatment groups (semaglutide 0.5 mg: 8 subjects [0.6%], semaglutide 1.0 mg: 5 subjects [0.3%], all comparators: 8 subjects [0.5%]).

Subgroup analyses-effects on HbA1c

The extent to which the exposure of semaglutide was affected by sex, age, race, ethnicity, body weight and renal function was evaluated in a population PK analysis. The analysis included data from five of the phase 3a trials (trials 3623, 3624, 3626, 4091 and 3744). Semaglutide exposure was only affected by body weight showing higher semaglutide exposure in subjects with a lower body weight.

In the clinical studies, the efficacy response to semaglutide (0.5 mg and 1.0 mg) was in general consistent across sub-populations. In a few of the subgroup analyses, there were some inconsistencies in the analyses between groups. However, the overall pattern suggested that these differences occurred by chance.

The overall HbA_{1c} response to semaglutide is considered similar for men and women.

The number of subjects ≥75 years of age at baseline was ≥74 subjects for each of the four treatment groups in the CVOT and <20 for each treatment group in all other trials. The estimated HbA_{1c} treatment differences for semaglutide vs comparator were generally comparable across the different age subgroups in all trials.

For all trials but the two Japanese trials, the majority of subjects identified themselves as White (64–84%), while Blacks or African-Americans (5–9%) and Asians (2–25% excluding the Japanese trials where all subjects were Asians) were represented to a lesser degree. All race subgroups

responded equally well to treatment with semaglutide. The Hispanic or Latino population was represented by 12−30% across the key efficacy trials and the CVOT. Overall, the HbA_{1c} response with semaglutide treatment across the six trials was considered comparable for the two ethnicity subgroups. In addition, the estimated HbA_{1c} treatment differences for semaglutide vs comparator were similar for the different subgroups of region across the key efficacy trials and the CVOT.

Overall, the HbA_{1c} response with semaglutide treatment was not affected by diabetes duration and body weight at baseline.

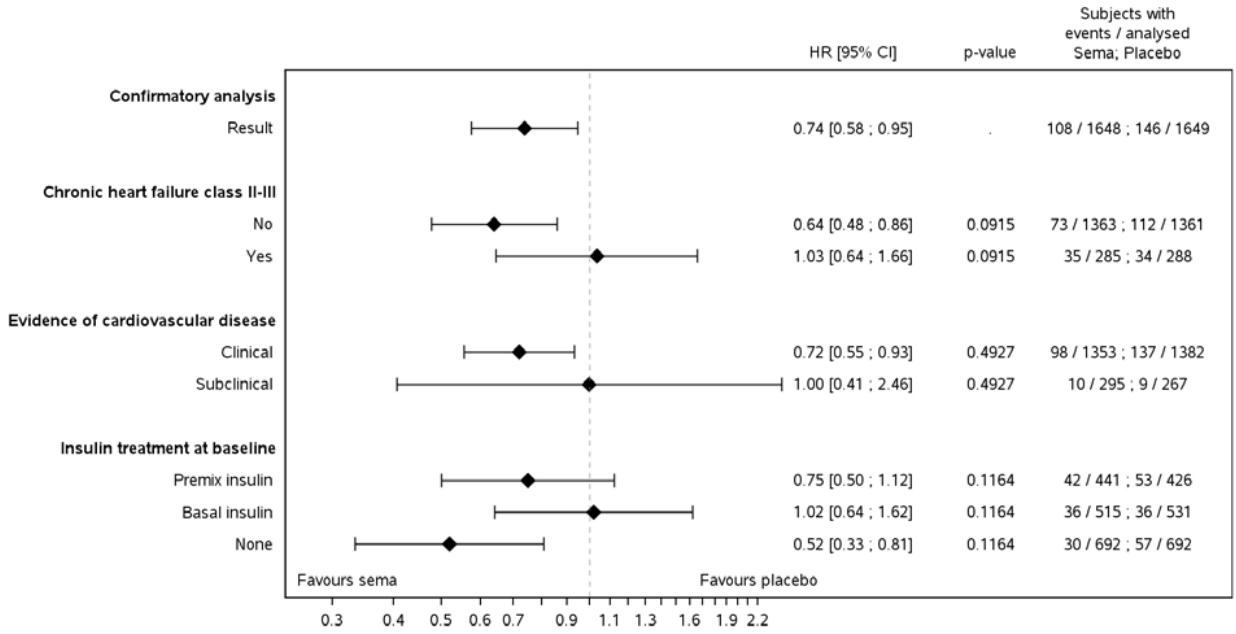
For all trials but the CVOT, the proportion of subjects with normal renal function and mild renal impairment ranged from 50.8−68.7% and 29.3−40.4%, respectively, while moderate renal impairment was seen for <9% of subjects. For the CVOT, the proportion of subjects with normal renal function, mild renal impairment and moderate renal impairment were comparable, while severe renal impairment and end-stage renal disease represented <4% of subjects. The patterns across trials were not consistent with dose nor did it correlate with the degree of renal impairment. The semaglutide treatment effect is therefore considered of a comparable magnitude across all subgroups of renal function.

While a larger HbA_{1c} reduction was seen for subjects on metformin+SU at baseline compared with subjects on metformin alone at baseline in trial 3624, both subgroups showed HbA_{1c} reductions above 1.3 %−points. In the CVOT, for subjects on SU monotherapy at baseline, estimated treatment differences of −1.74 %−points $[-2.28; -1.19]_{95\%CI}$ and −1.64 %−points $[-2.16; -1.12]_{95\%CI}$ were obtained with semaglutide 0.5 mg and 1.0 mg, respectively, compared with pooled placebo. For subjects on premix insulin at baseline, estimated treatment differences of −0.86 %−points $[-1.06; -0.66]_{95\%CI}$ and −1.37 %−points $[-1.57; -1.17]_{95\%CI}$ were obtained with semaglutide 0.5 mg and 1.0 mg, respectively, compared with pooled placebo. Thus, relevant treatment effects were seen across subgroups of background diabetes medication, and the treatment effects appeared consistent across trials.

Subgroup analyses-effects on cardiovascular risk

The results of most pre-specified subgroup analyses were consistent with the results of the primary analysis of time to first EAC-confirmed MACE. There were no differences between subgroups of sex, age, race, ethnicity, region, HbA1c at baseline, duration of diabetes, evidence of CV disease, renal impairment and BMI at baseline. Although not statistically significant, treatment effects were absent for patients with chronic heart failure class II-III and insulin treatment at baseline (p for interaction 0.09 and 0.12, respectively) (Figure 26).

Figure 26 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



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.

nn9535/nn9535-3744/freeze_20161007_ctr_er
09OCT2016:15:08:26 - zt_time2mace_subgrp.sas/f_stat_forest_mace_subgrp3.png

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.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The 5 key efficacy trials evaluated the efficacy and safety of semaglutide as mono- and combination therapy (primarily combinations with metformin, SU and/or insulin). In addition, semaglutide was compared with insulin glargine, a DPP-4 inhibitor and another long acting GLP-1 receptor agonist. The studies were performed in line with the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. A comparison to SU was not performed. SU is considered the next step after metformin by many guidelines and doctors. No trials with combination therapy with DPP-4-inhibitors or SGLT-2-inhibitors have been carried out. A combination with a DPP4-inhibitor is not rational, as the mechanisms of action of both products is similar. For semaglutide, specific combinations that are studied are mentioned in section 5.1 of the SmPC. As no interactions are expected between semaglutide and SGLT2-inhibitors, it is agreed that the current text in the SmPC is sufficient.

Two phase 3a trials evaluated semaglutide for treatment of T2D in Japanese subjects (trials 4092 and 4091). While safety was the primary endpoint for the Japanese trials, they were designed and conducted in a similar manner to the key efficacy trials.

The last phase 3a trial was a 104−week cardiovascular outcomes trial (CVOT, trial 3744) in a T2D population at high risk of CV events that investigated the effect of semaglutide on CV events as well as long-term safety and efficacy. The inclusion of individuals with a high cardiovascular risk in the CVOT may limit generalizability to the general diabetic population. Data suggest that semaglutide has effects on atherosclerosis, and effects on MACE might be largely obtained by affecting this process. In addition, other CV risk factors are also reduced, like HbA1c, body weight, blood lipids and blood pressure. However, whether this results in a reduction in MACE in subjects with less atherosclerosis and a lower CV risk is still unclear. In CVOT a number of subjects were included with risk factors "only". In these subjects, no effect on MACE was seen, but the numbers were too small to draw firm conclusions (10 events with semaglutide and 9 events with placebo).

Semaglutide was investigated at two dose levels (0.5 mg and 1.0 mg) in most phase 3a trials (dose selection is discussed in the end of the present section).

Trial duration is similar to that used in other registration studies and according to current EMA Guidelines. For semaglutide, the results of a CVOT are included in this application. We consider these data very important. However, the duration of 2 years is relatively short in comparison to several other cardiovascular outcome trials and also for a drug that is intended for long term diabetes treatment.

The statistical analysis of the key efficacy trials and the CVOT are similar to those used in other antidiabetic programs and according to current EMA Guidelines. The primary estimand of the key efficacy trials was the difference in effect as if all subjects were treated. The primary analysis, using MMRM, corresponds to this estimand and is acceptable. However, the primary analysis sets all data after rescue medication or treatment withdrawal to missing and assumes this will be missing at random (MAR). Therefore, sensitivity analyses were performed to test the robustness of the primary outcome and the assumption of MAR: using all in trial data, comparator-based multiple imputation analysis, a complete case, LOCF and per protocol analyses. The primary endpoint in the CVOT, time to MACE, was analysed using a Cox proportional hazards model, stratified for the factors used in randomisation. Multiplicity was handled using a pre-specified hierarchical testing schemes. Of note, superiority on time to MACE was not included in the predefined testing hierarchy. It is agreed with the Applicant that a test for MACE superiority could have been done without adjustment for multiplicity. However, the problem is that it was not predefined in the protocol as part of the hierarchical testing scheme. The superiority test for MACE was performed as one of a range of post-hoc tests. This means that the Applicant had the chance to choose any statistically significant test from the post-hoc analyses, which will lead to inflation of the type I error. A claim of superiority is not mentioned in the SmPC, the issue was not further pursued.

Efficacy data and additional analyses

Pivotal efficacy trials

In trial 3623 in drug naïve T2D subjects, semaglutide was associated with a clinically relevant decrease in HbA1c after 30 weeks (semaglutide 0.5 mg -1.43%; semaglutide 1.0 mg -1.53%) compared to placebo. In addition, there were changes in body weight (semaglutide 0.5 mg -2.75 kg; semaglutide 1.0 mg -3.56 kg).

In trial 3626 was performed in T2D subjects who had not achieved adequate glycaemic control on metformin, TZD or a combination of metformin/TZD. Compared to sitagliptin, semaglutide was associated with a clinically relevant decrease in HbA1c after 56 weeks (semaglutide 0.5 mg -0.77%; semaglutide 1.0 mg -1.06%). In addition, compared to sitagliptin, semaglutide was associated with a decrease in body weight (semaglutide 0.5 mg -2.35 kg; semaglutide 1.0 mg -4.20 kg). However, only 5.4% (N=43) of the patients was using a TZD as background medication in combination with semaglutide, and further in 68 subjects in one of the Japanese trials. Based on these limited numbers, no difference with other semaglutide combinations were observed in reducing HbA1c. Section 5.1 mentions the limited number of subjects on combination treatment with TZD, which is considered adequate.

In trial 3624, compared to exenatide ER, semaglutide 1.0 mg was associated with a clinically relevant decrease in HbA1c after 56 weeks of -0.62%. In addition, compared to exenatide ER, semaglutide 1.0 mg was associated with a clinically relevant decrease in body weight after 56 weeks of -3.78 kg. Use of metformin monotherapy ± SU was reported by the majority of the subjects. SU monotherapy, insulin +/- OADs and other background diabetes medication was reported by only a few patients (2.7%, 0.1% and 2.7% of the subjects, respectively). There were more premature treatment discontinuations due to gastrointestinal adverse events with semaglutide than with exenatide.

In trial 3625, compared to insulin glargine, semaglutide was associated with a clinically relevant decrease in HbA1c after 30 weeks (semaglutide 0.5 mg -0.38%; semaglutide 1.0 mg 0.81%). Rescue medication was used in 28 (2.58%) of the patients. Compared with patients treated with insulin glargine (5 [1.4%]), notably more patients treated with semaglutide 0.5 mg (14 [3.9%]) and with semaglutide 1.0 mg (9 [2.5%]) were treated with rescue medication. This might be explained by the fact that 92.5% of the patients in the insulin glargine treatment group increased the insulin glargine dose which was not accounted as Rescue medication (at week 30 mean insulin glargine dose was 29.2 IU with a maximum up to 112 IU). In addition, compared to insulin glargine, semaglutide was associated with a clinically relevant decrease in body weight after 30 weeks (semaglutide 0.5 mg -4.62 kg; semaglutide 1.0 mg -6.33 kg). Use of metformin ± SU was reported by almost all patients. Only 0.2% and 0.2% of the subjects reported use of SU monotherapy and other background diabetes medication, respectively. Premature treatment discontinuation was clearly higher with semaglutide compared to insulin glargine. This was due to a higher number of gastrointestinal adverse events, protocol violations and other adverse events with semaglutide.

In trial 3627 in subjects with T2D on basal insulin, semaglutide was associated with a clinically relevant decrease in HbA1c after 30 weeks (semaglutide 0.5 mg -1.35%; semaglutide 1.0 mg -1.75%) compared to placebo. In addition, compared to placebo, semaglutide was associated with a clinically relevant decrease in body weight after 30 weeks (semaglutide 0.5 mg -2.31 kg; semaglutide 1.0 mg -5.06 kg). From a mean baseline insulin dose of 37.74 IU across the 3 groups, significant reductions of insulin doses of 6% and 12% were seen at week 30 with semaglutide 0.5 mg and 1.0 mg, respectively, when compared to placebo. There was a higher number of gastrointestinal adverse events and other adverse events with semaglutide. All patients were using insulin with or without OADs.

In trial 3744 (cardiovascular outcome trial, COVT), the primary objective was to confirm that treatment with semaglutide does not result in an unacceptable increase in CV risk compared to placebo in T2D subjects. The secondary objectives were to assess the long-term safety and efficacy of semaglutide 0.5 mg and 1.0 mg once-weekly compared to placebo, both added on to standard-of-care, in T2D subjects at high risk of CV events. This was a long-term, double-blind, trial in subjects with T2D at high risk of CV events. A total of 3297 subjects were randomised. There was a higher number of premature

treatment discontinuation due to gastrointestinal adverse events with semaglutide 1.0 mg (9.4%) and semaglutide 0.5 mg (5.7%) compared to placebo (1.1%).

The trial reached its primary objective and demonstrated non-inferiority of semaglutide versus placebo in terms of MACE. The composite primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and 146 of 1649 (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for non-inferiority. Superiority was tested post hoc without a statistical penalty for multiple testing. This has been discussed elsewhere.

For MACE subcomponents, events of non-fatal MI (HR: 0.74 [0.51; 1.08]95%CI, p=0.1194) and non-fatal stroke (HR: 0.61 [0.38; 0.99]95% CI, p=0.0438) contributed to the overall favourable treatment effect of semaglutide on MACE. However, occurrence of CV death was similar with semaglutide and placebo (HR: 0.98 [0.65; 1.48]95%CI, p-value: 0.9181). This is rather unexpected. Based on biological plausibility it may be anticipated that treatment will beneficially influence all components in a similar way. Although the three individual components of the composite endpoint are clinically meaningful, CV death may be considered more relevant than non-fatal MI and non-fatal stroke. In response, the Applicant reasons that duration of the trial may have been too short for showing positive effects on CV-death. Similarly heterogeneous results have been observed for statins and PSK9-inhibitor. The explanation is considered acceptable.

The difference in MACE is primarily driven by a difference in the frequency of strokes. However, there was a baseline difference in prior stroke favouring semaglutide **(**Table 5**).** Number of subjects with prior stroke and an event were small, however, and confidence intervals were wide. Therefore, no firm conclusion can be drawn. The analyses adjusted by prior stroke were consistent with the primary MACE analysis. It is unlikely that the small difference in distribution at baseline has affected the outcome of the CV trial in a relevant way. The proportion of subjects that experienced an expanded MACE (3-point MACE plus revascularisation (coronary and peripheral), unstable angina requiring hospitalisation, or hospitalisation for heart failure) was lower with semaglutide (199 subjects, 12.1%) than with placebo (264 subjects, 16.0%). The hazard ratio for the expanded composite CV outcome (0.74 [0.62 ; 0.89]95% CI) was identical to that of the 3-component MACE. The individual components, events of non-fatal MI, non-fatal stroke, revascularisation, and unstable angina requiring hospitalisation, all contributed to the favourable treatment effect of semaglutide with hazard ratios below 1. However, hospitalisation for heart failure and all cause of death had a hazard ratio above 1. The Company reasons that heart failure is often due to non-atherosclerotic mechanisms, while semaglutide most probably affects atherosclerosis. Furthermore, numbers are too small for a firm conclusion. Numbers of all-cause death were similar for semaglutide and placebo (62 vs 60 events), mostly due to CV-death (44 vs 46 events). Numbers of non-CV death were small (18 vs 14). Results do not indicate that semaglutide has a beneficial or negative effect neither on CV-death nor on non-CV death.

The results of most pre-specified subgroup analyses were consistent with the results of the primary analysis of time to first EAC-confirmed MACE. However, several interactions between treatment effect and subgroups on time to first MACE may be identified. Treatment effects were absent for patients with chronic heart failure class II-III and lower for patients using insulin treatment at baseline (p for interaction 0.09 and 0.12, respectively). The Applicant reasons that effects on HbA1c, body weight and systolic blood pressure were seen in subjects with chronic heart failure class II-III and in subjects using insulin at baseline, suggesting that semaglutide is effective in these patients, and thus might be beneficial on MACE. Of note, conclusions drawn from subgroup analyses should be performed cautiously when subgroups are small, and in the statistical subgroup interaction test, the treatment differences were not statistically significant. At week 104, the mean glycated haemoglobin level in the semaglutide group, as compared with the placebo group, was 0.7% points lower in the group receiving

0.5 mg and 1.0% point lower in the group receiving 1.0 mg (estimated treatment difference) ($p<0.001$ for both comparisons). During the trial, significantly more patients in the placebo group than in the semaglutide group received additional antihyperglycaemic agents (including insulin) which were initiated approximately twice as frequently in the placebo group.

At week 104, the mean body weight in the semaglutide group, as compared with the placebo group, was 2.9 kg lower in the group receiving 0.5 mg and 4.3 kg lower in the group receiving 1.0 mg semaglutide ($p<0.001$ for both comparisons). In addition, mean systolic blood pressure in the semaglutide group, as compared with the placebo group, was 1.3 mm Hg lower in the group receiving 0.5 mg ($p=0.10$) and 2.6 mm Hg lower in the group receiving 1.0 mg ($p<0.001$). Changes in diastolic blood pressure were similar across treatment groups.

Supportive trials performed in Japanese patients

Trials 4091 and 4092 were both conducted in Japan. These studies are only considered supportive because they were performed in Japanese individuals only and efficacy was not a primary endpoint.

In trial 4092, the primary objective was to compare the safety of once-weekly dosing of semaglutide (0.5 and 1.0 mg) versus sitagliptin (100 mg) once daily, both as monotherapy during 30 weeks of treatment in Japanese T2D subjects. This was a randomised, open-label, active-controlled, 3-armed trial in subjects with T2D. There was a remarkably higher number of premature treatment discontinuation due to gastrointestinal adverse events with semaglutide 1.0 mg (9.8%) vs. semaglutide 0.5 mg (1%) and placebo (0%).

Compared to sitagliptin, semaglutide was associated with a clinically relevant decrease in HbA1c after 30 weeks (for semaglutide 0.5 mg -1.13%; for semaglutide 1.0 mg 1.44%). In addition, compared to placebo, semaglutide was associated with a clinically relevant decrease in body weight after 30 weeks (for semaglutide 0.5 mg -2.22 kg; for semaglutide 1.0 mg -3.88 kg).

In trial 4091, the primary objective was to compare the safety of once-weekly dosing of semaglutide in monotherapy or in combination with 1 OAD (either of SU, glinide, alpha-GI or TZD) vs OAD therapy during 56 weeks of treatment in Japanese T2D subjects who were insufficiently controlled on diet/exercise therapy or OAD monotherapy (either of SU, glinide, alpha-GI or TZD. This was a randomised, open-label, active-controlled, 3-armed trial. Similar to trial 4092, there was a remarkably higher number of premature treatment discontinuation due to gastrointestinal adverse events with semaglutide 1.0 mg (7.5%) vs. semaglutide 0.5 mg (2.9%) and additional OAD (0%). It can be speculated that Asian/Japanese patients on average have a lower mean weight and thus a higher exposure as compared to American/European patients. Based on this assumption, it cannot be excluded that the frequency of GI AEs including nausea tends to be higher in the Asian region but in this case, it is however, due to differences in weight rather than race. Overall, it is considered sufficiently documented that the rates of GI AEs do not differ substantially between Asians and non-Asians and it is considered justified not to include specific information regarding GI AEs in Asians in the SmPC.

Compared to additional OAD, semaglutide was associated with a clinically relevant decrease in HbA1c after 56 weeks (for semaglutide 0.5 mg -1.08%; for semaglutide 1.0 mg 1.37%). In addition, compared to placebo, semaglutide was associated with a clinically relevant decrease in body weight after 56 weeks (for semaglutide 0.5 mg -1.84 kg; for semaglutide 1.0 mg -3.59 kg).

Analyses of results performed across trials

Characteristics of the trial populations

Baseline demographic and disease characteristics of the trial populations studied were designed to be representative of the target population for treatment with semaglutide expected in the clinical practice, and were comparable across the treatment groups and across the phase 3a trials.

The mean age was comparable across trials and ranged from 53.7−58.8 years. With regard to race, the majority of subjects across all trials were White (64−84%), except for the two Japanese trials in which all subjects were Asian. Excluding the two Japanese trials, the proportion of Black or African American subjects across trials was only 5−9%, while 2−25% of subjects were Asian. For ethnicity, the Hispanic or Latino population represented 12−30% of the subjects across all trials, excluding the two Japanese trials.

Only 156 subjects of ≥75 years were included in the seven phase 3a trials (thus excluding the CVOT). As could be expected based on the inclusion criteria, the mean age (64.6 years) was higher for the CVOT population compared to the other seven phase 3a trials. A total of 321 subjects of ≥75 years were included in the CVOT. The mean diabetes duration (13.9 years) was longer and the mean baseline HbA_{1c} (8.7%) was higher in the CVOT compared with the other seven phase 3a trials. The mean renal function for the trial population was lower (eGFR: 76.13 mL/min/1.73 m^2) compared with the other phase 3a trials. Importantly, this was the only trial to include subjects (around 3%) with severe renal impairment, while moderate renal impairment accounted for 25% of subjects in the CVOT.

HbA1c

For all eight phase 3a trials, treatment with semaglutide 0.5 mg or 1.0 mg resulted in marked, sustained improvements in glycaemic control, as shown by a reduction in HbA1c, beginning already after 4 weeks of treatment and reaching nadir after 16−30 weeks. The reduction was maintained after long-term treatment of up to 104 weeks (in the CVOT). The magnitude of the reduction in HbA1c with semaglutide increased with increasing baseline HbA1c levels. In line with the reductions in HbA1c, the treatment target of an HbA1c <7% was reached for significantly more subjects with semaglutide 0.5 mg (57−74%) and 1.0 mg (67−79%) vs placebo (11−25%) and active comparators (36−40%) in the key efficacy trials.

Overall, 60-70% of patients in a European population have a response of a reduction of -1%-point in HbA_{1c}. In all pivotal trials, the maximum effect of reduction in HbA_{1c} was reached after 16 weeks' treatment; thereafter the HbA_{1c} level remained unchanged or increased a little.

