30 January 2020
EMA/95374/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rybelsus

International non-proprietary name: semaglutide

Procedure No. EMEA/H/C/004953/0000

Note

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

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AME	absorption, metabolism, excretion
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BCRP	breast cancer resistance protein
BG	blood glucose
BMI	body-mass index
CI	confidence interval
CKD	chronic kidney disease
CTR	clinical trial report
CVOT	cardiovascular outcomes trial
DDI	drug-drug interaction
DPP	dipeptidyl peptidase
DTSQs	Diabetes Treatment Satisfaction Questionnaire (status version)
EAC	event adjudication committee
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FHD	first human dose
FPG	fasting plasma glucose
GI	Gastrointestinal
GLP	glucagon-like peptide
HOMA	homeostatic model assessment
HR	hazard ratio
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IR	insulin resistance
MAA	Marketing Authorisation Application
MACE	major adverse cardiovascular event
MMRM	mixed model for repeated measurements
MTC	medullary thyroid carcinoma
NN	Novo Nordisk
PD	Pharmacodynamic
PIONEER	Peptide InnOvatioN for Early diabEtes tReatment
PRO	patient-reported outcomes
PT	preferred term
OAD	oral anti-diabetic drug
PK	Pharmacokinetic
PT	preferred term

PYE	patient-years of exposure
PYO	patient-years of observation
RA	receptor agonist
RI	renal impairment
SAE	serious adverse event
SAS	safety analysis set
SGLT	sodium-glucose co-transporter
SMPG	self-measured plasma glucose
SNAC	sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (salcaprozate sodium)
SOC	system organ class
SU	Sulphonylurea
TZD	Thiazolidinedione
ULN	upper limit of normal
UACR	urinary albumin-to-creatinine ratio

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 26 April 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Rybelsus, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

> "Rybelsus 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 combination with 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 legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0206/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0206/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant indicated the active substance semaglutide contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received Scientific advice from the CHMP on the development for the indication from the CHMP on 9 April 2015 (EMEA/H/SA/1359/3/2015/PED/III), 25 June 2015 (EMEA/H/SA/1359/4/2015/III), 26 January 2017 (EMEA/H/SA/1359/3/FU/1/2016/PED/III) and 18 May 2017 (EMEA/H/SA/1359/4/FU/1/2017/I). The Scientific advice pertained to the following Quality, Non-clinical and Clinical aspects:

- Adequacy of the adult formulation for application in children
- Adequacy of the comparability demonstration proposed for the drug substance used in Phase 3 studies vs. Phase 1/2
- Acceptability of a change in drug product dissolution testing
- Acceptability of the proposed starting materials for SNAC synthesis and the intended Quality documentation for SNAC (absorption enhancer, excipient)
- Adequacy of the proposed drug product differentiation strategy between tablet strengths
- Adequacy of a juvenile toxicity study in rats with s.c. semaglutide to support the use of orally administered semaglutide in paediatric patients with Type 2 Diabetes Mellitus
- Need for a non-clinical juvenile toxicity study with SNAC
- Adequacy of the non-clinical development plans for subcutaneously administered semaglutide, orally administered SNAC and orally administered semaglutide
- Adequacy of observed animal-to-human exposure ratios of SNAC for the intended clinical use in oral semaglutide; need for additional non-clinical studies to investigate mortality observations in non-clinical studies with high SNAC exposures; relevance of a correlation between SNAC plasma concentration and CSF lactate levels observed in rat studies to support the derivation of adequate animal-to-human exposure ratios for the intended clinical use of SNAC in oral semaglutide in the paediatric population (10-17 years of age) and to support monitoring of plasma lactate as a relevant means of monitoring effects on cellular respiration
- Sufficiency of proposed in-vitro evaluations of the drug interaction potential of semaglutide and SNAC
- Acceptability of a proposed 10-day dosing PK and tolerability trial design in children and adolescents with Type 2 Diabetes Mellitus aged 10 to less than 18 years of age
- Acceptability of a proposed safety and efficacy trial design in children and adolescents with Type 2 Diabetes Mellitus aged 10 to less than 18 years of age
- Adequacy of the proposed clinical pharmacology programme
- Adequacy of the proposed Phase 3 clinical study programme: number of exposed subjects, duration of exposure, study population, dose selection and escalation algorithm, design of a flexible dose adjustment trial, background medication in add-on trials, choice of comparators and their dosing, rescue criteria and management of patients requiring rescue treatment for data analysis, appropriateness of estimand definitions and MMRM as estimation method, sensitivity analyses, non-inferiority margins, statistical testing strategy, type-I error control, safety monitoring plans, immunogenicity assessment, cardiovascular safety
- Adequacy of a proposed renal impairment trial to support an indication in renally impaired patients with Type 2 Diabetes Mellitus
- Adequacy of evidence generation plans in patients with gastrointestinal comorbidities

Overall, the CHMP considered that the applicant did adhere to most of the advice and deviations were generally acceptable:

In the CHMP advice from 2015 (EMA/CHMP/SAWP/382906/2015), the Applicant proposed a clinical development programme including 6 pivotal studies, which were overall acknowledged. It was however noted that a lack of a direct comparison with metformin will preclude a first line indication according to the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2 2).

Some changes to the clinical development programme have been implemented: instead of the proposed comparator, canagliflozin, the Applicant has used another SGLT2 inhibitor, empagliflozin, as comparator. This is acceptable. Furthermore, in the renal impairment study, placebo was used as comparator instead of the proposed linagliptin. This might have increased the proportion of individuals initiating rescue medication. Additionally, the Applicant has conducted a study in insulin-dependent type 2 diabetes patients, in which oral semaglutide was compared with placebo. This is endorsed.

With regards to efficacy, the CHMP questioned the selected dose of 14 mg, as 40 mg has a markedly stronger effect on HbA_{1c} than 10 mg. In the dossier, no clear argumentation for the selection of 14 mg as the maximal dose is provided. Furthermore, a non-inferiority margin of HbA_{1c} of 0.3 was advised by the CHMP, however the Applicant has used 0.4% for the comparison with empagliflozin and liraglutide without proper justification (PIONEER 2 AND 4). For the comparison with sitagliptin (PIONEER 3), the Applicant used a non-inferiority margin of 0.3% thus following the advice by the CHMP. Please also refer to the section on Clinical efficacy in this report.

Regarding safety, the Applicant was advised to closely monitoring GI effects and gastric events over time as AEs of special interest due to the SNAC co-formulation. Furthermore, the Applicant was advised to perform a pre-defined meta-analysis of adjudicated relevant cardiovascular events from all clinical trials performed with semaglutide+SNAC to address this point. Instead, the Applicant has conducted a cardiovascular outcome trial to evaluated cardiovascular safety. This is endorsed.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Mark Ainsworth

The application was received by the EMA on	26 April 2019
The procedure started on	23 May 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 January 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	24 January 2020
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 Rybelsus on	30 January 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Type 2 diabetes (T2D) is a metabolic disease which is highly prevalent in western and worldwide societies, attributed to unhealthy lifestyle.

2.1.2. Epidemiology

T2D remains a substantial health care challenge that affects the individual patient and the society profoundly. The prevalence of the chronic and progressive metabolic disorder is expected to increase worldwide markedly; projections suggest that around 10% of the global adult population will be affected by 2045.

2.1.3. Aetiology and pathogenesis

Whereas Type 1 diabetes is the result of a total deficiency of the pancreatic insulin production, this deficiency is usually only relative in T2D. On the one hand, the body is 'resistant' to insulin and requires more insulin than in healthy subjects to counter hyperglycaemia. On the other hand, the pancreatic insulin secretion has an insufficient reserve to deliver this extra insulin.

Most subjects with T2D are overweight or obese, which is important in the aetiology as it increases insulin resistance.

2.1.4. Clinical presentation, diagnosis

The typical presentation of diabetes includes polyuria and polydipsia. However, many patients with T2D are asymptomatic and are diagnosed with screening or general investigations of aspecific complaints like fatigue. The diagnosis is made by measurement of hyperglycaemia.

2.1.5. Management

Massive weight loss, e.g. after bariatric surgery, can completely cure T2D. However, treatment is usually aimed at controlling glycaemia and CV risk.

To avoid the microvascular complications associated with the disease, it is a crucial aim to establish adequate glycaemic control as soon as possible after a T2D diagnosis. Furthermore, highlighting the need for a therapy that targets all aspects of the disease, many patients with T2D are at high cardiovascular risk and suffer from macrovascular complications and other co-morbidities (e.g. obesity).

The guidelines of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) for treatment of T2D have been developed in cooperation and are widely agreed. The major steps include lifestyle measures ('diet and exercise' to promote weight loss and a healthier diet). Primarily for

glycaemic control, metformin, other non-insulin hypoglycaemic agents and finally insulin (in various forms) are used. Cardiovascular (CV) risk factors should be treated aggressively.

Recently, SGLT-2 inhibitors (e.g. empagliflozin) and GLP-1 RAs (e.g. liraglutide) have shown not only improvements in glycaemic control but also a reduction in CV events in patients with T2D and high risk CV risk (e.g. based on a previous CV event).

2.2. About the product

Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and the cardiovascular system. Semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high.

Semaglutide has been authorised in the EU as Ozempic, for once weekly, subcutaneous (s.c.) use. Rybelsus has the same active substance, but is developed for oral use. To improve bioavailability, which is around 1%, an 'absorption enhancer' (SNAC) is added. SNAC has not been used in a commercial product in the EU yet.

2.3. Quality aspects

2.3.1. Introduction

The active substance contained in Rybelsus is semaglutide, a GLP 1 analogue with 94% sequence homology to human GLP 1. It is acylated and has two amino acid substitutions compared to human GLP-1. Semaglutide is produced using recombinant DNA technology in *Saccharomyces cerevisiae* followed by chemical modifications.

Semaglutide acts as a recombinant long-acting GLP 1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

Rybelsus is presented as tablets containing 3 mg, 7 mg or 14 mg of semaglutide formulated with salcaprozate sodium, povidone K90, microcrystalline cellulose and magnesium stearate.

The product is available in Alu/Alu blister cards with the following pack sizes:

- 3 mg tablets: 10, 30, 60 and 90 tablets;

- 7 mg tablets: 30, 60 and 90 tablets;

- 14 mg tablets: 30, 60 and 90 tablets.

2.3.2. Active Substance

General Information

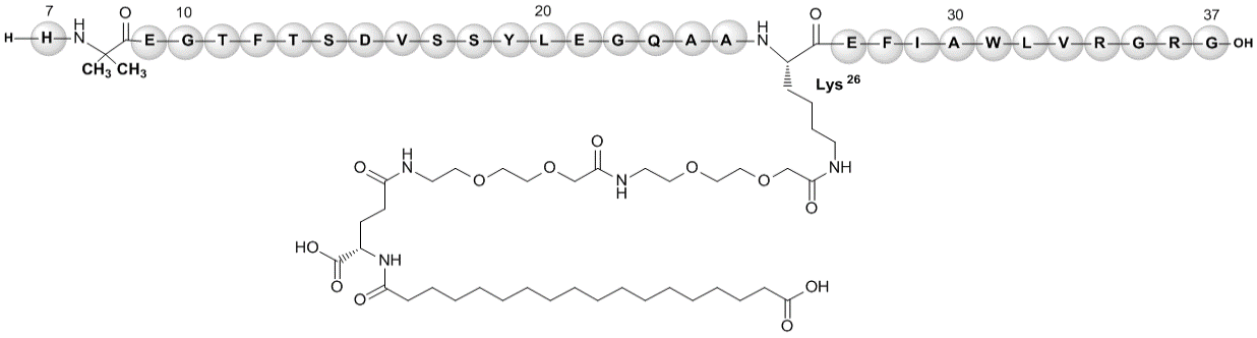
Semaglutide is a recombinant long acting glucagon-like peptide-1 (GLP-1) receptor agonist. The GLP-1 analogue is acylated at lysine 26 with a fatty diacid moiety and has two amino acid substitutions (Ala8 to Aib8 (2-aminoisobutyric acid), Lys34 to Arg34) compared to human GLP-1.

Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

Compared to human GLP-1, semaglutide has a prolonged half-life and the principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme by the amino acid substitution Ala8 to Aib8.

The structural formula of semaglutide is provided in Figure 1. The theoretical relative monoisotopic molecular mass of semaglutide is 4111.115 and the theoretical average molecular weight is 4113.58 g/mol.

Figure 1 - Structural formula of semaglutide



Semaglutide in Rybelsus is identical in structure to semaglutide in the authorised product Ozempic (EMEA/H/C/004174) for subcutaneous administration. However, the active substance manufacturing process for Rybelsus is based on a different yeast strain and the production process is optimised to accommodate the yeast strain and the need for larger capacity for an oral product. The applicant claimed "known active substance" status for this marketing authorisation application.

Manufacture, process controls and characterisation

Manufacture

Novo Nordisk A/S, Hallas Allé 1, DK-4400 Kalundborg, Denmark is responsible for production and quality control of the active substance except for the last step of the purification process (spray drying) which is performed at Hovione FarmaCiencia S.A., Quinta São Pedro, Sete Casas, PT- 2674-506 Loures, Portugal.

The manufacturing process for semaglutide active substance consists of:

- The fermentation process The recovery process,
- The synthesis of the acylating agent,
- The purification process.

All steps have been described and explained.

Control of materials

The construction of the expression plasmid and the generation of *S. cerevisiae* strain producing extended semaglutide precursor is described in sufficient detail. The cell bank system of master cell bank (MCB) and working cell bank (WCB) is explained and characterisation of the cell banks, as well as end-of-production cells and late extended culture, is reported. Stability results of MCB and WCB are available and the results show that the WCB and MCB are stable during storage. A protocol for establishing WCB was provided and is acceptable.

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

The choice of the starting materials is in line with regulatory expectations. Adequate specifications have been indicated.

A detailed listing is provided for all raw materials used in manufacture of the active substance. The designation and proposed specifications for some materials was considered too limited. The applicant has adjusted the information on raw materials by introducing additional requirements for materials with a medium risk rating.

Control of critical steps and intermediates

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

A set of critical operational parameters have been defined for the multistep process as has been supported by the evaluation studies in manufacturing process development. The recovery part of the process including the enzymatic cleavage does not include any critical operational parameters or controls. Upon request the robustness of this process step has been further supported by analytical data.

Process validation

Process validation, also referred to as PPQ, has been based on three consecutive commercial scale batches. The results from the PPQ of the critical and non-critical operational parameters, critical in-process tests, additional tests on in-process samples, and the results of the semaglutide active substance specification tests were all consistent for the fermentation, recovery, and purification batches and all acceptance criteria were fulfilled.

The PPQ study confirmed that the manufacturing process produces semaglutide active substance consistently and reproducibly on a commercial scale.

The process is therefore considered validated and ready for commercial production.

Reduction of product-related and process-related impurities were evaluated using data from the PPQ batches manufactured in commercial scale. The data showed that all the product-related impurities were effectively reduced to below the acceptance criteria demonstrating a consistent and robust manufacturing process.

Process justification studies for all steps of the active substance manufacturing process have been included. These process justification studies provide sufficient evaluation of the operational parameters and in-process controls. The conclusion on the criticality of processes and controls can be endorsed.

Manufacturing process development

The Applicant has sufficiently explained the development of the active substance manufacturing process. Analysis results of all batches are provided in Module 3 and comparability of clinical batches with commercial batches is supported in analytical studies.

The control strategy for semaglutide active substance consists of a planned set of controls which are derived from accumulated product and process understanding.

In general the control strategy for active substance is considered acceptable. The applicant has shown that the manufacture and control of the active substance ensure batches of consistently acceptable quality.

Characterisation

Structural characterisation and elucidation of the physicochemical properties of semaglutide have been performed using active substance batches representative of the manufacturing process intended for the commercial product. The results of the structural characterisation of semaglutide have confirmed the expected structural characteristics.

The bioactivity of semaglutide is determined by a cell-based bioactivity assay, which indirectly measures adenylate cyclase activation of the cloned human GLP-1 receptor. The bioactivity of isolated semaglutide related impurities has been investigated by isolation of the semaglutide main peak and major semaglutide related impurities from semaglutide active substance, followed by testing for content and purity of each peak by RP-HPLC and bioactivity. An evaluation of the correlation between the bioactivity and the content determined by RP-HPLC of semaglutide in active substance and finished product, including forced degraded samples, is provided. It is concluded that the RP-HPLC analytical procedure established for the determination of main peak content in the semaglutide active substance and finished product specifications offers a reliable measure of the bioactivity of semaglutide in both active substance and finished product. The Applicant has provided strong evidence that indeed the contents established with RP-HPLC strongly correlate with measured biologically activity results in active substance and finished product. RP-HPLC content, therefore, presents a reliable marker for bioactivity. This limited verification of biological activity is considered sufficiently justified by the characterisation studies and by the fact that semaglutide is a relatively well-characterised compound whose properties can be adequately monitored by physicochemical assays.

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

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

In fact, semaglutide for oral presentation is identical in structure and highly similar in purity to the semaglutide as approved for the parenteral presentation.

For process-related impurities reference is made to the process validation section.

An evaluation of potential extractables from the column resin material was performed and a leachable study was not deemed necessary.

Specification

The specification for the active substance includes control of identity, impurities, bioactivity and other general tests.

The semaglutide active substance specification acceptance criteria have been established based on one or more of the following considerations: active substance process capability, analytical variation, stability, and relation to the finished product manufacturing process and finished product specification.

The limits for impurities proposed for active substance routine release (i.e. process III lots) are wider compared to limits applied for active substance lots for the parenteral product (Ozempic uses active substance from process II). Comparability data presented under Manufacturing process development show that process III batches have the same or even lower levels of impurities compared to active substance process II lots used in clinical development of the oral formulation. The limits initially proposed for RP-HPLC resolved impurities and specific bioactivity are beyond the actual batch analysis results presented for the (39) process III batches and batches investigated in clinical studies. The wider limits for bioactivity have been justified by variability of the assay and limits for impurities have been tightened.

Analytical procedures

Adequate descriptions of analytical methods, including their system suitability criteria and evaluation have been provided. The proposed analytical methods have been sufficiently validated and are considered suitable for the control of the active substance.

The non-compendial methods were overall satisfyingly validated. Further details regarding the reference material used and regarding specificity of the specific bioactivity assay have been provided. Analytical development has been described and adequate comparative data between methods utilised during development has been presented.

It is noted that the analytical methods applied for Rybelsus are the same as those approved for Ozempic active substance.

The analytical results for all semaglutide active substance batches manufactured during clinical development are presented. All batch release data show compliance with the active substance specification for semaglutide, which was in force at the time for releasing the batches.

Batch analysis

Batch data from process I, II and III have been presented. All batch data are within specification acceptance limits in place at the time, and all batch data from process III are within current acceptance limits. A slight shift is observed in content, water content and particle size distribution for the PPQ and commercial batches from process III compared to the remaining process III batches. The Applicant has adequately described and justified this and provided reassurance that the shift has not negatively affected the quality of final finished product formulation.

Reference standards

The semaglutide reference material is produced by Novo Nordisk A/S and used in the analytical test of semaglutide (OG217) for oral formulation and semaglutide for subcutaneous formulation (approved product Ozempic).

The reference material hierarchy has been established according to Novo Nordisk A/S procedures, with a semaglutide primary reference material (PRM) and a semaglutide secondary reference material (SRM).

The documentation for the establishment of the current batches of PRM and SRM and the protocol for the establishment of future batches of PRM and SRM, is referred to the documentation submitted with the approved product Ozempic.

Certificates of analysis for semaglutide PRM batch and SRM batch are provided.

The current PRM and SRM, as well as the establishment of future reference preparations, have been well described, and upon request descriptions of analytical methods have been provided. The use of the same reference preparations for the Rybelsus and the Ozempic release controls is acceptable since the quality of the active substance is shown to be comparable.

The Applicant has explained that the reference material is stored at lower temperatures compared to the semaglutide active substance and controls are in place that the reference remains stable during storage.

Stability

Primary stability data consisting of six commercial scale batches of semaglutide active substance from Study A, Study B and Study C stored at long-term storage were provided

The stability data provided support the proposed shelf life for semaglutide active substance.

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented in tablets containing 3 mg, 7 mg or 14 mg of the active substance semaglutide. All three strengths are white to light yellow, oval shaped tablets (7.5 x 13.5 mm) debossed with respectively "3", "7" or "14" on one side and "*Novo*" on the other side of the tablet. The different tablet strengths are sufficiently visually distinguishable by their debossing. The excipients are salcaprozate sodium, microcrystalline cellulose, povidone K90 and magnesium stearate. The different tablet strengths have the same qualitative and quantitative composition with regards to the excipients and only differ with respect to the quantity of semaglutide. Except for salcaprozate sodium, the excipients are widely used in oral pharmaceutical dosage forms and are well known. The main excipient in the formulation is salcaprozate sodium, a novel excipient for which extensive information has been provided in the dossier (see below). The products are packed in Alu/Alu blister in an outer carton.

The aim of the formulation development was to develop an oral dosage form of semaglutide. The formulation design of the tablet was primarily driven by optimising the semaglutide bioavailability using salcaprozate sodium as an absorption enhancer. Formulations with different semaglutide to salcaprozate sodium ratios were tested in early phase 1 trials. Based on the clinical data, a fixed quantity of salcaprozate sodium per tablet was selected, irrespective of the semaglutide dose. Formulations with semaglutide contents ranging from 2.5 to 40 mg per tablet were tested in clinical trials and the amounts of 3, 7 and 14 mg semaglutide per tablet were selected for further development.

The changes made to the formulation and manufacturing process throughout the clinical development have been discussed in the dossier. No critical changes were made in the manufacturing process and formulation between the phase 3 clinical batches and commercial product. Any differences have been sufficiently discussed and justified. The manufacturing of semaglutide finished product has been transferred from the pilot facility to the commercial facility within the manufacturing site. A comparability study has been performed confirming that this change did not impact the quality and performance of the finished products. The batches used in the clinical studies are considered representative for the commercial product. The formulation development has been described in sufficient detail in the dossier.

The manufacturing process development has been described in sufficient details.

The Applicant has applied Quality by Design (QbD) principles in the development of the finished product manufacturing process. However, no design space was claimed. Critical steps in the manufacturing process were identified by a risk assessment. Guided by the risk assessment, process justification studies by multivariate or univariate experiments have been performed. The manufacturing process development studies support the proposed process ranges.

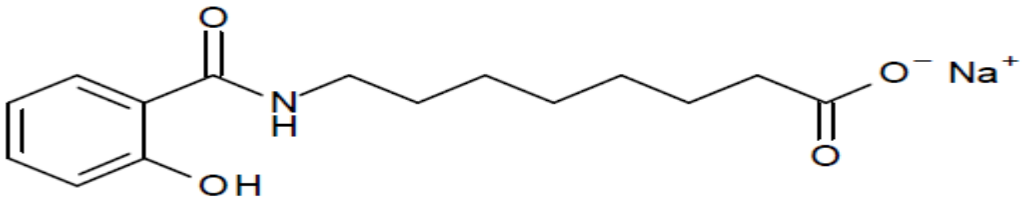
Given the sensitivity of the product to moisture and light, Alu/Alu blisters were selected as primary packaging due to the superior barrier properties. The suitability of this packaging was confirmed by the results of the formal stability studies.

Salcaprozate sodium

Salcaprozate sodium is a novel excipient that has been added to the formulation to enhance the bioavailability of semaglutide. Full quality details on the manufacture, characterisation and control of salcaprozate sodium have been provided in the dossier.

The chemical structure of salcaprozate sodium (molecular weight 301.22 g/mol) is reflect in Figure 2:

Figure 2 - Structure of salcaprozate sodium



Salcaprozate sodium is a white to almost white powder with a solubility of about 10 mg/ml at pH 2-4 to approximately 300 mg/ml at pH 8 in aqueous media. The excipient shows polymorphism and is manufactured as polymorphic form A anhydrate.

Manufacture of salcaprozate sodium

QbD principles were applied in the development of the manufacturing process. Critical steps in the manufacturing process were identified by a risk assessment and the impact of process variables on critical material attributes was investigated by several multivariate or univariate experiments. Based on these studies critical process parameters have been identified and process ranges have been determined. The process

justification studies have been adequately performed and finalized process ranges for critical and non-critical process parameters have been included in the manufacturing process description.

Control of salcaprozate sodium

The specification of salcaprozate sodium is acceptable.

The analytical procedures have been described in sufficient details and the in-house methods have been adequately validated. Batch analysis results on multiple full-scale batches have been provided confirming compliance with the proposed specification. Batches used for the phase 3 studies and onwards were all manufactured at production scale according to the finalised manufacturing process.

During the procedure, a Major Objection was raised regarding the fact that several of the potential impurities from the starting material synthesis contain structural alerts for mutagenicity (mostly alkyl halides). All actual and potential impurities from both starting materials should be evaluated for their mutagenicity and classified in accordance with the recommendations of ICH M7(R1) either based on literature or by performing a computational toxicology assessment based on two (Q)SAR prediction methodologies that complement each other (one expert rule-based and the second statistical-based). Any impurity that is classified into Class 1, 2 or 3 should be controlled to the TTC limit or compound-specific acceptable limit in the final excipient, a suitable intermediate or the starting material itself. For (potentially) mutagenic impurities measuring the related impurities is not considered sufficient as the purging of the actual impurities to levels below the TTC limits should be demonstrated by validated analytical methods.

In their response, the Applicant explained that the potential impurities from both starting materials have been evaluated for their mutagenicity and classified in accordance with the recommendations of ICH M7(R1) based on literature, (Q)SAR prediction methodologies or by Ames testing.

Ten potential impurities from the synthesis of the starting material were identified as (potentially) mutagenic. All impurities that were identified as (potential) mutagens are individually and routinely controlled in the starting material and by IPCs and purge factors. For the (potentially) mutagenic impurities that are structurally similar to the starting material it is assumed by the applicant that the same purge factor can be applied. This is considered reasonable, especially taking into account that these impurities will be present in the first step already at levels 250-500 folds lower than the starting material itself (based on their control limits).

For certain impurities the control limits in the specification were confirmed by actual spike and purge studies.

No (potentially) mutagenic impurities were identified from the synthesis of the starting material carsalam.

Overall, the provided discussion on the evaluation, control and carry-over of potential genotoxic impurities from the synthesis of the starting materials is considered satisfactory. The currently applied limits for (potentially) mutagenic impurities in the starting material specification are considered adequate to ensure that these impurities will not be carried over into the final salcaprozate sodium excipient in levels above the TTC limit of 5 ppm for individual mutagenic impurities (levels of most of these compounds will likely remain considerably below this TTC limit) and will not exceed the ICH M7 TTC limit for multiple mutagenic impurities (17 ppm) either.

This Major Objection is considered resolved.

Stability of salcaprozate sodium

Stability data have been provided on nine production scale batches of salcaprozate sodium that were stored at 25°C/60% RH (18-36 months) and 40°C/75% RH (6 months). The container closure system consists of a double bag system. The inner bag is a low-density polyethylene (LDPE) bag/liner closed using a zip tie and the outer bag is an aluminium laminated bag (Polyethylene terephthalate / Aluminium / Polyamide / Polyethylene) closed by heat sealing. The batches were evaluated for appearance, identity by X-ray powder diffraction (XRPD), assay, related impurities, water content, particle size and microbiological quality. Except for a slight increase in water content, no clear trends or changes were seen in any of the tested parameters at both conditions. The excipient was shown to be stable with low impurity levels. Photostability testing results showed that the excipient was not sensitive to light exposure. The claimed retest period of 36 months if stored at 15-25°C is justified.

Overall, the Rybelsus formulation is acceptable.

Manufacture of the product and process controls

Manufacture

The finished product is manufactured by Novo Nordisk A/S, Denmark. The main steps of the manufacturing process are granulation, mixing, compression and packaging. The manufacturing process has been described in sufficient detail in the dossier including process parameter settings for critical and non-critical process parameters and in-process control tests. Hold times for bulk intermediate have been laid down and justified.

The finished product is packed in Alu/Alu blisters. The blister materials are adequately controlled and are in compliance with the relevant Ph.Eur. monograph or EU Regulation on food contact materials.

Process controls

Process parameter ranges for the critical steps and tests and acceptance limits for the in-process controls have been laid down in the dossier and are supported by the manufacturing process development studies and process validation results.

Criticality is based on the evaluation of the impact of the individual process steps and parameters on the CQAs on basis of the cumulative data from production and development.

Specification tests and acceptance criteria have been set and descriptions of the in-house analytical procedures and corresponding validation reports have been provided.

Process validation

All the critical process parameters were within the established process ranges during PPQ. Results from in-process controls, PPQ additional tests and semaglutide finished product batch analysis show that the acceptance criteria were fulfilled for the PPQ batches (3 batches for each strength). The obtained results demonstrate that the manufacturing process performs as expected and that the manufacturing process for the three strengths of the semaglutide tablets (3 mg, 7 mg and 14 mg) is consistent and reproducible.

Product specification

The finished product specification includes tests for appearance (visual), uniformity of dosage units (RP-UHPLC), water content (KF), identity (by peptide mapping and RP-UHPLC retention time), assay semaglutide (RP-UHPLC), assay salcaprozate sodium (RP-UHPLC), high molecular weight proteins (HMWP) (SE-HPLC), impurities (RP-UHPLC), dissolution and microbiological quality. Upon request, the shelf-life limit for semaglutide assay of the 3 mg tablet was tightened.

Analytical procedures

The analytical procedure for dissolution is in accordance with Ph. Eur.2.9.3. During the development of the dissolution method, the following was investigated: sink conditions, agitation speed for the dissolution, the discriminating ability of the dissolution method and the choice and amount of surfactant. The investigations have been performed in accordance with the principles of "*Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/336031/2017)*.

Except for Appearance, all the non-pharmacopoeial analytical methods (identity, uniformity of dosage units, assay, impurities, HMWPs and dissolution) presented in the specifications for the semaglutide finished product have been validated. The validation was in accordance with ICH Q2(R1). The validation shows that the methods are suitable for their intended use, as all the acceptance criteria for the validation have been fulfilled.

Batch analysis

Batch analysis data on multiple batches of the 3 mg, 7 mg and 14 mg products that have been used in the phase 3, stability and PPQ studies have been provided as well as on all further batches that have been used in the clinical phase 1 and phase 2 studies. Batch results were consistent for all phase 3 batches and PPQ bathes and confirm compliance with the specification.

Reference standard

The same semaglutide reference standard is used as for the analysis of the active substance. This is acceptable.

Stability of the product

Stability data have been provided on three pilot scale batches of each product strength (primary stability batches) that were stored at 25°C/60% RH (30 months), 30°C/75% RH (30 months) and 40°C/75% RH (6 months) as well as on three or four production scale batches per strength (supportive stability batches) stored at the same storage conditions (3-12 months data available). The batches were packed in the commercial packaging. The conditions are according to the ICH recommendations. The following parameters were investigated: appearance, semaglutide assay, uniformity of dosage units, salcaprozate assay, HMWP, impurities, dissolution and microbiological quality.

For all three storage conditions, a decrease in semaglutide assay and an increase in impurities and HMWP levels were observed. No clear trends or changes were seen in any of the other parameters. All parameters remained within the specification limits.

Results of a photostability study in accordance with ICH Q1B showed a change in visual appearance of the unpacked samples. No further changes were seen and no changes were seen for the finished product packed in

its primary packaging. Results of forced degradation studies showed clear degradation under extreme conditions of heat and humidity.

The claimed shelf-life of 30 months with storage condition '*Store in the original blister package in order to protect from moisture and light*' is justified based on the presented stability data, the photostability studies and the forced degradation studies.

Post approval change management protocol(s)

The Applicant has submitted two Post Approval Change Management Protocols (PACMPs).

The 2 PACMPs are considered acceptable.

Adventitious agents

No animal- or human-derived material is used in the manufacture of Rybelsus and *S. cerevisiae* is not a natural host for mammalian viruses. Therefore no virus clearance study has been performed, which is acceptable.

All raw materials used in propagation and fermentation, recovery and purification steps, and in the synthesis of the acylation agent are tested and released by the Applicant according to established specifications and acceptance criteria. The MCB, WCB, end-of-production cell bank and late extended cell bank are all tested for microbial purity. Tests for possible contamination with bacteria and fungi during production are performed at release for both active substance and finished product which are tested for total aerobic microbial count, total yeast and mould count and *Escherichia coli*.

The adventitious agents safety evaluation is considered satisfactory.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

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

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

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

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality point of view, the marketing authorisation application for Rybelsus is considered approvable.

2.3.6. Recommendation(s) for future quality development

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

2.4. Non-clinical aspects

2.4.1. Pharmacology

Semaglutide

Primary pharmacodynamics: in vitro

Semaglutide is a long-acting human glucagon-like peptide-1 (GLP-1) receptor agonist, which specifically activates the GLP-1 receptor (GLP-1R). Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification. Semaglutide has a 94% structural homology to native GLP-1, a molecular weight of 4113,58 g/mol and is good soluble in an aqueous solution. Semaglutide is suitable for once-weekly administration in humans. The pharmacological mechanism of GLP-1R agonists is well described in the literature, with blood glucose lowering and body fat loss mediated by lowered intake of calories. The primary pharmacological target tissues for GLP-1R agonists are the pancreas (beta-cells), the gastrointestinal system and the brain. The amino acid sequence of GLP-1 is preserved in mammals, and only one receptor, the GLP-1R, has been identified. Rat and human GLP-1R have 90% homology and monkey and human 99%. The GLP-1R is a G-protein coupled receptor, and the cellular action of GLP-1 is mediated through the G-protein and subsequent activation of adenylate cyclase leading to increased cAMP accumulation.

Baby hamster kidney (BHK) cell membranes, stably expressing the human GLP-1 receptor, were used to characterize the *in vitro* pharmacological receptor effect of semaglutide using binding and functional studies on the human GLP-1 receptor. The binding affinity of semaglutide to the GLP-1 receptor, using the membrane preparation, was found to be influenced by albumin concentrations.
The results of the functional, receptor activating, studies, measuring cAMP production, using 0.1% BSA, showed that semaglutide is a GLP-1 receptor agonist with a potency of 0.15 nM, which is comparable to liraglutide and 8-fold less potent than GLP-1 itself.
In an *ex vivo* study using rat isolated perfused pancreas, semaglutide, stimulated insulin secretion dose-dependently. Two pancreas preparations were studied with increasing concentration of semaglutide, and the EC_{50} of insulin secretion was estimated to be ~14 nM.

Primary pharmacodynamics: in vivo

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

In male diabetic db/db mice, upon single or repeated 4-week sc dosing, semaglutide lowered blood glucose dose-dependently and had a long duration of action. The ED_{50} for lowering of blood glucose (6 hours

post-dosing) was estimated to be 1.2 µg/kg for semaglutide, whereas it was about 20-fold higher for liraglutide indicating that semaglutide was more potent *in vivo* than liraglutide. The maximal effect on blood glucose lowering was comparable for semaglutide and liraglutide and was obtained at 4 - 8 µg/kg for semaglutide in the 4-week study. The effect on body weight was maximal at a dose of 21 µg/kg.

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

GLP-1 and its analogues are, among other effects, able to reduce food intake, which is an important aspect in the treatment of obesity and diabetes. The subchronic efficacy of semaglutide on body weight reduction was evaluated in diet-induced obese (DIO) aged female rats, which were given chocolate in addition to normal chow for 9 months. Subcutaneous doses of 1.2 and 4.1 µg/kg once-daily for 77 days led to a dose-dependent, significant decrease in body weight, primarily from fat. Furthermore, semaglutide dose dependently decreased overall food intake, which mainly consisted of chocolate. Leptin, total cholesterol and free fatty acids were significantly decreased after treatment with semaglutide while plasma glucose, HbA1c, insulin, glucagon and triglycerides were not changed.
The effects of semaglutide on hypothalamic appetite signals were evaluated in high fat diet obese (DIO) mice. Dosing of semaglutide for 18 days (0.15 mg/kg, s.c., daily) significantly lowered body weight. This was associated with increased mRNA expression of the satiety peptide cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus (ARC) in the hypothalamus. Expression levels of the hunger peptides neuropeptide Y (NPY) and Agouti-related peptide (AGRP) in the ARC in hypothalamus were not different between semaglutide and vehicle but were lower than in the weight-matched vehicle group.

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

The access and neuronal interaction of semaglutide in the rodent (SD rat, C57BL mice) brain was investigated using peripherally administered fluorescently labelled semaglutide. Semaglutide was shown to have access to discrete brain regions expressing the GLP-1R including some of the well-defined circumventricular organs. Fluorescently labelled semaglutide also gained access to brain regions protected by the blood brain barrier (BBB) such as NTS (nucleus tractus solitarus) in the brain stem and in the hypothalamus, where it was present in CART positive neurons in the ARC. The fluorescent signal was lost in the GLP-1R Knock-Out (KO) mouse, suggesting dependence upon binding to the
GLP-1 receptor. Electrophysiological measurements of mouse brain slices revealed that semaglutide (100 nM) directly stimulated Pro-opiomelanocortin (POMC)/CART neurons and indirectly inhibited neural activity in neurons expressing NPY.

The effect of semaglutide on development of atherosclerosis was investigated in two hypercholesterolemic mouse models, the ApoE- and LDL-receptor KO mouse models, at sc doses of 4, 12 and 60 µg/kg administered once-daily for 13 or 17 weeks, respectively. These models are widely used to study plaque formation when on a western diet (WD) consisting of high fat and carbohydrate content and 0.2% cholesterol.
In the LDLr KO mouse model, semaglutide showed a significant, about two-third, reduction of aortic plaque area at all three dose levels tested. This effect was accompanied by a significantly reduced body weight gain and a

reduction in plasma TG levels with the highest dose, while plasma cholesterol and cholesterol lipoprotein levels were not changed by semaglutide treatment.
In the ApoE KO mouse, semaglutide treatment showed a significant attenuation of aortic plaque area at all three dose levels tested after 13 week daily treatment. This effect was accompanied by a significantly reduced body weight gain with all doses.
In conclusion, the development of WD-induced aortic plaque lesion areas was attenuated by semaglutide in both KO models at all dose levels. The effect was partially independent of reduced body weight gain.

Secondary pharmacodynamics

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

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

Safety pharmacology

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

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

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

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

The acute effect of semaglutide on cardiovascular function was studied in male conscious unrestrained cynomolgus monkeys equipped with telemetry transmitters and dosed subcutaneously with ascending doses of semaglutide. No effects related to semaglutide were observed on arterial blood pressure (systolic, diastolic and

mean) or the lead II ECG variables examined (RR, PR, QR, QTcF and QTcQ intervals or QRS duration). In conclusion, it was found that there were no clinically relevant findings in cynomolgus monkeys in single doses up to 470 µg/kg (about 14-fold above MRHD based on C_{max}).

In addition, in the repeat dose toxicology study at week 13, 26 and 52, the cardiac electrophysiology was monitored by ECG in male and female telemetered cynomolgus monkeys (10, 60 and 360 µg/kg twice-weekly sc). In this 52-week toxicity monkey study, a left-bundle-branch-block was observed in one female animal at high dose of 360 µg/kg (~27-fold above MRHD). The animal exhibited no clinical signs attributable to the ECG finding and histopathology revealed no correlating changes. Cardiac bundle-branch blocks are an ocional finding in monkeys and humans, and are in most cases a consequence of other underlying cardiac diseases. Although histopathology revealed no changes in the heart, the ECG finding was considered adverse. This issue is being addressed in the clinical part as a combined question.

A renal function study was performed to evaluate the acute effects of semaglutide on the renal system in the rat. Semaglutide caused an acute transient increase in diuresis during the first 8 hours after dosing at the highest doses (23 and 89 µg/kg) and a decrease in the diuresis parameters thereafter (8-24h). These observations are well known effects of GLP-1R agonists in the rat. Acute effects on diuresis have also been shown in humans with native GLP-1, but not following chronic administration of GLP-1R agonists. The NOAEL was determined to be 5 µg/kg.

Pharmacodynamic drug interactions

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

Oral Semaglutide

Safety pharmacology

As part of the oral semaglutide toxicology programme, ECG, heart rate and blood pressure was monitored in the 6-week and 17-week repeat dose toxicology studies in cynomolgus monkeys, which were given both semaglutide (0, 5, 20 mg/kg, QD, po) and SNAC (up to 300 mg/kg, QD, po) for the 6-weeks or 17-weeks. In both studies no toxicologically relevant treatment related effects on heart rate, blood pressure (systolic, diastolic, mean arterial), or ECG parameters (P, PR, QRS, ST, QT, QTc) were found.

SNAC

Oral administration of therapeutic peptides such as GLP-1 analogues is severely hindered by poor absorption across the gastrointestinal (GI) barrier and extensive degradation by proteolytic enzymes. To achieve acceptable bioavailability upon oral administration of semaglutide, the absorption enhancer SNAC is used to increase the uptake across the epithelium of the gastrointestinal tract. Salcaprozate sodium (SNAC) is a small fatty acid derivative with a molecular weight of 279 Da. Several examples exist in the literature describing SNAC's capacity to augment the absorption of compounds. However, as SNAC is a new excipient, a nonclinical programme has been conducted. The pharmacology studies summarised below, describe the application of SNAC for delivery of semaglutide via the oral route.

Primary pharmacodynamics: in vitro

Mechanistically, absorption enhancers can promote transport of drug molecules across the GI epithelium via modification of tight junctions (i.e. paracellular) and/or cell membrane perturbation (i.e. transcellular). *In vitro* experiments using monolayers of human gastric carcinoma epithelial NCI-N87 cell showed that SNAC increased the intracellular accumulation of semaglutide, which indicates that the effect of SNAC is mediated via the transcellular route. SNAC was found to interact with and incorporate in lipid membranes and, with increasing concentrations, increases the fluidity and permeability of the membrane.
It was found that moderate concentrations of SNAC were required to adequately enhance the *in vitro* gastric NCI-N87 epithelial permeability of semaglutide. A ~7-fold increase in the apparent permeability (P_{app}) of semaglutide was seen with 80 mM SNAC as compared to no SNAC.
In ex vivo studies, SNAC treatment (30 mM for 10 min) resulted in a transient 25% decrease in trans-epithelial electrical resistance (TEER) across gastric mucosa, which increased towards baseline at 60 min post-exposure to SNAC. The effects of SNAC on the increased apparent permeability (P_{app}) of semaglutide in the gastric epithelial NCI-N87 monolayers were also found to be transient. Semaglutide has a propensity to form oligomers, which could hinder efficient trans-epithelial passage. Increasing concentration of SNAC, however, resulted in a decrease in the apparent molecular mass, which suggests a shift in the oligomeric state of semaglutide towards its monomeric form. Furthermore, the effect of SNAC was size-dependent, with a diminishing effect on the transport of molecules above 4 kDa.
Incubation of oral semaglutide tablets containing SNAC in small volumes (1-30 mL) of simulated human gastric fluid (SGF) revealed that SNAC increased the pH of SGF from acidic to neutral within 5-15 min. This process may help to facilitate a high(er) pH in the localised stomach environment beneath the tablet and thereby confers enhanced protection of semaglutide from degradation by gastric enzymes, such as pepsin, whose action is most predominant at low pH. In contrast, semaglutide is rapidly degraded in the intestine as revealed by incubations with rat intestinal fluid.

Primary pharmacodynamics: in vivo

To support clinical observations of stomach absorption, mechanistic studies were performed in Beagle dogs. Upon intragastric dosing, comparable plasma levels of semaglutide were seen in dogs that underwent pyloric ligation as to normal dogs that had free access from the stomach to the intestine. In a separate study, using normal dogs, a higher semaglutide exposure (~2-fold) was observed in the splenic vein, draining only the gastric cavity, as compared to the portal vein, draining the gastrointestinal system.
In anaesthetised Beagle dogs, after intragastric dosing followed by aspiration of gastric fluid from underneath the oral semaglutide tablet, it was found that highest levels of both semaglutide and SNAC in gastric fluids were measured in and immediately around the tablet in the stomach. Both concentrations declined >10-fold within 6 cm from the tablet. In line with measurements in gastric fluid, semaglutide immunoreactivity was almost exclusively restricted to epithelial surfaces immediately under and around the site of tablet and absent in regions remote to the tablet surface. Moreover, semaglutide immunoreactivity was found to be mostly restricted to the surface mucous epithelial cell layer in the pit and neck regions of the gastric mucosa. Intracellular uptake of semaglutide was evident as well as detection within blood vessels of the lamina propria mucosae, already 5 minutes after dosing.
In rats, 10 min after oral dosing with semaglutide, a similar distribution was found using electron microscopy (EM), showing by immunohistochemistry reactivity in the cytoplasm among the mucous vesicles and the basal cytoplasm of the mucous cells indicating transcellular transport of semaglutide, while no immunoreactivity was found in the extracellular space under junctional complexes, indicating an absence of paracellular-directed

absorption.
The impact of food on the oral bioavailability was studied in Beagle dogs given oral semaglutide. Exposure (AUC) was decreased by ~60% and ~80%, when feeding 30 min or 15 min after dosing, respectively, compared with 240 min post-dose fasting.

Secondary pharmacodynamics

SNAC and its principal metabolites (E494, E506, E1245, E1246 and E1247) were tested in a broad range of in vitro and in vivo binding and functional assays (>160) including biochemical receptors, ion-channels and neurotransmitter transporters. Overall, no clinically relevant binding or activity of SNAC or its metabolites was identified.

Safety pharmacology

The safety pharmacology studies were designed to investigate the effect of SNAC on vital organ function (central nervous system, respiratory system and cardiovascular system).

The effect of a single dose of SNAC (250 - 1500 mg/kg) on the central nervous system was studied in the rat CNS (Irwin) test. In two studies no significant gross behavioural or physiological changes were observed, at 0.5, 4 and 24 h post-dose in rats receiving oral treatment with SNAC up to 750 mg/kg, representing >50-fold human Cmax exposure. At 1000 and 1500 mg/kg abnormal gait (walking on toes), decreased touch response and piloerection were observed. The acute effects of SNAC on respiratory rate and tidal volume were studied in male Sprague Dawley rats given oral doses up to 1000 mg/kg. SNAC, at 0.5 and 4 h after dosing, had no marked respiratory effects in male Sprague Dawley rats. Treatment with 1 mM SNAC (>100-fold above the average clinical C_{max}) did not induce an inhibition of hERG tail current in HEK293 cells stably transfected with hERG cDNA. In addition, the effect of SNAC and E506 (up to 200 µM) was tested on twelve cardiac ion channels. Inhibition of the cardiac ion channels was maximal 16% (SNAC) or 22% (E506) and did not display a clear dose-response relationship. Single oral doses of SNAC up to 600 mg/kg given to conscious telemetered rhesus monkeys did not reveal any effects on blood pressure, heart rate or in the measured electrocardiogram intervals (i.e., values for the QT- and RR-intervals, and derived QTc values).
Furthermore, ECG measurement was included in the repeated dose toxicity study in rhesus monkeys given SNAC orally for 13 weeks (1800 mg/kg, QD) or 9 months (200-600 mg/kg, QD). SNAC did not affect cardiovascular function in these rhesus monkeys after 13- or 39-weeks treatment.

