Amsterdam, 21 May 2026
EMADOC-1700519818-3184701
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on an extension of marketing authorisation

Wegovy

international non-proprietary name: semaglutide

Procedure No. EMA/X/0000296344

Marketing Authorisation Holder (MAH): Novo Nordisk A/S

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List of abbreviations

ADO	8-amino-3,6-dioxaoctanic acid
AAS	Atomic Absorption Spectrometry
ADME	Absorption, distribution, metabolism and excretion
Aib	2-aminoisobutyric acid
ALP	alkaline phosphatase
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ATP	active pharmaceutical ingrediënt
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
BRCP	breast cancer resistance protein
cAMP	cyclic adenosine monophosphate
CEP	Certificate of Suitability of the European Pharmacopoeia
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
CNS	central nervous system
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
CSF	cerebrospinal fluid
CYP	cytochrome P450
DDI	drug-drug interaction
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DPP-4	dipeptidyl peptidase-4
DRF	dose range finding
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ETC	electron transport chain
EU	European Union
FDA	US Food and Drug Administration
GD	gestation day
GI	Gastrointestinal
GLP	good laboratory practice
GLP-1	glucagon like peptide – 1
GLP-1R	glucagon like peptide – 1 receptor
HDPE	High Density Polyethylene
hERG	human ether-a-go-go related gene
HMWP	high molecular weight protein
i.v.	Intravenous
IC50	inhibitory concentration (at which 50% inhibition is observed)

ICH	International Conference on Harmonisation
IPC	In-process control
IR	Infrared
IU	International Units
LC-MS/MS	liquid chromatography tandem-mass spectrometry
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOCI	luminescent oxygen channelling immunoassay
LOD	Limit of Detection
LOQ	Limit of Quantification
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
MATE	multidrug and toxin extrusion (1 or 2k)
MEB	Medicines Evaluation Board
MPR	multidrug resistance-associated protein (2)
MRHD	maximum recommended human dose
MS	Mass Spectrometry
MTD	maximum tolerated dose
NAD	nicotinamide adenine dinucleotide (oxidised form)
NADH	nicotinamide adenine dinucleotide (reduced form)
ND	Not detected
NEP	neutral endopeptidase (neprilysin)
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP1B	organic anion transporting polypeptide
OCT	organic cation transporter
OECD	Organisation for Economic Co-operation and Development
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	pharmacokinetic
PP	Polypropylene
PPND	pre- and postnatal development
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
QTc	corrected Q-T interval in the electrocardiogram
QWBA	quantitative whole body autoradiography
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time

RSD	Relative standard deviation
s.c.	Subcutaneous
SNAC	salcaprozate sodium (USAN name)
SPC	Summary of Product Characteristics
TCA	tricarboxylic acid cycle
TGA	Thermo-Gravimetric Analysis
US	United State of America
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 2025-09-12, Novo Nordisk A/S submitted an extension of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (tablet), associated with four new strengths (1.5 mg, 4 mg, 9mg and 25 mg) and a new route of administration (oral use).

1.2. Legal basis and dossier content

The legal basis for this application refers to:

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

1.3. Scientific advice and protocol assistance

The Applicant received Scientific Advice on the development of semaglutide for weight management from the CHMP on 25/03/2021 (EMA/SA/0000051734). The Scientific Advice pertained to the following non-clinical and clinical aspects:

- Non-clinical strategy
- Clinical pharmacology plans – additional data generation requirements to complement available evidence from prior MA
- Evidence generation planned to demonstrate clinical efficacy and safety – complementing available evidence from PIONEER PLUS (NN9924-4635) and STEP1-4 (NN9536) studies with one additional pivotal safety and efficacy study
- Plans for pivotal safety and efficacy study: overall trial design, endpoints, population, sample size, safety data collection, statistical analysis plan, handling of missing data, estimands

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0347/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0347/2023 was not yet completed as some measures were deferred.

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal product Imcivree.

1.6. Steps taken for the assessment of the product

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

Rapporteur:	Patrick Vrijlandt
Co-Rapporteur:	Thalia Marie Estrup Blicher

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur:	Mari Thorn

The application was received by the EMA on	12 September 2025
The procedure started on	02 October 2025
The CHMP Rapporteur's first Assessment Report was received on	19 December 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	n/a
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	n/a
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 January 2026
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	29 January 2026
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 February 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 March 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2026
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	23 April 2026
The MAH submitted the responses to the CHMP List of Outstanding Issues on	28 April 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 May 2026
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 Wegovy on	21 May 2026
The CHMP adopted a report on similarity of Wegovy with Imcivree on (see Appendix on similarity)	21 May 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4. of this report.

1.7.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.5. of this report.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Wegovy (semaglutide) is not similar to Imcivree (setmelanotide) within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.7.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of tablets for oral use (1.5 mg, 4 mg, 9 mg and 25 mg) of Wegovy is favourable in the following indication(s):

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- *≥ 30 kg/m^2 (obesity), or*
- *≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.*

For trial results with respect to populations studied, see section 5.1.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Wegovy, subject to the conditions described in the following sections.

1.7.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.7.5. Other conditions and requirements of the marketing authorisation

1.7.5.1. 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.

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

1.7.6.1. Risk management plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

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

Not applicable.

2. Introduction

Therapeutic Context

Obesity

The worldwide prevalence of obesity has reached epidemic proportions and continues to increase at an alarming rate, affecting both adults and children, and populations in both developed and developing countries. Obesity is defined as abnormal or excessive fat accumulation that may impair health. BMI is the most convenient population-level measure of overweight and obesity currently available, while other anthropometric measures, including body composition and waist circumference can further substantiate the diagnosis and added risk associated with obesity. According to the WHO classification system, overweight in adults is defined as a BMI of ≥25 kg/m^2 and obesity is classified as a BMI of ≥30 kg/m^2.

Obesity is associated with several health-related complications. Most concerning, obesity increases the risk of developing cardiovascular disease and certain types of cancers, which are some of the leading causes of early death in these patients. In addition, obesity is a well-established risk factor for other serious conditions, including T2D, dyslipidaemia, hypertension, osteoarthritis, obstructive sleep apnoea, asthma/COPD, urinary incontinence, liver disease (MAFLD or MASH), and PCOS. Obesity is also characterised by functional limitations and psychological symptoms that reduce quality of life.

The risk of obesity-related complications and comorbidities increases with increasing BMI, and a weight loss of 5−10% has shown significant health benefits by improving obesity related comorbidities including slowing the progression to T2D, and improving physical functioning and quality of life. Studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in people with obesity, with or without T2D.

Current therapies

Lifestyle intervention in the form of diet and exercise is first line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss with diet and exercise alone. During weight loss, the restricted food and energy intake is counteracted by adaptive biological responses to weight loss. Changes in a range of hormones are associated with a drop in energy expenditure and increase in appetite observed after a weight loss. Some of these changes result in altered physiology that promotes weight regain.

Surgical treatments offer an effective alternative for some people with severe obesity, but bariatric surgery carries a risk in connection with the procedure and involves potential complications. Pharmacotherapy serves as a valuable adjunct to lifestyle intervention.

Since overweight and obesity often develop into a life-long problem, the availability of a wide range of therapeutic options with different modes of action is important. Before the availability of GLP-1 RAs, only a limited number of pharmacological options were approved for weight management; all showing modest weight loss, generally only in the range of around 5% and with side effects.

The worldwide approved injectable medicinal products for weight management contain GLP-1 RAs that include liraglutide (3 mg s.c. once daily, Saxenda), semaglutide (2.4 mg s.c. once weekly, Wegovy), and tirzepatide (5 mg, 10 mg, or 15 mg s.c. once weekly, Zepbound). These have shown clinically meaningful reductions in body weight with an acceptable safety and tolerability profile.