The effect of semaglutide on HbA1c and body weight were larger than those of exenatide o.w.. However, the effect of exenatide 2.0 mg o.w. on HbA1c (reduction of -0.92% from baseline) appears to be somewhat smaller than the effect seen in the DURATION (registration-)studies, which found a mean HbA1c reduction of 1.3%-point to 2.0%-point at Week 26-52. In addition, the effect of exenatide 2.0 mg o.w. on body weight (reduction of -1.85 kg from baseline) appears to be somewhat smaller than the effect seen in the DURATION studies, which found a mean weight reduction of 2.0-4.1 kg at Week 26-52.

Body weight

Semaglutide significantly reduced body weight in all eight phase 3 trials compared with placebo (both as monotherapy and in combination with insulin) or active comparators; sitagliptin, exenatide ER and insulin glargine. The reductions took place through the first 30 weeks of treatment, and the reduction in body weight was sustained through the entire treatment period of up to 104 weeks with reductions of up to 4.28 kg and 6.42 kg with semaglutide 0.5 mg and 1.0 mg, respectively.

Almost all patients (85-90%) had some degree of weight loss in the key efficacy trials. From the PD Trial 3685, is shown that 75% of the loss is body fat and 25% is lost from lean body mass. In the Japanese and CVOT studies approximately 80% had some degree of weight loss. Across trials, approximately 50% achieved a ≥5% weight loss and around 20% achieved a ≥10% weight loss for the high dose semaglutide. It is unknown if there are certain parameters that characterize patients with the greatest weight loss. In response, the Applicant presented results of the percentage of patients with ≥10% weight loss stratified on baseline BMI. In general, the group of patients with a BMI <25 kg/m^2 was small and therefore no firm conclusions can be made. Overall, it is agreed with the Applicant that there is no firm pattern indicating that patients with lower BMI have a more extensive weight loss. More patients treated with semaglutide 1.0 mg compared to semaglutide 0.5 mg experience a weight loss ≥10%; this is in accordance with the dose-dependent effect.

Cardiovascular risk (excluding the cardiovascular outcome trial)

The number of subjects with MACEs across the seven phase 3a trials (excluding the CVOT) were similar across the treatment groups (semaglutide 0.5 mg: 8 subjects [0.6%], semaglutide 1.0 mg: 5 subjects [0.3%], all comparators: 8 subjects [0.5%]).

Cardiovascular risk factors

Overall, in the key efficacy trials, systolic blood pressure decreased more with semaglutide 1.0 mg and 0.5 mg (ranging from -2.58 to -7.27 mmHg) vs comparators (ranging from -0.99 to -1.72 mmHg) at end-of-treatment. Likewise, diastolic blood pressure also decreased over time. Data for pulse rate across trials are evaluated and presented in the safety section. In several of trials, semaglutide 1.0 mg was associated with small improvements in blood lipids vs comparators.

DTSQ

For all trials investigating DTSQ, both doses of semaglutide significantly improved the summary score of treatment satisfaction and significantly lowered the perceived frequency of hyperglycaemia compared to placebo and active comparators; sitagliptin, exenatide ER and insulin glargine. There was no difference in the perceived frequency of hypoglycaemia with semaglutide vs comparators.

Subgroup analyses

In a population PK analysis, data from five phase 3a trials were included (trials 3623, 3626, 3624, 4091 and 3744). Semaglutide exposure was only affected by body weight showing higher semaglutide exposure in subjects with a lower body weight. However, in the clinical trials, the semaglutide efficacy was considered consistent across subgroups of baseline body weight.

The overall HbA1c response to semaglutide is considered similar for men and women.

Overall, the efficacy of semaglutide on HbA1c reduction was considered consistent across age groups. However, for subjects >75 years of age, the effects of semaglutide on HbA1c were lower in some trials but higher in others. These inconsistencies may be explained by the relatively small numbers of patients >75 years of age. This is adequately reflected in the SmPC.

The estimated HbA1c treatment differences for semaglutide vs comparator and the change from baseline in HbA1c with semaglutide treatment may be similar for the different race subgroups across all trials. However, for Asians and Blacks/African Americans, the effects of semaglutide on HbA1c were lower in some trials but higher in others. These inconsistencies may be explained by the relatively small numbers of patients in these race groups and for the Asian (Japanese) population, also due to the lower weight.

Overall, subjects with mild and moderate impaired renal function had clinically relevant treatment effects, but the effect tended to be smaller compared with subjects with normal renal function. The number of individuals with severe renal impairment and end-stage renal disease was too small to draw conclusions as these patients were excluded from most trials.

Overall, the HbA1c response across the different regions is considered comparable across trials.

Although subjects on metformin+SU at baseline showed a larger treatment effect than subjects on metformin monotherapy at baseline, both groups showed relevant HbA1c reductions. Similarly, subjects on SU monotherapy at baseline showed somewhat larger treatment effects compared to subjects on premix insulin at baseline. However, superiority was shown of both doses of semaglutide for both types of background diabetes medication. On request, the Applicant has presented a subgroup analysis of background diabetes medication stratified on mono, dual and triple therapy. The effect of semaglutide appears to be independent of baseline antidiabetic treatment including type and number of antidiabetic products.

In all trials, either no subjects or a relatively low number of subjects developed anti-semaglutide antibodies. The data did not indicate that formation of anti-semaglutide antibodies with or without GLP-1-cross-reacting properties hampered the HbA1c-lowering effect of semaglutide.

Dose selection

Based on the results from the dose-finding trial 1821 and the exposure response analysis from four phase 3a trials, the suggested lowest maintenance dose of semaglutide 0.5 mg is questionable. A lower maintenance dose of 0.4 mg shows at least 0.5 %−point reduction on HbA1c change from baseline and has probably a lower number of GI AEs (trial 1821) and is thus better tolerated. Therefore, semaglutide 0.4 mg may provide improved benefit/risk compared with 0.5 mg. Prior to initiating the phase 3a trials, the Applicant concluded that using maintenance doses of 0.5 and 1.0 mg were likely to result in better efficacy than the 0.4 mg and 0.8 mg. AE profile of nausea and vomiting could be further mitigated by applying a 4-week dose escalation regimen. There is no unequivocal evidence confirming that a better benefit/risk profile could be attained with semaglutide maintenance doses of 0.5 and 1.0 mg in the phase 3 trials as compared to 0.4 and 0.8 mg. Still, the confirmatory trials have demonstrated that maintenance doses of 0.5 and 1.0 mg have a positive benefit/risk profile. Both dose levels of semaglutide can be safe and efficacious and should be based on individual needs. The 1.0 mg dose is associated with an increased risk of side effects. Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide. This is mentioned in Section 4.8 of the SmPC.

The Applicant suggests that semaglutide treatment is initiated with a dose of 0.25 mg. After four weeks, the dose should be increased to 0.5 mg. After at least four weeks with a dose of 0.5 mg, the dose can be increased to 1.0 mg. This dose regimen is based on estimations from trial 1821 and tests in trial 3819. However, the study groups and design of these trials were not identical. Therefore, the suggested dose regimen is questionable. As shown in trial 1821, the incidence of GI AEs generally decreased within the first 12 weeks of treatment. Therefore, a 12 week dose escalation regimen might improve the GI tolerability and reduce withdraws. In the answer, the Applicant, based on the data obtained in the phase 3a programme, presented a time course-model for nausea to describe the prevalence of nausea over time for different escalation regiments. Data simulation supports the choice of escalation schedule as it demonstrates that four-week escalation, as compared to one-week and eight-week escalation, achieves the best balance between risk of subjects experiencing nausea and achieving glycaemic control.

It is questionable whether the additional effect on primary and secondary endpoints of semaglutide 1.0 mg vs. 0.5 mg is clinically relevant. Although semaglutide 1.0 mg vs. 0.5 mg shows clear benefit on HbA1c and body weight change from baseline, the estimated treatment differences were small (range: 0.10−0.43%−point HbA1c and 0.81−2.75 kg). Also, additional reduction on CV risk was small. Semaglutide 1.0 mg showed a higher number of AEs i(trials 3625 and 3627) and GI AEs (trials 3627, 3744 and4092) compared with 0.5 mg. Therefore, the question arises whether semaglutide 1.0 mg provides additional clinical benefit compared to 0.5 mg. Because of the higher number of (gastrointestinal) adverse events, the Applicant should provide information about tapering off the 1 mg maintenance dose to 0.5 mg when the 1.0 mg is not tolerated. The Applicant reasons that, as the semaglutide 1.0 mg maintenance dose is reached by stepwise progression from 0.25 to 0.5 mg, patients must first have demonstrated that they can tolerate the 0.5 mg dose before being dose-escalated to 1.0 mg. Thus, lowering the semaglutide dose from 1.0 mg to 0.5 mg may be carried out at discretion of the treating physician if deemed appropriate. This is acceptable.

2.5.4. Conclusions on clinical efficacy

In the key efficacy trials, both semaglutide 0.5 mg and 1.0 mg were superior in lowering HbA1c and body weight compared with placebo (both as monotherapy and in combination with insulin) or the respective comparators (i.e. sitagliptin, exenatide ER and insulin glargine). The reductions in HbA1c and body weight were sustained throughout the course of the treatment in all trials (up to 104 weeks in the CVOT). Both dose levels of semaglutide can be efficacious and should be based on individual needs.

Semaglutide was associated with a lower risk of cardiovascular events. However, occurrence of cardiovascular death was similar with semaglutide and placebo, which might be due to the relative short duration of the trial. Numbers of all-cause death were similar for semaglutide and placebo (62 vs 60 events), mostly due to CV-death (44 vs 46 events). Numbers of non-CV death were small (18 vs 14). Results do not indicate that semaglutide has a beneficial or negative effect on CV-death and non-CV death.

For heart failure the hazard ratio for MACE was above 1 and treatment effects were absent for patients with chronic heart failure class II-III Conclusions drawn from subgroup analyses should be performed cautiously when subgroups are small, and in the statistical subgroup interaction test, the treatment differences were not statistically significant.

2.5.5. Clinical safety

Safety methodology

The safety of semaglutide has been studied in a broad T2D population with different degrees of diabetic complications and which covered the continuum of T2D care. The safety evaluation was based on data from all completed and ongoing trials in the semaglutide s.c. OW development programme Safety was evaluated based on exposed patients using both the on-treatment observation period (i.e., treatment emergent events) and the in-trial observation period. For the majority of safety assessments, the primary focus was on the period where patients were considered exposed to trial product (i.e., the on-treatment observation period). Due to a potential long latency and diagnostic lead time, the evaluation of cardiovascular and microvascular disorders, neoplasms and fatal events focused primarily on data from the entire trial period regardless of treatment adherence (i.e., the in-trial observation period).

Pooling of trials

The evaluation of the safety profile of semaglutide (0.5 mg and 1.0 mg) was based both on data from the completed phase 3a trials of 30 to 56 weeks duration as well as data from the 2-year CVOT. Data from the CVOT were presented separately from the other phase 3a trials. Due to important differences in trial designs including size, duration and population it was evaluated not to be applicable and feasible to pool the CVOT with the other phase 3a trials. The primary evaluation of safety data from the 7 phase 3a trials excl. the CVOT were performed on pooled data from these trials (phase 3a pool). This was done to increase the level of evidence and was considered appropriate due to the overall consistency in trial design and safety results seen across the individual trials.

Safety monitoring and overview

Unblinded safety data were monitored by an external and independent Data Monitoring Committee (DMC) to protect patients enrolled in the trials from harm by providing a recommendation to the sponsor to modify the protocol or to terminate the trial if safety issues arise. The DMC performed ongoing evaluation of accumulated safety data from the CVOT at predefined time points and *ad-hoc* in accordance with written guidelines. The DMC did not identify any safety issues warranting changes in trial conduct. In addition, the DMC ensured adequate monitoring of CV safety across all phase 3a trials.

Patient exposure

The number of patients exposed in the phase 3a trials included a total of 8,093 patients of whom 4,792 patients received at least one dose of semaglutide. A total of 3,301 patients were included in comparator groups including 1,906 in placebo groups and 1,395 in active comparator groups (OAD: 120; sitagliptin: 510, Exenatide ER: 405; insulin glargine: 360). A total of 1,321 patients were exposed to semaglutide for 18 months or longer; the total exposure to semaglutide was 5,644 PYE; 2,712 PYE in the phase 3a trials and 2,932 PYE in the CVOT.

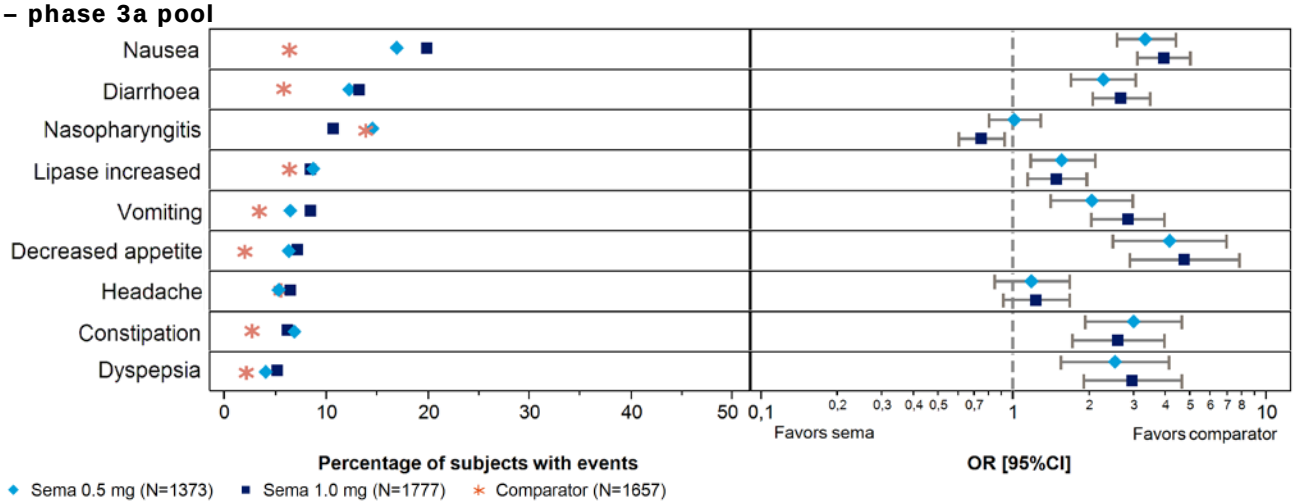
Adverse events

The proportion of patients reporting at least one AE was higher with semaglutide (0.5 mg and 1.0 mg) than comparators in the phase 3a pool and similar with semaglutide (0.5 mg and 1.0 mg) and placebo in the 2-year CVOT. The overall rate of AEs was higher with semaglutide than placebo and comparators across all phase 3a incl. the CVOT. The higher proportions and rates of AEs were mainly driven by gastrointestinal disorders.

All safety issues identified among commonly reported AEs or SAEs (Figure 27 and Figure 28) have previously been seen for other GLP-1 RAs, except for the adjudicated endpoint diabetic retinopathy complications in the CVOT. Overall, semaglutide had a safety profile similar in patients with T2D evaluated for glycaemic control (phase 3a pool) and in the more vulnerable population of patients with T2D at high risk of CV events (CVOT).

The most commonly reported AEs with semaglutide (0.5 mg and 1.0 mg) were gastrointestinal (GI) disorders including nausea, diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, abdominal distension, gastritis, gastro-oesophageal reflux disease, eructation and flatulence, which are known common side effects of GLP-1 RAs particularly at the start of treatment. The proportion of patients with GI AEs as well as the rate of events increased with semaglutide dose. This was reflected in more AEs and AEs leading to premature treatment discontinuation with semaglutide 1.0 mg than with semaglutide 0.5 mg. In addition to GI AEs, decreased appetite, decreased weight, fatigue (incl. asthenia), dizziness, dysgeusia (altered taste perception) and cholelithiasis occurred more frequently with semaglutide than with placebo and comparators and are evaluated to be likely related to semaglutide. In general, these reactions were mild or moderate in severity and of short duration. AEs of lipase and amylase increased were also reported more frequently with semaglutide (0.5 mg and 1.0 mg) than with placebo and active comparators, and are related to the general increase in lipase and amylase levels observed with semaglutide and other GLP-1 RAs.

Figure 27 Common (≥5% of patients) adverse events by preferred term - SAS on-treatment – phase 3a pool



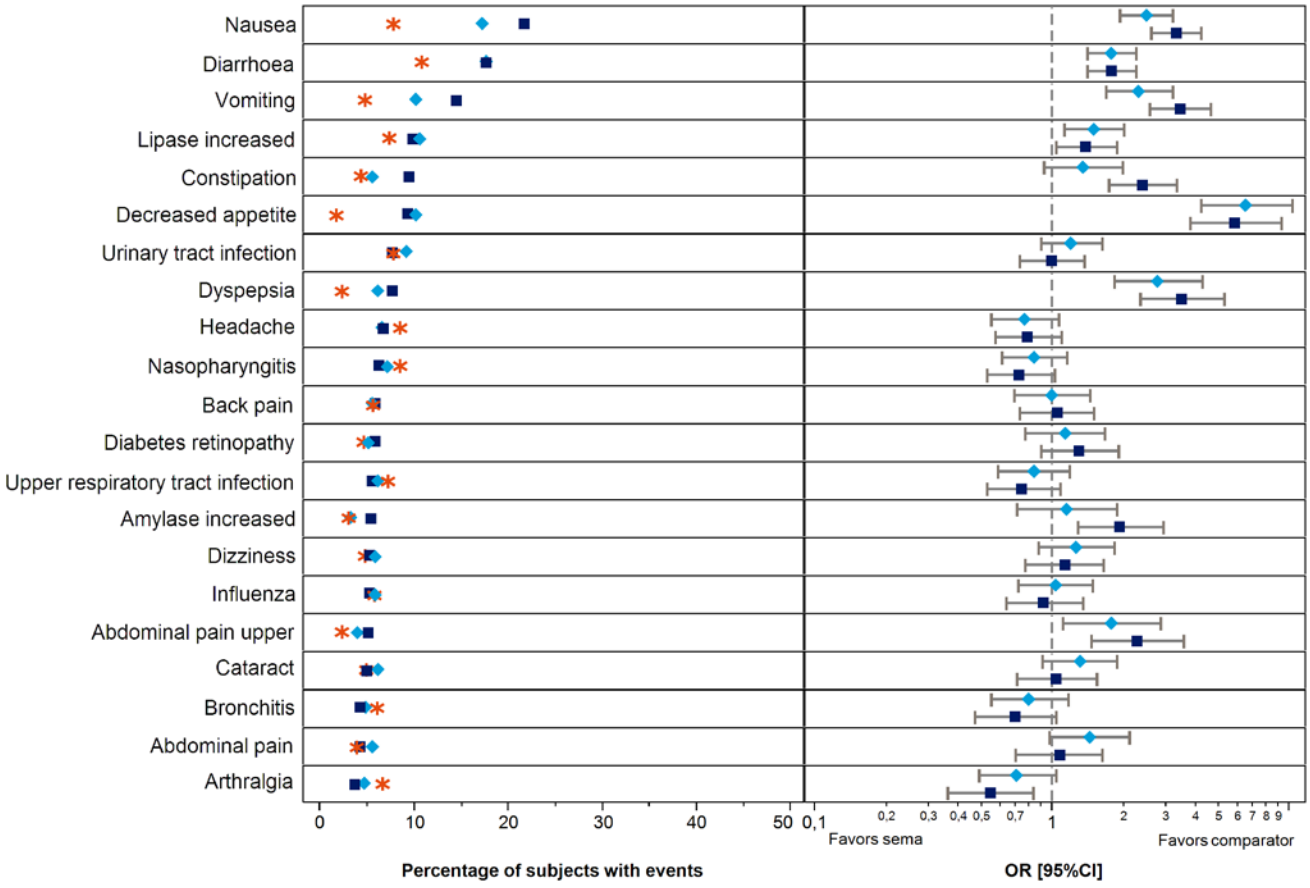
Notes: The percentage of patients is the Cochran-Mantel-Haenszel-adjusted percentage. The OR and the CIs are Cochran-Mantel-Haenszel exact method stratified by trial. On-treatment is defined as the observation period from the date of first dose to either the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first. Sorted by the highest frequency in the semaglutide 1.0 mg group. Comparators: exenatide ER; insulin glargine; oral anti-glycaemic drugs; sitagliptin, placebo.
Abbreviations: CI: confidence interval; N: number of patients; OR: odds ratio; SAS: safety analysis set; sema: semaglutide.

In trial 3624 where the safety profile of semaglutide 1.0 mg was compared with another once weekly GLP-1 RA (exenatide ER 2.0 mg), the overall proportion of patients reporting AEs and the event rate

were comparable in a head-to-head comparison. GI disorders were reported more frequently with semaglutide 1.0 mg than with exenatide ER 2.0 mg (41.8% vs. 33.3%) mainly driven by nausea, diarrhoea, vomiting, constipation and dyspepsia whereas events within the system organ class of 'general disorders and administration site conditions' were reported less frequently with semaglutide 1.0 mg than with exenatide ER 2.0 mg (10.1% vs. 29.9%) mainly driven by a greater proportion of patients with exenatide ER 2.0 mg who reported injection site reactions.

The semaglutide safety profile in patients at high CV risk (CVOT) generally resembled that observed in the more broad T2D population (phase 3a pool), albeit the incidences of especially deaths and CV events were higher reflecting a population at high risk of CV disease (Figure 28). In the CVOT, investigator-reported diabetic retinopathy and cataract were common AEs (i.e., reported as AEs in ≥ 5% of patients) both with semaglutide and placebo.

Figure 28 Common (≥5% of patients) adverse events by preferred term - SAS on-treatment – CVOT



Notes: On-treatment: on-set on or after the day of first randomised dose and not after the follow-up visit scheduled 5 weeks after the end-of-treatment.
Abbreviations: CI: confidence interval; N: number of patients; OR: odds ratio; SAS: safety analysis set; sema: semaglutide.

Serious adverse events and deaths

Serious adverse events

In the phase 3a pool the proportion of patients with serious adverse events (SAEs) were generally low, and slightly higher with semaglutide (0.5 mg: 6.6%; 1.0 mg: 6.7%) than with comparator products (5.8%). This difference was mainly explained by more GI SAEs with semaglutide. In the CVOT, the proportion of patients with SAEs was lower with semaglutide (0.5 mg: 32.1%; 1.0 mg: 29.3%) than with placebo (34.9%). In the CVOT the proportion of SAEs was slightly lower with semaglutide 1.0 mg than with 0.5 mg (0.5 mg: 32.1%; 1.0 mg: 29.3%). In line with the distribution of EAC-confirmed CV events described in the efficacy section, events within the SOC 'Cardiac disorders' were less common with semaglutide than with placebo.

Deaths

Across the semaglutide development programme, a total of 140 patients died. In the CVOT, a total of 123 patients (3.7%) with T2D and high risk of CV events died due to AEs that had onset during the 2-year in-trial period of the trial; 62 with semaglutide and 61 with placebo. In the 7 phase 3a trials in patients with T2D, a total of 16 patients died; 10 (0.3%) randomised to semaglutide, and 6 patients (0.4%) randomised to comparator products. In addition, one patient with T2D died during the follow-up period due to a traffic accident in the clinical pharmacology trial 3635. No deaths were reported in the individual trials in the period from DBL until the cut-off date 18 April 2016.

