11 November 2021
EMA/21773/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ozempic

International non-proprietary name: semaglutide

Procedure No. EMEA/H/C/004174/X/0021

Note

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

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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	tumor 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

Novo Nordisk A/S submitted on 29 December 2020 an extension of the marketing authorisation.

Extension application to add a new strength of 2 mg solution for injection in pre-filled pen.

The MAH applied for a change or addition of a new strength.

The MAH applied for the following indication for Ozempic the new strength:

Ozempic is indicated for the 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 trial 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.

Furthermore, the RMP is updated to version 6.1.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Not applicable, the currently approved Ozempic PIP (EMEA-001441-PIP01-13-M03) has not been updated since a new strength does not trigger the paediatric regulation. The currently approved PIP is included in the application.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege   Co-Rapporteur: Sinan B. Sarac

PRAC Rapporteur: Annika Folin

The application was received by the EMA on	29 December 2020
The procedure started on	21 January 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 April 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	20 May 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	16 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 September 2021
The PRAC Rapporteur's Updated Assessment Report was circulated to all PRAC and CHMP members on	23 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 September 2021
The CHMP Rapporteur's Updated Assessment Report was circulated to all CHMP and PRAC members on	07 October 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	14 October 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	19 October 2021
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 October 2021
The CHMP Rapporteur's Updated Assessment Report was circulated to all CHMP and PRAC members on	05 November 2021

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	11 November 2021

2. Scientific discussion

2.1. Problem statement

Semaglutide for once-weekly s.c. injection (Ozempic) is approved worldwide for the treatment of type 2 diabetes (T2D) at maintenance doses of 0.5 mg and 1.0 mg. Treatment with semaglutide improves glycaemic control, reduces body weight and reduces cardiovascular risk. Additionally, semaglutide is being developed for weight management using a once-weekly dose of 2.4 mg.

A third maintenance dose of once-weekly semaglutide s.c. 2.0 mg is developed for patients with T2D who may benefit from additional glucose-lowering and body weight loss as the disease progresses. In this application, data from the phase 3b Trial NN9535-4506 are presented to support the use of semaglutide 2.0 mg for the treatment of T2D.

2.1.1. Disease or condition

The claimed indication is:

Ozempic is indicated for the 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 applicant has not made any changes to the approved indication, however, the posology with regards to increase in dose to 2.0 mg has been amended.

2.1.2. Epidemiology

The global prevalence of diabetes is estimated to 9.3% with the majority being type 2 diabetes (reference: IDF 2019). The estimated number of persons living with diabetes in Europe is 59 million in 2019. Systematic reviews indicate that the relative risk of cardiovascular diseases (CVD) is between 1.6 and 2.6.

T2D remains a substantial health care challenge with a projected worldwide prevalence of 10.9% (700 million adults) by 2045. T2D is a progressive disease and persistent hyperglycaemia can lead to serious microvascular and macrovascular complications. Despite the availability of several treatments, optimising glycaemic control remains a challenge in many patients.

2.1.3. Aetiology and pathogenesis

Type 2 diabetes is a progressive metabolic disease primarily characterised by abnormal glucose metabolism.

The pathophysiology of type 2 diabetes is characterised by chronic hyperglycaemia caused by insulin resistance in the peripheral tissue, by reduced insulin production in the pancreatic beta-cells and by increased hepatic glucose release.

The pathogenesis is seemingly heterogeneous and also involves environmental, lifestyle, and genetic components. All of these factors contribute to chronic hyperglycaemia which, if left untreated, is associated with β-cell failure and increased risk of long-term micro-and macrovascular complications. Long-term glycaemic control is fundamental for the management of type 2 diabetes to prevent/slow down progression of β-cell failure and reduce the risk of type 2 diabetes-related complications.

2.1.4. Clinical presentation, diagnosis

Type 2 diabetes is chronic metabolic disease characterised by deficient insulin activity arising from decreased insulin secretion secondary to β-cell insufficiency, compromised insulin action in peripheral target tissue (insulin resistance), or a combination of these. The abnormal metabolic state is exacerbated by excess glucagon secretion, excess hepatic glucose production, altered metabolism of protein and lipids, and reduced incretin effect.

The symptoms of type 2 diabetes often develop gradually. Blood tests will be used to confirm the diagnosis. The tests measure the amount of sugar, or glucose, in the blood. The tests used are: Glycated haemoglobin (A1C) test (gold standard), fasting plasma glucose test, random plasma glucose test and oral glucose tolerance test.

2.1.5. Management

Several products are approved for the treatment type 2 diabetes: metformin, GLP-1 analogues, DPP4-inhibitors, SGLT2 inhibitors, sulphonylureas, thiazolidinediones, and insulin.

The ADA and EASD consensus report recommends a patient-centred approach for glycaemic management in type 2 diabetes. Patient characteristics and preferences are important factors for individualising treatment goals and strategies. Individualised HbA1c target, indicators of high-risk or established atherosclerotic cardiovascular disease, chronic kidney disease or heart failure of a patient, risk of hypoglycaemia, body weight and costs are main factors that should be considered in the treatment of patients with type 2 diabetes. The main goal of all the above-mentioned drug classes is to lower plasma glucose. However, even though several classes are combined, the patients' individualised goals are not always reached.

2.2. About the product

Semaglutide is a glucagon like peptide 1 receptor agonist (GLP-1 RA). 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 once weekly s.c. administration.

Semaglutide 2.68 mg/ml solution for injection is a clear and colourless solution filled in a 3 ml cartridge, assembled in a PDS290 pen-injector. The PDS290 pen-injector for semaglutide 2.68 mg/ml delivers doses (each dose 0.74 ml) of 2 mg (4 doses available).

The active ingredient, semaglutide, is a GLP-1 analogue substituted with a fatty acid side chain. Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) followed by chemical modification. The drug substance is identical to the already approved drug substance for Ozempic.

2.3. Type of Application and aspects on development

Semaglutide has been investigated in a comprehensive global clinical development programme (SUSTAIN) involving more than 11,000 subjects across 11 phase 3 trials, including a dedicated cardiovascular outcomes trial. In the SUSTAIN programme, semaglutide was investigated throughout the continuum of T2D care, from monotherapy in drug naïve patients with short disease duration to combination use with one or more OADs or basal insulin in patients in a later stage of T2D disease progression. Across the SUSTAIN trials, semaglutide demonstrated superior reduction in HbA$_{1c}$ and body weight compared to placebo and several active comparators. The cardiovascular outcomes trial (SUSTAIN 6) demonstrated a statistically significant reduction in the risk of major adverse cardiovascular events compared to placebo in subjects with T2D at high risk of or established cardiovascular diseases. Semaglutide has a safety profile consistent with the safety profile of the GLP-1 RA drug class.

Two maintenance doses of semaglutide are currently approved for the treatment of T2D: 0.5 mg and 1.0 mg. Across the SUSTAIN programme, larger reductions in HbA$_{1c}$ and body weight were consistently observed with semaglutide 1.0 mg than with 0.5 mg. However, it was observed that 20-30% of patients receiving semaglutide 1.0 mg did not achieve the treatment target of HbA$_{1c}$ <7.0%.

No CHMP scientific advices have been given for the current application.

2.4. Quality aspects

2.4.1. Introduction

The scope of this line extension application is to register a new 2 mg strength: solution for subcutaneous injection in a cartridge assembled in a disposable pre-filled pen (PFP) (also referred to as PDS290 pen injector), containing 8 mg semaglutide in 3 mL of solution (concentration 2.68 mg/mL). Each PFP is intended to deliver 4 doses of 2 mg. The pack sizes are 1 and 3 PFPs co-packaged with 4 and 12 NovoFine Plus needles, respectively.

The cartridge, PFP, and needles are the same as those in the currently authorised for Ozempic 1.34 mg/mL (0.25 mg, 0.5 mg and 1 mg) presentations:

- Cartridge (Type I glass) closed at the one end with a rubber plunger and at the other end with an aluminium cap;

- Cartridge assembled into a disposable PDS290 multi-dose pen injector - Disposable NovoFine Plus needles are co-packaged.

The qualitative and quantitative composition in excipients in the new presentations also remains unchanged.

The active substance semaglutide is a human glucagon-like peptide-1 (GLP 1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology. Module 3.2.S is not affected by this application.

2.4.2. Active Substance

Module 3.2.S is not affected by this application.

2.4.3. Finished Medicinal Product

Description of the product

Semaglutide 2 mg solution for injection is a clear and colourless solution filled in a 3 mL cartridge assembled in a PDS290 pen injector. NovoFine Plus 32G needles are co-packaged.

Semaglutide is formulated with the following compendial excipients: disodium phosphate, dihydrate (buffering agent), propylene glycol (tonicity agent), hydrochloric acid (pH adjustment to 7.4), sodium hydroxide (pH adjustment), and water for injections (solvent).

The average overfill volume is approximately 0.2 mL.

Pharmaceutical development

Finished product understanding has been achieved based on the Quality Target Product Profile (QTPP), prior knowledge gained during development of Ozempic 1.34 mg/mL presentations, formulation development studies, and risk assessment of the manufacturing process.

There were no changes made to the composition of the finished product during development.

Semaglutide 2.68 mg/mL solution for injection manufacturing process development is based on the manufacturing process of Ozempic 1.34 mg/mL finished products. Changes from the manufacturing processes for primary stability batches to finished products intended for the market are limited to batch size and the implementation of sterile filtration close to filling.

The primary container closure system is identical to the currently authorised 1 mg presentations. No new extractables and leachables studies have been performed, this is acceptable as the composition of the solution, the pH, and the primary container is identical, except for an increase of the relatively low peptide content.

Sterility of the finished product is obtained by filtration and filling under aseptic conditions. The antimicrobial preservative efficacy of phenol in semaglutide 2.68 mg/mL solution for injection has been tested according to Ph. Eur. Container closure integrity has been confirmed by microbial ingress tests. Semaglutide 2.68 mg/mL in the 3 mL cartridge is compatible with the PDS290 pen injector. There is no direct contact between the semaglutide solution for injection and the pen injector.

Manufacture of the product and process controls

The manufacturing sites for semaglutide 2.68 mg/mL solution for injection are listed and identical to the Ozempic 1 mg finished products.

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 pre-filtered using a bacteria-retaining filter with 0.45 μm pore size and a sterilising filter with ≤0.2 μm pore size. Sterile filtration at point of filling is carried out with a sterilising filter with ≤0.2 μm pore size. Filter specifications and filter validation documents are provided. Established ranges for process parameters based on data from process justification are also provided, these include temperature, stirring speed, stirring time, holding times and process time. Pre-treatment procedures of the primary packaging materials are provided. Caps and plungers are steam sterilised using Ph. Eur. 5.1.1. reference conditions ($\geq 121^0$C, $\geq$ 15 min) and cartridges are depyrogenated.

Assembly with the PDS290 pen injector for semaglutide 2.68 mg/mL is described in sufficient detail and identical to the assembly of semaglutide 1.34 mg/mL solution for injection. After final assembly, PDS290 pen injectors are labelled and packing in carton before the final release.

No reprocessing is foreseen.

Process controls

Critical steps and in-process controls (IPCs) have been assigned for the semaglutide finished product. The proposed actions for failing to meet acceptance criteria are considered acceptable. Adequate process controls are in place for the front and rear assembly and the final assembly. The dose accuracy of the finished products is controlled routinely.

Process validation

Validation activities have been performed to confirm that the manufacturing process for the 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 justification, b) Process validation programme, and c) Ongoing process verification.

The purpose of the process justification is to support the process parameters and limits for IPCs for the production scale manufacturing processes. The process justification was performed with scalable process parameters (batch size independent) and non-scalable process parameters (batch size dependent and/or equipment specific).

Three commercial scale batches of semaglutide 2.68 mg/mL solution for injection were manufactured and filled in 3 mL cartridges for process validation. Results from IPCs, extensive sampling , and batch analysis data demonstrate that the manufacturing process yields consistent and reproducible finished products.

Validation studies to control the essential functions of the PDS290 pen-injector for semaglutide 2.68 mg/mL solution for injection demonstrate that assembled pen-injectors of the required quality are consistently produced.

Product specification, analytical procedures, batch analysis

Specifications

Specifications include control of identity, impurities, content and other general tests.

The proposed acceptance criteria are based on prior knowledge from manufacturing and stability data of Ozempic 1.34 mg/mL presentations.

The proposed finished product specifications, including acceptance criteria for content of semaglutide and for impurities, are based on the approved specifications and limits for the semaglutide 1.34 mg/mL. These limits are sufficiently tight and considered approvable. n alignment with the currently authorised presentations for Ozempic, no release testing for bioactivity is proposed since the specific

bioactivity can be adequately monitored by the reverse phase-high performance liquid chromatography (RP-HPLC) content assay.

The specifications are considered acceptable.

Analytical procedures

Analytical procedures are described and validated according to relevant ICH guidelines, or reference is made to compendial requirements (Ph. Eur.). The non-pharmacopoeia analytical procedures in the finished product specification are identical to those used for the Ozempic 1.34 mg/mL.

Batch analyses

Analyses of all relevant finished product batches are provided. The results from the three process validation batches indicate that the manufacturing process for semaglutide 2.68 mg/mL solution for injection is under control.

Characterisation of impurities

The impurity profiles obtained for semaglutide 2.68 mg/mL solution for injection are comparable to the Ozempic 1.34 mg/mL. No new impurities were found to be generated, and the major degradation products characterised by liquid chromatography mass spectrometry (LC-MS) are the same.

The risk assessment for elemental impurities, in accordance with ICH Q3D, is considered approvable, and the levels found were consistently below 30% of the permissible daily exposure (PDE) value based on the worst-case finished product dosing.

According to the Applicant, a risk assessment for the potential presence of nitrosamine impurities in the finished product was performed. Only the conclusions are provided. This is acceptable considering that this application is a line extension, and the excipients or container closure system do not give rise to an increased risk in the formation of nitrosamine impurities.

Container closure system

The container closure system for semaglutide 2.68 mg/mL is currently used with Ozempic 1 mg presentations.

The 3 mL cartridge is made of colourless hydrolytic glass (Type 1 glass as defined by Ph. Eur.). The closure at one end of the cartridge is a cap that consists of a rubber disc and a seal of aluminium. The rubber disk is made of laminated rubber, with bromobutyl rubber (Type 1, Ph. Eur.) in contact with the finished product. The closure at the other end of the cartridge is a plunger made of chlorobutyl rubber (Type 1, Ph. Eur.). The laminated rubber and rubber plunger are not made with natural rubber latex.

Extractable and leachable studies and container closure integrity testing were part of the finished product development studies. Sterilisation procedures are described as part of the manufacturing process. Sufficient documentation is provided.

The cartridge is assembled in a PDS290 pen-injector. The PDS290 pen injector components are not in direct contact with the solution for injection. Overall, sufficient information has been provided to demonstrate that the pen injector fulfils the relevant ISO requirements.

The PDS290 pen injector was tested in a usability study and found to be safe and effective for the intended users, intended use and use environments with regards to handling and differentiation.

In addition, a Notified Body Opinion according to Article 117 of Regulation (EU) 2017/745 on Medical Devices was provided, confirming full compliance of the PDS290 pen injector with the relevant general safety and performance requirements.

The PDS290 pen-injector is co-packaged with compatible NovoFine Plus 32G needles (same needles as those currently authorised for Ozempic 1.34 mg/mL presentations).

Stability of the product

The stability test programme for the semaglutide finished product was performed according to current ICH guidelines.

No changes in formulation and primary container closure system were introduced between the production of the primary stability batches and process validation batches.

Long-term stability data for three primary stability batches and for one primary stability batch assembled in the device, and for the three process validation batches were performed. Only slight changes in content and impurities are observed; all results for these parameters remain within the proposed shelf life specification. No changes in the other stability parameters are observed. Furthermore, the stability is comparable for all batches tested. The proposed shelf life before first use of 24 months, when stored at 5°C ± 3°C, is considered acceptable.

An in-use simulation is performed to simulate patient usage. The proposed in-use period of 42 days below 30°C or in a refrigerator (5°C ± 3°C) after first opening is considered approvable.

The semaglutide solution for injection is considered photosensitive. Photo stability studies show that the pen-injector with the cap on provides adequate protection from light exposure. This consideration is reflected in the SmPC.

Post approval change management protocol(s)

A Post approval change management protocol (PACMP) is included to add a second manufacturing site for the semaglutide 2.68 mg/mL finished product (formulation, filling and inspection). The contents of the PACMP are well aligned with PACMPs recently accepted for additional finished product facilities for Ozempic and are considered acceptable.

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 transmissible spongiform encephalopathies (TSE) agents.

The finished product is considered to be safe with regards to virus, TSE agents, bacteria, mycoplasma, and fungi.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The pharmaceutical development, manufacturing process and controls are based on the currently authorised 1.34 mg/mL mg presentations. The quality of the finished product is controlled by adequate test methods and specifications. No major objection was identified during the procedure. The overall quality documentation provided in this line extension application is considered adequate and complies with existing guidelines.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Ozempic 2 mg solution for injection in pre-filled pen is considered acceptable when used in accordance with the conditions defined in the SmPC.

From a quality point of view, this line extension application is considered acceptable.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

Section on 'Ecotoxicity/environmental risk assessment' (ERA) has been assessed in the current procedure as a new ERA document was submitted.

2.5.1. Ecotoxicity/environmental risk assessment

The active substance is a peptide, which will not alter the concentration or distribution of the substance in the environment. Therefore, semaglutide is not expected to pose a risk to the environment.

2.5.2. Discussion on non-clinical aspects

In the current procedure a new ERA document was submitted, in which the applicant has adequately justified the absence of further studies to assess the environmental risk of semaglutide.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, semaglutide is not expected to pose a risk to the environment.