Oral anti-obesity therapies expand the scope for personalised weight management strategies. Currently available options—such as orlistat, naltrexone/bupropion, and phentermine/topiramate, have different mechanisms of action and demonstrate variable efficacy. However, their modest weight loss

outcomes and associated safety concerns may limit their clinical utility. In contrast, oral semaglutide 25 mg provides a pharmacological alternative. Its oral route of administration may enhance patient acceptance and adherence, thereby supporting its benefit-risk profile in the management of obesity.

2.1. Aspects of development

The efficacy and safety evaluation in this document is primarily based on results from the pivotal phase 3 confirmatory study OASIS 4 (NN9932 4954).

The data from the semaglutide s.c. 2.4 mg in STEP development programme (NN9536, Wegovy, STEP 1−4) will be used as supportive evidence for efficacy (data from STEP 1) and supportive evidence for safety data (all STEP 1−4 studies). The evaluations will also be supported by results from the phase 3 study, PIONEER PLUS (NN9924-4635), evaluating once-daily oral semaglutide of 14 mg, 25 mg, and 50 mg in participants with T2D and a BMI of at least 25 kg/m^2.The PIONEER and STEP studies have been assessed previously, and data have been added to the SmPC of Rybelsus and subcutaneous Wegovy.

2.2. Description of the product

Semaglutide is a GLP-1 analogue, classified as a GLP-1 RA, with 94% homology to human GLP-1. GLP-1 is an incretin hormone with multiple physiological actions, including stimulation of insulin secretion and inhibition of glucagon secretion in a glucose-dependent manner. The blood glucose-lowering effect of GLP-1 can provide glycaemic control. GLP-1 is a naturally occurring regulator of appetite and induces feelings of satiety and fullness and reduces the feeling of hunger via GLP-1 receptors in the brain. The effect is reduced energy intake that results in weight loss.

Semaglutide has shown therapeutic effect in chronic weight management, including weight loss and weight maintenance, due to its combined effects on body weight and glucose metabolism, mediated through specific activation of the GLP-1 receptor. Studies with semaglutide have shown reduced energy intake during an ad libitum meal, improved control of eating, less food cravings (for dairy and savoury foods), less desire for sweet food and less preference for high fat food compared to placebo.6 GLP-1 receptors are also expressed in the pancreas, heart, blood vessels, and kidneys and can thus mediate glucose lowering, cardiovascular and microvascular effects.

For oral administration, semaglutide has been co-formulated with SNAC in a tablet. SNAC transiently increases the transcellular permeability of the gastric epithelium to semaglutide and increases pH locally around the tablet, facilitating the semaglutide molecule absorption, which mainly occurs in the stomach after oral administration.

2.3. Inspection issues

2.3.1. GMP inspection(s)

No inspection required.

2.3.2. GLP inspection(s)

No inspection required.

2.3.3. GCP inspection(s)

No inspection required.

3. Quality aspects

Introduction

The purpose of this line extension is to introduce a tablet formulation for Wegovy, in addition to the approved solutions for injection.

The finished product (FP, also known as drug product) is presented as tablets containing 1.5 mg, 4 mg, 9 mg or 25 mg semaglutide as active substance.

Other ingredients are: salcaprozate sodium and magnesium stearate.

The product is available in Alu/Alu blister cards. Pack sizes of 10, 30 and 90 tablets in blisters.

The Wegovy tablet formulation dossier includes a full Module 3 quality documentation. As this is a new application, all the data has been assessed accordingly.

The applicant confirmed that the active substance AS and FP used for Wegovy tablets 1.5 mg, 4 mg, 9 mg and 25 mg are the same as those used for Rybelsus tablets (EMEA/H/C/004953).

3.1. Active substance

3.1.1. General information

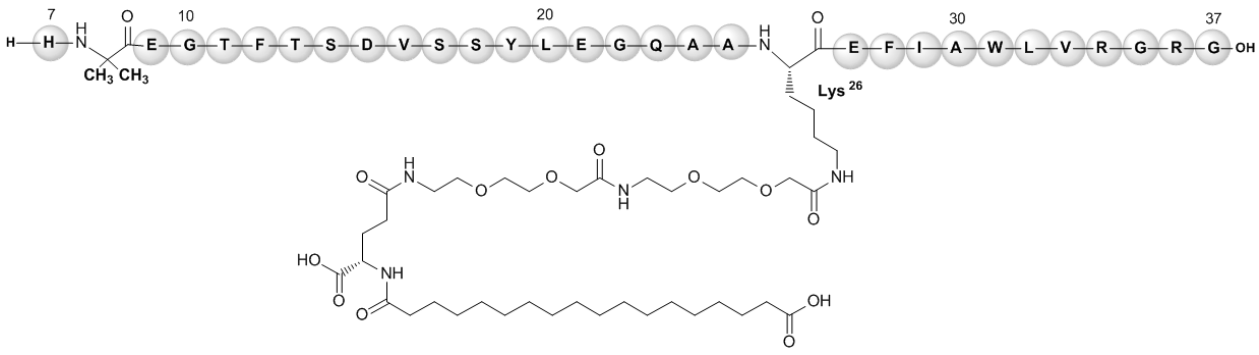
Semaglutide (INN) is a recombinant human glucagon-like peptide-1 (GLP-1) analog which corresponds to amino acids 7 – 37 of human GLP-1, and Ala at position 2 and Lys at position 28 are substituted by 2-amino-2-methylpropanoic acid and Arg, respectively, and Lys residue at position 20 is attached to 1,18-octadecanedioic acid via a linker which consists of a Glu and two 8-amino-3,6-dioxaoctanoic acids. Semaglutide is a modified peptide consisting of 31 amino acid residues.

Compared to human GLP-1, semaglutide has a prolonged half-life, and, by binding to albumin, a reduced renal clearance. Further, the amino acid substitution on position 8 from Ala to Aib stabilizes semaglutide against degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme.

The structural formula of semaglutide is given in Figure 1.

Semaglutide is produced using recombinant DNA technology in *Saccharomyces cerevisiae* followed by chemical modifications.

Figure 1: Structural formula of semaglutide



Semaglutide for oral administration is identical in structure to semaglutide for subcutaneous administration in the currently approved Wegovy presentations. The AS manufacturing process for semaglutide for oral administration is based on the same yeast strain and the production process is optimised to accommodate the need for larger capacity and formulation for an oral product. The applicant claimed "known active substance" status for this marketing authorisation application.

3.1.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The sites Novo Nordisk A/S Hallas Allé 1, Kalundborg DK and Novo Nordisk Pharmaceutical Industries LP, Clayton USA are responsible for production and quality control of the AS including the last step of the purification process. This last step (spray drying) is also performed at Hovione FarmaCiencia S.A., Loures, PortugalAll further Novo Nordisk sites involved in cell bank manufacture and storage and quality control activities are described. The sites involved in the manufacture and quality control of the active substance, and operate in accordance with EU GMP.

In addition to the AS itself, three other intermediates are isolated and storage conditions and shelf life are defined. The 3.2.S.2 Process description documents together with the information provided 3.2.S.2 documents on Critical In-process Controls and Non-Critical Operational Parameters provide a sufficiently detailed manufacturing process description.

Container closure system

The semaglutide AS, which is a solid AS, is stored in a double bag container closure system suitable for commercial scale. The container closure system used for storage of semaglutide AS is a double bag system. . The actual size of the AS containers, thickness of the foils and typical amounts of contents has been provided.

In view of the nature of the AS (dry powder) and the storage temperature the risk of interactions between AS and container is considered very low. Results of stability studies (discussed below) do not indicate any increase in moisture in the stored samples or any other trend.

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 (master cell bank (MCB), working cell bank (WCB)) is explained and characterisation of MCB, WCB as well as end-of-production cells and late extended cultures is reported. Stability results are available and show that the WCB and MCB are stable during storage.