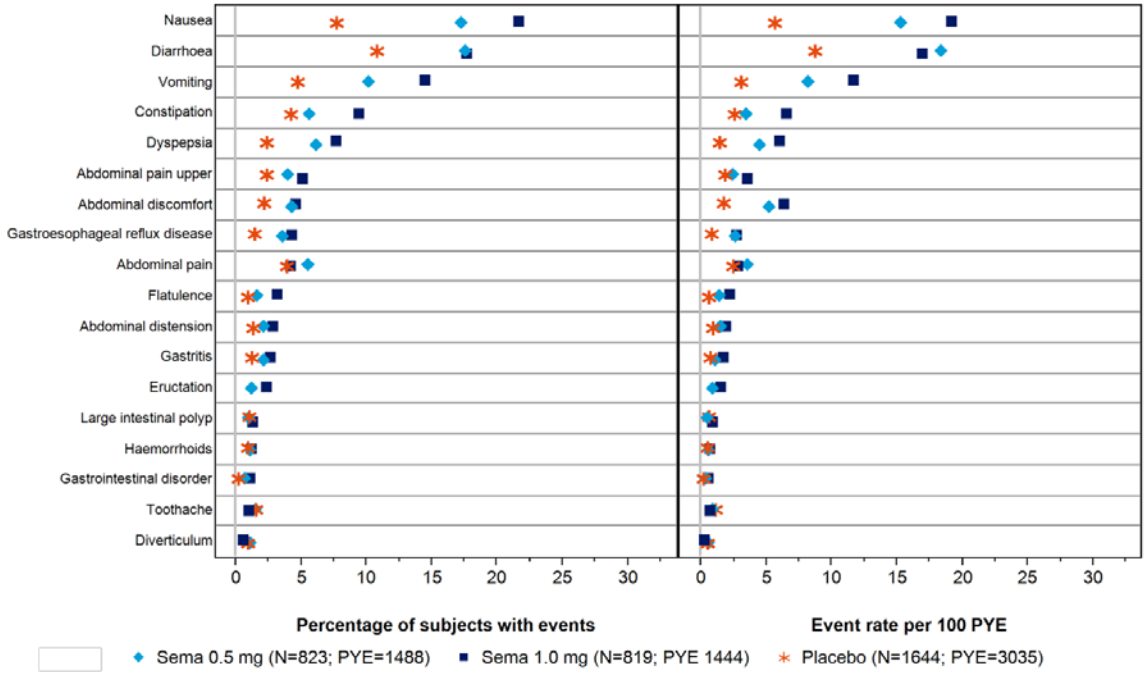
Fatal events occurred throughout the entire treatment period of the CVOT, with no clustering of events in any time interval and with similar patterns seen with semaglutide and placebo. All deaths were evaluated by the EAC and the cause of death was categorised as CV deaths, non-CV deaths or undetermined cause of death and further classified. As would be expected in patients with T2D at high risk of CV events, the majority of deaths were due to CV events including sudden cardiac death, undetermined cause of death and death due to acute MI as the most frequent causes, with no difference between treatments. For death classified by the EAC as 'undetermined cause of death', the investigator-reported term pertaining to the AE with fatal outcome indicated a CV cause in the majority of cases. In the analyses of composite CV endpoints, deaths with undetermined cause are considered CV deaths. *Post hoc* sensitivity analyses were performed excluding deaths with undetermined cause as CV events in the analyses of composite CV endpoints. There were no significant differences between semaglutide (0.5 mg and 1.0 mg pooled) and placebo (pooled) for EAC-confirmed all-cause mortality or CV-death.

Adverse events of special interest

Gastrointestinal (GI) disorders

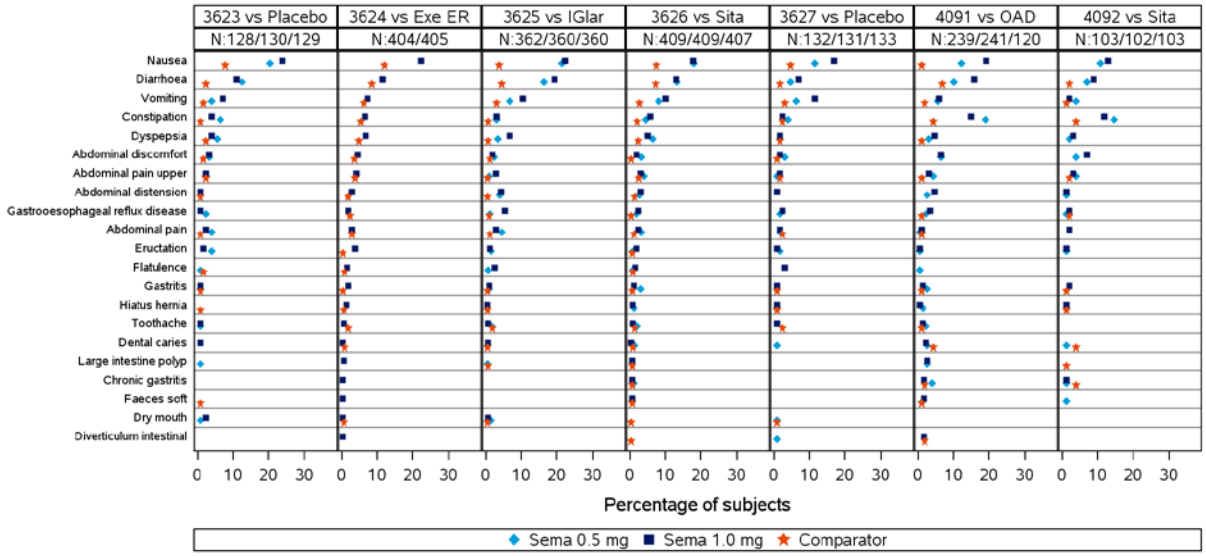
Across the semaglutide development programme, GI AEs were the most frequently reported AEs during treatment with semaglutide. The most frequent GI AEs were nausea, diarrhoea, vomiting, constipation, dyspepsia and abdominal pain (CVOT: Figure 29 and phase 3a pool: Figure 30). Nausea was reported in up to 20% of patients across trials.

Figure 29 Common (≥1%) GI AEs (MedDRA search) by preferred term – SAS on-treatment – CVOT



Note: Events are sorted by highest frequency in the sema 1.0 mg group. On-treatment: onset on or after the day of first randomised dose and not after the follow-up visit scheduled 5 weeks after the end-of-treatment.
Abbreviations: AE: adverse events; CVOT: cardiovascular outcomes trial; GI: gastrointestinal; SAS: safety analysis set; sema: semaglutide.

Figure 30 Common (≥1% of subjects) GI AEs (MedDRA search) by preferred term – SAS on-treatment – individual phase 3a trials excl. CVOT



Notes: Preferred terms sorted by the highest frequency with Sema 1.0 mg in the phase 3a pool based on the Cochran-Mantel-Haenszel-adjusted percentages, if no events then by semaglutide 0.5 mg. Comparator: mentioned after 'trial number vs'
Abbreviation: N: Number of subjects in the SAS in semaglutide 0.5 mg/semaglutide 1.0 mg/placebo.

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 3a trials (CVOT: Figure 29 and phase 3a pool: Figure 30).

GI AEs were not more prevalent in patients with mild, moderate or severe renal impairment for semaglutide vs. comparators. Patients with a higher exposure to semaglutide (as seen in patients with low body weight, low BMI, women and Asians) had more GI AEs than patients with a lower semaglutide exposure, as supported by exposure-response analyses. The proportion of patients reporting GI AEs were higher with increasing age both with semaglutide and placebo and comparator products.

GI AEs were reported as SAEs at a very low frequency with semaglutide (both doses) with only minor variations relative to placebo, the non-GLP-1 RA comparators or exenatide ER. Four (4) fatal GI AEs were reported in 3 subjects in trial CVOT, 1 in 1 subject on semaglutide 0.5 mg and 3 in 2 subjects on placebo.

GI AEs were typically of short duration and mild or moderate in severity. The duration of GI events were in general similar with semaglutide, placebo and active comparators. The proportion of patients with GI AEs and the corresponding rates were higher with semaglutide (0.5 mg and 1.0 mg) than with comparators including placebo, non-GLP-1 RA comparators and exenatide ER. A higher rate of GI AEs during the dose escalation period was reported with semaglutide than with exenatide ER in trial 3624.

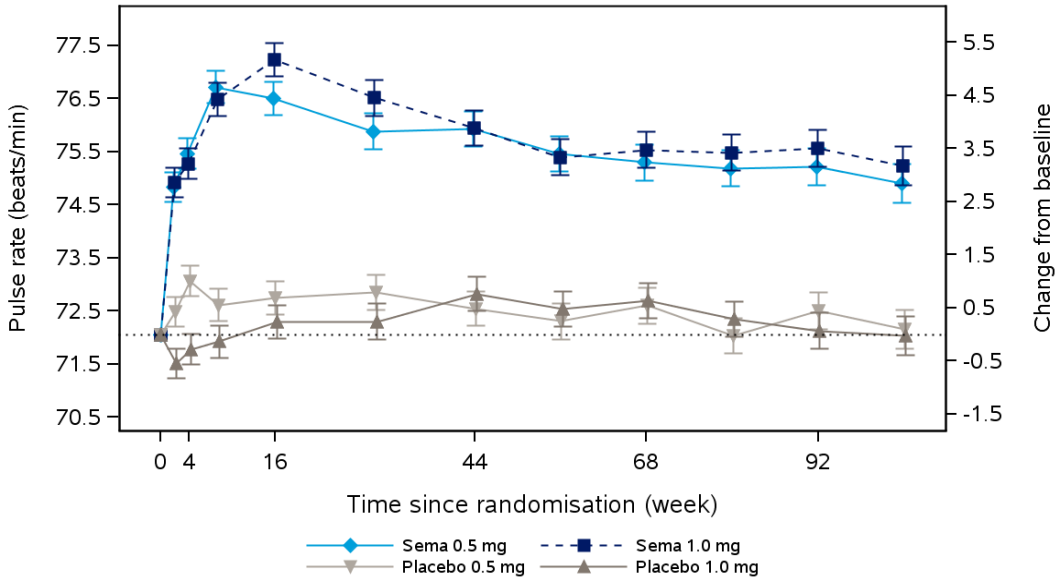
In a proportion of patients, GI AEs were the primary reason for premature treatment discontinuation (phase 3a pool: 0.5 mg: 3.9%; 1.0 mg: 5.9%). GI AEs leading to premature treatment discontinuation with semaglutide (0.5 mg and 1.0 mg) occurred mainly during the dose escalation period in the beginning of the trials.

CV safety

The general CV safety of semaglutide was established in the dedicated pre-approval CVOT, demonstrating that semaglutide is not associated with an increased CV risk but, on the contrary, reduces the risk of MACE in patients with T2D at high CV risk (see efficacy for details).

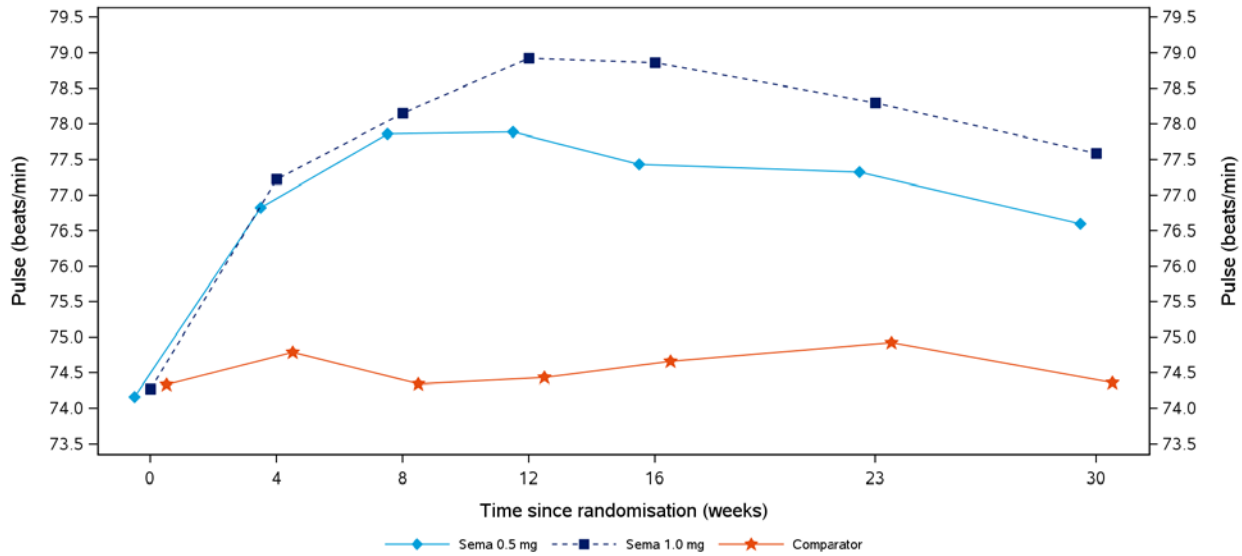
A non dose-related increase in resting pulse rate of 1 to 6 beats/minutes during treatment was seen across trials (Figure 31, Figure 32). The increase in pulse rate with semaglutide (1.0 mg) was not significantly different from the increase observed with exenatide ER 2.0 mg (Figure 33). No clinical consequences of increased pulse rate (e.g., increased angina pectoris, hospitalisation for heart failure, palpitations or discontinuation of treatment due to tachycardia) were identified in the semaglutide development programme. Furthermore, there was no increase in hospitalisation for heart failure, MACE or even increased mortality in the CVOT.

Figure 31 Estimated pulse rate (bpm) by treatment week - SAS on-treatment - CVOT



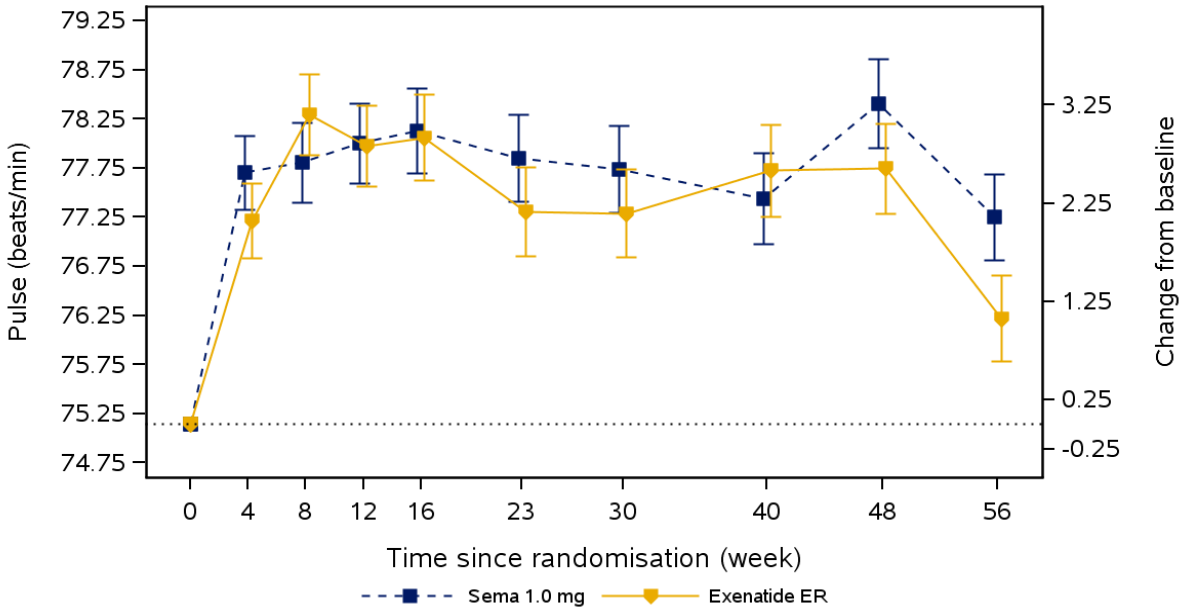
Note: Mean estimates (+/- error bar) are from a MMRM analysis with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/- 1 SEM. Dotted line is the average value at baseline for all subjects.
Abbreviations: MMRM: mixed model for repeated measurements; SEM: standard error of mean; sema: semaglutide.

Figure 32 Mean pulse rate (bpm) by treatment week – on-treatment – Phase 3a non-GLP-1 RA subset



Note: Trials (comparator) included: 3623 (placebo), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin).
Abbreviations: sema: semaglutide.

Figure 33 Mean pulse rate (bpm) by treatment week (weeks 0 to 30) – on-treatment – Trial 3624, semaglutide vs. exenatide ER



Exenatide ER: Exenatide Extended release,
Observed 'on-treatment' 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.

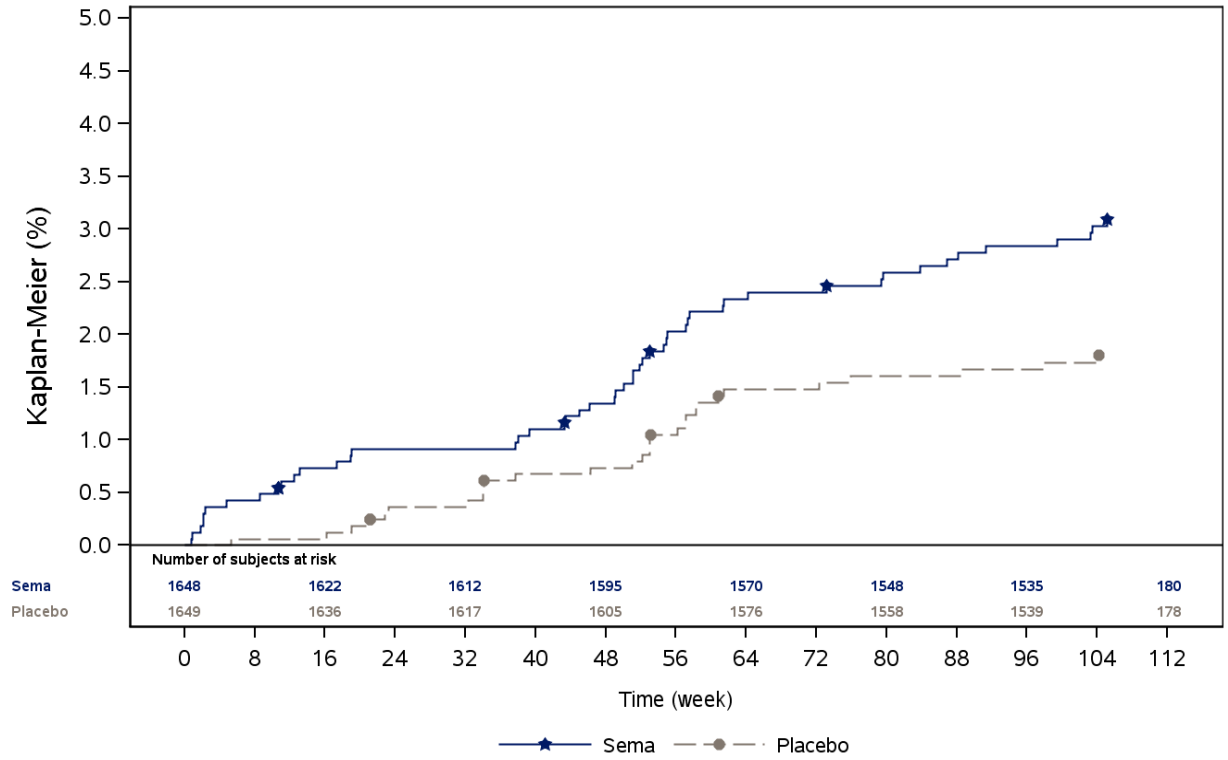
Abbreviations: Exe ER: exenatide extended release; sema: semaglutide.

Diabetic retinopathy

Diabetic retinopathy complications was an adjudicated composite endpoint in the CVOT, and events were confirmed based on fulfilment of one or more of the 4 criteria/components: i) need for retinal photocoagulation, ii) vitreous haemorrhage, iii) need for treatment with intravitreal agents and iv) 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). Fundoscopy/fundus photography performed according to local practice was scheduled at baseline, after 1 year of treatment, at premature treatment discontinuation visits and at end-of-treatment visits.

Of a total of 98 EAC confirmed events of diabetic retinopathy complications, 79 were identified as first event. A higher number of subjects treated with semaglutide (50 subjects) than with placebo (29 subjects) had first EAC confirmed event of diabetic retinopathy complications with no evidence of a difference between the semaglutide doses (semaglutide 0.5 mg: 25 subjects; semaglutide 1.0 mg: 25 subjects) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$). The treatment difference appeared early and persisted throughout the trial (Figure 34).

Figure 34 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. Patients are censored at their planned end-of-trial visit, last direct patient-site contact or all-cause death of the patient, whichever comes first. Numbers below the figure are patients at risk.
Abbreviations: EAC: event adjudication committee; sema: semaglutide

The imbalance was observed for all four components of the endpoint and was similar with semaglutide 0.5 mg and 1.0 mg. The majority of the eye examinations leading to EAC-confirmed events of diabetic retinopathy complications were based on routine examinations, and events were thus asymptomatic.

In the Kaplan Meier plots, the separation of the two curves was apparent immediately after trial initiation for time to first EAC confirmed events of all criteria for diabetic retinopathy complications.

Compared to the overall population, the patients who had EAC-confirmed events of diabetic retinopathy complications during the trial were characterised by a longer diabetes duration (17.53 years), a higher baseline HbA_{1c} (9.37%), more patients on insulins at baseline (75.9%), and more patients with pre-existing diabetic retinopathy (83.5%).

Among patients without pre-existing diabetic retinopathy, events of EAC-confirmed diabetic retinopathy complications were few and there was no imbalance in events of diabetic retinopathy complications between patients treated with semaglutide as compared with placebo (5 vs 4 events). Supporting a lack of effect in those patients without baseline retinopathy, no difference was observed in patients with a baseline fundoscopy evaluated to be normal.

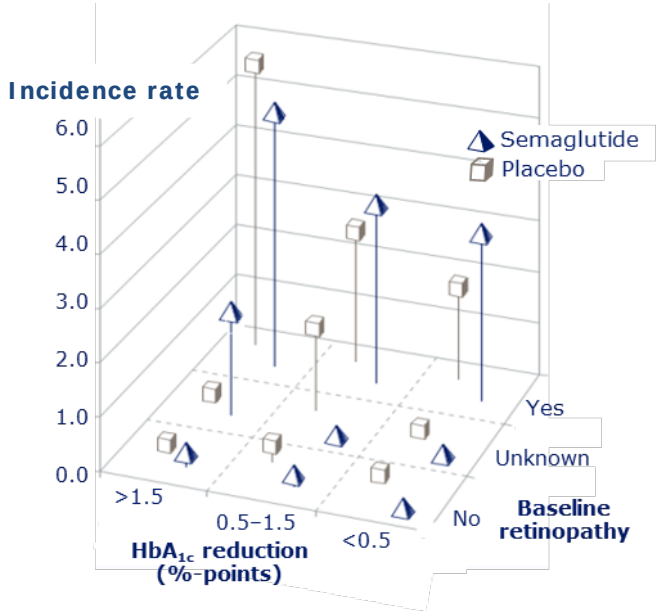
A more specific group with an increased risk of retinopathy complications using semaglutide was identified. This risk of retinopathy complications was only observed in patients with retinopathy at baseline treated with insulin. In patients without retinopathy, there was no effect of semaglutide on the development of retinopathy complications. Numbers needed to treat (3-point MACE) and numbers needed to harm (retinopathy complications) were 45 and 77 respectively for the total population, 19

versus 36 for subjects with baseline retinopathy, and 61 versus 456 for subjects without retinopathy at baseline.

For patients with diabetic retinopathy at baseline and treated with insulin, the number needed to treat is 17 for MACE, whereas the corresponding number needed to harm is 29 for diabetic retinopathy complications.

Rapid improvements in glycaemic control may be associated with a transient worsening of diabetic retinopathy. Semaglutide treatment generally provides a rapid initial decline in blood glucose, e.g., more pronounced and with a faster decline than with a basal insulin (as shown with IGlar in trial 3625). This initial decline was even more pronounced in the CVOT, likely due to a higher baseline HbA_{1c}. A *post-hoc* mediator analysis suggests that the effect of semaglutide in patients with pre-existing retinopathy could be explained in part by the HbA_{1c} reduction at week 16, indicating that a rapid initial decline in blood glucose was a likely mechanism causing this effect (Figure 35). Data suggest that semaglutide was associated with increased risk of retinopathy in patients with pre-existent retinopathy and only small HbA1c reductions (HbA1c reduction <0.5%points).