2.5.3. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted for this procedure which is acceptable. There are no objections to the approval from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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.

It is stated that The NN9535-4506 (SUSTAIN FORTE) trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice (GCP).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

This line-extension application concerns the application for an additional, higher maintenance dose of semaglutide 2.0 mg once-weekly s.c. for the treatment of T2D. The applicant submitted a phase 3 trial **(NN9535-4506)** as a pivotal trial to support this application. In this trial, sparse pharmacokinetic samples were collected, and pharmacokinetic parameters based on these samples were obtained using a population pharmacokinetic analysis. The applicant also submitted two supportive studies **NN9535-3687** (a bioequivalence study) and **NN9536-4374** (phase 3 trial with 2.4 mg semaglutide for weight indication as supportive safety evidence). The bioequivalence study **NN9535-3687** has been assessed before (initial marketing authorisation application). Also, reference was made to study **NN9535-3685 and NN9536-4455** that evaluated the influence of semaglutide 1.0 mg and 2.4 mg on gastric emptying.

The higher maintenance dose of semaglutide 2.0 mg once-weekly s.c. is delivered as in a prefilled disposable pen-injector belonging to the same PDS290 technology platform as the existing Ozempic doses. The concentration of the to-be-marketed product (for the 2.0 mg dose) is 2.68 mg/ml.

Methods

Validated LC-MS/MS bioanalytical methods, previously assessed in initial marketing authorisation application, were used to analyse semaglutide in plasma. In study **NN9535-3687,** standard non-compartmental pharmacokinetic parameters have been determined. A population pharmacokinetic analysis was conducted to estimate pharmacokinetic parameters in pivotal study **NN9535-4506**. The objectives were to evaluate the dose proportionality of the pharmacokinetics of semaglutide and the impact of covariates on semaglutide exposure.

Population PK model used to characterise PK data from phase 3 trial (NN9535-4506)

A one-compartment structural model with first-order absorption and first-order elimination was used to describe the pharmacokinetics of semaglutide. The absorption rate constant was fixed to a value of 0.0296 h^{-1}, based on earlier clinical pharmacology trials in normoglycaemic and type 2 diabetes subjects. Between-subject variability was included for CL/V and V/F and assumed to have a log-normal distribution. Residual variability was described by a proportional error model.

Covariate factors were implemented using the same factors as for the SUSTAIN population PK model, with two differences: First, the injection site was previously shown to have a negligible effect on PK,[1] and therefore, this data was not collected for this analysis. Second, the dose factor (originally testing 0.5 mg vs 1.0 mg) will, for this analysis, test an effect on exposure (CL/F) at 2.0 mg vs 1.0 mg. The covariate factors to be included for CL/F are sex, age group, race, ethnicity, body weight, renal function, and maintenance dose. Covariates were analysed using a "full covariate model" and assumed a power model structure. The population pharmacokinetic model was reduced by excluding covariates that were not considered significantly impact exposure ($p<0.05$).

The first-order conditional estimation with interaction as implemented in NONMEM version 7.3 was used to estimate model parameters. Non-parametric bootstrap was used to estimate standard errors. The population pharmacokinetic model was evaluated using standard goodness-of-fit plots, visual predictive checks, parameter uncertainty, shrinkage and plausibility of fixed model parameters.

A total of 3632 pharmacokinetic observations from 956 subjects (on-treatment) were evaluated for inclusion in the population pharmacokinetic dataset. 229 observations (6.3%) were excluded due to

values below the lower limit of quantification or inadequate dosing history. The final population pharmacokinetic model comprised 3403 pharmacokinetic observations from 944 subjects.

A visual predictive check of the model is displayed below in Figure 1. Model parameters are displayed in Table 1.

Figure 1. Visual predictive check for the final model of semaglutide PK

Data are observed (lines) and 95% CIs (shaded area, n=500) of simulated medians and 5th and 95th concentration percentiles versus time since first dose
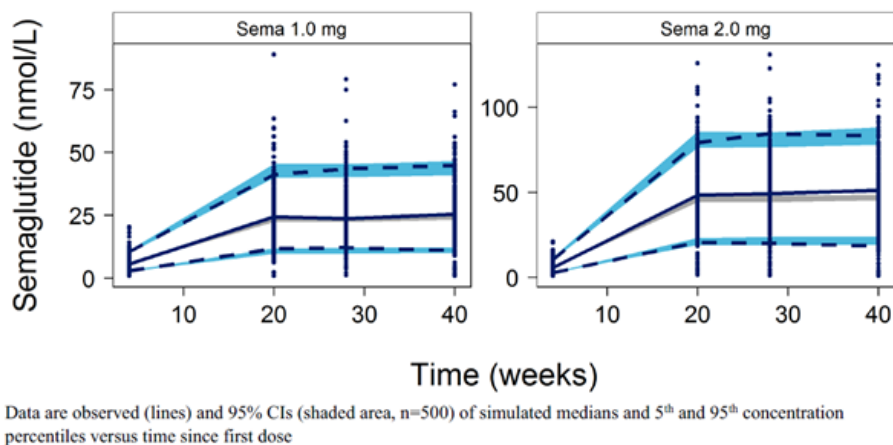
Table 1. Parameter estimates for the final PK model of semaglutide

param.name	param.descrip	Estimate	CI95. lower	CI95. upper	pct.RSE	IIV.pct. CV	Shrink age.pct
KA [1/h]	Absorption rate constant (ka)	0.0296	0.0296	0.0296	0	NA	NA
CL/F [L/h]	Apparent clearance (CL/F)	0.0475	0.0461	0.0488	1.43	13.9	23.3
V/F [L]	Apparent central volume (V/F)	15.9	14.4	17.6	5.23	18.1	82.6
BW EXP []	Body weight exponent on CL	0.764	0.704	0.821	3.86	NA	NA
MALE []	Sex factor on CL	1.07	1.04	1.1	1.44	NA	NA
RACE BLACK []	Black/Afr. Amercian factor on CL	0.922	0.849	0.995	4	NA	NA
RACE ASIAN []	Asian factor on CL	0.951	0.91	0.99	2.22	NA	NA
RENAL IMP. []	Mild-Mod renal imp. factor on CL	0.962	0.941	0.987	1.27	NA	NA
ETHNICITY HISPANIC []	Hispanic factor on CL	1.1	1.06	1.15	2.38	NA	NA
AGE65 CL []	Age (above 65) factor on CL	0.972	0.944	0.998	1.34	NA	NA

Absorption

The pharmacokinetics of 2 mg semaglutide has been characterised in the patients with type 2 diabetes, the intended target population. No healthy volunteer studies have been conducted with the 2mg dose. The observed semaglutide concentrations in phase 3 trial (NN9535-4506) are presented in (See Figure 2).

Figure 2. Observed semaglutide concentrations and model predictions versus time since first dose by planned treatment dose. (Pop PK of trial NN9535-4506)
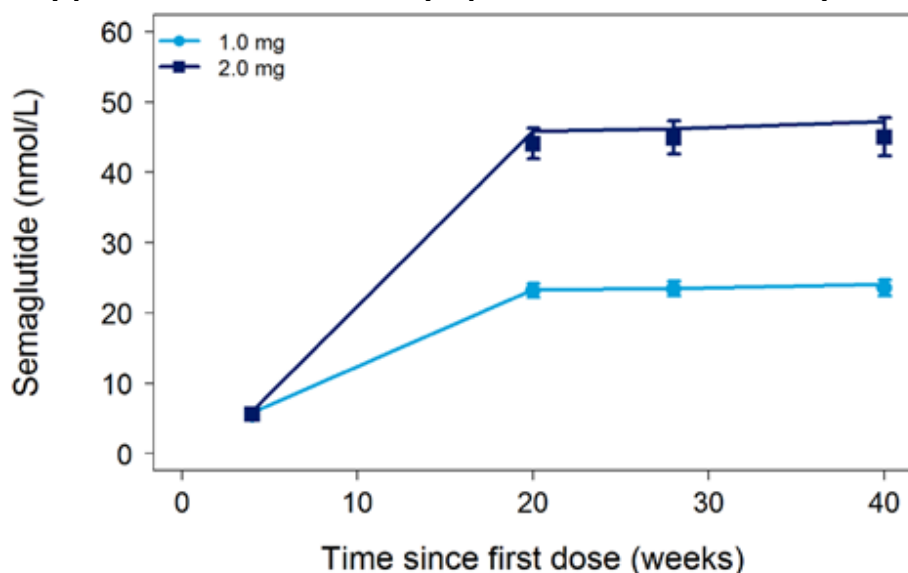
Points with error bars are geometric mean observations with 95% CIs. Lines are geometric mean population predictions for the corresponding observations obtained from the final population PK model

Study **NN9535-3687** investigated and compared the pharmacokinetics of following s.c. injection of 0.5 mg semaglutide with three different concentrations semaglutide (1 mg/mL, 3 mg/mL, and 10 mg/mL). Equivalence between semaglutide 1 mg/mL and 3 mg/mL was demonstrated for overall exposure (AUC_{0-inf}) and for C_{max}. 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}.

Distribution

No new information has been provided.

Elimination

No new information has been provided.

Dose proportionality and time dependencies

Dose proportionality

Dose proportionality was evaluated in the population pharmacokinetic analyses of the pivotal phase 3 trial. The geometric mean average concentration was estimated to be 27 nM [range: 14-56 nM] for the 1.0 mg and 54 nM [range: 28-102 nM] for the 2.0 mg dose.

Time dependency

During the Ozempic programme, it was shown that semaglutide steady-state exposure is stable over time, with accumulation ratios of approximately 2. Bodyweight was identified as the most influential covariate affecting semaglutide plasma exposure.

Variability

The population pharmacokinetic analyses of the pivotal phase 3 trial, based on trough concentrations, estimated an approximately 13.9% between-subject variability in AUC. Within-subject variability is

estimated to be 25.0% (CV), which was based on the residual error model of the population pharmacokinetic model.

Special populations

No new covariates have been identified in the population pharmacokinetic model for the 2.0 mg dose. Bodyweight was the predominant factor influencing the pharmacokinetics of semaglutide. Therefore, no new information is described here.

Pharmacokinetic interaction studies

The applicant conducted two studies to investigate het effect on gastrointestinal emptying, study **NN9535-3685** with semaglutide 1.0 mg and **NN9536-4455** with semaglutide 2.4 mg (to support the weight management indication), see tables below.

Table 2. Effect of semaglutide on gastric emptying – paracetamol AUC and C_{max} – primary analysis and *post-hoc* analysis – trial 4455

	Estimate	95% CI	p-value
PRIMARY ANALYSIS			
AUC paracetamol, 0–5h (ug*h/mL) Treatment ratio Sema 2.4 mg / Placebo	1.08	[1.02 ; 1.14]	0.0054
AUC paracetamol, 0–1h (ug*h/mL) Treatment ratio Sema 2.4 mg / Placebo	0.99	[0.87 ; 1.12]	0.8474
Cmax paracetamol, 0–5h (ug/mL) Treatment ratio Sema 2.4 mg / Placebo	0.94	[0.82 ; 1.07]	0.3299
POST-HOC ANALYSIS – adjusting for body weight at week 20			
AUC paracetamol, 0–5h (ug*h/mL) Treatment ratio Sema 2.4 mg / Placebo	1.05	[0.99 ; 1.12]	0.1218
AUC paracetamol, 0–1h (ug*h/mL) Treatment ratio Sema 2.4 mg / Placebo	0.94	[0.82 ; 1.06]	0.3069
Cmax paracetamol, 0–5h (ug/mL) Treatment ratio Sema 2.4 mg / Placebo	0.90	[0.79 ; 1.04]	0.1464

AUC: area under the curve; CI: confidence interval; Cmax: maximum concentration; Sema: semaglutide; tmax: time of maximum observed concentration.

Table 3. Effect of semaglutide on gastric emptying – paracetamol AUC and C_{max} – trial NN9535-3685

	FAS	N	Estimate	95% CI	p-value
Cmax paracetamol, 0–5h (ug/mL) Mean					
Sema 1.0 mg	30	28	13.44	[11.74 ; 15.38]	
Placebo	28	28	17.43	[15.23 ; 19.95]	
Treatment ratio					
Sema 1.0 mg / placebo			0.77	[0.67 ; 0.88]	0.0006
AUC paracetamol, 0–1h (ug*h/mL) Mean					
Sema 1.0 mg	30	28	8.68	[7.26 ; 10.38]	
Placebo	28	28	11.94	[9.98 ; 14.28]	
Treatment ratio					
Sema 1.0 mg / placebo			0.73	[0.61 ; 0.87]	0.0012
AUC paracetamol, 0–5h (ug*h/mL) Mean					
Sema 1.0 mg	30	28	37.94	[34.35 ; 41.91]	
Placebo	28	28	40.24	[36.43 ; 44.44]	
Treatment ratio					
Sema 1.0 mg / placebo			0.94	[0.88 ; 1.01]	0.1081

N: Number of subjects contributing to analysis, CI: Confidence interval, AUC: Area under the curve, Cmax: Maximum concentration, Subjects received 1500 mg paracetamol as part of the standardised breakfast.

2.6.2.2. Pharmacodynamics

No new information has been provided on the primary and secondary pharmacodynamics of semaglutide.

2.6.3. Discussion on clinical pharmacology

The higher maintenance dose of semaglutide 2.0 mg once-weekly s.c. is delivered as in a prefilled disposable pen-injector belonging to the same PDS290 technology platform as the existing Ozempic doses. The concentration of the to-be-marketed product (for the 2.0 mg dose) is 2.68 mg/ml.

In the pivotal phase 3 trial (**NN9535-4506**) this product was not administered. Instead, two injections of 1.0 mg (1.34 mg/mL) were administered. The switch to the to-be-marketed product 2.0 mg (2.68 mg/ml) is not expected to significantly influence the pharmacokinetics of semaglutide based on the results of the bioequivalence trial **NN9535-3687**. In this trial, different concentrations of semaglutide were evaluated at the same dose level of 0.5mg semaglutide. Bioequivalence between semaglutide 1 mg/mL and 3 mg/mL was demonstrated for overall exposure (AUC_{0-inf}) and C_{max}. Therefore, it can be considered reasonable that the proposed 2 mg dose with the 2.68 mg/mL formulation will provide equivalent exposures as the double administration of 1 mg dose with the 1.34 mg/mL formulations.

Based on trough concentrations after treatment with 1 mg and 2 mg dose of semaglutide in the phase 3 trial (NN9535-4506) and the previously conducted bioequivalence trial NN9535-3652, it can be concluded that semaglutide steady-state exposure (AUC and Cmax) increased approximately proportionally with the dose, in the dose range of 0.25-2.0 mg semaglutide.

During the Ozempic programme, it was shown that semaglutide steady-state exposure is stable over time with accumulation ratios of approximately 2 (study NN9535-3634). Bodyweight was identified as the most influential covariate affecting semaglutide plasma exposure.

As requested, the applicant provided an estimate of the within-subject variability of semaglutide 2 mg dose. The within-subject variability has been estimated using the population pharmacokinetic model. A proportional residual error model was used. The within-subject variability of semaglutide for the 2 mg dose is estimated to be about 25%, which is in line with previous observations in the SUSTAIN programme with a within-subject variability of 24% for the existing Ozempic doses (0.25, 0.5, and 1.0 mg/week).

The pharmacokinetics of semaglutide in patients with type 2 diabetes have been characterised for the 0.25, 0.5 and 1.0 mg dosages in previous Ozempic trials and up to 2.0-mg in pivotal phase 3 trial (NN9535-4506). The results in patients with type 2 diabetes are comparable between trials. No new covariates have been identified in the population pharmacokinetic model for the 2.0 mg dose. Bodyweight was the predominant factor influencing the pharmacokinetics of semaglutide. No differences in the pharmacokinetics of the higher 2.0 mg dose are to be expected as dose proportionality is demonstrated for the 2.0 mg.

Several drug-drug interaction studies were conducted in the clinical development program of 0.25, 0.5 and 1.0 mg semaglutide. In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters. The potential of semaglutide to delay gastric emptying may influence the absorption of concomitantly administered oral medical products.

No new drug-drug interaction studies have been provided for the 2.0 mg formulation. Upon request, the applicant justified that the potential effect of semaglutide 2.0 mg on the absorption of oral medicines is anticipated not to exceed that of semaglutide 1.0 mg. The applicant conducted two studies to investigate het effect on gastrointestinal emptying, study **NN9535-3685** with semaglutide 1.0 mg and **NN9536-4455** with semaglutide 2.4mg (to support the weight management indication). Based on data from these trials, semaglutide 2.4 mg (assessed at week 20) did not appear to further delay gastric emptying compared to semaglutide 1.0 mg (assessed at week 12). Accordingly, the influence the absorption of concomitantly administered oral medical products is expected to be similar between the existing 1.0 mg and the higher 2.0 mg dose level.

Upon request, the applicant assessed whether an increased incidence of anti-drug antibodies can be expected due to the higher 2.0 mg dose. In the SUSTAIN programme, the frequencies of antibody positive subjects for the existing Ozempic 1.0 mg were between 0% and 3.2%, and in study NN9536 with semaglutide 2.4 mg dose, for the weight management indication, 3% of subjects developed anti-semaglutide antibodies. As the incidence of ADAs was low and comparable between the different dose levels and no impact on efficacy and safety was observed, the incidence and impact of anti-drug antibodies is expected to be low with the semaglutide 2.0 mg dose as well.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of semaglutide 2.0 mg once-weekly s.c. has been appropriately characterised.

2.6.5. Clinical efficacy

Data from Trial 4506 is the pivotal study of efficacy and safety with semaglutide 2.0 mg.