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

The choice of the starting materials for the synthesis of acylating agent, DC18-γGlu-ADOADO-ONSu, resp. the dipeptide, Fmoc-His-Aib-OH, TFA 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 AS. The specifications include a test for identification and additional tests (assay, purity, impurities, function test) as appropriate for raw materials with a medium risk rating. The information provided is acceptable.

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 (HCP and hydrophilic/hydrophobic 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, however the robustness of this process step has been supported by analytical data.

The storage and shelf life of the intermediates and the re-test period of the acylating agent are adequately described. The acylation agent has a claimed shelf-life , and sufficient data to support this shelf-life has been provided. Sufficient information is provided.

Process validation and/or evaluation

The initial process performance qualification (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 AS specification tests were all consistent for the fermentation, recovery, and purification batches and all acceptance criteria were fulfilled.

The PV studies confirmed that the manufacturing process produces semaglutide AS consistently and reproducibly on a commercial scale and at the intended production lines. Furthermore, extensive manufacturing experience is gained from other Novo Nordisk recombinant yeast products, including semaglutide for oral use, as well as the experience gained from laboratory experiments. This knowledge has formed the basis for the PPQ design. 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. Overall, the process related impurities (DNA, HCP, solvents, salts, acids and acylating and ligating reagents) are reduced to a low level or below quantitation limits.

Process justification studies for all steps of the AS manufacturing process have been included. These process justification studies provide sufficient evaluation of the operational parameters and in-process controls. An adequate description of the HCP assay, including validation results, is provided. The conclusion on the criticality of processes and controls can be endorsed.

Control strategy for active substance

The basis of the control strategy is the critical quality attributes (CQAs) and the elements having an impact on the CQAs. The control strategy ensures process performance and product quality and includes the following elements:

- Critical Quality Attributes (CQAs) – the properties and characteristics of the AS that should be controlled to ensure product quality
- Process design – selection and design of the process steps to ensure the desired product quality and process performance
- Process justification – based on extensive knowledge from process characterisation, establishment of the final manufacturing process by process justification (PJ) studies and risk assessment (FMECA)
- In-process controls – critical and non-critical in-process controls
- Specification testing of AS

- Materials, selection and control; raw materials, API starting materials and acylating agent intermediate
- Facility and equipment – design and procedure control
- Continued process verification and maintenance of the validated state

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

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

Manufacturing process development

For semaglutide AS for oral formulation, the development of the manufacturing process has taken place in the period 2008 to 2018. The manufacturing process has been changed from a synthetic process (referred to as Process I) to a process based on expressing the semaglutide precursor in a recombinant strain of the yeast *S. cerevisiae* followed by chemical modifications (hereafter referred to as Process II). In order to increase productivity a new *S. cerevisiae* yeast strain expressing the extended semaglutide precursor was implemented together with an enzymatic cleavage step to handle the extension, leading to Process III. Process III material has been used for the clinical phase 3 of Wegovy tablet. The applicant has sufficiently explained the development of the AS.

Characterisation

Structural characterisation and elucidation of the physico-chemical properties of semaglutide have been performed using AS 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. Structural properties have been investigated by peptide mapping/LC-MS, Mass spectrometry (MS/MS), higher order structure by CD, and specific bioactivity. Furthermore, the physicochemical characteristics appearance, solubility, isoelectric point, UV absorbance and water absorption have been determined. The hydrophobic properties evaluated by RP-HPLC and the hydrodynamic volume evaluated by size exclusion high-performance liquid chromatography (SE-HPLC) were as expected.

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 company has provided strong evidence that indeed the contents established with RP-HPLC strongly correlate with measured biologically activity result in AS and FP and 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 physical-chemical 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.

Product-related impurities in semaglutide are classified into three groups: Hydrophilic impurities, Hydrophobic impurities 1, and Hydrophobic impurities 2. A specification limit is set for each group.

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

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An evaluation on the presence of any downstream-derived impurities in the AS, including the potential presence of column leachables, is provided.

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

3.1.3. Specification

The active substance specification for semaglutide, presented in Table 2 includes tests for: appearance (visual inspection), identity (peptide mapping and RP-HPLC), content (RP-HPLC), hydrophilic impurities (RP-HPLC), hydrophobic impurities 1 (RP-HPLC), hydrophobic impurities 2 (RP-HPLC), sum of impurities (RP-HPLC), high molecular weight proteins (SE-HPLC), specific bioactivity (cell based assay), water content (Karl Fischer - Ph. Eur.), particle size distribution (laser light diffraction - Ph. Eur.), total aerobic microbial count ((TAMC) microbial enumeration test - Ph. Eur.), total yeast and mould count ((TYMC) microbial enumeration test, Ph. Eur.) and escherichia coli (Ph. Eur.).

Analytical procedures and reference standards

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 AS control.

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 same methods are applied for semaglutide AS for oral use as those approved for semaglutide AS for subcutaneous use, and the secondary reference material (SRM) (see below) is formulated according to subcutaneous formulation and not oral semaglutide FP.

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

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

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 (s.c.) 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 SRM.

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 AS is shown to be comparable.

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

Batch analysis

Batch analysis data (n=43 commercial scale) of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life, in the proposed container.

Real time, real condition stability data on 15 commercial scale batches of active substance from the commercial manufacturing process stored in the intended container under accelerated conditions, according to the ICH guidelines, were provided.

The parameters tested are the same as for release. All available data are within the acceptance criteria and show no change over time.

Results of a primary stability study and stability studies of PPQ and process validation batches are presented. Batches are stored at proposed storage condition and at accelerated conditions. The stability studies cover the test parameters from the AS specification shown in Table 2.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

The finished product subject to this line extension is presented as a tablet containing respectively 1.5 mg, 4 mg and 9 mg and 25 mg of the active substance semaglutide. All three strengths are white to light yellow, round tablets (6.5 mm in diameter; 1.5 mg, 4 mg and 9 mg) or oval shaped tablets (6.8 mm x 12 mm; 25 mg). The different tablet strengths are sufficiently visually distinguishable by their debossing. The tablets are debossed with a unique identification "1.5", "4", "9" or "25". On one side and "novo" on the other side of the tablet.

No overages are used in the manufacture of the tablets.

Although full information is provided for 1.5, 4, 9, 25 and 50 mg FPs, the present application does not include the 50 mg as proposed presentation for marketing authorisation. The data on the 50 mg FP are considered as supportive for the 1.5, 4, 9 and, in particular, for 25 mg FPs and therefore included in this report.

The pharmaceutical development is a based on Rybelsus tablets and their development. The initial formulation of the Rybelsus tablets (3 mg, 7 mg, and 14 mg strengths, approved in 2020), was modified by removing the excipients microcrystalline cellulose and povidone K 90, which resulted in improved bioavailability, of the AS from the FP (for 1.5, 4, 9, 25 and 50 mg strengths).

The two formulations were shown to be bioequivalent. The Wegovy tablet formulation in the proposed strengths (1.5, 4, 9 and 25 mg) is identical formulations to their respective Rybelsus strength.

The optimisation of the ratio between semaglutide and the excipients salcaprozate sodium and magnesium stearate, performed during the development of Rybelsus, has been described. The intended commercial formulation is the same as that used during clinical studies.

Magnesium stearate is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. Salcaprozate sodium complies with in house specifications which are the same as those approved for Rybelsus; its quality considered acceptable. The list of excipients is included in section 6.1 of the SmPC.

Compatibility of the excipients (salcaprozate sodium and magnesium stearate) with the AS has been evaluated, and compatibility was confirmed.

The applicant has applied Quality by Design principles in the development of the FP and its manufacturing process. A quality target product profile (QTTP) has been established

Critical quality attributes (CQAs) have been derived from the QTTP.

The establishment of critical quality attributes and critical process parameters was done through a risk assessment, which has been sufficiently described 5.

The primary packaging is Alu/Alu blisters composed of a forming foil and a lid foil. The container closure system is the same as for previously approved Rybelsus tablets.