Figure 35 Mediator analysis of first EAC confirmed events of diabetic retinopathy complications by treatment, baseline diabetic retinopathy, and reduction in HbA1c at week 16 – FAS in trial - CVOT



Note: The figure shows observed incidence rates for first EAC-confirmed event of diabetic retinopathy complications (vertical axis) for subgroups of patients 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 patients with events divided by the total risk time. A patient's risk time is the time from randomisation until the patient's first EAC-confirmed event or censoring.
Abbreviations: EAC: event adjudication committee; PYR: patient years of risk time.

Systematic evaluation of diabetic retinopathy complications was only performed in the CVOT and not in the remaining phase 3a trials. Patients requiring active treatment for known proliferative retinopathy or maculopathy at baseline were excluded from these trials, and overall no safety concerns related to retinopathy were observed.

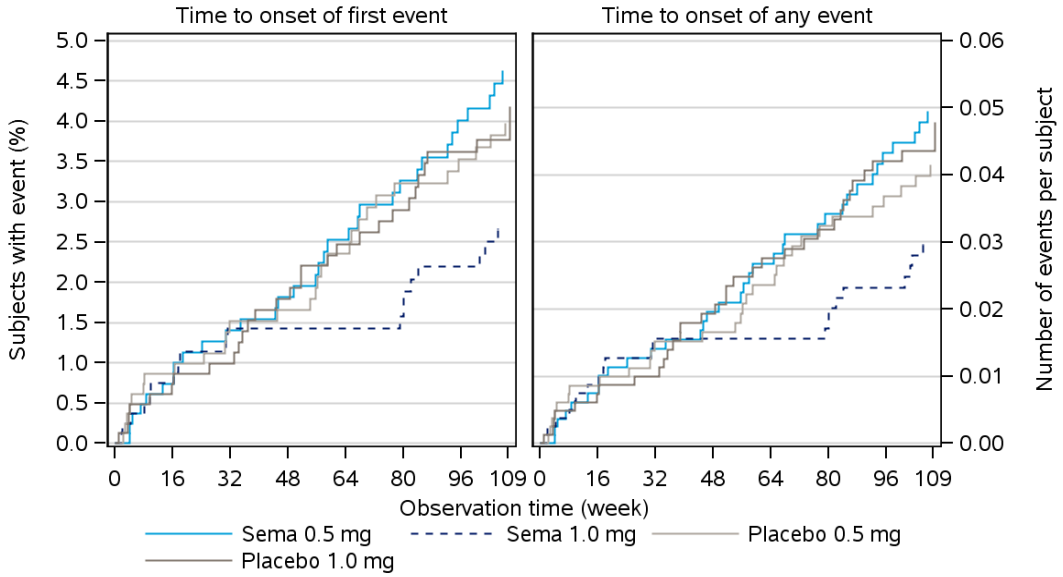
Renal safety

Based on the PK results from a special population trial (trial 3616) and the population PK analysis which included patients with various degrees of renal impairment as covariate (see PK Section), no dose adjustment of semaglutide is needed in patients with renal impairment. This is supported by the fact that semaglutide is extensively metabolised in humans prior to elimination and excretion in the urine and faeces with only 3% intact semaglutide excreted in urine supporting that no accumulation is expected in patients with impaired renal function.

In the CVOT, only patients requiring renal replacement therapy (chronic haemodialysis or chronic peritoneal dialysis) were excluded whereas patients with severe or end-stage renal disease were also excluded in the other phase 3a trials. In the phase 3a programme including more than 900 patients with moderate renal impairment, a little less than 100 patients with severe renal impairment and very few with end-stage renal impairment were included. Based on subgroup analyses, the safety profile of semaglutide (0.5 mg and 1.0 mg) appeared similar in patients with varying degrees of impaired renal function compared with patients with normal renal function.

In the CVOT, fewer AEs and SAEs related to acute renal failure were reported with semaglutide 1.0 mg than with semaglutide 0.5 mg and placebo; all cases were associated with pre-existing morbidity, e.g., chronic renal disease, and some were temporally associated with GI AEs that may have led to dehydration and, in turn, prerenal failure (Figure 36). In the phase 3a pool, AEs related to acute renal failure were very few and with no apparent difference between semaglutide and comparator products (Table 16).

Figure 36 Proportion of subjects with acute renal failure (narrow MedDRA search) event and mean number of events per subject 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.

Table 16 Acute renal failure (narrow MedDRA search) by preferred term – SAS on-treatment – phase 3a pool

System organ class High level group term 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	3	(0.2)	3	0.3	9	(0.5)	9	0.6	5	(0.3)	5	0.3
Renal and urinary disorders	3	(0.2)	3	0.3	9	(0.5)	9	0.6	5	(0.3)	5	0.3
Acute kidney injury					4	(0.2)	4	0.3	1	(<0.1)	1	<0.1
Renal failure	2	(0.2)	2	0.2	3	(0.2)	3	0.2	1	(<0.1)	1	<0.1
Renal impairment	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1	3	(0.2)	3	0.2

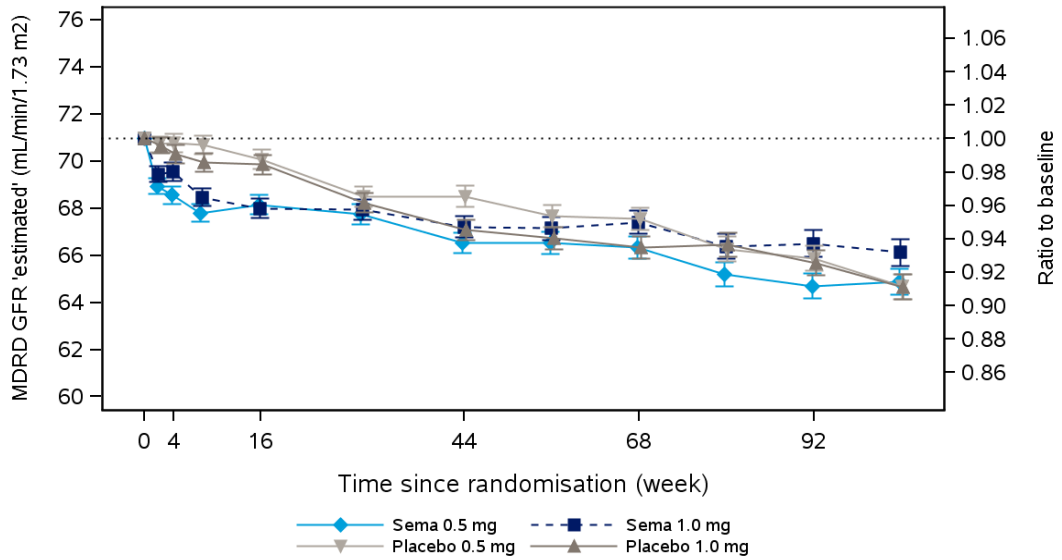
Notes: % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Trials (comparator) included: 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin)
Abbreviations: Adj: adjusted; E: number of events; N: number 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.

Semaglutide was consistently associated with an initial decrease in the estimated glomerular filtration rate (eGFR) (

Figure 37, Figure 38). In active-controlled phase 3a trials, the eGFR also decreased with the active comparators (same magnitude as with semaglutide), including sitagliptin, insulin glargine and OADs, suggesting that the decrease in eGFR was not related to properties of the incretin-based trial products. As observed in the CVOT, the decrease in eGFR was primarily seen in patients with normal renal function or mild impairment at baseline, whereas the decline was less marked in patients with moderate or severe impairment at baseline. In the CVOT, the eGFR decreased with placebo at a more constant and higher rate throughout the trial than with semaglutide; at end-of-treatment, the eGFRs did not differ significantly between semaglutide and placebo (

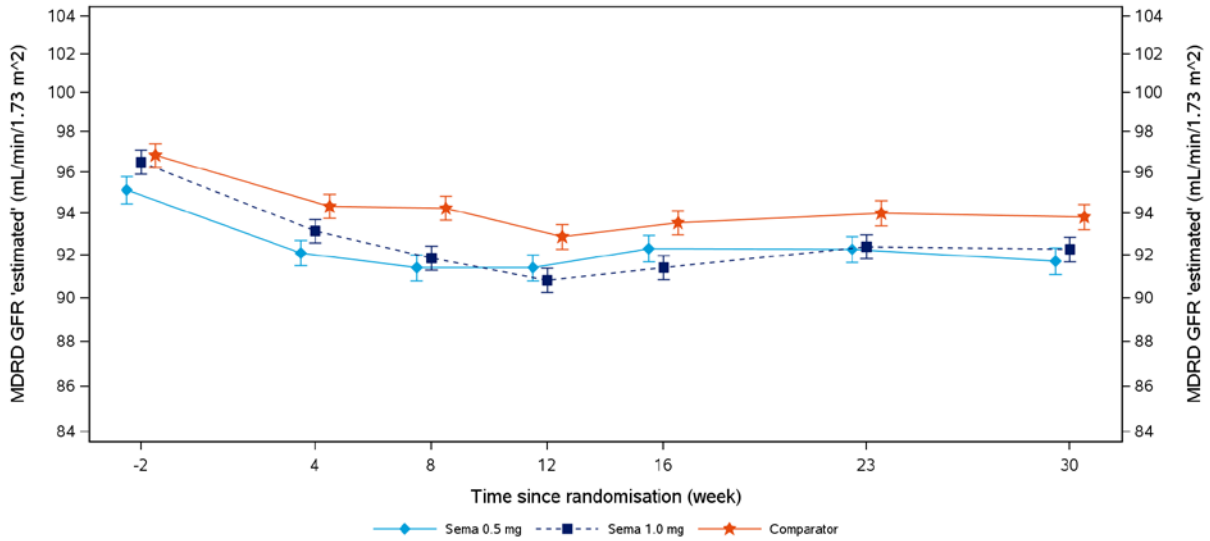
Figure 37). The effect seen with placebo likely reflects the expected decline of renal function over time in a population of patients with renal impairment.

Figure 37 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.

Figure 38 eGFR (mL/min/1.73 m^2) by treatment week (geometric mean) – SAS on-treatment - phase 3a pool

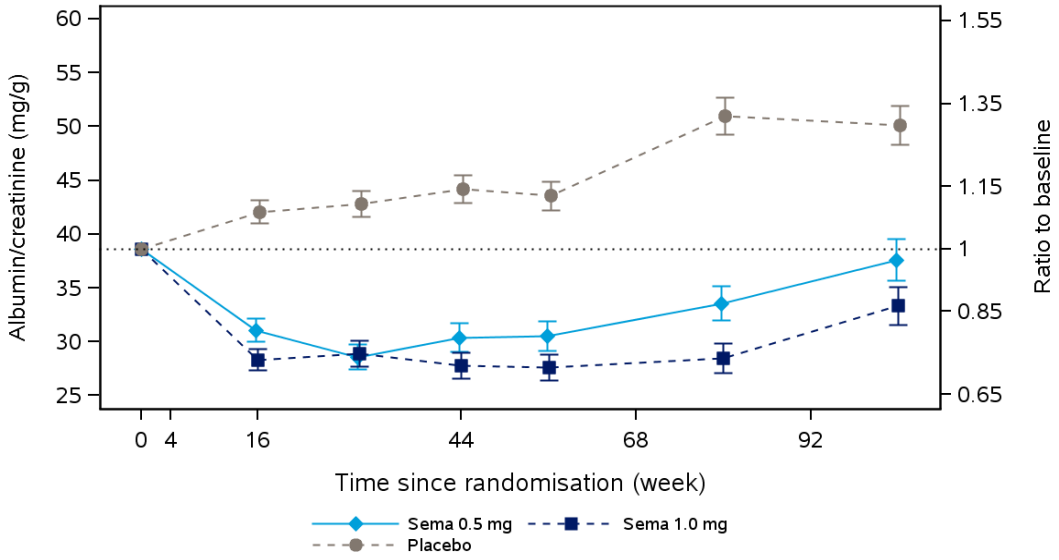


SAS, on-treatment observation period, observed data, Group geometric means (+/-error bars). Error bars are SD/sqrt(n), Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale. Phase 3a pool: trial (comparator): 3623 (placebo), 3624 (exenatide ER), 3625 (insulin glargine), 3626 (sitagliptin), 3627 (placebo), 4091 (OAD) and 4092 (sitagliptin), MDRD: modification of diet in renal disease, eGFR: estimated glomerular filtration rate.

In the CVOT, there was a decrease in urinary albumin-to-creatinine ratio (UACR) with semaglutide and UACR values below baseline values with semaglutide at end-of-treatment, whereas it had increased with placebo (Figure 39). In the phase 3a 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.

Time to new or worsening nephropathy was a secondary endpoint in the CVOT and was evaluated based on composite of 4 components (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine and eGFR $\leq$ 45 mL/min/1.73 m^2 per MDRD, need for continuous renal replacement therapy, and death due to renal disease) confirmed by an independent event adjudication committee (EAC). The incidence and rate of new or worsening nephropathy (first events and recurrent events) were lower with semaglutide (62 patients with 68 events) than with placebo (100 patients with 106 events). The time-to-event analyses of EAC-confirmed new or worsening nephropathy showed a 36% risk reduction with semaglutide relative to placebo.

Figure 39 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.

Pancreatitis

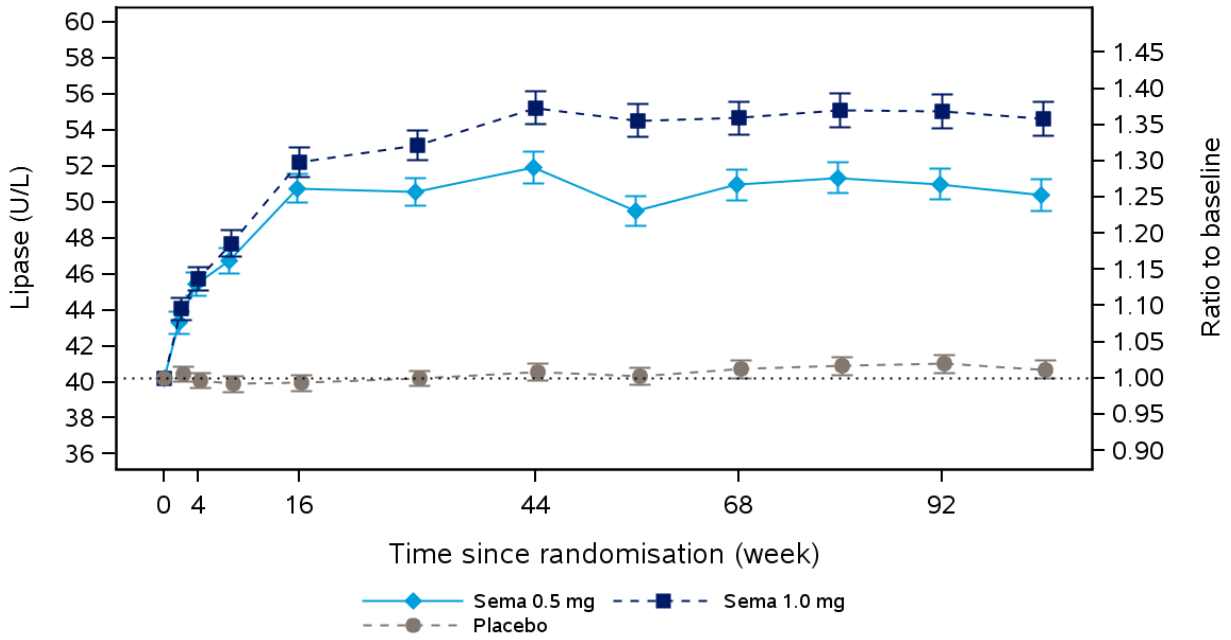
In the CVOT, the number of patients with EAC-confirmed acute pancreatitis was comparable with semaglutide (8 patients) and placebo (10 patients) and all events were classified as 'mild acute pancreatitis' based on the revised Atlanta criteria.

In the phase 3a pool, 5 events of pancreatitis were confirmed by the EAC with semaglutide 0.5 mg, 3 events with semaglutide 1.0 mg and 3 events with comparators. The event rate for EAC-confirmed pancreatitis was similar with semaglutide 1.0 mg and comparators, but higher with semaglutide 0.5 mg compared to semaglutide 1.0 mg or comparators. All comparator events occurred in trial 3624 with exenatide ER and no events were confirmed by the EAC for subjects receiving sitagliptin or non-incretin comparator products.

Levels of serum lipase and amylase increased with semaglutide, similar to what has been described with other incretin-based therapies. After an initial increase in lipase and amylase, the levels showed no further change for up to 2 years (Figure 40, Figure 41).

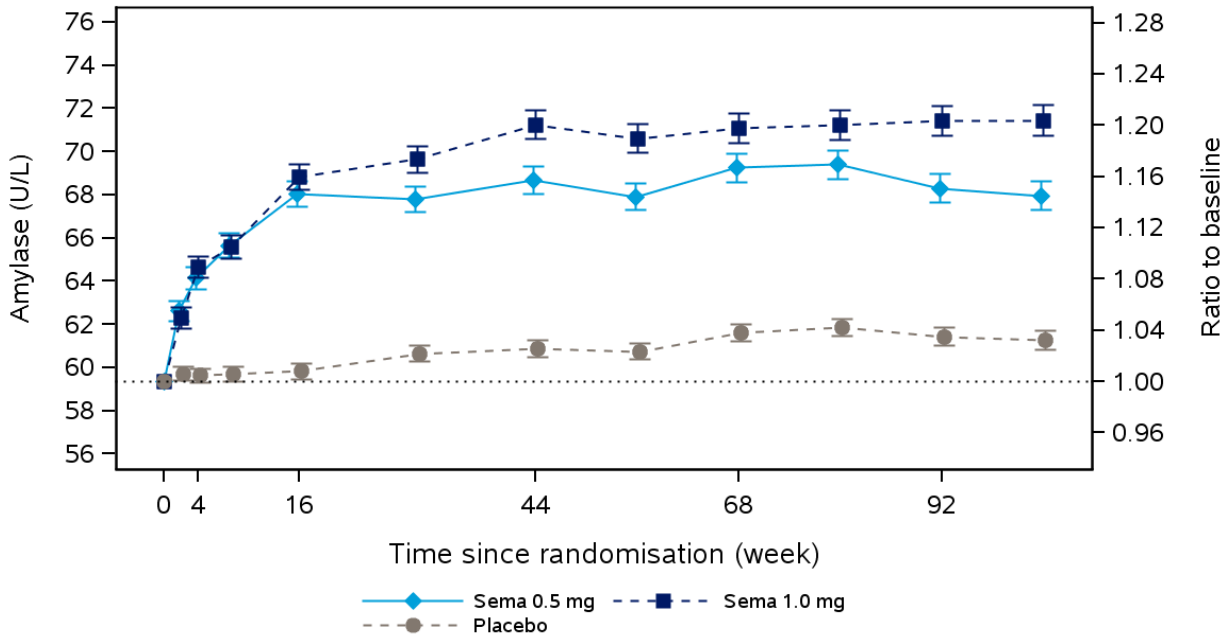
The evidence supports that, in the absence of other signs or symptoms of pancreatitis, elevation of lipase and amylase levels seen with semaglutide does not predict a later development of pancreatitis. This is in line with data obtained for liraglutide.

Figure 40 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.

Figure 41 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.

Gallstones

In the placebo-controlled 2-year CVOT, the proportion of patients with gallbladder-related adverse events were similar with semaglutide (0.5 mg: 3.5%; 1.0 mg: 3.2%) and placebo (3.4%). Conversely, in the phase 3a pool, gallbladder-related AEs were reported more frequently with semaglutide (0.5 mg: 1.3%; 1.0 mg: 1.7%) than with comparator products (0.8%); this difference was primarily driven by AEs of cholelithiasis, especially with semaglutide 1.0 mg. In the non-incretin subset, the proportion of subjects with cholelithiasis and the corresponding rates were 1.0% and 0.6% with semaglutide 0.5 mg and 1.0 mg, respectively. However, with the non-incretin comparators, no AEs of cholelithiasis were reported.

A total of 16 SAEs of cholelithiasis were reported across the phase 3a trials incl. the CVOT with no apparent difference between semaglutide and comparators. All but one SAEs of cholelithiasis led to cholecystectomy; there were 1-2 acute cholecystectomies with semaglutide and comparators, the rest were elective.

The increased risk of cholelithiasis with semaglutide is in line with data on liraglutide for weight management and the liraglutide CVOT which both observed an increased risk of cholelithiasis and cholecystitis whereas no increased risk was observed in phase 3a trials for liraglutide in T2D.Taken together, it is likely that there is a causal relationship between cholelithiasis and semaglutide.

Hepatic events

Across the phase 3a trials, small mean and median decreases from baseline within the normal reference range were observed for each of the hepatic analytes (ALT and AST); and the decreases were more pronounced with semaglutide (0.5 mg and 1.0 mg) than with all comparators.

Overall, the proportion of patients with ALT/AST >3x ULN and 5x ULN were similar with semaglutide (0.5 mg and 1.0 mg) and placebo/active comparator products and there was no pattern or clustering in the timing or duration of the ALT/AST peaks.

In the CVOT, the number of subjects with increases in ALT or AST >5xULN was slightly lower with semaglutide 0.5 mg than with semaglutide 1.0 mg albeit the total numbers were similar between semaglutide and placebo groups. In the phase 3a pool, there were more subjects with elevated ALT or AST levels >5xULN and >10xULN on semaglutide (0.5 mg and 1.0 mg) than on comparators. The number of subjects with ALP elevations 2x, 3x or 5xULN was well-balanced between both semaglutide doses and between semaglutide and comparators in the CVOT and the phase 3a pool. The number of subjects with TBL elevations 2x, 3x, 5x, 10xULN was well-balanced between both semaglutide doses and between semaglutide and comparators in the CVOT and the phase 3a pool.

Thorough screening for Hy's law was performed and no cases were identified. Hepatic disorders SAEs or severe AEs were infrequent and proportion of patients with events were similar with semaglutide and comparators Laboratory findings.

Neoplasms

Number and proportion of patients with individual type of neoplasms (benign and malignant) were low, see Figure 42.

In the CVOT, there was a tendency towards higher frequencies for benign neoplasm with semaglutide than with placebo (HR: 1.35 $[0.99; 1.84]_{95\%CI}$, p=0.0558). No apparent single types of benign

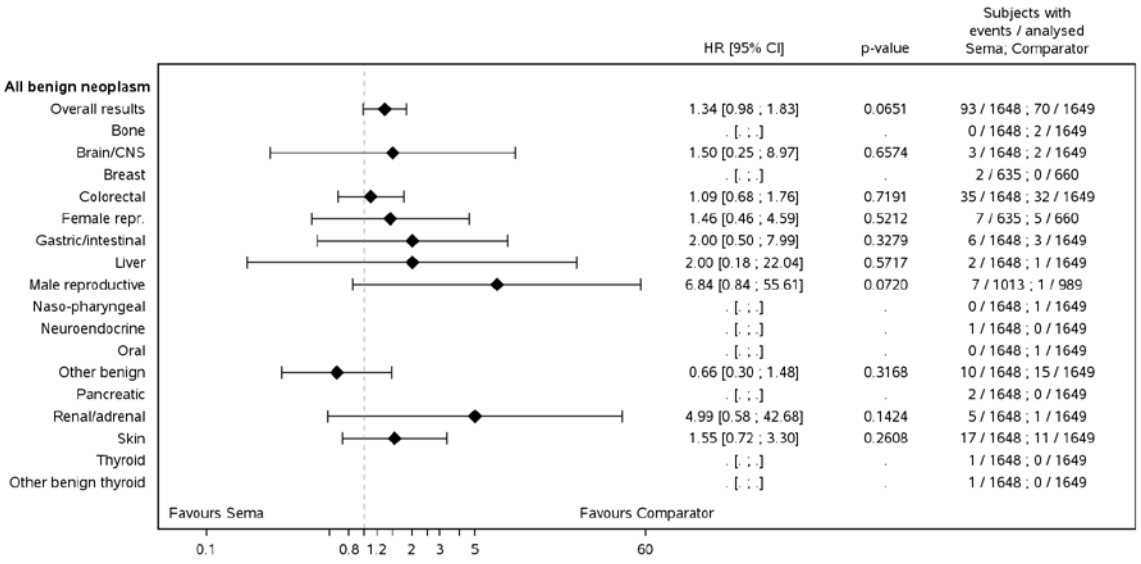
neoplasms were driving this difference (Figure 42). In the phase 3a pool, the proportion of patients with EAC-confirmed benign neoplasms was low and similar with semaglutide and comparator products (HR: 1.14 $[0.73; 1.78]_{95\%CI}$, p=0.5713).