The following data provide supportive evidence for this application:
Trial 3687: trial supporting the comparability of the intended *to-be-marketed* drug product for semaglutide 2.0 mg (semaglutide drug product concentration: 2.68 mg/mL) with the semaglutide drug product used in Trial 4506 (semaglutide drug product concentration: 1.34 mg/mL). Trial 3687 was submitted to the EMA.

Trial 4191: phase 2 dose-finding trial: Supportive evidence of safety is available from the clinical development programme for semaglutide 2.4 mg in weight management (STEP), comprising 4 phase 3a therapeutic confirmatory trials. One of the 4 trials in the programme investigated the efficacy and safety of semaglutide 2.4 mg in subjects with obesity or overweight and with T2D as a comorbidity (NN9536-4374, STEP 2).

2.6.5.1. Dose response study(ies)

To explore the potential of higher semaglutide doses, the phase 2 Trial NN9535-4191 (hereafter referred to as Trial 4191) was conducted. In Trial 4191, once-daily semaglutide s.c. doses up to 0.3 mg (equivalent to ~2.1 mg once-weekly) were investigated in 705 subjects with T2D. After 26 weeks, dose dependent and clinically relevant reductions in HbA_{1c} and body weight were observed (Table 4). Once-daily semaglutide s.c. was well-tolerated with no new safety concerns identified.

Table 4. Effect of semaglutide doses on HbA_{1c} and body weight – Trial 4191

Semaglutide s.c. OD dose	N	HbA_{1c}			Body weight		
		Baseline (%)	Week 26 (%)	Δ (%-point)	Baseline (kg)	Week 26 (kg)	Δ (kg)
0.05 mg	64	7.9	7.0	-1.1	93.4	91.4	-2.8
0.1 mg	63	7.9	6.7	-1.4	92.4	89.8	-4.4
0.2 mg	65	8.0	6.4	-1.7	98.1	87.5	-6.7
0.3 mg	63	8.2	6.2	-1.9	94.8	86.0	-8.2

Observed mean at baseline. Estimated mean at week 26. Δ: estimated change from baseline to week 26; OD: once-daily N: number of subjects.

Data from Trial 4191 and the SUSTAIN trials were included in the exposure-response model, which supported the hypothesis of additional glucose lowering and body weight loss with higher dose levels of semaglutide. With dose increase from semaglutide 1.0 mg to 2.0 mg, a reduction in HbA1c of 0.26%-points was predicted. Therefore, the increment from semaglutide 1.0 mg to 2.0 mg was expected to provide clinically meaningful differentiation on glycaemic control, with a higher likelihood of more patients achieving glycaemic targets.

Semaglutide drug product intended *to-be-marketed* for semaglutide 2.0 mg

Ozempic is currently marketed with the drug product concentration 1.34 mg/mL which was used in Trial 4506 (Table 5). The intended *to-be-marketed* product for semaglutide 2.0 mg has a drug product concentration of 2.68 mg/mL with dose-volume retained at 0.74 mL (Table 5). In Trial 4506, semaglutide 2.0 mg was administered as 2 separate injections of 1.0 mg, with 0.74 mL dose volume each. Except for the semaglutide concentration, the composition of semaglutide drug product 2.68 mg/mL is identical to the current drug product for Ozempic (1.34 mg/mL), also used in Trial 4506.

Table 5. Semaglutide drug product in Trial 4506 versus the *to-be-marketed* drug product for semaglutide 2.0 mg

| Dose group | Trial 4506 | | *To-be-marketed* drug product | |
	Semaglutide DPC	Dose volume	Semaglutide DPC	Dose volume
1.0 mg	1.34 mg/mL	0.74 mL	Not applicable	Not applicable
2.0 mg	1.34 mg/mL	0.74 mL + 0.74 mL[a]	2.68 mg/mL	0.74 mL

[a] In Trial 4506, semaglutide 2.0 mg was administered as 2 doses (2 separate injections) of 1.0 mg each with 0.74 mL dose volume. DPC: drug product concentration

Comparability between drug product intended *to-be-marketed* for semaglutide 2.0 mg vs. drug product in Trial 4506

A previously conducted trial (NN9535-3687, hereafter referred to as Trial 3687) supports the comparability of the current semaglutide drug product 1.34 mg/mL (used in Trial 4506) to the semaglutide drug product (2.68 mg/mL), intended *to-be-marketed* for the semaglutide 2.0 mg dose (details below).

The composition of the semaglutide drug products (1.0 mg/mL, 3.0 mg/mL and 10 mg/mL) tested in Trial NN9535-3687 was identical to the current Ozempic product, and to the drug product *to-be-marketed* for semaglutide 2.0 mg, except for the semaglutide concentration.

Summary of Trial 3687

Trial 3687 was a randomised, two-period, incomplete cross-over trial in healthy subjects investigating if the comparison of different semaglutide drug product concentrations (1 mg/mL, 3 mg/mL, and 10 mg/mL) met the bioequivalence criterion concerning the total exposure after single s.c. injections. To support the change in semaglutide drug product concentration from 1.34 mg/mL to 2.68 mg/mL (for the semaglutide 2.0 mg dose), only the comparison between the semaglutide drug product concentrations 1.0 mg/mL and 3.0 mg/mL is relevant and therefore presented in this document.

For the comparison between semaglutide drug product concentrations, 1.0 mg/mL and 3.0 mg/mL, the 90% confidence intervals (CIs) of the treatment ratios were fully contained within the bioequivalence

limits of 80-125% for both the total exposure and C_{max}. The treatment ratios for semaglutide drug product concentrations 1.0 mg/mL: 3.0 mg/mL were:

$AUC_{0-\infty}$: 1.02 [0.99; 1.05]$_{90\%CI}$

C_{max}: 0.91 [0.84; 1.00]$_{90\%CI}$

Hence, the comparison between semaglutide drug product concentrations of 1.0 mg/mL and 3.0 mg/mL in Trial 3687 met the equivalence criterion. These data support comparability between the semaglutide drug product concentrations of 1.34 mg/mL (used in Trial 4506) and 2.68 mg/mL (*to-be-marketed* drug product for semaglutide 2.0 mg) as the concentration range is contained within the concentration range tested in Trial 3687.

Further, bridging the semaglutide drug product concentrations based on Trial 3687 is considered appropriate as semaglutide exposure increased in a dose-proportional manner from 1.0 mg (administered with 1.34 mg/mL) to 2.0 mg (administered as 2 doses of 1.0 mg, 1.34 mg/mL) based on population PK data from Trial 4506.

In summary, the results from Trial 3687 support the change in drug product concentration from that used in Trial 4506 (1.34 mg/mL) to that of the intended *to-be-marketed* drug product for semaglutide 2.0 mg (2.68 mg/mL).

2.6.5.2. Main study(ies)

Trial 4506

Methods

Trial design

Trial 4506 was a multinational, multi-centre, randomised, double-blind, two-armed, active-comparator trial with a 49-week trial period (incl. screening, dose-escalation, 40 weeks treatment and 7 weeks follow-up). The trial design is shown schematically in Figure 3.

A total of 961 adults with T2D were randomised 1:1 to treatment with once-weekly semaglutide 2.0 mg or 1.0 mg.

Figure 3. Trial design of trial 4506
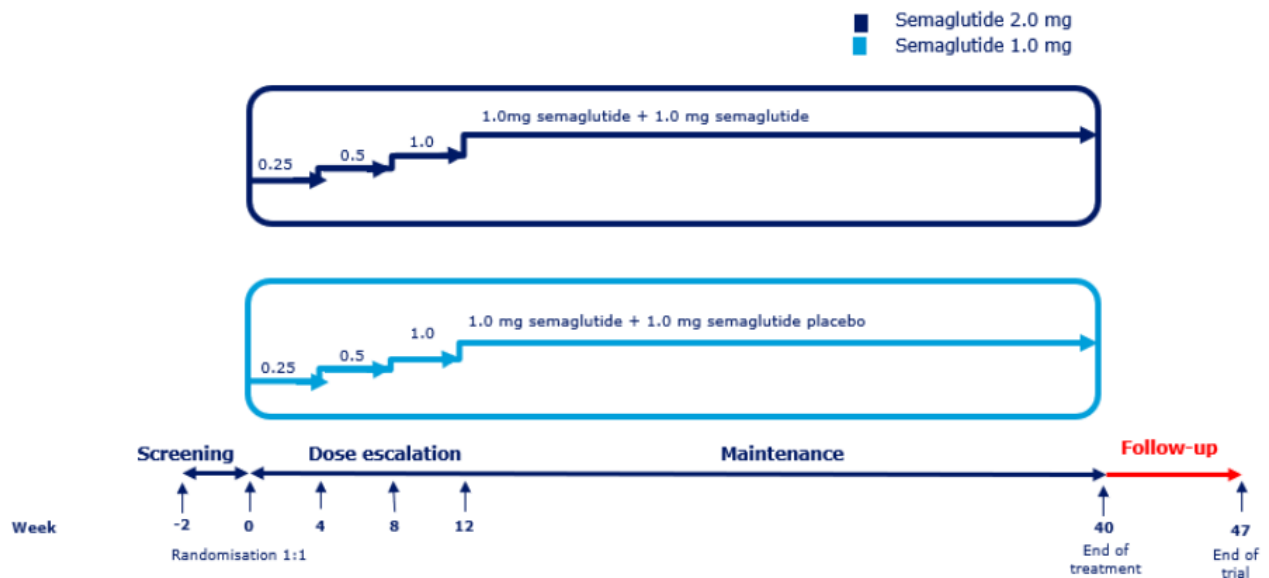
The trial was performed at 129 sites in 10 countries in Europe, North America and Asia (Japan). At baseline, randomisation was stratified by country (Japan/other).

- **Study Participants**

Subjects with T2D were enrolled in the trial.

Key inclusion and exclusion criteria are presented below. The complete list of eligibility criteria is provided in the trial protocol.

Inclusion criteria

- Male or female, age ≥18 years at the time of signing informed consent

- Diagnosed with T2D ≥180 days prior to the day of screening

- HbA$_{1c}$ of 8-10% (64−86 mmol/mol) (both inclusive)

- Stable daily dose(s) for 90 days prior to the day of screening of:

- Any metformin formulations (≥1500 mg or maximum tolerated or effective dose) alone or in combination with SU (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose)

Key exclusion criteria

Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes

Renal impairment measured as estimated glomerular filtration rate (eGFR) value of <30 mL/min/1.73 m2 according to CKD-EPI creatinine equation as defined by KDIGO 2012 classification

Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening

and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

- **Treatments**

Subjects were randomised 1:1 to receive treatment with (for a total of 2 weekly injections from week 12 onwards):

- semaglutide 1.0 mg + semaglutide 1.0 mg

- semaglutide 1.0 mg + placebo once weekly

- **Objectives / Outcomes/endpoints**

Objectives	Endpoints
Primary objective	Primary endpoint(s)
• To establish the superior effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with T2D, on a background of metformin with or without SU treatment.	Change from baseline (week 0) to week 40 in HbA_{1c} (%-point)
Secondary objectives	Secondary endpoints[a]
• To compare the effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly in subjects with T2D, on a background of metformin with or without SU treatment, on: Body weight Vital signs Hypoglycaemia General safety and tolerability	Change from baseline (week 0) to week 40 in body weight (kg)[#] Change from baseline (week 0) to week 40 in: 1 Fasting plasma glucose (FPG) (mmol/l) 2 Body mass index (BMI) (kg/m^2) 3 Waist circumference (cm) 4 HbA_{1c} < 7% at week 40 (yes/no) 5 HbA_{1c} ≤ 6.5% at week 40 (yes/no) 6 Weight loss ≥ 5% at week 40 (yes/no) 7 Weight loss ≥ 10% at week 40 (yes/no) 8 Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from first dose to week 40 9 Change from baseline (week 0) to week 40 in pulse (bpm)

a The confirmatory secondary endpoint is marked with a #, all other secondary endpoints are supportive secondary endpoints.

Estimands

Two estimand strategies were defined for this trial.

The hypothetical estimand strategy is considered the primary strategy, except in the US, where FDA has specifically requested the treatment policy estimand strategy to be the primary strategy.

For each endpoint, results based on the hypothetical estimand strategy will be presented first, followed by results based on the treatment policy estimand strategy where applicable.

Hypothetical estimand strategy

The hypothetical estimand addressing the primary objective was defined as the treatment difference in mean change from baseline to week 40 in HbA1c (%-point) of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised subjects with T2D, regardless of change in treatment dose and had they not discontinued treatment or initiated any rescue medication (anti-diabetic medications).

Other parameters that were evaluated by the hypothetical estimand strategy used the same hypothetical estimand as for the primary objective, however with "HbA1c (%)-point" replaced by the relevant parameter and unit.

Treatment policy estimand strategy

The treatment policy estimand addressing the primary objective was defined as the treatment difference in mean change from baseline to week 40 in HbA1c (%-point) of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised subjects with T2D, regardless of change in treatment dose, discontinuation of treatment and initiation of rescue medication (anti-diabetic medications).

Other parameters that were evaluated by the treatment policy estimand strategy used the same treatment policy estimand as for the primary objective, however with "HbA1c (%)-point" replaced by the relevant parameter and unit.

- **Sample size**

The sample size calculation was performed to ensure sufficient power for confirming superiority of once-weekly semaglutide 2.0 mg vs. once-weekly semaglutide 1.0 mg on change from baseline to week 40 in HbA1c (%-point) based on each estimand separately.

For the primary endpoint, an on-treatment HbA1c effect of -0.26%-point was predicted based on exposure-response modelling. The treatment policy estimand was assumed to reflect a 15% lower effect (based on results from the SUSTAIN phase 3a programme). With the adjusted HbA1c treatment effect of -0.22%-point and an SD of 1.1%-point, 964 randomised subjects would give 87% power to confirmed superiority of the primary endpoint based on the treatment policy estimand, and at least 87% power for confirming superiority for the primary endpoint based on the hypothetical estimand.

- **Randomisation and Blinding (masking)**

Blinding (masking)

The first 12 weeks during escalation all the trial products were packed open-label as all subjects followed the same treatment regimen in this period. From week 13, the subject was to receive the trial

product, which was packed open-label (which contained semaglutide), as well as the trial product which was packed blinded (and contained either semaglutide or placebo). The active drug and placebo drug were visually identical.

Randomisation

All subjects were centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product was dispensed/allocated at the trial visits summarised in the flowchart.

At screening, each subject was be assigned a unique 6-digit subject number which remained the same throughout the trial. Each site was assigned a 3-digit number and all subject numbers started with the site number.

- **Statistical methods**

An overview of statistical methods used for the analysis of trial 4506 is presented below.

Analysis sets and observation periods

Data selection for statistical analysis was selected first by the analysis population, and subsequently by events/data for those subjects based on the observation period.

For the evaluation of efficacy, one analysis set was defined:

Full analysis set: All randomised subjects. Subjects in the FAS were analysed according to the treatment to which they were assigned at randomisation.

For the evaluation of efficacy, the following observation periods were defined:

'On-treatment without rescue medication' observation period: this observation period is a sub-set of the 'on-treatment' observation period and represents the time period where subjects are considered treated with trial product but have not initiated any rescue medication. The observation period starts at the date of first dose of trial product and ends at the date of any of the following:

initiation of rescue medication

the date of last dose of trial product +14 days

'In-trial' observation period: This observation period is defined as the period from the date of randomisation to the first of the following dates, both inclusive:

Follow-up visit (P11)

Death

Subject withdrew informed consent

Last contact for subjects lost to follow-up

Confirmatory endpoints

Two confirmatory endpoints are defined in this trial

change from baseline (week 0) to week 40 in HbA$_{1c}$ (%-point)

change from baseline (week 0) to week 40 in body weight (kg)

For each estimand strategy, both endpoints were tested for superiority. The type-I error rate was controlled in the strong sense across the primary and confirmatory secondary hypotheses, separately for each estimand, at an overall two-sided alpha-level of 0.05.

The superiority of once-weekly semaglutide s.c. 2.0 mg versus once-weekly semaglutide s.c. 1.0 mg was evaluated hierarchically according to the sequence below (the treatment difference was defined as μ = [semaglutide 2.0 mg minus semaglutide 1.0 mg]):

1. Superiority of once-weekly semaglutide s.c. 2.0 mg versus 1.0 mg on change from baseline to week 40 in HbA1c
   H_0: $\mu \geq 0.0\%$-point against H_a: $\mu < 0.0\%$-point

2. Superiority of once-weekly semaglutide s.c. 2.0 mg versus 1.0 mg on change from baseline to week 40 in body weight
   H_0: $\mu \geq 0.0$ kg against H_a: $\mu < 0.0$ kg

Table 6. Statistical analyses of the confirmatory endpoints

Endpoint	Estimand	Analysis set	Observation period	Statistical model	Imputation approach	Sensitivity analysis
Primary endpoint						
Change in HbA1c (%-point)	Hypothetical	FAS	Ontreatment w/o rescue	ANCOVA	MAR within randomised treatment group	Tipping point analysis
	Treatment policy	FAS	In-trial	ANCOVA	MAR within group defined by randomised treatment and treatment status at week 40	One-way and two-way tipping point analyse
Confirmatory secondary endpoint						
Change in body weight (kg)	Hypothetical	FAS	Ontreatment w/o rescue	ANCOVA	MAR within randomised treatment group	Tipping point analysis
	Treatment policy	FAS	In-trial	ANCOVA	MAR within group defined by randomised treatment and treatment status at week 40	One-way and two-way tipping point analyse

Abbreviations: ANCOVA; analysis of covariance; FAS: full analysis set; MAR: missing at random

The primary (except US) hypothetical estimand was estimated based on FAS using post-baseline data collected up to and including week 40 from the 'on-treatment without rescue medication' observation period.