Pharmacodynamic drug interactions

Nonclinical pharmacodynamic drug interaction studies have not been conducted with SNAC.
It is reported that SNAC did not cause an increase in the exposure of co-administered drugs when co-administered at the same time but in separate tablets (with a SNAC-containing semaglutide formulation or in tablets containing SNAC-alone, See Clinical Pharmacology section).

2.4.2. Pharmacokinetics

Methods of analysis

Subcutaneous semaglutide

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

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

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

Oral semaglutide

The methods developed for analysis of semaglutide in plasma with LOCI or LC-MS/MS (rat and monkey) are the same as having been used for Ozempic.

SNAC

Several Liquid Chromatography Tandem Mass Spectrometry assays (LC-MS/MS) methods were developed and validated at different laboratories for the analysis of SNAC (mouse, rat, rabbit and monkey) and its metabolites (rat and mouse) in plasma. The methods were sufficiently validated with satisfactory assay performance, apart from a few minor deviations from the intra-assay accuracy. Storage of the metabolites in plasma generally resulted in values outside acceptance criteria, indicating that degradation has taken place. Nevertheless, since this will result in an underestimation of these metabolite concentrations (at most 20-30%), it is not considered to impact the nonclinical evaluation of SNAC.

Absorption

Subcutaneous semaglutide

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

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

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

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

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

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

Oral semaglutide

PK parameters following a single oral dose of semaglutide (co-administered with SNAC) were investigated in rats and monkeys. Absorption was rapid in all species, with time to maximum concentration (Tmax) being 2h in rat and 4h in monkey, compared to 1.5h in humans. Despite co-administration with SNAC, bioavailability was very low: only 0.16% in monkey, compared to ~1% in humans. However, since no test groups were included where semaglutide is administered orally without co-administration of SNAC, no quantitative data on how SNAC affects the PK of semaglutide is available, and therefore the added value of SNAC has not been demonstrated in animal studies. Moreover, also in the clinical studies, the beneficial effects of SNAC on semaglutide absorption have not been sufficiently demonstrated (see also clinical assessment report).

The pharmacokinetics were dose-proportional, and there was no clear gender effect.

Similar as following s.c. and i.v. administration, the mean dose-normalized concentration was lower in rat than in monkey and human, probably due to faster clearance. The terminal half-life following oral administration was estimated to be 4.3-8.1 hr in the rat, 44-51hr in the monkey and 145 hr in human, which is similar to values obtained after i.v. administration, indicating that the rate of elimination is not limited by the absorption rate from the stomach.

Variability in exposure (AUC and Cmax) following oral dosing was higher than after s.c. and i.v. dosing.

The pharmacokinetics following repeated dosing of oral semaglutide (co-administered with SNAC) was investigated in rats and monkeys. In the studies in rats (2, 6 and 26 weeks) exposure to semaglutide was not confirmed in all animals, but increased with dose (supraproportional). In contrast to s.c. administration, exposure decreased after repeated oral dosing compared to a single dose, although no anti-semaglutide antibodies were observed in the 6 and 26 week studies. In monkey, no clear relationship between dose and plasma exposure to semaglutide was observed at the investigated doses in the 2 week study, although in the 6

week study (using lower doses), Cmax and AUC0-24h increased with dose. In both species no or minor accumulation was observed. No gender differences were noted.

SNAC

PK parameters following a single oral dose of SNAC was investigated in mice, rats (intact and bile-cannulated) and monkeys. Absorption was very rapid in rodents, with time to maximum concentration (Tmax) being only 2-5 minutes and rapid in monkeys (Tmax 5-120 min). Although results from bile-cannulated rats indicate that SNAC is almost completely absorbed from the GI tract, bioavailability was low: 5-16% in rats and ~16% in monkeys, probably due to a significant first pass metabolism. In rodents, AUC generally increased more than proportional with dose, whereas Cmax increased proportionally to dose. Data indicate limited capacity of elimination (metabolism) at high exposure levels. The pharmacokinetics following repeated oral dosing of SNAC showed that exposure (AUC) increased more than proportional to dose at high doses, but remains proportional to dose when tested up to 12 times the human dose (i.e. 12 tablets with 300 mg SNAC). No accumulation was observed in mouse, rat, monkey and humans. No relevant gender differences were observed.

Distribution

Subcutaneous semaglutide

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

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

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

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

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

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

Oral semaglutide

No additional distribution studies were performed using the oral route. The Applicant has argued that the distribution of semaglutide is considered to be the same irrespective of the route of administration. In principle this is agreed, however the much higher oral dose compared to subcutaneous dose and direct exposure to the gastrointestinal tract, may have revealed another distribution pattern.

SNAC

The distribution of SNAC has been studied after single oral administration of ^{14}C-SNAC to male and female mice and rats (albino and pigmented). Radioactivity from ^{14}C-SNAC was rapidly and widely distributed throughout the body. Concentrations of radioactivity in nearly all tissues were less than those in plasma. Highest levels of radioactivity were found in the stomach, small intestines, liver, kidney, and bile duct. SNAC was transported rapidly but in small amounts over the blood brain barrier (brain:plasma 0.06). Blood:plasma ratios were approximately 0.6. SNAC does not bind to melanin or accumulate in pigmented tissues. No relevant gender differences were observed. In partially pigmented rats levels of radioactivity were still detectable after 168h in the skin (pigmented and unpigmented) and adipose tissue (white and brown fat). Tissue half-life for skin (pigmented) was calculated at 244 h. It is noted that the potential for accumulation of SNAC in unpigmented skin has not been sufficiently addressed by the Applicant. This is relevant as the potential for photo toxicity of SNAC has furthermore not been sufficiently addressed. An OC has been raised in the toxicological section for the Applicant to address the potential photo toxicity of SNAC taking into account the potential for accumulation in the unpigmented skin.

Equilibrium dialysis showed that the plasma protein binding of SNAC is moderate to high in mice, rat, rabbit and monkey and concentration independent up to concentrations of 30.000 ng/ml, but decreases thereafter, suggesting saturation of binding (free fraction 12-35%, 5.5-35%, 6.3-32% and 2.8-25%, respectively). Plasma binding of the two β-oxidised metabolites (E494 and E506) and the three glucuronised metabolites (E1245, E1246 and E1247) differs per species (lowest in mice), but is in general low to moderate (free fraction E94 and E506 15-66%, free fraction E1245, E1246 and E1247 57-100%). Plasma protein binding of SNAC and the metabolites is higher in humans (free fraction SNAC 1.6-3.1%, free fraction E94 and E506 7-15%, free fraction E1245, E1246 and E1247 9-59%) and essentially non-saturable up to 100.000 ng/ml. In humans, SNAC binds exclusively to albumin. It is noted that the increased free plasma concentrations of SNAC observed in the animals compared to humans combined with the non-linear kinetics in animals may have contributed to the increased mortality observed in the toxicological studies in animals after dosing with SNAC.

A tissue distribution study in pregnant rats at GD18 showed that SNAC is transferred over the placenta. Exposure in foetal tissue and placenta (assessed by AUCall tissue: maternal blood) were 0.4-0.6 fold maternal blood.

Metabolism

Subcutaneous semaglutide

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

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

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

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

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

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

Oral semaglutide

Plasma metabolite profiles of orally administered semaglutide (co-administered with SNAC) was investigated in male rats and monkeys. In rats, parent compound and two metabolites were observed in plasma, both after administration as oral solution and tablet. In monkeys, parent compound and one metabolite were observed in plasma. In both species, the same metabolites were observed following s.c. administration, however, with s.c. administration route 1 additional metabolite was found in rat plasma and 2 additional metabolites were found in monkey plasma. Following s.c. administration, metabolites observed in rat and monkey are predictive of human metabolites (all metabolites observed in human are also observed in rat and monkey). According to the applicant, the metabolites that are observed are products of proteolytic degradation of semaglutide. In rat and monkey, metabolites observed following oral administration are also observed following s.c. administration. Increases in ^{3}H-water and P8 are observed, probably due to increased degradation in the GI tract. Although there are no data showing the metabolite profile in human plasma following oral administration, it can be assumed that the metabolite profile in animals is representative of human metabolite profile, showing irrespective of route of administration a similar metabolite profile.

SNAC

The *in-vitro* metabolism of radiolabelled SNAC was studied in hepatocytes from rats, Rhesus monkeys and humans. In all species. it was shown that SNAC is metabolised by β-oxidation (resulting in metabolites E494 and

E506) and sequential O-glucuronidation (resulting in metabolites E1245, E1246 and E1247. Three UGT enzymes (UGT1A7, UGT1A8, and UGT2B7) were shown to be responsible for the glucuronidation. The *in-vivo* metabolism of semaglutide was investigated by metabolite profiling and LC-MS/MS of radiolabelled semaglutide in mouse, rat, monkey and human (plasma and excreta). Overall, the metabolic pathway in humans was found to be similar to that in the animal species, with the primary pathways of SNAC metabolism being β-oxidation, followed by O-glucuronidation of the β-oxidation metabolites, and direct O-glucuronidation of SNAC. The β-oxidised metabolites E494 and E506, and the glucuronides E1245, E1246 and E1247 are the principal metabolites formed.

In mice and rats, the twice β-oxidised metabolite E506, and its corresponding glucuronide E1247 accounted for 60-80% of plasma exposure, whereas in monkeys and humans the glucuronides E1245, E1246 and E1247 were the most abundant metabolites detected in plasma.

Some species differences were however detected in respect to metabolism of SNAC. Whereas unglucuronidated metabolites were predominately present in rats, the glucuronidated metabolites E1245 and E1247 were mainly formed in humans. The toxicity of the metabolites have been addressed by the Applicant *in vitro*, as described in the mechanistic studies section 4.7.6. It was found that unglucuronidated metabolites inhibited cellular respiration to a much lower extent than SNAC while glucuronidated metabolites have virtually no effect on cellular respiration. Hence, it seems that differences in metabolite pattern are unlikely to contribute to any important species differences in the sensitivity to SNAC toxicity.

Excretion

Subcutaneous semaglutide

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

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

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

Oral semaglutide

In male monkeys, excretion of semaglutide related material in faeces is more following oral administration than after an i.v. dose (48% vs 12.5% in faeces), which may be due to the non-absorbed semaglutide. In addition, the excretion of semaglutide in urine after oral administration is comparable to i.v. administration (14.8% vs 20.1% in urine).

SNAC

Excretion of orally administered ^{14}C-SNAC has been analysed in mice, rats (intact and bile duct cannulated), and humans. In all species, the majority of the radioactive dose is recovered in urine (87% in mice, 90% in intact rats and 82% in humans). In rats as well as humans, SNAC is predominantly excreted as the glucuronide conjugates (E1245, E1246, E1247).

In bile-cannulated rats, the amount excreted in urine was lower (71%), and 27% was excreted in bile, indicating enterohepatic recirculation occurs in intact rats.

Following oral administration of 500 mg SNAC to lactating female rats at approximately 10 days post-partum results have indicated that SNAC is transferred into rat milk with a AUC ratio of milk to maternal plasma of 5.3, indicating preferential sequestration of ^{14}C-SNAC and/or its radiolabelled metabolites into milk.

Pharmacokinetic drug interactions

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

2.4.3. Toxicology

Semaglutide

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

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

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

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

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

Additional repeated dose studies with semaglutide, usually in combination with SNAC, via the oral route of administration in rats using gavage and in monkeys using enterocoated capsules have been submitted in the current procedure. There are no additional toxicities identified for the oral administration of semaglutide as compared to the subcutaneous route, as most effects observed are secondary effects related to the pharmacological effect of reduced body weight gain and food consumption.

Semaglutide is not genotoxic in vitro or in vivo.

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

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

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

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

It is agreed that the mechanism demonstrated is specific for rats and could explain the malformations seen in the rat foetuses. Although undoubtedly this mechanism is responsible for most of the malformations observed, it cannot be excluded that other mechanisms that may not be rat specific are also involved. This is based on the

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

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

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

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

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

A juvenile study was performed where rats from the age of 21 days were dosed for 11 weeks. Apart from general signs of toxicity, sexual maturation and fertility were investigated. Sexual maturation was delayed for both sexes, but this did not coincide effects on fertility or mating performance. No histopathological findings were noted, and therefore it is considered likely that the delay is due to the decreased body weight gain of the treated

animals. No new findings were seen in these juvenile animals that were not seen in the adult animals. This study is of limited relevance in the current procedure, as the indication applied for is in adults only.

Although all impurities present in in the batch tested in the 26-week rat study are at lower percentages than the proposed specification limits, the effects seen are considered pharmacologically related to semaglutide or not relevant for humans. Since the exposure is sufficiently high in the rat study, the impurities are considered toxicologically qualified. Tightening of the limits is, however, requested, see quality AR.

SNAC

Repeated dose toxicity studies with SNAC were performed in rats (up to 52 weeks) and monkeys (up to 39 weeks). Doses used resulted in exposures in most studies far in excess of human exposure to SNAC. Exposures are compared to the human SNAC AUC after a dose of 300 mg, measured in trial 3991 of 1636 ng.h/ml. A 13-week study in mice was of limited value since only blood samples were taken from the high dose group to perform haematology and clinical chemistry.

The urinary system was a target organ of SNAC in both species. This was evident as changes in urine parameters (potassium, chloride, sodium, pH, plasma creatinine). Increased kidney weight was only seen in rats, but consistently across all studies. There were no accompanying histopathological changes in the kidney, however. The lowest dose at which effects on urine parameters were seen was 1200 mg/kg/day in cynomolgus monkeys which is presumably around 120-fold human exposure although TKs are only available for rhesus monkeys, and the lowest dose tested in rats of 90 mg/kg/day, presumably around 2-fold human exposure in rats although the TK is not available for this dose. The exposure margin for the effect on kidney weight is 32 for males and 19 for females. The effect on the urinary system could be pharmacologically related. It was, however, further shown that no synergistic renal effects are expected when SNAC and semaglutide is administered in combination. This is furthermore supported by no relevant or adverse findings in long-term carcinogenicity studies and clinical trials.

The liver also appeared as a target organ in both species. Effects seen were limited to increased liver weight in monkeys at the highest dose tested of 1800 mg/kg/day (~180-fold human exposure), and slight increases in ALP in SD rats at 250 mg/kg/day (7-fold human exposure) and increases liver weight in Wistar rats at 500 mg/kg/day (presumably ~18-fold human exposure). Considering the lack of histopathological findings relating to the liver, the inconsistency of the findings, and the high exposures, the liver effects are unlikely to be relevant humans.

Red blood cells and consequently haemoglobin and haematocrit were increased in rats only. However, the increase was slight and only occurred at the highest dose tested which was 26-fold and 11-fold for females and males respectively. It is unlikely that the effect on RBC's is relevant for humans.

Another rat-specific effect is a drop in globulin levels, seen in several of the studies. However, this effect was only seen at high doses, and not in the long-term 52 week study, and is therefore not likely to be relevant for humans.

A series of mechanistic studies, both in in-vitro and in-vivo were conducted to investigate the mortalities that occurred in all species after treatment with SNAC. In rats, high doses of SNAC resulted in reduced glucose and increased lactate levels (in both plasma and CSF), and reduced heart and liver ATP levels. These findings are in line with an effect of SNAC on cellular respiration. This was confirmed in in-vitro studies, where it was shown that SNAC can inhibit complex I in the electron transport chain in mitochondria, and thereby inhibit ATP formation, and increase the NADH/NAD+ ratio. This in turn results in increased glycolysis to generate ATP, and formation

of lactate from pyruvate to generate NAD^+. Mortality and clinical signs occurred only in animals with very high Cmax total of at least 500000 ng/ml (1790 µM). This corresponds to around 350 µM Cmax free in rats. It is therefore likely that cellular concentrations that are near the IC50 for inhibition of rat complex I of 558 µM are reached. In comparison, the IC50 for human complex I is 752 µM, which is far higher than the average free Cmax of SNAC in human of 0.069 µM, or even the highest free Cmax ever measured in human of 0.69 µM. Due to this large safety margin, the risk of inhibition of cellular respiration by SNAC as seen in some animals after high SNAC doses, is negligible in humans. The potency of the principle metabolites of SNAC towards inhibiting the cellular respiration of cells was furthermore investigated *in vitro*, which showed the metabolites was significantly less potent than SNAC, with a factor 10 or more.

A local tolerance study was performed in dogs, receiving a single dose of 300 mg in a tablet or liquid formulation. No adverse findings were seen in the dogs. This study is somewhat limited however due to the single dosing, and therefore only an acute effect could have been observed, while treatment will be chronic in patients. However, other data are available. There were no effects on the stomach of monkeys dosed up to 600 mg/kg/day corresponding to around 2400 mg/day for 39 weeks, or in monkeys dosed with 300 mg/day for 16 weeks, including detailed stomach examinations. In rats, however, the stomach was a target organ, with epithelial hyperplasia of the non-glandular stomach, consistently across most studies. The applicant argues that these findings were only present in animals that were terminated within 60 minutes post-dose, and not after 24 hours post-dose. Although it is not always clear from the study reports, it appears that for the 52-week study BNA00004, termination of the animals occurred 24 hours post-dose and stomach effects were indeed seen in these animals. However, the lack of acute effects in dogs and chronic effect in monkeys regarding the stomach, with appropriate dosing levels, it is unlikely that the stomach is the target organ in humans. No further studies are required.

SNAC is not genotoxic in vitro or in vivo.

Carcinogenicity of SNAC was studied in transgenic rasH2 mice for 6 months, and in SD rats for 2 years. There was no increase in tumour incidence in either study, and therefore is it concluded that SNAC has no carcinogenic potential when tested around clinical exposure and around 2-fold clinical exposure in male and females mice, and up to 32- and 22-fold clinical exposure in male and female rats. Although the exposure was rather low in the mouse study, it is considered sufficient due to the presence of the negative rat study.

There were no effects on male or female fertility in rats when treated up to 1000 mg/kg/day, with or without heparin. No TK data are available for this study, but exposure is assumed to be sufficient and around 10- to 20-fold human exposure based on TK data from the rat 26-week study.

Embryofoetal development was tested the pivotal rat study with a single dose group of 1000 mg/kg/day. However, additional dose groups of 500, 750 and 1000 were included that were dosed together with 5000 U/kg/day of heparin. There was a single mortality in the 1000 mg/kg/day group without heparin, but no treatment-related effects on embryofoetal development were observed.

In the DRF study in rabbits, a dose-dependent increase in mortality was observed, with all dam expired in the high dose. There were effects on embryofoetal development in the DRF study from 1500 mg/kg/day and higher, with increased early resorptions. In the pivotal rabbit study with a single dose group of 1000 mg/kg/day SNAC only, there were no effects on the F0 or on embryofoetal development. The NOAEL for both species is therefore 1000 mg/kg/day. No TK was performed in either study. For the rat, exposure is assumed to be sufficient and around 10- to 20-fold human exposure based on TK data from the rat 26-week study. However, for the rabbit there is no TK data available. Due to the lack of findings, there is no real concern for humans regarding embryofoetal toxicity.

A pre- and postnatal development study was performed in rats with a single dose group of 1000 mg/kg/day. However, additional dose groups of 500, 750 and 1000 were included that were dosed together with 5000 U/kg/day of heparin. There was a slight decrease in maternal body weight gain of the F0 animals. This could have resulted in increases in stillborn pups and pups dying at days 1-4 after birth. However, since the reduction in body weight was only slight, other causes cannot be ruled out. In the additional dose groups which included heparin however, no effects on pup survival were seen up to 750 mg/kg/day SNAC. Therefore, this dose can be considered the NOAEL for pre- and postnatal development. No TK data are available for this study, but exposure is assumed to be sufficient and around 25-fold human exposure based on TK data from the rat 52-week study. There were no effects on the F2 in any dose group.

An immunotoxicity study was performed in rats for 28 days with doses up to 500 mg/kg/day. There were no effects observed, and therefore, it is concluded that SNAC has no potential for immunotoxicity.

Three potential impurities of SNAC, α-methyl-SNAC, E655 and E1026, have been identified and included in the specification of SNAC with a maximum level of 0.15% according to ICH Q3A(R2) guideline. The impurities have been detected in SNAC batches in the range 0.01-0.03%. According to the Applicant, an evaluation of the impurities according to ICH M7 has been performed, which shows that the impurities are classified as Class 5 (non-mutagenic) impurities. Upon request, the documentation establishing the non-genotoxic potential of the impurities of SNAC according to ICH M7 was provided.

No studies to address photo toxicity have been submitted. However, the Applicant has shown that SNAC has an UV absorption peak at a wavelength of 301 nm, a molar extinction coefficient (MEC) of 4122 $L \times mol^{-1} \times cm^{-1}$ and was shown to be photostable. Further documentation was provided to investigate the phototoxic potential of SNAC according to ICH S10. Results from a 3T3 NRU *in vitro* assay performed with the structurally similar compound octyl salicylate resulted in negative predictions for phototoxicity. Furthermore, in silico evaluations of structurally similar compounds were conducted which also indicated a negative potential for phototoxicity. Based on the provided information, it is assessed that the weight of evidence points towards SNAC being of limited phototoxic potential.

2.4.4. Ecotoxicity/environmental risk assessment

Semaglutide

The active substance semaglutide is a GLP-1 analogue, substituted with a non-human amino acid Aib8. Semaglutide is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae) and chemical modification. Although a non-human amino acid has been included in the peptide, the molecule is expected to be readily biodegradable. Therefore, semaglutide is not expected to pose a risk to the environment.

Semaglutide is not expected to pose a risk to the environment, as it is a GLP-1 analogue with an aminoacid substitution and linked to a fatty diacid sidechain with two ADO spacers and one GLU spacer.

SNAC

No ERA has been provided for the excipient SNAC. The Applicant has provided a sufficient justification for not performing an ERA for the excipient SNAC and its metabolites, including a QSAR analysis. This is accepted.

2.4.5. Discussion on non-clinical aspects

Overall the pharmacodynamics studies showed that the oral formulation of semaglutide + SNAC is primarily disintegrated in the stomach, and absorption occurs only in very close proximity of the disintegrating tablet. No PD studies describing primary pharmacology of semaglutide delivered orally have been performed. This is due to the expectation that the effect of semaglutide is dependent on systemic exposure.

Oral semaglutide has been formulated in clinical studies using tablets with 300 mg SNAC. The amount of SNAC in the tablet is independent on the strength of the semaglutide tablet (3, 7 or 14 mg). The safety margins with respect to findings has been calculated on MHRD of both semaglutide and SNAC. Therefore the SmPC clearly states that only one tablet should be taken, e.g. it should not be recommended that two 7 mg tablets could be used instead of one 14 mg tablet.

From the pharmacokinetic point of view, the rat and monkey were the most relevant species regarding toxicology, as these had been utilised in prior applications too. The rat appears to be the most sensitive species regarding SNAC. However, the mouse shows limited exposure in the 26 weeks study, most likely due to non-optimal kinetic sampling, as SNAC is very rapidly absorbed, and the first blood sampling time point was at 30 minutes.

Large inter- and intra-variability has been observed across species following oral dosing of semaglutide, both regarding plasma levels of semaglutide and SNAC. This may have had an impact on findings in pharmacodynamic and toxicological studies, i.e. as it has sometimes not been possible to establish exposure of the tested animals, and this has been reflected in some of the conclusions of certain sections of the report.

The toxicology programme for semaglutide (p.o.) consisted of only repeat-dose studies of up to 6 months or 17 weeks duration (rats by gavage and cynomolgus monkey by capsules, respectively). All other studies were performed with s.c. administration and have been submitted previously in support of s.c. semaglutide (Ozempic). A full nonclinical study package has been presented for the active excipient SNAC, albeit some of the studies were performed previously in support of a different co-formulation with SNAC. Only the SNAC alone groups have been discussed in detail in the documents prepared by the Applicant, and in the non-clinical assessment reports. Semaglutide has an identified risk regarding reproduction, and C-cell carcinomas have been observed in the rodent studies. These findings are reflected, along with all other relevant findings, in the SmPC – which is in line with the approved SmPC for Ozempic. No SNAC data regarding the observed mortalities in all nonclinical species tested is included in the SmPC, which, based on the high safety margins for the observations of sudden death, can be accepted. Excretion of semaglutide and SNAC in rodent milk has been included in SmPC section 4.6.

2.4.6. Conclusion on non-clinical aspects

All non-clinical issues have been sufficiently addressed and there are no objections to registration of Rybelsus from a non-clinical point of view.

2.5. Clinical aspects

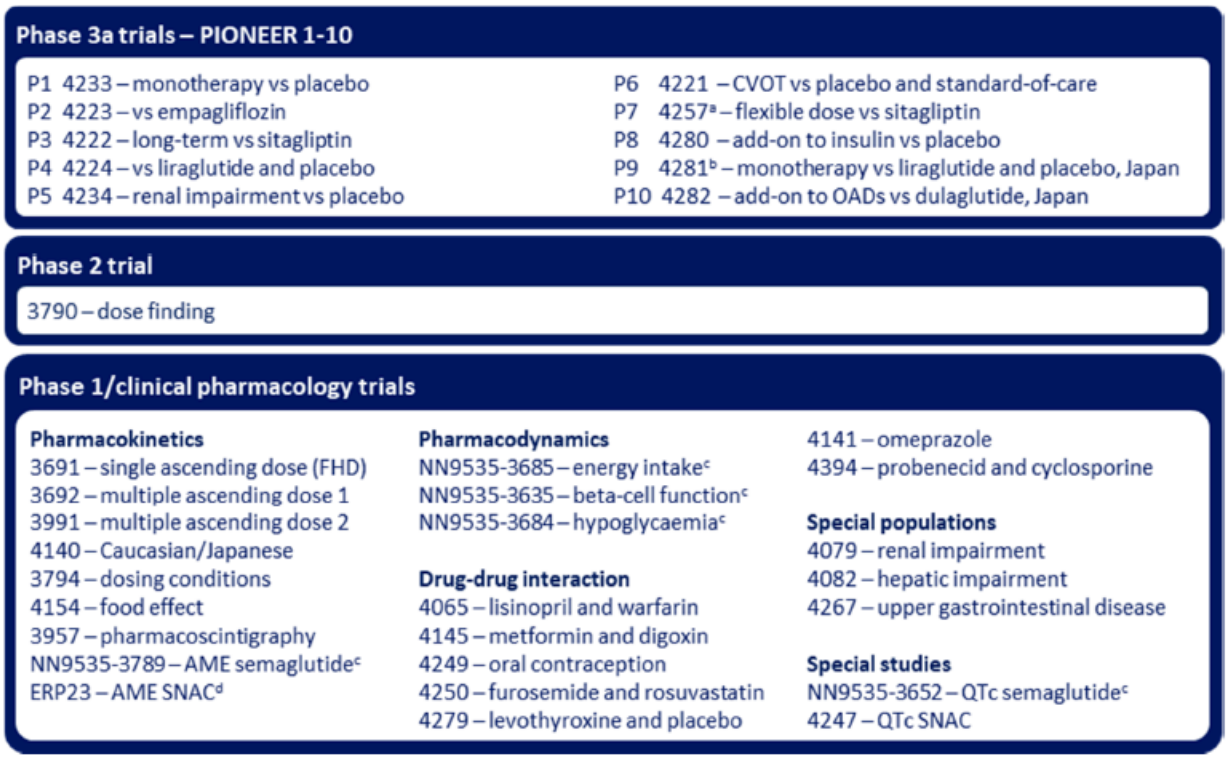
2.5.1. Introduction

The clinical development of oral semaglutide includes 24 completed Phase 1 studies and 6 Phase 3 studies. Some of the clinical pharmacology studies have been conducted with subcutaneously administered semaglutide and have been previously submitted and assessed during the marketing authorisation of Ozempic 0.25 mg, 5 mg, and 1 mg solution for injection in pre-filled pen (semaglutide s.c.), procedure EMEA/H/C/004174.

The clinical development programme comprised 18 clinical pharmacology trials, a phase 2 dose-finding trial and ten phase 3a trials (PIONEER 1–10) with oral semaglutide. The phase 3a trials included a total of 9543 randomised subjects, of whom 5707 were exposed to oral semaglutide. The programme included a dedicated cardiovascular outcomes trial (CVOT), PIONEER 6, to assess the cardiovascular safety of oral semaglutide. An overview of the clinical development programme of oral semaglutide is presented in Figure PK-3.

- Tabular overview of clinical studies

Figure PK-3 - Overview of clinical trials included in the oral semaglutide development programme



Notes: [a.] Includes an ongoing extension trial; [b.] phase 2/3 trial; [c.] trials with s.c. semaglutide for T2D (Ozempic®). The Novo Nordisk project number NN9535 is included for these trials; d. trial sponsored by Emisphere Technologies. Abbreviations: AME: absorption, metabolism and excretion; FHD: first human dose; QTc: corrected QT interval

GCP

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

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

2.5.2. Pharmacokinetics

Semaglutide is a potent human GLP-1 analogue. Compared to human native GLP-1, the semaglutide molecule has three minor but important modifications which make it suitable for clinical use. Oral semaglutide is aimed for once-daily administration. The pharmacokinetics of orally administered semaglutide has been investigated in healthy subjects and patients with T2D using single-dose studies, in repeat-dose studies, in subjects with renal and hepatic impairment, different races (Caucasian and Japanese) and several DDI studies. The pharmacokinetics of SNAC has been studied as well.

Orally administered semaglutide has a low absolute bioavailability and a highly variable absorption. Daily administration in combination with a long half-life reduces the day– to-day fluctuation of the exposure.

Methods

Two different types of validated assays were used to measure total semaglutide plasma concentrations. At first, a luminescent oxygen channelling immuno (LOCI) assay was used, but the assay was changed to an LC-MS/MS assay as it was found that measurements with the LOCI assay were influenced by a matrix effect. The LOCI assay was used in 1 study (3691) and the reduced sensitivity hampers conclusions drawn in that study. However, it was of no further concern, as the results of that study were not directly compared to others. For all other studies, plasma concentrations were measured with the appropriately validated LC-MS/MS assay. For the analysis of semaglutide in urine, an appropriately validated LC-MS/MS bioanalytical method has been used.

The bioanalytical methods used to determine SNAC and its beta oxidised, and glucuronide metabolites were appropriately validated and suitable.

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

The plasma concentration-time data for semaglutide were analysed by non-compartmental methods and standard pharmacokinetic parameters have been calculated. Descriptive statistics of pharmacokinetic variables have been provided for the pharmacokinetic studies. Acceptable standard statistical methods and software have been used.

Clinical population PK and PK-PD models were developed to gain insight into the PK properties and exposure-response relationships of semaglutide after oral dosing. In the population analysis, the applicant focusses on estimating the average concentration of semaglutide after oral administration, but did not evaluate the fluctuation in exposure within subjects. As a consequence, using the average concentration cannot be used to evaluate variability in treatment response in efficacy markers as HbA1c and safety parameters. The population models were not suitable to quantify the day –to- day variability of the bioavailability (F) most likely

due to lack of sampling in the absorption phase, lack of recording of drug intake conditions (such as time of administration and intake of fluid or meals).

For the drug-drug interaction program, the conventional no-effect boundaries of 0.80 and 1.25 were applied for both semaglutide and SNAC, except in the investigation of the impact on semaglutide PK of multiple other tablets in stomach and effect of cyclosporine and probenecid on SNAC PK.

Co-formulation with SNAC

Oral semaglutide is co-formulated in a tablet with SNAC. Based on in vitro data the applicant claims that the novel excipient SNAC is an absorption enhancer.

The in vitro tests 309788, BLMP150301, SBJJ100709, 309790, and 309791 have shown that SNAC increases the local pH around the tablet. This results in reduced pepsin activity and thereby reduced metabolism of semaglutide in the stomach. Further SNAC would lead to an increase in the gastric epithelial and transcellular permeability, resulting in better absorption of semaglutide.

Non clinical studies 309780 and 309771 have shown that high concentrations of semaglutide and SNAC are only found close to the tablet in vivo.

None of the submitted clinical or non-clinical studies investigated the absorption of semaglutide without SNAC.

The SNAC dose was selected based on study 3691. In this study, safety, tolerability and bioavailability of orally administered semaglutide (5 - 20 mg) formulated with different amounts (150 - 600 mg) of the absorption enhancer SNAC was investigated. No data was provided with orally administered semaglutide without SNAC. The main results of the study are presented in Table PK-1. It is not possible to draw any conclusions on the relationship between SNAC dose and uptake of semaglutide based on dose finding study 3691. This study is considered inconclusive due to several analytical and methodological issues. Only 39 of the 70 dosed subjects had any measurable concentration, probably due to an inappropriate bioanalytical assay (with reduced sensitivity, due to the presence of a matrix effect), further the small sample size, the different intake conditions (post dose 5 hour light lunch), and the absence of data on semaglutide without SNAC hamper the interpretation of study data. No SNAC dose- exposure relationship is visible. It has not been demonstrated that SNAC improves the bioavailability in vivo.

All other clinical studies have been conducted with a 300mg SNAC. As there are no clinical data on other strengths the selection of the 300mg dose is considered acceptable.

Table PK-1 Single-dose pharmacokinetics of semaglutide study 3691

Dose (mg)-	N(n)	AUC0-24h (nmol·h/L)	Cmax (nmol/L)	tmax (h)	t½ (h)	CL/F (L/h)	V/F (L)
Part 1:	84	AUC0-last					
Oral sema 5/150	10 (4)	14.32 (58.38)	1.75 (28.09)	2.00 (1.00-10.00)	-	-	-
Oral sema 15/450	10 (3)	2.54 (43.55)	0.93 (63.56)	2.00 (1.50-2.00)	-	-	-
Oral sema 10/600	10 (6)	151.52 (113.50)	3.36 (101.72)	2.25 (1.50-10.00)	-	-	-
Oral sema 20/600	10 (2)	740.13 (75.28)	2.31 (49.05)	174.00 (84.00-264.00)	-	-	-
Oral sema 2/300	10 (2)	22.79 (141.03)	2.72 (114.74)	1.00 (1.00-1.00)	-	-	-
Oral sema 5/300	10(6)	110.17	4.06	1.50	-	-	-

Dose (mg)-	N(n)	AUC0-24h (nmol·h/L)	Cmax (nmol/L)	tmax (h)	t½ (h)	CL/F (L/h)	V/F (L)
		(97.52)	(64.16)	(0.50-2.50)			
Oral sema 10/300	10 (8)	204.61 (102.48)	4.13 (88.16)	2.00 (0.50-168.00)	-	-	-
Part 2:	107						
Oral sema 2/300	24 (6)	13.07 (206.08)	1.67 (116.79)	1.25 (1.00-2.50)	6.25 (189.35)	15.53 (113.61)	302.14 (47.15)
Oral sema 5/300	24 (11)	46.01 (126.45)	2.21 (91.06)	1.50 (0.50-120.00)	7.94 (112.92)	12.31 (176.29)	526.34 (75.27)
Oral sema 10/300	24 (18)	138.37 (104.85)	4.18 (71.78)	1.50 (0.50-168.00)	24.69 (141.64)	8.57 (308.27)	696.90 (55.49)
i.v. sema 0.1/0	10 (10)	121.51 (28.50)	-	-	38.25 (38.20)	0.16 (28.26)	9.73 (27.86)
s.c. sema 0.4/0	10 (10)	1036.46 (47.43)	4.62 (18.61)	48.00 (42.00-72.00)	112.21 (103.25)	0.08 (36.77)	13.85 (14.83)

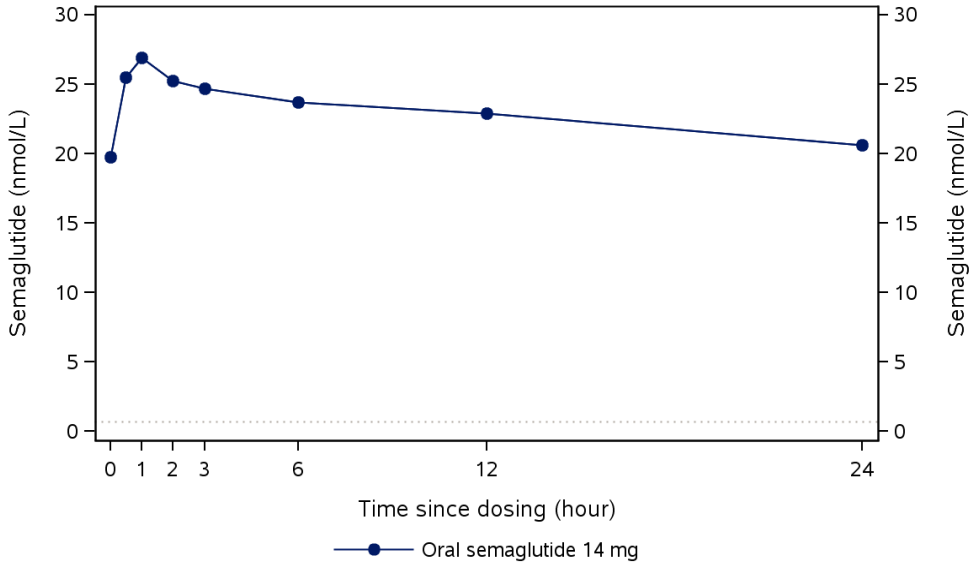
N (n) the total number of subjects dosed and (the number of subjects with measurable plasma concentrations).
Geometric means an (CV%) are presented, for tmax median and range is presented.

Absorption

Semaglutide is poorly absorbed and has a bioavailability of approximately 1% after oral administration. Several multiple dosing studies investigated whether it was possible to reach exposure levels with oral semaglutide co-formulated with 300 mg SNAC comparable to those associated with recommended therapeutic doses s.c. semaglutide (0.5−1.0 mg once weekly). The steady-state PK of semaglutide was investigated in trials 4279, 3991 and 4140, and by modelling of sparse-sampled PK from phase 3a trials.

In trial 4279, following a dose of 14 mg, the steady-state geometric mean AUC0-24h was 544 nmol*h/L (corresponds to Cavg: 22.7 nmol/L) and the geometric mean Cmax was 27.7 nmol/L (see Figure PK-4). In trial 3991, at steady state following 20 mg, AUC0-24h was 742 nmol*h/L (Cavg: 30.9 nmol/L) and the geometric mean Cmax was 37.1 nmol/L. In trial 4140, AUC0-24h was 1105 nmol*h/L (Cavg: 46.0 nmol/L) and the geometric mean Cmax was 53.5 nmol/L with oral semaglutide 20 mg.

Figure PK-4 - Semaglutide exposure at steady state – Trial 4279



Healthy subjects. Oral semaglutide 14 mg at steady-state. Geometric mean profile.

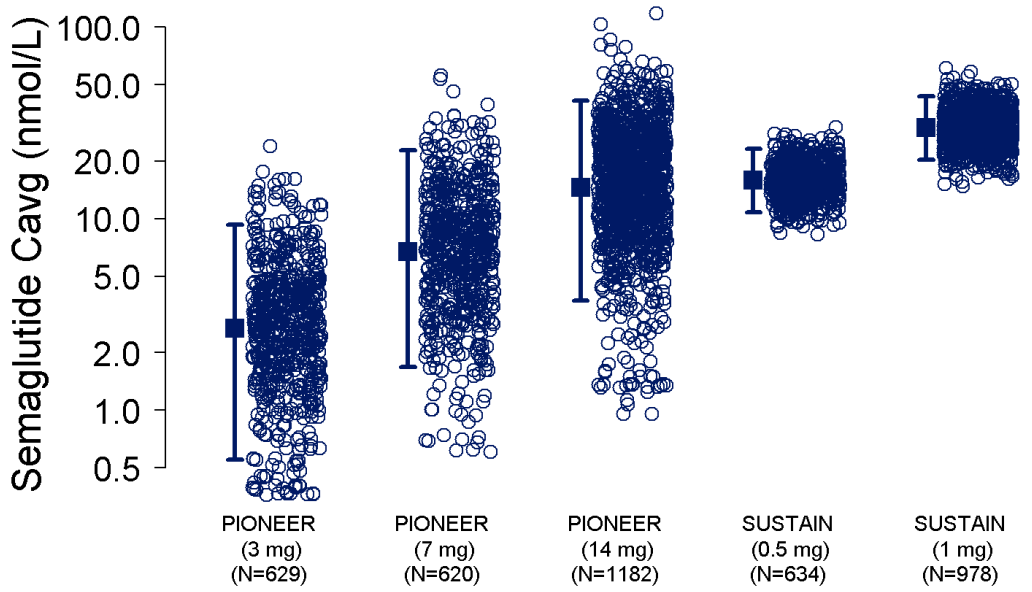
In studies 4065, 4145, 4229 and 4279 multiple doses oral semaglutide 3/7/14 mg have been administered. For the 14 mg strength the mean AUC0-24,ss and mean Cmax,ss were about 540 nmol*h/L and 28 nmol/L. The results of AUC and Cmax were consistent between studies but with high variability.

Oral semaglutide exposure at steady state compared to s.c. semaglutide

Model derived steady-state exposures were estimated based on population pharmacokinetic analysis III and from the s.c. semaglutide phase 3a trials SUSTAIN, see the Figure PK-5. *It should be noted that the model III does not accurately describe the pharmacokinetics of the oral formulation.*

The mean average concentration was comparable between oral semaglutide 14 mg and s.c. semaglutide 0.5 mg (Cavg: 14.6 vs 15.9 nmol/L). Due to the large variability of the absorption of the oral formulation, it is unclear if similar steady state exposure will be achieved in individual patients.

Figure PK-5 - Exposure of semaglutide – oral semaglutide (pioneer 1, 2, 3, 5, 8 and 9) vs. s.c. semaglutide (sustain 1,2,3, and 4) phase 3a trials – modelling



Dosing conditions

The absolute bioavailability of semaglutide dosed orally is approximately 1%. The bioavailability is dependent on dosing conditions and highly variable. Studies 4154, 3794 and 3957 were conducted to investigate the influence of food, the post-dose fasting period and the potential influence of the volume of water. The presence of food or larger volumes of water (>120 ml) in the stomach reduced the absorption of semaglutide. There was no difference between 50 ml or 120 ml of water. In study 3957 it has been shown that semaglutide is absorbed from the stomach. The bioavailability of semaglutide appears to increase with longer post-dose fasting. In study 3794 it was demonstrated that the bioavailability increases up to 120 minutes post dose fasting time. Due to the limited absorption and the influence of food and liquid intake thereon, strict dosing recommendations in the SmPC are considered being relevant. To ensure adequate oral semaglutide absorption and exposure, the recommended dosing conditions are as follows:

- Oral semaglutide should be taken on an empty stomach
- Oral semaglutide should be swallowed whole with up to half a glass of water equivalent to 120 ml. Do not split, crush or chew the tablet.
- Wait at least 30 minutes before the first meal or drink of the day or taking other oral medicinal products. Waiting less than 30 minutes may decrease the absorption of semaglutide.
- If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

Formulations used during clinical development

During the clinical development program the composition of the excipients in the tablet remained the same, however, the drug product strength and drug substance process changed. Bioequivalence between the two drug products with the two drug substances used in the clinical trials have not been demonstrated.

Distribution

The apparent volume of distribution of oral semaglutide at steady state (V_{ss}/F_{sema}) was evaluated in healthy subjects in trials 4140, 4065 and 4145; the mean values were between 14500 and 1900L. These values reflect the low bioavailability of oral semaglutide of approximately 1%. The absolute volume of distribution of semaglutide following IV injection was about 8 L and the apparent volume of distribution V/F following SC administration was 12.5L. These volumes are small and close to the blood volume, indicating that a high fraction of semaglutide is circulating in the blood.

The *in vitro* protein-binding, mainly to albumin, was approximately 99% in human plasma. The unbound fraction was 0.19% and 0.36% in human samples of healthy volunteers (*in vitro* studies 208380 and 213228). The high protein binding prevents semaglutide from being rapidly eliminated from the circulation. Semaglutide passes the placental barrier, blood-brain barrier and is secreted in breast milk, see preclinical section.

Elimination

Semaglutide is extensively metabolised but has a long half-life. The t½ following oral administration of semaglutide was approximately one week, which is in line with previous findings. The apparent clearance of oral semaglutide at steady state (CL_{ss}/F_{sema}) was between 4.5-8 L/h.

In the mass balance study with s.c. semaglutide the cumulative recovery of total radioactivity was 75% of the administered dose; hereof 53.0% in urine, 18.6% in faeces and 3.2% in expired air. In urine unchanged semaglutide accounted for 3.1% of the administered dose (study 3789, semaglutide s.c.). The mean CL/F of semaglutide following s.c. use was approximately 0.05 L/h in patients with T2D as compared to about 0.035 L/h in healthy subjects. This difference is largely attributable to differences in BMI. Mean t½ was approximately 155 hours (149 to 165 hours) in subjects with T2D and comparable to that in healthy volunteers.

Semaglutide is extensively metabolised into many different metabolites by proteolytic degradation of the peptide backbone and beta-oxidation of the fatty acid side-chain. Its most abundant metabolites were P3 (detected in plasma) and U6 and U7 (detected in urine) (study 214379). Semaglutide is almost completely metabolised and degraded into peptides, amino acids and fatty acid fragments. All metabolites accounted for less than 10% of the total amount of semaglutide related material and are not expected to have any activity. One semaglutide isomer (P3C) has been identified and although it is considered likely that it has some activity it is not expected to be of clinical relevance as its concentration is low (<7.7%).

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

Dose Proportionality

Dose proportionality has been assessed in several clinical pharmacology studies. However, due to the large variability in absorption and bioavailability of semaglutide in combination with the limited number of subjects in these trials, the studies are not very suitable for the assessment of dose proportionality. Dose proportionality has also been evaluated via population PK modelling (see Figure PK-5) however none of the submitted models adequately describes the pharmacokinetics of oral semaglutide. Therefore, dose proportionality is not confirmed

but there was no indication of deviation from dose proportionality and clinical data response indicate that there is an increased response with increasing dose.