Malignant neoplasms were equally distributed with semaglutide and placebo (HR: 0.94 $[0.67; 1.32]_{95\%CI}$, p= 0.7228) in the CVOT with no apparent differences for any types of malignant neoplasms. In the phase 3a pool there was a tendency towards more malignant neoplasms (HR: 1.61 $[0.74; 3.49]_{95\%CI}$, p=0.2264) with semaglutide than with comparators; however, numbers were low and the difference was not significant. Also, there were no single types of malignant neoplasms driving this difference.

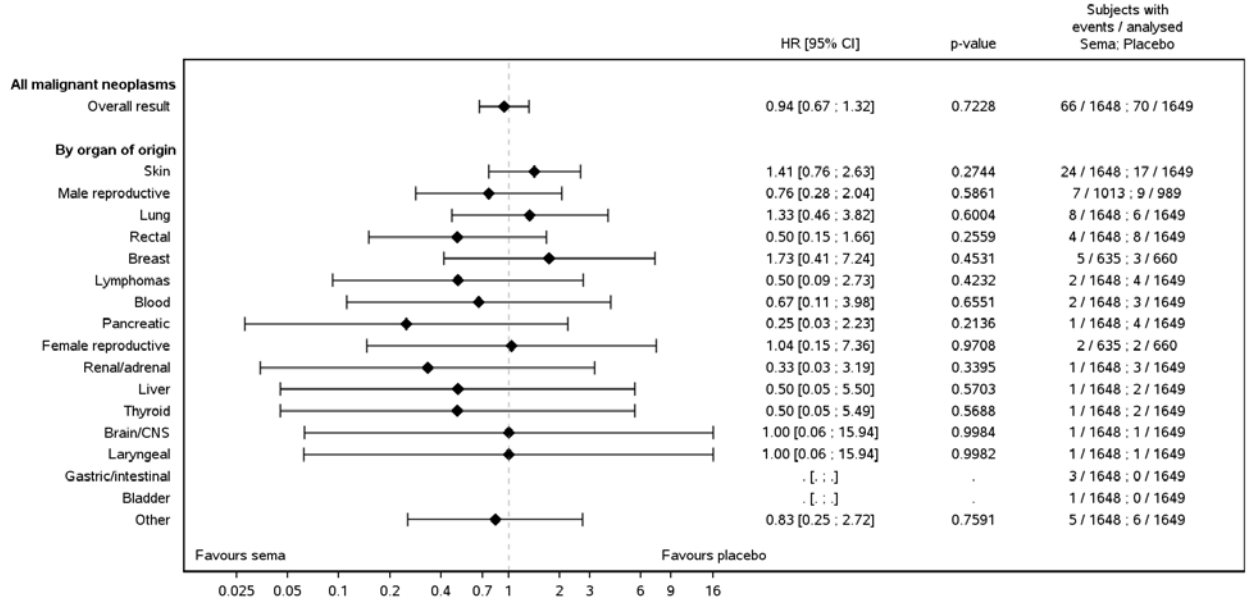
Both benign and malignant skin neoplasms occurred in a higher proportion of patients and at a higher rate with semaglutide 1.0 mg than with semaglutide 0.5 mg and placebo in the CVOT. The difference was driven by malignant skin neoplasms arising from 2 different cell types (basal and squamous cell carcinoma) and 1 case of malignant melanoma was identified. The full treatment differences for both benign and malignant skin neoplasms appeared early in the CVOT, making a drug-related effect unlikely. No differences were seen for neither benign nor malignant neoplasms in the phase 3a pool.

Figure 42 *Post hoc* analyses of first benign (top) and malignant (bottom) neoplasms by organ of origin – FAS in-trial – CVOT

Benign neoplasms



Malignant neoplasms



Notes: Estimated HRs and associated CIs are from a Cox proportional hazard model with treatment as a fixed factor. HRs give comparison of sema versus placebo. All EAC-confirmed thyroid neoplasms were in subcategory 'other' (than C-cell related), HRs, CIs and p-values for 'gastric/intestinal and bladder are not shown due to events only occurring in the semaglutide groups. Women contribute to breast and female reproductive. Men contribute to male reproductive.
Abbreviations: CI: confidence interval; CNS: central nervous system; HR: hazard ratio.
Cross-reference: Summary 2.7.4, Figures 2-82 and 2-85.

No cases of MTC were identified during the semaglutide development programme. Calcitonin is considered a biomarker for increased thyroid C-cell mass and activation. Calcitonin levels were assessed at baseline (to exclude patients likely to have pre-existing C-cell neoplasia) and at regular intervals during the semaglutide phase 3a trials to identify patients at risk of having C-cell neoplasia. Overall, minor fluctuations in calcitonin levels were observed throughout the phase 3a trials with no clinically relevant difference between semaglutide and placebo or semaglutide and comparators.

Across the CVOT and phase 3a trials a small proportion of subjects had post-baseline events of calcitonin ≥20 ng/L both with semaglutide, placebo and pooled comparators. Proportion of subjects with post-baseline calcitonin levels >ULN, >20 ng/mL, >50 ng/L and >100 ng/L were comparable with semaglutide, placebo and pooled comparators.

In the semaglutide clinical development programme, the incidence of pancreas cancer with semaglutide was low (5 cases: 3 malignant, 2 benign) and appeared not to be different from placebo and comparator products (7 cases; 6 malignant, 1 benign).

Episodes of hypoglycaemia

Episodes of hypoglycaemia were generally infrequent with semaglutide treatment when used as monotherapy or in combination with OADs excl. SU. In the semaglutide phase 3a clinical development programme, no episodes of severe hypoglycaemia were observed when semaglutide s.c. was used as monotherapy (Table 17).

Episodes of severe hypoglycaemia were infrequent when semaglutide was administered concomitantly with OADs excl. SU and primarily observed when semaglutide was used with an SU or insulin with no apparent differences between semaglutide and comparators including placebo.

Table 17 Episodes of ADA severe hypoglycaemia by baseline background medication – SAS on-treatment – phase 3a trials incl. CVOT

	Sema 0.5 mg				Sema 1.0 mg				Comparators/Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Monotherapy												
Phase 3a trials (a)												
N and PYE (year)	299	226			300	215			237	157		
Severe episodes	0	(0.0)			0	(0.0)			0	(0.0)		
Add-on to other OADs												
Phase 3a trials (b)												
N and PYE (year)	687	659			910	874			851	845		
Severe episodes	0	(0.0)			1	(0.1)	1	0.1	3	(0.3)	3	0.3
CVOT												
N and PYE (year)	118	204.2			124	207.0			256	464.5		
Severe episodes	1	(0.8)	1	0.5	0	(0.0)	0	0.0	1	(0.4)	1	0.2
Add-on to SU												
Phase 3a trials (c)												
N and PYE (year)	255	196			436	377			435	380		
Severe episodes	2	(0.8)	4	2.3	5	(1.2)	11	3.0	4	(0.9)	4	1.0
CVOT												
N and PYE (year)	230	420.1			219	399.1			434	808.2		
Severe episodes	3	(1.3)	3	0.7	3	(1.4)	3	0.8	2	(0.5)	4	0.5
Add-on to insulin												
Phase 3a trials (d)												
N and PYE (year)	132	84			131	82			133	84		
Severe episodes	0	(0.0)			2	(1.5)	2	2.4	0	(0.0)		
CVOT												
N and PYE (year)	358	653.3			345	599.6			678	1248.1		
Severe episodes	8	(2.2)	8	1.2	3	(0.9)	7	1.2	14	(2.1)	23	1.8
Add on to SU + insulin												
CVOT												
N and PYE (year)	117	210.7			131	238.2			276	514.0		
Severe episodes	2	(1.7)	3	1.4	3	(2.3)	3	1.3	9	(3.3)	12	2.3

Notes: a: Monotherapy subgroup comprises patients from trials 3623, 3626, 3624, 4092 and 4091. b: 'Add-on to other OADs' subgroup comprises patients from trials 3623, 3626, 3624, 3625 and 4091. c) 'Add-on to SU' subgroup comprises patients from trials 3626, 3624, 3625 and 4091.d: 'Add-on to insulin' subgroup comprises patients from trials 3624 and 3627. Comparator in the CVOT is placebo. The on-treatment summary of hypoglycaemic episodes comprises treatment-emergent events from the hypo form reported with onset on or after the day of first randomised dose to date of last dose plus 42 days. The subgroups are based on the baseline medication. The patients included in each subgroup only consist of those patients from a trial, who fulfil the criteria. For phase 3a trials (excl. CVOT) the table only contain data from the on-treatment period without rescue medication and % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Abbreviations: ADA: American Diabetes Association; E: Number of events, N: Number of patients from safety analysis set experiencing at least one event, OAD: Oral anti-glycaemic drug, PYE, PYE: Patient years of exposure is calculated from the time of first drug date to the follow-up visit or first drug date of second treatment in crossover trials, R: Event rate per 100, SU: Sulfonylurea, %: Percentage of patients experiencing at least one event

A similar picture was seen with regards to background medication and frequencies of hypoglycaemia based on Novo Nordisk defined 'severe or BG confirmed symptomatic episodes of hypoglycaemia' in phase 3 trials. No difference between semaglutide and comparators was evident in patients on monotherapy as well as on a background of OADs excl. SU. For patients on SU and insulin, episodes were reported at higher frequencies with semaglutide than with placebo; the difference was due to more BG confirmed symptomatic episodes in the setting of lower achieved mean $HbA_{1c.}$.

In the CVOT where semaglutide was administered in addition to standard-of-care, changes to background medication were allowed during the trial reflecting a real-life setting. Across all background medications, there were no significant differences between semaglutide and placebo with respect to number of episodes or patients experiencing episodes of severe or BG confirmed symptomatic hypoglycaemia, including nocturnal episodes. However, for patients on SU and insulin, episodes of severe or blood glucose confirmed symptomatic hypoglycaemia were reported at higher frequencies

with semaglutide than with placebo. Overall, severe episodes of hypoglycaemia were infrequent with semaglutide (0.5 mg: 1.7%, 1.0 events per 100 PYE; 1.0 mg: 1.1%, 0.9 events per 100 PYE) and placebo (1.6%, 1.3 events per 100 PYE).

Laboratory findings

The following laboratory parameters have been described above: lipase and amylase, liver tests (ALT, AST, ALP, and total bilirubin), renal function tests (eGFR, creatinine, UACR, urea), calcitonin, anti-semaglutide antibodies.

No clinically relevant mean changes in haematology parameters (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential cell count [eosinophils, neutrophils, basophils, monocytes and lymphocytes]) were observed from baseline to end-of-treatment in any of the treatment groups (semaglutide 0.5 mg, semaglutide 1.0 mg or placebo) based on mean changes and ratios to baseline.

No clinically relevant mean changes in the biochemistry parameters (albumin, sodium, potassium, creatine kinase, calcium total and calcium [albumin corrected]) were observed from baseline to end-of-treatment in any of the treatment groups based on mean values, changes from baseline, or ratios to baseline.

Safety in special populations

AEs in subgroups

The AE profile in subgroups of patients based on intrinsic factors (sex, baseline age, race, ethnicity, baseline BMI, baseline body weight, baseline hypertension, baseline CV history, baseline renal function, baseline hepatic function) and extrinsic factors (region, tobacco use and anti-glycaemic background medication) was explored. The applicant has provided detailed data for elderly patients in the mandatory table (Table 19 and Table 19). The safety profile of semaglutide was consistent across all subpopulations of patients treated with semaglutide including elderly and patients with renal impairment and heart failure.

Table 18 Adverse events by age - Ph 3a pool - on-treatment – safety analysis set

	Sema 0.5 mg		Sema 1.0 mg		Comparator	
	N	(%)	N	(%)	N	(%)
18-64 years	1034		1372		1248	
All events	758	72.7	997	72.3	840	67.5
Serious AEs	66	6.3	90	6.6	60	4.8
Fatal	6	0.6	2	0.1	4	0.4
(prolonged) hospitalization	57	5.4	80	5.9	55	4.4
Life-threatening	10	1.0	13	1.0	10	0.8
Disability/incapacity	0		3	0.2	0	
Other (medically significant)	10	1.0	15	1.1	7	0.6
AE leading to premature discontinuation	49	4.8	106	7.7	37	2.9
Psychiatric disorders (SOC)	37	3.6	31	2.2	41	3.3
Nervous system disorders (SOC)	118	11.5	181	13.2	137	10.9
Accidents and injuries (SMQ, narrow scope)	51	4.6	66	4.7	49	4.0
Cardiac disorders (SOC)	24	2.3	47	3.4	29	2.3
Vascular disorders (SOC)	38	3.7	53	3.9	44	3.5
Cerebrovascular disorders (narrow SMQ)	54	4.9	75	5.3	54	4.4
Infections and infestations (SOC)	379	35.8	435	31.2	421	34.4
Collapse [1]	40	3.8	53	3.9	30	2.5
Decreased appetite (PT)	62	5.9	94	6.7	25	2.0
65-74 years	294		348		355	
All events	222	74.9	260	73.8	259	73.1
Serious AEs	21	7.1	24	7.0	31	8.6

Fatal	0		1	0.3	2	0.6
(prolonged) hospitalization	21	7.1	22	6.4	22	6.1
Life-threatening	4	1.3	4	1.3	7	1.8
Disability/incapacity	0		0		0	
Other (medically significant)	3	1.0	6	1.8	6	1.7
AE leading to premature discontinuation	26	8.9	44	12.5	12	3.2
Psychiatric disorders (SOC)	9	3.1	14	3.9	10	2.8
Nervous system disorders (SOC)	43	14.3	41	11.8	46	12.5
Accidents and injuries (SMQ, narrow scope)	16	5.3	15	4.2	16	4.6
Cardiac disorders (SOC)	15	5.0	18	5.2	20	5.5
Vascular disorders (SOC)	10	3.5	15	4.4	15	3.9
Cerebrovascular disorders (narrow SMQ)	21	7.0	16	4.5	18	5.2
Infections and infestations (SOC)	85	27.9	105	29.7	125	35.5
Collapse [1]	22	7.4	17	5.0	18	5.2
Decreased appetite (PT)	20	6.7	29	7.9	10	2.6
75-84 years	45		57		52	
All events	35	76.3	44	77.8	36	68.8
Serious AEs	5	11.9	4	6.5	4	6.9
Fatal	1	2.7	0		0	
(prolonged) hospitalization	4	9.0	4	6.5	4	6.9
Life-threatening	1	2.7	1	1.4	1	1.6
Disability/incapacity	0		1	1.4	0	
Other (medically significant)	1	2.9	1	2.4	0	
AE leading to premature discontinuation	9	19.4	6	11.1	2	3.0
Psychiatric disorders (SOC)	2	2.7	0		2	3.2
Nervous system disorders (SOC)	4	7.4	11	22.6	7	10.7
Accidents and injuries (SMQ, narrow scope)	3	8.6	7	12.3	3	5.4
Cardiac disorders (SOC)	2	5.5	4	6.7	2	4.6
Vascular disorders (SOC)	2	3.7	4	7.5	4	6.8
Cerebrovascular disorders (narrow SMQ)	4	10.0	8	13.7	4	6.8
Infections and infestations (SOC)	13	24.0	15	25.3	17	36.1
Collapse [1]	2	4.2	9	19.1	4	7.1
Decreased appetite (PT)	5	12.1	8	15.0	0	
>= 85 years	0		0		2	
All events	0		0		1	50.0
Serious AEs	0		0		0	
Fatal	0		0		0	
(prolonged) hospitalization	0		0		0	
Life-threatening	0		0		0	
Disability/incapacity	0		0		0	
Other (medically significant)	0		0		0	
AE leading to premature discontinuation	0		0		0	
Psychiatric disorders (SOC)	0		0		0	
Nervous system disorders (SOC)	0		0		0	
Accidents and injuries (SMQ, narrow scope)	0		0		0	
Cardiac disorders (SOC)	0		0		0	
Vascular disorders (SOC)	0		0		0	
Cerebrovascular disorders (narrow SMQ)	0		0		0	
Infections and infestations (SOC)	0		0		1	50.0
Collapse [1]	0		0		0	
Decreased appetite (PT)	0		0		0	

Table 19 Adverse events by age - 3744, CVOT - on-treatment – safety analysis set

	Sema 0.5 mg N	(%)	Sema 1.0 mg N	(%)	Comparator N	(%)
18-64 years	442		412		843	
All events	387	87.6	358	86.9	733	87.0
Serious AEs	122	27.6	117	28.4	274	32.5
Fatal	11	2.5	14	3.4	17	2.0
(prolonged) hospitalization	110	24.9	102	24.8	252	29.9
Life-threatening	44	10.0	37	9.0	79	9.4
Disability/incapacity	2	0.5	7	1.7	9	1.1
Other (medically significant)	18	4.1	19	4.6	45	5.3
AE leading to premature discontinuation	41	9.3	40	9.7	50	5.9
Psychiatric disorders (SOC)	27	6.1	31	7.5	43	5.1
Nervous system disorders (SOC)	90	20.4	87	21.1	210	24.9
Accidents and injuries (SMQ, narrow scope)	49	11.1	44	10.7	105	12.5
Cardiac disorders (SOC)	76	17.2	70	17.0	154	18.3
Vascular disorders (SOC)	42	9.5	44	10.7	109	12.9
Cerebrovascular disorders (narrow SMQ)	62	14.0	51	12.4	137	16.3
Infections and infestations (SOC)	180	40.7	165	40.0	367	43.5
Collapse [1]	41	9.3	31	7.5	88	10.4
Decreased appetite (PT)	39	8.8	28	6.8	14	1.7
65-74 years	307		324		638	

All events	277	90.2	288	88.9	579	90.8
Serious AEs	112	36.5	93	28.7	238	37.3
Fatal	9	2.9	6	1.9	23	3.6
(prolonged) hospitalization	101	32.9	78	24.1	216	33.9
Life-threatening	33	10.7	20	6.2	75	11.8
Disability/incapacity	3	1.0	5	1.5	11	1.7
Other (medically significant)	23	7.5	17	5.2	32	5.0
AE leading to premature discontinuation	36	11.7	57	17.6	36	5.6
Psychiatric disorders (SOC)	18	5.9	20	6.2	42	6.6
Nervous system disorders (SOC)	82	26.7	79	24.4	154	24.1
Accidents and injuries (SMQ, narrow scope)	40	13.0	32	9.9	81	12.7
Cardiac disorders (SOC)	59	19.2	39	12.0	135	21.2
Vascular disorders (SOC)	38	12.4	41	12.7	80	12.5
Cerebrovascular disorders (narrow SMQ)	47	15.3	42	13.0	107	16.8
Infections and infestations (SOC)	148	48.2	141	43.5	323	50.6
Collapse [1]	41	13.4	37	11.4	66	10.3
Decreased appetite (PT)	34	11.1	32	9.9	9	1.4
75-84 years	71		76		154	
All events	65	91.5	69	90.8	133	86.4
Serious AEs	30	42.3	27	35.5	56	36.4
Fatal	4	5.6	2	2.6	4	2.6
(prolonged) hospitalization	27	38.0	24	31.6	54	35.1
Life-threatening	8	11.3	7	9.2	16	10.4
Disability/incapacity	0		1	1.3	4	2.6
Other (medically significant)	5	7.0	3	3.9	4	2.6
AE leading to premature discontinuation	18	25.4	18	23.7	23	14.9
Psychiatric disorders (SOC)	9	12.7	8	10.5	9	5.8
Nervous system disorders (SOC)	19	26.8	24	31.6	36	23.4
Accidents and injuries (SMQ, narrow scope)	9	12.7	10	13.2	23	14.9
Cardiac disorders (SOC)	16	22.5	10	13.2	36	23.4
Vascular disorders (SOC)	12	16.9	7	9.2	17	11.0
Cerebrovascular disorders (narrow SMQ)	9	12.7	13	17.1	25	16.2
Infections and infestations (SOC)	30	42.3	30	39.5	54	35.1
Collapse [1]	14	19.7	13	17.1	23	14.9
Decreased appetite (PT)	11	15.5	13	17.1	5	3.2
>= 85 years	3		7		9	
All events	3	100.0	7	100.0	8	88.9
Serious AEs	0		3	42.9	6	66.7
Fatal	0		1	14.3	0	
(prolonged) hospitalization	0		3	42.9	5	55.6
Life-threatening	0		1	14.3	4	44.4
Disability/incapacity	0		1	14.3	1	11.1
Other (medically significant)	0		0		0	
AE leading to premature discontinuation	0		4	57.1	1	11.1
Psychiatric disorders (SOC)	0		1	14.3	1	11.1
Nervous system disorders (SOC)	0		1	14.3	4	44.4
Accidents and injuries (SMQ, narrow scope)	0		1	14.3	1	11.1
Cardiac disorders (SOC)	0		1	14.3	2	22.2
Vascular disorders (SOC)	0		0		1	11.1
Cerebrovascular disorders (narrow SMQ)	0		1	14.3	2	22.2
Infections and infestations (SOC)	2	66.7	5	71.4	5	55.6
Collapse [1]	0		1	14.3	0	
Decreased appetite (PT)	0		3	42.9	0	

Immunological events

Semaglutide has a high homology (94%) to endogenous GLP-1 and is therefore expected to have a low immunogenic potential. Allergic reactions were reported by a low (4–6%) proportion of patients. Most of the allergic reactions were of mild or moderate severity, did not lead to premature treatment discontinuation and no differences between semaglutide and placebo/comparators were observed.

In the CVOT, the most frequently reported AEs related to allergic reactions were the PTs rash, rhinitis allergic, urticaria, dermatitis and eczema; the proportion of subjects and rate of events of these PTs were similar across the semaglutide and placebo treatment groups. The most frequently reported AEs related to allergic reactions generally reflected the PTs reported for CVOT and overall were similar across treatment groups.

Injection site reactions were reported by a low (approximately 1%) proportion of patients with semaglutide and were not recurrent in those individuals. Most injections site reactions were of mild or moderate severity, did not lead to premature treatment discontinuation and no differences between semaglutide and placebo and non-exenatide comparators was observed.

In trial 3624, injection site reactions were reported in fewer patients with semaglutide 1.0 mg (1.2%) than with exenatide ER 2.0 mg (22.0%).

Anti-semaglutide antibody formation was low in the phase 3a trials; the proportion of subjects that tested positive for anti-semaglutide antibodies was 1.9% in CVOT, 1.0% in the phase 3a pool and 2.2% in the pool of placebo-controlled trials. In patients that did test positive, the antibody response was low (up to 15.90 % bound semaglutide related to total semaglutide [B/T]) and appeared to be transient as very few patients (less than 0.4%) had anti-semaglutide antibodies at the follow-up visit performed at least 5 weeks after last dose. No patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect and no effect on semaglutide exposure, HbA_{1c} or semaglutide safety profile were identified and no association with immunogenicity-related AEs were evident (see efficacy).

In trial 3624, 3.2% (13 of 404) of patients were tested positive for anti-semaglutide antibodies, none of the antibodies were neutralising to semaglutide or endogenous GLP-1. In contrast, anti-exenatide antibodies were confirmed in the majority (87.7%, 355 of 405) of patients treated with exenatide ER 2.0 mg, in which 39 had a neutralising effect on exenatide and none on endogenous GLP-1.

Safety related to drug-drug interactions and other interactions

See PK section.

Discontinuation due to AES

Discontinuation due to AES is described in the efficacy section; patient disposition.

Post marketing experience

Not applicable.

2.5.6. Discussion on clinical safety

The primary focus of the safety evaluation is on the data from the eight completed phase 3a 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. The phase 3a trials were designed to evaluate the efficacy and safety of semaglutide in a relatively broad population of subjects with T2D 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.