Imputation of missing data was handled by multiple imputation (MI), assuming that missing data were missing at random (MAR). The imputation was performed separately within each treatment group defined by randomised treatment. First, intermittent missing values were imputed using a Markov Chain Monte Carlo (MCMC) method, to obtain a monotone missing data pattern, generating 500 complete data sets. Secondly, a sequential conditional linear regression approach for imputing monotone missing values was implemented starting with the first visit after baseline and sequentially

continuing to the last planned visit at week 40. The model used for imputation included the baseline and post-baseline HbA1c values observed prior to the visit in question as covariates.

The 500 complete datasets were analysed using an analysis of covariance (ANCOVA) with treatment and stratification as fixed factors and the baseline HbA1c as a covariate. Rubin's rule was applied to obtain inference.

Results

- **Participant flow**

Of the 961 randomised subjects, 97.1% completed the trial and 92.5% completed treatment, equally balanced between the two treatment arms. Few subjects discontinued treatment due to AEs (4.6% and 4.4% in the semaglutide 1.0 mg and 2.0 mg arm, respectively). See Table 7 for details.

Table 7. Subject disposition - summary - all subjects

	Sema 1.0 mg		Sema 2.0 mg		Total	
	N	(%)	N	(%)	N	(%)
Screened					1515	
Screening failures					540	(35.6)
Not assigned					14	(0.9)
Randomised	481		480		961	
Exposed	480	(99.8)	479	(99.8)	959	(99.8)
Analysis sets						
Full analysis set	481	(100)	480	(100)	961	(100)
Safety analysis set	480	(99.8)	479	(99.8)	959	(99.8)
Treatment completers [1]	**447**	**(92.9)**	**442**	**(92.1)**	**889**	**(92.5)**
Without rescue medication	428	(89.0)	435	(90.6)	863	(89.8)
With rescue medication	19	(4.0)	7	(1.5)	26	(2.7)
Premature trial product discontinuation – primary reason	**34**	**(7.1)**	**38**	**(7.9)**	**72**	**(7.5)**
Exposed						
Adverse event(s)	22	(4.6)	21	(4.4)	43	(4.5)
Violation of inclusion and/or exclusion criteria	0		0		0	
Intention of becoming pregnant	0		0		0	
Participation in another clinical trial [2]	0		0		0	
Subject withdrawal from trial	3	(0.6)	6	(1.3)	9	(0.9)
Lost to follow-up	2	(0.4)	4	(0.8)	6	(0.6)
Pregnancy	0		0		0	
Other	6	(1.2)	6	(1.3)	12	(1.2)
Due to COVID-19	1	(0.2)	2	(0.4)	3	(0.3)
Other	5	(1.0)	4	(0.8)	9	(0.9)
Not exposed						
Violation of inclusion and/or exclusion criteria	1	(0.2)	0		1	(0.1)
Lost to follow-up	0		1	(0.2)	1	(0.1)
Trial completers [3]	**471**	**(97.9)**	**462**	**(96.3)**	**933**	**(97.1)**
Withdrawal from trial – primary reason	**10**	**(2.1)**	**18**	**(3.8)**	**28**	**(2.9)**
Lost to follow-up	3	(0.6)	10	(2.1)	13	(1.4)
Withdrawal by subject	6	(1.2)	6	(1.3)	12	(1.2)
Died	1	(0.2)	2	(0.4)	3	(0.3)

'Not assigned': subjects who are eligible to participate in the trial, but never randomised, '[1]': subjects who completed treatment with the trial product according to the end-of-trial form, '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product, '[3]': subjects who attended the final scheduled visit, 'primary reason': according to the end-of-trial form, 'Rescue medication' is defined as the use of new anti-diabetic medication as an add-on to trial product and used for more than 21 days with the initiation at or

after randomisation and before last day on trial product, and/or intensification of anti-diabetic medication (a more than 20% increase in dose relative to baseline) for more than 21 days with the intensification at or after randomisation and before last day on trial product, %: proportion of randomised subjects except for screening failures where it is the proportion of screened subjects.

- **Recruitment / Baseline data**

Subjects enrolled in this trial had a mean age of 58 years, mean HbA$_{1c}$ of 8.9%, mean duration of diabetes of 9.5 years and a mean body weight of 99.3 kg. Approximately 74% of subjects had a BMI ≥30 kg/m^2 and 58.6% of the population was male. At baseline, all subjects were treated with metformin, and approximately half of subjects were treated with SU.

- **Numbers analysed / Outcomes and estimation**

At the end of the treatment visit (week 40), 95.9% and 96.9% of treatment completers in the semaglutide 2.0 and 1.0 mg arm, respectively, were at target doses.

Overall, few subjects (2.9%) initiated rescue medication, predominantly constituting SU or SGLT2 inhibitor classes, during the course of the treatment. A greater proportion of subjects in the semaglutide 1.0 mg arm required the use of rescue medication compared to the semaglutide 2.0 mg arm (4.2% vs. 1.7% subjects).

Change in HbA$_{1c}$

Semaglutide 2.0 mg was superior to semaglutide 1.0 mg for the primary endpoint of change from baseline to week 40 in HbA$_{1c}$, as evaluated by the hypothetical and treatment policy estimands (Table 8).

Table 8. Change in HbA$_{1c}$ from baseline to week 40

	HbA$_{1c}$ (%)			Estimated treatment difference	p-value
	Baseline	Week 40	Δ		
Hypothetical estimand – on treatment without rescue medication observation period					
Semaglutide 2.0 mg	8.9	6.7	-2.2	-0.23% [-0.36;-0.11]$_{95\% CI}$	0.0003
Semaglutide 1.0 mg	8.8	6.9	-1.9		
Treatment policy estimand – in trial observation period					
Semaglutide 2.0 mg	8.9	6.8	-2.1	-0.18% [-0.31;-0.04]$_{95\% CI}$	0.0098
Semaglutide 1.0 mg	8.8	7.0	-1.9		

Observed mean at baseline. Estimated mean at week 40. Δ: estimated change from baseline to week 40 in %-point; CI: confidence intervals

The mean change in HbA$_{1c}$ over the duration of the trial for both treatment arms is presented in Figure 4 for the on-treatment without rescue medication observation period. The mean HbA$_{1c}$ values for the treatment arms started to separate after escalating to semaglutide 2.0 mg at week 12. A similar

pattern in HbA1c reduction over the duration of the trial was observed for the in-trial observation period.

Figure 4. HbA1c change from baseline by week - mean plot - observed and estimated - on-treatment without rescue medication - full analysis set
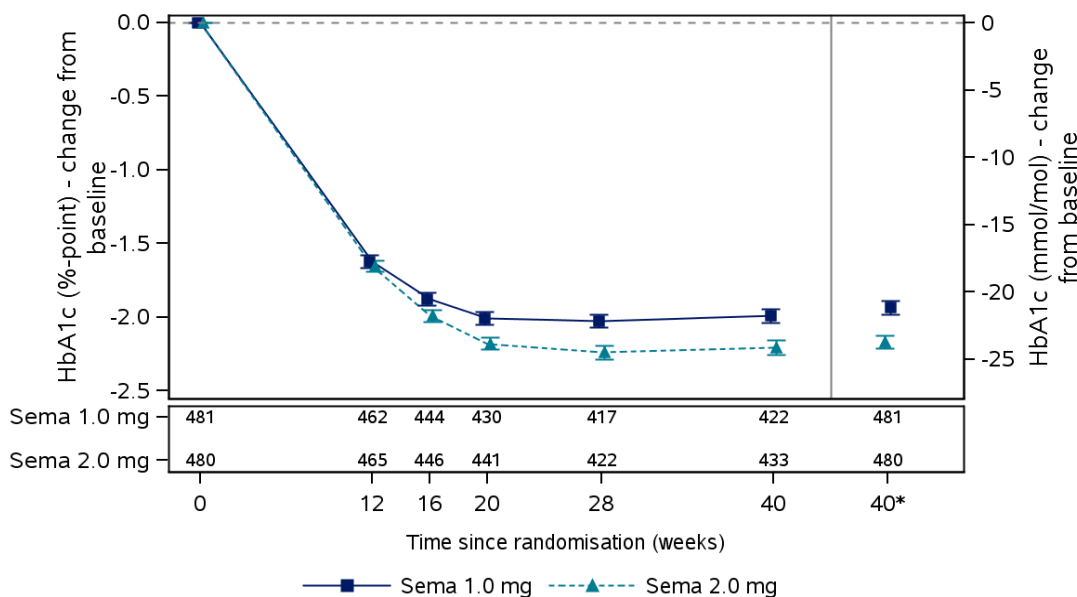
Data from the on-treatment without rescue medication period. Error bars are +/- standard error of the mean. '*': the estimated mean and the corresponding error bars are from the primary analysis. Numbers shown in the lower panel represent the number of subjects contributing to the means.

HbA1c <7.0% or ≤6.5%

At baseline, mean HbA1c was 8.9% and 8.8% in the semaglutide 2.0 and 1.0 mg treatment arms, respectively. A greater proportion of subjects achieved HbA1c target levels (ADA: <7.0% or AACE: ≤6.5%) at week 40 with semaglutide 2.0 mg compared to semaglutide 1.0 mg, as evaluated by the hypothetical estimand (Table 9). The odds of achieving HbA1c targets were statistically significant favouring semaglutide 2.0 mg, as evaluated using the hypothetical estimand (Table 9). Similar results were observed for HbA1c targets evaluated by the treatment policy estimand. (64.4% vs 55.8% for HbA1c<7%; 49.4% vs 37.1% for HbA1c <6.5%).

Table 9. Proportions of subjects achieving HbA1c targets at week 40

	• Proportion of subjects with HbA1c <7.0%	• Proportion of subjects with HbA1c ≤6.5%
• Hypothetical estimand – on-treatment without rescue medication observation period		
• Semaglutide 2.0 mg	• 67.6%	• 51.7%
• Semaglutide 1.0 mg	• 57.5%	• 38.5%
• Estimated odds ratio; p-value	• 1.60 [1.21; 2.13]95%CI; 0.0010	• 1.80 [1.36; 2.36]95%CI; <0.0001

HbA1c in subgroups

Semaglutide 2.0 mg provided consistently improved glycaemic control compared to semaglutide 1.0 mg across pre-specified dichotomous subgroups defined by baseline HbA1c and BMI (Figure 5) and across additional subgroups defined by intrinsic and extrinsic factors (Figure 6).

Figure 5. Change in HbA₁c from baseline to week 40 by pre-specified subgroups

Demographic or Disease Factor		ETD [95% CI] - % points	Semaglutide 2.0 mg, N	Semaglutide 1.0 mg, N
Hypothetical estimand – on treatment without rescue medication observation period				
HbA₁c (%)	<9.0	-0.20 [-0.37; -0.04]	282	278
	≥9.0	-0.28 [-0.48; -0.08]	198	203
BMI (kg/m²)	<30	-0.15 [-0.40; 0.10]	113	135
	≥30	-0.26 [-0.41; -0.11]	367	346
BMI (kg/m²)	<35	-0.28 [-0.45; -0.11]	280	281
	≥35	-0.17 [-0.37; 0.02]	200	200
Treatment policy estimand – in-trial observation period				
HbA₁c (%)	<9.0	-0.17 [-0.35; 0.01]	282	278
	≥9.0	-0.19 [-0.39; 0.02]	198	203
BMI (kg/m²)	<30	-0.09 [-0.36; 0.17]	113	135
	≥30	-0.20 [-0.36; -0.05]	367	346
BMI (kg/m²)	<35	-0.20 [-0.37; -0.03]	280	281
	≥35	-0.15 [-0.36; 0.06]	200	200

Scale: -1.0 — 0.0 — 1.0. ← Favours semaglutide 2.0 mg | Favours semaglutide 1.0 mg →

BMI: body mass index; ETD: estimated treatment difference; N: number of subjects contributing to the analysis

Figure 6. Change in HbA₁c from baseline to week 40 by intrinsic and extrinsic factors – hypothetical estimand

Demographic or Disease Factor		ETD [95% CI] - % points	Semaglutide 2.0 mg, N	Semaglutide 1.0 mg, N
Age (years)	<65	-0.23 [-0.38; -0.09]	342	348
	65-<75	-0.24 [-0.50; 0.02]	122	115
	≥75	-0.14 [-0.85; 0.58]	16	18
Sex	Female	-0.15 [-0.35; 0.05]	201	197
	Male	-0.29 [-0.45; -0.13]	279	284
BMI (kg/m²)	<25	-0.53 [-1.08; 0.02]	21	33
	25-<30	-0.06 [-0.34; 0.22]	92	102
	30-<35	-0.37 [-0.59; -0.15]	167	146
	≥35	-0.17 [-0.37; 0.02]	200	200
Body weight (kg)	<70	0.02 [-0.43; 0.48]	33	45
	70-<90	-0.28 [-0.53; -0.03]	117	144
	90-<110	-0.25 [-0.46; -0.05]	192	159
	≥110	-0.26 [-0.49; -0.02]	138	133
Race	White	-0.27 [-0.40; -0.13]	420	427
	Asian	-0.34 [-0.80; 0.13]	33	36
	Other	0.55 [-0.06; 1.15]	27	18
Ethnicity	Not Hispanic/Latino	-0.25 [-0.38; -0.11]	428	422
	Hispanic/Latino	-0.10 [-0.48; 0.27]	52	59
HbA₁c (%)	<8.0%	-0.29 [-0.83; 0.26]	29	25
	8.0 -<8.5%	-0.24 [-0.50; 0.03]	98	120
	8.5 -<9.0%	-0.18 [-0.41; 0.05]	155	133
	9.0 -<9.5%	-0.23 [-0.49; 0.04]	99	119
	≥9.5%	-0.32 [-0.61; 0.02]	99	84
Diabetes duration (years)	<10	-0.26 [-0.42; -0.10]	298	270
	≥10	-0.18 [-0.38; 0.02]	182	211
Renal function (mL/min/1.73 m²)	Normal	-0.24 [-0.40; -0.08]	316	309
	Mild impairment	-0.23 [-0.46; 0.0]	150	147
	Moderate impairment	-0.20 [-0.89; 0.48]	14	25
Region	North America	-0.14 [-0.36; 0.08]	158	171
	Europe	-0.26 [-0.42; -0.10]	297	285
	Asia (Japan)	-0.48 [-1.02; 0.06]	25	25

Scale: -2.0 — -1.0 — 0.0 — 1.0 — 2.0. ← Favours semaglutide 2.0 mg | Favours semaglutide 1.0 mg →

Data from the on-treatment without rescue medication observation period analysed using the hypothetical estimand strategy.

BMI: body mass index; ETD: estimated treatment difference; N: number of subjects contributing to the analysis.

Fasting plasma glucose

The reduction in FPG was consistent with the observed reduction in HbA$_{1c}$. The change from baseline to week 40 in mean FPG levels was statistically significantly greater with semaglutide 2.0 mg compared to semaglutide 1.0 mg as evaluated by the hypothetical estimand (Table 10). However, the difference between semaglutide 2.0 mg and semaglutide 1.0 mg was not statistically significant as evaluated by the treatment policy estimand.

Table 10. Change in FPG from baseline to week 40

	Baseline mmol/L (mg/dL)	Week 40 mmol/L (mg/dL)	Δ mmol/L (mg/dL)	ETD mmol/L (mg/dL)	p-value
Hypothetical estimand – on treatment without rescue medication observation period					
Semaglutide 2.0 mg	10.7 (193.0)	7.4 (133.3)	-3.4 (-61.1)	-0.327 [-0.614 ; -0.039]$_{95\%CI}$ (-5.89 [-11.06 ; -0.71]$_{95\%CI}$)	0.0259
Semaglutide 1.0 mg	10.9 (195.9)	7.7 (139.2)	-3.1 (-55.3)		
Treatment policy estimand – in trial observation period					
Semaglutide 2.0 mg	10.7 (193.0)	7.5 (135.8)	-3.3 (-58.6)	-0.213 [-0.520; 0.093]$_{95\%CI}$ (-3.85 [-9.36; 1.67]$_{95\%CI}$)	0.1717
Semaglutide 1.0 mg	10.9 (195.9)	7.8 (139.6)	-3.0 (-54.8)		

Observed mean at baseline. Estimated mean at week 40. Δ: estimated change from baseline to week 40; CI: confidence intervals; ETD: estimated treatment difference.

Body weight

Change in body weight

Semaglutide 2.0 mg was superior to semaglutide 1.0 mg for the secondary confirmatory endpoint of change from baseline to week 40 in body weight as evaluated by the hypothetical estimand; however, superiority could not be confirmed with the treatment policy estimand (Table 11).

Table 11. Change in body weight from baseline to week 40

	Body weight (kg)			Estimated treatment difference	p-value
	Baseline	Week 40	Δ		
Hypothetical estimand – on treatment without rescue medication observation period					
Semaglutide 2.0 mg	100.1	92.4	-6.9	-0.93 [-1.68; -0.18]$_{95\%CI}$	0.0155
Semaglutide 1.0 mg	98.6	93.3	-6.0		
Treatment policy estimand – in trial observation period					
Semaglutide 2.0 mg	100.1	92.9	-6.4	-0.77 [-1.55; 0.01]$_{95\%CI}$	0.0535

	Body weight (kg)			Estimated treatment difference	p-value
	Baseline	Week 40	Δ		
Semaglutide 1.0 mg	98.6	93.7	-5.6		

Observed mean at baseline. Estimated mean at week 40. Δ: estimated change from baseline to week 40; CI: confidence intervals

Body weight decreased to a larger extent with semaglutide 2.0 mg than with semaglutide 1.0 mg after escalation to semaglutide 2.0 mg at week 12. Mean body weight continued to show a downward trend at the last treatment visit for both treatment arms (Table 12). A similar pattern in body weight reduction over the duration of the trial was observed for the in-trial observation period.