Time dependency

Steady-state exposure of semaglutide was reached after 4–5 weeks of once daily administration; due to its long half-life, semaglutide slowly accumulates, with an accumulation ratio of 12.6 at steady state based on the clinical pharmacology PK model. Time dependency has only been investigated by the applicant with the use of the population pharmacokinetic modelling. These models do not adequately describe the pharmacokinetics of semaglutide. Time dependency cannot be excluded.

Variability

A high variability has been observed for semaglutide after oral administration, this is in line with the low absolute bioavailability (around 1%). Due to the long half-life of semaglutide, the variability following repeated doses is reduced, compared to variability following a single dose. In healthy subjects a high between subject variability (with CV% around 70%) was observed at steady-state dose levels of semaglutide 10-40 mg daily. For lower doses the variability appeared to be even higher for the 5 mg dose (a total CV% of 389% was calculated (study 3692).The within- and between-subject variability in steady-state exposure were measured over 3 days in two clinical pharmacology trials, Trials 3991 and 4140. At steady-state, the within-subject variability in exposure (AUC0-24h and Cmax) appeared consistently lower than the between-subject variability. For AUC0-24h, the within-subject variability ranged 13.3%–32.6% and the between-subject variability ranged 34.8–74.0%. As a result of the high variability, there is overlap in exposure ranges between the different dose levels. In the phase 3 populations the between subject variability appears to be higher. The observed trough concentrations ranged from approximately 1 nmol/L to 100 nmol/L in different patients, with estimated between subject variability of more than 100% CV. Within-subject variability could not be reliably estimated based on the provided models. It has been shown that food intake and intake with a large volume of water affects the bioavailability of orally administered semaglutide. Up to now, no other covariates have been identified that could explain the high variability in bioavailability. Probably adherence to the dosing instructions is the most critical factor for appropriate absorption. (see *dosing conditions*).

In contrast with very high variability of orally administered semaglutide, the within- and between subject variability in the pharmacokinetics of s.c. semaglutide was low. A within-subject variability of 5–10% and between-subject variability of 17-24% were observed after subcutaneous administration of semaglutide. Thus, most of the high variability of orally administered semaglutide can be attributed to low and unpredictable absorption of semaglutide.

Pharmacokinetics in the target population

Exposure of semaglutide appeared higher in the clinical pharmacology trials than in the phase 3a trials, possibly due to an off-site effect. In Trial 3991, the steady state PK parameters of semaglutide were similar in healthy subjects and patients with T2D. In the phase 3a trials, the estimated apparent bioavailability was approximately 0.4%; corresponding to approximately half of the estimated absolute bioavailability from clinical pharmacology trials. Semaglutide PK is comparable between healthy subjects and patients with T2D. The difference in bioavailability between PK trials and phase 3 trials could be linked to non-adherence to the recommended dosing conditions. Off-site dosing was associated with 34-48% lower exposure compared to on-site dosing.

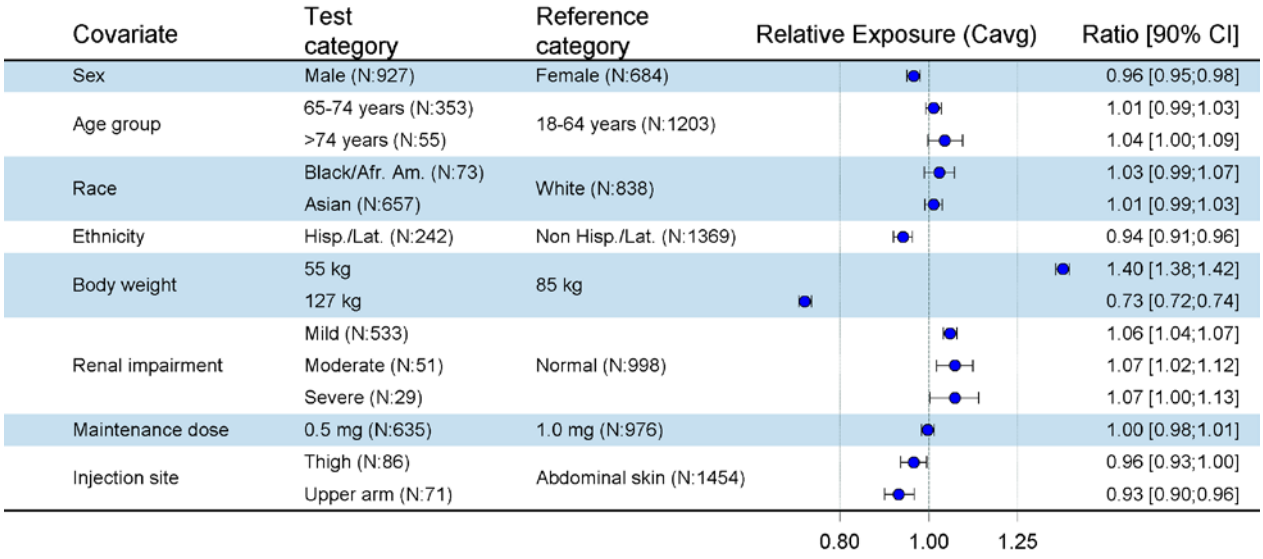
In the target population, the mean steady-state concentrations following oral administration of 3 mg and 7 mg and 14 mg semaglutide were approximately 2.7 nmol/L, 6.7 nmol/L, and 14.6, respectively. With 90% of subjects treated with semaglutide 14 mg having an average concentration between 3.7 and 41.3 nmol/L. For the 14 mg dose, the mean steady-state concentrations were close to the mean values achieved following s.c. administration of 0.5 mg semaglutide (16 nmol/L). For the 3mg and 7mg formulation, the C_{avg} was lower. There is no equivalent dose of Rybelsus for 1.0 mg s.c. semaglutide injection once weekly.

Special populations

The applicant submitted 5 population PK and exposure response models for the oral formulation. However, these models do not correctly describe the pharmacokinetics of oral semaglutide and should not be used for any interpretation of the data. The assessment of covariates on pharmacokinetics and pharmacodynamics of oral semaglutide should rely on the results of the standard non-compartmental studies and the population models submitted in the application procedure of semaglutide s.c.

Based on results from these previously conducted Population PK studies with semaglutide s.c. no dose adjustment of oral semaglutide is required for patients based on intrinsic factors of age, sex, body weight, race, ethnicity, upper GI disease, renal function or hepatic function (Figure PK-6).

Figure PK-6 - Effect of covariates on exposure based on population PK studies for semaglutide s.c.



The applicant conducted four phase I studies in patients with renal or hepatic impairment, subjects with upper gastrointestinal diseases and subjects with different races (Caucasian vs Japanese subjects).

The effect of renal impairment on semaglutide exposure was evaluated in study **4079**. The study included subjects with normal renal function and mild, moderate and severe renal impairment and subjects with ESRD (requiring haemodialysis). A 10-day dosing regimen was used starting with oral semaglutide 5 mg for 5 days, followed by oral semaglutide 10 mg for 5 days. Although hampered by the high variability of the absorption and the low power of the study no consistent effect of renal function was observed.

The effect of hepatic impairment on semaglutide exposure was evaluated in study **4082**. Subjects with normal hepatic function and mild, moderate and severe hepatic impairment (defined according to Child-Pugh classification) were included. A 10-day dosing regimen was used starting with oral semaglutide 5 mg for 5 days,

followed by oral semaglutide 10 mg for 5 days. Semaglutide exposure was similar across the hepatic function groups; no relationship was observed between AUC0-24h or Cmax and the degree of hepatic function.

Upper gastrointestinal disease did not appear to affect semaglutide exposure, about 15% higher exposure has been observed in a dedicated PK study **4267**. This change is not expected to be clinically relevant.

A clinical pharmacology trial was conducted to investigate PK of semaglutide in Japanese and Caucasian subjects (trial **4140**). Semaglutide exposure was about 30% lower in Japanese subjects when compared to Caucasians. Clinical pharmacology trial 4140 was a relatively small trial (n=48). When taking into account the highly variable semaglutide absorption, this study is not very suitable for the assessment of differences between populations. It is preferred to use an appropriate population PK model to assess the differences between races. Based on the population PK models of the s.c. formulation, it can be concluded that race has no relevant effect on the exposure of semaglutide. Therefore no meaningful differences in elimination and distribution are expected for the oral formulation.

Population PK analysis with semaglutide s.c. showed that exposure of semaglutide was inversely correlated to body weight. For oral semaglutide a similar trend was observed in the phase 3 studies. Patients with high body weight have a relatively low exposure, but exposures are in the effective range.

In the phase 3 trials, males had 18 % lower exposure compared to females, contrary to results from clinical pharmacology trials. The difference was still present after correction for baseline body weight. In previous population studies with the s.c. formulation sex did not have a relevant influence on distribution and excretion of semaglutide. Further in the studies with the oral formulation no clinically relevant differences in glycaemic response between male and female subjects were observed, Therefore the observed difference does not appear to be clinically relevant.

The number of subjects exposed to trial product in the phase 3a trials is presented by age group in Table PK-2 . Age had no effect on the pharmacokinetics of semaglutide, as evaluated in the population PK studies, elderly patients (>75 years). A higher proportion of subjects ≥75 years of age reported concomitant illnesses and concomitant medications. The proportion of subjects prematurely discontinuing trial product increased with age (see paragraph 3.3.12). Discontinuation occurred primarily upon dose escalation, however this was not clearly related to dose level or exposure.

Table PK-2 Number of subjects exposed to trial product (oral semaglutide and comparators) by age groups – phase 3a trials (PIONEER 1–10)

	Number of subjects age 18-<65 years/ Number of subjects in total	Number of subjects age 65–74 years/ Number of subjects in total	Number of subjects age 75–84 years/ Number of subjects in total	Number of subjects age ≥85 years/ Number of subjects in total
Phase 3a trials (incl. PIONEER 6)	5785/9534	3019/9534	706/9534	24/9534

Semaglutide has not been studied in paediatric patients.

In patients with obesity and T2DM, bariatric surgery is not uncommon. The use of oral semaglutide has not been investigated in patients with bariatric surgery. It is not possible to predict if semaglutide exposure will be higher (due to decreased gastric metabolism by peptidase) or lower (due to decreased gastric surface) than in patients without bariatric surgery. Due to unpredictability of the absorption and the lack of evidence administration of the

oral semaglutide formulation is not recommended, however the s.c. formulation may be considered in patients with bariatric surgery.

It was not possible to identify a subgroup with low exposure. It cannot be excluded that cultural or behavioural differences between populations may have attributed to variation in semaglutide absorption. However, investigations of the impact of behavioural and cultural factors are not possible with the available data. Adherence to the dosing conditions was not monitored in the phase 3a trials.

Drug interactions

In vitro

All Semaglutide in vitro drug interaction studies submitted in the current application have been previously submitted and assessed. No clinically relevant drug-drug interactions related to inhibition and induction of CYP enzymes or drug transporters by semaglutide are anticipated based on in vitro studies.

In vivo

Semaglutide as perpetrator drug

The company investigated if oral semaglutide influences the absorption of some concomitantly administered oral drugs in interaction studies 4065, 4145, 4249, 4250, 4279 and 4141. The company evaluated drugs with different solubility and permeability properties and/or narrow therapeutic indices that are commonly used by subjects with T2D (see table PK 3). A 33% increase of levothyroxine exposure has been observed which could be clinically relevant and could be resolved with monitoring of the thyroid parameters and dose adjustments for levothyroxine. Modest changes in pharmacokinetics were observed in the drug-drug interaction studies with metformin, furosemide and rosuvastatin, these changes are considered not clinically relevant. However, the changes in the PK of rosuvastatin and potential INR changes of warfarin when co-administered with oral semaglutide could also be clinically relevant. The pharmacokinetics of lisinopril, S-warfarin and R warfarin, digoxin, ethinylestradiol and levonorgestrel was not affected by concomitant administration of oral semaglutide. Oral semaglutide co-administration did not affect exposures of the victim drugs if the two-sided 90% confidence interval for the ratio (with/without oral semaglutide) fell entirely within the no-effect interval (0.80; 1.25).

An increase in AUC but no effect on Cmax was observed for metformin (32%) and levothyroxine (33%). An increase on AUC (28%) and a decrease on Cmax (-34%) was observed for furosemide. An increase in both AUC (41%) and Cmax (10%) was observed for rosuvastatin. The results of the interaction studies are summarised in Table PK–3.

No clinical relevant interaction is expected with other drug that delay gastrointestinal motility.

Table PK–3 Drug-drug interaction: Effect of oral semaglutide – treatment ratios of victim drug exposure – Trials 4065, 4145, 4249, 4250, 4279

Trial	Victim drug[a,b]	N	AUC[c] Ratio[e] (90% CI)	C_{max}[d] Ratio[e] (90% CI)
4065	lisinopril (20 mg)	46	1.07 (0.99; 1.15)	0.96 (0.88; 1.06)
4065	S-warfarin (25 mg)	46	1.08 (1.04; 1.12)	0.88 (0.83; 0.94)
4065	R-warfarin (25 mg)	46	1.11 (1.06; 1.15)	0.91 (0.86; 0.96)
4145	metformin (850 mg)	31	1.32 (1.23; 1.43)	0.98 (0.90; 1.06)

4145	digoxin (500 µg)	31	1.03 (0.96; 1.11)	0.98 (0.89; 1.09)
4249	ethinylestradiol (0.03 mg)	25	1.06 (1.01; 1.10)	0.97 (0.90; 1.05)
4249	levonorgestrel (0.15 mg)	25	1.06 (0.97; 1.17)	0.95 (0.87; 1.05)
4250	furosemide (40 mg)	39	1.28 (1.16; 1.42)	0.66 (0.53; 0.82)
4250	rosuvastatin (20 mg)	33	1.41 (1.24; 1.60)	1.10 (0.94; 1.28)
4279	levothyroxine (600 µg)[f]	43	1.33 (1.25; 1.42)	0.88 (0.81; 0.94)

[a] single dose for lisinopril, warfarin, digoxin, furosemide, rosuvastatin and levothyroxine and multiple doses for metformin (twice daily for 3.5 days) and ethinylestradiol/levonorgestrel (once daily for 8 days). [b] oral semaglutide (20 mg in trials 4065 and 4145 and 14 mg in trials 4249, 4250, 4279) at steady state used as perpetrator drug. [c] $AUC_{0-\infty}$ for lisinopril, S- and R-warfarin, digoxin, furosemide and rosuvastatin; AUC_{0-12h} for metformin; AUC_{0-24h} for ethinylestradiol and levonorgestrel; baseline-corrected AUC_{0-48h} for levothyroxine. [d] baseline-corrected C_{max} for levothyroxine. [e] estimated treatment ratio (with/without co-administration of oral semaglutide). [f] measured as baseline-corrected T4. The conclusion that oral semaglutide co-administration did not affect exposures of the victim drugs was declared if the two-sided 90% confidence interval for the ratio (with/without oral semaglutide) fell entirely within the no-effect interval (0.80; 1.25). N: number of subjects contributing to analysis

Although co-administration of semaglutide at steady state did not affect the mean INR values, the individual INR measurements of some patients appeared to be affected. Therefore frequent monitoring of INR is recommended upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives.

The estimated treatment ratio (with/without oral semaglutide) of the mean incremental AUC of INR and maximum INR response were:

- $iAUC_{INR}$, 0 144h: 1.00 $[0.93; 1.06]_{90\%CI}$
- INR_{max}: 0.98 $[0.96; 1.01]_{90\%CI}$

Semaglutide is a GLP-1 receptor agonist which delays gastric emptying. This has been shown in an interaction study with paracetamol and semaglutide s.c. The observed effects in some of the DDI studies may be attributed to this delayed gastric emptying.

Semaglutide as victim drug

In study 4279, it was shown that the presence of multiple other tablets in the stomach affected the PK of oral semaglutide. AUC0-24h and Cmax were 34% and 32% lower when oral semaglutide was co-administered with 5 oral placebo tablets compared to when administered alone.

Co-treatment of oral semaglutide with a drug that increases gastric pH has been investigated in study 4141. A 15% increase of semaglutide exposure was observed, which was not statistically significant and is not expected to be clinically relevant taking into account the high variability of semaglutide.

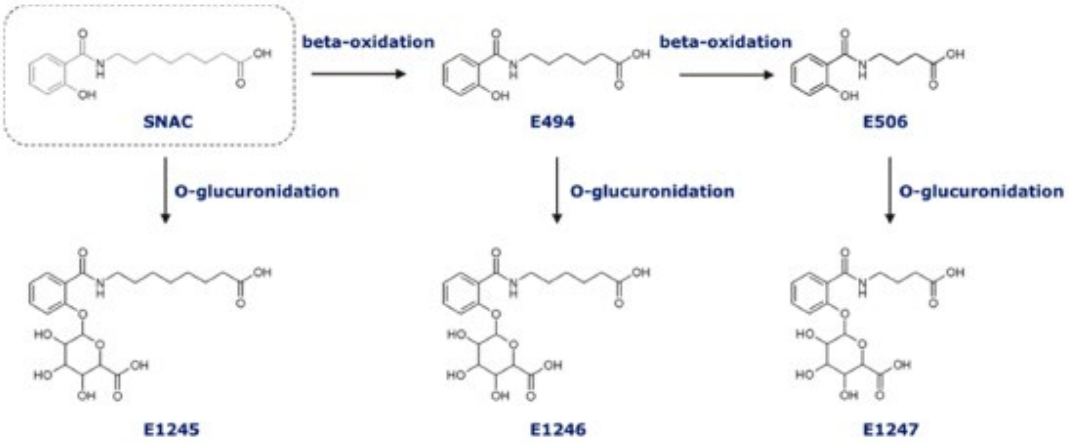
Pharmacokinetics of SNAC

The pharmacokinetics of SNAC are consistent across trials. SNAC is quickly absorbed with a t_{max} of 0.5-1 hour. Due to a short half-life, no accumulation is observed after multiple doses of SNAC. Food has some effect on SNAC absorption.

SNAC is distributed through-out well-perfused tissues, cross placental barrier and is secreted in milk. The apparent volume of distribution (Vss/F) of SNAC at steady state was approximately 500 L. At least 82% of the SNAC was absorbed and recovered from urine in the human mass balance study and it can be concluded that SNAC is extensively distributed into the tissues. This is in line with non-clinical observations.

SNAC is extensively metabolised and rapidly eliminated, with a t½ of approximately 2 hours. It is metabolised via β-oxidation and glucuronidation. A total of five metabolites of SNAC were detected in plasma. The metabolites of SNAC are rapidly eliminated and do not accumulate (Figure 6a).

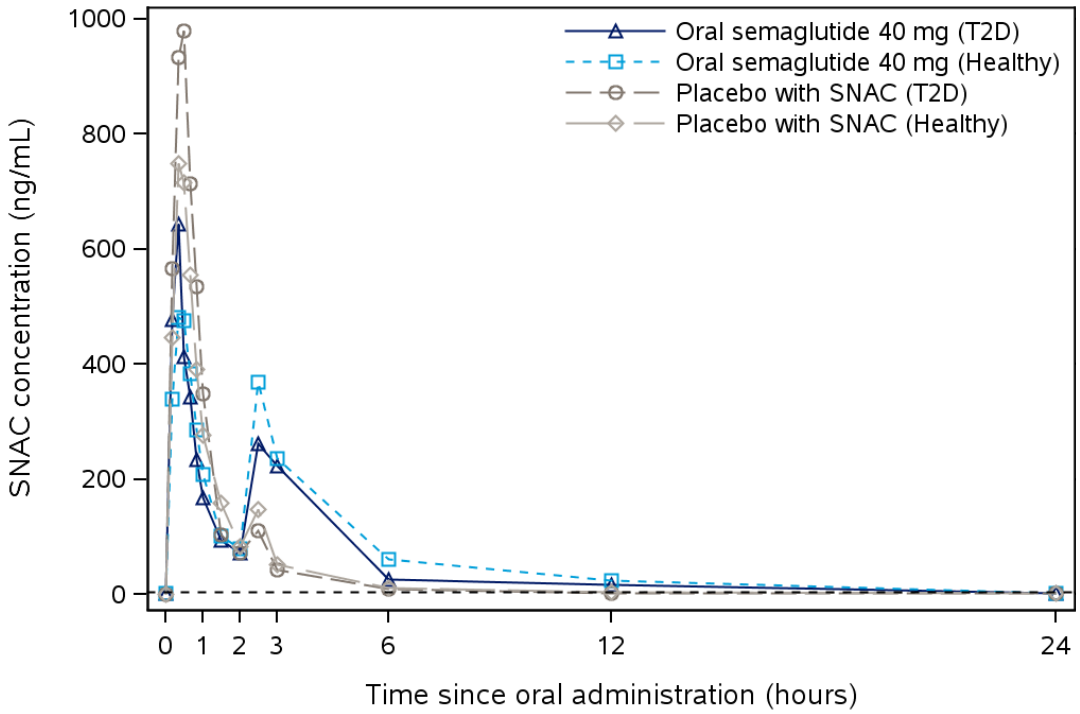
Figure 6a - Metabolism pathways of SNAC



Subjects who were dosed with placebo tablets containing SNAC (and not semaglutide) appeared to have higher maximum SNAC concentration, see Figure PK-7 (grey lines). The 2nd peak occurs shortly after the first post-dose meal (at 2 hours post dose).

Additionally, the PK of SNAC is similar between healthy subjects and patients with T2D. AUC0-24h of SNAC was 1074 ng*h/mL, Cmax was 1092 ng/mL and median tmax was 0.3 hour. In terms of CV%, variability of AUC0-24h ranged 21–54% and Cmax ranged 44−191%.

Figure PK-7 - SNAC exposure – healthy subjects vs. subjects with T2D – Trial 3991



---: Reference line for lower limit of quantification
Values below lower limit of quantification are imputed.

Interaction with SNAC

Several in vitro studies were conducted to investigate the potential interactions of the absorption enhancer SNAC. Based on the presented in vitro studies for SNAC can be concluded that SNAC and metabolites E494 and E506 were substrates for OATP1B1 and OATP1B3. Metabolites E1245, E1246 and E1247 were substrates for MRP2. Further SNAC is a substrate for the BCRP transporter. The metabolite E1245 was a substrate of MRP2 and OAT3, E494 was a substrate of BCRP and OAT3, E1246 was a substrate of MRP2 and OAT3, E506 was a substrate of OAT1 and OAT3, and E1247 was a substrate of MRP2 and OAT3. Consequently, in vivo investigations were performed.

The clinical drug-drug interaction studies also tested interaction with SNAC (alone). The DDI studies did not demonstrate any relevant interaction potential of the absorption enhancer SNAC per se. The results for SNAC are presented in Table PK–4.

Table PK–4 Drug-drug interaction: Effect of SNAC – treatment ratios of victim drug exposure – Trials 4065, 4145, 4249, 4250, 4279

Trial	Victim drug[a,]	N	AUC[b] Ratio[e] (90% CI)	C_{max}[c] Ratio[e] (90% CI)
4065	lisinopril (20 mg)	50	0.95 (0.89; 1.01)	0.89 (0.81; 0.97
4065	S-warfarin (25 mg)	37	1.04 (1.02; 1.07)	0.94 (0.88; 1.01)
4065	R-warfarin (25 mg)	37	1.06 (1.03; 1.08)	0.96 (0.90; 1.02)
4145	metformin (850 mg)	32	1.05 (0.99; 1.12)	1.06 (0.98; 1.14)
4145	digoxin (500 µg)	32	0.96 (0.91; 1.01)	0.82 (0.73; 0.92)
4249	ethylenestradiol (0.03 mg)	25	1.04 (1.00; 1.09)	1.13 (1.07; 1.19)
4249	levonorgestrel (0.15 mg)	25	1.13 (1.06; 1.19)	1.08 (1.01; 1.15)

4250	furosemide (40 mg)	40	0.99 (0.91; 1.07)	0.90 (0.74; 1.11
4250	rosuvastatin (20 mg)	40	0.97 (0.91; 1.02)	0.92 (0.82; 1.02)
4279	levothyroxine (600 µg)f	45	0.97 (0.90; 1.04)	0.85 (0.79; 0.92)

[a] single doses for lisinopril, warfarin, digoxin, furosemide, rosuvastatin and levothyroxine and multiple doses for metformin (twice daily for 3.5 days) and ethylenestradiol/levonorgestrel (once daily for 8 days). [b] AUC0–∞ for lisinopril, S- and R-warfarin, digoxin, furosemide and rosuvastatin, AUC0-12h for metformin, AUC0–24h for ethinylestradiol and levonorgestrel, and baseline-corrected AUC0-48h for levothyroxine. [c] baseline-corrected Cmax for leveothyroxine. d estimated treatment ratio (with/without co-administration of SNAC). e data shown for S- and R-warfarin are based on a sensitivity analyses that excluded 12 subjects who were incorrectly dosed with 1 warfarin tablet instead of 5 tablets in the warfarin with SNAC dosing period. f measured as baseline corrected T4. The conclusion that SNAC co-administration did not affect exposures of the victim drugs was declared if the two-sided 90% confidence interval for the ratio (with/without SNAC) fell entirely within the no-effect interval (0.80; 1.25) N: number of subjects contributing to the analysis

Drug-drug interaction study 4394 investigated the potential for SNAC to be a victim of UGT-mediated drug interaction and the potential for SNAC to be a victim of a DDI via inhibition of these transporters by either probenecid (index inhibitor of OAT1 and OAT3) or cyclosporine (index inhibitor of BCRP and inhibitor of MRP2). No interactions with these drugs were observed.

2.5.3. Pharmacodynamics

The Applicant has submitted data from trial 4248, which investigated the effect of oral semaglutide on energy balance, appetite (including body composition, energy intake, rating of appetite, control of eating, food cravings and food preferences) and on lipid metabolism in subjects with T2D. Further, to provide additional evidence for the mechanisms of HbA_{1c} and body weight lowering effect of semaglutide, data included and evaluated in the once-weekly s.c. semaglutide submission, supporting the approval of Ozempic are referenced here. In addition, the effects of semaglutide administered orally on fasting glycaemic parameters are included (trial 3991 in Table PD–5). Further, a QT study 4247 investigated the potential effects of SNAC on QTc interval and cardiac repolarisation.

Table PD–5 Clinical pharmacology trials investigating pharmacodynamic parameters

Trial ID	**N**	**Dose**	**Key assessments**
			Pharmacodynamic *methods* and parameters presented
Study with oral semaglutide			
Subjects with T2D			
4248	*15*	*14mg*	*Standard blood sampling, before (while fasting) a standardised breakfast and up to 5 hours postprandial (day 2) and before a fat-rich breakfast and up to 8 hours postprandial* **Glucose metabolism** • Glucose • Insulin • C-peptide • Glucagon • HbA1c **Lipid metabolism** • Lipids **Body weight and composition** **Gastric emptying** **Energy balance and appetite** • Energy intake • Ratings of appetite • Control of eating, food cravings and food preferences
Healthy subjects and subjects with T2D			
3991	*23*	*40 mg*	*Standard blood sampling*

Trial ID	N	Dose	Key assessments	
			Pharmacodynamic *methods* and parameters presented	
			Glucose metabolism • Glucose (fasting) • Insulin (fasting) • C-peptide (fasting)	• Glucagon (fasting) • HbA1c **Body weight** • Body weight
Studies with s.c. semaglutide				
Subjects with T2D				
NN 9535-3635	75	1.0 mg	*Intravenous glucose tolerance test, meal stimulation test (24 hours), arginine stimulation test, graded glucose infusion test*	
			Glucose metabolism • Glucose (fasting and postprandial) • Insulin (fasting and postprandial) • C-peptide (fasting and postprandial)	• Glucagon (fasting and postprandial) • Insulin secretion rate (ISR) • HbA1c
NN 9535-3684	38	1.0 mg	*Hypoglycaemic clamp*	
			Counter-regulation during hypoglycaemia • Glucagon (fasting and clamp) • C-peptide (fasting and clamp) • Adrenaline (clamp) • Noradrenaline (clamp) • Cortisol (clamp) • Growth hormone (clamp)	• Glucose infusion rate (clamp) • Hypoglycaemic symptoms (clamp) • Recognition of hypoglycaemia (clamp) • Cognitive function tests (clamp) **Glucose metabolism** • Glucose (fasting) • HbA1c
Subjects with obesity				
NN 9535-3685	30	1.0 mg	*Standardised and fat-rich meal tests and ad libitum meals, control of Eating Questionnaire (CoEQ), Leeds Food Preference Task (LFPT), indirect calorimetry, air displacement plethysmography*	
			Gastric emptying • Gastric emptying **Energy balance and appetite** **Appetite** • Energy intake	• Energy expenditure • Control of eating/food cravings • Food preference • Body composition **Lipid metabolism** • Lipids

N: number of subjects exposed to trial product
4248 trial with oral semaglutide: PD assessments were performed at the end of each 12-week treatment period, (including an 8-week dose escalation (3 mg oral semaglutide/placebo for 4 weeks followed by 7 mg oral semaglutide/placebo for 4 weeks) and subsequent administration of 14 mg oral semaglutide/placebo for 4 weeks).
. For trial 3991 assessments performed after 10 weeks of oral semaglutide 40 mg treatment (including two 1-weekly and one 2-weekly dose escalation steps) with a two hours post-dose fasting period (longer than the post-dose fasting period of 30 min used in the phase 3a trials). NN9535 trials with subcutaneous dosing (NN9535-3635, NN9535-3684 and NN9535-3685) assessments performed after 12 weeks of s.c. semaglutide 1.0 mg treatment (including two 4-weekly dose escalation steps).

The pharmacodynamic parameters shown in Table PD–5 evaluated the pharmacological effects of semaglutide on fasting and postprandial glucose, insulin, C-peptide, and glucagon response, as well as beta-cell function. Specifically, the glucose-dependency of these effects was evaluated. In addition, the effects of semaglutide on gastric emptying and lipid metabolism were evaluated. Furthermore, as semaglutide induces body weight loss, the mechanism of action behind this was evaluated by means of assessing the effect of semaglutide on appetite, energy intake and energy expenditure. In addition, the impact of semaglutide on body composition, control of eating and food preferences was evaluated.

The NN 9535 trials were already assessed during the marketing authorisation application of Ozempic. For the assessment of these trials, reference is made to the European Public Assessment Report (EPAR) of Ozempic (Procedure No. EMEA/H/C/004174/0000), p 40-44. A summary is provided below.

Glucose metabolism

The effect of semaglutide on glucose metabolism was assessed in subjects with T2D in trials 4248, 3991, NN9535-3635 and NN9535-3684. Specifically, the effects of semaglutide on fasting and postprandial glucose, insulin, C-peptide, and glucagon response, as well as beta-cell function were investigated. Further, the glucose-dependency of these effects was evaluated, including both the response to hyper- and hypo-glycaemic conditions.

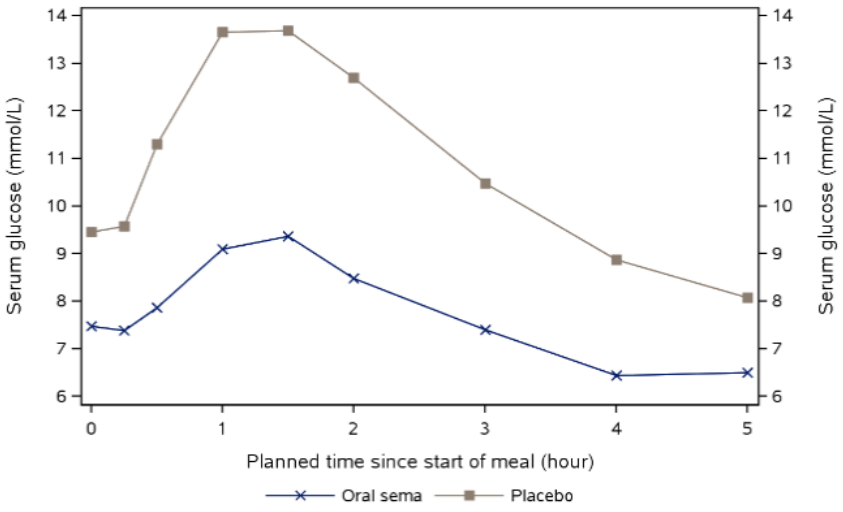
In summary, semaglutide treatment, as compared with placebo, lowered fasting and postprandial blood glucose by improving multiple aspects of beta-cell function, including insulin secretion, and by reducing both fasting and postprandial glucagon concentrations, all in a glucose-dependent manner. The mechanism of postprandial blood glucose lowering also involved a delay in gastric emptying.

Counter-regulation during hypoglycaemia was comparable between semaglutide and placebo treatment. This was based on responses in concentrations of glucagon and C-peptide, and in glucose need during the hypoglycaemic clamp (AUC_{GIR}). A decreased recognition of hypoglycaemia was observed with semaglutide compared to placebo. However, the risk of hypoglycaemia during semaglutide treatment is low due to the glucose-dependent mode of action.

Glucose response

In study 4248 the estimated serum glucose concentrations were statistically significantly lower with oral semaglutide than placebo, both when fasting (pre-meal) and for all endpoints assessed during the 5 hours after the standardised breakfast meal. The fasting serum glucose concentration was 22% lower and the area under the serum glucose concentration-time curve from 0 to 5 hours (AUC_{0-5h}) was 29% smaller with oral semaglutide than with placebo and both differences were statistically significant.

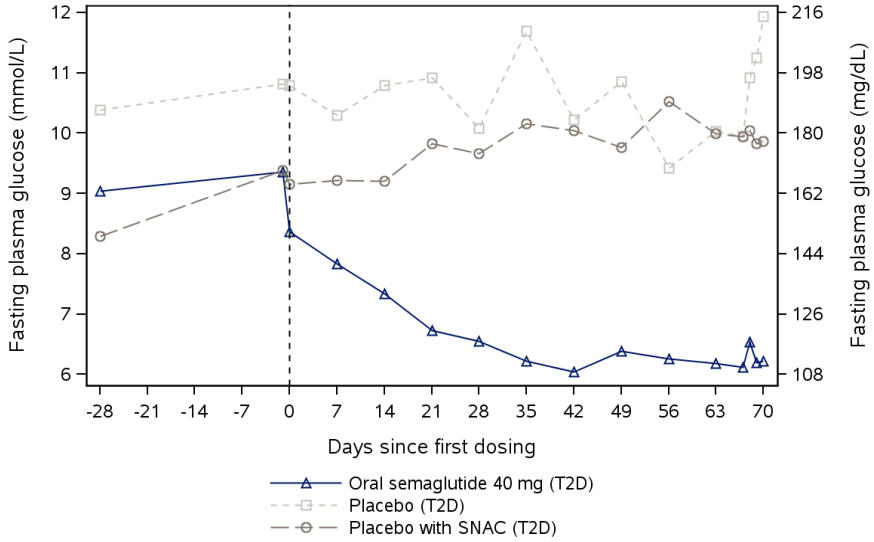
Figure PD–8 - Glucose profiles during standardised breakfast – oral semaglutide 14 mg – trial 4248



Semaglutide lowered fasting plasma glucose in subjects with T2D in trial 3991; a mean decrease of 2.3 mmol/L was demonstrated after 10 weeks of oral semaglutide treatment. Further, data from trial 3991 suggest an early onset (i.e. within the first week of treatment) on lowering of fasting plasma glucose with oral semaglutide (Figure PD-9). Note that the starting dose in trial 3991 was 5 mg oral semaglutide. The fasting plasma

glucose-lowering effect of oral semaglutide is further supported by observations from the phase 3a trials. Similar results were observed for s.c. semaglutide.

Figure PD-9 - Fasting plasma glucose (mmol/L) in subjects with T2D – oral semaglutide up to 40 mg – Trial 3991



Dose escalation of oral semaglutide was used: 5 mg for 1 week followed by 10 mg for 1 week and then 20 mg for two weeks before reaching a maintenance dose of 40 mg. Mean plot is shown.

Insulin response

In study 4248 fasting insulin concentrations were statistically significantly higher with oral semaglutide compared to placebo for the fat-rich meal only. Serum insulin concentrations tended to be lower with oral semaglutide than with placebo during the 5 hours of the standardised meal test but were not statistically significantly different. Fasting serum C-peptide concentration was statistically significantly higher with oral semaglutide compared to placebo.

An effect of oral semaglutide on fasting insulin and C-peptide was not observed in subjects with T2D in trial 3991. In the phase 3a trials, small changes were observed at week 26 in fasting insulin levels (+8%, +8% and -3% for oral semaglutide doses of 3, 7 and 14 mg, respectively) and fasting C-peptide (+9%, +10% and +5%). In the trials investigating pharmacodynamic effects of semaglutide, fasting insulin and C-peptide increased by 30% and 23%, respectively, after treatment with s.c. semaglutide 1 mg, as compared with placebo.

Glucagon response

T2D is associated with inappropriately high glucagon secretion both at fasting and at postprandial conditions, contributing to high hepatic glucose output. The ability of semaglutide to counter this undesired effect was investigated in subjects with T2D during various glucose metabolism tests.

In study 4248 the estimated plasma glucagon concentrations were lower with oral semaglutide than with placebo during the 5 hours of the standardised meal test. The area under the plasma glucagon

concentration-time curve from 0 to 5 hours (AUC_{0-5h}) was 29% smaller with oral semaglutide than with placebo and the difference was statistically significant. No data were presented for the fat-rich meal.

An effect of oral semaglutide on fasting glucagon was not observed in subjects with T2D in trial 3991. However, in the phase 3a trials, fasting glucagon levels decreased by 9% and 10% from baseline to week 26 with oral semaglutide 7 mg and 14 mg, respectively. In the trials investigating pharmacodynamic effects of semaglutide, glucagon decreased by 8%−21% after treatment with s.c. semaglutide 1 mg, as compared with placebo.

Body weight and body composition

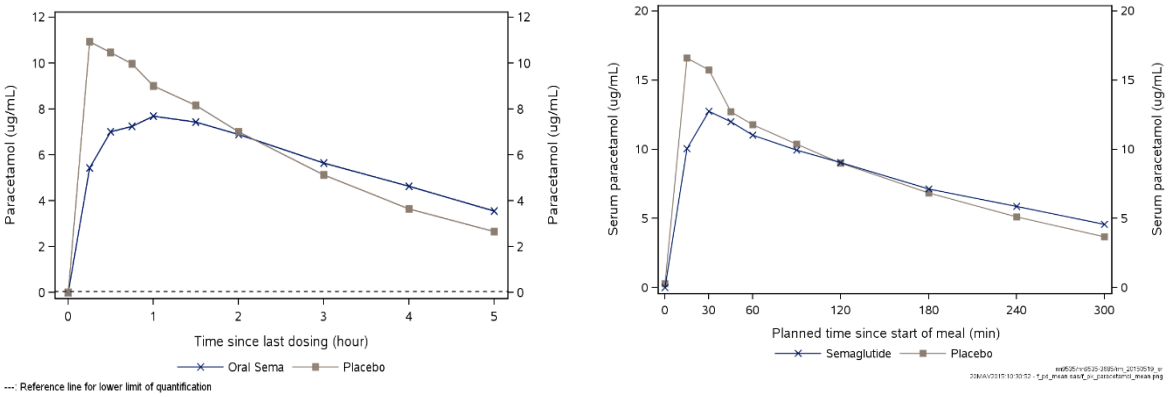
In trial 4248, a mean weight loss of 2.7 kg was seen with oral semaglutide and 0.1 kg with placebo. This weight loss was primarily due to a loss of body fat mass of 2.6 kg. Body lean mass did not decrease. In the clinical pharmacology trial with oral semaglutide subjects with T2D had a reduction in body weight after 10 weeks as would be expected from the observation on effect of semaglutide on body weight in the phase 3a trials.

Gastric emptying

Gastric emptying was assessed by the paracetamol absorption technique in trials 4248 and NN9535-3685.

In trial 4248, paracetamol AUC_{0-1h} were 31% lower (p=0.0050) for subjects when treated with oral semaglutide compared with placebo, whereas no statistically significant difference was observed for AUC_{0-5h} . In trial NN9535-3685, paracetamol AUC_{0-1h} were 27% lower (p=0.0012) for subjects when treated with s.c. semaglutide compared with placebo, whereas no statistically significant difference was observed for AUC_{0-5h}

Figure PD-10 - Gastric emptying - paracetamol concentration profile at steady state of treatment - mean plot – trials 4248 (left; oral semaglutide) and NN9535-3685 (right; s.c. semaglutide)



Lipid metabolism

In trial 4248, fasting LDL and total cholesterol levels were statistically significant lower during treatment with oral semaglutide than with placebo. Fasting HDL levels were not statistically significantly different between the two treatments. Triglycerides, VLDL cholesterol and ApoB48 appeared to be lower with oral semaglutide than with placebo, both when fasting and during the 8 hours following a fat-rich breakfast. The fasting triglycerides, VLDL cholesterol and ApoB48 concentration was 19%, 20% and 25% lower, respectively, and the area under the concentration-time curve from 0 to 8 hours (AUC_{0-8h}) was 24%, 21% and 30% smaller, respectively, with oral semaglutide than with placebo and all differences were statistically significant. The company did not present data on the lipid concentrations after a standard breakfast.

Energy balance and appetite

Energy intake, ratings of appetite, control of eating, food cravings and food preferences were assessed in trial NN9535-3685 and trial 4248, using Visual Analogue Scale (VAS) ratings and the overall appetite score (OAS).A significant reduction in energy intake with semaglutide and a semaglutide-induced suppression of appetite is reported. However, both studies are small and confidence intervals wide. Therefore, conclusions on the effect on energy balance and appetite are not possible.

Cardiac repolarisation as assessed by QTc

The potential effect on the QT interval was evaluated in two thorough QT/QTc trials: one QTc trial with semaglutide s.c. 1.5 mg (trial NN9535-3652) and one trial with SNAC 3.6 g (trial 4247). For the assessment of trial NN9535-3652, reference is made to the Ozempic EPAR.

The geometric mean exposure (C_{avg}) in the QTc assessment for semaglutide was 4-fold higher than C_{avg} of oral semaglutide 14 mg in the phase 3a trials (59.1 nmol/L vs 14.6 nmol/L). A dose of SNAC 3.6 g (12-fold the SNAC content of 300 mg in the oral semaglutide tablet) was used for the QTc evaluation of SNAC, with exposures exceeding the highest observed $C_{max.}$for SNAC. No prolongation of the QTc interval was observed with semaglutide or SNAC, indicating that treatment with oral semaglutide will not affect cardiac repolarisation.

There was no prolongation of QTcI (QT interval individual corrected for heart rate) at steady state of semaglutide 1.5 mg; the upper limits of the 11 two-sided 90% CIs (equivalent to the upper limits of the one-sided 95% CIs) for the estimated mean treatment differences were all below 10 msec. The upper limit of the two-sided 90% CI for the maximum time-matched estimated mean treatment difference in QTcI was 0.29 msec. Similar to the result for QTcI, no prolongation of QTcL and QTcF was observed at any of the three dose levels. For QTcB, however, a prolongation was observed at all dose levels, which was not considered clinically relevant. The prolongation observed with QTcB is as expected with an increase in HR; QTcB is therefore no longer recommended as a correction method in QT/QTc trials.

Semaglutide treatment was associated with a prolongation of the PR interval at all dose levels, but there was no indication of a dose- or time-dependency. The maximum increase in the estimated mean treatment difference between subjects treated with semaglutide and placebo in baseline-adjusted PR interval was 10.02 ms $[6.15; 13.89]_{95\%\ CI}$, observed at 30 hours after dose in subjects treated with s.c. semaglutide 1.5 mg.

Relevance of exposure in QTc assessment for oral semaglutide

The exposure of semaglutide s.c. 1.5 mg at which the QTc assessment was made in trial NN9535-3652 was considered relevant to justify that no unacceptable prolongation of the QTc interval would be expected after treatment with oral semaglutide. The semaglutide concentrations following semaglutide s.c. 1.5 mg were about 4 fold higher than the mean through concentrations after treatment with oral semaglutide 3, 7 and 14 mg. The median semaglutide concentration in the QTc trial was above 90% of the observed concentrations resulting from treatment with oral semaglutide 14 mg. Further, there was no exposure-response relationship between QTc and semaglutide concentration. The QTc trial NN9535-3652 was therefore considered adequate to support oral semaglutide doses of 7 and 14 mg.

QTc assessment for SNAC

The potential effects of SNAC on QTc interval and cardiac repolarisation were tested in dedicated thorough QTc trial 4247. ECGs were recorded for 12 hours after dosing with a supra-therapeutic dose of SNAC 3.6gr (12-fold the SNAC content of oral semaglutide). SNAC 3.6 g did not have an impact on cardiac repolarisation.

Immunogenicity

Immunogenicity was assessed throughout the oral semaglutide clinical development programme.

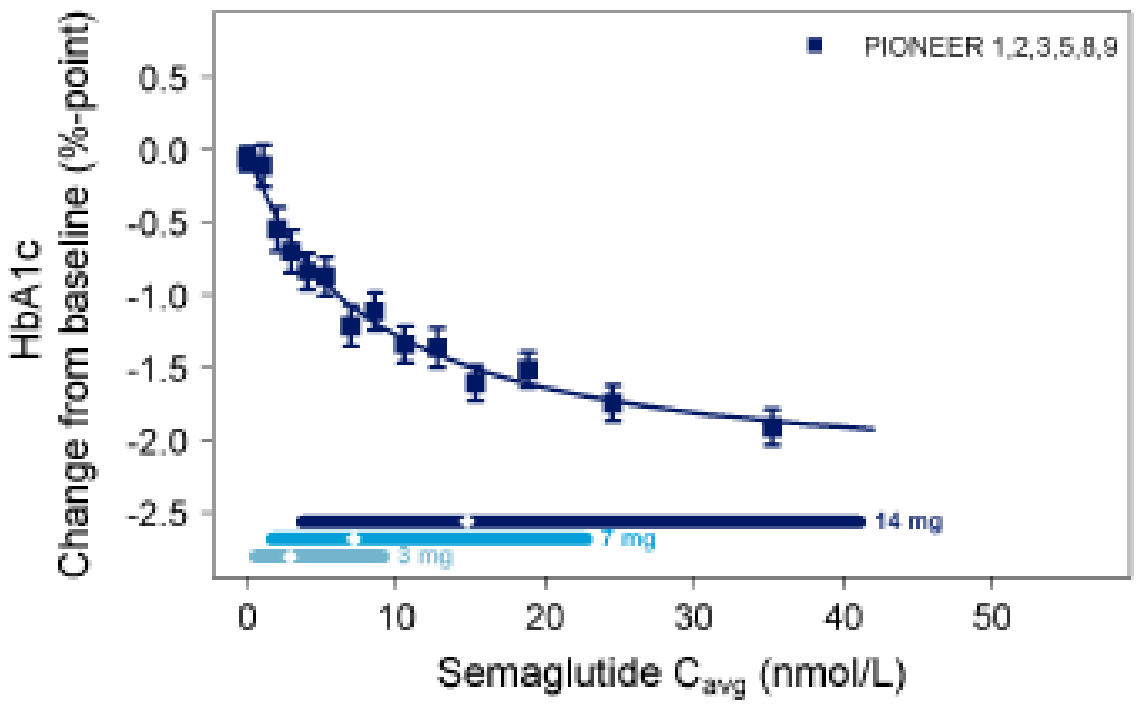
The proportion of patients that tested positive for anti-semaglutide antibodies at any time point post-baseline was low (0.5% [14 out of 2924 patients]) and no patients had anti-semaglutide *in vitro* neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 *in vitro* neutralising effect at end-of-trial. Anti-semaglutide antibodies do not appear to affect semaglutide exposure.