Total exposure to semaglutide was 2712 PYE (n=3150 patients) in the phase3a trials and 2932 PYE (n=1642 patients) in the CVOT. Exposure is considered sufficient to evaluate the semaglutide safety profile in the target population. However, the high risk population in the CVOT trial is not representative of the general population. In addition, effects of treatment with semaglutide >2 years are unknown.

Characteristics were generally well-balanced across the semaglutide (0.5 mg and 1.0 mg) and placebo/comparator treatment groups.

Adverse events CVOT

In the 2-year CVOT, nearly 90% of subjects had at least one AE during the treatment period. The proportion of subjects with AEs was similar with semaglutide (0.5 mg: 88.9%; 1.0 mg: 88.2%) and placebo (88.4%), whereas, the rate of events per 100 PYE was higher in subjects treated with semaglutide (0.5 mg: 334.7 events per 100 PYE; 1.0 mg: 350.2 events per 100 PYE) than with placebo (313.2 events per 100 PYE). The majority of AEs were of mild or moderate severity. Approximately 22% of subjects had severe AEs both with semaglutide (0.5 mg and 1.0 mg) and placebo. The proportions of subjects with AEs reported as recovered or recovering were similar with semaglutide (0.5 mg and 1.0 mg) and placebo. Also, proportion of AEs that were recovered and not-recovered at the end of the trials were similar between semaglutide and placebo. The AEs reported with semaglutide (0.5 mg and 1.0 mg) were generally consistent with those reported for other drugs in the GLP-1 RA class. AEs were reported in a higher proportion of subjects with semaglutide than with placebo in the GI disorders SOC and for PTs of lipase increased, amylase increased, decreased appetite, diabetic retinopathy, and dizziness. Headache, nasopharyngitis, upper respiratory tract infection, bronchitis, and joint pain (arthralgia) were reported in a lower proportion of subjects with semaglutide (0.5 mg and 1.0 mg) than with placebo.

A total of 123 subjects (3.7%) had fatal AEs that had onset during the 2-year in-trial period of the CVOT. The proportion of subjects with fatal events (with onset during the in-trial period) was similar with semaglutide (0.5 mg and 1.0 mg) and placebo.

SAEs were most frequently reported in the SOC cardiac disorders across all treatment groups. The proportion of subjects reporting SAEs within this SOC and the corresponding rate were generally lower with semaglutide than placebo (in particular with semaglutide 1.0 mg) confirming the results from the 'time-to-first CV event' analyses. However, SAE's coronary artery disease, cardiac failure and vascular therapeutic procedures (particularly cardiac interventions) were higher with semaglutide (0.5 mg and 1.0 mg) than with placebo in the phase 3a pool. In the CVOT, the opposite was seen with fewer reports of the HLGT 'vascular therapeutic procedures' with semaglutide than with placebo. The Applicant has investigated the conditions leading to the procedures, and states that at HLGT level there were fewer imbalances in the conditions that are treated with vascular therapeutic procedures. According to the Applicant, local treatment practices and availability of treatment options may have amplified a chance finding here.

Subjects discontinued treatment prematurely due to AEs throughout the trial both with semaglutide and placebo with the highest frequencies and rates in the first months after treatment initiation. The pattern for subjects discontinuing treatment prematurely due to AEs reflects that the prevalence of GI AEs was highest during the initial months and that these were the main drivers of premature treatment discontinuation due to AEs.

Adverse events pool of phase 3a trials

In the pool of phase 3a trials, the proportion of subjects reporting any AE during the treatment period was approximately 70%. The proportion of subjects with AEs and the corresponding rates were higher with semaglutide (0.5 mg and 1.0 mg) than with comparator products (73.4 and 72.7% vs 68.7%).

The majority of AEs were of mild or moderate severity. Approximately 6% of subjects in the semaglutide groups (0.5 mg and 1.0 mg) and 4.4% in the comparators group had severe events.

AEs reported with semaglutide (0.5 mg and 1.0 mg) were generally consistent with those reported for other drugs in the GLP-1 RA class. The majority of AEs were reported as recovered. The proportions of subjects with AEs reported as not recovered or recovering were similar with semaglutide (0.5 mg and 1.0 mg) and comparator products. Also, proportion of AEs that were recovered and not recovered at the end of the trials were similar between semaglutide and placebo. In the phase 3a pool, a total of 16 subjects died due to AEs with onset during the in-trial period for the individual subject. A total of 10 subjects (0.3%) randomised to semaglutide died, and 6 subjects (0.4%) randomised to comparator products died.

The proportion of subjects with SAEs and the corresponding rate were higher with semaglutide (0.5 mg and 1.0 mg) than with comparator products. SAEs within the SOC of gastrointestinal disorders were reported by a higher proportion of subjects with semaglutide 0.5 mg (1.3%, 2.1 events per 100 PYE) than with semaglutide 1.0 mg (0.7%, 1.0 events per 100 PYE) and comparator products (0.5%, 0.8 events per 100 PYE) driven by pancreatitis. The proportion of subjects who discontinued treatment prematurely due to AEs was higher with semaglutide than with comparator products. The proportion of subjects who discontinued treatment prematurely due to AEs was higher with semaglutide 1.0 mg than with semaglutide 0.5 mg indicating a dose-response. The proportions of subjects who discontinued treatment prematurely due to gastrointestinal disorders were higher with semaglutide (0.5 mg: 3.9%; 1.0 mg: 5.9%) than with comparators (0.9%).

Gastrointestinal disorders

Gastrointestinal disorders, particularly nausea, vomiting and diarrhoea, are the most common side effects of GLP-1 RAs and these side effects are typically of short duration. Across the semaglutide development programme, gastrointestinal AEs were the most frequently reported AEs during treatment with semaglutide. The most frequent gastrointestinal AEs were nausea, diarrhoea, vomiting, constipation, dyspepsia and abdominal pain. The frequencies (%) and rates of gastrointestinal AEs were higher with both doses of semaglutide compared to all comparators, including the only other GLP-1 RA studied, Exenatide ER.

There was a dose-dependent increase in gastrointestinal AEs with semaglutide across the CVOT and most of the phase 3a trials. This also included a dose-dependent increase in gastrointestinal AEs leading to premature treatment discontinuation.

Gastrointestinal AEs were not more prevalent in patients with mild, moderate or severe renal impairment for semaglutide vs. comparators.

Patients with a higher exposure to semaglutide (as seen in patients with low body weight, low BMI, women and Asians) had more gastrointestinal AEs than patients with a lower semaglutide exposure, as supported by exposure-response analyses. The fact that patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide is mentioned in Section 4.8 of the SmPC.

Pulse rate

Similar to other GLP-1 RA, an increase in resting pulse rate of 1 to 6 beats/minutes during treatment was seen across trials. However, based on the results obtained in the semaglutide CVOT as well as in

the liraglutide LEADER trial, the increase in pulse rate does not seem to result in an increased CV risk after a follow up of 2 years. When assessed by office measurements, semaglutide seems to antagonize the beta-blocker-induced pulse rate reduction. As beta-blockers were not a randomised treatment in the CVOT, the implications hereof cannot be assessed. Extrapolation of the CV outcome results to subjects without established CV disease remains difficult. In these subjects the differences in office HR were larger than in the whole population. Possible longer term effects are unknown.

Diabetic retinopathy

A significantly increased risk of EAC-confirmed events of diabetic retinopathy complications was observed with semaglutide (50 [3.0%] patients) as compared with placebo (29 [1.8%] patients) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$). The treatment difference appeared early and persisted throughout the trial The imbalance was observed for all four components of the endpoint (need for retinal photocoagulation, vitreous haemorrhage, need for treatment with intravitreal agents and onset of diabetes-related blindness) and was similar with semaglutide 0.5 mg and 1.0 mg.

Exenatide has been associated with transient worsening of diabetic retinopathy in a case series (Varadhan et al. Diabetes Res Clin Pract. 2014;103(3):e37-9). In addition, in the liraglutide CVOT, the HR for the composite endpoint reflecting diabetic retinopathy complications, although not statistically significant, disfavoured liraglutide (HR: 1.15 [0.87; 1.52] 95%CI, p=0.33).

Compared to the overall population, the patients who had EAC-confirmed events of diabetic retinopathy complications during the trial were characterised by a longer diabetes duration (17.53 years), a higher baseline HbA_{1c} (9.37%), more patients on insulins at baseline (75.9%), and more patients with pre-existing diabetic retinopathy (83.5%). Among patients without pre-existing diabetic retinopathy, events of EAC-confirmed diabetic retinopathy complications were few and there was no imbalance in events of diabetic retinopathy complications between patients treated with semaglutide as compared with placebo (5 vs 4 events).

A more specific group with an increased risk of retinopathy complications using semaglutide was identified. This risk of retinopathy complications was only observed in patients with retinopathy at baseline treated with insulin. In patients without retinopathy and no insulin use, there was no effect of semaglutide on the development of retinopathy complications. Numbers needed to treat (3-point MACE) and numbers needed to harm (retinopathy complications) were 45 and 77 respectively for the total population, 19 versus 36 for subjects with baseline retinopathy, and 61 versus 456 for subjects without retinopathy at baseline.

Complications for patients with diabetic retinopathy at baseline and treated with insulin, complications the number needed to treat is 17 for MACE, whereas the corresponding number needed to harm is 29 for diabetic retinopathy complications.

Semaglutide treatment generally provides a rapid initial decline in blood glucose levels. The company refers to studies in patients with type 1 diabetes that reported an association between rapid glucose lowering and worsening of retinopathy. If this association is applicable to the effects of semaglutide, this would be reassuring. In type 1 diabetes, the early worsening of retinopathy is transient, largely resolving after 1 to 2 years (DCCT Research Group. Ophthalmology 1995;102:647-661; Dahl-Jørgensen et al. Br Med J (Clin Res Ed) 1985;290:811-815), and there is clear evidence of benefit from glucose lowering in the following years (DCCT Research Group. Ophthalmology 1995;102:647-661). However, the fact that the increased risk of retinopathy complications with semaglutide does not

decrease in the course of the 2 year trial is worrisome and suggests that other mechanisms than rapid glucose lowering may play a role.

An increased risk was observed in patients with pre-existing diabetic retinopathy at baseline and co-use of insulin. Among patients without pre-existing diabetic retinopathy or insulin use, the frequency of diabetic retinopathy complications was low and similar with semaglutide and placebo. Data suggest that semaglutide was associated with increased risk of retinopathy complications in patients with pre-existent retinopathy and only small HbA1c reductions (HbA1c reduction <0.5%points).

The follow up might have been too short to show benefits of improved glycaemic control. However, there might have been other possibilities, such as a direct deleterious effect on the retina. Observations do not permit definite conclusions regarding the underlying mechanism of action. The occurrence of early worsening in patients with only small reductions in HBA_{1C} remains unexplained. However, it is agreed that net clinical benefit over time due to improved glycaemic control is likely. A long-term PASS study should be conducted to examine this. The Applicant proposes to add a warning in section 4.4, similar to that of insulins. In general this can be accepted. However, the text should be somewhat amended.

Systematic evaluation of diabetic retinopathy complications was only performed in the CVOT and not in the remaining phase 3a trials.

Renal safety

In the CVOT, fewer AEs and SAEs related to acute renal failure were reported with semaglutide 1.0 mg than with semaglutide 0.5 mg and placebo. In the phase 3a pool, AEs related to acute renal failure were very few and with no apparent difference between semaglutide and comparator products.

Semaglutide was consistently associated with an initial decrease in the estimated glomerular filtration rate (eGFR). As observed in the CVOT, the eGFR decreased with placebo at a more constant and higher rate throughout the trial than with semaglutide; at end-of-treatment, the eGFRs did not differ significantly between semaglutide and placebo. The effect seen with placebo likely reflects the expected decline of renal function over time in a population of patients with renal impairment, and the fact that this was not seen with semaglutide, excludes a negative effect of semaglutide on GFR. There was a decrease in urinary albumin-to-creatinine ratio (UACR) with semaglutide in the CVOT. In the phase 3a trials excluding the CVOT, the UACR was similar with semaglutide and placebo.

A causal relationship between acute renal failure and semaglutide is unlikely, and semaglutide may delay the progression of UACR.

Pancreatitis

No indications of semaglutide-induced acute pancreatitis have been observed in any of the repeat dose toxicity studies in mice, rats and monkeys or the 2-year carcinogenicity studies in mice and rats.

In line, in the CVOT, the number of patients with EAC-confirmed acute pancreatitis was comparable with semaglutide (8 patients) and placebo (10 patients). These results may be supported by recent results from the liraglutide CVOT where acute pancreatitis occurred in 18 liraglutide-treated patients and in 23 placebo-treated patients, as well as results from the lixisenatide CVOT where pancreatitis occurred in 5 patients in the lixisenatide group and in 8 in the placebo group. However, in the phase 3a pool, 8 semaglutide-treated patients had EAC-confirmed events of pancreatitis and 3 events were confirmed in patients treated with exenatide ER, while no events were reported with placebo. There

was a striking difference in the pattern of Exocrine pancreas conditions. A total of 8 events belonging to this HLGT are registered among the semaglutide treated patients (R=0.4) as compared to none in the comparator group The Applicant has addressed this imbalance and it has been documented that no dose response or temporal clustering was present. This weakens the assumption of a causal relationship with treatment. Further, reassuringly all but two of the events of pancreatitis were considered mild.

Levels of serum lipase and amylase increased with semaglutide, similar to what has been described with other incretin-based therapies. After an initial increase in lipase and amylase, the levels showed no further change for up to 2 years. The mechanisms underlying these associations are not clear. In the absence of other signs or symptoms of pancreatitis, elevation of lipase and amylase levels seen with semaglutide did not predict a later development of pancreatitis. This is in line with data obtained for liraglutide.

Taken together, levels of serum lipase and amylase increased with semaglutide. However, although the majority of confirmed events of pancreatitis were accompanied by increased lipase/amylase, the finding of increased lipase/amylase in isolation was a poor predictor of pancreatitis.

Gallbladder-related adverse events

In the placebo-controlled 2-year CVOT, the proportion of patients with gallbladder-related adverse events were similar with semaglutide (0.5 mg: 3.5%; 1.0 mg: 3.2%) and placebo (3.4%). However, in the phase 3a pool, gallbladder-related AEs were reported more frequently with semaglutide (0.5 mg: 1.3%; 1.0 mg: 1.7%) than with comparator products (0.8%); this difference was primarily driven by AEs of cholelithiasis, especially with semaglutide 1.0 mg. In the non-incretin subset, the proportion of subjects with cholelithiasis and the corresponding rates were 1.0% and 0.6% with semaglutide 0.5 mg and 1.0 mg, respectively. However, with the non-incretin comparators, no AEs of cholelithiasis were reported.

The increased risk of cholelithiasis with semaglutide is in line with data on liraglutide for weight management and the liraglutide CVOT which both observed an increased risk of cholelithiasis and cholecystitis. There was no clear pattern between extensive weight loss and events of cholelthiasis, events were seen in patients with weight gain as well as those with weight loss. Also, there did not seem to be an increasing number of events with increasing amounts of weight loss. In addition, there was no clear temporal pattern in the occurrence of cholelithiasis as the events were dispersed across the duration of the trials. The lack of a temporal pattern supports that these events were not set-off by the rapid or extensive weight loss usually observed with semaglutide treatment during the first 16 weeks of the trials. The incidence rates of cholelithiasis in a T2DM cohort have been reported to be 1.2 events per 100 PYE. The rate of cholelithiasis reported in the CVOT and phase 3a pool d with semaglutide were thus lower than, or on par with, the rate of cholelithiasis in a T2DM population in general.

Hepatic analytes

Across the phase 3a trials, small mean and median decreases from baseline within the normal reference range were observed for each of the hepatic analytes (ALT and AST); and the decreases were more pronounced with semaglutide (0.5 mg and 1.0 mg) than with all comparators. In addition, in the CVOT, the number of subjects with increases in ALT or AST >5xULN was slightly lower with semaglutide 0.5 mg than with semaglutide 1.0 mg albeit the total numbers were similar between

semaglutide and placebo groups. However, in the phase 3a pool, there were more subjects with elevated ALT or AST levels >5xULN and >10xULN on semaglutide (0.5 mg and 1.0 mg) than on comparators.

Neoplasms

In the CVOT, there was a tendency towards higher frequencies for benign neoplasm with semaglutide than with placebo (HR: 1.35 [0.99; 1.84]95%CI, p=0.0558). No apparent single types of benign neoplasms were driving this difference. The difference between semaglutide and placebo was seen within the first 40 weeks in the trial indicating a relatively short lead time. In the phase 3a pool, the proportion of patients with EAC-confirmed benign neoplasms was low and similar with semaglutide and comparator products (HR: 1.14 [0.73; 1.78]95%CI, p=0.5713).

Malignant neoplasms were equally distributed with semaglutide and placebo (HR: 0.94 [0.67; 1.32]95%CI, p= 0.7228) in the CVOT with no apparent differences for any types of malignant neoplasms. In the phase 3a pool there was a tendency towards more malignant neoplasms (HR: 1.61 [0.74; 3.49]95%CI, p=0.2264) with semaglutide than with comparators; however, numbers were low and the difference was not significant. Also, there were no single types of malignant neoplasms driving this difference.

Thyroid neoplasms

No cases of MTC were identified during the semaglutide development programme. Similar to other long-acting GLP-1 RAs, carcinogenicity studies show evidence of effects in rodents that are not mirrored in clinical trials in humans. However, the clinical trials in the semaglutide programme are of relatively short duration compared to the expected latency of MTCs.

Calcitonin is considered a biomarker for increased thyroid C-cell mass and activation. Calcitonin levels were assessed at baseline (to exclude patients likely to have pre-existing C-cell neoplasia) and at regular intervals during the semaglutide phase 3a trials. Overall, minor fluctuations in calcitonin levels were observed throughout the phase 3a trials with no clinically relevant difference between semaglutide and placebo or semaglutide and comparators..

Pancreatic neoplasms

In the semaglutide clinical development programme, the incidence of pancreas cancer with semaglutide was low (5 cases: 3 malignant, 2 benign) and appeared not to be different from placebo and comparator products (7 cases; 6 malignant, 1 benign). However, a follow up of only 2 years is relatively short. In addition, the liraglutide CVOT malignant pancreatic neoplasms were confirmed in 13 patients in the liraglutide group and 5 in the placebo group. The Applicant has presented an analysis of the relative risk for pancreatic carcinoma in 6 CVOTs with the use of increatin-based medications: 5 of the 6 trials showed a relative risk below 1 and the liraglutide trial (LEADER) was the only one with a relative risk above 1. For semaglutide the Applicant keeps pancreatic cancer as an important potential risk in the RMP and pancreatic cancer will be monitored. This is considered adequate, and similar to liraglutide, no additional text in the SmPC is needed.

Hypoglycaemia

Despite significant improvement in glycaemic control with HbA1c levels reduced to a greater extent with semaglutide than with all comparators, semaglutide does not increase the risk of hypoglycaemia unless combined with either SU or insulin.

Subgroups

Overall, the trial population did not display markedly different AE profiles for semaglutide (0.5 mg and 1.0 mg) relative to comparators, when divided into subgroups. Impaired renal or hepatic function, sex, CV history or baseline hypertension did not substantially affect semaglutide-associated treatment differences.

However, treatment differences with semaglutide were seen for AEs of decreased appetite (PT) in the following subgroups: baseline age ≥75 years; Asian race; non-Hispanic/Latino ethnicity; baseline body weight <70 kg; and baseline BMI <25 kg/m2. Accordingly, the treatment differences for weight decreased (PT) were most pronounced among subgroups of baseline body weight <70 kg and baseline BMI <25 kg/m2. The Applicant has provided detailed safety data in the Table “Adverse events in subgroups by age”.

Clinical data in patients with hepatic impairment are not available. The clinical pharmacology trial (trial 3651) demonstrated that the exposure to semaglutide is similar in subjects with hepatic impairment and subjects with normal hepatic function. No data in diabetic patients are presented. The SmPC should mention that caution should be exercised in severe hepatic impairment, as there are no data presented on the use of GLP1-RAs in these patients. Hepatic impairment must be considered missing information in the RMP.

Immunological reactions

The most frequently reported AEs related to allergic reactions were the PTs rash, rhinitis allergic, urticaria, dermatitis and eczema; the proportion of subjects and rate of events of these PTs were similar across the semaglutide and placebo treatment groups.

Injection site reactions were reported by a low (approximately 1%) proportion of patients with semaglutide and were not recurrent in those individuals. A causal relationship between injection site reactions and semaglutide cannot be excluded, although the risk is evaluated as low, especially in comparison to exenatide ER.

The proportion of subjects that tested positive for anti-semaglutide antibodies was 1.9% in CVOT, 1.0% in the phase 3a pool and 2.2% in the pool of placebo-controlled trials. No effects on semaglutide exposure, HbA1c or semaglutide safety profile were identified and no association with immunogenicity-related AEs were evident. However, long term effects of these antibodies are unknown.

Additional safety data

Data from a completed phase 2 trial (Trial 9924 3790) in the oral semaglutide development programme is included as supportive data as semaglutide s.c. OW is included as comparator. In the semaglutide sc arm, semaglutide compared to placebo was associated with a relatively high risk of hypoglycaemia (17.4 vs 11.3%). In addition, there were more adverse events leading to premature treatment discontinuation (14.5 vs. 1.4%).

2.5.7. Conclusions on clinical safety

The safety profile of semaglutide is generally consistent with those reported for other drugs in the GLP-1 RA class. However, there are several specific safety issues.

The rates of gastrointestinal adverse events were higher with semaglutide compared to all comparators, including the only other GLP-1 RA studied, Exenatide ER. There was a dose-dependent increase in gastrointestinal adverse events leading to premature treatment discontinuation (up to 9%).

A significantly increased risk of diabetic retinopathy complications was observed with semaglutide as compared with placebo. This increased risk was particularly marked in patients with pre-existing diabetic retinopathy at baseline and co-use of insulin. Among patients without pre-existing diabetic retinopathy or insulin use, the frequency of diabetic retinopathy complications was low but numerically the relative risk was similar between semaglutide and placebo. The Applicant ascribes the increased incidence of retinopathy complications to early worsening of diabetic retinopathy following intensified glycaemic control. However, in contrast to what would be expected on the basis of previous studies with intensive glucose lowering using insulin, the increased risk of diabetic retinopathy complications with semaglutide suggests not to decrease in the course of the 2 year trial. In addition, data suggest that semaglutide was associated with retinopathy in patients with only small HbA1c reductions. A persistent deleterious effect of semaglutide on the retina independent of glucose lowering cannot be excluded. Therefore, a warning in section 4.4, similar to that of insulins, has been added. In addition, a post-authorization safety study will be performed.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Severe hypoglycaemia in combination with other anti-glycaemic agents Acute gallstone disease Diabetic retinopathy complications
Important potential risks	Serious allergic reactions Acute pancreatitis Malignant neoplasm Pancreatic cancer Medullary thyroid cancer
Missing information	Pregnancy and lactation Patients with end-stage renal disease Patients with NYHA Class IV Patients with severe hepatic impairment

Pharmacovigilance plan

Study / activity Type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned or started)	Date for submission of interim or final reports (planned or actual)
MTC registry MTC- 22341 Category 3	A medullary thyroid cancer case series registry to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace	Medullary thyroid cancer	Planned (ongoing for liraglutide)	Final report 2033
Epidemiological database study Category 3	To estimate the risk of pancreatic cancer in users of semaglutide.	Pancreatic cancer	Planned	Annual status reports After start of study Final report 5 years after start of study
Clinical trial Category 3	Randomised clinical trial to evaluate the long-term effects of semaglutide on diabetic retinopathy progression in subjects with T2DM	Diabetic retinopathy complications	Planned	Protocol submission: March 2018

The protocol of the category 3 Randomised clinical trial to evaluate the long-term effects of semaglutide on diabetic retinopathy progression in subjects with T2DM is requested to be submitted for review by PRAC as part of a Post-Authorisation Measure, by end of March 2018.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe hypoglycaemia in combination with other anti-glycaemic agents	**Text in proposed SmPC** Dosing recommendations and precautions are included in SmPC Sections 4.2 and 4.4, respectively. In addition, the risk is listed in Section 4.8 of the SmPC. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Acute gallstone disease	**Text in proposed SmPC** Listed in Section 4.8 **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Diabetic retinopathy complications	**Text in proposed SmPC** Warning is included in Section 4.4. Listed in Section 4.8 **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Serious allergic reactions	**Text in proposed SmPC** Hypersensitivity is included as a contraindication in Section 4.3. 'Anaphylactic reactions' is listed in Section 4.8. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Acute pancreatitis	**Text in proposed SmPC** Warning is included in Section 4.4. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Malignant neoplasm	**Text in proposed SmPC** None **Additional routine risk minimisation:** No further risk minimisation is warranted.	None
Pancreatic cancer	**Text in proposed SmPC** None **Additional routine risk minimisation:** No further risk minimisation is warranted.	None
Medullary thyroid	**Text in proposed SmPC**	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
cancer	The nonclinical findings are described in Section 5.3. **Additional routine risk minimisation:** No further risk minimisation is warranted.	
Pregnancy and lactation	**Text in proposed SmPC** Recommendations regarding pregnancy and breast-feeding are included in Section 4.6 of the SmPC. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Patients with end-stage renal disease	**Text in proposed SmPC** The lack of data on the use in this population is addressed in Section 4.2. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Patients with congestive heart failure NYHA IV	**Text in proposed SmPC** The lack of data on the use in this population is addressed in Section 4.4. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None
Patients with severe hepatic impairment	**Text in proposed SmPC** The limited amount of data on the use in this population is addressed in Section 4.2. **Additional routine risk minimisation:** By the legal status of the product; prescription only	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD) of 05.12.2017 and the first Data Lock Point to be 31.05.2018. The new EURD list entry will therefore be introduced in line with this request.