Input materials

The suitability of the pre-existing quality requirements for semaglutide, salcaprozate sodium, and magnesium stearate were evaluated at the time of the development of the manufacturing process for the 1.5, 4, 9 and 25 mg tablets, and found to be acceptable.

3.2.2. Manufacture of the product and process controls

The bulk FPs for all product presentations are manufactured and quality controlled (chemical/physical testing) by Novo Nordisk. Novo Nordisk A/S in Bagsværd (Denmark) is responsible for the batch release of all presentations.

All sites involved in manufacture and QC testing of the FP operate in accordance with EU GMP.

The manufacturing process consists of the following steps: blending , granulation, tableting, packaging (primary and secondary).

The ranges for critical process parameters and limits for process controls have been adequately justified.

Packaging

The semaglutide tablets are filled into the primary packaging, which is in turn placed into secondary packaging.

Reprocessing is not foreseen.

Critical process parameters (CPPs) and their operating ranges for the manufacturing of semaglutide 1.5 mg, 4 mg, 9 mg and 25 mg tablets have been justified. All operating ranges for the critical process parameters can be classified as PARs. The suitability of the ranges has been validated through DoE studies using commercial scale equipment.

Quality by Design (QbD)

The applicant has defined a design space, containing different operating ranges for the critical process parameters of the critical process steps.

The design space for blending, granulation and tableting processes, using the same equipment as for commercial manufacturing, results in acceptable product quality. The ranges have been justified based on Design of Experiment (DOE) studies.

The applicant has provided clarification on the DOE conducted. Full factorial designs containing centre points have been used where multiple CPPs are to be varied simultaneously, which is considered an acceptable approach.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Process validation / verification

Process validation

The manufacturing process is a non-standard process.

Traditional process validation has been conducted on three consecutive batches of each strength (six validation batches in total) at the proposed commercial scale range, which was found acceptable. Moreover, the applicant commits to perform continued process verification, supplemental to traditional process verification, for which high level description was provided. This was found acceptable.

Overall, it has been demonstrated that the manufacturing process is capable of producing the FP of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Container closure system

The primary packaging is Alu/Alu blisters composed of a forming foil and a lid foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.2.3. Product specification

The finished product specification include the following tests: appearance (visual inspection), identity semaglutide (RP-UHPLC), assay semaglutide (RP-UHPLC), assay salcaprozate sodium (RP-UHPLC), uniformity of dosage units (RP-UHPLC), impurities (including hydrophilic, hydrophobic 1, hydrophobic 2 and sum of impurities, all by RP-UHPLC), high molecular weight proteins (SE-HPLC), water content (Karl Fisher - Ph. Eur.), dissolution (RP-UHPLC), microbial tests (TAMC, TYMC, *E. Coli*) (Ph. Eur.).

The specification tests and limits were set in line the approved specification of the authorised Rybelsus strengths, the relevant ICH and Ph. Eur. requirements, and are acceptable.

The potential presence of elemental impurities in the FP has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. All batches of semaglutide FP tested for elemental impurities and used in the elemental impurities risk assessment were manufactured by the manufacturing process proposed for commercial manufacture. Batch analysis data on 3 batches of 9 mg tablets and 3 batches of 50 mg tablets produced at Durham US site (highest strength representative of highest possible exposure) using a validated ICP-MS method was provided,

demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the FP specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the FP has been performed with respect to the changes made compared to the already approved strengths and considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in semaglutide 1.5 mg, 4 mg, 9 mg and 25 mg tablets. Therefore, no additional control measures are deemed necessary.

Analytical procedures and reference standards

The analytical methods used have generally been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. . An improved analytical procedure for SE-UHPLC has been introduced. Method validation and comparability with the previous method is demonstrated.

Batch analysis

Batch analysis data for the 1.5 mg, 4 mg, 9 mg, 25 mg and 50 mg strengths were provided. Data from more than 3 commercial scale batches per strength were provided. The results are within the specifications and confirm consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.2.4. Stability of the product

A shelf-life of 36 months is proposed for the FP, along with the storage conditions: 'store in the original package in order to protect from moisture and light'.

Stability data from 3 primary stability batches (commercial scale) per each strength stored for up to 24 months under long-term (25 °C/ 60%RH) and intermediate (30 °C/ 75%RH) conditions and for 6 months under accelerated conditions (40 °C/ 75%RH). Stability data for 13 supporting stability batches at commercial scale was provided up to 36 months under long-term and intermediate conditions. The batches used in the stability studies are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The specification parameters tested are the same as for release. All tested parameters are within the proposed acceptance criteria. Batches showed an increase in impurities under all storage conditions, however, they remained well within the proposed acceptance criteria.

As part of the forced degradation studies, the FP was found to degrade under elevated heat and humidity (75 °C/ 75% RH).

Photostability studies performed in line with ICH Q1B. The applicant applied a bracketing approach where the lowest and highest strength have been investigated. Discoloration of the tablets occurred under light exposure. This justifies the proposal to store the product protected from light.

Based on available stability data, the shelf-life of 3 years stored in the original blister package in order to protect from light and moisture and without any special temperature storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

3.2.5. Post-approval change management protocols

The Applicant has submitted several Post Approval Change Management Protocols (PACMPs). However, many were obsolete as their changes were already implemented in the submission, with the exception of two PACMPs. These two protocols describe 1) the use of an alternative for the purification facilities; and 2) the addition of a manufacturing site for the 25 mg and 50 mg FPs. The PACMPs provided with the submission are in accordance with the EMA *Questions and answers on post approval change management protocols* (EMA/CHMP/CVMP/QWP/586330/2010) and considered approvable.

3.2.6. Adventitious agents

No animal or human derived material is used in the manufacture of Rybelsus and the 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 Master cell bank, Working cell bank, 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 AS and FP which are tested for Total aerobic microbial count, Total yeast and mould count and *Escherichia coli*.

The adventitious agents safety evaluation is considered satisfactory.

3.3. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. A design space has been proposed for the manufacture of the finished product, which contains different operating ranges for the critical process parameters of the critical process steps. This is acceptable.

3.3.1. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The line extension is considered approvable from a quality point of view.

3.4. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

Introduction

All pivotal non-clinical safety studies (safety pharmacology and toxicology studies) were conducted in conformance with the principles of Good Laboratory Practice (GLP)

Oral semaglutide

To evaluate semaglutide for oral administration to humans, a nonclinical safety programme has been conducted in line with the recommendations in the concurrent draft FDA guideline 'Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route'. This is justified given that the FDA guidance is in line with principles of the ICH M3 guideline and EMA expectations for non-clinical development. The programme includes repeat dose toxicity studies in rat and monkey with oral semaglutide, the same two species as used in the s.c. programme. Based on the final version of the guideline, issued in 2015, the completed repeat dose toxicity testing programme in rat (26-week) and monkey (17-week) was still found appropriate to support the marketing authorisation for oral semaglutide. These studies have been carried out using SNAC as an absorption enhancer, except for the 17-week monkey study where semaglutide was formulated together with another absorption enhancer (sodium caprate). The nonclinical programme also comprises assessment of local tolerability (gastrointestinal tract) after oral dosing of semaglutide. Further, the pharmacokinetic of semaglutide dosed orally in a formulation with SNAC has been investigated after single and/or repeat dose administration in rats, dogs and cynomolgus monkeys. Finally, single dose in *vivo* metabolism studies after oral dosing of semaglutide in a formulation with SNAC to rats and cynomolgus monkeys have been completed.