Table 12. Body weight change from baseline by week - mean plot - observed and estimated - on-treatment without rescue medication - full analysis set
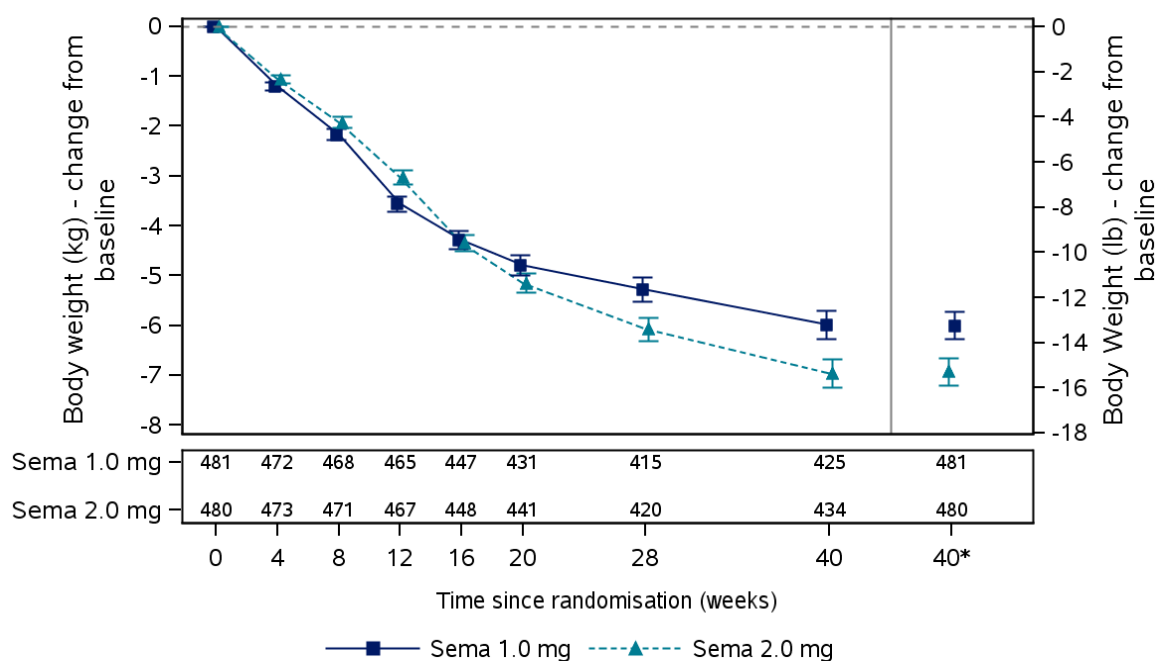
Data from the on-treatment without rescue medication period. Error bars are +/- standard error of the mean. '*': the estimated mean and the corresponding error bars are from the primary analysis. Numbers shown in the lower panel represent the number of subjects contributing to the means.

Body weight loss ≥5% or ≥10.0%

At baseline, the mean body weight was 100.1 kg and 98.6 kg in the semaglutide 2.0 and 1.0 mg treatment arms, respectively. A greater proportion of subjects achieved weight loss ≥5% or ≥10.0% at week 40 with semaglutide 2.0 mg compared to semaglutide 1.0 mg. The odds of achieving body weight loss ≥5.0% or ≥10.0% were statistically significant in favour of semaglutide 2.0 mg as evaluated using the hypothetical estimand strategy (Table 13). Statistical analysis using the treatment policy estimand was not performed.

Table 13. Proportions of subjects achieving body weight loss ≥5.0% or ≥10.0% at week 40 – hypothetical estimand

• Parameter	• Proportion of subjects with body weight loss ⩾ 5.0%	• Proportion of subjects with body weight loss ⩾ 10.0%
• Semaglutide 2.0 mg	• 59.2%	• 28.4%
• Semaglutide 1.0 mg	• 51.3%	• 22.6%
• Estimated odds ratio; p-value	• 1.41 [1.08; 1.84]$_{95\%CI}$; 0.0115	• 1.40 [1.03; 1.90]$_{95\%CI}$; 0.0314

Data based on the on-treatment without rescue medication observation period analysed using the hypothetical estimand strategy

Blood pressure

After 40 weeks of treatment, a reduction in blood pressure was observed for both doses of semaglutide, with the reduction in systolic blood pressure being clinically meaningful (Table 14).

Table 14. Change in blood pressure from baseline to week 40

	• Baseline	• Week 40	• Δ
• Diastolic blood pressure (mmHg)			
• Semaglutide 2.0 mg	• 81.3	• 80.6	• -0.8
• Semaglutide 1.0 mg	• 80.4	• 80.3	• -0.4
• Systolic blood pressure (mmHg)			
• Semaglutide 2.0 mg	• 134.3	• 129.3	• -5.3
• Semaglutide 1.0 mg	• 134.5	• 130.4	• -4.5

Baseline, week 40 and Δ: observed mean values presented; Data from the on-treatment without rescue medication observation period; Δ: change from baseline to week 40.

- **Summary of main efficacy results**

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 15. Summary of Efficacy for trial NN9535-4506

Title	Efficacy and safety of semaglutide 2.0 mg s.c. once-weekly compared to semaglutide 1.0 mg s.c. once-weekly in subjects with type 2 diabetes
Study identifier	Trial ID: NN9535-4506 UTN: U1111-1224-5162 www.clinicaltrials.gov identifier: NCT03989232 EudraCT number: 2018-004529-96
Data cut-off date	20 November 2020
Design	This was a multinational, multi-centre, randomised, double-blind, two-armed, active-comparator trial with a 49-week trial period (incl. screening, dose escalation, treatment and follow-up).

	Duration of main phase:	The trial period was 49 weeks with 2 weeks screening period. The treatment duration of the trial was 40 weeks, with an additional 7 weeks of follow-up.

Hypotheses	**Primary objective:**
	
	 • To establish the superior effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with T2D, on a background of metformin with or without SU treatment.
	
	 Secondary objectives:
	
	 • To compare the effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly in subjects with T2D, on a background of metformin with or without SU treatment, on
	     o body weight
	     o vital signs
	     o hypoglycaemia
	     o general safety and tolerability	

Treatments groups	Semaglutide 2.0 mg	480 randomised subjects
	Semaglutide 1.0 mg	481 randomised subjects
Endpoints and definitions	**Primary endpoint:** Change from baseline (week 0) to week 40 in HbA$_{1c}$ (%-point)	
	Confirmatory secondary endpoint: Change from baseline (week 0) to week 40 in body weight (kg)	

	Supporting secondary endpoints:
	
	 • Change from baseline (week 0) to week 40 in:
	     o Fasting plasma glucose (FPG) (mmol/l)
	     o Body mass index (BMI) (kg/m2)
	     o Waist circumference (cm)
	 • HbA$_{1c}$<7% at week 40 (yes/no)
	 • HbA$_{1c}$≤6.5% at week 40 (yes/no)
	 • Weight loss≥5% at week 40 (yes/no)
	 • Weight loss≥10% at week 40 (yes/no)
	 • Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from first dose to week 40
	 • Change from baseline (week 0) to week 40 in pulse (bpm)	

	Data from all randomised subjects in the FAS were included in the analyses. The presented results are for the hypothetical estimand which estimates the absolute treatment difference in mean change from baseline to week 40 of semaglutide 2.0 mg versus semaglutide 1.0 mg, both as an add-on to metformin with or without SU, in all randomised subjects with T2D, regardless of change in treatment dose and had they not discontinued treatment or initiated any rescue medication (anti-diabetic medications). Continuous endpoints were analysed using a linear regression (ANCOVA) model with treatment and stratification factor as fixed factors and baseline value as covariate applying Rubin's rule to draw inference. The ETD between semaglutide 2.0 mg and semaglutide 1.0 mg was reported together with the associated two-sided 95% CI and corresponding p-value.	
Results and Analysis		
Analysis description	**Primary Analysis Hypothetical estimand**	
Analysis set	The full analysis set included all randomised subjects	

Results		Semaglutide 1.0 mg	Semaglutide 2.0 mg
	Number of subjects (FAS)	481	480
	Change in HbA$_{1c}$ (%-points)	-1.9 (95% CI -3.4 ; -0.1)	-2.2 (95% CI -3.7 ; -0.4)
	ETD		-0.23
	95% CI		-0.36; -0.11
	P-value (ANCOVA)		0.0003
Analysis description	**Secondary confirmatory analysis**		
Analysis set	The full analysis set included all randomised subjects		
Results		Semaglutide 1.0 mg	Semaglutide 2.0 mg
	Number of subjects (FAS)	481	480
	Change in body weight (kg)	-6.0	-6.9
	ETD		-0.93
	95% CI		-1.68; -0.18
	P-value (ANCOVA)		0.0155
Analysis description	**Primary Analysis treatment policy estimand**		
Results		Semaglutide 1.0 mg	Semaglutide 2.0 mg
	Change in HbA$_{1c}$ (%-points)	-1.9	-2.2
	ETD		-0.18
	95% CI		-0.31; -0.04
	P-value (ANCOVA)		0.0098
Analysis description	**Primary Analysis treatment policy estimand**		
Results		Semaglutide 1.0 mg	Semaglutide 2.0 mg
	Change in body weight (kg)	-5.6	-6.4
	ETD		-0.77
	95% CI		-1.55; -0.01
	P-value (ANCOVA)		0.0535

2.6.5.3. Clinical studies in special populations

No new covariates have been identified in the population pharmacokinetic model for the 2.0 mg dose (under 'Pharmacokinetics').

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

To explore the potential of higher semaglutide doses, the phase 2 Trial NN9535-4191 (hereafter referred to as Trial 4191) was conducted. In Trial 4191, once-daily semaglutide s.c. doses up to 0.3 mg (equivalent to ~2.1 mg once-weekly) were investigated in 705 subjects with T2D.

Data from Trial 4191 and the SUSTAIN trials were included in the exposure-response model. With dose increase from semaglutide 1.0 mg to 2.0 mg, a reduction in HbA1c of 0.26%-points was predicted. In addition, an additional reduction in body weight of a least 2.5 kg is to be expected.

Trial 4506 was a multinational, multi-centre, randomised, double-blind, two-armed, active-comparator trial with a 49-week trial period (incl. screening, dose-escalation, 40 weeks treatment and 9 weeks follow-up). A total of 961 adults with T2D were randomised 1:1 to treatment with once-weekly semaglutide 2.0 mg or 1.0 mg. Subjects with T2D were enrolled in the trial (HbA1c of 8-10%). Patients were treated with metformin alone or in combination with SU. The trial design is acceptable, the primary objective was to establish the superior effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with T2D, on a background of metformin with or without SU treatment.

- Secondary objectives were to compare the effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly in subjects with T2D, on a background of metformin with or without SU treatment, on: body weight, vital signs, hypoglycaemia and general safety and tolerability.

Of the 961 randomised subjects, 97.1% completed the trial and 92.5% completed treatment, equally balanced between the two treatment arms.

Subjects enrolled in this trial had a mean age of 58 years, mean HbA1c of 8.9%, mean duration of diabetes of 9.5 years and a mean body weight of 99.3 kg. Approximately 74% of subjects had a BMI ≥30 kg/m2, and 58.6% of the population was male. Characteristics were comparable between treatment groups. Baseline HbA1c was somewhat higher than that in most other studies with semaglutide.

Overall, few subjects (2.9%) initiated rescue medication, predominantly constituting SU or SGLT2 inhibitor classes, during the course of the treatment. A greater proportion of subjects in the semaglutide 1.0 mg arm required use of rescue medication compared to the semaglutide 2.0 mg arm (4.2% vs. 1.7% subjects).

Efficacy data and additional analyses

The estimated mean HbA1c reduced to 6.7% from a relatively high baseline value of 8.9% (estimated mean change from baseline of -2.2%-point, hypothetical estimand). Comparatively, in the semaglutide 1.0 mg arm, the estimated mean change from baseline was -1.9%-point. Similar results were observed using the treatment policy estimand strategy. The estimated treatment difference in HbA1c reduction between 1.0 and 2.0 mg was modest (0.23%, hypothetical estimand; 0.18%, treatment policy estimand), especially when the relatively high baseline HbA1c is taken into account. A modest additional proportion of subjects achieved HbA1c target levels at week 40 with semaglutide 2.0 mg compared to semaglutide 1.0 mg (treatment estimand 64.4% vs 55.8% for target HbA1c<7%).

Semaglutide 2.0 mg was superior to semaglutide 1.0 mg for the secondary confirmatory endpoint of change from baseline to week 40 in body weight as evaluated by the hypothetical estimand (-0.93 [-1.68; -0.18]95%CI, p=0.0155). However, superiority could not be confirmed with the treatment policy estimand (-0.77 [-1.55; 0.01]95%CI, p=0.0535). The reduction in body weight of 0.8-0.9 kg is less than expected from the dose-finding study (-2.5 kg).

After 40 weeks of treatment, a reduction in blood pressure was observed for both doses of semaglutide. There were no relevant differences between the 1.0 mg and the 2.0 mg dose.

Trial 3687 was a randomised, two-period, incomplete cross-over trial in healthy subjects investigating if comparison of different semaglutide drug product concentrations (1 mg/mL, 3 mg/mL, and 10 mg/mL) met the bioequivalence criterion with respect to the total exposure after single s.c. injections.

These data support comparability between the semaglutide drug product concentrations of 1.34 mg/mL (used in Trial 4506) and 2.68 mg/mL (to-be-marketed drug product for semaglutide 2.0 mg) as the concentration range is contained within the concentration range tested in Trial 3687.

2.6.7. Conclusions on the clinical efficacy

The estimated treatment difference in HbA1c reduction between 1.0 and 2.0 mg was modest (approximately 0.2%), especially when the relatively high baseline HbA1c is taken into account. In general, results with respect to HbA1c were similar across pre-specified subgroups.

Semaglutide 2.0 mg was statistically superior to semaglutide 1.0 mg for body weight as evaluated by the hypothetical estimand; however, superiority could not be statistically confirmed with the treatment policy estimand.

2.6.8. Clinical safety

Safety methodology

The safety evaluation is based on the safety analysis set (SAS) primarily using the on-treatment observation period as this represents the period when subjects were considered exposed to the trial product. The in-trial observation period was used for deaths and adverse events (AEs) related to the safety focus areas with potentially long latency between onset and diagnosis.

2.6.8.1. Patient exposure

Exposure was defined as the time from first date to last date of dose of trial product plus the ascertainment window of 49 days (both dates inclusive).

A total of 959 subjects were exposed to trial products, with 479 subjects exposed to semaglutide 2.0 mg and 480 subjects to semaglutide 1.0 mg. The duration of exposure and observation based on the on-treatment and in-trial observation periods, respectively, was comparable between the treatment arms:

semaglutide 2.0 mg: 409.9 PYE and 431.0 PYO

semaglutide 1.0 mg: 411.2 PYE and 433.7 PYO

2.6.8.2. Adverse events

An overview of AEs reported for the on-treatment observation period is presented in Table 16.

A slightly higher proportion of subjects experienced AEs in the semaglutide 2.0 mg treatment arm compared to the semaglutide 1.0 mg treatment arm; while the event rates were similar between the treatment arms:

- semaglutide 2.0 mg: 56.8% subjects; 189.1 events per 100 PYE

- semaglutide 1.0 mg: 52.3% subjects; 201.4 events per 100 PYE

No difference between the treatment arms was observed in terms of the proportion of subjects with SAEs, severe AEs or AEs leading to premature treatment discontinuation. In both treatment arms, the majority of the AEs were non-serious, of mild or moderate severity, and reported as recovered. The

steepest increase in the number of subjects reporting their first AE was during the dose-escalation period.

Table 16. Overview of adverse events – on-treatment

	Sema 1.0 mg				Sema 2.0 mg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	480				479				959			
Exposure time (year)	411.2				409.9				821.1			
Events	251	(52.3)	828	201.4	272	(56.8)	775	189.1	523	(54.5)	1603	195.2
Serious												
Yes	25	(5.2)	40	9.7	21	(4.4)	29	7.1	46	(4.8)	69	8.4
No	241	(50.2)	788	191.6	264	(55.1)	746	182.0	505	(52.7)	1534	186.8
Severity												
Severe	26	(5.4)	37	9.0	19	(4.0)	29	7.1	45	(4.7)	66	8.0
Moderate	111	(23.1)	216	52.5	108	(22.5)	194	47.3	219	(22.8)	410	49.9
Mild	199	(41.5)	575	139.8	215	(44.9)	552	134.7	414	(43.2)	1127	137.3
Relationship to trial product												
Probable	88	(18.3)	210	51.1	109	(22.8)	255	62.2	197	(20.5)	465	56.6
Possible	84	(17.5)	159	38.7	105	(21.9)	164	40.0	189	(19.7)	323	39.3
Unlikely	195	(40.6)	459	111.6	180	(37.6)	356	86.9	375	(39.1)	815	99.3
Outcome												
Fatal	1	(0.2)	1	0.2	2	(0.4)	2	0.5	3	(0.3)	3	0.4
Not recovered	93	(19.4)	156	37.9	98	(20.5)	152	37.1	191	(19.9)	308	37.5
Recovered with seq.	0				3	(0.6)	3	0.7	3	(0.3)	3	0.4
Recovering	9	(1.9)	10	2.4	3	(0.6)	3	0.7	12	(1.3)	13	1.6
Recovered	220	(45.8)	660	160.5	236	(49.3)	614	149.8	456	(47.5)	1274	155.2
Unknown	1	(0.2)	1	0.2	1	(0.2)	1	0.2	2	(0.2)	2	0.2
Leading to premature treatment discontinuation	22	(4.6)	22	5.4	21	(4.4)	21	5.1	43	(4.5)	43	5.2
Action taken												
Drug withdrawn	22	(4.6)	33	8.0	21	(4.4)	48	11.7	43	(4.5)	81	9.9
Drug interrupted	6	(1.3)	10	2.4	11	(2.3)	20	4.9	17	(1.8)	30	3.7
Dose reduced	17	(3.5)	33	8.0	22	(4.6)	43	10.5	39	(4.1)	76	9.3
Dose not changed	229	(47.7)	688	167.3	236	(49.3)	609	148.6	465	(48.5)	1297	158.0
Not applicable	33	(6.9)	64	15.6	38	(7.9)	55	13.4	71	(7.4)	119	14.5

MedDRA version 23.0.