2.5.4. Exposure - Response relationship

Population pharmacokinetics (PK) and exposure-response analyses of the oral formulation have been presented. For semaglutide s.c. a correlation between C_{avg} and response has been shown. It should be noted that the underlying pharmacokinetic models do not describe within subject variability, the estimates of C_{avg} only roughly describe the pharmacokinetics and are not considered accurate estimates. For the oral formulation, a similar relationship between exposure and response is observed for the s.c. formulation.

There was a clear exposure-response relationship with respect to change from baseline in HbA1c (Figure PD–11).

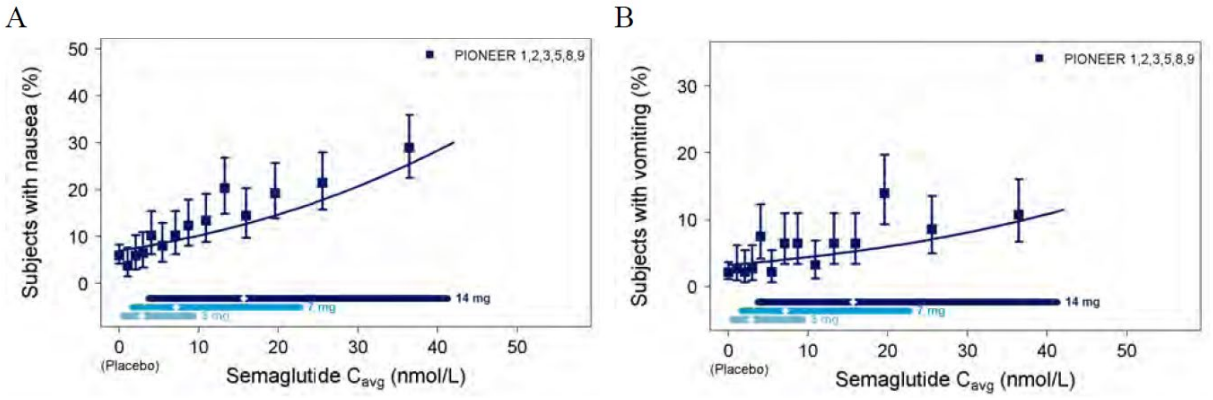
Figure PD-11 - HbA1c response at week 26 versus exposure of semaglutide for all subjects – PIONEER 1, 2, 3, 5, 8 and 9



Data are mean HbA1c response values with 95% CI obtained after 26 weeks of treatment versus exposure expressed as quantiles of Cavg (plus placebo at Cavg of 0 nmol/L). The lines through data represent covariate-adjusted model-derived exposure-response relations for each population. Horizontal lines with diamonds along the x-axes represent median and 90% exposure ranges

The company also developed exposure response models to evaluate the safety of semaglutide. The exposure-response relationship for gastrointestinal adverse events (nausea, vomiting) For s.c. semaglutide also the relationship with the occurrence of diarrhoea, constipation, pulse rate and calcitonin concentration have been evaluated. An exposure response was observed for gastrointestinal adverse events. Pulse rate and calcitonin concentration showed no significant results.

Figure PD-12 - Proportion of subjects reporting nausea (A) or vomiting (B) at any time during oral semaglutide treatment versus exposure- PIONEER 1, 2, 3, 5, 8 and 9



Data are proportions of subjects with 95% CI during 26 weeks of treatment versus exposure expressed as quantiles of Cavg values plus placebo (at Cavg of 0 nmol/L). Lines through data represent covariate-adjusted model-derived relations.
The horizontal lines with diamonds along the x-axes represent medians and 90% exposure ranges. Data from PIONEER1, 3, 5, 8, 9.

2.5.5. Discussion on clinical pharmacology

Despite co-formulation with salcaprozate sodium (SNAC), oral semaglutide has a very low bioavailability (<1%) and high variability.

The applicant claims that SNAC is an absorption enhancer based on *in vitro* data. Although it has not been demonstrated that SNAC improves the bioavailability in vivo it has been shown that semaglutide is absorbed in the presence of SNAC, all clinical studies have been conducted in the presence of SNAC and no apparent disadvantages of co-formulation of SNAC have been detected in these studies. Therefore it can be accepted that oral semaglutide is co-formulated with a new excipient SNAC, although its absorption enhancing effect has not been confirmed in vivo.

The absorption enhancing effect of SNAC has not been shown appropriately for the following reasons:

- *In vitro* studies 309788, BLMP150301, SBJJ100709, 309790, and 309791 show that SNAC increases the pH around the tablet and increases permeability of gastric cells when concentrations are sufficiently high. These studies could be used to support a mechanism of action but they do not demonstrate the additive value of SNAC in the clinical situation.
- Clinical dose finding trial 3691 has several methodological and analytical issues. Due to this it is not possible to draw any conclusions on the relationship between SNAC dose and uptake of semaglutide .
- The non clinical studies 309780 and 309771 have shown that high concentrations of semaglutide and SNAC are only found close to the tablet. This finding is not unique for this specific tablet or active substance, nor solely related to the presence of SNAC. High concentrations of any active substance are found close to a dissolving tablet and lower concentrations further away from the tablet.
- None of the submitted clinical or non-clinical studies investigated the absorption of semaglutide without SNAC.
- It cannot be assumed that semaglutide is not absorbed without SNAC. Semaglutide is not a normal peptide but a modified GLP analogue, designed to have altered pharmacokinetics. Systemically the

modifications prevent semaglutide inactivation by DPP4 and increase binding to albumin. Due to modifications semaglutide is possibly absorbed.

- The semaglutide absorption is low (bioavailability <1%) and highly variable. If SNAC possesses any absorption enhancing properties at all, this effect is not impressive, semaglutide absorption is still very low and unpredictable.

The relation between the amount of SNAC and absorption of semaglutide is unclear. No convincing evidence was given to show that 300 mg SNAC is the most optimal dose. The interpretation of the SNAC dose-finding study (3691) data is hampered due to several methodological and analytical issues. However, the lack of appropriate SNAC dose finding data is considered acceptable as all clinical studies have been conducted with a 300mg SNAC dose and it has been shown that the achieved semaglutide steady state levels are adequate in most patients.

Methods

Clinical population PK and PK-PD models were developed to gain insight in the PK properties and exposure-response relationships of semaglutide after oral dosing. The Population PK models do not describe the pharmacokinetics of orally administered semaglutide correctly as PK models failed to converge, indicating that the models do not accurately describe the data. It was not possible to use these models to quantify the day –to-day variability of the bioavailability (F) most likely due to the lack of sampling in the absorption phase. Also, adherence to the dosing instructions has not been recorded in clinical studies. Therefore , the contribution of this covariate could not be analysed.

Also, the population pharmacokinetic models focus on estimating the average concentration of semaglutide after oral administration and did not evaluate fluctuation in exposure within subjects. Estimating an average concentration throughout a long-term trial does not adequately reflect the within subject variability throughout this trial. As a consequence, using the average concentration to evaluate variability in treatment response in HbA1c dose not adequately reflect the influence of variability in exposure. From several analyses submitted before, it is clear that the within subject variability in the bioavailability of oral semaglutide is high as several models indicated a CV higher than 100%. Between-subject variability on bioavailability is usually estimated lower (approximately 50 – 80%) in these models than within-subject variability. Indicating that variability within an individual in exposure to oral semaglutide is higher than variability between subjects.

Because the population PK models were used as a basis for the exposure response models also these models cannot be completely trusted. The assessment of the pharmacokinetics and pharmacodynamics of oral semaglutide mainly relies on the results of the standard non-compartmental studies, and on the characterisation of semaglutide pharmacokinetics following s.c. administration. The previously submitted studies on semaglutide s.c. have also been used to describe the influence of covariates on distribution and excretion of semaglutide; other factors than water intake and timing to food intake and post-dose fasting period length on the absorption remains unpredictable due to the large variability of semaglutide absorption.

Pharmacokinetics oral semaglutide

The clinical development programme is comprehensive and includes 18 overall adequately designed and performed clinical pharmacology trials, *in vitro* studies with both semaglutide and SNAC and PK modelling including data from the clinical pharmacology and Phase 3 trials.

Different formulations and three different drug substance processes have been used during clinical development. Process I has been used in one early study and the manufacturing processes II and III result in a very similar quality of the semaglutide drug.

The estimated Cavg for the clinical pharmacology trials and Phase 3 trials, 32.8 nmol/L and 14.6 nmol/L for the 14 mg doses respectively. The Phase 1 and Phase 3 studies were conducted with drug substances from two different processes. Any quality differences due to the use of different processes are not likely to be the cause of the differences in Cavg. A likely contributing cause is the different populations included in clinical pharmacology and phase 3 trials, with mainly healthy volunteers in clinical pharmacology trials and TD2 subjects in phase 3 trials including differences in body weight, which is known to have significant impact on exposure. Most important is probably the impact of supervised dosing, which emphasises the importance of high compliance for exposure of oral semaglutide.

As all clinical phase 3 studies have been conducted with process III and the to-be-marketed oral semaglutide formulations contain process III drug substance there is sufficient pharmacokinetic data to support this application. Although different strengths have been used in the clinical pharmacology program the data collected with the processes II products can still be used to describe the pharmacokinetics of oral semaglutide.

The absolute bioavailability of semaglutide dosed orally is highly variable and approximately 1%. The bioavailability is dependent on dosing conditions, such as amount of concomitant water intake, food intake and post-dose fasting period.

Due to the large variability there are patients with a high exposure using a 3 mg or 7 mg dose. These patients could already achieve maximum effects on these lower dosages.

An important concern identified in the pharmacokinetic evaluation of oral semaglutide is the risk of low exposure and resulting negative impact on efficacy. There appears to be a considerable difference in bioavailability between clinical pharmacology trials and phase 3 trials. The bioavailability appears to be only half of what is found in the clinical pharmacology trials (0.4 vs 0.8 % for the proposed dosing regimen).Overall, the presented population modelling is not suitable to quantify the day –to- day variability of the bioavailability (F) due to the lack of sampling in the absorption phase, the between subject variability in bioavailability is estimated to be about 100%CV with trough concentrations ranging from approximately 1 nmol/L to 100 nmol/L. In the models it was estimated that approximately 2-4% of patients will not have any exposure. None of the models was able to identify covariates that could explain the high variability in the oral absorption of semaglutide. The estimation of within subject variability on bioavailability was not reliable.

Further, the lower bioavailability in the phase 3 trials is possibly related to low compliance to the dosing regimen, supported by a well-established "on-site dosing effect" in both healthy volunteers and patients with T2D. Compliance is highly important for the exposure of oral semaglutide. Patients with low compliance for the strict dosing regimen will probably not achieve adequate exposure necessary for adequate efficacy. About 10 % of the population is expected to have exposures below 5.8 nMI. It was difficult to unequivocally identify a subpopulation or risk factor that noticeably predicts low exposure. As for all T2D treatments, clinical response to treatment and achievement of treatment goal should be regularly evaluated by the treating physician. Failure to achieve an adequate treatment effect could be due to inadequate exposure.

Relevant information on variability and inadequate treatment effect has been included in the SmPC (sections 4.4 and 5.2).

Special populations

Various special populations have been evaluated by the applicant (e.g. renal/hepatic impairment, gender, race/ethnicity, age, weight and subjects with the presence of anti-semaglutide antibodies) and have been included in the population models. However, none of the models describe the pharmacokinetics of orally administered semaglutide correctly; all PK models terminated. The assessment of the covariates on the pharmacokinetics of oral semaglutide should rely on the results of the standard non-compartmental studies and previously conducted population PK- studies for semaglutide s.c.. The high variability of the semaglutide absorption should be considered for the interpretation of the clinical pharmacology studies in special populations. The studies in patients with renal or hepatic impairment, subjects with upper gastrointestinal diseases and subjects with different races had standard population sizes (between 8 and 36 subjects). Due to the high variability of semaglutide absorption, these studies are only suitable to detect large differences between populations. Therefore, the interpretation of these studies should be made with caution.

Based on population PK studies of semaglutide s.c. and the clinical pharmacology studies no dose adjustment of oral semaglutide appears to be required for patients based on intrinsic factors of age, sex, body weight, race, ethnicity, upper GI disease, renal function or hepatic function.

Interactions

In general, interactions were adequately investigated. However, there are some issues remaining.

In study 4279 was shown that the presence of multiple other tablets in the stomach affected the PK of oral semaglutide. The impact of the interaction should be described in section 4.5. To reduce the variability of semaglutide exposure, the concomitant intake of other medication should be avoided.

The concomitant use of other drugs that need to be administered on an empty stomach may be problematic in clinical practice. The company has decided to advise a 30 minute post-fasting period due to compliance reasons, although it has been shown that semaglutide absorption improves with a longer fasting period. The applicant advises to administer other drugs after the 30 minutes have passed. For other drugs that require dosing in the fasting state this would imply additional post dose fasting. Longer postdose fasting could be problematic for compliance to dosing instructions of both drugs, and could result in an increased uptake of semaglutide thus a lower dose could be required, this may be resolved with down titration. The applicant sufficiently justified that the risk of hypoglycaemia is expected to be low. Overall it can be concluded that it is possible to use other drugs that also need to be administered on an empty stomach but that this may be problematic in clinical practice.

Pharmacokinetic interaction with levothyroxine (33% increase) was identified for which the consideration to monitor thyroid parameters during treatment with semaglutide is reflected in the SmPC. However, the dosing conditions of oral semaglutide mentioned in the SmPC that no other oral treatments should be co-administered, highly affects patients using levothyroxine as this implies that these patients need to be in a fasted state for another 30 minutes before breakfast. This may impact the adherence of both medicines and moreover due to longer post dose fasting, increased uptake of semaglutide is expected and a lower dose could be required.

NEP inhibition could lead to a relevant interaction. However, as degradation of semaglutide is not only based on NEP, the impact of NEP interactions is expected to be limited. No safety concerns were seen in the small amount of patients treated with the NEP-inhibitor valsartan/sacubitril.

In the drug-drug interaction program the applicant evaluated the potential interaction with drugs with a moderate (metformin F: 50%) or low bioavailability (lisinopril F: 25%), but no drugs with a very low bioavailability (F:1%).

Pharmacokinetics SNAC

The pharmacokinetics SNAC is characterised appropriately. SNAC is quickly absorbed, with a tmax of 0.5-1 hour. Due to a short half-life of 2 hours, no accumulation is observed after multiple doses of SNAC. SNAC is metabolised via either step-wise β-oxidation or conjugation with glucuronic acid. None of the SNAC metabolites- as SNAC itself - have pharmacological activity. The variability of SNAC exposure is moderate.

The absorption enhancing effect of SNAC has not been convincingly shown. If SNAC possesses any absorption enhancing properties at all, this effect is not impressive.

Based on in vitro tests SNAC would increase the pH around the tablet and increase local permeability of gastric cells. Theoretically, assuming that his mechanism of action is correct, SNAC could only be expected to enhance the uptake of other drugs if tablets are taken at the same time and end up at the same location in the stomach.

Pharmacodynamics

The semaglutide PD properties were investigated in the clinical pharmacology programme of semaglutide s.c. No new clinical pharmacology studies have been conducted to investigate the PD properties of the oral formulation of semaglutide. The effects on HbA1c and body weight observed in the previously conducted PD studies are in line with the results from the phase 3 PIONEER trials. The results of gastric emptying study 1821, submitted for semaglutide s.c. but not for the oral semaglutide application are also considered relevant.

Pharmacodynamic measures were evaluated with oral semaglutide in PK/PD phase I trial 3991, which includes a population of healthy volunteers and patients with T2D. No effect of oral semaglutide on fasting insulin, C-peptide and fasting glucagon was observed in the healthy volunteers; the findings in the few T2D subjects are overall in line with previous findings for semaglutide.

The pharmacodynamic investigations of semaglutide impact on energy balance and appetite have primarily been conducted with s.c. semaglutide. It is not evident that these results also apply to oral semaglutide where e.g. dosing has to be coordinated with food intake. The Applicant referred to the PD outcomes of trial NN9535-3685, which included investigations of the effect of s.c. semaglutide on energy balance and appetite in subjects with obesity. The Applicant has submitted data from the recently completed trial 4248, which investigated the effect of oral semaglutide on energy balance, appetite (including body composition, energy intake, rating of appetite, control of eating, food cravings and food preferences) and on lipid metabolism in subjects with T2D. The design of the study 4248 is comparable to study NN9535-3685, besides lack of assessment of energy expenditure in trial 4248, but a notable difference is that subjects with T2D were included in the oral treatment study (trial 4248) and obese non-diabetic subjects in the s.c. treatment study (NN9535-3685).

A similar delay of gastric emptying is observed with oral and s.c. semaglutide compared to placebo, in trials 4248 and NN9535-3685.

In study 4248 the mean weight loss after 12-weeks treatment was 2.7 kg compared to 5.0 kg in study NN9535-3685. In both studies, the weight loss was mainly loss of body fat and not lean body mass. Energy intake was reduced in both studies, 39 % with oral semaglutide and 18 % with sc semaglutide.

Lipid metabolism (LDL, triglycerides, VLDL cholesterol and ApoB48) were investigated in study 4248. Triglycerides, VLDL cholesterol and ApoB48 appeared to be lower with oral semaglutide after a fat-rich breakfast this is similar to s.c. semaglutide and could be reflected in the SmPC. However, numerical values should be presented with 95 % confidence intervals.

Adequately conducted QTc studies with supra-therapeutic doses of both semaglutide and SNAC and moxifloxacin as positive control have confirmed that there is no QTc prolonging potential of either semaglutide or SNAC.

Exposure response relationship

Both glycaemic response, as well as gastro-intestinal adverse effects, are dose dependent. However, the large pharmacokinetic variability hampers study of this relation with population modelling.

2.5.6. Conclusions on clinical pharmacology

The pharmacokinetics of oral semaglutide was generally well characterised. Oral Semaglutide has a very low bioavailability and highly variable absorption.

The added value of SNAC has only been demonstrated in vitro. Although it has not been demonstrated that SNAC improves the bioavailability in vivo it has been shown that semaglutide is absorbed in the presence of SNAC, all clinical studies have been conducted in the presence of SNAC and no apparent disadvantages of co-formulation of SNAC have been detected in these studies. Therefore it can be accepted that oral semaglutide is co-formulated with a new excipient SNAC, although its absorption enhancing effect has not been confirmed in vivo.

Further, the absorption of semaglutide is affected by drug intake conditions. Food, administration with large amounts of water and concomitant administration of other tablets decreases bioavailability. Due to the high variability in the absorption of semaglutide, an important concern identified in the pharmacokinetic evaluation of oral semaglutide is the risk of low exposure and resulting negative impact on efficacy. The high variability of the absorption is possibly related to (non)compliance to the rather strict dosing regimen. These issues are clearly reflected in SmPC sections 4.4 and 5.2.

The pharmacodynamics of oral semaglutide has been adequately investigated, but the impact on appetite of oral semaglutide cannot be assessed based on the presented PK/PD studies. The studies were small and the exposure ranges of oral semaglutide are wide and therefore the clinical response remains unpredictable. The SmPC has been revised during the procedure to only reflect those PD effects documented for oral semaglutide.

2.6. Clinical efficacy

2.6.1. Dose response study

In all ten phase 3a trials, fixed semaglutide doses were evaluated. Three oral semaglutide doses (3, 7 and 14 mg) were investigated in five phase 3a trials (PIONEER 1, 3 and 8−10). Four trials investigated oral semaglutide 14 mg only (PIONEER 2 and 4–6). For evaluation of efficacy results relating to phase 3 dose selection and dose-escalation, results from the dose-finding trial 3790 were used.

Trial 3790 – dose-finding

Title

Multiple dose trial examining dose range, escalation and efficacy of oral semaglutide in subjects with type 2 diabetes.

Objectives

The primary objective was to compare the efficacy on glycaemic control of oral semaglutide vs placebo as add-on to metformin or as monotherapy. The secondary objectives were to compare the efficacy on glycaemic control, to compare safety and tolerability of three dose-escalation schemes using a single end dose level, and to compare parameters of efficacy, safety and tolerability, and population PK after 26 weeks of treatment.

Trial design and treatment regimen

A 26-week, randomised, partially-blinded, parallel-group, dose range, dose-escalation, multi-centre trial. The oral semaglutide and oral placebo arms were double-blinded: the s.c. semaglutide arm was not blinded. A total of 632 subjects were randomised in an equal manner into one of the 9 treatment arms: oral semaglutide 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, 40 mg S (slow dose escalation), 40 mg F (fast dose escalation), placebo and s.c. semaglutide 1 mg once weekly.

Trial subjects

A total of 632 subjects were randomised (mean age: 57 years, HbA_{1c}: 7.9%, body weight: 92.3 kg, diabetes duration: 6.3 years). A total of 583 subjects (92%; 87−96% across treatment arms) completed the trial, a total of 492 subjects (78%; 64−92% across treatment arms) completed the treatment and a total of 463 subjects (73%; 64−83% across treatment arms) completed the treatment without administration of rescue medication.

Efficacy results

HbA_{1c} and body weight were analysed using the hypothetical estimand (comparable to the secondary analysis of continuous endpoints in phase 3).

In subjects with T2D with or without metformin as background treatment, dose-dependent reductions from baseline in estimated HbA_{1c} were seen with all oral semaglutide doses (Table E-6). The reductions in HbA_{1c} after 26 weeks of treatment were greater with all oral semaglutide doses and s.c. semaglutide 1.0 mg compared to placebo (Figure E-13). No statistically significant differences in HbA_{1c} between the dose-escalation schemes 40 mg, 40 mg S and 40 mg F were seen.

A dose-dependent reduction in estimated body weight was seen with oral semaglutide (Table E-6). The weight loss after 26 weeks of treatment was greater with oral semaglutide ≥10 mg and s.c. semaglutide 1.0 mg vs placebo. With oral semaglutide 40 mg F, the estimated weight loss was greater than with 40 mg S. No significant differences were seen between the other dose-escalation schemes.

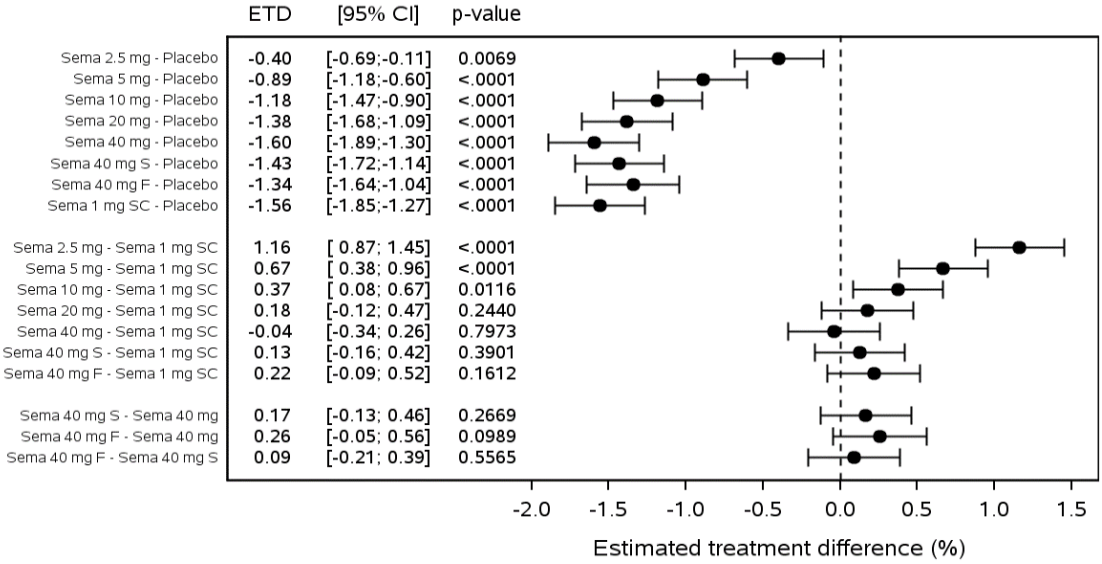
As reflected in the standard errors (Table E-6) and in the slope of the cumulative distribution functions; there were no notable differences in variability of the efficacy response, despite the large pharmacokinetic variability.

Table E-6 Trial 3790 dose-finding – change from baseline in HbA_{1c} and body weight

		HbA_{1c} (%)			Body weight (kg)		
	FAS	N	Baseline	eCFB (SE) at week 26	N	Baseline	eCFB (SE) at week 26
Placebo	71	51	8.00	-0.31 (0.10)	51	93.76	-1.18 (0.55)
Oral sema 2.5 mg	70	56	7.99	-0.71 (0.10)	56	93.62	-2.06 (0.53)
Oral sema 5 mg	70	58	7.80	-1.20 (0.10)	57	93.09	-2.65 (0.53)
Oral sema 10 mg	69	57	7.80	-1.49 (0.10)	57	91.76	-4.80 (0.54)
Oral sema 20 mg	70	48	7.86	-1.69 (0.11)	47	93.81	-6.14 (0.57)
Oral sema 40 mg	71	46	8.05	-1.91 (0.11)	46	90.85	-6.89 (0.56)
Oral sema 40 mg S	70	52	7.96	-1.74 (0.10)	51	93.25	-6.05 (0.54)
Oral sema 40 mg F	70	44	7.77	-1.65 (0.11)	44	91.98	-8.16 (0.58)
Sema 1 mg SC	69	48	7.77	-1.87 (0.11)	46	88.80	-6.43 (0.55)

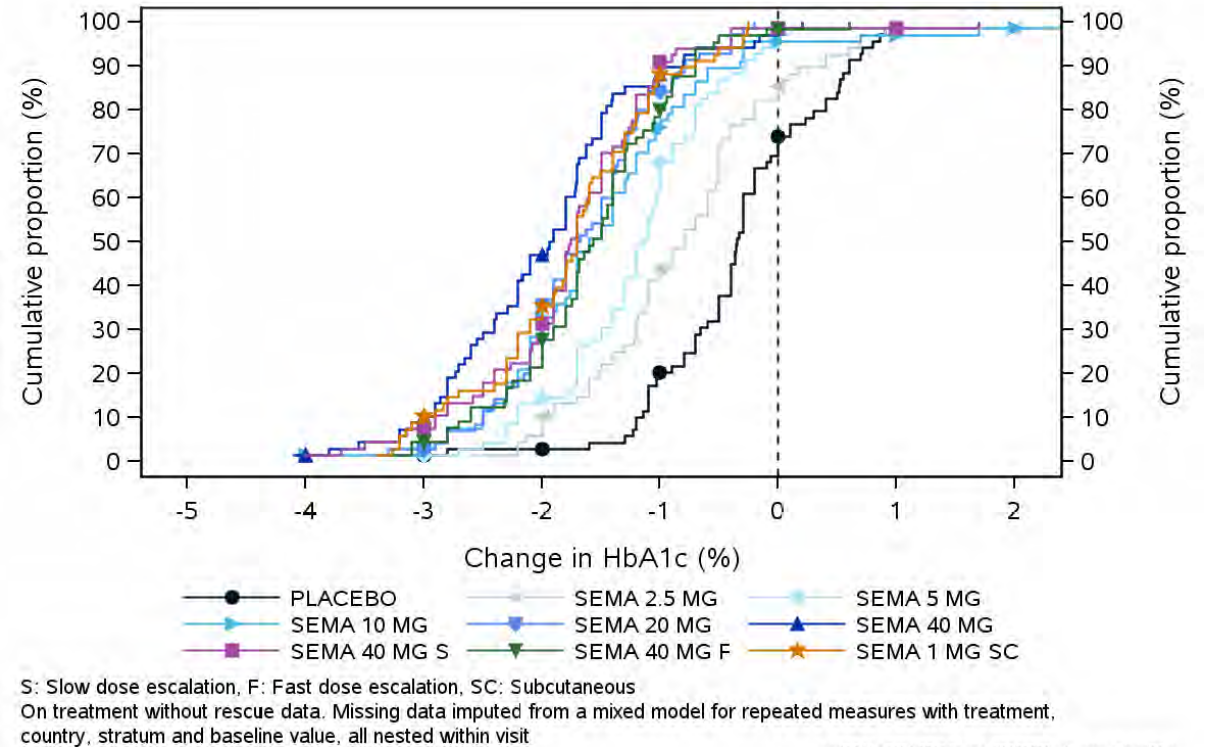
N: Number of subjects contributing to analysis. Analysis of observed on-treatment without rescue data. S: slow dose escalation; F: fast dose escalation; SC: subcutaneous CFB: Estimated change from baseline

Figure E-13 - Trial 3790 dose-finding – change in HbA_{1c} after 26 weeks of treatment – estimated treatment differences



ETD: estimated treatment difference; CI: confidence interval; S: slow dose escalation; F: fast dose escalation; SC: subcutaneous

Figure E-14 - Change in HbA1c (%) after 26 weeks of treatment - cumulative distribution function – full analysis set



S: Slow dose escalation, F: Fast dose escalation, SC: Subcutaneous
On treatment without rescue data. Missing data imputed from a mixed model for repeated measures with treatment, country, stratum and baseline value, all nested within visit

Safety

In this 26-week dose-finding trial in subjects with T2D, no unexpected safety issues were identified. The proportion of subjects with AEs and the number of AEs showed an increasing trend with increasing oral semaglutide doses (from 67.1%/142 AEs with oral semaglutide 2.5 mg to 85.7%/245 AEs with oral semaglutide 40 mg F) and were higher with oral semaglutide ≥10 mg than with placebo. The difference to placebo was mainly driven by higher proportions of subjects with oral semaglutide ≥10 mg reporting nausea, diarrhoea and vomiting; these events were mostly of mild or moderate severity. The proportion of subjects who discontinued treatment prematurely due to an AE was higher with oral semaglutide compared to placebo and higher with oral semaglutide 20 mg, 40 mg and 40 mg F compared to oral semaglutide 2.5 mg, 5 mg, 10 mg and 40 mg S. The most frequently reported AEs leading to treatment discontinuation were within the system organ class (SOC) 'gastrointestinal disorders' (125 out of the 180 AEs). AEs within this SOC were reported by higher proportions of subjects with oral semaglutide 20 mg, 40 mg and 40 mg F (21.4%, 18.3% and 21.4%) than with oral semaglutide 2.5 mg, 5 mg, 10 mg and 40 mg S (4.3%, 4.3%, 11.6% and 11.4%) and s.c. semaglutide 1.0 mg (11.6%).

No apparent differences between treatment arms were seen with respect to hypoglycaemia.

Conclusion

From trial 3790 it can be concluded that both efficacy (in terms of HbA1c reduction and weight loss) and safety (driven by gastro-intestinal adverse events) are dose dependent. This information was used to select doses for Phase 3, according to the Applicant based on a benefit-risk evaluation and modelling data from the dose finding

trial. It remains unclear how the large variability in exposure of oral semaglutide was taken into account for dose selection. However, the applicant considers prediction of low and high absorption unfeasible since only 18.1% of the variability is explained by covariates.

2.6.2. Main studies

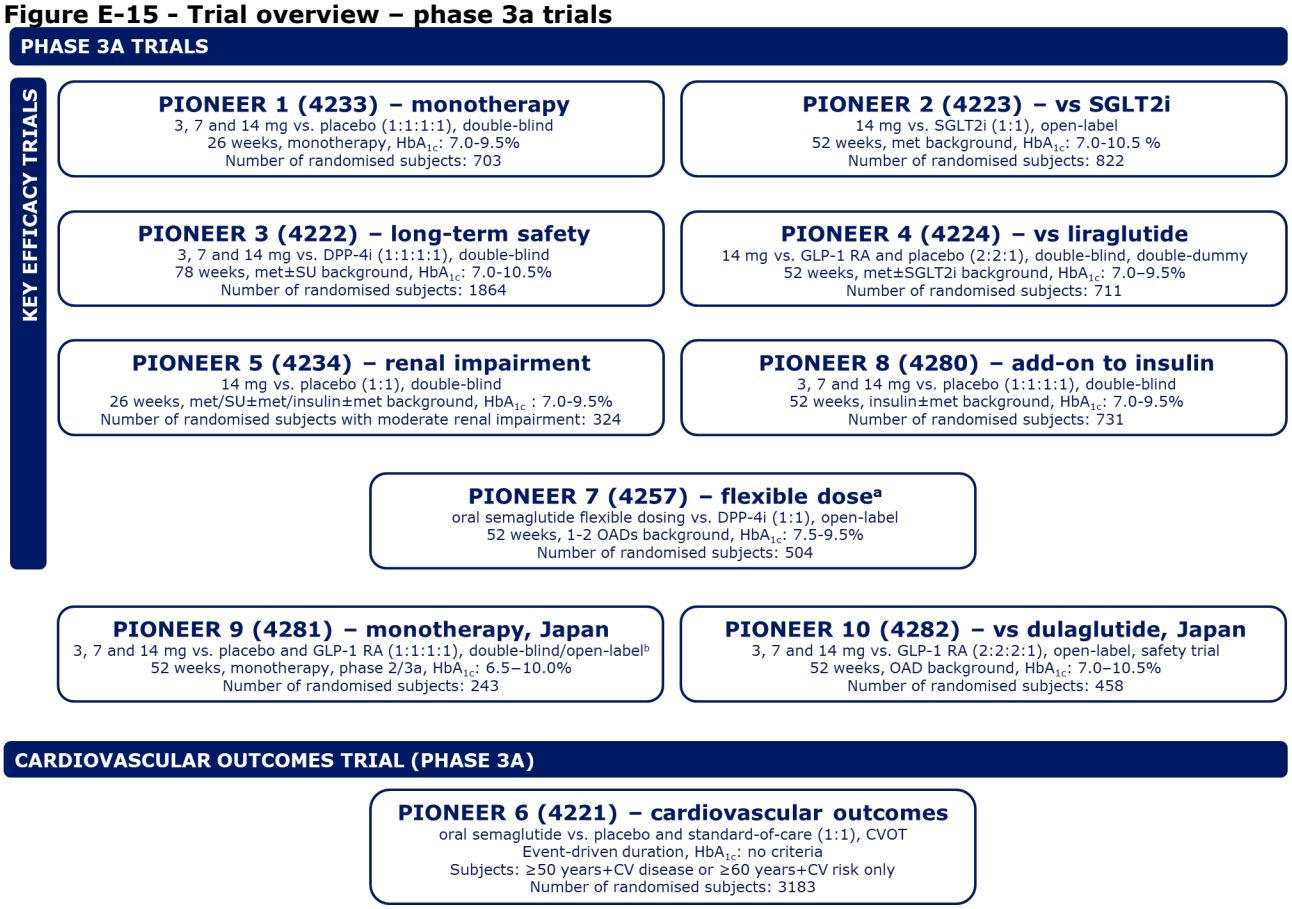
The oral semaglutide clinical development programme (NN9924) was initiated to develop the first orally administered GLP-1 analogue. For oral administration, semaglutide has been co-formulated with a SNAC (300 mg) in a tablet formulation. Semaglutide for once-weekly s.c. injection is approved worldwide for the treatment of T2D (Ozempic), and it reduces body weight.

The clinical development programme comprised 18 clinical pharmacology trials, a phase 2 dose-finding trial and ten phase 3a trials (PIONEER 1–10) with oral semaglutide. The phase 3a trials included a total of 9543 randomised subjects, of whom 5707 were exposed to oral semaglutide. The programme included a dedicated cardiovascular outcome trial (CVOT), PIONEER 6, to assess the cardiovascular safety of oral semaglutide.

Of the phase 3a trials, PIONEER 1–5 and 7–8 are regarded as the key efficacy trials. These seven trials share an overall similarity in objectives, design features and trial procedures, have similar eligibility criteria, and explore a relevant range of comparators. Notably, PIONEER 7 differed in design from the other key efficacy trials with respect to the primary endpoint, the dose-escalation and dosing scheme. Therefore, PIONEER 7 is presented as the last key efficacy trial (i.e. after PIONEER 8) in tables and figures (Figure E-15).

PIONEER 9 and 10 were conducted solely in Japan to fulfil Japanese requirements. PIONEER 6 was a pre-approval cardiovascular outcome trial (CVOT) designed and conducted according to regulatory guidance and advice. The efficacy of oral semaglutide is evaluated based primarily on data from the key efficacy trials.

Figure E-15 - Trial overview – phase 3a trials



a. investigates the flexible use of oral semaglutide 3, 7 and 14 mg; b. double-blind vs placebo; open-label vs GLP-1 RA; CV: cardiovascular; CVOT: CV outcomes trial; RA: receptor agonist

This document focuses on the key efficacy trials; findings from the two Japanese trials are mentioned only if relevantly different from the findings from the key efficacy trials. In PIONEER 6, efficacy parameters (HbA_{1c} and body weight) were evaluated using descriptive statistics only.

For details of the individual studies, reference is made to the summaries in the section "Summary of main efficacy results".

Methods

Study Participants

The key efficacy trials included relevant subgroups of the T2D population, based on pre-trial background therapy. Details per trial are specified in the section "Summary of main efficacy results".

Treatments

The precise treatments per trial are specified in the section "Summary of main efficacy results". The trials compared one or more doses of oral semaglutide to placebo or active comparators.

Objectives

The precise objectives per trial are specified in the section "Summary of main efficacy results". In short, most trials were designed to show superior or non-inferior glycaemic control in comparison to placebo or active comparators.

PIONEER-6, the CVOT, aimed to show that hazard ratio of the risk of Major Adverse Cardiovascular Events (MACE) was below 1.8.

Outcomes/endpoints

In all key efficacy trials, the primary endpoint evaluated the effect of the trial products on glycaemic control estimated based on the around 3-month average blood glucose concentration (HbA_{1c}). These analyses were supported (among others) by glucose measurements and responder analyses.

Weight-loss was pre-defined as a confirmatory, secondary endpoint.

PIONEER-7 used a flexible dosing regimen in an active-controlled, open-label design. Here, the primary endpoint was the fraction of participants reaching an HbA_{1c} target of below 7%.

In PIONEER-6, the CVOT, the endpoint was MACE, a composite of cardiovascular (CV) mortality, nonfatal stroke and nonfatal myocardial infarction.

Randomisation and blinding (masking)

The randomisation was performed in IV/WRS and included allocation of dispensing unit numbers to be dispensed to the subject. All trials were blinded unless masking of active comparator or titration scheme was not feasible (notably open-label trial PIONEER 7), which is acceptable.

Statistical methods

In the key efficacy trials and Japanese trials, the treatment effect is quantified using two estimands for each efficacy endpoint: the treatment policy estimand and the hypothetical estimand. The treatment policy estimand addresses the trial objectives by taking into account the following intercurrent events: initiation of rescue medication; and premature discontinuation of the trial product, while the hypothetical estimand disregards any effects of rescue medication and premature treatment discontinuation. The chosen estimands are properly explained.

The treatment policy estimand estimates the treatment effect regardless of premature trial product discontinuation or the use of additional anti-diabetic medication. The treatment policy estimand was used to establish whether oral semaglutide was associated with a statistically significant treatment effect vs the comparator when including any potentially confounding effects pertaining to the period after discontinuation of trial product and to any additional anti-diabetic medication. All superiority or non-inferiority claims are based on the treatment policy estimand; therefore, this estimand is the basis of analyses presented in the SmPC for all claims.

The hypothetical estimand estimates the treatment effect without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not

require additional anti-diabetic medication. The hypothetical estimand was used to assess the magnitude of an established treatment effect.

For the primary analyses, the use of the in-trial observation period for the primary estimand (treatment policy) is endorsed. The use of the on-treatment observation period without rescue medication for the supplementary estimands (hypothetical estimands) is agreed.

Across the trials, the following analysis sets were specified: A full analysis set (FAS) comprised of all randomised subjects based on the trial product they were randomised to receive; A safety analysis set (SAS) comprised of all randomised subjects who received at least one dose of trial product based on the trial product they actually received. The FAS was used for the evaluation of the efficacy endpoints and the SAS was used for the evaluation of the safety endpoints. For the key efficacy trials with active comparators except PIONEER 7 (i.e. PIONEER 2–4), a per-protocol analysis set was also defined.

The primary analysis in the efficacy trials was performed using an ANCOVA model with treatment, region and strata as fixed effects and baseline value as covariate. Missing data in the primary analysis was handled by retrieved dropout multiple imputation, assuming missing at random within subgroups defined by randomised treatment, treatment status at week 26 (including discontinuation and/or use of rescue medication. The impact of missing data was evaluated using sensitivity analysis: two pattern mixture models using comparator-based imputation for all discontinuations and one for AE-related discontinuations.

The primary analysis in the CVOT trial (PIONEER 6) was performed using Cox proportional hazards model stratified by cardiovascular disease at screening.

For the hypothetical estimand, the primary analysis was based on a mixed model for repeated measurements, including all post-baseline values from the on-treatment without rescue medication observation period collected. The independent categorical fixed effects were treatment, region (PIONEER 1–8), strata (PIONEER 3–10) and interaction between strata (PIONEER 5 and 8), and the baseline value as a covariate, all nested within visit.

For the key efficacy trials, the confirmatory hypotheses were controlled for multiplicity using a graphical pre-defined weighted Bonferroni closed testing strategy. The strategy was used to preserve the overall type I error rate in the strong sense at a nominal two-sided 5% significance level (for the treatment policy estimand only).

For binary endpoints a logistic regression model with similar covariates and missing data handling as the primary analysis. For time to event endpoints the analysis used a Cox proportional hazards model, again with similar covariates.

In the key efficacy trials, confirmatory hypotheses were tested for each applicable oral semaglutide dose vs comparator(s) for the primary endpoint and confirmatory secondary endpoints using the primary treatment policy estimand. In PIONEER 6, the confirmatory endpoint (time from randomisation to first occurrence of a MACE) was first tested for non-inferiority (margin 1.8), and then for superiority. The overall type I error rate was controlled at a nominal two-sided 5% significance level using a graphical pre-defined weighted Bonferroni closed testing strategy.

Results

Participant flow

The characteristic data for the participant flow is shown in Table E-7. With higher doses of oral semaglutide, less subjects needed rescue medication, but more discontinued – often due to adverse events. Discontinuations were usually higher with semaglutide than with comparators.

Table E-7 Subject disposition – overview – all subjects – phase 3a trials

	P1 4233	P2 4223	P3 4222	P4 4224	P5 4234	P8 4280	P7 4257	P9 4281	P10 4282	P6 4221
Randomised subjects (N)										
Total	703	822	1864	711	324	731	504	243	458	3183
Oral sema 3 mg	175		466			184		49	131	
Oral sema 7 mg	175		466			182		49	132	
Oral sema 14 mg	175	412	465	285	163	181		48	130	
Oral sema flex/var							253			1591
Empa 25 mg		410								
Sita 100 mg			467				251			
GLP1-RA				284				48	65	
Placebo	178			142	161	184		49		1592
Treatment completers (%)*										
Total	89.6	85.6	84.0	86.4	84.6	84.0	87.1	95.1	92.4	87.4
Oral sema 3 mg	93.1		83.3			87.0		91.8	94.7	
Oral sema 7 mg	89.7		85.0			81.3		98.0	93.2	
Oral sema 14 mg	86.3	82.3	80.9	84.6	81.6	79.6		93.8	88.5	
Oral sema flex/var							83.4			84.7
Empa 25 mg		89.0								
Sita 100 mg			86.9				90.8			
GLP1-RA				87.3				91.7	93.8	
Placebo	89.3			88.0	87.6	88.0		100.0		90.1
With rescue medication (%)										
Total	6.0	8.8	21.7	10.8	6.2	23.8	9.1	13.6	7.6	NA
Oral sema 3 mg	6.3		31.1			27.2		14.3	16.0	
Oral sema 7 mg	2.3		20.4			18.1		10.2	6.1	
Oral sema 14 mg	1.1	7.0	8.8	6.3	3.7	16.0		8.3	0.8	
Oral sema flex/var							3.2			NA
Empa 25 mg		10.5								
Sita 100 mg			26.3				15.1			
GLP1-RA				6.0				4.2	7.7	
Placebo	14.0			29.6	8.7	33.7		30.6		NA
Premature trial product discontinuation (%)										
Total	10.4	14.4	16.0	13.6	15.4	16.0	12.9	4.9	7.6	12.6
Oral sema 3 mg	6.9		16.7			13.0		8.2	5.3	
Oral sema 7 mg	10.3		15.0			18.7		2.0	6.8	
Oral sema 14 mg	13.7	17.7	19.1	15.4	18.4	20.4		6.3	11.5	
Oral sema flex/var							16.6			15.3
Empa 25 mg		11.0								
Sita 100 mg			13.1				9.2			
GLP1-RA				12.7				8.3	6.2	
Placebo	10.7			12.0	12.4	12.0		0.0		9.8
Adverse event(s) (%)										
Total	4.0	7.9	7.1	9.3	10.5	8.2	6.3	1.6	5.0	9.1
Oral sema 3 mg	2.3		5.6			7.1		2.0	3.8	
Oral sema 7 mg	4.0		6.0			8.8		2.0	6.1	
Oral sema 14 mg	7.4	10.9	11.6	11.6	14.7	14.4		4.2	6.2	
Oral sema flex/var							8.7			11.6
Empa 25 mg		4.9								
Sita 100 mg			5.4				4.0			
GLP1-RA				9.5				0.0	3.1	
Placebo	2.2			4.2	6.2	2.7		0.0		6.5
Withdrawal from trial (%)										
Total	5.7	4.3	5.7	3.7	3.1	4.7	3.8	2.5	2.2	0.3
Oral sema 3 mg	3.4		7.1			5.4		6.1	2.3	
Oral sema 7 mg	8.0		6.4			4.9		0.0	1.5	
Oral sema 14 mg	6.9	2.9	5.8	2.8	3.1	3.3		2.1	2.3	
Oral sema flex/var							4.7			0.3
Empa 25 mg		5.6								
Sita 100 mg			3.4				2.8			

GLP1-RA				3.5				4.2	3.1	
Placebo	4.5			5.6	3.1	4.9		0.0		0.3

* subjects who completed treatment with trial product according to the end-of-trial form;
NA: not applicable; N: number of subjects; %: proportion of randomised subjects.