2.7. New Active Substance

The applicant declared that semaglutide has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers semaglutide to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ozempic (semaglutide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit risk assessment

3.1. Therapeutic Context

3.1.1. Disease or condition

Type 2 diabetes (T2D) is a progressive chronic metabolic disease primarily characterised by abnormal glucose metabolism. Close to 9% (415 million) of adults worldwide have diabetes with T2D accounting for ~90% of the diabetes cases. Glycaemic control is fundamental for the management of T2D to reduce the risk of T2D-related microvascular and macrovascular complications. CV disease is the leading cause of death in patients with diabetes, and CV morbidity is more prevalent in patients with diabetes than in those without.

3.1.2. Available therapies and unmet medical need

There are several classes of medicinal products for the treatment of T2D. All products have been shown to reduce blood glucose level and to improve HbA1c. Based on the extensive therapeutic experience (including possible CV benefits), metformin is currently recommended as first-line treatment for all patients with T2D, unless contraindications apply (most notably, GFR <30 ml/min). Recently, empagliflozin (SGLT2-inhibitor) and liraglutide (GLP-1 receptor agonist) have shown to be

superior compared to placebo in reducing 3-point MACE in patients with established CV disease in a CV outcome trial.

Semaglutide is a GLP-1 RA that is structurally similar to liraglutide but modified to have a longer half-life. The extended half-life is primarily obtained by increased albumin binding, which slows the degradation of semaglutide in plasma and results in decreased renal clearance prolonging the half-life of semaglutide to approximately 1 week making it suitable for once weekly s.c. administration.

3.1.3. Main clinical studies

The efficacy and safety of semaglutide as mono- and combination therapy (primarily combinations with metformin, SU and/or insulin) were evaluated in 5 key efficacy trials. In addition, semaglutide was compared with insulin glargine, a DPP-4 inhibitor and another long acting GLP-1 receptor agonist (exenatide ER). Semaglutide was investigated at two dose levels (0.5 mg and 1.0 mg) in most phase 3a trials.

- In trial 3623 (**SUSTAIN 1**), the primary objective was to demonstrate superiority of once-weekly dosing of 2 dose levels of semaglutide vs placebo on glycaemic control after 30 weeks of treatment in drug naïve T2D subjects. This was a randomised, double blind, parallel group, placebo controlled, 4 armed trial in adult T2D subjects treated with diet and exercise.
- In trial 3626 (**SUSTAIN 2**), the primary objective was to compare the effect of once-weekly dosing of 2 dose levels of semaglutide vs sitagliptin 100 mg once-daily on glycaemic control after 56 weeks of treatment. This was a randomised, double-blind, 4-armed trial in T2D subjects who had not achieved adequate glycaemic control on metformin, TZD or a combination of metformin/TZD.
- In trial 3624 (**SUSTAIN 3**), the primary objective was to compare the effect of semaglutide 1.0 mg once-weekly vs exenatide ER 2.0 mg once-weekly on glycaemic control after 56 weeks of treatment. This was a randomised, open-label, 2-armed trial in subjects with T2D. The trial was open label.
- In trial 3625 (**SUSTAIN 4**), the primary objective was to compare the effect of once-weekly dosing of 2 dose levels of semaglutide vs insulin glargine once-daily on glycaemic control after 30 weeks of treatment in insulin-naïve T2D subjects. This was a randomised, open-label, 3-armed trial in insulin-naïve T2D subjects. The trial was open label.
- In trial 3627 (**SUSTAIN 5**), the primary objective was to demonstrate superiority of once-weekly dosing of 2 dose levels of semaglutide vs placebo on glycaemic control in subjects with T2D on basal insulin. This was a randomised, double-blind, 4-armed trial in subjects with T2D.

The last phase 3a trial (trial 3744; **SUSTAIN 6**) was a 104−week cardiovascular outcomes trial (CVOT). The primary objective was to confirm that treatment with semaglutide does not result in an unacceptable increase in CV risk compared to placebo in T2D subjects. The secondary objectives were to assess the long-term safety and efficacy of semaglutide 0.5 mg and 1.0 mg once-weekly compared to placebo, both added on to standard-of-care. This was a double-blind trial in subjects with T2D at very high risk of CV events.

Two additional phase 3a trials evaluated semaglutide for treatment of T2D in Japanese subjects (trials 4092 and 4091). While safety was the primary endpoint for the Japanese trials, they were designed and conducted in a similar manner to the key efficacy trials.

- In trial 4092 (JPN), the primary objective was to compare the safety of once-weekly dosing of semaglutide (0.5 and 1.0 mg) versus sitagliptin (100 mg) once daily, both as monotherapy during 30 weeks of treatment in Japanese T2D subjects. This was a randomised, open-label, active-controlled, 3-armed trial in subjects with T2D.
- In trial 4091 (JPN), the primary objective was to compare the safety of once-weekly dosing of semaglutide in monotherapy or in combination with 1 OAD (either of SU, glinide, alpha-GI or TZD) vs OAD therapy during 56 weeks of treatment in Japanese T2D subjects who are insufficiently controlled on diet/exercise therapy or OAD monotherapy (either of SU, glinide, alpha-GI or TZD. This was a randomised, open-label, active-controlled, 3-armed trial in T2D subjects insufficiently controlled on diet/exercise therapy or OAD monotherapy.

3.2. Favourable effects

Once weekly dosing regimen

In the pharmacokinetic studies, it has been demonstrated that the semaglutide formulations are suitable for once weekly administration. The absorption of semaglutide after subcutaneous injection is slow and Tmax is reached between 24-36 hours post-dosing. After a single dose of semaglutide s.c. the systemic concentrations were maintained at about the same level for about 7 days. Steady state concentrations were achieved after 4-5 weeks.

HbA1c

In all eight phase 3a trials, treatment with semaglutide 0.5 mg or 1.0 mg resulted in a reduction in HbA1c, starting after 4 weeks of treatment and reaching nadir after 16−30 weeks (see Effects Table below). The reduction was maintained after long-term treatment of up to 104 week in the CVOT. The reductions in HbA1c obtained with semaglutide were 1.09−1.87 %−points with semaglutide 0.5 mg and 1.41−2.18 %−points with semaglutide 1.0 mg and superior across trials with semaglutide vs placebo or active comparators.

Body weight

Semaglutide reduced body weight in all eight phase 3 trials compared with placebo (both as monotherapy and in combination with insulin) or active comparators; sitagliptin, exenatide ER and insulin glargine. The reductions of up to 4.28 kg and 6.42 kg with semaglutide 0.5 mg and 1.0 mg, respectively took place through the first 30 weeks of treatment. The reduction in body weight was sustained through the entire treatment period of up to 104 weeks in the CVOT.

MACE

In CVOT trial 3744, (SUSTAIN 6), the primary objective was reached and non-inferiority of semaglutide versus placebo in terms of MACE was demonstrated. The composite primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and 146 of 1649 (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for non-inferiority and P=0.02 for superiority).

For MACE components, CV death was similar with semaglutide and placebo (HR: 0.98 [0.65; 1.48]$_{95\%CI}$, but events of non-fatal MI (HR: 0.74 [0.51; 1.08]$_{95\%CI}$, p=0.1194) and non-fatal stroke (HR: 0.61 [0.38; 0.99]$_{95\%CI}$, p=0.0438) favoured semaglutide.

The proportion of subjects that experienced an expanded MACE (3-point MACE plus revascularisation (coronary and peripheral), unstable angina requiring hospitalisation, or hospitalisation for heart failure) was lower with semaglutide (199 subjects, 12.1%) than with placebo (264 subjects, 16.0%; HR 0.74 [0.62; 0.89]$_{95\%\ CI}$).

The number of subjects with MACEs across the seven phase 3a trials (excluding the CVOT) were similar across the treatment groups (semaglutide 0.5 mg: 8 subjects [0.6%], semaglutide 1.0 mg: 5 subjects [0.3%], all comparators: 8 subjects [0.5%]).

Other endpoints

Overall, in the key efficacy trials, systolic (and diastolic) blood pressure decreased more with semaglutide 1.0 mg and 0.5 mg (systolic blood pressure ranging from -2.58 to -7.27 mmHg) vs comparators (ranging from -0.99 to -1.72 mmHg) at end-of-treatment.

Subgroups body weight and sex

In a population PK analysis, semaglutide exposure was only affected by body weight showing higher semaglutide exposure in subjects with a lower body weight. However, in the clinical trials, the semaglutide efficacy was consistent across subgroups of baseline body weight. In addition, the overall HbA1c response to semaglutide was not influenced by sex and region.

3.3. Uncertainties and limitations about favourable effects

Dose selection

Dose-response modelling was used to select the semaglutide maintenance doses of 0.5 mg and 1.0 mg for the phase 3 programme. There is no unequivocal evidence for a better benefit/risk profile with semaglutide 0.5 and 1.0 mg in the phase 3 trials as compared to 0.4 and 0.8 mg. Still, the confirmatory trials have provided evidence for maintenance doses of 0.5 and 1.0 mg. Both dose levels can be safe and efficacious and should be based on individual needs. The 1.0 mg dose is associated with an increased risk of side effects. Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide. This is mentioned in Section 4.8 of the SmPC.

Comparators

Semaglutide was compared to several active comparators that may be considered a next step after lifestyle and metformin. However, a comparison to SU was not performed. SU is considered the next step after metformin by many guidelines and doctors.

In trial 3624 (SUSTAIN 3), compared to exenatide ER, semaglutide 1.0 mg was associated with a decrease in HbA1c after 56 weeks of -0.62%. In addition, compared to exenatide ER, semaglutide 1.0 mg was associated with a decrease in body weight after 56 weeks of -3.78 kg. However, the effect of

exenatide 2.0 mg once weekly on HbA1c (reduction of -0.92% from baseline) appears to be somewhat smaller than the effect seen in the DURATION studies, which found a mean HbA1c reduction of 1.3%-point to 2.0%-point at Week 26-52. The reason for this difference is unclear. In addition, the effect of exenatide 2.0 mg once weekly on body weight (reduction of -1.85 kg from baseline) appears to be somewhat smaller than the effect seen in the DURATION studies, which found a mean weight reduction of 2.0-4.1 kg at Week 26-52. The Applicant has presented the results for 3 DURATION trials and pointed out that the change in HbA_{1c} and weight at 23 weeks resembles the changes observed in Trial 3624. However, the two DURATION trials with the greatest HbA_{1c}-reduction were omitted because these trials would not resemble Trial 3624. Although this argumentation is not agreed, the trial met its primary objectives.

Subgroups

Several subgroups were relatively small and/or demonstrated inconsistent results.

Although the number of subjects ≥75 years of age at baseline was more than 74 subjects for each of the four treatment groups in the CVOT, there were less than 20 individuals >75 years of age for each treatment group in all other trials. Efficacy of semaglutide on HbA1c reduction was consistent across most age groups. However, in comparison to other age groups, the effects of semaglutide on HbA1c for subjects >75 years of age were lower in some trials but higher in others. Due to the relatively small numbers of patients >75 years of age, efficacy in these patients is uncertain.

With regard to race, the majority of subjects across all trials were White (64−84%), except for the two Japanese trials in which all subjects were Asian. Excluding the two Japanese trials, the proportion of Black or African American subjects across trials was only 5−9%, while 2−25% of subjects were Asian. For Asians and Blacks/African Americans, the effects of semaglutide on HbA1c were not consistent. The 2 trials from Japan provide supportive evidence for efficacy in Asians, but efficacy in Blacks/African Americans is uncertain.

The mean renal function for the CVOT population was lower (eGFR: 76.13 mL/min/1.73 m^2) compared with the other phase 3a trials. This was the only trial to include subjects (around 3%) with severe renal impairment, while moderate renal impairment accounted for 25% of subjects in the CVOT. In several trials, the treatment effect tended to be 0.1-0.3% smaller in subjects with mildly and moderately impaired renal function compared with subjects with normal renal function. Due to the relatively small numbers of patients with severe renal impairment and end-stage renal disease, efficacy in these patients is uncertain. This is adequately addressed in the updated SmPC.

No trials with combination therapy with DPP-4-inhibitors or SGLT-2-inhibitors have been carried out. A combination with DPP-4 inhibitors is not rational, as the mechanism of action is similar for both products. In SUSTAIN 2, only 5.4% (N=43) of the patients were using a TZD as background medication in combination with semaglutide. Efficacy of semaglutide on a background of a TZD or SGLT-2-inhibitors is not well established.

Cardiovascular risk

For a drug that is intended for long term diabetes treatment, the duration of the CVOT (2 years) is relatively short (also in comparison to several other cardiovascular outcome trials). Longer term safety is uncertain.

The inclusion of only individuals with a very high CV risk in the CVOT makes it uncertain whether the results may be generalized to the general diabetic population. In the CVOT a number of subjects were included with T2DM and risk factors “only”. In these subjects, no effect on MACE was observed, but the numbers were too small to draw firm conclusions (10 events with semaglutide and 9 events with placebo).

Semaglutide had a favourable effect on events of non-fatal MI and non-fatal stroke. However, the occurrence of CV death was similar with semaglutide and placebo (HR: 0.98 $[0.65; 1.48]_{95\%CI}$). Based on biological plausibility it may be anticipated that treatment will beneficially influence all components in a similar way. The Applicant reasons that duration of the trial may have been too short for showing positive effects on CV-death. Similar results have been observed for statins and PCSK9-inhibitors.

The difference in MACE is primarily driven by a difference in the rate of strokes. However, there was a baseline difference in prior stroke favouring semaglutide. To further clarify this, subgroup analyses in patients with prior stroke for the primary and secondary endpoints for MACE were requested during the procedure. Also, additional analyses for MACE where patients with previous strokes or prior MI were excluded were requested. Point estimates for the hazard ratios were in line with those seen for all subjects. However, effect on MACE seems to be more consistent in subjects without prior stroke than in subjects with prior stroke. This is even more so for the individual components of MACE. The number of subjects with prior stroke and an event were small, and confidence intervals were wide. Therefore, no firm conclusion can be drawn. The analyses adjusted by prior stroke were consistent with the primary MACE analysis. It is unlikely that the small difference in distribution at baseline has affected the outcome of the CVOT in a relevant way. For prior myocardial infarction, results were more consistent. Effect was seen both in subjects without and with prior MI. Similarly, almost all individual components of the expanded MACE contributed to the favourable treatment effect of semaglutide with hazard ratios below 1, but hospitalisation for heart failure had a hazard ratio above 1.

All-cause mortality also had a hazard ratio above 1. Analyses including all-cause mortality should supplement analyses based on endpoints that include only CV mortality. Any analysis that ‘censors’ patients who die from non-CV causes effectively makes an assumption of continued treatment effect after death and hence provides treatment effects that are difficult to understand. In additional analyses however, no influence of such informative censoring due to non-CV mortality was observed. These analyses therefore support the primary analysis.

The results of most pre-specified subgroup analyses in the CVOT were consistent with the results of the primary analysis of time to first EAC-confirmed MACE. However, treatment effects were absent for patients with chronic heart failure class II-III and lower for patients using insulin treatment at baseline requires (p for interaction 0.09 and 0.12, respectively) The Applicant reasons that effects on HbA1c, body weight and systolic blood pressure were seen in subjects with chronic heart failure class II-III and in subjects using insulin at baseline. This could be extrapolated to MACE. Moreover, conclusions drawn from subgroup analyses should be performed cautiously when subgroups are small also considering the non-statistically significant subgroup interaction test. For use of insulin at baseline, the populations of subjects using insulin at baseline are similar in terms of demography and CV history. Subgroups were small, and it is unlikely that there is a true difference in effects on MACE in subjects with T2D using premix or basal insulin at baseline.

3.4. Unfavourable effects

For safety evaluation, results of the phase 3 trials were pooled, but results for the CVOT population were described separately. Total exposure to semaglutide was 2712 PYE (n=3150 patients) in the phase 3a trials and 2932 PYE (n=1642 patients) in the CVOT.

Adverse events pool of phase 3a trials

The proportion of subjects with AEs and the corresponding rates were higher with semaglutide (0.5 mg and 1.0 mg) than with comparator products (73.4 and 72.7% vs 68.7%). The proportions of subjects with AEs reported as not recovered or recovering were similar with semaglutide (0.5 mg and 1.0 mg) and comparator products.

In the phase 3a pool, a total of 16 subjects died due to AEs with onset during the in-trial period for the individual subject. A total of 10 subjects (0.3%) randomised to semaglutide died, and 6 subjects (0.4%) randomised to comparator products died.

The proportion of subjects who discontinued treatment prematurely due to AEs was higher with semaglutide than with comparator products. The proportion of subjects who discontinued treatment prematurely due to AEs was higher with semaglutide 1.0 mg than with semaglutide 0.5 mg indicating a dose-response. The proportions of subjects who discontinued treatment prematurely due to gastrointestinal disorders were higher with semaglutide (0.5 mg: 3.9%; 1.0 mg: 5.9%) than with comparators (0.9%).

Adverse events CVOT

The proportion of subjects with AEs was similar with semaglutide (0.5 mg: 88.9%; 1.0 mg: 88.2%) and placebo (88.4%). The proportions of subjects with AEs reported as recovered or recovering were similar with semaglutide (0.5 mg and 1.0 mg) and placebo.

A total of 123 subjects (3.7%) had fatal AEs that had onset during the 2-year in-trial period of the CVOT. The proportion of subjects with fatal events (with onset during the in-trial period) was similar with semaglutide (0.5 mg and 1.0 mg) and placebo.

Subjects discontinued treatment prematurely due to AEs throughout the trial both with semaglutide and placebo with the highest frequencies and rates in the first months after treatment initiation. The prevalence of GI AEs was highest during the initial months and these events were often the reason for premature treatment discontinuation due to AEs.

Gastrointestinal disorders

The rates of gastrointestinal adverse events were higher with semaglutide compared to all comparators, including the only other GLP-1 RA studied, exenatide ER. There was a dose-dependent increase in gastrointestinal adverse events leading to premature treatment discontinuation (up to 9%). Patients with a higher exposure to semaglutide (as seen in patients with low body weight, low BMI, women and Asians) had more gastrointestinal AEs, particularly nausea, than patients with a lower semaglutide exposure, as supported by exposure-response analyses.

Diabetic retinopathy

Although not observed in the preclinical studies, a significantly increased risk of EAC-confirmed events of diabetic retinopathy complications was observed with semaglutide (50 [3.0%] patients) as compared with placebo (29 [1.8%] patients) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$) in the CVOT. The treatment difference appeared early and persisted throughout the trial. The imbalance was observed for all four components that were predefined (need for retinal photocoagulation, vitreous haemorrhage, need for treatment with intravitreal agents and onset of diabetes-related blindness) and was similar with semaglutide 0.5 mg and 1.0 mg. Compared to the overall population, the patients who had events of diabetic retinopathy complications during the trial were characterised by a longer diabetes duration (17.53 years), a higher baseline HbA_{1c} (9.37%), use of insulins at baseline (75.9%) and pre-existing diabetic retinopathy (83.5%). Among patients without pre-existing diabetic retinopathy, there was no imbalance in events of diabetic retinopathy complications between patients treated with semaglutide as compared with placebo (5 vs 4 events).

Systematic evaluation of diabetic retinopathy complications was only performed in the CVOT and not in the remaining phase 3a trials.

Renal safety

Semaglutide was consistently associated with an initial decrease in the estimated glomerular filtration rate (eGFR), but at end-of-treatment the eGFRs did not differ significantly between semaglutide and placebo. There was a decrease in urinary albumin-to-creatinine ratio (UACR) with semaglutide in the CVOT. In the phase 3a trials excluding the CVOT, the UACR was similar with semaglutide and placebo. In the CVOT, fewer AEs and SAEs related to acute renal failure were reported with semaglutide 1.0 mg than with semaglutide 0.5 mg and placebo. In the phase 3a pool, AEs related to acute renal failure were very few and with no apparent difference between semaglutide and comparator products.

Semaglutide was not associated with acute renal failure or progression of UACR.

Gallbladder-related adverse events

In the phase 3a pool, gallbladder-related AEs were reported more frequently with semaglutide (0.5 mg: 1.3%; 1.0 mg: 1.7%) than with comparator products (0.8%); this difference was primarily driven by AEs of cholelithiasis, especially with semaglutide 1.0 mg. In the CVOT, the proportion of patients with gallbladder-related adverse events was similar with semaglutide (0.5 mg: 3.5%; 1.0 mg: 3.2%) and placebo (3.4%). In the non-incretin subset, the proportion of subjects with cholelithiasis and the corresponding rates were 1.0% and 0.6% with semaglutide 0.5 mg and 1.0 mg, respectively. With the non-incretin comparators, no AEs of cholelithiasis were reported.

There was no clear pattern between extensive weight loss and events of cholelithiasis, events were seen in patients with weight gain as well as those with weight loss. Also, there did not seem to be an increasing number of events with increasing amounts of weight loss. In addition, there was no clear temporal pattern in the occurrence of cholelithiasis as the events were dispersed across the duration of the trials. The lack of a temporal pattern supports that these events were not set-off by the rapid or extensive weight loss usually observed with semaglutide treatment during the first 16 weeks of the trials.

The incidence rates of cholelithiasis in a T2DM cohort have been reported to be 1.2 events per 100 PYE.16 The rate of cholelithiasis reported in the phase 3a pool and the CVOT with semaglutide were thus lower than, or on par with, the rate of cholelithiasis in a T2DM population in general.

Thus, cholelithiasis may be causally related to semaglutide, but the nature of the events reported do not support the need for cholelithiasis to be included in Section 4.4 of the SmPC. Cholelithiasis is adequately listed as an important identified risk in the RMP.

Thyroid neoplasms

No cases of MTC were identified during the semaglutide development programme. However, the clinical trials in the semaglutide programme are of relatively short duration compared to the expected latency of MTCs. Calcitonin is considered a biomarker for increased thyroid C-cell mass and activation. Calcitonin levels were assessed at baseline (to exclude patients likely to have pre-existing C-cell neoplasia) and at regular intervals during the semaglutide phase 3a trials. Overall, minor fluctuations in calcitonin levels were observed throughout the phase 3a trials with no clinically relevant difference between semaglutide and placebo or semaglutide and comparators.