'Relationship to trial product': as judged by the investigator, N: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, R: events per 100 years of exposure, seq.: sequelae.

As expected for the GLP-1 RA drug class, gastrointestinal disorders were the most frequently reported AEs in both treatment arms (Figure 7). For most system organ classes (SOCs), the proportions of subjects with events and the event rates with semaglutide 2.0 mg were similar to or lower than with semaglutide 1.0 mg. Compared to the semaglutide 1.0 mg arm, slightly more subjects in the semaglutide 2.0 mg arm reported AEs across SOCs of gastrointestinal disorders, metabolism and nutrition disorders, investigations, vascular disorders and blood and lymphatic system disorders (Figure 7). The most common AEs reported by ≥5.0% subjects by preferred terms (PTs) were nausea, diarrhoea, vomiting, decreased appetite and dyspepsia (Figure 8). The majority of the common AEs were non-serious, of mild or moderate severity, and with outcome reported as recovered.

Infections and infestations are the second most frequent AEs affecting 16.9% of the subjects in both treatment arms, i.e. there is no difference between the dosing groups. The listing by preferred terms are spread across a large number of different infections and infestations.

Figure 7. Adverse events by system organ class – on-treatment

System organ class	Semaglutide 1.0 mg (N=480; PYE=411.2) N (%)	E	R	Semaglutide 2.0 mg (N=479; PYE=409.9) N (%)	E	R
Gastrointestinal disorders	148 (30.8)	353	85.8	163 (34.0)	346	84.4
Infections and infestations	81 (16.9)	107	26.0	81 (16.9)	95	23.2
Metabolism and nutrition disorders	29 (6.0)	36	8.8	37 (7.7)	39	9.5
Investigations	21 (4.4)	27	6.6	29 (6.1)	36	8.8
Nervous system disorders	47 (9.8)	59	14.3	28 (5.8)	37	9.0
Eye disorders	22 (4.6)	23	5.6	26 (5.4)	30	7.3
Vascular disorders	14 (2.9)	14	3.4	22 (4.6)	24	5.9
General disorders and administration site conditions	22 (4.6)	26	6.3	21 (4.4)	25	6.1
Musculoskeletal and connective tissue disorders	33 (6.9)	44	10.7	18 (3.8)	22	5.4
Respiratory, thoracic and mediastinal disorders	16 (3.3)	18	4.4	17 (3.5)	23	5.6
Injury, poisoning and procedural complications	13 (2.7)	18	4.4	16 (3.3)	19	4.6
Skin and subcutaneous tissue disorders	13 (2.7)	15	3.6	14 (2.9)	15	3.7
Cardiac disorders	12 (2.5)	16	3.9	12 (2.5)	16	3.9
Renal and urinary disorders	16 (3.3)	21	5.1	12 (2.5)	13	3.2
Blood and lymphatic system disorders	4 (0.8)	4	1.0	9 (1.9)	9	2.2
Psychiatric disorders	9 (1.9)	10	2.4	6 (1.3)	6	1.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (1.3)	10	2.4	4 (0.8)	5	1.2
Reproductive system and breast disorders	3 (0.6)	3	0.7	4 (0.8)	4	1.0
Surgical and medical procedures	4 (0.8)	5	1.2	3 (0.6)	3	0.7
Ear and labyrinth disorders	4 (0.8)	5	1.2	3 (0.6)	3	0.7
Hepatobiliary disorders	6 (1.3)	6	1.5	3 (0.6)	3	0.7
Endocrine disorders	3 (0.6)	3	0.7	1 (0.2)	1	0.2
Immune system disorders	3 (0.6)	3	0.7	1 (0.2)	1	0.2
Congenital, familial and genetic disorders	2 (0.4)	2	0.5	0		

Proportion of subjects (%)
0   10   20   30   40

■ Sema 1.0 mg   ▲ Sema 2.0 mg

Figure 8. Adverse events by preferred term - most frequent (≥5%) - on-treatment

■ Sema 1.0 mg (N = 480 ; PYE = 411.2)
▲ Sema 2.0 mg (N = 479 ; PYE = 409.9)

Sorted in descending order by preferred term based on total proportion of subjects with at least one event in the semaglutide 2.0 mg arm. N: number of subjects; PYE: patient-years of exposure.

nn9535/nn9535-4506/ctr_20201204_er
04DEC2020:14:39:57 - fsumae.sas/fsum5pctot.png
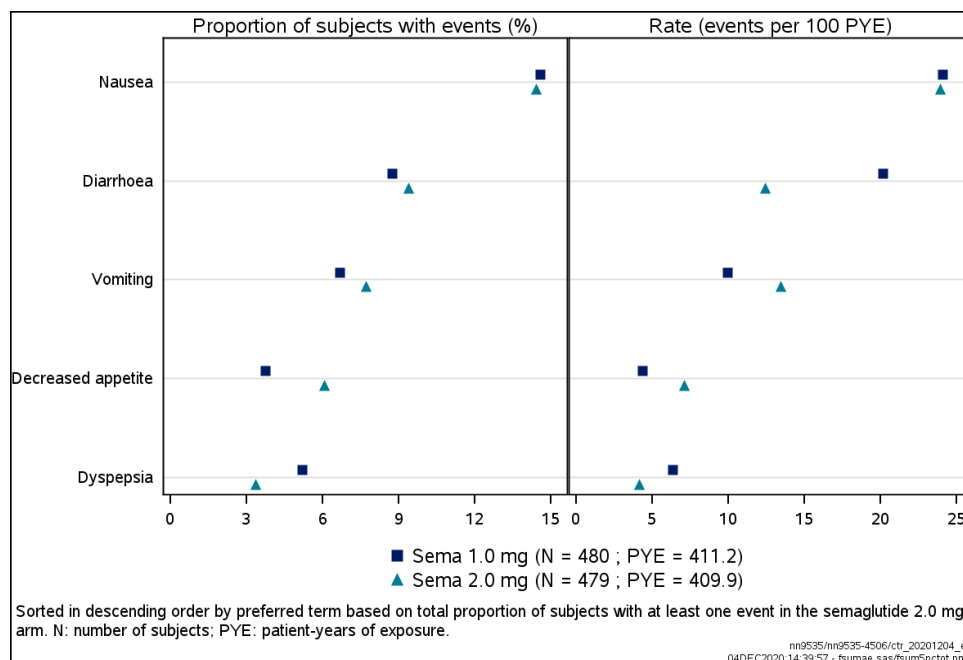
Details on common AEs reported by ≥5%.

Safety focus areas

Based on the disease, drug class, and regulatory feedback and requirements, safety focus areas of special interest were pre-defined for the evaluation of safety with semaglutide 2.0 mg. An overview of the results for the safety focus areas in presented in Figure 9 and summarised in subsequent sections.

Figure 9. Overview of results for the safety focus areas

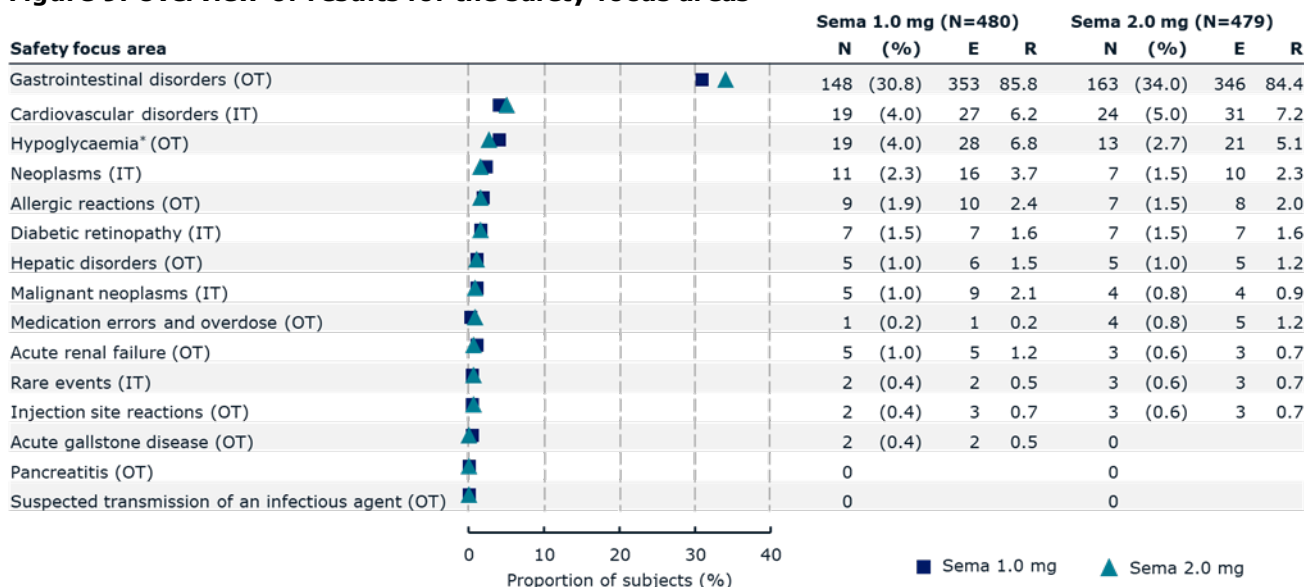| Safety focus area				Sema 1.0 mg (N=480)				Sema 2.0 mg (N=479)			
				N	(%)	E	R	N	(%)	E	R
Gastrointestinal disorders (OT)				148	(30.8)	353	85.8	163	(34.0)	346	84.4
Cardiovascular disorders (IT)				19	(4.0)	27	6.2	24	(5.0)	31	7.2
Hypoglycaemia* (OT)				19	(4.0)	28	6.8	13	(2.7)	21	5.1
Neoplasms (IT)				11	(2.3)	16	3.7	7	(1.5)	10	2.3
Allergic reactions (OT)				9	(1.9)	10	2.4	7	(1.5)	8	2.0
Diabetic retinopathy (IT)				7	(1.5)	7	1.6	7	(1.5)	7	1.6
Hepatic disorders (OT)				5	(1.0)	6	1.5	5	(1.0)	5	1.2
Malignant neoplasms (IT)				5	(1.0)	9	2.1	4	(0.8)	4	0.9
Medication errors and overdose (OT)				1	(0.2)	1	0.2	4	(0.8)	5	1.2
Acute renal failure (OT)				5	(1.0)	5	1.2	3	(0.6)	3	0.7
Rare events (IT)				2	(0.4)	2	0.5	3	(0.6)	3	0.7
Injection site reactions (OT)				2	(0.4)	3	0.7	3	(0.6)	3	0.7
Acute gallstone disease (OT)				2	(0.4)	2	0.5	0			
Pancreatitis (OT)				0				0			
Suspected transmission of an infectious agent (OT)				0				0			

Proportion of subjects (%)
0 10 20 30 40

■ Sema 1.0 mg   ▲ Sema 2.0 mg

*Severe or BG-confirmed symptomatic hypoglycaemia episodes.

N: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events/episodes; R: events/episodes per 100 patient-years of exposure/observation. OT: on-treatment observation period. IT: in-trial observation period. MedDRA version 23.0.

Gastrointestinal disorders

The proportion of subjects with AEs related to gastrointestinal disorders was slightly higher with semaglutide 2.0 mg (34.0%) compared to semaglutide 1.0 mg (30.8%); while, the event rates were similar in the treatment arms (84.4 vs. 85.8 events per 100 PYE) (Figure 9).

The most frequently reported PTs reported by ≥5% of subjects in both treatment arms were nausea, diarrhoea, vomiting and dyspepsia. The majority of AEs were non-serious, of mild or moderate severity and were reported as recovered. A higher proportion of AEs related to gastrointestinal disorders with semaglutide 2.0 mg compared to semaglutide 1.0 mg were judged as probably or possibly related to trial product by the investigator. In the semaglutide 2.0 mg arm, 12 subjects reported severe AEs related to gastrointestinal disorders compared to 8 subjects in the semaglutide 1.0 mg arm. Severe events in the semaglutide 2.0 mg treatment arm were mainly vomiting.

The incidence of premature treatment discontinuation due to AEs related to gastrointestinal disorders was similar between the two treatment arms (3.3% vs 2.7% of subjects for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively).

SAEs related to gastrointestinal disorders were reported in both treatment arms:

- semaglutide 2.0 mg: 3 subjects reported 3 events (PTs: colitis, constipation and oesophagitis)
- semaglutide 1.0 mg: 2 subjects reported 3 events (PTs: abdominal pain, nausea and vomiting)

Cardiovascular disorders

The proportion of subjects with AEs related to cardiovascular disorders was 5.0% in the semaglutide 2.0 mg arm and 4.0% in the semaglutide 1.0 mg arm with comparable event rates between the treatment arms (Figure 9).

In both treatment arms, the majority of AEs related to cardiovascular disorders were non-serious, mild or moderate in severity and judged by the investigator as unlikely related to trial product with outcome

reported as recovered. Most of the identified events were reported within the cardiac disorders SOC, where minor imbalances across PTs were observed between the treatment arms.

A total of 3 events led to premature treatment discontinuation:

- semaglutide 2.0 mg: 1 SAE (atrial fibrillation) and 1 non-serious AE (syncope)

- semaglutide 1.0 mg: 1 SAE (acute myocardial infarction)

The proportion of subjects with SAEs related to cardiovascular disorders was similar in both treatment arms:

semaglutide 2.0 mg: 6 subjects (1.3%) reported 9 events

semaglutide 1.0 mg: 8 subjects (1.7%) reported 9 events

Pulse rate

The change in pulse rate was investigated as a supportive secondary endpoint. Pulse rate increased in the 2.0 and 1.0 mg arms and with no statistically significant difference between the arms (+3.6 vs +2.6 beats/min, respectively, p=0.06)

Hypoglycaemic episodes

The number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemia episodes (Novo Nordisk classification) from the first dose to week 40, was a supportive secondary safety endpoint. There were no statistically significant differences in the rate or odds of experiencing severe or blood glucose-confirmed symptomatic hypoglycaemia episodes between the treatment arms (Table 17). The majority of severe or blood glucose-confirmed symptomatic hypoglycaemia episodes occurred when the trial product was used in combination with SU or insulin.

Table 17. Severe or BG-confirmed symptomatic hypoglycaemia episodes

	N (%)	Odds ratio	E	R	Rate ratio
Semaglutide 2.0 mg	13 (2.7)	0.69 [0.34;1.38]$_{95\%CI}$	21	5.1	0.79 [0.34;1.81]$_{95\%CI}$
Semaglutide 1.0 mg	19 (4.0)		28	6.8	

Data from the on-treatment observation period.

CI: confidence interval; E: number of events; N: number of subjects with at least one episode; %: proportion of subjects with at least one episode; R: episodes per 100 patient years of exposure

Of the 49 treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemia episodes, 3 episodes were classified as severe based on the ADA 2018 classification:

- semaglutide 2.0 mg: 2 subjects reported 2 events (both episodes occurred while the subjects were concomitantly treated with SU, and one subject had prematurely discontinued treatment 30 days prior to the episode)

- semaglutide 1.0 mg: 1 subject reported 1 event (occurred while the subject was treated with insulin and had prematurely discontinued treatment 49 days prior to the episode)

Neoplasms

Overall, 18 subjects reported 26 AEs related to neoplasms during the trial. The proportion of subjects with AEs related to all neoplasms (benign and malignant) and the event rates were low in both treatment arms (Figure 9). In all, 7 events were serious (all malignant), 4 were severe (all malignant), and 22 were mild or moderate in severity. All events were assessed as unlikely related to trial product by the investigator and none led to premature treatment discontinuation.

Nine (9) subjects reported a total of 13 AEs related to malignant neoplasms during the trial with no notable treatment difference. One subject in the semaglutide 1.0 mg treatment arm reported 4 events of squamous cell carcinoma (at different locations) and 1 event of basal cell carcinoma, accounting for the higher event rate in the semaglutide 1.0 mg arm (Figure 9). Except for one subject with 4 events of squamous cell carcinoma and 1 event of basal cell carcinoma, all AEs related to malignant neoplasms were single events reported in single subjects, with no clustering in SOCs/PTs, tissue or organ of origin. Also, there was no clustering in SOCs/PTs, tissue or organ of origin for the benign neoplasms.

Allergic reactions

The proportion of subjects reporting AEs related to allergic reactions and the event rates were low and similar between the treatment arms (Figure 9). The most frequently reported AEs were in the skin and subcutaneous tissue disorders SOC. Except for 1 event, all events were non-serious, and the majority were mild in severity. The SAE (urticaria) was reported in the semaglutide 1.0 mg arm and was judged unlikely to related to trial product by the investigator and the subject recovered from the event.

Diabetic retinopathy

Fourteen (14) subjects reported a total of 14 AEs related to diabetic retinopathy during the trial (Figure 9). The proportion of subjects with these AEs and the corresponding event rates were similar between the treatment arms. The most frequently reported AE was diabetic retinopathy, and the remaining events were distributed across several PTs. The majority of events were mild in severity and judged as unlikely related to trial product by the investigator. Since the majority of events with additional data collection were reported in connection with the end of treatment eye examination, the outcome for most AEs related to diabetic retinopathy were reported as not recovered. No SAEs were reported, and no events led to premature treatment discontinuation.