Baseline data

The key efficacy trials and Japanese trials included a total of 6358 subjects (FAS), mainly from Europe (37.3%), North America (26.4%) and Asia (23.1%); 45.0% were women. In the key efficacy and Japanese trials, 24.9% (1582 subjects) of the subjects were 65 to less than 75 years of age and 5.0% (321 subjects) were 75 years or older. Most (85.6%) had a BMI >25 kg/m^2, i.e. were overweight or obese.

Trial populations across the key efficacy trials ranged from early T2D (mean diabetes duration: 3.5 years in PIONEER 1) to long-standing T2D with or without insulin treatment (e.g. PIONEER 5 and PIONEER 8 with a mean diabetes duration of 14–15 years). Mean baseline HbA_{1c} ranged from 8.0% to 8.3%. All trials also included subjects with mild renal impairment (ranging from 9.6% to 39.0% of subjects across trials) and subjects with upper GI disease (13.8–27.5% across trials). The subjects in PIONEER 5 represented a population with T2D and moderate renal impairment (see section "Clinical studies in special populations").

Baseline characteristics in the Japanese trials were generally similar to those of the key efficacy trials, although the mean body weight and BMI were lower in the Japanese subjects and more men (74.5–78.6%) than women (21.4–25.5%) were included.

PIONEER 6 (CVOT) included 3183 subjects in the FAS, mainly from North America (34.7%), Europe (30.1%), Asia (16.4%) and South America (12.1%). Compared to the other phase 3a trials, and in line with the selection criteria, a larger proportion of subjects (45.2%) were 65 to less than 75 years of age, or 75 years or older (411 subjects, 12.9%) in this CVOT.

The background antidiabetic medication in the key efficacy trials and Japanese trials ranged from no background medication to insulin treatment, reflecting the treatment principles applied from early to late-stage T2D (Table E-8). An overview of other baseline characteristics is presented in Table E-9.

Table E-8 Background antidiabetic medication – all phase 3a trials

	Key efficacy trials							Japanese trials		CVOT
	P1	P2	P3	P4	P5	P8	P7	P9	P10	P6
FAS	703	821	1863	711	324	731	504	243	458	3183
No background treatment, %	100							100		1.4
Metformin only, %		100	52.9	74.3	23.8		37.5			14.3
SU ± metformin, %			47.1		40.7		48.4		32.1	16.1
SGLT2i ± metformin, %				25.7			10.1		17.0	2.0
Insulin ± OADs, %					35.5	100	0.2			60.9
TZD ± metformin, %							2.6		17.2	0.5
Other, %							1.2		33.6	4.8

The start and stop dates of the anti-diabetic medication were before and after the date of the screening visit, respectively. Insulin: basal insulin (P5 and P8), basal bolus (P8) or premix (P8), various insulin regimens were used in P6. For the evaluation of efficacy in subgroups, the following categories are used: No background treatment, metformin only, SU ± metformin, SGLT2i ± metformin, insulin ± OADs, other.
FAS: number of subjects in full analysis set; %: proportion of subjects.

Table E-9. Demographics and baseline characteristics across main trials

Trial/ Characteristic	Key efficacy trials							CVOT
Study No. N ()	**4233 P1** (703)	**4223 P2** (822)	**4222 P3** (1864)	**4224 P4** (711)	**4234 P5** (324)	**4257 P7** (504)	**4280 P8** (731)	**4221 P6** (3183)
General								
Sex (%, men/women)	51/49	50/50	53/47	52/48	48/52	57/43	54/46	68/32
Age (years) (SD)	55 (11)	58 (10)	58 (10)	56 (10)	70 (8)	57 (10)	61 (10)	66 (7)
Race (%) White/ Black or Afr.Am/ Asian	75/5/17	86/7/6	71/9/13	73/4/13	96/4/0	76/9/14	53/7/35	72/6/20
HbA_{1c} (%) (SD)	8.0 (0.7)	8.1 (0.9)	8.3 (0.9)	8.0 (0.7)	8.0 (0.7)	8.3 (0.6)	8.2 (0.7)	8.2 (1.6)
Diabetes duration (years) (SD)	3.5 (4.9)	7.4 (6.1)	8.6 (6.0)	7.6 (5.5)	14.0 (8.0)	8.8 (6.2)	15.0 (8.1)	14.9 (8.5))
BMI (kg/m^2) (SD)	31.8 (6.6)	32.8 (6.1)	32.5 (6.4)	33.0 (6.3)	32.4 (5.4)	31.5 (6.3)	31.0 (6.7)	32.2 (6.5)
Renal function								
Normal renal function, N (%) eGFR ≥90 mL/min/1.73 m^2	518 (73.7)	546 (66.5)	1314 (70.5)	499 (70.2)	NA	362 (71.8)	432 (59.1)	919 (28.9)
Mild renal impairment, N (%) eGFR 60−<90 mL/min/1.73 m^2	179 (25.5)	268 (32.6)	528 (28.3)	207 (29.1)	31 (9.6)	140 (27.8)	285 (39.0)	1389 (43.6)
Moderate renal impairment, N (%) eGFR 30−<60 mL/min/1.73 m^2	6 (0.9)	7 (0.9)	19 (1.0)	4 (0.6)	285 (88.0)	2 (0.4)	14 (1.9)	827 (26.0)
Severe renal impairment, N (%) GFR 15−<30 mL/min/1.73 m^2	NA	NA	NA	NA	8 (2.5)	NA	NA	28 (0.9)
End stage renal impairment N (%) eGFR <15 mL/min/1.73 m^2 ()	NA	NA	NA	NA	NA	NA	NA	1 (<0.1)

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

Numbers analysed

Almost all randomised patients (except two) were included in the full analysis set. The two exceptions were one subject randomised to oral semaglutide 14 mg in PIONEER-2 and one subject randomised to oral semaglutide 7 mg in PIONEER-3.

Outcomes and estimation

Glycaemic control

HbA_{1c} change from baseline

Oral semaglutide dose-dependently reduced HbA_{1c} across all PIONEER trials; the reductions were 0.6 to 0.9 %-points for 3 mg, 0.8 to 1.2 %-points for 7 mg and 1.0 to 1.4 %-points for 14 mg in the key efficacy trials (Figure E-16, Figure E-17). Oral semaglutide 7 and 14 mg were statistically significantly superior to most comparators, except that vs liraglutide 1.8 mg, oral semaglutide 14 mg was non-inferior but not superior at week 26 (PIONEER 4). Oral semaglutide 3 mg was statistically significantly superior to placebo, whereas non-inferiority vs sitagliptin 100 mg could not be confirmed.

The conclusions and results were consistent across estimands. When excluding the potentially confounding effects of any additional anti-diabetic medication and assuming that subjects stayed on trial product, the HbA_{1c} reductions were 0.5 to 0.8, 1.0 to 1.3, 1.1 to 1.5 and 1.4 %-points with oral semaglutide 3, 7, and 14 mg and flexible dose, respectively (hypothetical estimand; Figure E-17Figure E).

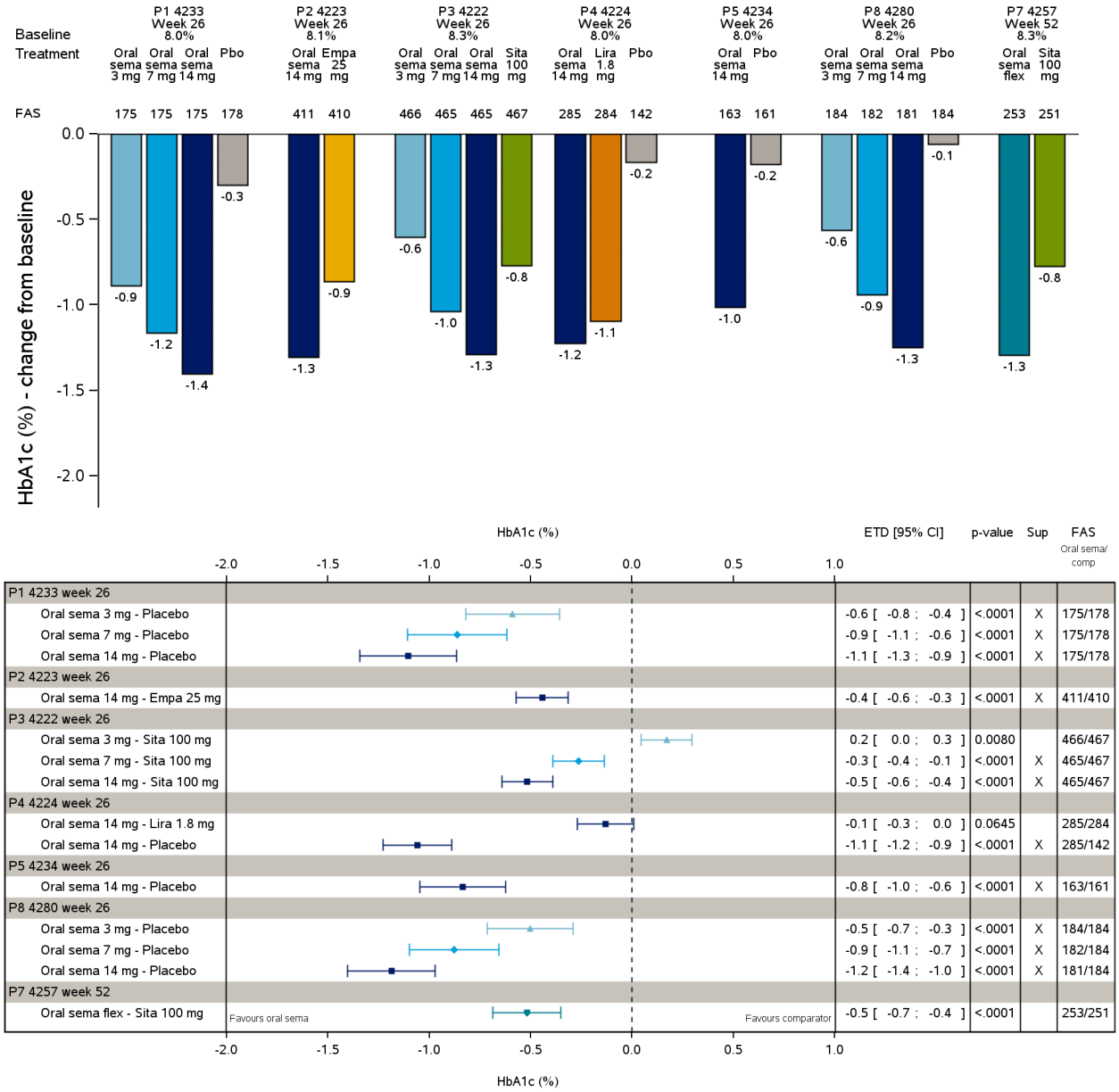
The robustness of these conclusions was consistently confirmed by the pre-defined sensitivity analyses.

Thus, compared against most of the contemporary second-line treatment options for T2D (except liraglutide), oral semaglutide 7 and 14 mg was statistically significantly superior in improving glycaemic control. The improvements started early (around week 4-8) and were sustained throughout the duration of the trials, including the 78-week PIONEER 3 trial (Figure E-17, Figure E–18). Furthermore, the improvements were seen across various T2D disease stages, from T2D managed by diet and exercise (PIONEER 1) to insulin-requiring T2D (PIONEER 8).

HbA_{1c} <7.0%

A high proportion of the subjects achieved the recommended HbA1c levels <7.0% (59 to 80% with oral semaglutide 14 mg monotherapy in PIONEER 1; Figure E-19). Oral semaglutide used according to a response-driven flexible dose regimen was superior to sitagliptin 100 mg in enabling subjects to achieve HbA_{1c} <7.0% (PIONEER 7).

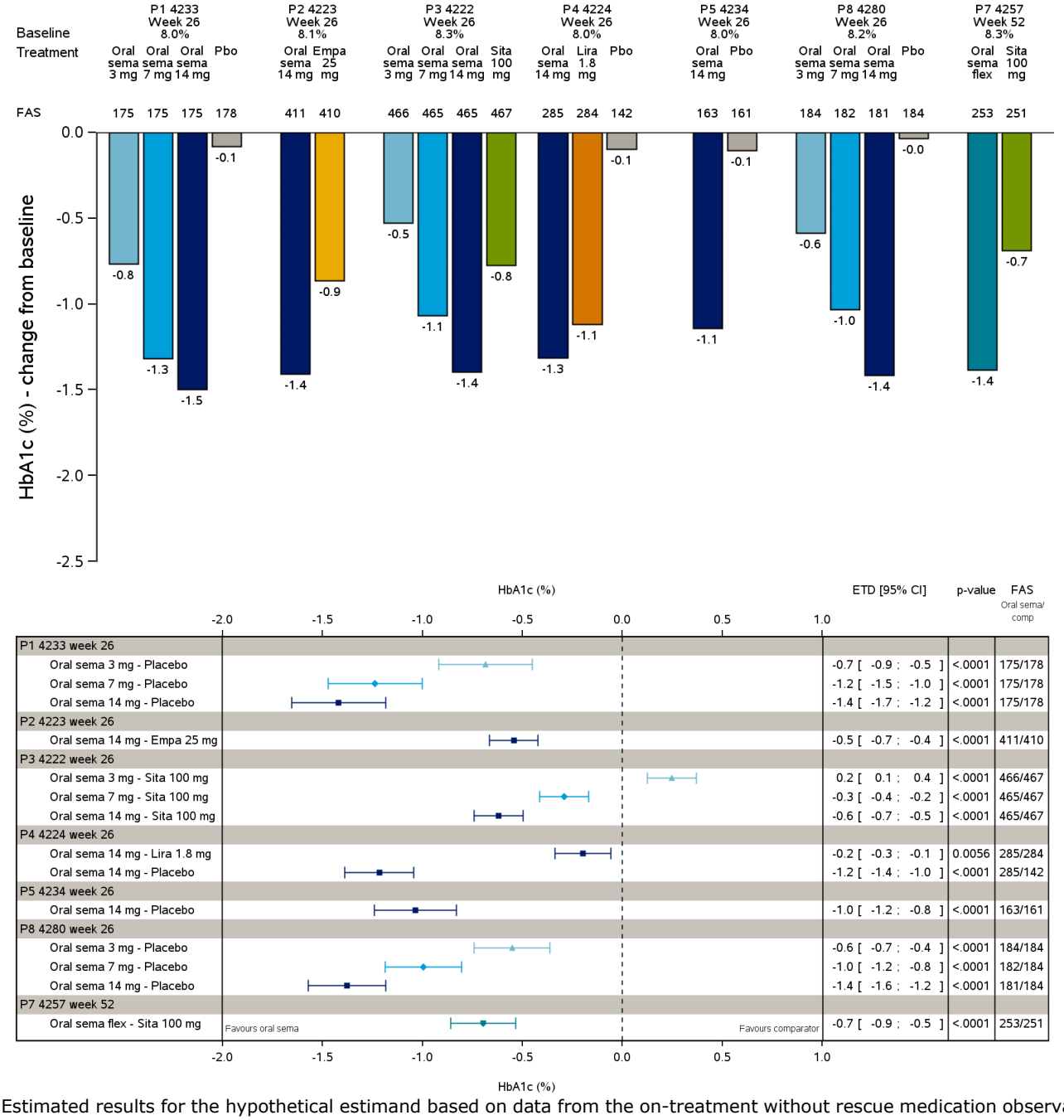
Figure E-16 - Estimated change in HbA_{1c} (%-points) – treatment policy estimand - key efficacy trials



Estimated results for the treatment policy estimand based on data from the in-trial observation period. Note that even though the change from baseline in HbA_{1c} was statistically significantly greater with oral semaglutide flex than with sitagliptin 100 mg in PIONEER 7 at week 52, superiority is not claimed because the endpoint was not confirmatory; for the confirmatory binary endpoint in PIONEER 7 (proportion of subjects achieving HbA_{1c} <7.0%), superiority of oral semaglutide flex vs sitagliptin 100 mg was confirmed.

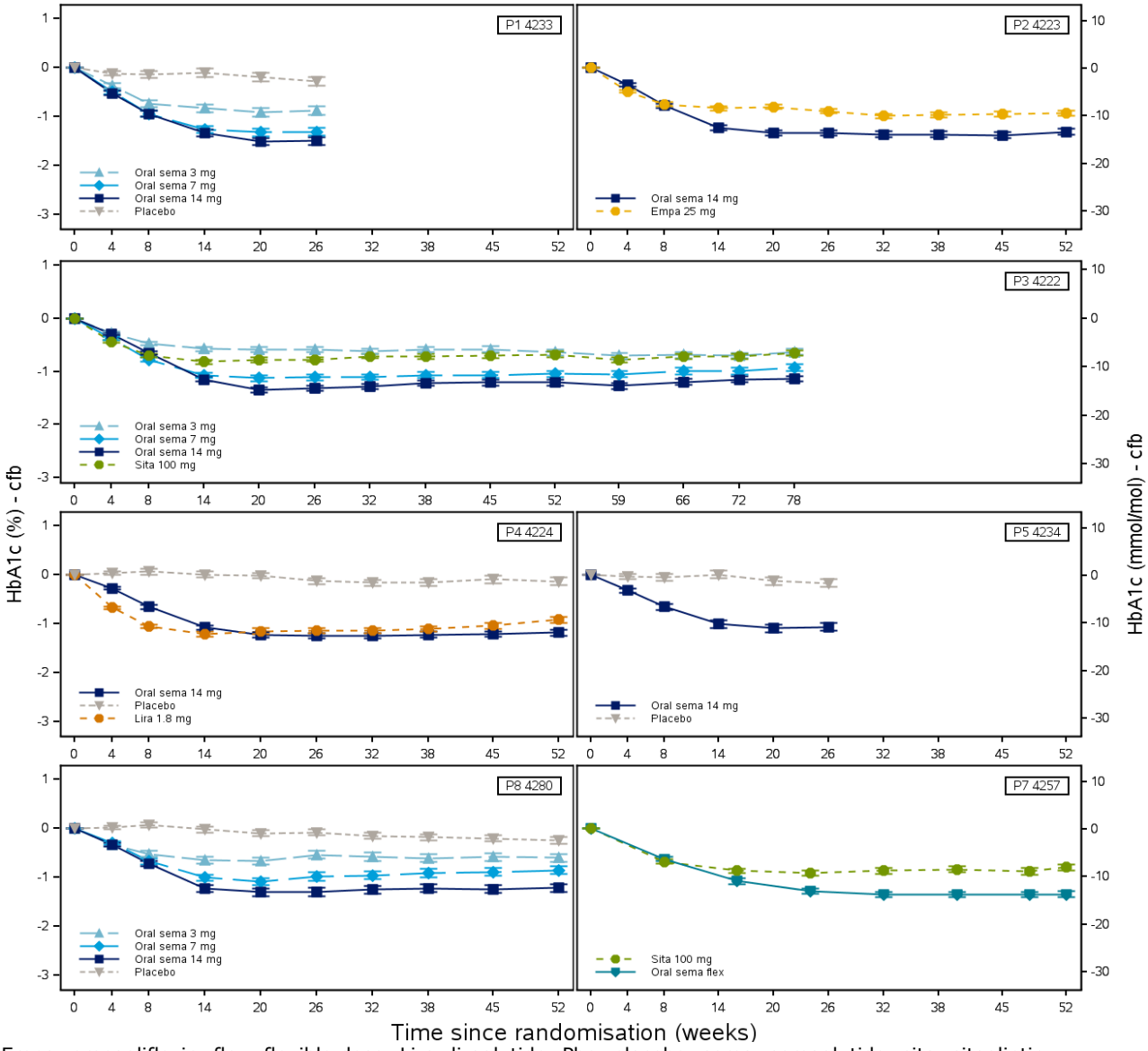
Empa: empagliflozin; FAS: full analysis set; flex: flexible dose; Lira: liraglutide; Pbo: placebo; sema: semaglutide; sita: sitagliptin; Sup: superiority

Figure E-17 - Estimated change in HbA1c (%-points) – hypothetical estimand – key efficacy trials



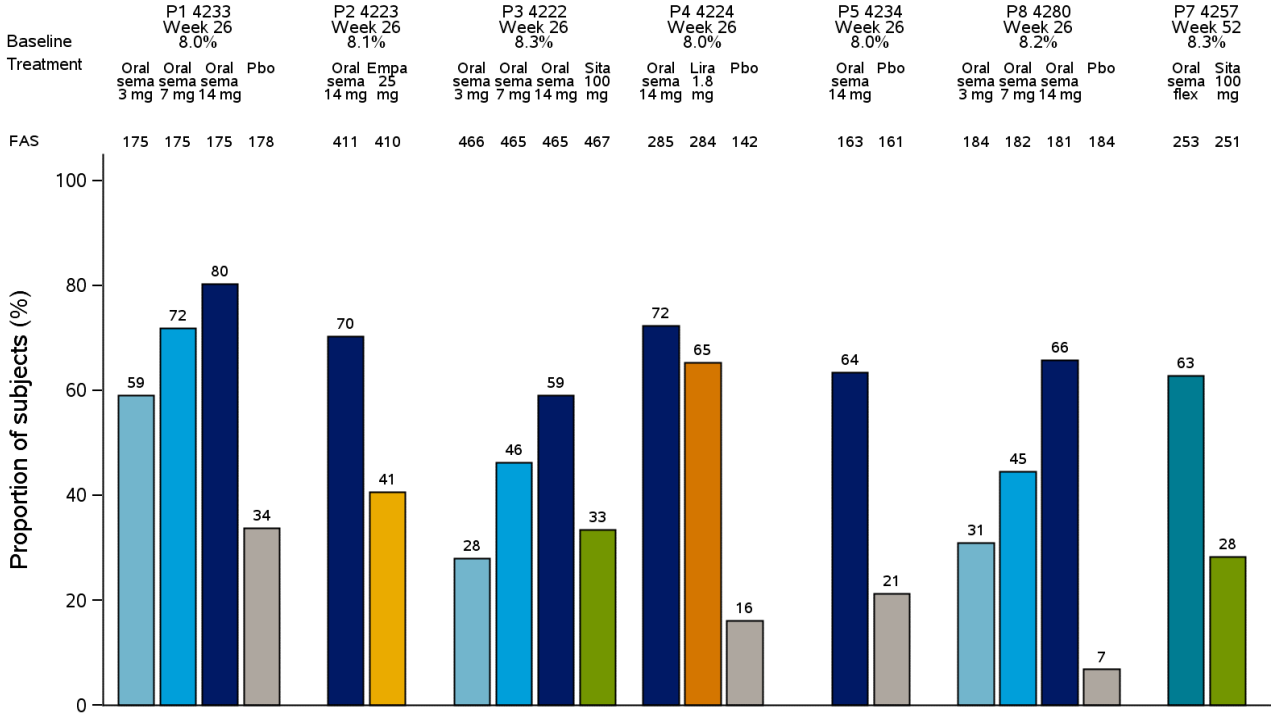
Estimated results for the hypothetical estimand based on data from the on-treatment without rescue medication observation period. Empa: empagliflozin; FAS: full analysis set; flex: flexible dose; Lira: liraglutide; Pbo: placebo; sema: semaglutide; sita: sitagliptin.

Figure E-18 - HbA_{1c} – observed change by week – in-trial – key efficacy trials



Empa: empagliflozin; flex: flexible dose; Lira: liraglutide; Pbo: placebo; sema: semaglutide; sita: sitagliptin.

Figure E-19 - Observed proportion of subjects achieving HbA_{1c} <7.0% – on-treatment without rescue medication – key efficacy trials

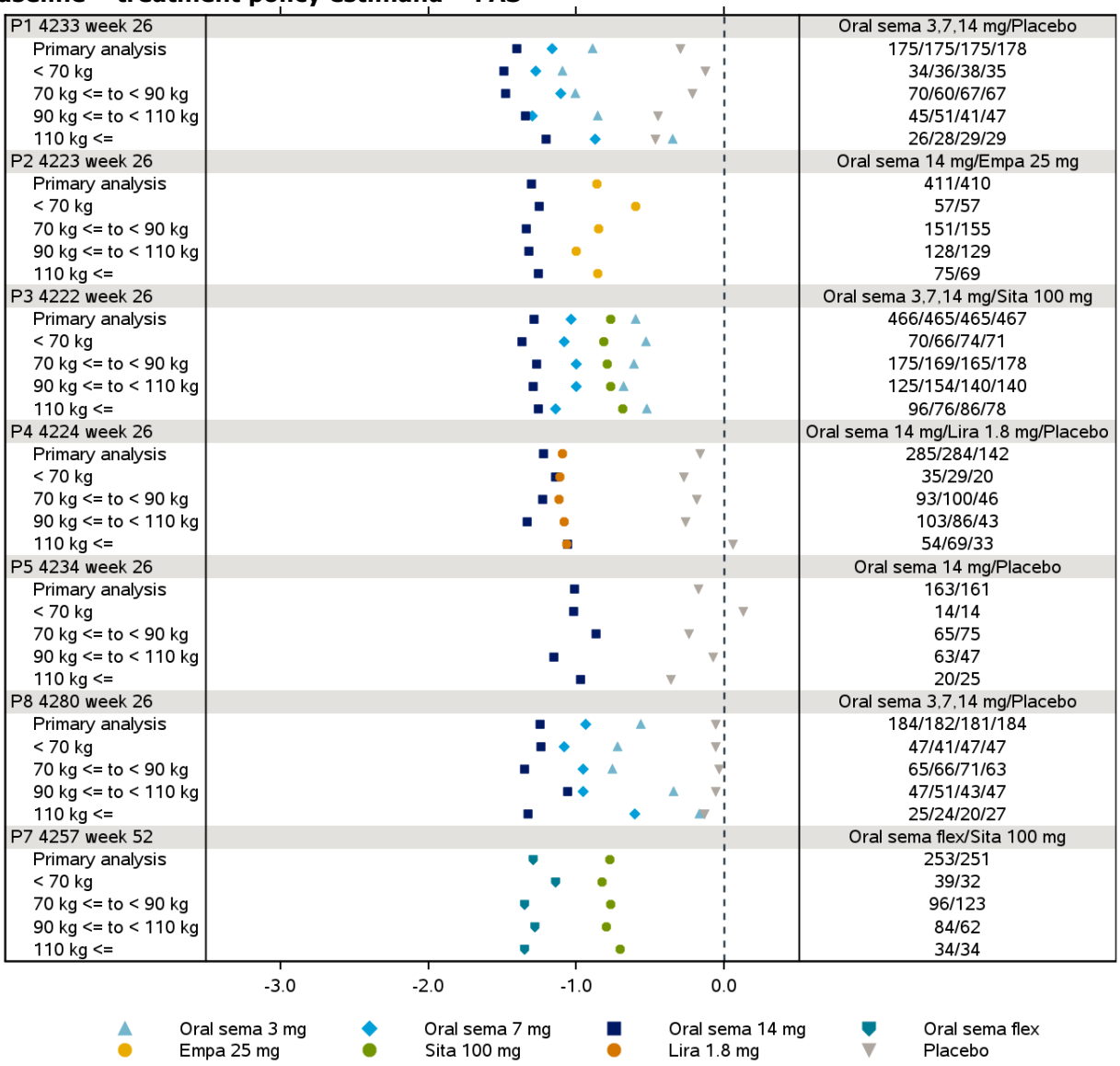


Empa: empagliflozin; flex: flexible dose; Lira: liraglutide; Pbo: placebo; sema: semaglutide; sita: sitagliptin.

HbA_{1c} response across trial population subgroups

The applicability of the HbA_{1c} results across a relevant range of trial population segments (by demography, disease factors and background medication use) was supported by subgroup analyses. The analyses qualified the population PK-based exposure-response modelling that suggested an effect on semaglutide exposure of body weight. The subgroup analyses did not suggest that the effect of oral semaglutide on HbA_{1c} differs by baseline body weight supporting that all individuals irrespective of the baseline body weight could be able to achieve clinically relevant HbA_{1c} reductions with oral semaglutide. Upon request, to explain this clear difference from observation with s.c. semaglutide, the applicant provided additional analyses (both as subgroup and based on dose-response modelling) which demonstrated no clear relationship between baseline body weight and efficacy on weight reduction and glycaemic parameters. In addition, the treatment effect of oral semaglutide on HbA_{1c} was consistent across all the other evaluated subgroups (sex, age, race, ethnicity, region, baseline hba1c, diabetes duration, body weight, BMI, eGFR, upper gastrointestinal disease, antidiabetic background medication). For an example, see Figure E-20.

Figure E-20 - HbA1c (%) change from baseline by body weight – dot plot – estimated change from baseline – treatment policy estimand – FAS



Data from the in-trial observation period. Treatment policy estimand: Analysis of covariance (ANCOVA) using data irrespectively of premature discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation; pattern was defined by treatment arm and treatment status (premature trial product discontinuation and/or initiation of rescue medication).
FAS: number of subjects in full analysis set.

Other glycaemia-related results

Supporting the HbA_{1c}-related improvements, glucose-metabolism-related parameters were dose-dependently improved with oral semaglutide. Oral semaglutide (all doses) reduced fasting as well as self-measured plasma glucose concentrations, including post-prandial concentrations and across-meal concentration increments. These improvements appeared to be sustained throughout the duration of the trials. In line with findings from clinical pharmacology trials, oral semaglutide increased insulin and C-peptide concentrations, and decreased pro-insulin and glucagon concentrations, suggesting a normalising effect on the beta-cell function as also supported by the observed increases in HOMA-B indices and improved the insulin sensitivity (HOMA-IR).

Corroborating the glycaemic benefits of oral semaglutide, subjects on oral semaglutide needed glucose-lowering medication in addition to or instead of trial product later than subjects on sitagliptin 100 mg (oral semaglutide 7, 14 mg and flexible dose) and placebo (all doses). Moreover, when evaluating oral semaglutide used as add-on to insulin in subjects with insulin-requiring T2D, the total daily insulin dose required to attain a pre-defined FPG target was lower with oral semaglutide 7 and 14 mg than with placebo.

These findings support that oral semaglutide improves long-term glycaemic control, the more short-term glucose metabolism as well as the beta-cell function.

Effect on body weight and related parameters

Weight loss is another objective in the management of T2D, which is intimately associated with overweight and obesity. The weight-lowering effect of semaglutide is well documented mechanistically and clinically, and the weight loss largely represents loss of predominantly fat tissue. It contributes to improved glycaemic control (e.g. via improved peripheral insulin sensitivity) and reduced cardiovascular risk.

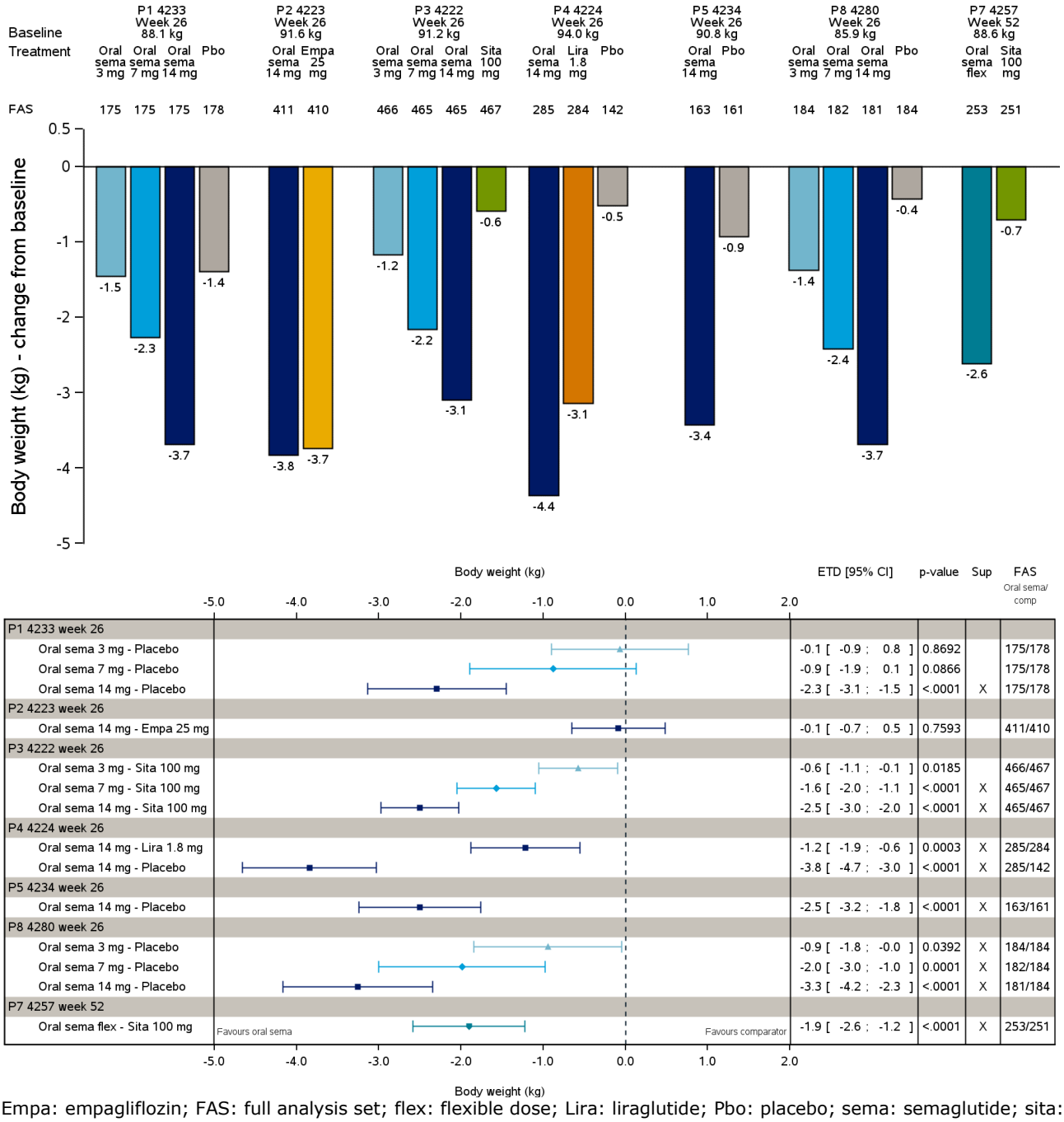
Body weight

Body weight was reduced by 1.2 to 1.5 kg with oral semaglutide 3 mg, 2.2 to 2.4 kg with 7 mg and 3.1 to 4.4 kg with 14 mg in the key efficacy trials at week 26 (Figure E-21).

Oral semaglutide 14 mg was superior to comparators except for empagliflozin 25 mg. Oral semaglutide 7 mg and the flexible dose regimen were superior to sitagliptin 100 mg and to placebo, and oral semaglutide 3, 7 and 14 mg used as an add-on to insulin were superior to placebo.

Across the key efficacy trials, the maximum body weight reduction was achieved around week 26 to 32, and the reduction was sustained throughout the duration of the trials, including the 78-week PIONEER 3 trial.

Figure E-21 - Estimated change in body weight (kg) – treatment policy estimand – key efficacy trials



Empa: empagliflozin; FAS: full analysis set; flex: flexible dose; Lira: liraglutide; Pbo: placebo; sema: semaglutide; sita: sitagliptin; Sup: superiority

≥5% and ≥10% weight loss

A weight loss of at least 5% is considered clinically meaningful and helps improve glycaemic control in patients with T2D.

The proportion of subjects across the key efficacy trials who had achieved a clinically meaningful weight loss of ≥5% by week 26 was consistently greater with oral semaglutide 7 and 14 mg than with placebo and active comparators (up to 46% with 14 mg). The proportion of subjects across the key efficacy trials who had achieved a weight loss of ≥10% at week 26 was consistently greater with oral semaglutide 7 and 14 mg than with all comparators.

Ancillary analyses

N/A

2.6.3. Summary of main efficacy results

Table 10 Trial NN9924-4233 (PIONEER 1)

Trial NN9924-4233 – PIONEER 1 – Monotherapy		
Title	Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only	
Study identifier	Protocol number: NN9924-4233 EudraCT number: 2015-005622-19	
Data cut-off date	30 January 2018	
Design	This was a randomised, double-blind, placebo-controlled multinational, multi-centre efficacy and safety trial with a 26-week treatment period (including an 8-week dose escalation period). A total of 704 adults with type 2 diabetes treated with diet and exercise only were planned to be randomised 1:1:1:1 to once-daily treatment with oral semaglutide (3, 7 or 14 mg) or placebo. Randomisation was stratified by country (Japan/non-Japan). The total maximum trial duration for the individual subject was approximately 33 weeks, comprising a 2-week screening period, a 26-week treatment period and a 5-week follow-up period. Subjects were to follow a dose-escalation regimen, where all subjects started at 3 mg and were dose escalated in 4-week increments until the final maintenance dose was reached. Dose escalation was blinded for all treatment arms and dose levels. Subjects were scheduled to attend 8 visits at the trial site; in addition, 1 phone contact with the investigator was scheduled 2 weeks after randomisation. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. All efforts were made to collect data on all randomised subjects, including subject who prematurely discontinued trial product or initiated additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	26 weeks 2 weeks
Objectives	Primary objective: To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo on glycaemic control in subjects with type 2 diabetes treated with diet and exercise only. Secondary objectives: To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo on body weight in subjects with type 2 diabetes treated with diet and exercise only. To compare the safety and tolerability of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo in subjects with type 2 diabetes treated with diet and exercise only.	
Treatment groups	Oral semaglutide 3 mg	175 subjects randomised
	Oral semaglutide 7 mg	175 subjects randomised
	Oral semaglutide 14 mg	175 subjects randomised
	Placebo	178 subjects randomised
Endpoints and	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%-points)	

Trial NN9924-4233 – PIONEER 1 – Monotherapy	
definitions	Confirmatory secondary endpoint: Change from baseline to week 26 in body weight (kg)
	Supportive secondary endpoints: Change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumptions that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4233 – PIONEER 1 – Monotherapy					
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.				
Results		Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
	Number of subjects (FAS)	175	175	175	178
HbA_{1c}	Change from baseline to week 26, %-points	−0.9	−1.2	−1.4	−0.3
	ETD [95% CI] vs placebo	−0.6 [−0.8; −0.4] *	−0.9 [−1.1; −0.6] *	−1.1 [−1.3; −0.9] *	
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26	55.1	68.8	76.9	31.0
	EOR [95% CI] vs placebo	3.09 [1.91; 4.99] #	5.79 [3.50; 9.59] #	8.36 [4.86; 14.41] #	
Body weight	Change from baseline to week 26, kg	−1.5	−2.3	−3.7	−1.4
	ETD [95% CI] vs placebo	−0.1 [−0.9; 0.8]	−0.9 [−1.9; 0.1]	−2.3 [−3.1; −1.5] *	
FPG	Change from baseline to week 26, mmol/L	−0.90	−1.55	−1.82	-0.18
	ETD [95% CI] vs placebo	−0.72 [−1.19; −0.25] $	−1.37 [−1.95; −0.79] $	−1.64 [−2.12; −1.17] $	

* superiority vs placebo confirmed (controlled for multiplicity)
$ reduction statistically significantly greater with oral semaglutide than with placebo ($p<0.05$)
# odds for achieving the target statistically significantly greater with oral semaglutide than with placebo ($p<0.05$).

Table 11 Trial NN9924-4223 (PIONEER 2)

Trial NN9924-4223 – PIONEER 2 – vs. SGLT-2 inhibitor		
Title	Efficacy and safety of oral semaglutide versus empagliflozin in subjects with type 2 diabetes mellitus	
Study identifier	Protocol number: NN9924-4223 EudraCT number: 2015-005209-36	
Data cut-off date	05 July 2018	
Design	This was a multinational, multi-centre, randomised, open-label, active-controlled efficacy and safety trial with a 52-week treatment period (including an 8-week dose escalation period). A total of 816 adults with type 2 diabetes treated with metformin were planned to be randomised 1:1 to once-daily treatment with oral semaglutide 14 mg or empagliflozin 25 mg. The total maximum trial duration for the individual subject was approximately 59 weeks, comprising a 2-week screening period, followed by a 52-week randomised treatment period and a follow-up period of 5 weeks. All subjects were to follow a dose-escalation regimen. Subjects randomised to oral semaglutide started at 3 mg from week 0 to week 4, and were dose escalated to 7 mg from week 4 to week 8, the maintenance dose of 14 mg once daily was to be taken from week 8 to week 52. Subjects randomised to empagliflozin were initiated at 10 mg once-daily and the dose was escalated after 8 weeks to the maintenance dose of 25 mg. Subjects were scheduled to attend 13 visits at the trial site; in addition, 1 phone contact with the investigator was scheduled 2 weeks after randomisation. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. All efforts were made to collect data on all randomised subjects, including subject who prematurely discontinued trial product or initiated additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	52 weeks 2 weeks
Objectives	Primary objective: To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on glycaemic control in subjects with type 2 diabetes. Secondary objectives: To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on body weight in subjects with type 2 diabetes. To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, in subjects with type 2 diabetes.	
Treatment groups	Oral semaglutide 14 mg	412 subjects randomised
	Empagliflozin 25 mg	410 subjects randomised
Endpoints and definitions	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%-points)	
	Confirmatory secondary endpoint: Change from baseline to week 26 in body weight (kg)	
	Supportive secondary endpoints: Change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)	
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of	

Trial NN9924-4223 – PIONEER 2 – vs. SGLT-2 inhibitor	
	additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4223 – PIONEER 2 – vs. SGLT-2 inhibitor			
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.		
Results		Oral semaglutide 14 mg	Empagliflozin 25 mg
	Number of subjects (FAS)	411	410
HbA_{1c}	Change from baseline to week 26, %-points ETD [95% CI] vs empagliflozin	−1.3 −0.4 [−0.6; −0.3] *	−0.9
	Change from baseline to week 52, %-points ETD [95% CI] vs empagliflozin	−1.3 −0.4 [−0.5; −0.3] §	−0.9
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26 EOR [95% CI] vs empagliflozin	66.8 3.39 [2.47; 4.65] #	40.0
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 52 EOR [95% CI] vs empagliflozin	66.1 2.71 [1.99; 3.69] #	43.2
Body weight	Change from baseline to week 26, kg ETD [95% CI] vs empagliflozin	−3.8 −0.1 [−0.7; 0.5]	−3.7
	Change from baseline to week 52, kg ETD [95% CI] vs empagliflozin	−3.8 −0.2 [−0.9; 0.5]	−3.6
FPG	Change from baseline to week 26, mmol/L ETD [95% CI] vs empagliflozin	−1.99 0.02 [−0.24; 0.28]	−2.01
	Change from baseline to week 52, mmol/L ETD [95% CI] vs empagliflozin	-2.01 0.08 [-0.20; 0.36]	-2.09

* superiority vs empagliflozin confirmed (controlled for multiplicity);
§ reduction statistically significantly greater with oral semaglutide than with sitagliptin ($p<0.05$);
# odds for achieving the target statistically significantly greater with oral semaglutide than with empagliflozin ($p<0.05$).

Table 12 Trial NN9924-4222 (PIONEER 3)

Trial NN9924-4222 – PIONEER 3 – vs. DPP-4 inhibitor		
Title	Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes mellitus	
Study identifier	Protocol number: NN9924-4222 EudraCT number: 2015-001351-71	
Data cut-off	29 May 2018	
Design	This was a randomised, double-blind, double-dummy, active-controlled, trial with four arms comparing efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg once-daily with sitagliptin 100 mg once-daily. A total of 1860 adults with type 2 diabetes inadequately controlled on metformin alone or in combination with SU were planned to be randomised 1:1:1:1 to once-daily treatment with oral semaglutide (3 mg, 7 mg or 14 mg) or sitagliptin 100 mg. Randomised treatment was given with metformin alone or in combination with SU as background medication. The total maximum trial duration for the individual subject was approximately 85 weeks, comprising a 2-week screening period, a 78-week treatment period and a 5-week follow-up period. Subjects randomised to oral semaglutide were to follow a dose-escalation regimen, in which all subjects started at 3 mg; then the dose was escalated in 4-week increments until the maintenance dose was reached. Dose escalation was blinded for all treatment arms and dose levels. Subjects were scheduled to attend 16 visits at the trial site; in addition, 1 phone contact with the investigator was scheduled at 2 weeks after randomisation. All efforts were to be made to keep subjects on trial product, but the subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. Diligent efforts were made to collect data on all randomised subjects despite potential premature discontinuation of trial product or initiation of additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	78 weeks 2 weeks
Objectives	Primary objective: To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on glycaemic control in subjects with type 2 diabetes. Secondary objectives: To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on body weight in subjects with type 2 diabetes. To compare the long-term safety and tolerability of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, in subjects with type 2 diabetes.	
Treatment groups	Oral semaglutide 3 mg	466 subjects randomised
	Oral semaglutide 7 mg	466 subjects randomised
	Oral semaglutide 14 mg	465 subjects randomised
	Sitagliptin 100 mg	467 subjects randomised
Endpoints and definitions	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%- points)	
	Confirmatory secondary endpoint: Change from baseline to week 26 in body weight (kg)	
	Supportive secondary endpoints: Change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)	

Trial NN9924-4222 – PIONEER 3 – vs. DPP-4 inhibitor	
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4222 – PIONEER 3 – vs. DPP-4 inhibitor					
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.				
Results		Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Sitagliptin 100 mg
	Number of subjects (FAS)	466	465	465	467
HbA_{1c}	Change from baseline to week 26, %-points ETD [95% CI] vs sitagliptin	−0.6 0.2 [0.0; 0.3] [a]	−1.0 −0.3 [−0.4; −0.1] *	−1.3 −0.5 [−0.6; −0.4] *	−0.8
	Change from baseline to week 78, %-points ETD [95% CI] vs sitagliptin	−0.6 0.0 [-0.1; 0.2]	−0.8 −0.1 [−0.3; 0.0]	−1.1 −0.4 [−0.6; −0.3] §	−0.7
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26 EOR [95% CI] vs sitagliptin	26.7 0.74 [0.54; 1.02]	43.8 1.97 [1.46; 2.66] #	56.4 3.23 [2.39; 4.37] #	32.3
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 78 EOR [95% CI] vs sitagliptin	26.8 0.88 [0.65; 1.20]	38.9 1.61 [1.19; 2.16] #	44.9 2.01 [1.50; 2.69] #	29.4
Body weight	Change from baseline to week 26, kg ETD [95% CI] vs sitagliptin	−1.2 −0.6 [−1.1; −0.1] §	−2.2 −1.6 [−2.0; −1.1] *	−3.1 −2.5 [−3.0; −2.0] *	−0.6
	Change from baseline to week 78, kg ETD [95% CI] vs sitagliptin	-1.8 -0.8 [-1.5; -0.1] §	-2.7 -1.7 [-2.3; -1.0] §	-3.2 -2.1 [-2.8; -1.5] §	-1.0
FPG	Change from baseline to week 26, mmol/L ETD [95% CI] vs sitagliptin	−0.75 0.10 [−0.20; 0.40]	−1.18 −0.32 [−0.63; −0.02] §	−1.69 −0.84 [−1.14; −0.54] §	−0.86

Trial NN9924-4222 – PIONEER 3 – vs. DPP-4 inhibitor					
	Change from baseline to week 78, mmol/L ETD [95% CI] vs sitagliptin	-0.95 -0.11 [-0.45; 0.22]	-1.00 -0.17 [-0.52; 0.17]	-1.71 -0.88 [-1.20; -0.55] §	-0.83

* superiority vs sitagliptin confirmed (controlled for multiplicity);
# odds for achieving the target statistically significantly greater with oral semaglutide than with sitagliptin (p<0.05);
§ reduction statistically significantly greater with oral semaglutide than with sitagliptin (p<0.05).
[a] reduction statistically significantly greater with dulaglutide than with oral semaglutide 3 mg (p<0.05).