SNAC

The nonclinical safety evaluation of SNAC is made as a stand-alone programme. SNAC is considered a novel excipient, and the conducted nonclinical programme is in accordance with the US FDA's 'Guidance for Industry - Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients', which is overall in line with the recommendations given in the ICH M3 guideline to support chronic administration to humans. The nonclinical programme includes a mode-of-action programme for SNAC comprising *in vitro* and *in vivo* studies assessing its function as absorption enhancer, a safety pharmacology programme, pharmacokinetic evaluations as well as distribution, metabolism, and excretion studies. Further, a toxicology programme including, single and repeat dose toxicity studies of up to 52 weeks duration, genotoxicity, carcinogenicity, reproductive- and developmental toxicity, local GI tract tolerability, and immunotoxicity studies have been conducted. Finally, studies to elucidate the underlying mechanism for the observed SNAC-related mortality in animals have been carried out. *In vivo* nonclinical safety studies were conducted in mice, rats and monkeys. Rats and rabbits were used in the developmental toxicity studies.

Analytical methods

Semaglutide

The methods developed for analysis of semaglutide in plasma with LOCI or LC-MS/MS (rat and monkey) are the same as have been used for s.c. semaglutide in the original MAA of Wegovy.

SNAC

Several using 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 in the SNAC assays generally resulted in values outside acceptance criteria (studies 209037, 215297, 215303, 215298), indicating that degradation has taken place at the end of this period. Nevertheless, the applicant claimed stability of SNAC metabolites in plasma during storage over these periods of time. Overall, there seems to be a decline in metabolite concentrations, indicating that the concentrations in the mechanistic non-clinical studies may be underestimated (at most 20-30%). Since the exposure margins of SNAC metabolites in the non-clinical toxicity studies were already sufficient, it is agreed that an underestimation of these metabolite concentrations do not impact the nonclinical evaluation of SNAC.

4.1. Pharmacology

4.1.1. Pharmacodynamics

4.1.1.1. Primary pharmacodynamics

Oral semaglutide

The non-clinical pharmacology evaluation of subcutaneously administered semaglutide was made during the original MAA of Wegovy. Since the pharmacological response of semaglutide is considered independent of the route of administration, no additional pharmacology studies with oral administration of semaglutide are needed.

SNAC

The pharmacology of the new excipient SNAC was fully evaluated. 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 (GI) 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 non-clinical 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

The primary pharmacodynamics of SNAC was investigated *in vitro* and *in vivo*. Mechanistically, absorption enhancers can promote transport of drug molecules across the gastro-intestinal (GI) epithelium via modification of tight junctions (i.e. paracellular) and/or cell membrane perturbation (i.e. transcellular). In vitro experiments using human gastric carcinoma epithelial NCI-N87 monolayers 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 incorporates in lipid membranes and, upon increasing concentrations, increases the fluidity and permeability of the membrane.

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. Using the gastric epithelial NCI-N87 monolayers, the effects of SNAC on

the increased apparent permeability (P_{app}) of semaglutide were similarly found to be transient. This effect of SNAC was size-dependent, with a diminishing effect on the transport of molecules above 4 kDa.

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 is consistent with a shift in the oligomeric state of semaglutide towards its monomeric form.

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.

4.1.1.2. Secondary pharmacodynamics

Oral semaglutide

The secondary pharmacology evaluation of subcutaneously administered semaglutide was made during the original MAA of Wegovy. Since the secondary pharmacology is considered independent of the route of administration, no additional studies with oral administration of semaglutide are needed.

SNAC

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.

4.1.1.3. Safety pharmacology

Oral semaglutide

Regarding safety pharmacology, cardiovascular endpoints were included in the repeat-dose toxicity studies with oral semaglutide. ECG, heart rate and blood pressure were 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

The safety pharmacology studies were designed to investigate the effect of SNAC on vital organ function (central nervous system, respiratory system and cardiovascular system). All studies were performed according to the ICH S7A and S7B guidelines and according to good laboratory practise (GLP) except for one supportive *in vitro* cardiac ion channel study (130130.DCC).

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. 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. Mortality, observed at 1000 mg/kg in one animal, was considered SNAC related without a clear indication of a respiratory system component.

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 ECG 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.

4.1.1.4. Pharmacodynamic drug interactions

Semaglutide

Non-clinical 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.

SNAC

Non-clinical pharmacodynamic drug interaction studies have not been conducted with SNAC, which is agreed upon. 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).

4.1.2. Pharmacokinetics

The non-clinical PK evaluation of subcutaneously administered semaglutide was performed during the original MAA of Wegovy. In this line extension of Wegovy, the PK of oral semaglutide has been evaluated in the species used in the repeat-dose toxicity studies; Sprague Dawley rat and cynomolgus monkey. Furthermore, the metabolism and excretion of semaglutide have been evaluated *in vivo* in the same species. The studies used an absorption enhancer (SNAC) to increase oral bioavailability of semaglutide. The PK of the new excipient SNAC was fully evaluated.

4.1.2.1. Absorption

Oral semaglutide

PK parameters following a single oral dose of semaglutide (co-administered with SNAC) was 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 1.25% in humans (Table 11). However, since no test groups were included in which semaglutide is administered orally without co-administration of SNAC, no quantitative data on how SNAC affects the PK of semaglutide are 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).

Table 1 Interspecies comparison of dose-normalised (1 mg/kg/day) mean pharmacokinetic parameters.

Species	oral administration (steady-state)						i.v. administration (single dose)		
	C_{max} (nmol/L)	t_{max} (h)	$AUC_{(0-24h)}$ (h×nmol/L)	C_{avg} (nmol/L)	$t_{½}$ (h)	F (%)	CL (L/h/kg)	V_z (L/kg)	$t_{½}$ (h)
Rat	8.6	2	39	1.6	6.5	-	-	-	-
Monkey	12.0	4	220	9.1	60	0.16	0.0022	0.18	54
Human	-	-	7629	318	-	1.25	0.0004	0.08	137

Data from studies: Rat: 208300, 208301 (both studies group 3 and 4), 210196. Monkey: 208302, 209157, 209115 (i.v. data incl. F). Human oral PK based on population PK analysis in OASIS 4 (Phase 3 Modelling Report (M 5.3.3.5)), NN9535-3687 (i.v. data). C_{max}, AUC_{0-24h}, C_{avg} and F and mean values, $t_{½}$ and t_{max} are median values.

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.

It is noted that in the rat studies (2831 and 210196, but not 2830), the exposure of SNAC seems to be higher when administered without semaglutide (Cmax up to 39 times higher, AUC up to 11 times higher).

The pharmacokinetics following repeated dosing of oral semaglutide (co-administered with SNAC) was investigated in rats and monkeys. In the studies in rat (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 monkey (Tmax 5-120 min). Although results from bile-cannulated rats indicate SNAC is almost completely absorbed from the GI tract, bioavailability was low: 5-16% in rats and ~16% in monkey, probably due to 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.

4.1.2.2. Distribution

Oral semaglutide

No additional distribution studies were performed using the oral route, which is agreed upon.

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 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.

Equilibrium dialysis showed that the plasma protein binding of SNAC is moderate to high in mice, rat, rabbit and monkey (free fraction 12-35%, 5.5-35%, 6.3-32% and 2.8-25%, respectively) and concentration independent up to concentrations of 30.000 ng/ml, but decreases thereafter, suggesting saturation of binding. 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.

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.

4.1.2.3. Metabolism

Oral semaglutide

Plasma metabolite profiles of orally administered semaglutide (co-administered with SNAC) were investigated in male rats and monkeys. The Applicant states that the metabolic profile between rats and monkeys following oral and s.c. administration were similar and further that the human metabolic profile after s.c. administration was similar to the profiles of rats and monkeys. Upon request, a table was provided with quantitative descriptions of metabolite profiles including all metabolite peaks observed in animals, irrespective of route of administration. The data indicate that 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. Increase in 3H 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.

4.1.2.4. Excretion

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 conjugate (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 a single oral administration of ^{14}C-SNAC to female rats at approximately 10 days post-partum, milk concentrations were elevated in comparison to maternal blood, resulting in mean maximum milk to maternal blood ratio of 21.

4.1.2.5. 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.