Hypoglycaemia

Despite significant improvement in glycaemic control with HbA1c levels reduced to a greater extent with semaglutide than with all comparators, semaglutide did not increase the risk of hypoglycaemia unless combined with either SU or insulin.

Immunological reactions

In all trials, either no subjects or a relatively low number of subjects developed anti-semaglutide antibodies. Formation of anti-semaglutide antibodies with or without GLP-1-cross-reacting properties hampered the HbA1c-lowering effect of semaglutide.

Injection site reactions were reported by a low (approximately 1%) proportion of patients with semaglutide and were not recurrent in those individuals. A causal relationship between injection site reactions and semaglutide cannot be excluded, although the risk is evaluated as low, especially in comparison to exenatide ER (22.0%).

3.5. Uncertainties and limitations about unfavourable effects

Retinopathy

The mechanism explaining the increased risk of retinopathy is uncertain. Semaglutide treatment generally provides a rapid initial decline in blood glucose levels. The company refers to studies in patients with type 1 diabetes that reported an association between rapid glucose lowering and worsening of retinopathy. If this association were applicable to the effects of semaglutide, this would be reassuring. In type 1 diabetes, the early worsening of retinopathy is transient, resolves after 1 to 2 years and there is clear evidence of benefit from glucose lowering in the following years (DCCT Research Group. Ophthalmology 1995;102:647; N Engl J Med 1993;329:977; the Oslo study, Dahl-Jørgensen et al. Br Med J (Clin Res Ed) 1985;290:811) (Figure 43).

However, the fact that the increased risk of retinopathy with semaglutide does not decrease in the course of the 2 year trial (Figure 44) is worrisome and suggests that other mechanisms than rapid glucose lowering may play a role. The Applicant suggests that the largest separation of the semaglutide and placebo curves is manifested during the first year of the CVOT and that the two curves are more parallel during the second year. However, in figures presented in the response document a further separation can be observed after the first year. In addition, a mediator analysis, shows that a marked decrease in HbA1c is a risk factor for development of retinopathy. However, the effect is much stronger in placebo-treated patients than in semaglutide-treated patients; among those treated with semaglutide, some are affected by retinopathy without much improvement in HbA1c.

Figure 43 Cumulative incidence of progressive retinopathy in patients with type 1 diabetes and very mild to moderate nonproliferative retinopathy who were treated with either conventional (dashed blue line) or intensive (solid red line) insulin therapy for nine years (DCCT: Ophthalmology 1995;102:647-661 and N Engl J Med 1993;329:977).

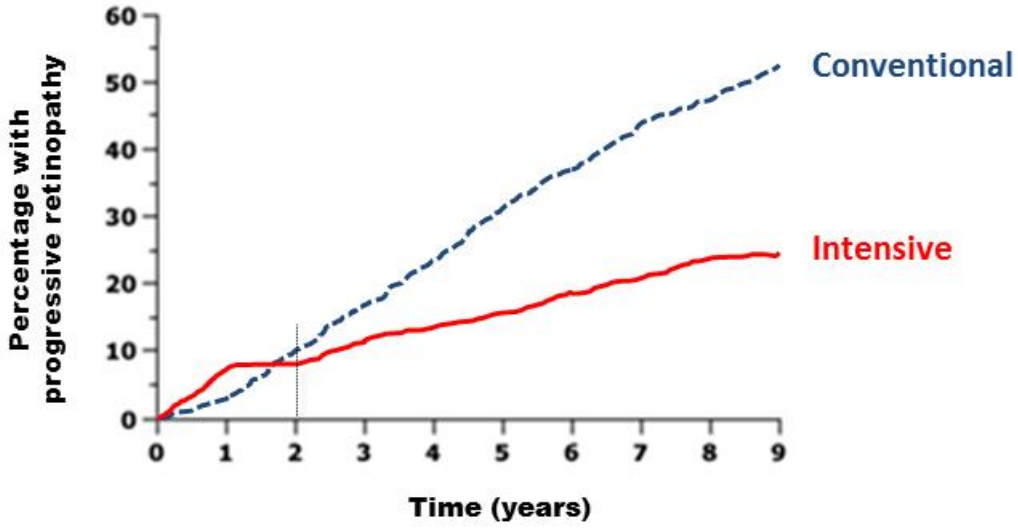
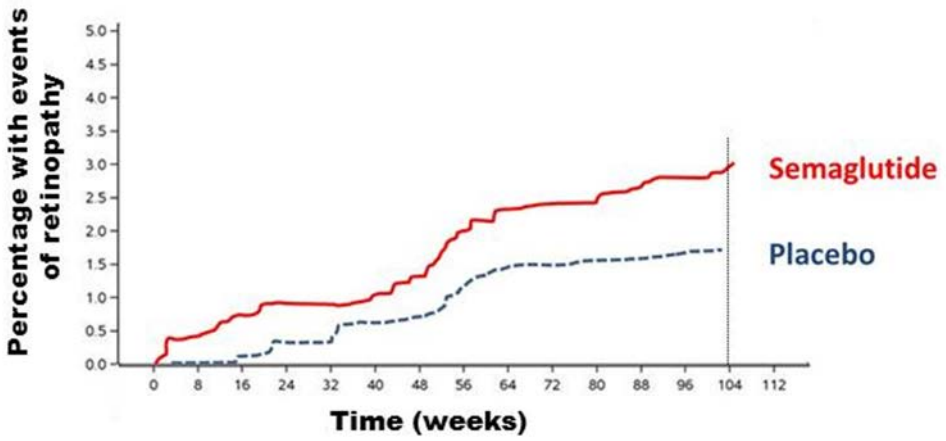


Figure 44 Time to first EAC-confirmed events of diabetic retinopathy complication in patients with type 2 diabetes at increased cardiovascular risk who were treated with either placebo (dashed blue line) or semaglutide (solid red line) for two years- (FAS in trial – CVOT).



A more specific group with an increased risk of retinopathy complications using semaglutide was identified. This risk of retinopathy complications was only observed in patients with retinopathy at baseline treated with insulin. In patients without pre-existing retinopathy, there was no effect of semaglutide on the development of retinopathy complications. Numbers needed to treat (3-point MACE) and numbers needed to harm (retinopathy complications) were 45 and 77 respectively for the total population, 19 versus 36 for subjects with baseline retinopathy, and 61 versus 456 for subjects without retinopathy at baseline.

For patients with diabetic retinopathy at baseline and treated with insulin, the number needed to treat is 17 for MACE, whereas the corresponding number needed to harm is 29 for diabetic retinopathy complications.

Effect of dose on tolerability

Based on the results from the dose-finding trial 1821 and the exposure response analysis from four phase 3a trials, it is uncertain whether the maintenance dose of semaglutide 0.5 mg is the optimal dose. A lower maintenance dose of 0.4 mg demonstrated a relevant decrease in HbA1c and a lower number of GI AEs. The population PK analysis showed a significant effect of body weight on the exposure of semaglutide. Patients with a relatively low body weight, and thus a higher exposure to semaglutide, appear to have a higher incidence of GI events and a lower chance that these adverse events subside over time due to tolerance.

Weight loss was most pronounced in the first two to three months of treatment. It is unknown how much GI side effects such as nausea and vomiting contribute to this weight loss. Furthermore, although weight loss is a known effect of GLP1-agonists the mechanism behind the weight loss with semaglutide is not entirely clear, as there did not seem to be an effect on appetite sensation. The weight loss could contribute to the observed decrease in systolic blood pressure, but why this did not translate into a decrease in diastolic blood pressure remains unknown**.**

It is uncertain whether the additional effect of semaglutide 1.0 mg vs. 0.5 mg is clinically relevant. Although semaglutide 1.0 mg vs. 0.5 mg shows benefit on HbA_{1c} and body weight change from baseline, the estimated treatment differences were small (range: 0.10−0.43%−point HbA1c and

0.81−2.75 kg). Also, the additional reduction of CV risk was small (HR 0.77 vs. 0.71). Semaglutide 1.0 mg showed a higher number of AEs (trials 3625 and 3627) and GI AEs (trials 3627, 4092 and 3744) compared with 0.5 mg

Although the population PK demonstrated an inverse relationship between body weight and semaglutide exposure, the weight of the patient is not reflected in the proposed posology of semaglutide. The treating physician can select one of two dose levels of semaglutide based on the degree of glycaemic control

Pulse rate

In the QTc study, the effect of semaglutide on the pulse rate appeared dose-dependent and was usually between 8 and 11 bpm. In the CVOT, this did not seem to result in an increased CV risk after a follow up of 2 years. When assessed by office measurements, semaglutide seems to antagonize the beta-blocker-induced pulse rate reduction. As beta-blockers were not a randomised treatment in the CVOT, the implications hereof cannot be assessed. Extrapolation of the CV outcome results to subjects without established CV disease remains difficult. In these subjects, the differences in office HR were larger than in the whole population. Therefore, the effects of a higher pulse in patients with relatively low CV risk are uncertain.

Other

In the phase 3a pool, 8 semaglutide-treated patients had events of pancreatitis and 3 events were confirmed in patients treated with exenatide ER, while no events were reported with placebo. In the CVOT, the number of patients with acute pancreatitis was comparable between semaglutide (8 patients) and placebo (10 patients). With regard to GI disorders, there was a striking difference in Exocrine pancreas conditions. A total of 8 events belonging to this HLGT were registered among the semaglutide treated patients (R=0.4) as compared to none in the comparator group. Levels of serum lipase and amylase increased with semaglutide. In the absence of other signs or symptoms of pancreatitis, elevation of lipase and amylase levels seen with semaglutide did not predict a later development of pancreatitis. The lack of a dose-response or temporal clustering, weakens the assumption of a causal relationship with treatment.

On the basis of PK data, the SmPC states that no dose adjustment is required for patients with hepatic impairment. The clinical pharmacology trial (trial 3651) demonstrated that the exposure to semaglutide is similar in subjects with hepatic impairment and subjects with normal hepatic function. No data in diabetic patients are presented. Therefore, caution should be exercised in severe hepatic impairment, as there are no data presented on the use of GLP1-RAs in these patients. The SmPC states that the experience in patients with severe hepatic impairment is limited and that thus caution should be exercised when treating these patients. The text is considered adequate. Hepatic impairment is considered missing information in the RMP.

Malignant neoplasms were equally distributed with semaglutide and placebo (HR: 0.94 [0.67; 1.32]$_{95\%CI}$) in the CVOT with no apparent differences for any types of malignant neoplasms. In the phase 3a pool there were more malignant neoplasms (HR: 1.61 [0.74; 3.49]$_{95\%CI}$) with semaglutide than with comparators; however, numbers were low. There were no single types of malignant neoplasms driving this difference.

3.6. Effects Table

Table 20 Effects Table for semaglutide in the treatment of type 2 diabetes mellitus

Effect	Short Description	Unit	Sema 0.5	Sema 1.0	Control	Uncertainties/ Strength of evidence	References (Study nr)
Favourable Effects							
HbA1c	Mean change in HbA1c from baseline	%	-1.45	-1.55	Pla: -0.02	Treatment effects were clinically relevant, but uncertain for several subgroups and only slightly better with sema 1.0 mg vs. 0.5 mg	3623
			-1.32	-1.61	Sita: -0.55		3626
				-1.54	Exe: -0.92		3624
			-1.21	-1.64	Glarg: -0.83		3625
			-1.45	-1.85	Pla: -0.09		3627
			-1.27	-1.78	Pla: -0.41		CVOT
Body weight	Mean change in body weight from baseline	kg	-3.73	-4.53	Pla: -0.98	Treatment effects were clinically relevant, but uncertain for several subgroups and only slightly better with sema 1.0 mg vs. 0.5 mg	3623
			-4.28	-6.13	Sita: -1.93		3626
				-5.63	Exe: -1.85		3624
			-3.47	-5.17	Glarg: +1.15		3625
			-3.67	-6.42	Pla: -1.36		3627
			-3.57	-4.88	Pla: -0.62		CVOT
MACE	First MACE; subjects with events	N (%)	108 (6.6)		146 (8.9)	Obtained in population at high CV risk and lower/absent for several subgroups	CVOT
		HR vs placebo	0.74 (0.58, 0.95)		-		
	Non-fatal MI; subjects with events	N(%)	47 (2.9)		64 (3.9)		
		HR vs placebo	0.74 (0.51, 1.08)		-		
	Non-fatal Stroke; subjects with events	N(%)	27 (1.6)		44 (2.7)		
		HR vs placebo	0.61 (0.38, 0.99)		-		
	CV Death; subjects with events	N(%)	44 (2.7)		46 (2.8)	Unexpected that there was no effect on CV death	
		HR vs placebo	0.98 (0.65, 1.48)		-		
Unfavourable Effects							
GI-side effects	Incidence	%	41.7	42.2	Comp 18.5	More GI side effects with sema 1.0 mg vs. 0.5 mg	Pooled trials
		Rate	116.8	147.4	Comp 38.4		
		%	50.4	52.0	Pla 34.3		CVOT
		Rate	81.2	94.9	Pla 40.5		
Retinopathy	Incidence	%	3	3.0	1.8	Negative effect of semaglutide was absent in individuals without retinopathy at baseline	CVOT
		Rate	1.6	2.0	1.1		
Severe hypoglycaemia	Incidence	%	1.7	1.1	1.6	For patients on SU and insulin, episodes of hypoglycaemia were reported at higher frequencies with semaglutide.	
		Rate	1	0.9	1.3		
All cause mortality		N(%)	62 (3.8)		60 (3.6)		CVOT
		HR vs placebo	1.05 (0.74, 1.50) -				

Effect	Short Description	Unit	Sema 0.5	Sema 1.0	Control	Uncertainties/ Strength of evidence	References (Study nr)
Pulse rate	Mean placebo corrected change at most sensitive timepoint	Beats per minute	8.48	9.66	N/A		QTc trial

Abbreviations: Sema: semaglutide; Pla: placebo; Sita: sitagliptin; Exe: exenatide LAR; Glarg: insulin glargine; CVOT: cardiovascular outcome trial

Severe hypoglycaemia defined as severe hypoglycaemia according to the ADA classification (requiring the assistance of another person) or BG confirmed by a plasma glucose measurement <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important favourable effects observed were decreases in HbA1c and body weight in comparison to placebo and several active comparators. In addition, there were clinically relevant decreases in systolic blood pressure. Despite this improvement in glycaemic control, it is important for patients that semaglutide does not increase the risk of hypoglycaemia unless combined with either SU or insulin.

The main goal in the treatment of diabetes is to reduce the progression of microvascular and macrovascular complications. It is therefore important that semaglutide had a favourable effect on non-fatal MI and non-fatal stroke, but it is rather unexpected that the occurrence of CV death was similar with semaglutide and placebo. Based on biological plausibility it would have been expected that semaglutide treatment will beneficially influence all components in a similar way. Although the three individual components of the composite endpoint are clinically meaningful, CV death is considered more clinically relevant than non-fatal MI and non-fatal stroke. Importantly, the effect of semaglutide on several other important outcome measures was negative. Hospitalisation for heart failure, all-cause mortality, SAEs of coronary artery disease, SAEs of cardiac failure and vascular therapeutic procedures (particularly cardiac interventions) were higher with semaglutide than with placebo. The duration of the trial may have been too short to show positive effects on CV-death. Similarly heterogenous results have been observed for statins and PSK9-inhibitors. Results do not indicate that semaglutide has a beneficial or negative effect on CV-death and non-CV death. Heart failure is often due to non-atherosclerotic pathomechanisms, while semaglutide most probably affects atherosclerosis. Furthermore, numbers are too small for a firm conclusion. For some Preferred Terms imbalances were seen, while no differences were observed for related PTs or high-level group terms. The explanation given by the Applicant for these discrepancies is considered acceptable.

Treatment of 1648 patients with semaglutide in the CVOT resulted in a reduction in the number of major cardiovascular events of 38 (number needed to treat 45), but was also associated with an additional 21 events of serious retinopathy (number needed to harm 77). Therefore, retinopathy is considered a very important risk. The imbalance was observed for all four predefined components of the combined endpoint and was similar with semaglutide 0.5 mg and 1.0 mg, suggesting that the increased risk with semaglutide is a robust finding. Only for the subgroup of patients with diabetic retinopathy at baseline and treated with insulin, semaglutide was associated with a significantly increased risk of relevant retinopathy complications. In these patients, the number needed to treat is

17 for MACE, whereas the corresponding number needed to harm is 29 for diabetic retinopathy complications. Among patients without pre-existing diabetic retinopathy or insulin use, the frequency of diabetic retinopathy complications was low and similar with semaglutide and placebo (number needed to treat 61, number needed to harm 456).

In line with semaglutide, exenatide has also been associated with (transient) worsening of diabetic retinopathy in a case series (Varadhan et al. Diabetes Res Clin Pract. 2014;103(3):e37-9). In addition, in the liraglutide CVOT (Victoza, procedure EMEA/H/C/001026/II/0042), the HR for the composite endpoint reflecting diabetic retinopathy complications, although not statistically significant, disfavoured liraglutide (HR: 1.15 [0.87; 1.52] 95%CI, p=0.33).

In type 1 diabetes, a rapid improvement of glycaemic control is thought to be associated with progression of diabetic retinopathy. However, contrary to this experience, the increased risk of retinopathy with semaglutide does not decrease in the course of the 2 year trial. This is worrisome and suggests that other mechanisms than rapid glucose lowering may play a role. Moreover, semaglutide was associated with retinopathy in patients with only small HbA1c reductions. Thus, a persistent deleterious effect of semaglutide on the retina independent of glucose lowering cannot be excluded.

Observations do not permit definite conclusions regarding the underlying mechanism of action. The occurrence of early worsening in patients with only small reductions in HbA1C remains unexplained. However, it is agreed that net clinical benefit over time due to improved glycaemic control is likely. A long-term PASS study will be conducted to examine this. In this double-blinded, placebo-controlled study, the development and progression of diabetic retinopathy in terms of ≥2 steps ETDRS progression in either eye at year 5 is suggested to be studied in approximately 1000 patients with inadequately controlled T2D (e.g. defined as an HbA1c ≥7.5%) treated with semaglutide once-weekly versus placebo once-weekly, both added to standard-of-care. In addition, the Applicant has added a warning in section 4.4, similar to that in the product information of insulins. The primary endpoint will be proportion of patients with diabetic retinopathy at five years. However, time-to-event or similar endpoints elucidating the time-response were advised to be included as secondary endpoint(s).

Treatment effects on CV outcomes were absent for patients with chronic heart failure class II-III and lower for patients using insulin treatment at baseline. The Applicant emphasizes that effects on HbA1c, body weight and systolic blood pressure were seen in these subjects. For use of insulin at baseline, the populations of subjects using insulin at baseline are similar in terms of demography and CV history. Subgroups were small, and it is unlikely that there is a true difference in effects on MACE in subjects with T2D using premix or basal insulin at baseline.

Although the gastrointestinal adverse events with semaglutide were typically of limited duration and are reversible after stopping treatment, it is important that the percentage of patients that prematurely discontinued semaglutide because of GI AEs was relatively large. Patients with a higher exposure to semaglutide had more GI AEs than patients with a lower semaglutide exposure. Dose finding studies suggest that a lower dose selection might have been associated with acceptable efficacy outcomes and lower rates of premature discontinuation. In addition, it is possible that a 12 week dose escalation regimen (instead of 8 weeks) might have improved the GI tolerability and reduced withdrawals.

There is no unequivocal evidence for a better benefit/risk profile with semaglutide maintenance doses of 0.5 and 1.0 mg in the phase 3 trials as compared to 0.4 and 0.8 mg. The confirmatory trials have demonstrated that maintenance doses of 0.5 and 1.0 mg have a positive benefit/risk profile. Both dose levels of semaglutide can be safe and efficacious and should be based on individual needs. The 1.0 mg dose is associated with an increased risk of side effects. Patients with low body weight may experience

more gastrointestinal side effects when treated with semaglutide. This is mentioned in Section 4.8 of the SmPC.

The higher incidence of adverse events with the 1.0 mg dose could be acceptable if the additional efficacy of semaglutide 1.0 mg vs. 0.5 mg is clinically relevant. However, in the studies treatment differences were rather small. Therefore, the Applicant was invited to explain the clinical relevance of the differences. If the differences are clinically relevant, it is important to provide information about tapering off the 1 mg maintenance dose to 0.5 mg when the 1.0 mg is not tolerated. The Applicant reasons that, as the semaglutide 1.0 mg maintenance dose is reached by stepwise progression from 0.25 to 0.5 mg, patients must first have demonstrated that they can tolerate the 0.5 mg dose before being dose-escalated to 1.0 mg. Thus, lowering the semaglutide dose from 1.0 mg to 0.5 mg may be carried out at discretion of the treating physician if deemed appropriate.

It is unknown how much of the weight loss is associated with GI AEs. There is little doubt that semaglutide is associated with GI AE and these include nausea and vomiting. The frequency and severity is reduced by titrating the dose over an 8 week period, but the largest observed weight loss coincides with the treatment period where GI AEs are also most pronounced.

Previous studies have shown that liraglutide is associated with an increased risk of cholelithiasis and cholecystitis. In addition, in the liraglutide CVOT malignant pancreatic neoplasms were confirmed in 13 patients in the liraglutide group and 5 in the placebo group. Semaglutide may also be associated with an increased risk of cholelithiasis, and the effect of semaglutide on pancreatitis and pancreatic cancer cannot be excluded. Observations indicate that semaglutide use may be related to cholelithiasis. Absolute numbers are small. Cholelithiasis is adequately listed as a common adverse reaction in the SmPC and as an important identified risk in the RMP. Pancreatic cancer is listed as an important potential risk in the RMP. The risks may be small, but risks may be higher with longer term use of semaglutide which may have serious consequences.

The effect of semaglutide on the pulse rate did not seem to result in an increased CV risk after a follow up of 2 years in high CV risk patients. However, the effects of a higher pulse in patients with relatively low CV risk are uncertain.

For a drug that is intended for long term diabetes treatment, the duration of the CVOT (2 years) is relatively short (also in comparison to several other cardiovascular outcome trials). Long term follow up based on a comprehensive RMP is important. In addition, the inclusion of individuals with a high CV risk in the CVOT may limit generalizability to the general diabetic population (in the CVOT a number of subjects were included with risk factors “only”. In these subjects, no effect on MACE was seen, but the numbers were too small to draw firm conclusions, with 10 events with semaglutide and 9 events with placebo). This is an important knowledge gap for low risk patients.

Semaglutide was not compared to SU. SU is considered the next step after metformin by many guidelines and doctors. Therefore, the lack of a trial comparing semaglutide with SU may be considered important. However, in the CVOT, the patients in the placebo group were treated in accordance with the standard of care, including SU.

3.7.2. Balance of benefits and risks

Semaglutide was studied in a number of placebo- and comparator-controlled trials. The most important favourable effects observed were considerable decreases in HbA1c and body weight in comparison to placebo and several active comparators. Except for the combination with sulphonylurea or insulin, improved glycaemic control was achieved without an increase of the risk of hypoglycaemia.

Gastrointestinal adverse events were frequent and clinically relevant, but expected with this product class. Semaglutide may be linked to an increased risk of cholelithiasis, and an association with pancreatitis and pancreatic cancer cannot be excluded. Semaglutide was also studied in a separate cardiovascular outcome trial in patients with type 2 diabetes and a high cardiovascular risk; semaglutide showed a beneficial effect on some outcomes relevant to macrovascular disease, but the effect was neutral with regard to cardiovascular death and death from any cause. Events of serious retinopathy were more frequent with semaglutide use, and mostly seen in patients with diabetic retinopathy at baseline and treated with insulin. This will be further investigated in a long-term, large scale post authorisation study. On balance, the described benefits therefore outweigh the risks for the indicated patient population with type 2 diabetes.

3.8. Conclusions

The overall benefit-risk balance of Ozempic is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ozempic is favourable in the following indication:

Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product

within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that semaglutide is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0095/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.