Table 13 Trial NN9924-4224 (PIONEER 4)

Trial NN9924-4224 – PIONEER 4 – vs. GLP-1 RA		
Title	Efficacy and safety of oral semaglutide versus liraglutide and versus placebo in subjects with type 2 diabetes mellitus	
Study identifier	Protocol number: NN9924-4224 EudraCT number: 2015-005210-30	
Data cut-off	30 May 2018	
Design	This was a randomised, double-blind, double-dummy, active- and placebo-controlled multinational, multi-centre trial with a 52-week treatment period (including an 8-week dose escalation period). A total of 690 adults with T2D on background anti-diabetic medication (metformin alone or metformin in combination with a SGLT-2 inhibitor) were planned to be randomised 2:2:1 to once-daily treatment with oral semaglutide 14 mg, liraglutide 1.8 mg (s.c. injection) or placebo, respectively. Randomisation was stratified based on antidiabetic background medication at screening (metformin alone or in combination with a SGLT-2 inhibitor) and descent (Japanese subjects/non-Japanese subjects). The total maximum trial duration for the individual subject was approximately 59 weeks, comprising a 2-week screening period, followed by a 52-week randomised treatment period and a follow-up period of 5 weeks. Subjects were to follow a dose-escalation regimen, where subjects started at 3 mg and were dose escalated in 4-week increments until the final maintenance dose was reached. Subjects randomised to liraglutide/liraglutide placebo were initiated at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The background medication (metformin alone or in combination with a SGLT-2 inhibitor) was to be maintained at the stable, pre-trial dose and frequency during the whole treatment period unless rescue medication was needed. Subjects were scheduled to attend 12 visits at the trial site; in addition, 2 phone contacts with the investigator were scheduled 2 weeks and 6 weeks after randomisation. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. Diligent efforts were made to collect data on all randomised subjects despite potential discontinuation of premature trial product or initiation of additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	52 weeks 2 weeks
Objectives	Primary objective: To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a SGLT-2 inhibitor, on glycaemic control in subjects with type 2 diabetes. Secondary objectives: To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a SGLT-2 inhibitor, on body weight in subjects with type 2 diabetes. To compare the safety and tolerability of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a SGLT-2 inhibitor, in subjects with type 2 diabetes.	
Treatment groups	Oral semaglutide14 mg	285 subjects randomised
	Liraglutide 1.8 mg	284 subjects randomised
	Placebo	142 subjects randomised
Endpoints and definitions	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%-points)	
	Confirmatory secondary endpoint: Change from baseline to week 26 in body weight (kg)	
	Supportive secondary endpoints: Change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)	

Trial NN9924-4224 – PIONEER 4 – vs. GLP-1 RA	
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4224 – PIONEER 4 – vs. GLP-1 RA				
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.			
Results		Oral semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
	Number of subjects (FAS)	285	284	142
HbA_{1c}	Change from baseline to week 26, %-points ETD [95% CI] vs liraglutide vs placebo	–1.2 −0.1 [−0.3; 0.0] [$] –1.1 [–1.2; –0.9] *	–1.1	–0.2
	Change from baseline to week 52, %-points ETD [95% CI] vs liraglutide ETD [95% CI] vs placebo	–1.2 −0.3 [−0.5; -0.1] [$] –1.0 [–1.2; –0.8] [§]	–0.9	–0.2
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26 EOR [95% CI] vs liraglutide EOR [95% CI]vs placebo	67.6 1.31 [0.91; 1.89] 17.10 [9.50; 30.77] [#]	61.8	14.2
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 52 EOR [95% CI] vs liraglutide EOR [95% CI] vs placebo	60.7 1.33 [0.93; 1.91] 11.36 [6.40; 20.19] [#]	55.0	15.0
Body weight	Change from baseline to week 26, kg ETD [95% CI] vs liraglutide ETD [95% CI] vs placebo	–4.4 –1.2 [–1.9; –0.6] * –3.8 [–4.7; –3.0] *	–3.1	–0.5
	Change from baseline to week 52, kg ETD [95% CI] vs liraglutide ETD [95% CI] vs placebo	-4.3 –1.3 [–2.1; –0.5] [§] -3.3 [–4.3; –2.4] [§]	–3.0	–1.0
FPG	Change from baseline to week 26, mmol/L ETD [95% CI] vs liraglutide ETD [95% CI] vs placebo	–2.00 –0.13 [–0.41; 0.14] –1.64 [–1.99; –1.28] [§]	–1.87	–0.36

Trial NN9924-4224 – PIONEER 4 – vs. GLP-1 RA				
	Change from baseline to week 52, mmol/L ETD [95% CI] vs liraglutide ETD [95% CI] vs placebo	−1.88 −0.41 [−0.74; −0.08] [§] −1.19 [−1.58; −0.79] [§]	−1.47	−0.70

[$] non-inferiority vs liraglutide confirmed (controlled for multiplicity; superiority could not be confirmed);
* superiority vs liraglutide/placebo confirmed (controlled for multiplicity);
[#] odds for achieving the target statistically significantly greater with oral semaglutide than with liraglutide / placebo ($p<0.05$);
[§] reduction statistically significantly greater with oral semaglutide than with placebo ($p<0.05$).

Table 14 Trial NN9924-4234 (PIONEER 5)

Trial NN9924-4234 – PIONEER 5 – Renal impairment		
Title	Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus and moderate renal impairment	
Study identifier	Protocol number: NN9924-4234 EudraCT number: 2015-005326-19	
Data cut-off date	11 July 2018	
Design	This was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial with a 26-week treatment period (including an 8-week dose escalation period) comparing the efficacy and safety of oral semaglutide with placebo in subjects with type 2 diabetes and moderate renal impairment inadequately controlled on metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin. A total of 324 adults with type 2 diabetes inadequately controlled on metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin, were planned to be randomised 1:1 to once-daily treatment with oral semaglutide (14 mg) or placebo, as add-on to their background medication The total maximum trial duration for the individual subject was approximately 33 weeks, comprising a 2-week screening period, a 26-week treatment period and a 5-week follow-up period. Randomisation was stratified based on renal function and anti-diabetic background medication at screening to ensure an even distribution of the two treatment arms within strata. Subjects were to follow a dose-escalation regimen, where subjects started at 3 mg and were escalated after 4 weeks to a dose of 7 mg and then, after a further 4 weeks, to the maintenance dose of 14 mg. Dose escalation was blinded for each treatment arm. Subjects were scheduled to attend 8 visits at the trial site; in addition, 1 phone contact with the investigator was scheduled 2 weeks after randomisation. Subjects taking insulin also had 5 phone visits at which the insulin dose could be titrated based on 3 prior self-measured plasma glucose readings. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. All efforts were made to collect data on all randomised subjects, including subject who prematurely discontinued trial product or initiated additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	26 weeks 2 weeks
Objectives	Primary objective: To compare the effect of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on glycaemic control in subjects with type 2 diabetes and moderate renal impairment. Secondary objectives: To compare the effect of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on body weight in subjects with type 2 diabetes and moderate renal impairment. To compare the safety and tolerability of once daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin in subjects with type 2 diabetes and moderate renal impairment.	
Treatment groups	Oral semaglutide 14 mg	163 subjects randomised
	Placebo	161 subjects randomised

Trial NN9924-4234 – PIONEER 5 – Renal impairment	
Endpoints and definitions	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%-points)
	Confirmatory secondary endpoint: Change from baseline to week 26 in body weight (kg)
	Supportive secondary endpoints: Change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4234 – PIONEER 5 – Renal impairment			
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.		
Results		Oral semaglutide 14 mg	Placebo
	Number of subjects (FAS)	163	161
HbA_{1c}	Change from baseline to week 26, %-points	−1.0	−0.2
	ETD [95% CI] vs placebo	−0.8 [−1.0; −0.6] *	
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26	57.8	22.6
	EOR [95% CI] vs placebo	5.50 [3.20; 9.44] #	
Body weight	Change from baseline to week 26, kg	−3.4	−0.9
	ETD [95% CI] vs placebo	−2.5 [−3.2; −1.8] *	
FPG	Change from baseline to week 26, mmol/L	−1.54	−0.37
	ETD [95% CI] vs placebo	−1.17 [−1.70; −0.65] $	

* superiority vs placebo confirmed (controlled for multiplicity);
# odds for achieving the target statistically significantly greater with oral semaglutide than with placebo (p<0.05);
$ reduction statistically significantly greater with oral semaglutide than with placebo (p<0.05).

Table 15 Trial NN9924-4221 (PIONEER 6, CVOT)

Trial NN9924-4221 – PIONEER 6 – Cardiovascular outcomes trial		
Title	A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes mellitus	
Study identifier	Protocol number: NN9924-4221 EudraCT number: 2015-003563-10	
Data cut-off date	02 November 2018	
Design	This was a randomised, double-blind, placebo-controlled, multinational, multi-centre, cardiovascular outcomes trial (CVOT) designed to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard-of-care in subjects with type 2 diabetes and with high risk of cardiovascular events. Subjects were randomised to once-daily treatment with oral semaglutide or placebo (1:1) in addition to standard-of-care. The total maximum trial duration for the individual subject was up to 82 weeks, comprising a 3-weeks screening period, a treatment period and a 5-week follow-up period. The duration of the treatment period was event driven and therefore individual, because the treatment period continued until a pre-specified number of at least 122 first EAC-confirmed MACEs comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke had been accrued. If treatment with the trial product was associated with unacceptable side effects (as judged by the investigator), treatment pauses, dose reductions and extensions of dose escalation periods were allowed. To minimise potential confounding effects of differential glycaemic levels on trial outcomes, the use of open-label glucose-lowering medication was encouraged to promote glycaemic equipoise between the two treatment groups and to help patients reach clinically appropriate HbA_{1c} targets. In addition, standard-of-care medication was to be provided for management of CV risk factors. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued at the discretion of the investigator due to a safety concern. All efforts were made to collect data on all randomised subjects, including subjects who prematurely discontinued trial product. The subject was to remain in the trial regardless of lack of compliance with trial treatment, lack of adherence to the visit schedule, missed assessments, or development of comorbidities. Potential MACEs were adjudicated and evaluated by an external event adjudication committee (EAC) in an independent and blinded manner.	
	Duration of treatment Duration of screening period	Event-driven (until at least 122 first EAC-confirmed MACEs had been accrued) Up to 3 weeks
Objectives	Primary objective: To confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events. Secondary objectives: To compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.	
Treatment groups	Oral semaglutide 14 mg	1591 subjects randomised
	Placebo	1592 subjects randomised
Endpoints and definitions	Primary endpoint: Time from randomisation to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke	
	Secondary endpoints: Time from randomisation to first occurrence of an expanded composite	

Trial NN9924-4221 – PIONEER 6 – Cardiovascular outcomes trial	
	MACE endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or hospitalisation for heart failure
	Supportive secondary endpoints: Time from randomisation to first occurrence of each of the individual components in the expanded composite MACE endpoint Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke
	Data from all randomised subjects in the FAS regardless of any use of additional anti-diabetic medication and of permanent trial product discontinuation were analysed using a stratified Cox proportional hazards model from which the resulting hazards ratios are presented below. A hierarchical testing strategy was used for the primary endpoint and comprised a test for non-inferiority vs placebo (margin 1.8) as the first test followed by a test for superiority vs placebo. The type-1 error rate was controlled at 5% (two-sided) across the pre-specified tests for the primary endpoint.

Primary analysis

Trial NN9924-4233 – PIONEER 6 – Cardiovascular outcomes trial			
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.		
Results		Oral semaglutide	Placebo
	Number of subjects (FAS)	1591	1592
Primary endpoint 3-component first MACE	Subjects with events HR [95% CI]	61 0.79 [0.57; 1.11]	76
• Cardiovascular death	Subjects with events HR [95% CI]	15 0.49 [0.27; 0.92] *	30
• Non-fatal MI	Subjects with events HR [95% CI]	37 1.18 [0.73; 1.90]	31
• Non-fatal stroke	Subjects with events HR [95% CI]	12 0.74 [0.35; 1.57]	16
Composite of first all-cause death, non-fatal MI and non-fatal stroke	Subjects with events HR [95% CI]	69 0.77 [0.56 ;1.05]	89
All-cause death	Subjects with events HR [95% CI]	23 0.51 [0.31; 0.84] *	45

HR = Hazard ratio vs placebo
***** statistically significant (p<0.05)

Table 16 Trial NN9924-4257 (PIONEER 7)

Trial NN9924-4257 – PIONEER 7 – Flexible dose adjustment (main phase)		
Title	Efficacy and safety of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin in subjects with type 2 diabetes mellitus	
Study identifier	Protocol number: NN9924-4257 EudraCT number: 2015-005593-38	
Data cut-off date	Main phase: 15 May 2018 An extension phase is currently ongoing and is not part of the present application (blinded safety data contribute to the safety evaluation).	
Design	The main phase was a 52-week randomised, open-label, active-controlled, 2-arm, parallel-group, multi-centre, multi-national treatment period with an initial 2-week screening period and, for subjects that did not continue in the extension phase, a 5-week follow-up period. A total of 500 subjects with type 2 diabetes were planned to be randomised 1:1 to flexible dosing (3, 7 or 14 mg) of oral semaglutide once-daily or 100 mg sitagliptin once-daily as add-on to their anti-diabetic background medication. The total maximum duration of the main phase was 54 weeks for subjects who continued in the extension phase or 59 weeks for subjects who did not continue in the extension phase, comprising a 2-week screening period, a 52-weeks treatment period and for subjects that did not continue in the extension phase, a 5-week follow-up period. Subjects randomised to oral semaglutide initiated treatment on the 3 mg dose level and were to maintain this dose for the first 8 weeks. For the remaining of the treatment period, the dose of oral semaglutide was adjusted every 8 weeks according to dose adjustment criteria based on the subject's individual HbA_{1c} response (to reach the treatment target of HbA_{1c} < 7.0%) and tolerability (events of nausea or vomiting). Subjects randomised to sitagliptin 100 mg were to maintain the same dose throughout the trial. Subjects were scheduled to attend 10 visits at the trial site; in addition, 1 phone contact with the investigator was scheduled 4 weeks after randomisation. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. All efforts were made to collect data on all randomised subjects, including subjects who prematurely discontinued trial product or initiated additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	52 weeks 2 weeks
Objectives	Primary objective: To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on glycaemic control in subjects with type 2 diabetes. Secondary objectives: To compare the effect of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs on body weight in subjects with type 2 diabetes. To compare the safety and tolerability of once-daily dosing of oral semaglutide using a flexible dose adjustment based on clinical evaluation versus sitagliptin once daily, both in combination with 1-2 OADs in subjects with type 2 diabetes.	
Treatment groups	Oral semaglutide flexible dose	253 subjects randomised
	Sitagliptin	251 subjects randomised
Endpoints and	Primary endpoint: If a subject after week 52 achieved (yes/no) HbA_{1c} <7.0% (<53 mmol/mol).	
	Confirmatory secondary endpoint: Change from baseline to week 52 in body weight (kg)	

Trial NN9924-4257 – PIONEER 7 – Flexible dose adjustment (main phase)	
definitions	Supportive secondary endpoints: Change from baseline to week 52 in fasting plasma glucose (FPG); Change from baseline to week 52 in HbA_{1c}
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4257 – PIONEER 7 – Flexible dose adjustment (main phase)			
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.		
Results		Oral semaglutide flexible dose	Sitagliptin 100 mg
	Number of subjects (FAS)	253	251
HbA_{1c}	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 52 EOR [95% CI] vs sitagliptin	58.2 4.40 [2.89; 6.70] #	25.2
	Change from baseline to wk 52, %-points ETD [95% CI] vs sitagliptin	−1.3 −0.5 [−0.7; −0.4] *	−0.8
Body weight	Change from baseline to week 52, kg ETD [95% CI] vs sitagliptin	−2.6 −1.9 [−2.6; −1.2] #	−0.7
FPG	Change from baseline to wk 52, mmol/L ETD [95% CI] vs sitagliptin	−2.22 −0.78 [−1.20; −0.37] *	−1.44

superiority vs placebo confirmed (controlled for multiplicity);
* reduction statistically significantly greater with oral semaglutide than with placebo ($p<0.05$).

Table 17 Trial NN9924-4280 (PIONEER 8)

Trial NN9924-4280 – PIONEER 8 – Insulin add-on		
Title	Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with insulin	
Study identifier	Protocol number: NN9924-4280; EudraCT number: 2016-000988-16	
Data cut-off	03 October 2018	
Design	This was a randomised, double-blind, placebo-controlled, four-armed, parallel-group, multicentre, multinational efficacy and safety trials with a 52-week treatment period (including an 8-week dose escalation period). A total of 720 adults with type 2 diabetes on stable treatment with insulin with or without metformin treatment were planned to be randomised 1:1:1:1 to once-daily treatment with oral semaglutide (3, 7 or 14 mg) or placebo. The total maximum trial duration for the individual subject was approximately 59 weeks, comprising a 2-week screening period, a 52-week treatment period and a 5-week follow-up period. The 52-week randomised treatment period was split into two treatment periods; an initial 26-week fixed insulin treatment period where the insulin treatment was restricted, followed by a 26-week period where the insulin treatment was adjustable without any restrictions. The randomisation was stratified based on descent (Japanese/non-Japanese) and background metformin medication and background insulin medication at screening to ensure an even distribution of the four treatment arms within strata. Subjects were to follow a dose-escalation regimen, where all subjects started at 3 mg and were dose escalated in 4-week increments until the final maintenance dose was reached. Dose escalation was blinded for all treatment arms and dose levels. Subjects were scheduled to attend 12 visits at the trial site; in addition, 7 phone contacts with the investigator were scheduled. All efforts were to be made to keep subjects on trial product; however, subjects were free to withdraw from the trial at will and trial product could be discontinued prematurely at the discretion of the investigator due to a safety concern. All efforts were made to collect data on all randomised subjects, including subjects who prematurely discontinued trial product or initiated additional anti-diabetic medication.	
	Duration of treatment Duration of screening period	52 weeks 2 weeks
Objectives	Primary objective: To compare the effect of once-daily dosing of three dose levels of oral semaglutide (3 mg, 7 mg and 14 mg) versus placebo on glycaemic control in subjects with type 2 diabetes treated with insulin. Secondary objectives: To compare the effect of once-daily dosing of three dose levels of oral semaglutide (3 mg, 7 mg and 14 mg) versus placebo on body weight in subjects with type 2 diabetes treated with insulin. To compare the safety and tolerability of once-daily dosing of three dose levels of oral semaglutide (3 mg, 7 mg and 14 mg) versus placebo in subjects with type 2 diabetes treated with insulin.	
Treatment groups	Oral semaglutide 3 mg	184 subjects randomised
	Oral semaglutide 7 mg	182 subjects randomised
	Oral semaglutide 14 mg	181 subjects randomised
	Placebo	184 subjects randomised
Endpoints and definitions	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%- points)	
	Confirmatory secondary endpoint: Change from baseline to week 26 in body weight (kg)	
	Supportive secondary endpoints: Change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)	

Trial NN9924-4280 – PIONEER 8 – Insulin add-on	
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4280 – PIONEER 8 – Insulin add-on					
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.				
Results		Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Placebo
	Number of subjects (FAS)	184	182	181	184
HbA_{1c}	Change from baseline to week 26, %-points ETD [95% CI] vs pbo	−0.6 −0.5 [−0.7; −0.3] *	−0.9 −0.9 [−1.1; −0.7] *	−1.3 −1.2 [−1.4; −1.0] *	−0.1
	Change from baseline to week 52, %-points ETD [95% CI] vs pbo	−0.6 −0.4 [−0.6; −0.2] $	−0.8 −0.6 [−0.8; −0.4] $	−1.2 −0.9 [−1.1; −0.7] $	−0.2
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26 EOR [95% CI] vs pbo	28.4 5.61 [2.77; 11.37] #	42.5 12.37 [6.12; 25.00] #	58.4 22.52 [11.14; 45.51] #	6.8
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 52 EOR [95% CI] vs pbo	28.9 4.02 [2.13; 7.58] #	39.6 7.21 [3.84; 13.54] #	54.2 12.96 [6.91; 24.32] #	9.3
Body weight	Change from baseline to week 26, kg ETD [95% CI] vs pbo	−1.4 −0.9 [−1.8; −0.0] *	−2.4 −2.0 [−3.0; −1.0] *	−3.7 −3.3 [−4.2; −2.3] *	−0.4
	Change from baseline to week 52, kg ETD [95% CI] vs pbo	−0.8 −1.3 [−2.4; −0.3] $	−2.0 −2.5 [−3.6; −1.4] $	−3.7 −4.3 [−5.3; −3.2] $	0.5
FPG	Change from baseline to week 26, mmol/L ETD [95% CI] vs pbo	−0.22 −0.52 [−1.08; 0.04]	−1.08 −1.38 [−1.93; −0.83] $	−1.33 −1.62 [−2.17; −1.07] $	0.29
	Change from baseline to week 52, mmol/L ETD [95% CI] vs pbo	−0.66 −0.53 [−1.05; -0.01] $	−1.03 −0.90 [−1.42; −0.39] $	−1.58 −1.45 [−1.96; −0.94] $	−0.13

* superiority vs placebo confirmed (controlled for multiplicity);

[#] odds for achieving the target statistically significantly greater with oral semaglutide than with placebo ($p<0.05$);
[$] reduction statistically significantly greater with oral semaglutide than with placebo ($p<0.05$).

Table 18 Trial NN9924-4281 (PIONEER 9)

Trial NN9924-4281 – PIONEER 9 – Japan Monotherapy		
Title	Dose-response, safety and efficacy of oral semaglutide versus placebo and versus liraglutide, all as monotherapy in Japanese subjects with type 2 diabetes mellitus	
Study identifier	Protocol number: NN9924-4281 Japanese trial registration number: JapicCTI-173489	
Data cut-off	11 October 2018	
Design	This trial was a combined phase 2 dose-response and phase 3a safety and efficacy trial. It was a randomised, double-blind placebo-controlled and open-label active-controlled, 5-arm, parallel−group, multi-centre, single-country (Japan) monotherapy trial with a 52-week treatment period (including an 8-weeks dose escalation period). A total of 240 adult Japanese subjects with type 2 diabetes were planned to be randomised 1:1:1:1:1 to receive once-daily treatment with oral semaglutide (3 mg, 7 mg or 14 mg), oral placebo or liraglutide s.c. injection (0.9 mg). Only subjects treated with diet and exercise therapy alone or with OAD monotherapy (half maximum approved dose or below) were to be included in this trial. Subjects treated with diet and exercise alone were randomised to trial product after a 2-week screening period, while subjects treated with a pre-trial OAD had an 8-week screening and wash-out period, where the pre-trial OAD was to be discontinued at screening and washed-out before randomisation. Randomisation was stratified by pre-trial treatment at screening (with or without OAD). The total maximum duration of the trial was 59 weeks for subjects treated with diet and exercise prior to the trial and 65 weeks for subjects treated with a pre-trial OAD. Subjects were to follow a dose-escalation regimen, where subjects treated with oral semaglutide and placebo started at 3 mg and were dose escalated in 4-week increments until the final maintenance dose was reached. Treatment with once-daily liraglutide s.c. injection followed a weekly dose escalation regimen until the maintenance dose of 0.9 mg was reached in week 3. Dose escalation was blinded for all treatment arms and dose levels	
	Duration of treatment Duration of screening period	52 weeks 2 weeks
Objectives	Primary objective: To assess the dose-response relationship of once-daily dosing of three dose levels (3, 7 and 14 mg) of oral semaglutide versus placebo as monotherapy on glycaemic control in Japanese subjects with type 2 diabetes. Secondary objectives: To compare the safety and tolerability of once-daily dosing of three dose levels (3, 7 and 14 mg) of oral semaglutide versus placebo and versus once-daily 0.9 mg liraglutide subcutaneously, all as monotherapy in Japanese subjects with type 2 diabetes. To compare the effect of once-daily dosing of three dose levels (3, 7 and 14 mg) of oral semaglutide versus placebo and versus once-daily 0.9 mg liraglutide subcutaneously, all as monotherapy on glycaemic control and body weight in Japanese subjects with type 2 diabetes.	
Treatment groups	Oral semaglutide 3 mg Oral semaglutide 7 mg Oral semaglutide 14 mg Placebo Liraglutide 0.9 mg	49 subjects randomised 49 subjects randomised 48 subjects randomised 49 subjects randomised 48 subjects randomised
Endpoints and definitions	Primary endpoint: Change from baseline to week 26 in HbA_{1c} (glycosylated haemoglobin) (%-points)	
	Confirmatory secondary endpoint: Not applicable	
	Supportive secondary endpoints: Change from baseline to week 26 in body weight (kg); change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)	

Trial NN9924-4281 – PIONEER 9 – Japan Monotherapy	
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4281 – PIONEER 9 – Japan Monotherapy						
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.					
Results		Oral semaglutide			Placebo	Lira
		3 mg	7 mg	14 mg		0.9 mg
	Number of subjects (FAS)	49	49	48	49	48
HbA_{1c}	Change from baseline to week 26, %-points ETD [95% CI] vs placebo ETD [95% CI] vs lira 0.9 mg	−1.1 −0.8 [−1.1; −0.5] * 0.2 [−0.1; 0.5]	−1.6 −1.2 [−1.5; −0.9] * −0.2 [−0.5; 0.1]	−1.8 −1.4 [−1.7; −1.1] * −0.4 [−0.7; −0.1] *	−0.4	−1.4
	Change from baseline to week 52, %-points ETD [95% CI] vs placebo ETD [95% CI] vs lira 0.9 mg	−0.9 −0.8 [−1.2; −0.5] * 0.3 [−0.1; 0.6]	−1.4 −1.3 [−1.6; −1.0] * −0.2 [−0.6; 0.1]	−1.5 −1.4 [−1.7; −1.0] * −0.3 [−0.7; 0.1]	−0.1	−1.2
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26 EOR [95% CI] vs placebo EOR [95% CI] vs lira 0.9 mg	52.2 5.99 [2.20; 16.33] # 0.83 [0.35; 1.98]	69.4 16.41 [5.74; 46.91] # 2.28 [0.92; 5.61]	80.9 24.10 [7.96; 73.02] # 3.34 [1.26; 8.86] #	16.3	53.3
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 52 EOR [95% CI] vs placebo EOR [95% CI] vs lira 0.9 mg	43.5 4.95 [1.77; 13.90]* 0.68 [0.28; 1.63]	63.3 14.40 [4.99; 41.60]* 1.97 [0.81; 4.76]	72.3 17.27 [5.86; 50.86]* 2.36 [0.94; 5.91]	14.3	48.9
Body weight	Change from baseline to week 26, kg ETD [95% CI] vs placebo ETD [95% CI] vs lira 0.9 mg	−0.6 0.6 [−0.3; 1.5] -0.5 [−1.5; 0.4]	−1.1 0.0 [−0.8; 0.9] −1.1 [−2.0; −0.2]*	−2.4 −1.2 [−2.1; −0.4]* −2.3 [−3.2; −1.4]*	−1.1	-0.0
	Change from baseline to week 52, kg ETD [95% CI] vs placebo ETD [95% CI] vs lira 0.9 mg	−0.3 0.3 [−0.8; 1.4] −0.3 [−1.5; 0.8]	−0.8 −0.2 [−1.3; 0.9] −0.9 [−2.0; 0.3]	−2.6 −2.0 [−3.1; −0.9]* −2.7 [−3.8; −1.5]*	−0.6	0.0

Trial NN9924-4281 – PIONEER 9 – Japan Monotherapy						
FPG	Change from baseline to week 26, mmol/L ETD [95% CI] vs placebo ETD [95% CI] vs lira 0.9 mg	−1.69 −0.95 [−1.48; -0.42]* 0.33 [−0.20; 0.87]	−1.89 −1.15 [−1.66; −0.64]* 0.13 [−0.40; 0.66]	−2.54 −1.80 [−2.32; −1.28]* −0.52 [−1.05; 0.02]	−0.74	−2.02
FPG	Change from baseline to week 52, mmol/L ETD [95% CI] vs placebo ETD [95% CI] vs lira 0.9 mg	−1.04 −0.86 [−1.45; -0.26]* 0.91 [0.28; 1.53][a]	−2.01 −1.82 [−2.39; −1.26]* −0.06 [−0.67; 0.54]	−2.29 −2.11 [−2.68; −1.54]* −0.35 [−0.96; 0.27]	−0.18	−1.94

* reduction statistically significantly greater with oral semaglutide than with placebo/liraglutide (lira) ($p<0.05$);
[#] odds for achieving the target statistically significantly greater with oral sema than with placebo/liraglutide (lira) ($p<0.05$).
[a] reduction statistically significantly greater with dulaglutide than with oral semaglutide 3 mg ($p<0.05$).

Table 19 Trial NN9924-4282 (PIONEER 10)

Trial NN9924-4282 – PIONEER 10 – Japan OAD combination		
Title	Safety and efficacy of oral semaglutide versus dulaglutide both in combination with one OAD in Japanese subjects with type 2 diabetes mellitus	
Study ID	Protocol number: NN9924-4282; Japanese trial registration number: JapicCTI-173485	
Data cut-off	09 August 2018	
Design	This was a randomised, open-label, active-controlled, parallel-group, multi-centre, single-country trial with a 52-week treatment period (including an 8-week dose-escalation period). A total of 455 Japanese adults with type 2 diabetes inadequately controlled on one OAD were planned to be randomised (2:2:2:1) to once-daily oral semaglutide 3, 7 or 14 mg, or once-weekly s.c. dulaglutide 0.75 mg as add-on to their background OAD medication. The background OAD medication consisted of one of the following: SU, glinide, TZD, α-GI or SGLT-2 inhibitor as monotherapy. Subjects were stratified based on the type of OAD background medication (147 subjects in the strata of SU monotherapy and 77 subjects in the strata of each of the remaining OAD monotherapy [glinide, TZD, α-GI and SGLT-2 inhibitor]) in this trial. The total maximum trial duration for the individual subject was approximately 59 weeks, comprising a 2-week screening period, a 52-week treatment period and a 5-week follow-up period. Randomisation was stratified based on the type of background OAD medication (SU/glinide/TZD/ α-GI/SGLT-2 inhibitor) to ensure a 2:2:2:1 distribution of the 4 treatment arms within each stratum. Subjects were to follow a dose-escalation regimen, where all subjects started at 3 mg and were dose escalated in 4-week increments until the final maintenance dose was reached. Dose escalation was blinded for all treatment arms and dose levels.	
	Duration of treatment Duration of screening period	52 weeks 2 weeks
Objectives	Primary objective: To compare the safety and tolerability of once-daily dosing of three dose levels (3, 7 and 14 mg) of oral semaglutide versus once-weekly 0.75 mg dulaglutide subcutaneously both in combination with one OAD (SU, glinide, TZD, α-GI or SGLT-2 inhibitor) in Japanese subjects with type 2 diabetes. Secondary objectives: To compare the effect of once-daily dosing of three dose levels (3, 7 and 14 mg) of oral semaglutide versus once-weekly 0.75 mg dulaglutide subcutaneously both in combination with one OAD (SU, glinide, TZD, α-GI or SGLT-2 inhibitor) on glycaemic control and body weight in Japanese subjects with type 2 diabetes.	
Treatment groups	Oral semaglutide 3 mg	131 subjects randomised
	Oral semaglutide 7 mg	132 subjects randomised
	Oral semaglutide 14 mg	130 subjects randomised
	Dulaglutide 0.75 mg	65 subjects randomised
Endpoints and definitions	Primary endpoint: Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks (57 weeks equals the 52-week treatment period plus the 5-week follow-up period including the 3-day visit window).	
	Confirmatory secondary endpoint: Not applicable	
	Supportive secondary endpoints: Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks. Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks (yes/no) Change from baseline to week 26 in body weight (kg); change from baseline to week 26 in fasting plasma glucose (FPG); HbA_{1c} below 7.0% (53 mmol/mol) at week 26 (yes/no)	
	Data from all randomised subjects in the FAS were included in the analyses; the presented results are for the hypothetical estimand (on-treatment without rescue medication observation period), which estimates the treatment effects without the potentially confounding effects of additional anti-diabetic medication based on the assumption that subjects stayed on trial product and did not require rescue medication. Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment, stratification and region as categorical fixed effects and the baseline value as a covariate (all nested within visit); changes from baseline and estimated treatment differences (ETDs) are presented. Binary endpoints (evaluating e.g. the proportion of subjects achieving a target) were analysed using logistic regression after	

Trial NN9924-4282 – PIONEER 10 – Japan OAD combination	
	handling missing data; observed proportions and estimated odds ratios (EOR) are presented.

Primary analysis (treatment policy estimand)

Trial NN9924-4282 – PIONEER 10 – Japan OAD combination					
Analysis set	The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.				
Results		Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Dulaglutide 0.75 mg
	Number of subjects (FAS)	131	132	130	65
HbA_{1c}	Change from baseline to week 26, %-points	−1.1	−1.7	−2.0	−1.5
	ETD [95% CI] vs dulaglutide	0.4 [0.1; 0.7] [a]	−0.1 [−0.4; 0.1]	−0.4 [−0.7; −0.2] *	
	Change from baseline to week 52, %-points	−0.9	−1.4	−1.7	−1.4
	ETD [95% CI] vs dulaglutide	0.5 [0.2; 0.8] [a]	-0.1 [-0.3; 0.2]	-0.3 [-0.6; -0.1] *	
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 26	46.1	75.0	82.0	70.3
	EOR [95% CI] vs dulaglutide	0.26 [0.13; 0.54] [b]	1.233 [0.64; 2.77]	2.63 [1.20; 5.73] [#]	
	HbA_{1c} <7.0% (53 mmol/mol), % subjects at week 52	34.1	59.7	70.9	50.8
	EOR [95% CI] vs dulaglutide	0.41 [0.21; 0.80] [b]	1.51 [0.78; 2.92]	3.07 [1.53; 6.16] [#]	
Body weight	Change from baseline to week 26, kg	−0.2	−1.0	−2.2	0.3
	ETD [95% CI] vs dulaglutide	−0.5 [−1.3; 0.4]	−1.3 [−2.2; −0.5] *	−2.5 [−3.3; −1.7] *	
	Change from baseline to week 52, kg	0.0	−0.9	−1.6	1.0
	ETD [95% CI] vs dulaglutide	−0.9 [−1.9; −0.0] *	−1.9 [−2.8; −0.9] *	−2.6 [−3.5; −1.6] *	
FPG	Change from baseline to week 26, mmol/L	−1.37	−2.18	−2.63	−2.05
	ETD [95% CI] vs dulaglutide	0.68 [0.25; 1.10] [a]	−0.13 [−0.57; 0.30]	−0.58 [−1.01; −0.16] *	
	Change from baseline to week 52, mmol/L	−1.11	−1.97	−2.02	−1.65
	ETD [95% CI] vs dulaglutide	0.54 [−0.01; 1.09]	−0.32 [−0.86; 0.22]	−0.37 [−0.92; 0.17]	

* reduction statistically significantly greater with oral semaglutide than with dulaglutide ($p<0.05$);
[#] odds for achieving the target statistically significantly greater with oral semaglutide than with dulaglutide ($p<0.05$);
[a] reduction statistically significantly greater with dulaglutide than with oral semaglutide 3 mg ($p<0.05$);

[b] odds for achieving the target statistically significantly greater with dulaglutide than with oral semaglutide 3 mg ($p<0.05$).

2.6.4. Analysis performed across trials (pooled analyses and meta-analysis)

Effect on cardiovascular risk

PIONEER 6 confirmed cardiovascular safety of oral semaglutide assessed as major cardiac adverse events (MACE): HR vs placebo: 0.79 [0.57; 1.11]$_{95\%CI}$ < 1.8; Figure E-22).

Across the two CVOTs with semaglutide (PIONEER 6 and SUSTAIN 6), similar endpoints and methods for the evaluation of cardiovascular risk were applied, and the baseline characteristics of the enrolled populations were also similar. The findings in PIONEER 6 are consistent with those in SUSTAIN 6 (HR vs placebo: 0.74 [0.58; 0.95] $_{95\%CI}$; Figure E-23).

Figure E-22 - Time to first MACE and individual components – PIONEER 6

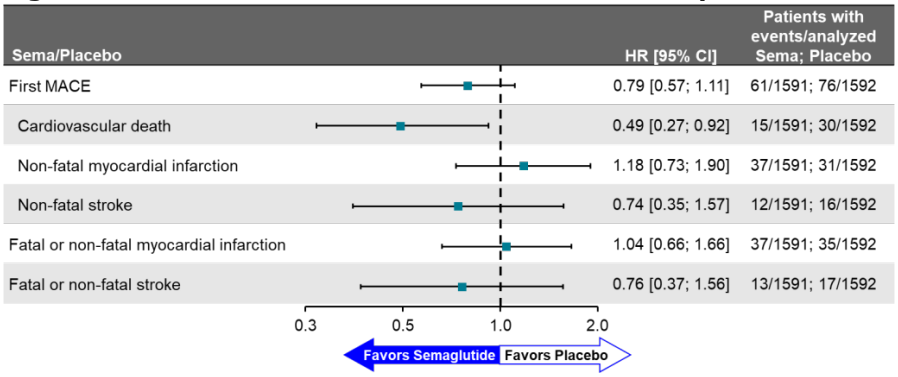
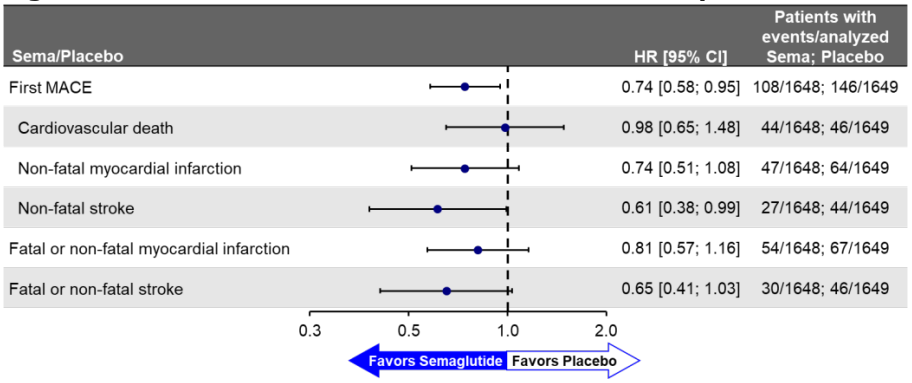


Figure E-23 - Time to first MACE and individual components – SUSTAIN 6



FAS in-trial. Estimated HRs and corresponding CIs are from separate Cox proportional hazards models with treatment as fixed factor and stratified by baseline cardiovascular status as well as by insulin treatment and renal function in SUSTAIN 6. Patients were censored at the end of the in-trial observation period. Cardiovascular death includes undetermined cause of death. CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular event; sema: semaglutide.

Further results in support of the conclusions included results from analyses of all-cause death, non-fatal stroke and non-fatal myocardial infarction and of an expanded MACE endpoint as well as an analysis of data pooled from the two CVOTs. Finally, results were consistent across subgroups.

2.6.5. Clinical studies in special populations

Renal impairment

In trial NN9924-4234 – PIONEER 5, the primary objective was to demonstrate superiority of semaglutide in patients with impaired renal function compared to placebo in subjects with T2D inadequately controlled on metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin. This trial was a randomised, double blind, placebo controlled multinational, multicentre trial. A total of 324 subjects were randomised. Only 8 subjects (2.5%) had a severe renal impairment (eGFR 15<= to < 30 mL/min/1.73m^2), 88% had a moderate renal impairment, and 9.6% a mild renal impairment.

Premature treatment discontinuation was higher in the semaglutide arm (18.4% versus 12.4% in placebo, Table E-7). This was largely due to gastrointestinal adverse events with semaglutide.

Compared to placebo, semaglutide was associated with a clinically relevant decrease in HbA1c after 26 weeks (-1.0 % versus -0.2%).

Hepatic impairment

According to the 10-day pharmacokinetic study in subjects with hepatic impairment, semaglutide exposure was similar across the hepatic function groups. However, clinical data in patients with hepatic impairment are not presented.

Elderly subjects

In the key efficacy and Japanese trials, 24.9% (1582 subjects) of the subjects were 65 to less than 75 years of age and 5.0% (321 subjects) were 75 years or older. According to subgroup analyses, the anti-hyperglycaemic efficacy was not age-dependent.

Participation of elderly subjects in the trials is shown below.

Table E-20 Participation of elderly in completed phase 3a trials – oral semaglutide

Phase 3a pool								
	Oral semaglutide				**All comparators**			
	N		**SYE**		**N**		**SYE**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	1,609	1,278	1,772	1,371	836	728	900	779
65–74 years	564	466	587	483	313	239	322	243
75–84 years	110	80	104	66	56	63	50	53

≥85 years	2	7	1	4	0	1	0	1
Total	**2,285**	**1,831**	**2,464**	**1,924**	**1,205**	**1,031**	**1,272**	**1,076**

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose response study

A dose-response study has been conducted and based on modelling of data doses of 3, 7 and 14 mg have been selected for the phase 3a studies.

Trial 3790 (NN9924-3790) was a 26-week, randomised, partially-blinded, parallel-group, dose range, dose-escalation, multi-centre trial. The oral semaglutide and oral placebo arms were double-blinded: the s.c. semaglutide arm was not blinded. A total of 632 patients were randomised in an equal manner into one of the 9 treatment arms: oral semaglutide 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, 40 mg S (slow dose escalation), 40 mg F (fast dose escalation), placebo and s.c. semaglutide 1 mg once weekly.

Based on biomodelling of data from the phase 2 dose-finding trial (3790), oral semaglutide 3, 7 and 14 mg were selected for confirmatory testing in the phase 3 programme (PIONEER) because the Applicant considered these doses to have the optimal benefits/risks profile. The increments between the three doses were expected to provide clinically meaningful differentiation between their effects on glycaemic control with acceptable gastrointestinal side effects. According to the modelling, the dose-dependency of the anti-hyperglycaemic effect is less steep at oral semaglutide doses >10 mg.

The dose-escalation regimen was also based on trial 3790, which tested three different time periods between the dose escalations (2, 4 and 8 weeks). The Applicant selected the 4-week escalation regimen as the compromise between marked efficacy and acceptable gastrointestinal tolerability. This is in line with the regimen for s.c. semaglutide (Ozempic). Based on the modelling, an estimated change in HbA1c of 1.64%-point was expected by 14 mg oral semaglutide. However, the observed changes in the phase 3 trials were smaller (1.0-1.4%-point). This might be due to lower absorption in "real life" compared to the highly controlled dose finding study. It is noted that the Applicant had chosen a dose that does not seem to provide the same plasma concentration as Ozempic. Based on the data from the Applicant, the predicted plasma concentrations for s.c. semaglutide 1 mg is 29 nmol/l 95% CI: 17-40, whereas it is 19 nmol/l 95% CI: 5.3-67.6 for oral semaglutide 14 mg. As the expected plasma concentrations for oral semaglutide 14 mg are lower than for s.c. semaglutide 1.0 mg with an even more pronounced difference observed in the phase 3a studies, a similar effect on HbA1c and cardiovascular disease could be questioned, which is reflected in the SmPC. Moreover, the observed concentrations of semaglutide in the phase 3a trials are also lower than the predicted values (14.6 nmol/l in the phase 3a trials compared with the predicted 19 nmol/l). This indicates that the absorption "in real life" is lower than expected. This might in some patients lead to lack of effect. Hence, a statement in the SmPC that treating physicians should be aware of a possible lack of response caused by minimal absorption and low absolute bioavailability due to the high variability in absorption, or by poor compliance to the dosing regimen; this is no included as advice in section 4.4 of the SmPC.

Main studies

In all key efficacy trials, the primary endpoint evaluated the effect of the trial products on glycaemic control estimated based on the average blood glucose concentration (HbA_{1c}) at about 3 months. This is the CHMP-recommended endpoint in the 'Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus' (CPMP/EWP/1080/00) and acceptable. These analyses were supported (among others) by glucose measurements and responder analyses.

Overall, the inclusion and exclusion criteria for the pivotal studies are acceptable and reflect a heterogeneous type 2 diabetes population without recent cardiovascular events (within 180 days), present ischaemic heart disease, heart failure (NYHA IV), recent proliferative retinopathy or maculopathy requiring acute treatment, or malignancies during the past 5 years. The inclusion criterion for HbA_{1c} differed across studies, which is in line with previous assessments of glucose lowering drugs. One of the studies was a dedicated renal impairment study, which included type 2 diabetes patients with eGFR between 30-59 ml/min/1.73m^2, which is endorsed.

In 3 of the pivotal trials, placebo was used as the only comparator, and in 4 of the pivotal trials active comparators were used at relevant doses (empagliflozin 25 mg, liraglutide 1.8 mg, and sitagliptin 100 mg). This is overall acceptable, as the comparators reflect commonly used glucose-lowering treatments. The Japanese studies used GLP-1 RA as comparators in submaximal doses.