4.2. Toxicology

4.2.1. Single-dose toxicity

Oral semaglutide

General toxicity studies with s.c. semaglutide are described in the original MAA of Wegovy. No single dose toxicity studies were performed with oral semaglutide.

SNAC

In single dose studies with SNAC, mortalities occurred after high doses of 2000 mg/kg in the mouse, and 1500 mg/kg in the rat.

4.2.2. Repeat-dose toxicity

Oral semaglutide

General toxicity studies with s.c. semaglutide are described in the original MAA of Wegovy. 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.

In monkeys reduced thymus size and/or low thymus weights were observed in all studies. This may represent a stress-related finding caused by the dosing procedure, as well as the reduced food consumption and body weight. Changes in urinary parameters were observed throughout the studies combined with changes in kidney weights in some cases. The Applicant argues that the urinary effects correlates with known inhibitory effects of GLP-1 receptor agonists on the sodium reabsorption from the proximal tubules. In studies where SNAC was tested alone, effects on renal function was also observed, possibly due to excretion of sodium from the SNAC molecule. No synergistic effects are expected when SNAC and semaglutide are administered in combination, as no additive or synergistic effects are seen on the affected urinary parameters in the studies investigating semaglutide and SNAC in combination. This is furthermore supported by no relevant or adverse findings in long-term carcinogenicity studies and clinical trials.

In rats given oral semaglutide, mortalities were observed after 2 and 26 weeks. Some were related to reduced body weight and food consumption due to semaglutide but the majority were related to SNAC at a concentration of 900 mg/kg, which is consistent with the findings in the studies conducted with SNAC only.

The lowest NOAEL for oral semaglutide was found in the 26 week rat study and was 20 mg/kg/day (0.9-fold exposure margin) based on the premature deaths of two animals (60 mg/kg/day) which were probably due to exaggerated pharmacodynamic effects on food consumption and body weight.

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.

Mortality occurred in both rats and monkeys, though at doses much higher than clinically relevant doses. This is further discussed in section 5.2.8 (See "Mechanistic studies").

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), slight increases in ALP in SD rats at 250 mg/kg/day (7-fold human exposure) and increased 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 for humans.

The stomach was a target organ in the rat but not in monkeys, and these findings are further discussed in section "Local tolerance".

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 had an exposure margin of at least 11-fold. It is unlikely that the effect on RBC 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.

4.2.3. Genotoxicity

Oral semaglutide

The genotoxicity evaluation of semaglutide has been described in the original MAA of Wegovy. Semaglutide is not genotoxic *in vitro* or *in vivo*.

SNAC

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

4.2.4. Carcinogenicity

Oral semaglutide

Since the carcinogenic potential of semaglutide is considered independent of the route of administration, no additional studies with oral administration of semaglutide are needed.

SNAC

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 female mice, respectively, and up to 32- and 22-fold clinical exposure in male and female rats. Although the exposures were rather low in the mouse study, it is considered sufficient due to the presence of the negative rat study.

Mortality was increased in the mid and high dose female rats (survival of 26 and 25% as compared to 39% control animals). There was no treatment-related cause of death identified however.

4.2.5. Developmental and reproductive toxicity

Oral semaglutide

The evaluation of the reproductive and developmental toxicity of semaglutide has been described in the original MAA of Wegovy. The systemic effects of oral semaglutide, including reproductive and developmental effects, are considered independent of administration route and therefore adequately qualified in the s.c. programme. In the rat and monkey, no principle metabolites specific to the oral administration route were observed, and the metabolite profiles were similar when oral administration was compared to s.c. administration. Based on this, no reproductive and developmental toxicity

studies with oral administration of semaglutide have been conducted. Also, no studies on juvenile animals have been performed with oral semaglutide.

SNAC

There were no effects on male or female fertility in rats when treated with SNAC up to 1000 mg/kg/day, with or without heparin.

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. 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. Additional dose groups of 500, 750 and 1000 were included that were dosed together with 5000 U/kg/day of heparin. In these groups, no effects on pup survival was 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.

The need for juvenile toxicity studies on SNAC has been discussed as part of the paediatric investigation plan (PIP) with EMA/PDCO as well as the FDA. Both agencies have waivered studies in juvenile animals with SNAC for the present application, which is agreed.

4.2.6. Toxicokinetics and exposure margins

Oral semaglutide

The pharmacokinetics of oral semaglutide were studied primarily in rats and monkeys. Following oral administration, semaglutide (combined with SNAC) Tmax is 2 hr in rats and 4 hr in monkeys, and slightly faster in humans (1.5hr). The oral bioavailability of semaglutide co-administered with SNAC is low: 0.16% in monkeys, compared to 1% in humans. Plasma protein binding (mainly albumin) is >99% in al species. Following single or multiple oral dosing in rats and monkeys exposure increased with the dose. In humans, a dose proportional increase was observed in the therapeutic range. No or minor plasma AUC accumulation was observed following repeated oral dosing of semaglutide. Semaglutide is mainly distributed to blood and highly perfused tissues. Terminal half-life was estimated to be 4.3-8.1 hr in the rat and 44-51hr in the monkey. In humans the half-life was approximately 1 week. No clear gender differences were observed in the pharmacokinetics of semaglutide.

Exposure margins were recalculated based on human AUC exposure at the MRHD of 25 mg oral semaglutide/day. Human exposure seems more than dose-proportionally increased with the 25 mg/day dose as compared to the 14 mg/day dose, resulting in reduced safety margins for the non-clinical toxicity studies. The 26-week s.c. rat study has a sufficiently large safety margin (9.8x at the NOAEL), however, 26-week oral rat study and all repeat-dose monkey studies have low safety margins (<2.2x at the NOAEL). The DART studies in rat as well as monkey have low safety margins (<1x at the NOAEL), except for the juvenile s.c. rat study (8.1x at the NOAEL). Nevertheless, serum concentrations increased approximately dose proportionally in the non-clinical toxicity studies with (oral) semaglutide and adequate exposure was achieved in the animals to evaluate safety. The non-clinical toxicity profile of semaglutide is well-understood and oral administration of semaglutide was well-tolerated as most findings were expected and related to the PD of semaglutide. Therefore, the interpretation of the toxicity studies remains unchanged. No changes to sections 4.6 or 5.3 of the SmPC are needed.

SNAC

The pharmacokinetics of SNAC were studied primarily in mice, rats and monkeys. The absorption of SNAC following oral administration was rapid in rodents and monkeys (Tmax 2-5 and 5-120 minutes), which is similar to humans (0.5-1hr). Plasma protein binding is moderate to high in all species. Plasma clearance in animals is high (11.2-1.4 and 0.4-0.8 L/hr/kg in monkeys and rats, respectively), compared to 197-293 L/h in humans. Following multiple oral dosing AUC increased more than dose proportional at high doses, but dose proportional at doses up to 3600 mg. In humans AUC increased in a proportional manner at doses between 1.2 and 3.6 g, whereas Cmax appeared to increase less than dose proportional (lower doses not investigated). No accumulation was observed in mouse, rat, monkey and humans. The oral bioavailability of SNAC in humans was not investigated, but was 5-16 and 15%, respectively in rats and monkeys. No relevant gender differences were observed. SNAC is extensively distributed to tissues. 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. SNAC is predominantly excreted via urine as the glucuronide conjugates, with a plasma terminal half-life of 2.5h in monkeys, compared to 1.5hr in humans.

The applicant used the Cmax and AUC from trial 4267 for the calculations of the exposure margins. However, the highest AUC and Cmax at the clinical dose of 300 mg SNAC were found in trial 3991 and 4140, respectively (AUC 1636 h*ng/ml; Cmax 1683 ng/ml). Adequate exposure was maintained to evaluate safety in the toxicologic studies. Doses used resulted in exposures in most studies far in excess of human exposure to SNAC. Exposure multiples calculated for the NOAELs (based on the AUC or Cmax from trials 3991 and 4140) were up to 25 or 49 for the repeated dose toxicity studies. Developmental and reproductive toxicity pivotal studies in rats and rabbits were conducted with one dose level of 1000 mg/kg/day of SNAC only, which is higher than the NOAELs in the repeated dose toxicity studies.