Medication errors

Overdose because of medication errors occurred in 5 patients, i.e. 5 events in 4 patients in the semaglutide 2.0 mg arm and 1 event in the semaglutide 1.0 mg arm.

2.6.8.3. Serious adverse event/deaths/other significant events

Three deaths were reported during the trial:

- semaglutide 2.0 mg: 2 subjects; events: head injury and death (reason unknown)

- semaglutide 1.0 mg: 1 subject; event: neuromyelitis optica spectrum disorder

The proportions of subjects reporting SAEs and the corresponding event rates were comparable between the treatment arms:

- semaglutide 2.0 mg: 4.4% subjects; 7.1 events per 100 PYE

- semaglutide 1.0 mg: 5.2% subjects; 9.7 events per 100 PYE

SAEs were distributed across multiple SOCs and PTs with no clustering observed in either treatment arm.

The SAEs that were deemed possibly or probably related to the study drug by the investigator included constipation (1 patient), oesophagitis (1 patient), nausea (1 patient), vomiting (1 patient), atrial fibrillation (1 patient), myocardial infarction (1 patient), cholelithiasis (1 patient), weight decrease (1 patient), dehydration (1 patient) and neuromyelitis optica spectrum disorder (1 patient).

2.6.8.4. Laboratory findings

Apart from the pancreatic enzymes lipase and amylase, no notable change over the course of the trial was observed in any of the biochemistry or haematology laboratory parameters

In both treatment groups, mean (geometric) levels of lipase increased by 30% and amylase increased by 20%. The increase in lipase and amylase occurred during the initial 20 weeks of treatment, followed by a slight further increase in mean levels during the rest of the on-treatment period. There were no AEs related to pancreatitis.

2.6.8.5. Safety in special populations

An overview of the results for the safety of semaglutide 2.0 mg in the subgroups investigated is provided in Figure 10.

Apart from the subgroups presented here, no other parameters for safety in special group and situations were evaluated for trial 4506.

Overall, the trial population did not display markedly different AE profiles for semaglutide 2.0 mg relative to semaglutide 1.0 mg, when divided into subgroups by the described intrinsic and extrinsic factors Figure 10).

Figure 10. Adverse events – by intrinsic and extrinsic factors – on treatment

Demographic or Disease Factor		Sema 1.0 mg, Total N	Sema 2.0 mg, Total N	Sema 1.0 mg n	(%)	E	R	Sema 2.0 mg n	(%)	E	R
Age (years)	<65	347	341	175	(50.4)	556	184.8	191	(56.0)	530	178.3
	65-<75	115	122	63	(54.8)	225	233.2	72	(59.0)	205	203.1
	≥75	18	16	13	(72.2)	47	337.7	9	(56.3)	40	343.5
Sex	Female	197	201	104	(52.8)	388	236.2	114	(56.7)	351	207.8
	Male	283	278	147	(51.9)	440	178.2	158	(56.8)	424	176.0
BMI (kg/m²)	<25	33	21	19	(57.6)	65	234.9	16	(76.2)	61	346.7
	25-<30	102	91	57	(55.9)	178	209.2	49	(53.8)	143	186.0
	30-<35	146	167	80	(54.8)	303	238.1	92	(55.1)	253	179.1
	≥35	199	200	95	(47.7)	282	164.8	115	(57.5)	318	182.6
Body weight (kg)	<70	45	33	25	(55.6)	83	220.4	25	(75.8)	78	289.4
	70-<90	144	116	81	(56.3)	325	271.8	64	(55.2)	199	205.4
	90-<110	159	192	81	(50.9)	241	172.1	95	(49.5)	272	163.9
	≥110	132	138	64	(48.5)	179	157.1	88	(63.8)	226	188.2
Race*	White	426	420	210	(49.3)	709	194.0	230	(54.8)	649	180.8
	Asian	36	32	27	(75.0)	82	261.8	24	(75.0)	81	292.9
	Black/African American	17	26	13	(76.5)	36	265.5	17	(65.4)	41	183.7
Ethnicity	Not Hispanic/Latino	421	427	217	(51.5)	697	193.4	243	(56.9)	673	183.9
	Hispanic/Latino	59	52	34	(57.6)	131	258.1	29	(55.8)	102	232.5
HbA₁c (%)	<8.0%	25	29	17	(68.0)	76	359.2	19	(65.5)	60	236.9
	8.0-<8.5%	120	97	63	(52.5)	186	180.8	55	(56.7)	137	168.5
	8.5-<9.0%	133	155	61	(45.9)	220	194.4	86	(55.5)	243	183.2
	9.0-<9.5%	119	99	69	(58.0)	198	196.8	53	(53.5)	150	172.6
	≥9.5%	83	99	41	(49.4)	148	201.8	59	(59.6)	185	221.0
Diabetes duration (years)	<10	269	297	127	(47.2)	397	171.7	150	(50.5)	427	166.7
	≥10	211	182	124	(58.8)	431	239.4	122	(67.0)	348	226.4
Renal function (mL/min/1.73m²)	Normal	309	315	151	(48.9)	536	200.1	173	(54.9)	500	183.8
	Mild impairment	146	150	84	(57.5)	247	203.2	90	(60.0)	262	205.1
	Moderate impairment	25	14	16	(64.0)	45	206.6	9	(64.3)	13	128.0
Region	North America	171	158	122	(71.3)	454	321.0	117	(74.1)	365	274.0
	Europe	284	297	107	(37.7)	313	126.3	138	(46.5)	343	134.2
	Asia (Japan)	25	24	22	(88.0)	61	276.9	17	(70.8)	67	318.7

Proportion of subjects (%): 0 25 50 75 100

■ Sema 1.0 mg   ▲ Sema 2.0 mg

*The categories 'Other' and 'American Indian or Alaska native' have been omitted from this output, due to too few subjects.

Abbreviations: %: proportion of subjects with at least one event within the subgroup, N: total number of subjects in subgroup, n: number of subjects with at least one event within the subgroup, E: number of events, R: event rate per 100 patient-years of exposure.

Baseline age

Overall, the treatment differences for all AEs, SAEs and severe AEs were similar across subgroups of age. However, there appeared to be a slightly more pronounced treatment difference in the reporting of AEs leading to premature treatment discontinuation of trial product in subjects with age ≥75 years, albeit the number of events was low (5 subjects [31.3%] vs 2 subjects [11.1] for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively) More pronounced treatment differences in the reporting of AEs among subjects ≥75 years were seen for:

- Diarrhoea (2 subject [12.5%] vs 1 subject [5.6%] for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively)

- Vomiting (3 subjects [18.8%] vs 1 subject [5.6%] for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively)

Baseline body weight

Overall, the treatment differences for all AEs, SAEs, severe AEs and AEs leading to premature treatment discontinuation of the trial product were similar across body weight subgroups. However,

there appeared to be a slightly more pronounced treatment difference in the reporting of all AEs and AEs leading to premature treatment discontinuation of trial product in the lowest baseline body weight category, albeit the number of subjects within this subgroup was low (all AEs: 25 subjects [75.8%] vs 25 subjects [55.6%]; AEs leading to premature treatment discontinuation: 5 subjects [15.2%] vs 2 subjects [4.4%] for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively). More pronounced treatment differences in the reporting of AEs among subjects with a baseline body weight of <70 kg was seen for:

- Nausea (11 subjects [33.3%] vs 7 subjects [15.6%] for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively)

The more pronounced treatment difference in reporting of AEs of nausea and AEs leading to premature treatment discontinuation among subjects with a baseline body weight of <70 kg could be related to the higher exposure in these subjects or the low number of subjects in this subgroup.

Baseline renal function

Overall, no treatment differences were observed in reporting of AEs, SAEs, severe AEs and AEs leading to premature treatment discontinuation of trial product across subgroups of baseline renal function. For subjects with moderate renal impairment there were overall more pronounced treatment differences in the reporting of AEs within:

- Vomiting (3 subjects [21.4%] vs 0 subjects for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively).

2.6.8.6. Immunological events

Reference is made to results from the NN9536 semaglutide s.c. 2.4 mg (STEP) programme, where anti-drug antibodies (ADAs) were assessed for all subjects included in the STEP 1 and STEP 2 trials. STEP 2 trial included subjects with T2D and overweight or obesity. In this trial, 1% (4/396) of exposed subjects developed ADAs at the semaglutide 1.0 mg dose, whereas 3% (12/401) of exposed subjects developed ADAs at the 2.4 mg dose. No influence of ADAs on body weight and HbA1c was observed.

2.6.8.7. Safety related to drug-drug interactions and other interactions

The potential of high dose semaglutide to delay gastric emptying may influence the absorption of concomitantly administered oral medical products (described under 'Pharmacokinetics').

2.6.8.8. Discontinuation due to adverse events

The proportion of subjects with AEs leading to premature discontinuation was low and similar in both the treatment arms (4.4% of subjects in the semaglutide 2.0 mg arm and 4.6% of subjects in semaglutide 1.0 mg arm). AEs leading to premature discontinuation were predominantly gastrointestinal disorders (3.3% of subjects in the semaglutide 2.0 mg arm and 2.7% of subjects in semaglutide 1.0 mg arm).

2.6.8.9. Post marketing experience

The safety profile of the lower dose semaglutide is well established from marketing authorisation studies and post-marketing experience. The safety data were in line with the safety and tolerability profile of the GLP 1 RA drug class with no new or unexpected findings. The higher incidence of patients experiencing gastrointestinal adverse events is considered manageable: the higher dose of semaglutide can be tapered to 1 mg.

2.6.9. Discussion on clinical safety

Trial 4506, a total of 959 subjects were exposed to trial products, with 479 subjects exposed to semaglutide 2.0 mg and 480 subjects to semaglutide 1.0 mg. Exposure was defined as the time from first date to last date of dose of trial product plus the ascertainment window of 49 days (both dates inclusive).

Adverse events

A slightly higher proportion of subjects experienced AEs in the semaglutide 2.0 mg treatment arm compared to the semaglutide 1.0 mg treatment arm; while, the event rates were similar between the treatment arm (56.8% subjects; 189.1 events per 100 PYE vs 52.3% subjects; 201.4 events per 100 PYE).

As expected for the GLP-1 RA drug class, gastrointestinal disorders were the most frequently reported AEs in both treatment arms. Compared to the semaglutide 1.0 mg arm, slightly more subjects in the semaglutide 2.0 mg arm reported AEs across SOCs of gastrointestinal disorders. Nausea occurred in similar proportions of patients when treated with semaglutide 1 mg and 2 mg, respectively, diarrhoea and vomiting in higher proportions on semaglutide 2 mg. The gastrointestinal adverse reactions led to treatment discontinuation in similar proportions in the semaglutide 1 mg and 2 mg treatment groups.

Infections and infestations are the second most frequent AEs affecting 16.9% of the subjects in both treatment arms, i.e. there is no difference between the dosing groups. There was no consistent pattern of any types of infections and no suggestion of a cause-effect association with the high dose semaglutide in the available data.

Events of special interest

The proportion of subjects with AEs related to gastrointestinal disorders was slightly higher with semaglutide 2.0 mg (34.0%) compared to semaglutide 1.0 mg (30.8%).

The proportions of subjects reporting SAEs and the corresponding event rates were comparable between the treatment arms. Three deaths were reported during the trial:(semaglutide 2.0 mg: 2 subjects; semaglutide 1.0 mg: 1 subject).

The proportion of subjects with AEs related to cardiovascular disorders was 5.0% in the semaglutide 2.0 mg arm and 4.0% in the semaglutide 1.0 mg arm with comparable event rates between the treatment arms. A CV outcome trial was conducted with the lower dose semaglutide, which did not indicate an increased risk. However, trial 4506 was not designed to evaluate impact of the high dose semaglutide on CV risk reduction. In addition, the difference vs semaglutide 1.0 mg was not due to MACE events, but mainly due to events of palpitations (5 subjects vs 1 subject) and atrial fibrillation (2 subjects vs 1 subject). Although it is unknown whether or not the CV benefit demonstrated in SUSTAIN 6 for semaglutide 0.5 mg and 1.0 mg also is applicable for semaglutide 2.0 mg, there is no indication of an increased risk of cardiovascular events.

Pulse rate increased in both treatment arms and tended to be higher with semaglutide 2.0 mg (1 beat/min, p=0.055).

There were no statistically significant differences in the rate or odds of experiencing severe or blood glucose-confirmed symptomatic hypoglycaemia episodes between the treatment arms. Most episodes occurred on concomitant treatment with SU or insulin.

Nine (9) subjects reported a total of 13 AEs related to malignant neoplasms during the trial with no notable treatment difference.

Fourteen (14) subjects reported a total of 14 AEs related to diabetic retinopathy during the trial. The proportion of subjects with these AEs and the corresponding event rates were similar between the treatment arms. However, the concern remains that the underlying pathological mechanism of retinopathy in conjunction with semaglutide treatment, including the relationship to time and dose, is not fully understood. Since patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from study 4506, a potential dose-related effect of the higher dose of 2.0 mg on retinopathy in patients with pre-existing unstable diabetic retinopathy or maculopathy cannot be excluded based on study 4506 data. The Applicant has updated SmPC section 4.4, stating that there is no experience with semaglutide 2.0 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy, and that treatment with semaglutide 2.0 mg is not recommended in these patients.

Overdose because of medication errors occurred in 5 patients.

In both treatment groups, mean (geometric) levels of lipase increased by 30% and amylase increased by 20%.

Subgroup analyses

The subgroups investigated in study 4506 was based on the following intrinsic factors: age, sex, BMI, body weight, race, ethnicity, HbA_{1c}, diabetes duration, renal function, and the following extrinsic factor: region. Previously investigated subgroups based on CV history, hypertension and hepatic function in the initial dossier on semaglutide 0.5 and 1.0 mg were provided upon request. Based on the data, no dose adjustment for safety reasons is recommended in any of the subgroups investigated.

Overall, the trial population did not display markedly different AE profiles for semaglutide 2.0 mg relative to semaglutide 1.0 mg, when divided into subgroups. However, there were more adverse events in patients in the lowest body weight (and BMI) subgroup. This was added to the SmPC.

Overall, the treatment differences for all AEs, SAEs and severe AEs were similar across subgroups of age. However, there appeared to be a slightly more pronounced treatment difference in the reporting of AEs leading to premature treatment discontinuation of trial product in subjects with age ≥75 years, albeit the number of events was low (5 subjects [31.3%] vs 2 subjects [11.1] for semaglutide 2.0 mg vs semaglutide 1.0 mg, respectively). More pronounced treatment differences in the reporting of AEs among subjects ≥75 years were seen for: diarrhoea (12.5% vs 5.6%) and vomiting (18.8% vs 5.6%).

There appeared to be a slightly more pronounced treatment difference in the reporting of all AEs and AEs leading to premature treatment discontinuation of trial product in the lowest baseline body weight category, albeit the number of subjects within this subgroup was low (all AEs: 75.8% vs 55.6%; AEs leading to premature treatment discontinuation (15.2% vs 4.4%). More pronounced treatment differences in the reporting of AEs among subjects with a baseline body weight of <70 kg was seen for nausea (33.3% vs 15.6%).

Overall, no treatment differences were observed in reporting of AEs, SAEs, severe AEs and AEs leading to premature treatment discontinuation of trial product across subgroups of baseline renal function.

2.6.10. Conclusions on the clinical safety

The safety data were in line with the safety and tolerability profile of the GLP 1 RA drug class with no new or unexpected findings. A higher proportion of subjects experienced AEs in the semaglutide 2.0 mg treatment arm compared to the semaglutide 1.0 mg treatment arm. As expected for the GLP-1 RA drug class, gastrointestinal disorders were the most frequently reported AEs in both treatment arms. Compared to the semaglutide 1.0 mg arm, more subjects in the semaglutide 2.0 mg arm reported AEs across SOCs of gastrointestinal disorders. However, since patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from study 4506, a dose-related effect of 2.0 mg on retinopathy cannot be excluded. The Applicant has updated SmPC section 4.4, stating that there is no experience with semaglutide 2.0 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy, and that treatment with semaglutide 2.0 mg is not recommended in these patients.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	Pancreatic cancer Medullary thyroid cancer
Missing information	Pregnancy and lactation Patients with severe hepatic impairment

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk) **– semaglutide s.c. and oral semaglutide**				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk) **– semaglutide s.c. and oral semaglutide**				
None				
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA) **– semaglutide s.c. and oral semaglutide**				
MTC-22341		Medullary thyroid cancer	**Semaglutide s.c.**	
			Submitted protocol	January 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry *Ongoing*	A medullary thyroid cancer case series registry of at least 15 years duration 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.		Final report	May 2035
			Oral semaglutide	
			Submitted protocol	November 2020
			Final report	February 2037
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes *Ongoing*	The study will evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D.	Pancreatic cancer	**Semaglutide s.c.**	
			Adopted protocol	20 Sep 2018
			Final report	September 2025
			Oral semaglutide	
			Adopted protocol	Pending
			Final report	September 2025
NN9535-4352 Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes (FOCUS). *Ongoing*	The study will assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy	Diabetic retinopathy complications	Adopted protocol	19 Nov 2018
			Final report	November 2025

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risk Diabetic retinopathy complications	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and in the PL Sections 2 and 4. *Additional risk minimisation measures:* None
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None

Safety concern	Risk minimisation measures
Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Non-clinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None
Missing information: Pregnancy and lactation	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None
Missing information: Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 6.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC. Details on the Novo Nordisk pharmacovigilance system master file and the qualified person responsible for pharmacovigilance (QPPV) can be found in the original marketing authorisation application. This is regarded acceptable.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ozempic doses of 0.25 mg, 0.5 mg and 1 mg. The bridging report submitted by the MAH has been found acceptable.