Five of the seven pivotal studies were double-blinded of which two were additionally double-dummy trials. This is overall acceptable. PIONEER-7 used a flexible dosing regimen in an active-controlled, open-label design. Here, the primary endpoint was the fraction of participants reaching an HbA_{1c} target of below 7%.

Weight-loss was pre-defined as a confirmatory, secondary endpoint. In most trials, the type 1 error was protected for HbA_{1c} (as the change from baseline) and weight loss.

In PIONEER-6, the CVOT, the endpoint was MACE, a composite of cardiovascular (CV) mortality, nonfatal stroke and nonfatal myocardial infarction. The primary objective of this trial was to establish an upper bound of the 95% confidence interval of the hazard ration for MACE below 1.8. This approach is compliant with the 'Reflection paper on assessment of cardiovascular safety profile of medicinal products' (EMA/CHMP/50549/2015).

Semaglutide was investigated at three dose levels (3, 7 and 14mg) in most phase 3a trials. Trial duration is similar to that used in other registration studies.

For semaglutide, the results of a CVOT were included in this application. While CHMP considered this data to be of importance however, the mean duration of 16 months is relatively short for a drug that is intended for long term diabetes treatment and in comparison to several other cardiovascular outcome trials. The inclusion of one dose of semaglutide, namely 14mg, in individuals with a high cardiovascular risk in the CVOT trial, may also limit the generalizability to the general diabetic population.

The Applicant presented two estimands which address the treatment effect of oral semaglutide after the initiation of additional anti-diabetic medication or premature investigational treatment discontinuation in different ways. The estimand definition and the handling of intercurrent events were adequate. In the treatment policy estimand, the effect of oral semaglutide is estimated accepting premature discontinuation of oral semaglutide and/or the initiation of additional anti-diabetic medication. As stated in the diabetes GL (CPMP/EWP/1080/00 Rev. 2), the inclusion of data after start or changes in the use of additional glucose-lowering medication complicates the estimation of the sole treatment effect of oral semaglutide. On the other hand, this estimand reflects what could be expected if oral semaglutide is used in clinical practice, where changes in anti-diabetic treatment and treatment discontinuation are likely to occur. The two estimands address

different aspects of the efficacy of the compound. The choice of the treatment policy estimand as the primary estimand can be accepted provided that the results are supported by the hypothetical estimand.

The hypothetical estimand disregards the observations collected after investigational treatment discontinuation and/or the initiation of additional anti-diabetic medication. According to the diabetes GL (CPMP/EWP/1080/00 Rev. 2), patients who discontinued the investigational treatment but not make changes in the other glucose-lowering medication should be included in the analysis until initiation/change in other glucose-lowering products. It would have been preferred that the hypothetical estimand did not treat "premature investigational treatment discontinuation" as an intercurrent event. However, the inclusion of this intercurrent event is not expected to have a significant impact since the number of patients who discontinued investigational treatment and did not immediately started rescue is negligible.

The Applicant considered it scientifically and clinically warranted to focus the information to the prescribers on estimated effects not confounded by other anti-diabetic medication. On that basis, they considered it appropriate to present numerical results for the hypothetical estimand in the SmPC instead of the treatment policy estimand. However, the CHMP was of the view that the hypothetical estimand is only supportive of the primary analysis and therefore should not be used in the SmPC. Although it was agreed with the Applicant that the hypothetical estimand confers important information that may also be relevant to prescribers, the lack of statistical robustness, in the view of the CHMP, invalidated this approach. In this programme, the differences between the two estimands were numerically small (compare Figure E-16 and Figure E-17). From a clinical perspective, it is most relevant to understand which treatment effect may be achieved even when the prescription is not fully followed. Therefore, the effect of oral semaglutide when discontinuation of investigational product or changes in other anti-diabetic treatment can occur was considered by CHMP as the most relevant treatment effect to be communicated to clinical practitioners. Therefore, all claims are presented as results from treatment policy estimand in the SmPC in section 5.1. The trial results after 52 or 78 weeks have been accepted for inclusion in the SmPC because the persistence of effect is important to the prescribers, although these results may have less statistical robustness, e.g. not included separately in the statistical hierarchies.

The sample size calculations were based on former trials for semaglutide and took into account relevant intercurrent events. The sample size calculations are overall agreed. The Applicant did not justify their choice of the non-inferiority margin (0.4) for the study Pioneer 2 and Pioneer 4, given that the EMA GL (CPMP/EWP/1080/00 Rev. 1) and Scientific Advice (EMEA/H/SA/1359/4/2015/III) recommended to use a non-inferiority margin of 0.3% (3 mmol/mol).

The statistical analysis was appropriate; weighted Bonferroni closed testing procedures were employed to preserve the type-1 error.

The conduct of the studies is claimed to be GCP compliant and used state-of-the-art methods. The assessment did not raise important concerns in this regard.

Efficacy data and additional analyses

In PIONEER 7, subjects randomised to oral semaglutide initiated treatment on the 3 mg dose level and were to maintain this dose for the first 8 weeks. For the remaining treatment period, the dose of oral semaglutide was adjusted every 8 weeks according to dose adjustment criteria based on the subject's individual HbA_{1c} response and tolerability (moderate to severe events of nausea or vomiting). At end-of-trial (52 weeks), the majority of subjects were on oral semaglutide 7 mg (28%) or 14 mg (52%); 10% had discontinued treatment and 8% were

on the 3 mg dose. Accordingly, oral semaglutide 3 mg has been chosen as an escalation dose that patients should use to initiate treatment before escalating to the 7 or 14 mg treatment doses in line with the dose-escalation regimen used in the PIONEER trials.

Main trials

Ten phase 3a trials (PIONEER 1–10) were performed with oral semaglutide. The phase 3a trials included a total of 9543 randomised subjects, of whom 5707 were exposed to oral semaglutide. Baseline demographics and disease characteristics of the trial populations studied represented a broad T2D population as seen in clinical practice. An overview of the baseline characteristics is given in Table E-9. Although elderly (>65 years) are well represented, the representation of subjects above 85 years is only 9 subjects.

Participant flow

The number of treatment completers and trial completers across the trials were high and acceptable. Overall, the participant flow is adequately described and assumptions for the sample size calculations in PIONEER 1-10 are fulfilled. Based on the presented data the discontinuations were unlikely to have impacted the study results to a relevant degree.

PIONEER 1 (Trial 4233; Monotherapy) in drug naïve T2D subjects, semaglutide was associated with a clinically relevant decrease in HbA1c after 26 weeks (semaglutide 3mg -0.6%; 7mg -0.9%, and 14mg -1.1%) compared to placebo. In addition, there were changes in body weight (semaglutide 3mg -0.1kg; 7mg -0.9kg; 14mg -2.3kg versus placebo).

PIONEER 2 (Trial 4223) was performed in T2DM subjects who had not achieved adequate control on metformin. Compared to SGLT-2 inhibitor, semaglutide 14mg was associated with a clinically relevant decrease in Hba1c after 52 weeks (-0.4% [-0.6 - -0.3]). Superiority of oral semaglutide 14 mg vs empagliflozin 25 mg in reducing body weight was not confirmed.

PIONEER 3 (Trial 4222) compared three doses of semaglutide to sitagliptin in T2DM subjects who had not achieved adequate control on metformin or SU treatment. Superiority of oral semaglutide 7 mg and 14 mg vs sitagliptin 100 mg was confirmed (semaglutide 7mg: -0.3%; semaglutide 14mg: -0.5% vs sitagliptin) at week 26. For oral semaglutide 3 mg, non-inferiority vs sitagliptin 100 mg could not be confirmed and the decrease in HbA1c was statistically significantly smaller with oral semaglutide 3 mg than with sitagliptin 100 mg. The decrease in body weight from baseline at week 26 was statistically significantly greater with oral semaglutide 3 mg, 7 mg and 14 mg than with sitagliptin 100 mg.

In PIONEER 4 (Trial 4224) T2DM subjects on background anti-diabetic medication (metformin alone or in combination with a SGLT-2 inhibitor) were randomised to once daily treatment with a dose-escalation regimen to semaglutide 14mg, liraglutide 1.8mg or placebo, respectively. Superiority of oral semaglutide 14 mg vs placebo and non-inferiority of oral semaglutide 14 mg vs liraglutide 1.8 mg in reducing HbA1c were both confirmed, based on the treatment policy estimand; superiority of oral semaglutide 14 mg vs liraglutide 1.8 mg could not be confirmed (Hba1c: -0.1% [-0.3 – 0.0]). Body weight was significantly reduced in semaglutide vs liraglutide (-1.2kg [-1.9 - -0.6]). There were more premature treatment discontinuations with semaglutide than liraglutide (12.6 vs 9.2%) with a higher incidence of gastro-intestinal disorders.

PIONEER 5 (Trial 4234) subjects with T2DM and moderate renal impairment were randomised to oral semaglutide 14mg or placebo on a background of metformin and/or SU, basal insulin alone, or metformin in

combination with basal insulin. A clinically relevant change in Hba1c after 26-weeks was demonstrated with semaglutide 14mg: Hba1c -0.8% [-0.1 - -0.6], compared to placebo. The difference in body weight was -2.5kg in favour of semaglutide.

In PIONEER 6, (CVOT, Trial 4221) the primary objective was to assess the cardiovascular safety (Hazard ratio < 1.8) of oral semaglutide versus placebo when added to standard-of-care in subjects with T2DM and with high risk of cardiovascular events. The secondary objectives were to assess the long-term safety and efficacy of semaglutide 14mg compared to placebo, both added on to standard-of-care, in T2D subjects at high risk of CV events. A total of 3183 subjects were randomised.

The trial reached its primary objective and demonstrated non-inferiority of semaglutide versus placebo in terms of MACE. The composite primary outcome occurred in 61 of 1591 patients (4.1%) in the semaglutide group and 76 of 1592 (4.8%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.57 – 1.11; P<0.001 for noninferiority. Superiority was not confirmed with the upper bound of the 95% CI being below 1.0 (p=0.1749).

The Applicant has presented a combined analysis of cardiovascular risk reduction. Although across the two CVOTs with semaglutide (PIONEER 6 and SUSTAIN 6), similar endpoints and methods for the evaluation of cardiovascular risk were applied, and the baseline characteristics of the enrolled populations may be comparable, the duration of the trials differed markedly. The additional arguments given by the applicant to claim established CV risk reduction are reassuring and supportive, however not confirmatory as the CVOT PIONEER 6 did not show a statistically significant cardiovascular risk reduction. Due to the large variability in exposure and the different route of administration, it remains uncertain if the exposure obtained with oral semaglutide is sufficient to exhibit the cardiovascular effect and it remains questionable to extrapolate the results of s.c. semaglutide.

PIONEER 7 (Trial 4257) subjects with T2DM were randomised to flexible dosing (3, 7 or 14 mg) of oral semaglutide once-daily or 100 mg sitagliptin once-daily as an add-on to their anti-diabetic background medication. More patients in the flexible dosing semaglutide group achieved an Hba1c < 7% compared to subjects receiving sitagliptin (58.3% vs 25.2%). A clinically relevant difference in weight loss was observed in favour of semaglutide (-1.9 [-2.6 - -1.2kg]. More subjects in the semaglutide flexible dosing arm discontinued treatment prematurely compared to sitagliptin (11.9 vs 6.8%). This difference was mainly driven by more gastrointestinal AEs in the oral semaglutide flexible dosing group.

PIONEER 8 (Trial 4280) in subjects with T2DM on basal and/or bolus insulin with or without metformin, semaglutide was associated with a clinically relevant decrease in HbA1c after 26 weeks (semaglutide 3 mg – 0.5%; semaglutide 7 mg -0.9%; semaglutide 14mg -1.2%) compared to placebo. In addition, compared to placebo, semaglutide was associated with a clinically relevant decrease in body weight after 26 weeks (semaglutide 3 mg -0.9 kg; semaglutide 7 mg -2.0 kg; semaglutide 14mg -3.3kg). From a mean baseline insulin dose of 58 IU across the 4 groups, significant reductions of insulin doses of 8IU, 16IU and 17IU were seen at week 26 with semaglutide 3mg, 7mg and 14mg, respectively, when compared to placebo. There was a dose-related higher number of premature discontinuations, gastrointestinal adverse events and other adverse events with semaglutide compared to placebo.

PIONEER 9 and 10 were conducted in Japan only, according to Japanese requirements, and are considered supportive for the efficacy evaluation.

Analyses of results performed across trials

Oral semaglutide dose-dependently reduced HbA_{1c} across all PIONEER trials; the reductions were 0.6 to 0.9 %-points for 3 mg, 0.8 to 1.2 %-points for 7 mg and 1.0 to 1.4 %-points for 14 mg in the key efficacy trials (Figure E-16, Figure E-17). The results are supported by responder analyses, glucose measurements, sensitivity analyses and subgroup analyses.

Although body weight is an important covariate for exposure (Figure PK-6), there is no clear relation between glycaemic efficacy and baseline body weight (Figure E-20). This may be due to the high interindividual variation in exposure (due to variation in absorption), which may be much larger than the variation introduced by extrinsic factors such as body weight. This is a clear difference with s.c. use of semaglutide. Additional analyses provided by the applicant did not show a clear relationship between efficacy on weight reduction (absolute and relative) and baseline body weight.

Body weight was reduced dose-dependently by 1.2 to 1.5 kg with oral semaglutide 3 mg, 2.2 to 2.4 kg with 7 mg and 3.1 to 4.4 kg with 14 mg in the key efficacy trials at week 26.

Special populations

Renal impairment

Based on pharmacokinetic considerations, no dose adaptation is required for renal impairment. PIONEER-5 (Table 14) included primarily subjects with moderate renal impairment (88%). Compared to placebo, semaglutide was associated with a clinically relevant decrease in HbA1c after 26 weeks (-1.0 % versus -0.2%). However, only 8 subjects (2.5%) had a severe renal impairment (eGFR 15<= to < 30 mL/min/1.73m^2). For this reason, the newly proposed SmPC does not recommend semaglutide in patients with end stage renal disease and mentions that experience in patients with severe renal impairment is limited. This is in alignment with the Ozempic SmPC.

Hepatic impairment

According to the 10-day pharmacokinetic study in subjects with hepatic impairment, semaglutide exposure was similar across the hepatic function groups. However, clinical data in patients with hepatic impairment are not presented.

Elderly subjects

In the key efficacy and Japanese trials, 24.9% (1582 subjects) of the subjects were 65 to less than 75 years of age and 5.0% (321 subjects) were 75 years or older. However, the number of trial subjects above 85 years exposed to oral semaglutide was only 9. According to subgroup analyses, the anti-hyperglycaemic efficacy was not age-dependent.

2.6.7. Conclusions on clinical efficacy

The Applicant has established the efficacy of oral semaglutide for the treatment of T2D in a comprehensive development program. The evidence for CV risk reduction is incomplete.

Subgroups of patients >85 years of age and patients with severe renal impairment and end-stage renal disease were too small for a benefit-risk evaluation. This is adequately reflected in the SmPC with the additional note

that there is limited experience of oral semaglutide in patients ≥75 years and older, and in patients with severe renal impairment. Oral semaglutide is not recommended in patients with end stage renal disease.

2.7. Clinical safety

The primary focus of the safety analysis was on data from the ten PIONEER phase 3a trials, representing 6311 patient-years exposure. The safety analysis took further into account the experience with subcutaneously used semaglutide.

The safety and tolerability evaluation was based on assessments of standard parameters. Furthermore, a focused evaluation was done for a range of focus areas defined based on experience with the GLP-1 RA drug class and on regulatory advice and requirements.

In PIONEER 6, a targeted approach to safety data reporting was applied; data were collected systematically for serious AEs, AEs leading to treatment discontinuation and a few other AE categories of special interest whereas other non-serious AEs were not reported systematically.

An external event adjudication committee (EAC) performed ongoing adjudication of events belonging to pre-defined event categories. The purpose of the adjudication was for independent external medical experts to review the events in a consistent and blinded manner according to standardised criteria as outlined in an EAC charter.

The applicant's approach to the analysis of safety is agreed.

Patient exposure

Exposure by pool and by trial is presented in Table S-21. The 'Oral sema' column represents the pooled oral semaglutide doses. Please note that in this table 'Comparator' is the pool of active and placebo comparator for the phase 3a pool, but only the active comparator for the individual trials. The total exposure to oral semaglutide in the on-treatment observation period was 4379 PYE in the phase 3a pool (PIONEER 1−5 and 7-10), 1197 PYE in the placebo pool (PIONEER 1, 4, 5 and 8) and 1932 PYE in PIONEER 6. In addition to the exposure in the phase 3a trials, 977 subjects were exposed to oral semaglutide for 148.8 subject years of exposure (SYE) in 17 clinical pharmacology trials (Table S-21).

Table S-21 Total exposure – phase 3a trials and pools

SAS	Oral sema 3 mg		Oral sema 7 mg		Oral sema 14 mg		Oral sema[a]		Comparator[b]		Placebo	
	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE
Phase 3a pool							4116	4379	2236	2335		
Placebo pool							1519	1197			665	523
Placebo dose pool	359	288	356	274	356	267					362	290
P1 4233	175	101	175	98	175	96	525	296			178	101
P2 4223					410	400	410	400	409	420		
P3 4222	466	662	464	669	465	650	1395	1981	466	687		
P4 4224					285	281	285	281	284	285	142	143
P5 4234					163	89	163	89			161	90
P7 4257							253	238	250	247		
P8 4280	184	186	181	176	181	170	546	532			184	190
P9 4281	49	50	49	53	48	50	146	153	48	51	49	54
P10 4282	131	139	132	138	130	133	393	410	65	68		
P6 4221 (FAS)							1591	1932			1592	1987

N: number of subjects; PYE: patient-years of exposure Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8. Placebo dose pool: PIONEER 1 and 8. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).

[a] In PIONEER 1-5 and 8-10 this column is the pooled oral semaglutide data across the doses used in the individual trials. In PIONEER 7 and 6, subjects were allowed to delay dose escalation of oral semaglutide to 14 mg and to decrease the dose if experiencing unacceptable AEs. 1 subject in the placebo group of PIONEER 6 was not exposed to trial product.
[b]'Comparator' for the phase 3a pool: sitagliptin, empagliflozin, liraglutide and placebo; 'Comparator' for the individual trials only includes the active comparator.

The total exposure to oral semaglutide in the on-treatment observation period was 4379 PYE in the phase 3a pool (PIONEER 1−5 and 7-10), 1197 PYE in the placebo pool (PIONEER 1, 4, 5 and 8) and 1932 PYE in PIONEER 6. The reported exposure is sufficient for an adequate safety analysis. However, although 1165 patients were treated for at least 17 months in the phase 3a trials and another 400 in PIONEER 6, exposure beyond 82 weeks (the highest exposure in PIONEER 6) is extremely limited.

Adverse events

The rate of AEs was higher with oral semaglutide versus comparator in the phase 3a pool (3.02 v 2.59 events per PYE) and versus placebo in the placebo pool (3.57 v 2.65 events per PYE).

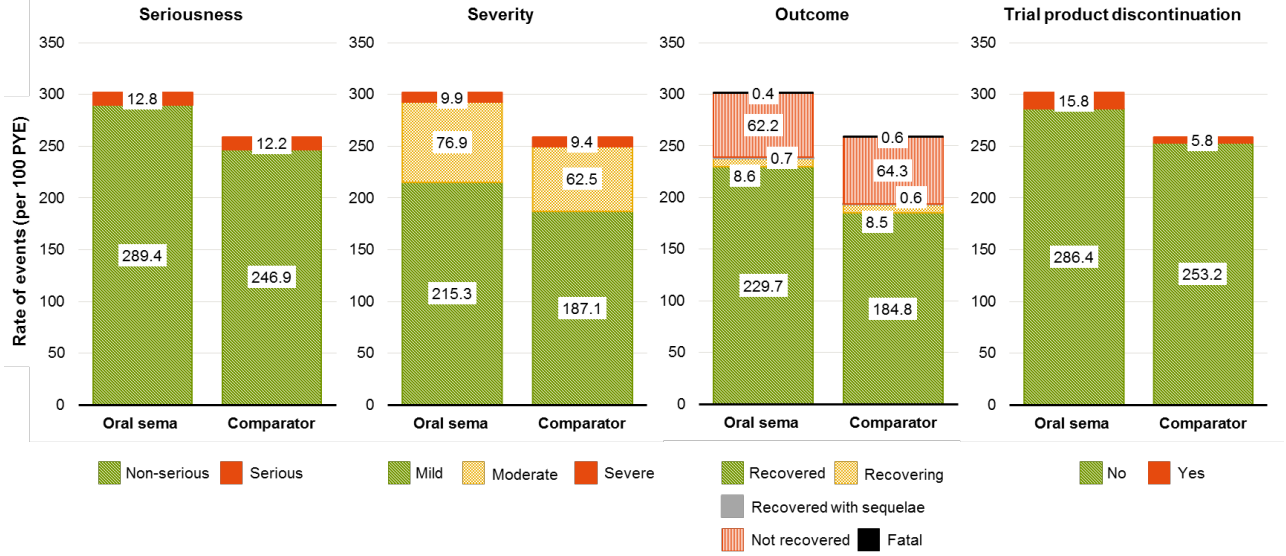
Table S-22 Total AEs – phase 3a pool and placebo pool – on-treatment

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	3087	(74.9)	12459	302.2	1616	(73.0)	6004	259.0
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	1072	(71.3)	4055	356.7	438	(65.9)	1358	264.5

Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator' for the phase 3a pool: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'Comparator' for the placebo pool only includes the placebo arms.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure; E: number of events.

Most of the AEs reported with oral semaglutide were mild, non-serious and recovered by the end of the trials. The rates of non-serious, mild and recovered AEs, and AEs leading to premature treatment discontinuation were higher with oral semaglutide than with comparator (Figure S-24). This difference was driven primarily by gastrointestinal (GI) AEs, which were more frequently reported with oral semaglutide, and which most often were non-serious, mild, recovered and the most common AEs leading to premature treatment discontinuation with oral semaglutide (Figure S-25) for the distribution of AEs by SOCs. Most of the AEs reported with oral semaglutide were dose-dependent with the highest percentage of AEs in the semaglutide 14 mg group. In this latter group, the highest rate of premature discontinuation was observed (Figure S-26) compared to placebo, semaglutide 3 and 7 mg, and to the active comparators: liraglutide, dulaglutide, sitagliptin and empagliflozin. This difference was driven primarily by GI AEs.

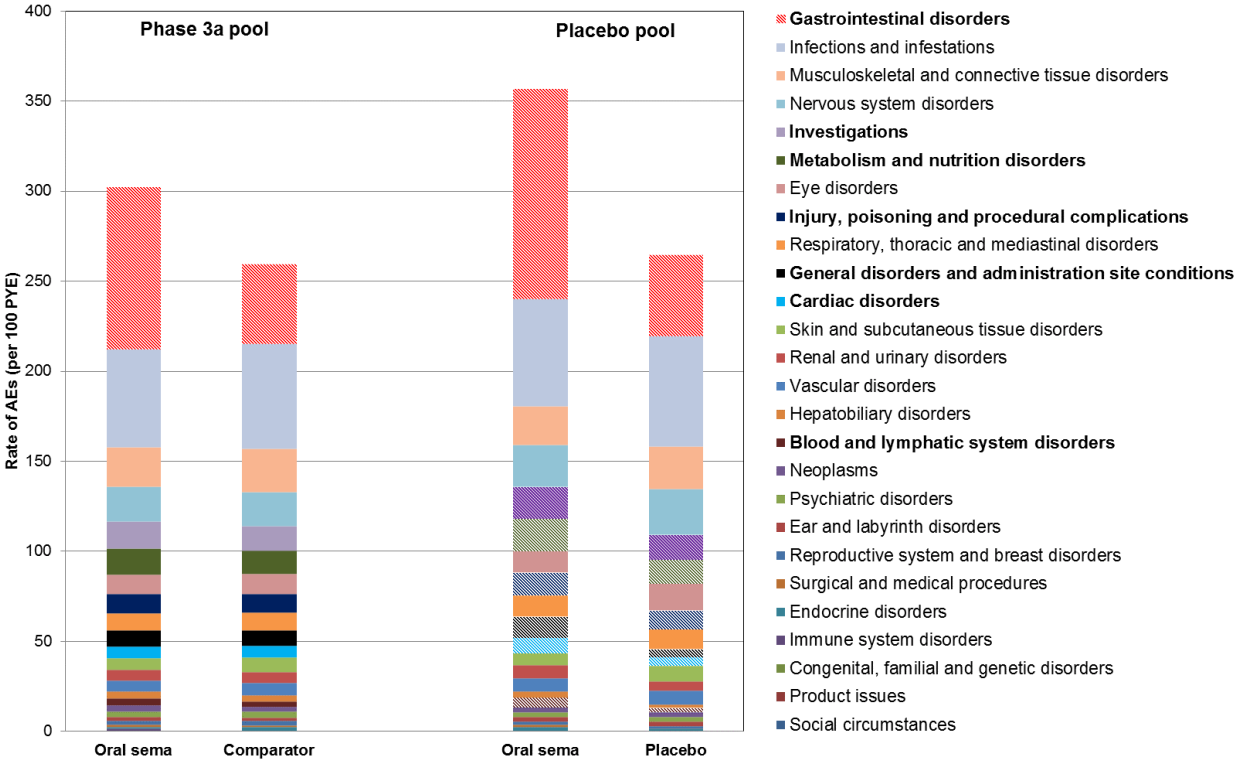
Figure S-24 - Adverse events by seriousness, severity, outcome and premature trial product discontinuation – phase 3a pool – on-treatment



Phase 3a pool: PIONEER 1-5 and 7-10. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. The rate is the Cochran-Mantel-Haenszel adjusted event rate per 100 patient-years of exposure. Events with unknown outcome are not included.

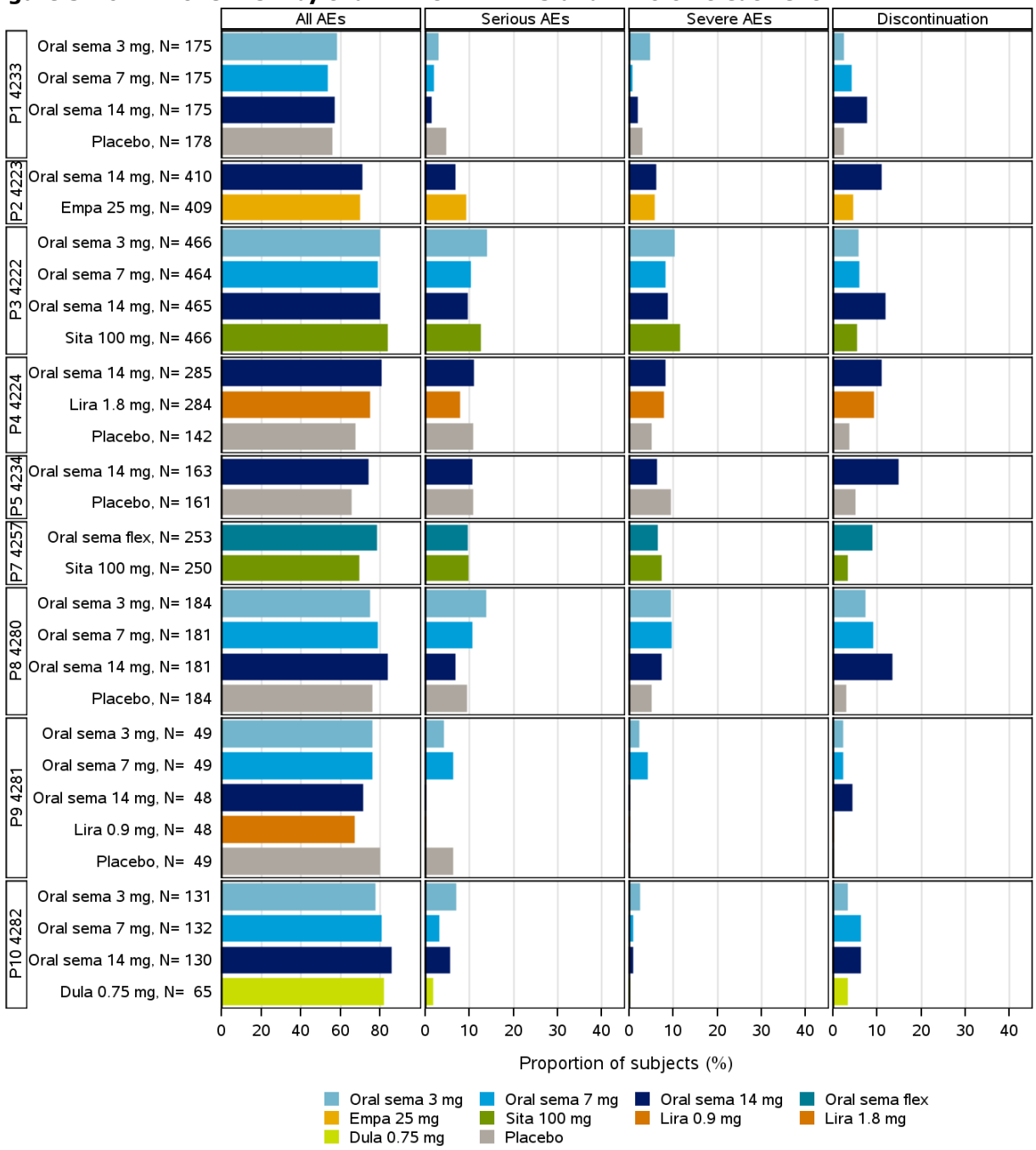
Gastrointestinal disorders were the most frequently reported AEs by SOC with oral semaglutide and were the primary driver of differences between oral semaglutide and comparator and placebo (Figure S-25). This difference was primarily driven by nausea, diarrhoea, vomiting and constipation. Gastrointestinal AEs are well-known side-effects of GLP-1 RAs.

Figure S-25 - Rate of AEs by SOC – phase 3a pool and placebo pool – on-treatment



SOCs are ordered by frequency from highest to lowest with oral semaglutide in the phase 3a pool. Bars were shaded and legend bolded for SOCs where the differences between oral semaglutide and comparator or placebo were greater than 2 AEs/100 PYE.

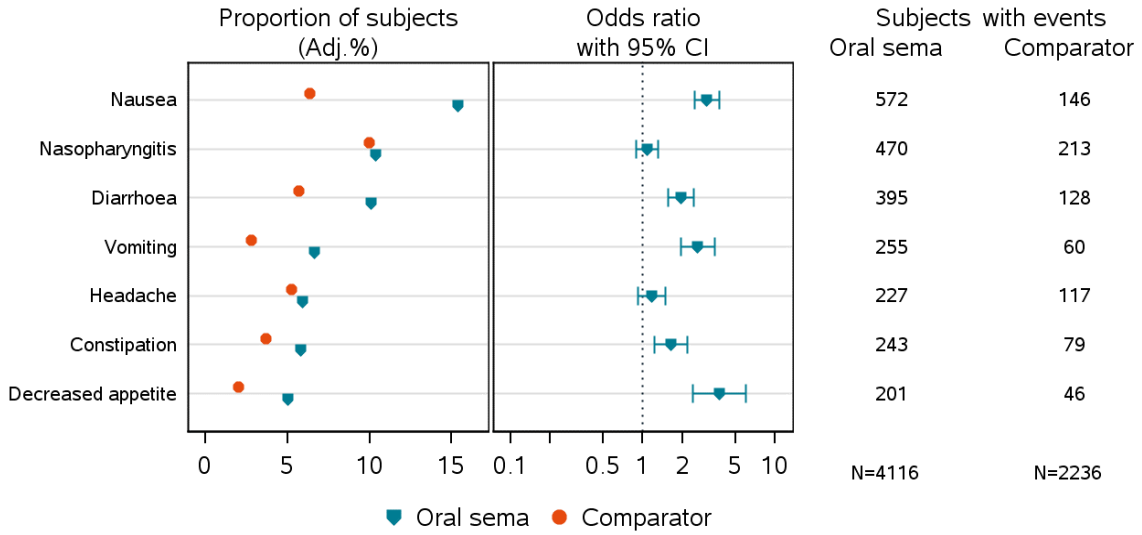
Figure S-26 - AE overview by trial – PIONEER 1-5 and 7-10 on treatment



'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects

In the phase 3a pool, the most frequent PTs (reported by ≥5% of subjects) that were more common with oral semaglutide than comparator included: nausea, diarrhoea, vomiting, constipation and decreased appetite (Figure S-27). In the placebo dose pool, a dose-response was seen for nausea, diarrhoea, decreased appetite and vomiting.

Figure S-27 - Most frequent AEs (≥ 5% of subjects) – statistical analysis by PT – phase 3a pool – on-treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
Sorted in descending order by preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%); CI: confidence interval; N: number of subjects.

Of the 39 PTs reported by more than 1% and less than 5% of subjects on oral semaglutide, the following were reported by a higher proportion of subjects (>0.5%) on oral semaglutide than the comparator, respectively:

- Dyspepsia: 4.0% vs 1.6%
- Abdominal pain: 3.3% vs 1.8%
- Abdominal pain upper: 3.3% vs 1.8%
- Abdominal discomfort: 2.7% vs 1.4%
- Gastro-oesophageal reflux disease: 2.6% vs 0.8%
- Gastroenteritis: 2.1% vs 1.0%
- Abdominal distension: 1.9% vs 1.3%
- Flatulence: 1.3% vs 0.7%

These are all believed to be part of the class-effect of GLP-1 RAs on the GI system.

In the placebo pool, the following PTs were reported more frequently with oral semaglutide than placebo (>0.5%) besides those mentioned in Figure S-27 and the list above:

- Lipase increased: 2.5% vs 0.6%
- Asthenia:1.7% vs 0 subjects
- Fatigue: 1.4% vs 0.5%
- Blood creatinine phosphokinase increased: 1.3% vs 0.6%
- Fall: 1.3% vs 0.7%
- Eructation: 1.2% vs 0 subjects

Asthenia is not listed in the proposed SmPC, but fatigue is listed with the frequency 'common'.

Gastrointestinal disorders are described above.

Renal disorders: Events of acute kidney injury were equally frequent in the between oral semaglutide and comparators in the phase 3a pool (<0.5% of the subjects in each group).

Hepatic disorders: The most common event was hepatic steatosis. There was no indication of oral-semaglutide-induced liver toxicity (no cases of Hy's law).

Gall-bladder related disorders: The proportion of subjects with gallbladder-related disorders was identical for oral semaglutide and comparators (1.3% in both groups; phase 3a pool). However, the frequency of cholelithiasis was greater for oral semaglutide than with placebo (10 events and 1 event, respectively, corresponding to 0.6% and 0.1% of the subjects in the placebo pool. Cholelithiasis is listed in section 4.8 of the SmPC.

Pancreatitis: The proportion of subjects with events of pancreatitis across the PIONEER trials was similar across oral semaglutide and comparators (both 0.2%). A warning regarding pancreatitis is included in section 4.4 of the SmPC. According to the SmPC, caution should be exercised in patients with a history of pancreatitis.

Cardiovascular safety: In PIONEER 6, the frequency of major adverse cardiovascular events (MACEs, comprising cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) was lower with oral semaglutide than with placebo (61 subjects [3.8%] and 76 subjects [4.8%]; hazard ratio of 0.79 $[0.57;1.11]_{95\%CI}$ ($p<0.0001$; non-inferiority margin 1.8), primarily driven by a lower incidence of stroke and cardiovascular death with oral semaglutide. Based on the available data for the GLP1-RA class and the data presented for oral semaglutide (primarily PIONEER-6), there is no concern for cardiovascular safety.

Neoplasms: The proportion of subjects with neoplasms (malignant and non-malignant) was slightly higher with oral semaglutide than with comparators (6.4% and 5.7%, respectively, in the phase 3a pool); 1.4% and 1.0% of the subjects were diagnosed with malignancy. Only 210 patients were treated for 18 months or more in the phase 3a pool; roughly 400 patients were treated for 18 months in PIONEER 6. This is insufficient for a thorough assessment of the risk of neoplasms. However, based on the numerical imbalance, follow up of these data is needed. Neoplasms remain an adverse event of special interest and should be included as an important potential risk in the RMP (**OC RMP, Safety Spec**).

Hypoglycaemia: The rate of hypoglycaemia was greater with oral semaglutide than with comparators: severe hypoglycaemia (0.3 and 0.1 episodes per 100 PYE, respectively; phase 3a pool), clinically significant hypoglycaemia (19.9 and 17.8 episodes per 100 PYE; phase 3a pool) asymptomatic (75.2 and 57.8 episodes per 100 PYE), respectively. A higher rate of clinically relevant and severe episodes was observed for elderly subjects.

Diabetic retinopathy: The proportion of subjects with AEs and event rates related to diabetic retinopathy were greater with oral semaglutide than with comparators including placebo. The events were in general non-serious and of mild severity. Most of the events were non-proliferative diabetic retinopathy, were identified by routine examinations and did in general not require treatment.

Diabetic retinopathy complications were considered an adverse effect of Ozempic after SUSTAIN 6. Proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation, was an exclusion criterion in the clinical trials. Despite careful control, the signal for SUSTAIN-6 seems to be independently confirmed in both the Phase 3a pool and PIONEER 6. Therefore, diabetic retinopathy must be considered an adverse reaction to oral semaglutide, with an excess

risk difference between 0.5 and 1.0% in the first year. Retinopathy is discussed in a warning in the proposed SmPC. In addition, diabetic retinopathy is included as an adverse drug reaction in the SmPC, and as an important identified risk in the RMP.

Pregnancy: With oral semaglutide, 7 pregnancies have been documented, all 7 with no known associated congenital anomalies or related AEs. However, due to the limited information, potential risks during pregnancy and lactation cannot be excluded.

Lactic acidosis: In animals, mortality was observed in all toxicology species when SNAC was administered at high doses (≥200 mg/kg depending on the species). Events of lactic acidosis (6 with oral semaglutide [3 were SAEs, all in PIONEER 6] and 3 [all SAEs] with comparators) occurred in relation with other conditions that can precipitate lactic acidosis such as pneumonia, acute kidney injury and sepsis.

Serious adverse events and deaths

Serious AEs: The proportions of subjects with SAEs and rates of SAEs were similar for oral semaglutide and comparator in the phase 3a pool and for oral semaglutide and placebo in the placebo pool (Table S-23). This pattern was observed across the trials and pools.

In PIONEER 6 the proportion of subjects reporting SAEs during the trial was lower with oral semaglutide (18.9% of subjects) than with placebo (22.5% of subjects) (Table S-23).

Table S-23 Total SAEs – phase 3a pool, placebo pool and PIONEER 6 – on-treatment

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
SAEs	345	(8.6)	518	12.8	202	(9.0)	282	12.2
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
SAEs	114	(7.9)	184	16.3	57	(8.3)	78	14.5
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
PIONEER 6								
Number of subjects	1591				1592			
Observation time (years)	1932				1987			
SAEs	301	(18.9)	545	28	358	(22.5)	618	31

Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
'Comparator' for the phase 3a pool: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'Comparator' for the placebo pool and PIONEER 6: placebo.
N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure; E: number of events; R: event rate/100 patient-years of observation.

The most frequently reported SAEs in the phase 3a pool were within the SOCs: cardiac disorders, neoplasms and infections and infestations. There were no marked differences in proportions of subjects or rates of SAEs by SOC across treatment groups. A similar pattern in the reporting of SAEs was seen in the placebo pool. The cardiac disorders SOC and the nervous system disorders SOC had the most SAEs reported with oral semaglutide, while the nervous system disorders SOC and the infections and infestations SOC were the most common SOCs with

placebo. No unexpected clustering or patterns were identified among SAEs in PIONEER 6. As expected in the population enrolled in this trial, SAEs were most frequently reported in the SOC Cardiac disorders both with oral semaglutide and placebo.

Deaths: In the phase 3a pool, 30 subjects died during the in-trial period (Table S-24). In the placebo pool, there were 11 subjects with fatal AEs. The proportion of subjects with fatal AEs was similar with oral semaglutide (0.4%) and comparators (0.5%) in the phase 3a pool, and similar with oral semaglutide (0.6%) and placebo (0.4%) in the placebo pool. There were no apparent differences with respect to cause of death as classified by the EAC.

In PIONEER 6, a total of 71 subjects had fatal AEs with onset during the in-trial period (Table S-24). The proportion of subjects with fatal AEs was lower with oral semaglutide (1.6%) than with placebo (2.9%). The rate of 'all-cause death' was also lower with oral semaglutide than with placebo (1.1 vs 2.2 deaths per 100 PYO), driven primarily by a lower rate of EAC confirmed cardiovascular death (0.5 vs 1.1 deaths per 100 PYO).

Table S-24 Total fatal AEs and EAC-confirmed deaths – phase 3a pool, placebo pool and PIONEER 6 – in-trial

	Oral sema				Comparator/Placebo			
	N (Adj.%)		E	Adj.R	N (Adj.%)		E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Observation time (years)	4719				2452			
Fatal AEs	17	(0.4)	21	0.4	13	(0.5)	16	0.6
EAC confirmed death								
Cardiovascular death	5	(0.1)	5	0.1	5	(0.2)	5	0.2
Undetermined cause of death	6	(0.1)	6	0.1	3	(0.1)	3	0.1
Non-cardiovascular death	6	(0.1)	6	0.1	5	(0.2)	5	0.2
Placebo pool								
Number of subjects	1519				665			
Observation time (years)	1292				548			
Fatal AEs	8	(0.6)	8	0.7	3	(0.4)	3	0.5
EAC confirmed death								
Cardiovascular death	2	(0.2)	2	0.3	1	(0.1)	1	0.2
Undetermined cause of death	4	(0.2)	4	0.3	1	(0.1)	1	0.2
Non-cardiovascular death	2	(0.1)	2	0.1	1	(0.1)	1	0.1
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
PIONEER 6								
Number of subjects	1591				1592			
Observation time (years)	2101				2081			
Fatal AEs	25	(1.6)	30	1	46	(2.9)	57	3
EAC confirmed death								
All-cause death	23	(1.4)	23	1.1	45	(2.8)	45	2.2
Cardiovascular death	10	(0.6)	10	0.5	23	(1.4)	23	1.1
Undetermined cause of death	5	(0.3)	5	0.2	7	(0.4)	7	0.3
Non-cardiovascular death	8	(0.5)	8	0.4	15	(0.9)	15	0.7

- Phase 3a pool: PIONEER 1-5 and 7-10.'Comparator' for the phase 3a pool: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. Placebo pool: PIONEER 1,4,5 and 8, 'Comparator' for the placebo pool and PIONEER 6: placebo. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
- EAC: event adjudication committee; N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure; E: number of events; R: event rate/100 patient-years of observation.

For 3 subjects in PIONEER 6, the investigator reported date of onset of the fatal AEs was within the in-trial period for the subjects, while the date of death according to the EAC was after the in-trial period. This explains the difference between the number of subjects with fatal AEs (71 subjects) for the in-trial period and the number of deaths during the in-trial period based on EAC confirmation (68 deaths) (Table S-24). One subject, who died before randomisation, is not shown.

The fatal AEs were distributed on multiple SOCs and PTs for oral semaglutide and for comparators. For oral semaglutide, the most frequent fatal AEs belonged to the cardiac disorders SOC (0.2%) and for comparators to the neoplasms SOC (0.2%).

The EAC classification for the 68 deaths during the in-trial period of PIONEER 6 is summarised in Table S-25. The mortality difference was driven by cardiovascular causes.

Table S-25 EAC confirmed deaths – PIONEER 6 – in-trial

	Oral sema				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1591				1592			
Observation time (years)	2101				2081			
All-cause death	23	(1.4)	23	1.1	45	(2.8)	45	2.2
Cardiovascular and undetermined cause of death	15	(0.9)	15	0.7	30	(1.9)	30	1.4
Cardiovascular death	10	(0.6)	10	0.5	23	(1.4)	23	1.1
Acute myocardial infarction	0				4	(0.3)	4	0.2
Sudden cardiac death	8	(0.5)	8	0.4	14	(0.9)	14	0.7
Heart failure	0				2	(0.1)	2	0.1
Stroke	1	(0.1)	1	0.0	1	(0.1)	1	0.0
Cardiovascular procedure	0				1	(0.1)	1	0.0
Other	1	(0.1)	1	0.0	1	(0.1)	1	0.0
Undetermined cause of death	5	(0.3)	5	0.2	7	(0.4)	7	0.3
Non-cardiovascular death	8	(0.5)	8	0.4	15	(0.9)	15	0.7
Renal causes	0				1	(0.1)	1	0.0
Malignancy	5	(0.3)	5	0.2	8	(0.5)	8	0.4
Infection	3	(0.2)	3	0.1	2	(0.1)	2	0.1
Non-CV procedure or surgery	0				1	(0.1)	1	0.0
Pulmonary causes	0				2	(0.1)	2	0.1
Other	0				1	(0.1)	1	0.0

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 observation; EAC: event adjudication committee.

Laboratory findings and vital signs

Across the trials, values of haematological parameters were stable over time and similar across treatment groups. Across the trials, values of biochemistry parameters not related to safety focus areas were stable over time and similar across treatment groups.

Renal function as assessed by the eGFR was stable with either oral semaglutide or comparators (ratios to baseline were 0.99 at end-of-treatment for the phase 3a pool), and no dose-response relationship for eGFR or creatinine was observed. In PIONEER 5 (moderate renal impairment), the UACR did not change relevantly and any changes did not differ between groups.

Creatine kinase: Due to findings of high creatine kinase levels for two subjects in the phase 2 trial (3790), creatine kinase concentrations and related AEs were a focus area in the PIONEER trials. However, no concern regarding creatine kinase was identified based on biochemistry.

Amylase and lipase activity increased during the initial 14 weeks with oral semaglutide treatment and then plateaued; these elevations were not associated with development of pancreatitis and are consistent with observations for other GLP-1 RAs.

Electrocardiography: There were no noteworthy findings in the assessment of ECGs.

Blood pressure: In the phase 3a trials, systolic blood pressure modestly decreased from baseline to end of treatment with oral semaglutide (1−7 mmHg), in a dose-dependent manner, which is comparable with results from semaglutide s.c. Diastolic blood pressure showed a minor decrease (0−3 mmHg) with oral semaglutide.