4.2.7. Local tolerance

Oral semaglutide

No dedicated local tolerance studies with oral semaglutide were performed, which is agreed.

SNAC

A local tolerance study with SNAC 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. The relevance of this study is somewhat limited given the single dosing, 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 SNAC 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 target organ in humans. No further studies are required.

4.2.8. Other toxicity studies

Immunotoxicity

Oral semaglutide

No dedicated immunotoxicity studies with oral semaglutide were performed, which is agreed.

SNAC

An immunotoxicity study with SNAC 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 at clinically relevant exposures.

Impurities

Oral semaglutide

No dedicated impurity studies were performed. Impurity ratios have been calculated based on a human drug dose of 25 mg oral semaglutide/day. At the NOAEL from the 26-week oral toxicity study in rats (210196), all specified impurity groups were tested in amounts at least 5-fold higher than the highest amounts for a daily 25 mg oral semaglutide dose (MRHD) in a 70 kg subject. The impurities can therefore be considered toxicologically qualified at the proposed specification levels.

SNAC

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%. A QSAR-based evaluation of the impurities according to ICH M7 has been performed, which shows that the impurities are classified as Class 5 (non-mutagenic) impurities.

Mechanistic studies

A series of mechanistic studies with SNAC, both in in-vitro and in-vivo, were conducted to investigate the mortalities that occurred in all species. 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 the mitochondrial complex I in the electron transport chain, 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 a Cmax free of around 350 µM 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 were significantly less potent than SNAC, with a factor 10 or more.

Phototoxicity

Upon request, the Applicant provided an evaluation of the phototox potential of SNAC, in line with ICH S10. The compound has an UV absorption peak at a wavelength of 301 nm and a molar extinction coefficient (MEC) of 4122 $L \times mol^{-1} \times cm^{-1}$ and was shown to be photostable. 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 point towards SNAC being of limited phototoxic potential. No further information is required.

4.2.9. Ecotoxicity/environmental risk assessment

The active substance is a non-natural peptide and is excreted by humans in amounts <10% of the dose. Therefore, no phase II risk assessment or definitive PBT assessment is warranted.

Semaglutide is not expected to pose a risk to the environment.

4.3. Overall discussion and conclusions on non-clinical aspects

4.3.1. Discussion

No procedure-specific non-clinical documentation was provided in support of the current application of oral semaglutide intended for weight management. The non-clinical documentation was based on the non-clinical package submitted in the Rybelsus procedure (EMEA/H/C/004953), which was considered also to support the indication of weight management. This approach was discussed and accepted in a scientific advice (EMA/SA/0000051734) given that no unexpected clinical safety issues occurred during the planned clinical trial. In the advice, the Applicant was recommended to perform careful clinical monitoring bearing in mind the lack of a safety margin from non-clinical data. No indication of unexpected clinical safety issues with oral semaglutide in clinical trials in support of the weight management indication has been provided by the Applicant, and the non-clinical documentation provided was identical to the one submitted for Rybelsus supplemented with a procedure-specific Addendum. In this, exposure margins to NOAELs in toxicity studies were re-calculated to account for the increased clinical exposure to semaglutide and impurities following administration of 25 mg tablets

in the OASIS 4 clinical trial compared to 14 mg which was the highest strength of oral semaglutide at the time of initial approval of Rybelsus (PIONEER trials).

The non-clinical profile of the active excipient SNAC in animals was characterised for Rybelsus and the Applicant did not provide any further information in support of the current application. 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.

Pharmacology

No new PD studies describing primary or secondary pharmacology of semaglutide delivered orally have been performed. This is due to the expectation that the effect of semaglutide is dependent on systemic exposure. The primary PD studies with SNAC demonstrated increased lipid membrane permeability and fluidity. It was furthermore shown 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.

In secondary PD studies, SNAC and its principal metabolites did not show clinically relevant off-target binding or activity.

Regarding safety pharmacology, no dedicated studies were performed with oral semaglutide. The Applicant justified that the safety margins derived from the safety pharmacology studies described in the EPAR for subcutaneous semaglutide (Wegovy 2.4 mg/week) are also considered applicable to oral semaglutide (Rybelsus 25 mg/day), and consequently to the applied-for product.

Cardiovascular endpoints were included in the repeat-dose toxicity studies with oral semaglutide in monkeys. No toxicologically relevant treatment-related effects were found providing a safety margin at least 1.7-fold to the estimated clinical exposure at the MRHD. Standard safety pharmacology studies performed with SNAC did not reveal any changes to CNS, respiratory or cardiovascular parameters at clinically relevant exposure levels.

Pharmacokinetics

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 week 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 metabolite profile in animals is similar after oral and subcutaneous (s.c.) administration and is considered representative of the human metabolite profile.

Toxicology

The toxicology programme for oral semaglutide consisted of only repeat-dose studies of up to 6 months in rat or 17 weeks in monkey. There are no additional toxicities identified for the oral administration of semaglutide as compared to the s.c. route, as most effects observed are secondary effects related to the pharmacological effect of reduced body weight gain and food consumption. All

other studies were performed with s.c. administration and have been submitted previously in support of s.c. semaglutide.

Exposure margins were recalculated based on human AUC exposure at the MRHD of 25 mg oral semaglutide/day, resulting in reduced safety margins for the non-clinical toxicity studies. Since the approval of Rybelsus 14 mg tablets, oral semaglutide has been approved in strengths of up to 50 mg resulting in similar (low) exposure margins. Also, subcutaneous semaglutide has been approved for weight management with similar clinical exposure levels. Hence, though the Applicant did not comment on the potential clinical relevance of the lowered safety margins, they are, considering the generally mild repeat-dose toxicity profile in animal studies, the adequate descriptions of carcinogenicity and reproductive findings in the SmPC, and the extensive clinical experience with semaglutide, considered acceptable without further justification.

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.

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 and is therefore similar for Rybelsus and the applied for product. The safety margins with respect to findings have been calculated based on MHRD of both semaglutide and SNAC. Therefore it is important that the SmPC clearly states that only one tablet should be taken a day. As it appears that for oral semaglutide the clinical exposure level is higher in the weight management patient population compared to the type 2 diabetes population (at least following higher doses i.e. 25 and 50 mg), it is noted that the clinical exposure level of SNAC in the weight management patient population was not presented or used in the SNAC exposure margin calculations. Nevertheless, it is expected that the exposure to SNAC is unchanged.

Target organs of SNAC in both rat and monkey were the urinary system and liver. Given the lack of histopathological findings and/or high safety margins, the relevance for humans is likely low.

No SNAC data regarding the observed mortalities in all nonclinical species tested are included in the SmPC, which, based on the high safety margins for the observations of sudden death, can be accepted. Excretion of SNAC in rodent milk has been included in SmPC section 4.6.

4.3.2. Conclusions

The non-clinical dossier largely supports chronic oral dosing up to 25 mg semaglutide for the line extension of Wegovy. The pharmacology, pharmacokinetics and toxicology of oral semaglutide and SNAC have been adequately described.

5. Clinical aspects

Introduction

5.1.1. GCP aspects

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

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

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.3.3.).