2.9.2. 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 Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

T2D remains a substantial health care challenge with a projected worldwide prevalence of 10.9% (700 million adults) by 2045. T2D is a progressive disease, and persistent hyperglycaemia can lead to serious microvascular and macrovascular complications. Despite the availability of several treatments, optimising glycaemic control remains a challenge in many patients.

3.1.2. Available therapies and unmet medical need

Semaglutide for once-weekly s.c. injection (Ozempic) is approved worldwide for treatment of type 2 diabetes (T2D) at maintenance doses of 0.5 mg and 1.0 mg. Semaglutide has been investigated in a comprehensive global clinical development programme (SUSTAIN) involving more than 11,000 subjects across 11 phase 3 trials, including a dedicated cardiovascular outcomes trial.

Two maintenance doses of semaglutide are currently approved for the treatment of T2D: 0.5 mg and 1.0 mg. Across the SUSTAIN programme, larger reductions in HbA_{1c} and body weight were consistently observed with semaglutide 1.0 mg than with 0.5 mg. However, it was observed that 20-30% of patients receiving semaglutide 1.0 mg did not achieve the treatment target of HbA_{1c} <7.0%.

A third maintenance dose of once-weekly semaglutide s.c. 2.0 mg is developed for patients with T2D who can benefit from additional glucose-lowering and body weight loss as the disease progresses. In this application, data from the phase 3b Trial NN9535-4506 are presented to support the use of semaglutide 2.0 mg for the treatment of T2D. Additionally, semaglutide is being developed for weight management using a once-weekly dose of 2.4 mg.

The present indication remains unchanged by this line extension. The proposed update of the posology reads as follows:

After at least 4 weeks with a dose of 1 mg once weekly, the dose can be increased to 2 mg once weekly to further improve glycaemic control.

3.1.3. Main clinical studies

Dose finding

To explore the potential of higher semaglutide doses, the phase 2 Trial NN9535-4191 (hereafter referred to as Trial 4191) was conducted. In Trial 4191, once-daily semaglutide s.c. doses up to 0.3 mg (equivalent to ~2.1 mg once-weekly) were investigated in 705 subjects with T2D. Data from Trial 4191 and the SUSTAIN trials were included in the exposure-response model. With dose increase from semaglutide 1.0 mg to 2.0 mg, a reduction in HbA1c of 0.26%-points was predicted. In addition, an additional reduction in body weight of a least 2.5 kg is to be expected.

Pivotal study

Trial 4506 was a multinational, multi-centre, randomised, double-blind, two-armed, active-comparator trial with a 49-week trial period (incl. screening, dose-escalation, 40 weeks treatment and 9 weeks follow-up). A total of 961 adults with T2D were randomised 1:1 to treatment with once-weekly semaglutide 2.0 mg or 1.0 mg. Subjects with T2D were enrolled in the trial (HbA1c of 8-10%). Patients were treated with metformin alone or in combination with SU. The trial design is acceptable.

- The primary objective was to establish the superior effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with T2D, on a background of metformin with or without SU treatment.

- Secondary objectives were to compare the effect of semaglutide s.c. 2.0 mg once-weekly versus semaglutide s.c. 1.0 mg once-weekly in subjects with T2D, on a background of metformin with or without SU treatment, on body weight, vital signs, hypoglycaemia and general safety and tolerability.

Of the 961 randomised subjects, 97.1% completed the trial, and 92.5% completed treatment, equally balanced between the two treatment arms.

Subjects enrolled in this trial had a mean age of 58 years, mean HbA1c of 8.9%, mean duration of diabetes of 9.5 years and a mean body weight of 99.3 kg. Approximately 74% of subjects had a BMI ≥30 kg/m2, and 58.6% of the population was male. Characteristics were comparable between treatment groups. Baseline HbA1c was somewhat higher than that in most other studies with semaglutide.

Overall, few subjects (2.9%) initiated rescue medication, predominantly constituting SU or SGLT2 inhibitor classes, during the treatment. A greater proportion of subjects in the semaglutide 1.0 mg arm required use of rescue medication compared to the semaglutide 2.0 mg arm (4.2% vs. 1.7% subjects).

3.2. Favourable effects

Pivotal study

The estimated mean HbA1c reduced to 6.7% from a relatively high baseline value of 8.9% (estimated mean change from baseline of -2.2%-point, hypothetical estimand). Comparatively, in the semaglutide 1.0 mg arm, the estimated mean change from baseline was -1.9%-point. Similar results were observed using the treatment policy estimand strategy. The estimated treatment difference in HbA1c reduction between 1.0 and 2.0 mg was 0.23% (hypothetical estimand) and 0.18% (treatment policy estimand).

A greater proportion of subjects achieved HbA1c target levels (ADA: <7.0% or AACE: ≤6.5%) at week 40 with semaglutide 2.0 mg compared to semaglutide 1.0 mg, as evaluated by the treatment estimand (64.4% vs 55.8% for HbA1c<7%; 49.4% vs 37.1% for HbA1c <6.5%).

In general, results concerning HbA1c were similar across pre-specified subgroups.

Semaglutide 2.0 mg was superior to semaglutide 1.0 mg for the secondary confirmatory endpoint of change from baseline to week 40 in body weight as evaluated by the hypothetical estimand (-0.93 [-1.68; -0.18]95%CI, p=0.0155). However, superiority could not be confirmed with the treatment policy estimand (-0.77 [-1.55; 0.01]95%CI, p=0.0535).

After 40 weeks of treatment, a reduction in blood pressure was observed for both doses of semaglutide. There were no relevant differences between the 1.0 mg and the 2.0 mg dose.

STEP 2 trial with semaglutide 2.4 mg (other procedure)

One of the 4 trials in the clinical development programme for semaglutide 2.4 mg in weight management (NN9536-4374, STEP 2) investigated the weight-reducing potential and the safety of semaglutide s.c. 2.4 mg administered once weekly as an adjunct to a reduced-calorie diet and increased physical activity in subjects with type 2 diabetes (T2D) and overweight or obesity (BMI ≥27 kg/m2) as compared to placebo. The dose in the weight loss programme (2.4 mg) is higher than that used in pivotal study 4191 (2.0 mg), and the study will be assessed in detail in a separate procedure. However, study results may be used for comparison purposes in the present application. For the treatment policy estimand, the estimated treatment difference in HbA1c between semaglutide 2.4 mg and semaglutide 1.0 mg (supportive secondary endpoint) was −0.15% [−0.34; 0.04]95% CI. With respect to body weight, the estimated treatment difference was −2.65% [−3.66; −1.64]95% CI for semaglutide 2.4 mg vs semaglutide 1.0 mg.

Comparability study

Trial 3687 was a randomised, two-period, incomplete cross-over trial in healthy subjects investigating if comparing different semaglutide drug product concentrations (1 mg/mL, 3 mg/mL, and 10 mg/mL) met the bioequivalence criterion concerning the total exposure after single s.c. injections. These data support comparability between the semaglutide drug product concentrations of 1.34 mg/mL (used in Trial 4506) and 2.68 mg/mL (to-be-marketed drug product for semaglutide 2.0 mg) as the concentration range is contained within the concentration range tested in Trial 3687.

3.3. Uncertainties and limitations about favourable effects

The estimated treatment difference in HbA1c reduction between 1.0 and 2.0 mg was modest (0.23%, hypothetical estimand; 0.18%, treatment policy estimand), especially when the relatively high baseline HbA1c is taken into account. A modest additional proportion of subjects achieved HbA1c target levels at week 40 with semaglutide 2.0 mg compared to semaglutide 1.0 mg (hypothetical treatment estimand (64.4% vs 55.8% for target HbA1c<7%). This modest effect is in line with the small additional HbA1c lowering effect of semaglutide 2.4 mg compared to 1.0 mg in STEP2 (-0.15%; weight management clinical development programme).

Concerning body weight, superiority could not be confirmed with the treatment policy estimand. In addition, the additional reduction in body weight of 0.8-0.9 kg is less than expected from the dose-finding study (-2.5 kg). The additional reduction in body weight is also less than that observed in in STEP2 (-2.6 kg), but this may be explained by the higher dose in STEP2.

In the submitted trial, semaglutide was studied as an add-on to metformin (and SU) but not in combination with other antihyperglycemic agents (in contrast to the phase 3 studies where semaglutide was given as an add-on to various background medications). However, it is considered likely that the incremental benefit of the higher dose is maintained when used in combination with other glucose-lowering medications.

3.4. Unfavourable effects

Pivotal trial

Trial 4506, a total of 959 subjects were exposed to trial products, with 479 subjects exposed to semaglutide 2.0 mg and 480 subjects to semaglutide 1.0 mg.

A higher proportion of subjects experienced AEs in the semaglutide 2.0 mg treatment arm compared to the semaglutide 1.0 mg treatment arm; while, the event rates were similar between the treatment arm (956.8% subjects; 189.1 events per 100 PYE vs 52.3% subjects; 201.4 events per 100 PYE).

As expected for the GLP-1 RA drug class, gastrointestinal disorders were the most frequently reported AEs in both treatment arms. Compared to the semaglutide 1.0 mg arm, more subjects in the semaglutide 2.0 mg arm reported AEs across SOCs of gastrointestinal disorders. Nausea occurred in similar proportions of patients when treated with semaglutide 1 mg and 2 mg, respectively, diarrhoea and vomiting in higher proportions on semaglutide 2 mg. The gastrointestinal adverse reactions led to treatment discontinuation in similar proportions in the semaglutide 1 mg and 2 mg treatment groups.

Subgroup analyses

Overall, the trial population did not display markedly different AE profiles for semaglutide 2.0 mg relative to semaglutide 1.0 mg when divided into subgroups.

Greater proportions of patients in the oldest age-group >=75 years, and in the lowest BMI group <25 kg/m2 and in the lowest body weight group <70 kg experienced gastrointestinal AEs.

Events of special interest

The proportion of subjects with AEs related to gastrointestinal disorders was higher with semaglutide 2.0 mg (34.0%) compared to semaglutide 1.0 mg (30.8%).

The proportions of subjects reporting SAEs and the corresponding event rates were comparable between the treatment arms. Three deaths were reported during the trial:(semaglutide 2.0 mg: 2 subjects; semaglutide 1.0 mg: 1 subject).

Nine (9) subjects reported a total of 13 AEs related to malignant neoplasms during the trial with no notable treatment difference.

Fourteen (14) subjects reported a total of 14 AEs related to diabetic retinopathy during the trial. The proportion of subjects with these AEs and the corresponding event rates were similar between the treatment arms.

In both treatment groups, mean (geometric) levels of lipase increased by 30% and amylase increased by 20%, but there were no AEs related to pancreatitis.

STEP 2 trial with semaglutide 2.4 mg (other procedure)

The STEP 2 trial (one of the 4 trials in the clinical development programme for semaglutide 2.4 mg in weight management (NN9536-4374)) may also be used for comparison purposes with respect to safety in the present application. In this study, 403 subjects with T2D were exposed to semaglutide 2.4 mg for 533 PYE. In general, the safety profile of semaglutide 2.4 mg was consistent with the 2.0 mg dose.

3.5. Uncertainties and limitations about unfavourable effects

The proportion of subjects with AEs related to cardiovascular disorders was 5.0% in the semaglutide 2.0 mg arm and 4.0% in the semaglutide 1.0 mg arm with comparable event rates between the treatment arms. The pulse rate increased in both treatment arms and tended to be higher with

semaglutide 2.0 mg (1 beat/min, p=0.055). A CV outcome trial was conducted with the lower dose semaglutide, which did not indicate an increased risk, but the higher dose situation is unclear However, trial 4506 was not designed to evaluate impact of the high dose semaglutide on CV risk reduction. In addition, the difference vs semaglutide 1.0 mg was not due to MACE events, but mainly due to events of palpitations (5 subjects vs 1 subject) and atrial fibrillation (2 subjects vs 1 subject). Although it is unknown whether or not the CV benefit demonstrated in SUSTAIN 6 for semaglutide 0.5 mg and 1.0 mg also is applicable for semaglutide 2.0 mg, there is no indication of an increased risk of cardiovascular events.

Retinal disorders were included as a safety focus area for the STEP 2 trial (diabetes patients) in the semaglutide 2.4 mg for the weight management programme. In STEP 2, subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were not eligible for enrolment in the trial. A total of 85 AEs of retinal disorders were identified by the pre-defined MedDRA search. These events were reported by a larger proportion of subjects with semaglutide 1.0 mg and 2.4 mg compared to placebo (6.2%, 6.9% and 4.2%, respectively).

The Company provided data on the effects of semaglutide on DRP and MACE in patients with "uncontrolled or potentially unstable diabetic retinopathy" in SUSTAIN 6 (semaglutide 0.5 and 1.0 mg in patients with diabetes). The estimated HRs in the 'uncontrolled or potentially unstable diabetic retinopathy' subpopulation in SUSTAIN 6 are consistent with those in the overall population. However, the absolute effects are of a different magnitude. In the 'uncontrolled or potentially unstable diabetic retinopathy' subpopulation for every 100 patients that were treated, semaglutide prevented 3 MACE events, but caused 6 events of serious DRP. Therefore, a strong warning in the SmPC was required.

Interactions

Uncertainties also exist with regard to potential interactions (delay of gastric emptying and of intestinal transit) of high dose semaglutide with concomitantly administered oral drugs.

The rate or odds of experiencing severe or blood glucose-confirmed symptomatic hypoglycaemia episodes were comparable between the treatment arms. However, this was based on a post-hoc defined analysis.

3.6. Effects Table

Table 18. Effects Table for Ozempic 2 mg

Effect	Short Description	Unit	Sema 2 mg	Sema 1 mg	Treatment difference/ Strength of evidence	References
Favourable Effects						
HbA1c	HbA1c reduction from baseline to Week 40	% points	-2.2	-1.9	**SoE:** Primary endpoint <u>Hypothetical</u> estimand LS mean difference (95% CI) -0.23% (-0.36, -0.11), p=0.0003; <u>Treatment policy</u> estimand -2.1 vs -1.9; -0.18% (-0.31, -0.04), p=0.0098	Trial 4506

Effect	Short Description	Unit	Sema 2 mg	Sema 1 mg	Treatment difference/ Strength of evidence	References
Body Weight	Body Weight reduction from baseline to Week 40	kg	-6.9	-6.0	**SoE:** Secondary endpoint <u>Hypothetical</u> estimand LS mean difference (95% CI) -0.93 kg (-1.68, -0.18), p=0.0155; <u>Treatment policy</u> estimand -6.4 vs -5.6 kg; -0.77 kg (-1.55, 0.01), p=0.053	Trial 4506
Unfavourable Effects						
Treatment emergent AEs		n(%)	272 (56.8)	251 (52.3)		Trial 4506
All SAEs		n(%)	21 (4.4)	25 (5.2)		
AEs leading to discontinuation		n(%)	21 (4.4)	22 (4.6)		
Deaths		n(%)	2 (0.4)	1 (0.2)		
Several focus areas						
Gastrointestinal AEs		%	34.0	30.8		Trial 4506
CV disorders AEs		%	5.0	4.0		
Heart rate	Change from baseline at Week 40	bpm	3.6	2.6	Irrelevant as the largest (end of night) increase is not reported	
Hypoglycaemia episodes AEs	Severe or BG-confirmed symptomatic	n(%)	13 (2.7)	19 (4.0)	Rate ratio 0.79 [0.34;1.81]95%CI	
Diabetic retinopathy AEs		n(%)	7 (1.5)	7 (1.5)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In principle, the proposed study design and conducted pivotal does not directly reflect the way in which the higher dose will be applied in clinical practice. A forced titration study design targeting a certain cut-off would be more appropriate. However, for additional desirable glycaemic control, the dosage can be increased; initially up to 1 mg and now up to 2 mg once weekly.

The higher HbA1c range at baseline led to the inclusion of a subgroup of patients for whom treatment intensification is more important, and these patients may benefit more from treatment with the higher semaglutide dose. Although study 4506 was not specifically performed in the target population, the results support the use of the higher dose in patients that are not sufficiently controlled with the lower dose.

Body weight is an important endpoint for patients with type 2 diabetes. The reduction in body weight of 0.8-0.9 kg is small.

The safety profile of the lower dose semaglutide is well established from marketing authorisation studies and post-marketing experience. The safety data were in line with the safety and tolerability profile of the GLP 1 RA drug class with no new or unexpected findings. The higher incidence of patients experiencing gastrointestinal adverse events is considered manageable: the higher dose of semaglutide can be tapered to 1 mg. However, the concern remains that the underlying pathological mechanism of retinopathy in conjunction with semaglutide treatment, including the relationship to time and dose, is not fully understood. Since patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from study 4506, the observation of no difference between the 1.0 mg and 2.0 mg treatment arms with respect to the proportions of subjects having diabetic retinopathy at the end-of-study eye examination, overall, or subjects experiencing new onset or worsening of diabetic retinopathy from baseline to end-of-study, may only apply to this selected patient population without pre-existing unstable diabetic retinopathy or maculopathy. In combination with data from the STEP2 trial, a potential dose-related effect of the higher dose of 2.0 mg on retinopathy in patients with pre-existing unstable diabetic retinopathy or maculopathy cannot be excluded. The Applicant has updated SmPC section 4.4, stating that there is no experience with semaglutide 2.0 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy, and that treatment with semaglutide 2.0 mg is not recommended in these patients.

The effect of the higher dose semaglutide on CV risk is not clear, but there is no suggestion of an increased risk of cardiovascular events.

3.7.2. Balance of benefits and risks

The effect size of additional efficacy afforded by the higher dose may be beneficial for some patients.

The overall B/R for the new higher dose strength of semaglutide (2 mg) is considered positive.

The application is approvable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Ozempic is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Ozempic 2 mg solution for injection in pre-filled pen, is favourable in the following indication(s):

Ozempic is indicated for the 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 trial 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 extension(s) of the marketing authorisation for Ozempic subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (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.