Pulse rate: Across trials, a dose-dependent increase in pulse rate was observed with oral semaglutide, with the greatest increase observed with the 14 mg dose. The pulse rate increases observed with oral semaglutide were comparable to what was reported with semaglutide s.c. (1−6 bpm). Based on the findings in the QTc trial, the mean highest changes for the highest dose group were 11.10 bpm $[9.58; 12.62]_{90\%CI}$ (see Ozempic EPAR). Adverse events of increased heart rate were higher in the placebo pool for oral semaglutide (11 (0.7%) vs 3 (0.4%)), without apparent dose-dependency.

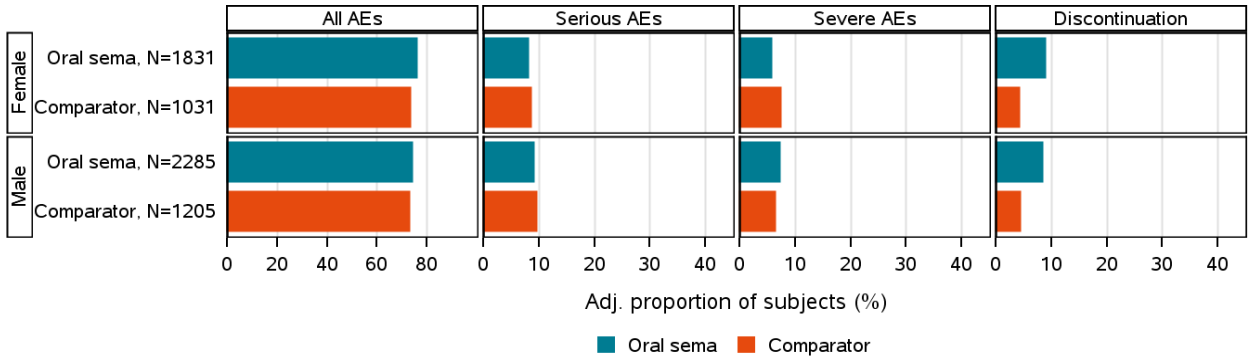
Based on the totality of data, including the effect on blood pressure and the CVOTs SUSTAIN-6 and PIONEER-6, it is unlikely that the (potential) adverse effect on pulse rate outweighs the apparent cardiovascular benefits of semaglutide. Therefore, the issue of potential adverse effect on the pulse rate is not further pursued.

Safety in special populations

Gender

An AE overview is presented for the phase 3a pool by sex in Figure S-28. Safety was comparable for both treatment groups. While proportions of subjects with AEs leading to premature trial product discontinuation were larger with oral semaglutide vs comparator, the treatment differences were comparable in males vs females.

Figure S-28 - AE overview by sex – bar plot – phase 3a pool – on-treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

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21JAN2019:15:08:48 - f_bar_ae.sas/f_bar_ae_sex_3a_ot.png

Age

The proportion of subjects with oral semaglutide who had AEs leading to premature trial product discontinuation increased with age, and while a similar tendency was seen with comparator, the differences between age groups were larger with oral semaglutide than with comparator. The differences were mainly explained by a higher frequency of GI AEs and decreased appetite (PT) with oral semaglutide in the older age groups compared to comparators. It should be noted that older subjects may have more advanced diabetes, e.g. using more insulin (Figure S-29). Therapeutic experience in patients ≥75 years of age is limited which is reflected SmPC (section 4.2).

Figure S-29 - AE overview by age groups – bar plot – phase 3a pool – on-treatment

Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%).

The treatment differences were larger in the older age groups compared to subjects of <65 years:

- Gastrointestinal disorders SOC (mainly driven by PTs nausea, diarrhoea, vomiting, constipation)
- Decreased appetite (PT)
- Weight decreased (PT)
- Fall (PT)

More elderly subjects (≥75 years) with oral semaglutide vs comparator experienced a fall (7 vs 1 subjects). According to the Applicant, case evaluation of the individual events did not indicate an association between the falls and event types that could potentially be caused by oral semaglutide, such as GI AEs or hypoglycaemic episodes. However, causality is not (yet) considered excluded.

Renal impairment

PIONEER-5 (Table 14) included subjects (n=324) with primarily moderate renal impairment (88%) and T2D (inadequately controlled on metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin). Premature treatment discontinuation was higher in the semaglutide (oral: 14 mg) arm (18.4% versus 12.4% in placebo, Table E-7). This was largely due to GI AEs with semaglutide. More severe or blood glucose confirmed symptomatic hypoglycaemic episodes were observed in the semaglutide arm compared to placebo (5.5% versus 1.9%).

The PIONEER 5 trial and the CVOT trial (PIONEER 6) were the only trials that included subjects (8 and 28 patients, respectively) with severe renal impairment (15≤ eGFR [mL/min/1.73m^2] <30). Due to this relatively small number of patients, safety in these patients is uncertain. This is reflected in the SmPC.

Hepatic impairment

The Applicant has provided an analysis of subjects with abnormal liver function tests. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide.

Immunological events

Immunogenicity was a focus area in the PIONEER trials, considering that oral semaglutide as a protein-based drug may be associated with immune and allergic reactions. However, considering the high homology of semaglutide (94%) to endogenous GLP-1, the immunogenic potential of the oral semaglutide is expectedly low. Anti-semaglutide antibodies were evaluated by default in PIONEER 1-5 and 9; in the other trials, anti-semaglutide antibodies were measured on suspicion of trial-product-related hypersensitivity reactions.

Across the PIONEER trials, the proportion of subjects reporting immunogenicity-related AEs was lower with oral semaglutide than with comparators (2.9% and 4.6%, respectively, in the phase 3a pool). Rash, eczema and dermatitis were the most frequent events with oral semaglutide (each reported by <1.0% of the subjects). Most events were non-serious, mild or moderate in severity and considered unlikely to be related trial product. No dose-response with regards to such AEs was observed for oral semaglutide.

Across PIONEER 1-5 and 9, a low proportion (0.5%; 14 subjects in total) of subjects were tested positive for anti-semaglutide antibodies post-baseline; the positive tests were predominantly a single finding (12 subjects) or transient (2 subjects). None of samples for the 6 reported cases of severe acute hypersensitivity that prompted anti-semaglutide antibody assessment were found to be positive for anti-semaglutide IgE or binding antibodies. Finally, the presence of anti-semaglutide antibodies did not impact the semaglutide plasma concentration.

Safety related to drug-drug interactions and other interactions

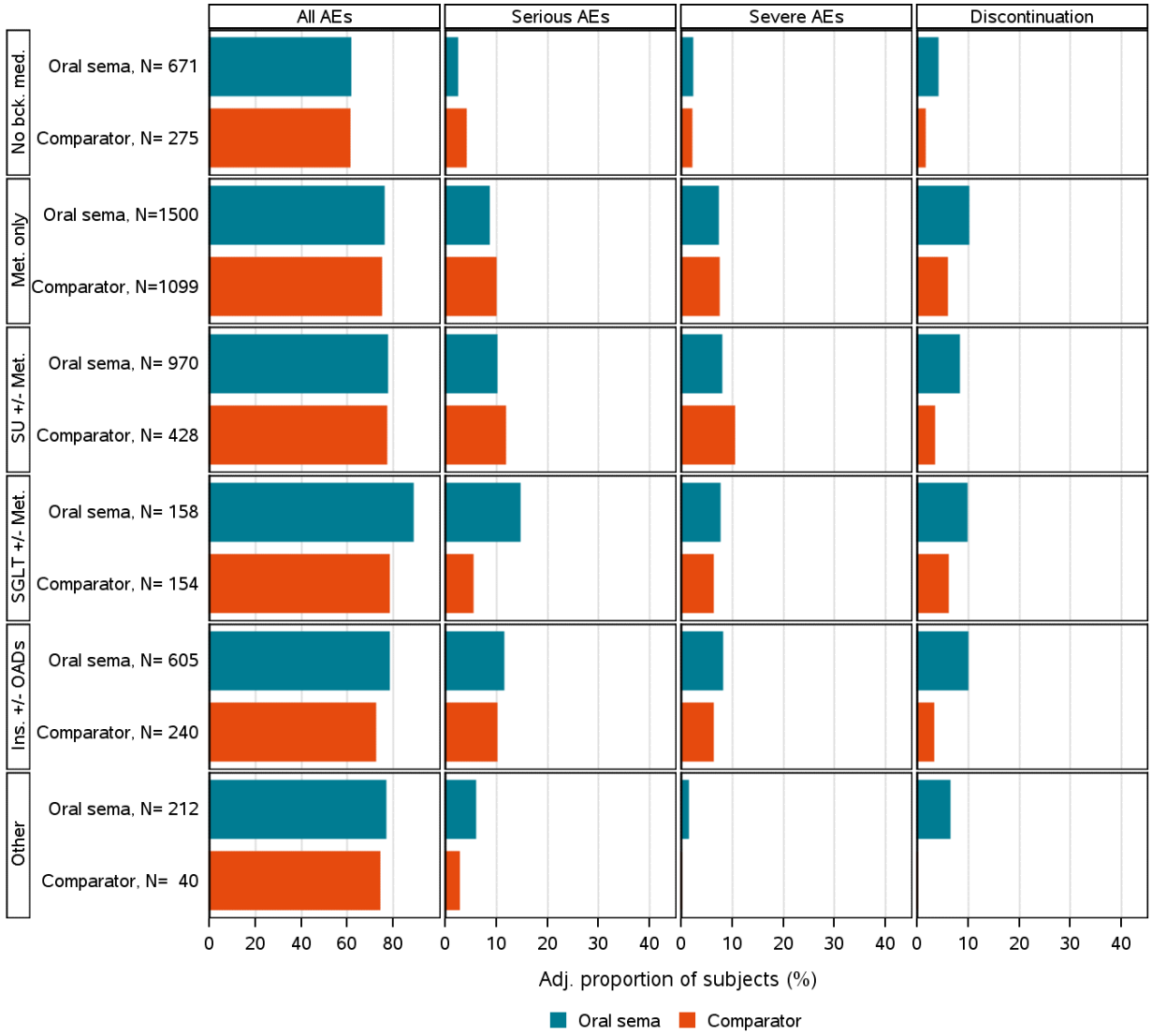
Anti-diabetic background medication:

An AE overview by anti-diabetic background medication is presented for the phase 3a pool in Figure S-30. The proportions of subjects with SAEs were higher with oral semaglutide vs comparator for SGLT-2i±metformin and

other, comparable for insulin±OADs and SU±metformin, and lower for oral semaglutide than comparator for no background medication or metformin only.

Treatment difference with oral semaglutide vs comparator was more pronounced for GI AEs and PTs decreased appetite and lipase increased in the subgroup taking insulin±OADs as anti-diabetic background medication. Evaluating the risk of hypoglycaemic episodes by anti-diabetic background medication, more episodes of hypoglycaemia were seen with oral semaglutide as well as comparators, when taken together with insulin or SU.

Figure S-30 - AE overview by anti-diabetic background medication – bar plot – phase 3a pool – on-treatment



Phase 3a pool: PIONEER 1-5 and 7-10.
'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator': sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.
'Discontinuation': AEs leading to premature discontinuation of trial product; N: number of subjects; Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%); Met.: Metformin; SU: sulphonylurea; SGLT: sodium-glucose cotransporter-2 inhibitor; Ins.: insulin; OAD: oral antidiabetic drug.

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21JAN2019:15:09:23 - f_bar_ae.sas/f_bar_ae_diamed_3a_ot.png

Other concomitant medications:

According to the Applicant and based on *in vitro* studies, no clinically relevant drug–drug interactions were anticipated with semaglutide. The assessment of potential safety issues was therefore only based on the PK studies.

However, a PK interaction was noted for levothyroxine with a 33% increase of total exposure after a single dose of levothyroxine. The Applicant reflected this interaction in the SmPC.

Discontinuation due to AES

Gastrointestinal disorders (mainly nausea vomiting, diarrhoea and different terms for abdominal pain) were the most frequent AEs leading to premature treatment discontinuation with oral semaglutide in the phase 3a pool, the placebo pool (Table S-26) and in PIONEER 6.This pattern is consistent with that reported for semaglutide s.c. and the GLP-1 RA class.

Table S-26 AEs leading to permanent trial product discontinuation - Placebo pool

	Oral sema				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	132	(9.3)	242	22.0	22	(3.2)	28	5.6
Non-serious adverse events	121	(8.6)	224	20.5	12	(1.7)	16	3.0
SAEs	12	(0.8)	18	1.5	11	(1.6)	12	2.6
Fatal	2	(0.1)	2	0.1	0			

Post marketing experience

Not applicable. Information based on (clinical trial and post marketing) experiences with Ozempic is reflected throughout the dossier.

2.7.1. Discussion on clinical safety

The description of the safety profile of oral semaglutide is primarily based on the pooled analysis of Phase 3a trials, including 4116 subjects treated with oral semaglutide and 2236 subjects treated with active comparator or placebo. The mean, individual observation time was slightly above one year in both groups; therefore, the experience corresponds to 4379 and 2335 patient-years exposure.

Oral semaglutide is not associated with an increased risk of fatal events. The proportion of subjects with fatal AEs was similar with oral semaglutide and comparator (0.4% vs 0.5% of subjects) in the phase 3a pool and similar with oral semaglutide and placebo (0.6% vs 0.4% of subjects) in the placebo pool. There were no apparent differences between oral semaglutide and comparators (phase 3a pool) or between oral semaglutide and placebo (placebo pool) with respect to the cause of death as classified by the event adjudication committee (EAC). Results from PIONEER-6 suggest a lower risk for all-cause death compared with placebo. A total of 71 randomised subjects in PIONEER 6 had fatal AEs with onset during the in-trial period. The proportion of subjects with fatal AEs was lower with oral semaglutide (25 subjects (1.6%)) than with placebo (46 subjects (2.9%)). The types of AEs with fatal outcome were similar between oral semaglutide and placebo, however lower frequencies were seen with oral semaglutide vs placebo for fatal events of cardiovascular disorders (0.6% vs

1.6% of subjects), infections and infestations (0.3% vs 0.6% of subjects) and general disorders (0.1% vs 0.5% of subjects) The frequency of fatal events across the PIONEER trials seemed to be in line with the expectations for a trial population of subjects with T2D.

Overall, the safety profile of oral semaglutide is similar to that of s.c. semaglutide (Ozempic). The Applicant specifically analysed several safety focus areas:

The pattern observed for **GI AEs** was in line with what was expected for the GLP-1 RA drug class, and the frequency and the nature of the GI AEs were similar to those observed for s.c. semaglutide (Ozempic).

No concern with regards to **renal safety** in relation to treatment with oral semaglutide was identified. Clinical pharmacology, PK modelling and phase 3a evidence (including data from s.c. semaglutide, Ozempic) do not indicate a need for dose-adjustment in patients with renal impairment. It is acknowledged that GI side effects may lead to dehydration and thus affect renal function. However, the PIONEER 5 trial and the CVOT trial (PIONEER 6) were the only trials that included subjects (8 and 28 patients, respectively) with severe renal impairment (15≤ eGFR [mL/min/1.73m^2] <30). Due to the relatively small number of patients, safety in these patients is uncertain. This is reflected in the SmPC.

The frequency of **cholelithiasis** was greater with oral semaglutide than with placebo (10 events and 1 event, respectively, corresponding to 0.6% and 0.1% of the subjects in the placebo pool). The risk of gallbladder-related disorders, including cholecystitis was similar to the comparators in the phase 3a pool. The gallbladder-related disorders were related to weight loss. The frequency of **pancreatitis** was low (MedDRA search) and there was no difference between oral semaglutide and neither the comparator nor the placebo group. In the CVOT, there were 4 EAC-confirmed events of acute pancreatitis, one with oral semaglutide, 3 with placebo. In line with evidence for s.c. semaglutide (Ozempic), oral semaglutide was not associated with increased risk of acute pancreatitis versus comparators.

No indication of an increased risk of **cardiovascular events** has been detected for orally or subcutaneously administered semaglutide, which is in line with the data for some marketed GLP-1 RAs.

Both the proportion of subjects with **neoplasms** (malignant and non-malignant) (6.4% and 5.7%, respectively, in the phase 3a pool) of (adjudicated) malignant neoplasms 1.4% and 1.0% were higher with oral semaglutide than with comparator. Only 210 patients were treated for 18 months or more in the phase 3a pool; roughly 400 patients were treated for 18 months in PIONEER 6. This is insufficient for a thorough assessment of the risk of neoplasms. Based on the numerical imbalance, follow up of these data is needed. Neoplasms remain an adverse event of special interest and are included as an important potential risk in the RMP.

With regards to prostate cancer, the numbers as well as the difference between the oral semaglutide group and the Comparator group are small and the clinical pattern do not support a causal relationship.

Similarly, with regard to gastric polyps the numbers are small and it is agreed that there is no pattern indication for a causal relation between treatment with oral semaglutide (+SNAC) and gastric polyps.

The risk of severe or clinically significant **hypoglycaemia** was low with oral semaglutide but appears to be higher when used in combination with other glucose-lowering medication (SUs and insulins), which themselves are associated with an increased risk of hypoglycaemia. This should be viewed in the context of the marked improvements in glycaemic control and blood glucose concentrations demonstrated with oral semaglutide. Overall, nocturnal hypoglycaemia occurred more commonly in the oral semaglutide group than in the placebo group (Placebo pool). A similar pattern though less pronounced was observed in the Phase 3a pool with more nocturnal hypoglycaemic episodes in the oral semaglutide group compared to the Comparator group. It is reassuring that severe (Level 3) episodes were only reported in 10 patients treated with oral semaglutide.

Considered a total exposure time of 4,692 years this is acceptable. Further, hypoglycaemia is included as a common adverse reaction in the Tabulated list of adverse reactions in section 4.8 of the SmPC and also described in more detail in the last part of the adverse reaction section of the SmPC.

Because of the increased risk of retinopathy with subcutaneous semaglutide (SUSTAIN), patients with pre-existing proliferative retinopathy or maculopathy requiring acute treatment were excluded. Nevertheless, in the PIONEER trials the proportion of subjects with AEs of **diabetic retinopathy** and related complications as well as the event rates were greater with oral semaglutide than with placebo (oral semaglutide: 3.8% placebo 2.9%; CVOT: semaglutide 7.1%, control 6.3%). Analysis of data from the Phase 3a pool regarding baseline risk factors for developing diabetic retinopathy does not present a clear pattern. Specifically, there was no apparent indication of a correlation between the magnitude of the HbA1c reduction and the risk of diabetic retinopathy, neither for patients treated with oral semaglutide nor for patients treated with comparators. No dose-response relationship was observed for oral semaglutide in the large long-term safety trial PIONEER 3, nor in the 4 other trials with three oral semaglutide doses. However, these trials with a short duration and/or lack of a placebo group may not be sensitive enough for relevant assessments of a chronic complication such as retinopathy. In the PIONEER trials, there was not an increased risk in the following four endpoints (1) treatment with retinal photocoagulation, (2) treatment with intravitreal agents, (3) Vitreous haemorrhage, (4) Onset of retinal blindness. The events were in general non-serious and of mild severity, and there was no indication of an increase in severity with oral semaglutide compared with comparators. Most of the events were non-proliferative diabetic retinopathy, were identified by routine examinations and did in general not require treatment.

Taken together, these data suggest that semaglutide increased the risk of diabetic retinopathy, in the trials that mostly had an observation time of up to 18 months.

The careful follow-up that was specified in the protocol was usually adequate to address this risk. There is a warning about 'diabetic retinopathy' in the Ozempic label and 'diabetic retinopathy complications' is included in its adverse effects table ('common'). Because it cannot be excluded that the risk of diabetic retinopathy complications identified in SUSTAIN 6 also applies to oral semaglutide, the safety concerns in the risk management plan of oral semaglutide were aligned to that of Ozempic to include diabetic retinopathy complications as an adverse drug reaction in the SmPC and as an important identified risk in the RMP.

The applicant updated the SmPC that, despite the exclusion of high risk patients, retinopathy risk was higher with oral semaglutide. The trials with a short duration and/or lack of a placebo group are not sensitive enough for a thorough assessment of a chronic complication such as retinopathy. In the placebo-controlled CV outcome trial (with a longer follow up), an increased risk of retinopathy with oral semaglutide was found (7.1% (113 of 1591 patients) with oral semaglutide and 6.3% (101 of 1592) with placebo).

Due to the large variability in exposure and supported by the drug-drug interaction studies as provided by the Applicant, clinically relevant **drug-drug interactions** may be unlikely. However, for levothyroxine, effects could be measurable, based on a relatively large PK effect (33% increase in total exposure following administration of a single dose levothyroxine). The interaction is reflected in section 4.5 of the SmPC.

Due to the potential inhibition of cellular respiration caused by (excessive doses of) SNAC, arterial and venous **lactate levels** were measured in a Phase II clinical pharmacology trial (Trial 4247) and in the PIONEER 1 and 2 trials. Further, lactic acidosis was included as a safety focus area for all Phase 3a trials.

Overall, only few cases of lactic acidosis and blood lactate increase were reported in both the Phase 3a pool and in the PIONEER 6. There were no reported cases in the Placebo pool. The Applicant stated that for all reported cases in the oral semaglutide group, confounding factors (respiratory disease, decreased renal function or

infections) were reported concomitantly. Thus, the Applicant concluded that based on concurrent medical conditions that can precipitate lactic acidosis, these events were not considered related to the trial product. CHMP agreed that the overall risk can be considered low, also among patients with concurrent medical conditions predisposing for lactic acidosis. With regard to concomitant treatment with metformin, the Applicant states that available data do not suggest an increased risk of lactic acidosis. It is agreed that the majority of patients included in the Phase III studies were concomitantly treated with metformin and the overall frequency of lactic acidosis was low. Thus, CHMP agreed that concomitant treatment with metformin is not associated with a notably risk of lactic acidosis and therefore, additional information regarding this e.g. in the SmPC or RMP is not warranted. It is reassuring that scatter plots of SNAC concentration and lactate concentrations do no indicate neither a dose-effect nor a concentration-effect relation and also do not increase over time.

There was no indication of an **immunogenicity-related concern** for oral semaglutide. Though, it is reassuring that the anti-semaglutide antibody formation did not affect the semaglutide plasma concentrations. In addition, no patients were tested positive for anti-semaglutide antibodies with endogeneous GLP-1 neutralising effect.

2.7.2. Conclusions on clinical safety

In general, treatment with oral semaglutide is safe. The safety profile is dominated by GI AEs, that may be associated with treatment discontinuation.

2.8. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Diabetic retinopathy complications
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer • Neoplasms (malignant and non-malignant)
Missing information	• Pregnancy and lactation • Patients with severe hepatic impairment

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA) **– semaglutide s.c. and oral semaglutide**				
MTC-22341 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	Medullary thyroid cancer	**Semaglutide s.c.**	
			Submitted protocol	January 2019
			Final report	May 2035
			Oral semaglutide	
			Submitted protocol	November 2020

	carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace.		Final report	February 2037
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of Ozempic® (semaglutide s.c.) and Rybelsus® (oral semaglutide) in patients with type 2 diabetes Ongoing	The study will evaluate whether exposure to Ozempic® increases the risk of pancreatic cancer in patients with T2DM.	Pancreatic cancer	**Semaglutide s.c.**	
			Adopted protocol	20 Sep 2018
			Final report	Septembe r 2025
			Oral semaglutide	
			Adopted protocol	Pending
			Final report	Septembe r 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
NN9535-4321 FLOW – Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease	To monitor and further characterise the neoplasms in subjects treated with s.c. and oral semaglutide	Neoplasms (malignant and non-malignant)	Final report	February 2025
NN9535-4352 FOCUS – Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes			Final report	May 2026
NN9535-4386 SUSTAIN 11 – Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add-on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes			Final report	July 2021
NN9535-4430 A trial investigating the effect of semaglutide on atherosclerosis in patients with cardiovascular disease and type 2 diabetes			Final report	March 2022
NN9535-4506 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			Final report	February 2021
NN9535-4416			Final report	May 2023

SePra – Long term comparative effectiveness of once-weekly semaglutide versus standard of care in a real-world adult US population with type 2 diabetes - a randomised pragmatic clinical trial				
EX9924-4473 SOUL – Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes			Final report	January 2025

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
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
Important potential risk; Neoplasms (malignant and non-malignant)	*Routine risk minimisation measures:* None *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

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.4 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the 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.

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rybelsus (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

Rybelsus is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with 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.

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

There are several classes of medicinal products for the treatment of T2D. All products have been shown to reduce blood glucose level and to improve HbA1c. Based on the extensive therapeutic experience (including possible CV benefits), metformin is currently recommended as first-line treatment for all patients with T2D, unless contraindications apply (most notably, GFR <30 ml/min). Recently, SGLT2-inhibitors and GLP-1 receptor agonists have shown to be superior compared to placebo in reducing 3-point MACE in patients with established CV disease in CV outcomes trials.

Semaglutide is a GLP-1 RA that is structurally similar to liraglutide (approved as Victoza) but modified to have a longer half-life. It is approved as Ozempic for once weekly s.c. administration. However, many patients are reluctant to use parenteral therapies; for such patients, oral semaglutide as proposed here could be of benefit.

3.1.3. Main clinical studies

Ten phase 3a trials (PIONEER 1–10) were performed with oral semaglutide. The phase 3a trials included a total of 9543 randomised subjects, of whom 5707 were exposed to oral semaglutide. The programme included a dedicated CV outcome trial (CVOT), PIONEER 6, to assess the CV safety of oral semaglutide. The subjects across the phase 3a trials represented a broad population of subjects with T2D at various disease stages. Subjects with T2D and with relevant co-morbidities were investigated in two specific trials: moderate renal impairment in PIONEER 5, and established CV disease, or risk factors for CV disease, in PIONEER 6.

The active comparators in the phase 3a trials comprised GLP-1 RAs other than semaglutide (liraglutide and dulaglutide, both for s.c. injection), a DPP-4 inhibitor (sitagliptin) and an SGLT2 inhibitor (empagliflozin). Three oral semaglutide doses (3, 7 and 14 mg) were investigated in five phase 3a trials (PIONEER 1, 3 and 8−10). Four

trials investigated oral semaglutide 14 mg only (PIONEER 2 and 4–6). Dose escalation was used to mitigate gastrointestinal (GI) side effects, based on experience from the phase 2 dose-finding trial (trial 3790) and from the GLP-1 RA drug class in general.

PIONEER 1 (Trial 4233; Monotherapy) was a randomised, double-blind, placebo-controlled efficacy and safety trial with a 26-week treatment period (including an 8-week dose escalation period). Adults with type 2 diabetes treated with diet and exercise only were randomised to once-daily treatment with oral semaglutide (3, 7 or 14 mg) or placebo.

PIONEER 2 (Trial 4223; vs. SGLT-2 inhibitor) was a randomised, open-label, active-controlled efficacy and safety trial with a 52-week treatment period (including an 8-week dose escalation period). Adults with T2D treated with metformin were randomised to once-daily treatment with oral semaglutide 14 mg or empagliflozin 25 mg.

PIONEER 3 (Trial 4222; vs. DPP-4 inhibitor) was a randomised, double-blind, double-dummy, active-controlled trial with four arms comparing efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg once-daily with sitagliptin 100 mg once-daily. Adults with T2D inadequately controlled on metformin alone or in combination with SU were randomised to once-daily treatment with oral semaglutide (3 mg, 7 mg or 14 mg) or sitagliptin 100 mg.

PIONEER 4 (Trial 4224; vs. GLP-1 RA) was a randomised, double-blind, double-dummy, active- and placebo-controlled trial with a 52-week treatment period (including an 8-week dose escalation period). Adults with T2D on background anti-diabetic medication (metformin alone or metformin in combination with a SGLT-2 inhibitor) were randomised to once-daily treatment with oral semaglutide 14 mg, liraglutide 1.8 mg (s.c. injection) or placebo, respectively.

PIONEER 5 (Trial 4234; Renal impairment) was a randomised, double-blind, placebo-controlled, parallel-group trial with a 26-week treatment period (including an 8-week dose escalation period) comparing the efficacy and safety of oral semaglutide with placebo in subjects with T2D and moderate renal impairment inadequately controlled on metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin. Adults with T2D inadequately controlled on metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin, were planned to be randomised 1:1 to once-daily treatment with oral semaglutide (14 mg) or placebo, as an add-on to their background medication.

PIONEER 6, (CVOT, Trial 4221) was a randomised, double-blind, placebo-controlled, CV outcomes trial (CVOT) designed to assess the CV safety (Hazard ratio <1.8) of oral semaglutide versus placebo when added to standard-of-care in subjects with T2D and with a high risk of CV events. Subjects were randomised to once-daily treatment with oral semaglutide or placebo in addition to standard-of-care. The duration of the treatment period was event driven; until a pre-specified number of at least 122 first EAC-confirmed MACEs comprising CV death, non-fatal myocardial infarction or non-fatal stroke was accrued.

PIONEER 7 (Trial 4257; Flexible dose adjustment (main phase)) was a 52-week randomised, open-label, active-controlled, 2-arm, parallel-group, treatment period with an initial 2-week screening period and, for subjects that did not continue in the extension phase, a 5-week follow-up period. Subjects with T2D were randomised to flexible dosing (3, 7 or 14 mg) of oral semaglutide once-daily or 100 mg sitagliptin once-daily as an add-on to their anti-diabetic background medication.

PIONEER 8 (Trial 4280; Insulin add-on) was a randomised, double-blind, placebo-controlled, four-armed, parallel-group efficacy and safety trials with a 52-week treatment period (including an 8-week dose escalation

period). Adults with T2D on stable treatment with insulin with or without metformin treatment were randomised to once-daily treatment with oral semaglutide (3, 7 or 14 mg) or placebo.

PIONEER 9 and 10 were conducted in Japan only, according to Japanese requirements, and are considered supportive for the efficacy evaluation.

3.2. Favourable effects

In all key efficacy trials, the primary endpoint evaluated the effect of the trial products on glycaemic control estimated based on the average blood glucose concentration (HbA_{1c}) after 3 months. Oral semaglutide dose-dependently reduced HbA_{1c} across all PIONEER trials; the reductions were 0.6 to 0.9 %-points for 3 mg, 0.8 to 1.2 %-points for 7 mg and 1.0 to 1.4 %-points for 14 mg in the key efficacy trials (Figure E-16, Figure E-17). The results are supported by responder analyses, glucose measurements, sensitivity analyses and subgroup analyses.

Weight-loss was pre-defined as a confirmatory, secondary endpoint. In most trials, the type 1 error was protected for HbA_{1c} (as the change from baseline) and weight loss. Body weight was reduced dose-dependently by 1.2 to 1.5 kg with oral semaglutide 3 mg, 2.2 to 2.4 kg with 7 mg and 3.1 to 4.4 kg with 14 mg in the key efficacy trials at week 26.

The conduct of the studies as stated by the applicant was GCP compliant and used state-of-the-art methods. The assessment did not raise important concerns in this regard.

3.3. Uncertainties and limitations about favourable effects

The intra- and inter-patient variability (CV 100 %) in exposure is high and much larger than with s.c. semaglutide. Both the (glycaemic) efficacy and tolerability (measured as GI AEs) are exposure-related. The intra- and inter-patient variability in exposure creates uncertainty about the 'right' dose for the individual patient. Due to the high variability in the absorption of semaglutide, an important concern identified in the pharmacokinetic evaluation of oral semaglutide is the risk of low exposure and resulting negative impact on efficacy. It has been demonstrated that SNAC is an absorption enhancer in vitro, however its absorption enhancing effect has not been confirmed in vivo. Based on the available data the influence of SNAC on semaglutide absorption or variability is unknown.

The Applicant has presented a combined analysis of CV risk reduction. Although across the two CVOTs with semaglutide (PIONEER 6 and SUSTAIN 6), similar endpoints and methods for the evaluation of CV risk were applied, and the baseline characteristics of the enrolled populations may be comparable, the duration of the trials differed markedly. The additional arguments given by the Applicant to claim established CV risk reduction are reassuring and supportive, however not confirmatory as the CVOT PIONEER 6 did not show a statistically significant CV risk reduction. Due to the large variability in exposure, the different route of administration, and taken into account that not all patients will tolerate the highest dose of 14 mg, it remains uncertain if the exposure obtained with oral semaglutide is sufficient for the entire population to exhibit the CV effect. Moreover, it remains questionable to extrapolate the results of s.c. semaglutide. Therefore, the the indication wording is restricted to 'treatment of T2D to improve glycaemic control' and CV events are presented in SmPC section 5.1 based on the PIONEER 6 trial only.

Baseline demographics and disease characteristics of the trial populations studied, represented a broad T2D population as seen in clinical practice. Although elderly (>65 years) are well represented, of subjects >85 years

only 9 were exposed to oral semaglutide. In addition, the PIONEER 5 trial and the CVOT trial (PIONEER 6) were the only trials that included subjects (8 and 28 patients, respectively) with severe renal impairment (15≤ eGFR [mL/min/1.73m^2] <30). Efficacy information in subjects with severe renal or severe hepatic impairment is very limited. This has been adequately reflected in the SmPC.

3.4. Unfavourable effects

The description of the safety profile of oral semaglutide is primarily based on the pooled analysis of Phase 3a trials, including 4116 subjects treated with oral semaglutide and 2236 subjects treated with placebo or active comparator. The mean, individual observation time was slightly above one year in both groups; therefore the experience corresponds to 4379 and 2335 patient-years exposure.

Gastrointestinal AEs are experienced by 38.7% of patients (compared to 21.0% for placebo). This is driven by nausea (27.4 vs 9.8%), diarrhoea (18.1 vs 8.5%), vomiting (14.9 vs 3.3%) and constipation (10.6 vs 4.0%). Prevalence of nausea peaked at 16 weeks. Discontinuation due to GI AEs was 6.9 vs 1.1%. The incidence of GI AEs was dose-dependent with the highest rates observed in the semaglutide 14 mg arm.

No indication of an increased risk of **cardiovascular events** has been detected for oral semaglutide. In the CVOT PIONEER-6, the Hazard ratio for major adverse cardiac events (MACE) was clearly below 1.8. (HR 0.79 [0.57; 1.11]; the hazard ratios for the components were CV death: 0.49; non-fatal myocardial infarction: 1.18; non-fatal stroke: 0.74). Oral semaglutide was not associated with an increased risk of (all-cause) fatal events. The frequency of fatal events across the PIONEER trials seemed to be in line with the expectations for a trial population of subjects with T2D.

The risk of severe or clinically significant **hypoglycaemia** was low with oral semaglutide but may be higher when used in combination with other glucose-lowering medication (SUs and insulins), which themselves are associated with an increased risk of hypoglycaemia. This should be viewed in the context of the marked improvements in glycaemic control and blood glucose concentrations demonstrated with oral semaglutide.

In the PIONEER trials, the proportion of subjects with AEs of **diabetic retinopathy** and related complications as well as the event rates were greater with oral semaglutide than with placebo (oral semaglutide: 3.8% placebo 2.9%; CVOT: semaglutide 7.1%, control 6.3%). Almost all the AEs were events of diabetic retinopathy. No dose-response relationship was apparent for oral semaglutide. The events were in general non-serious and of mild severity, and there was no indication of an increase in severity with oral semaglutide compared with comparators. Most of the events were non-proliferative diabetic retinopathy, were identified by routine examinations and did in general not require treatment. These data suggest that semaglutide increased the risk of diabetic retinopathy, in the trials that mostly had an observation time of up to 18 months. The careful follow-up that was specified in the protocol was usually adequate to address this risk.

The frequency of **cholelithiasis** was greater with oral semaglutide than with placebo (10 events and 1 event, respectively, corresponding to 0.6% and 0.1% of the subjects in the placebo pool). The risk of gallbladder-related disorders, including cholecystitis was similar to the comparators in the phase 3a pool.

There was no indication of an **immunogenicity-related concern** for oral semaglutide.

The safety profile of oral semaglutide is similar to that of semaglutide s.c. (Ozempic) and other GLP-1 RAs. Oral semaglutide was not associated with increased risk of **acute pancreatitis** vs comparators.

3.5. Uncertainties and limitations about unfavourable effects

The PIONEER 5 trial and the CVOT trial (PIONEER 6) were the only trials that included subjects (8 and 28 patients, respectively) with severe renal impairment (15≤ eGFR [mL/min/1.73m^2] <30). Due to the relatively small number of patients, safety in these patients is uncertain which is adequately reflected in the SmPC and aligned with the Ozempic SmPC. PIONEER 5 included primarily subjects with moderate renal impairment. In this trial, premature treatment discontinuation was higher in the semaglutide arm (18.4% versus 12.4% in placebo). This was largely due to GI AEs with semaglutide. More severe or blood glucose confirmed symptomatic hypoglycaemic episodes were observed in the semaglutide arm compared to placebo (5.5% versus 1.9%). Adverse events rates were higher in patients with renal impairment compared to other trials, both in active and control arms.

Experience with the use of semaglutide in patients with severe hepatic impairment is limited, which is adequately reflected in the SmPC.

Both the proportion of subjects with **neoplasms** (malignant and non-malignant) (6.4% and 5.7%, respectively, in the phase 3a pool) of (adjudicated) malignant neoplasms 1.4% and 1.0% were higher with oral semaglutide than with comparator. Only 210 patients were treated for 18 months or more in the phase 3a pool; roughly 400 patients were treated for 18 months in PIONEER 6. This is insufficient for a thorough assessment of the risk of neoplasms. Neoplasms remain an AE of special interest and are included as an important potential risk in the RMP.

3.6. Effects Table

Table BR-27 Effects Table for oral semaglutide in treatment of type 2 diabetes.

Effect	Short Description	Unit	Oral sema	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HbA1c reduction	CFB to week 26	%-points	3 mg: -0.9 7 mg: -1.2 14 mg: -1.4	pbo: -0.3	SoE Diff −0.1 [−0.9; 0.8] −0.9 [−1.1; −0.6] * −1.1 [−1.3; −0.9] * Responders HbA1c<7: 55, 69, 77 vs 31%	PIONEER 1 (background diet & exercise)
	CFB to week 52	%-points	14 mg: -1.3	empa: -0.9	SoE Diff −0.4 [−0.5; −0.3] * Responders HbA1c<7: 66 vs 43%	PIONEER 2 (background metformin)
	CFB to week 78	%-points	3 mg: -0.6 7 mg: -0.8 14 mg: -1.1	sita: -0.8	SoE Diff 0.0 [-0.1; 0.2] −0.1[−0.3; 0.0] * −0.4 [−0.6; −0.3] * Responders HbA1c<7: 27, 39, 45 vs 32%	PIONEER 3 (background metformin with or without sulphonylurea)
	CFB to week 52	%-points	14 mg: -1.2	lira -0.9 pbo -0.2	SoE Diff −0.3 [−0.5;-0.1] * −1.0 [−1.2; −0.8] * Responders HbA1c<7: 61 vs 55%	PIONEER 4 (background metformin with or without SGLT2 inhibitor)
	CFB to week 26	%-points	14 mg: -1.0	pbo -0.2	SoE Diff −0.8 [−1.0; −0.6] * Responders HbA1c<7: 58 vs 23%	PIONEER 5 (Subjects with renal impairment)
	CFB to week 52	%-points	Flex: -1.3	sita: -0.8	SoE Diff −0.5 [−0.7; −0.4] Responders HbA1c<7%: 58 vs 25% (primary endpoint *)	PIONEER 7 Open label, Treat to target (HbA1c < 7%)
	CFB to week 52	%-points	3 mg: -0.6 7 mg: -0.8 14 mg: -1.2	pbo: -0.2	SoE Diff −0.4 [−0.6; −0.2] * −0.6 [−0.8; −0.4] * −0.9 [−1.1; −0.7] * Responders HbA1c<7: 28, 44, 58 vs 7%	PIONEER 8 (background insulin, 26-weeks fixed dose, followed by 26 weeks flexible dose)
Weight loss	CFB to end of treatment	kg	3 mg: -0.8 to -1.8 7 mg: -2.0 to -2.7 14 mg: -3.2 to -4.3	pooled -0.5 to -3.6	SoE Confirmatory endpoint in phase 3a program. Most results statiscially significant.	PIONEER 1-5, 7-8

Effect	Short Description	Unit	Oral sema	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Serious adverse events	Event rate	Events per 100 PYO	16.3	pbo: 14.5	SoE Similarly, no relevant difference in PIONEER 6: Subjects with events [N (%)] sema fFlex: 301 (18.9); pbo: 358 (22.5)	Placebo pool
CV events	3-point MACE	Subjects with events	Flex: 61	pbo: 76	SoE HR 0.79 [0.57; 1.11] non-inferior to 1.8* HR per component: CV death 0.49 Non fatal MI: 1.18 Non-fatal stroke: 0.74 All cause mortality N (%) sema flex: 23 (1.4%); pbo: 45 (2.8%)	PIONEER 6
Gastro-intestinal adverse effects	Event rate	Events per 100 PYO	116.9	pbo: 45.1	As percentage: 38.7 v 21.0%. Driven by nausea (27.4 vs 9.8), diarrhea (18.1 vs 8.5), vomiting (14.9 vs 3.3), constipation (10.6 vs 4.0) . Prevalence of nausea peaked at 16 weeks. Discontinuation due to GI AEs 6.9 vs 1.1%.	Placebo pool
Hypoglycaemia	Event rate (ADA 2018 classification)	Events per 100 PYO	184.0	pbo: 137.7	SoE Severe 0.6 vs 0.2 Significant 42.1 vs 34.4 Alert 141.3 vs 103.1	Placebo pool
Cholelithiasis	Subjects with events	N (%)	10 (0.6%)	pbo: 1 (0.1%)	SoE Class effect for GLP-1 RAs	Placebo pool
Diabetic retinopathy	Event rate	Events per 100 PYO	4.9	pbo: 3.5	SoE Similarly, higher in PIONEER 6: Subjects with events [N (%)] sema flex:113 (7.1); pbo: 101 (6.3). Unc: Signal for diabetic retinopathy complications seen in SUSTAIN 6	Placebo pool
Neoplasms	Subjects with events	N (%)	69 (4.7)	pbo: 28 (4.2)	SoE Similar in phase 3a pool (6.4 vs 5.7%); Malignant 1.4 vs 1.0%. Unc due to short observation periods	Placebo pool
Falls	Subjects with events	N (%)	17 (1.3)	pbo: 5 (0.7)	Unc Elderly ≥ 75 years: 7 (3.5) vs 1 (1.2) (Phase 3a pool)	Placebo pool

Abbreviations:

CFB	change from baseline	GI	gastro-intestinal	sema	semaglutide
CV	cardio-vascular	HR	hazard ratio	sita	sitagliptin 100 mg
CVOT	cardio-vascular outcome trial	lira	liraglutide 1.8 mg	SoE	Strength of evidence
Diff	treatment difference	pbo	placebo	Unc	Uncertainties
empa	empagliflozin 25 mg	PYO	patient years observed	*	p < 0.05

flex flexible dosing

Notes
PIONEER 6(CVOT): subjects were treated with oral semaglutide 14 mg, but lower doses allowed based on tolerability Placebo pool: PIONEER 1, 4, 5 and 8.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Glycaemic control has been a main goal of therapy in type 2 diabetes for many years. According to the 'Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus' (CPMP/EWP/1080/00), glycaemic control as reflected by HbA1c is the preferred primary endpoint in clinical trials. Oral semaglutide has proven efficacy on this endpoint by showing clinically relevant and statistically significant superiority to placebo and active controls in the PIONEER program on a variety of background therapies. The improvement of glycaemic control is associated with a weight reduction of 0.8 to 4.3 kg, which was assessed as a confirmatory endpoint throughout the program.

In addition, a reduction of long-term complications is another goal of treatment. For macrovascular complications, PIONEER 6 has shown cardiovascular safety in terms of a hazard ratio for major adverse cardiovascular events (MACE) below 1.8 (HR 0.79 [0.57; 1.11]). The point estimate for MACE was below 1, suggesting cardiovascular benefit, but the trial was underpowered to reach statistical significance. In the trial, cardiovascular and all-cause mortality were markedly reduced. However, the robustness of this mortality finding is questioned as this benefit was not found in the trial with subcutaneous semaglutide.

Importantly, for microvascular complications, long-term glycaemic control may be the most important preventive measure. However, in the PIONEER program, the exposure studied is limited to 18 months. In this period, more adverse events of diabetic retinopathy occurred with semaglutide than with control. This could be due to rapid improvement of glycaemic control, but a causal implication of semaglutide has not been excluded. The risk can be mitigated by intensive screening for retinopathy. Therefore, the SmPC (section 4.4) clarifies that it cannot be excluded that the risk of diabetic retinopathy complications identified in SUSTAIN 6 may also apply to oral semaglutide**.**

The safety profile of oral semaglutide is largely in line with the safety profile of subcutaneous semaglutide. Gastro-intestinal adverse effects occur in 38.7% of patients (vs 21.0% with placebo), driven by nausea, diarrhoea, vomiting and constipation. Prevalence of nausea peaked at 16 weeks and seems to improve thereafter.

Serious adverse events are comparable to control. Oral semaglutide does not cause hypoglycaemia, but when taken with insulin or sulphonylureas, hypoglycaemia may occur. The SmPC suggests preventive dose reduction in these patients.

In the PIONEER program, a numerical imbalance in (both benign and malignant) neoplasms was observed. The short duration of the trials weakens the precision of the findings and questions a causal relationship with (oral) semaglutide; however, follow-up is required and outlined in the pharmacovigilance plan.

3.7.2. Balance of benefits and risks

Oral semaglutide dose-dependently reduces HbA_{1c} and contributes to weight loss but also frequently elicits gastro-intestinal adverse effects. The proposed dose improves glycaemic control in a large proportion of patients, but the rate of discontinuation due to gastro-intestinal adverse effects was 6.9%.

The contribution of the new excipient SNAC to the bioavailability of semaglutide has been investigated in vitro but has not been confirmed in vivo. The pharmacokinetic variability both within and between patients is considerable. This variability is much larger than the variability with semaglutide s.c. (Ozempic), is incompletely explained, and is presumably due to variability in absorption. This variability implies a trade-off for the individual patient between the certainty of exposure and convenience of oral treatment compared to injection. Both the benefits and the unfavourable effects are closely related to the exposure. The intra-patient variability is mitigated by daily dosing, which is frequent compared to the long half-life of one week.

Overall, oral semaglutide controls hyperglycaemia effectively but, at the same time, is associated with the disadvantage of frequent gastro-intestinal adverse effects. Still, it can be a suitable treatment option for many patients.

3.8. Conclusions

The overall B/R of Rybelsus is positive.

4. Recommendations

Outcome

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

> "Rybelsus is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise
>
> - as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
> - in combination with other medicinal products for the treatment of diabetes.
>
> For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.".

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0206/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.