5.1.2. Tabular overview of clinical trials

Table 2: Tabular overview of main clinical studies

Study / programme ID	Participants randomised / exposed	Brief description of study design
Completed studies		
Pivotal confirmatory study:		
Oral semaglutide 25 mg weight management		
OASIS 4 phase 3 (Study 4954)	N=307/306 (204 exposed to oral semaglutide 25 mg)	64-week, randomised, double-blind, placebo-controlled study investigating efficacy and safety of oral semaglutide 25 mg versus placebo once daily as an adjunct to a reduced-calorie diet and increased physical activity in adults with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) with ≥1 comorbidity, without T2D
Primary supportive studies:		
Semaglutide s.c. 2.4 mg weight management		
Phase 3 pool of the STEP programme (STEP 1−4)	N=4585 / 4581 (2650 exposed to semaglutide s.c. 2.4 mg)	68-week, randomised, double-blinded, placebo-controlled studies investigating semaglutide s.c. 2.4 mg versus placebo once-weekly as an adjunct to lifestyle intervention. 1. STEP 1: Study NN9536-4373 (weight management) 2. STEP 2: Study NN9536-4374 (weight management in T2D) 3. STEP 3: Study NN9536-4375 (weight management with intensive behavioural therapy) 4. STEP 4: Study NN9536-4376 (sustained weight management)
Oral semaglutide 25 mg and 50 mg weight management in T2D		
PIONEER PLUS phase 3 (Study NN9924-4635)	N=1606 / 1602 (534 exposed to oral semaglutide 25 mg; 534 exposed to oral semaglutide 50 mg)	68-week, randomised, double-blind study to confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on HbA_{1c} reduction and body weight reduction in adults with T2D and BMI ≥25 kg/m^2
Other supportive studies:		
Oral semaglutide 50 mg weight management		

OASIS 1 phase 3 (Study 4737)	N=667 / 667 (334 exposed to oral semaglutide 50 mg)	68-week, randomised, double-blind, placebo-controlled study comparing the efficacy, safety and tolerability of oral semaglutide 50 mg versus placebo once daily, as an adjunct to reduced-calorie diet and increased physical activity, in adults with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) with ≥1 comorbidity, without T2D
OASIS 2 phase 3 (Study 4738)	N=201 / 200 (134 exposed to oral semaglutide 50 mg)	68-week, randomised, double-blind, placebo-controlled study investigating efficacy and safety of oral semaglutide 50 mg versus placebo once daily as an adjunct to a reduced-calorie diet and increased physical activity in East Asian adults with obesity (BMI ≥35 kg/m^2) with ≥1 comorbidity or overweight (BMI ≥27 kg/m^2 to <35 kg/m^2) with ≥2 comorbidities, with/without T2D
OASIS 3 phase 3 (Study 4861)	N = 199/199 (100 exposed to oral semaglutide 50 mg)	44-week, randomised, double-blind, placebo-controlled study comparing the efficacy, safety and tolerability of oral semaglutide 50 mg versus placebo once daily, as an adjunct to reduced-calorie diet and increased physical activity, in Chinese adults with overweight (BMI ≥ 24.0 kg/m^2) or obesity (BMI ≥ 28.0 kg/m^2), at least one weight related comorbidity, both with and without T2D.

Abbreviations: BMI = body mass index; FPFV = first participant first visit; HbA_{1c} = glycosylated haemoglobin; LPLV = last participant last visit; N = number of participants; s.c. = subcutaneous; T2D = type 2 diabetes.

5.2. Clinical pharmacology

5.2.1. Methods

A large number of validation reports relating to immunogenicity, bioanalysis of semaglutide, SNAC and/or metabolites thereof in plasma and urine were re-submitted in support of this variation. Moreover, some were concerning co-administered drugs in DDI studies. Overall, the bioanalytical program appears to have been developing over time as especially the PK method for semaglutide was validated after change of platform from LOCI to LC-MS/SM, when changing from without to with stable labelled internal standard and again when applying the protein precipitation sample preparation method to robotics.

Six studies are considered important for this application. All six studies conducted a successful incurred sample reproducibility test for semaglutide and the pass rate of batches in general was high. All study samples were analysed within established long-term stability at -20°C. Hence, the bioanalytical program for semaglutide appear in good control.

The bioanalytical assay with LLOQ of 0.729 nmol/l, used for the new studies (4873, OASIS 1, OASIS 4, OASIS 2, PIONEER PLUS, NN9924-4633), as well as the bioanalytical assay used for other Rybelsus NN9924 studies referred to in this application was sufficiently validated. The LC-MS/MS bioanalytical methods for the analysis of semaglutide and urine are considered appropriately validated and suitable for the analysis of semaglutide.

The reports supporting the bioanalytical validation program for SNAC were resubmitted in this variation application. The bioanalytical methods for plasma SNAC have been used extensively in the Rybelsus development program. Therefore, it is anticipated that validations still hold, hence validation reports will not be assessed here.

A multi-tiered approach has been used to assess the anti-semaglutide and neutralizing antibodies. In general, the assay validation was adequately performed. The employed four-tiered strategy including a screening, confirmatory, cross reactivity to endogenous glucagon-like peptide-1 (GLP-1) and neutralization assay is in agreement with the draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev. 1). Validation of immunogenicity methods was performed before 2019. Hence validation reports are anticipated to have been assessed in previous submissions. Anti-semaglutide antibody development and hypersensitivity markers was investigated in subject with suspected hypersensitivity reactions in OASIS 2 (50 mg), but not in the phase 3 study OASIS 4 (25 mg). Here samples were collected but not analysed as no hypersensitivity reactions occurred. Hence, classical ADA screening in all subjects was not performed. This is acceptable, since semaglutide is well-characterised and has already been administered to a vast number of patients.

In conclusion, the bioanalytical program is vast but well-established. All bioanalytical methods and reports assessed showed acceptable performance of batch pass rate and ISR.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Absorption, distribution, metabolism and excretion (ADME) of semaglutide is being discussed, for a large part based on PK data already provided in support of the Rybelsus dossier. Sparse PK data obtained from the OASIS Phase 3 studies in support of this Wegovy application were included in popPK models aimed at investigating covariates affecting semaglutide PK upon poral dosing. Semaglutide PK is considered to be characterised to a sufficient extent, with only some remarks made to the SmPC section 5.2.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

Evaluation and qualification of models. Four popPK models were used in support of the current application:

- Population pharmacokinetic analysis of high dose oral semaglutide in healthy subject clinical pharmacology trials NN9924-4564 and NN9924-4633 (popPK Study NN9924-4564+4633)
- NN9924-3794, NN9924-3957, N9924-4079, NN9924-4082, NN9924-4141, NN9924-4154, NN9924-4279 and NN9924-4267 Population pharmacokinetic analysis of semaglutide dosed orally – a meta-analysis of data from healthy subject clinical pharmacology trials (popPK clinical pharmacology).
- PopPK and exposure-response meta-analysis of NN9932: OASIS 1, OASIS 2 and OASIS 4. Study Phase: 3 (popPK Phase 3)
- Pharmacometric modelling report Oral Semaglutide. Exposure-response analysis and simulations for MACE NN9535-3744 (SUSTAIN 6), NN9924-4221 (PIONEER 6), EX9536-4388 (SELECT), EX9924-4473 (SOUL), and NN9535-4321 (FLOW) (popPK CV)

Both the clinical pharmacology PopPK models based on healthy subject PK data and the Phase 3 PopPK models based on T2D and obese patient PK data are provided as supportive evidence in this application. All PopPK models applied a two-compartment structure with first-order absorption and elimination, consistent with previous models for oral semaglutide (Rybelsus). Several parameters were fixed based on previous semaglutide popPK analysis of clinical pharmacology trials.

All models provide a reasonable description of the observed PK. The adequate fit is confirmed by the provided GOF plots and VPC plots.

Sparse PK data obtained from the OASIS Phase 3 studies in support of this Wegovy application were included in popPK models aimed at investigating covariates affecting semaglutide PK upon poral dosing. Only the new Rybelsus strengths 1.5 mg, 4 mg and 9 mg (sema D) are now available in EU. No clinical data with the reduced tablet strengths and formulation D were included in the modelling population. Based on bioequivalence study, the oral exposure data in the model population in the Phase 3 OASIS modelling report seem translatable to exposure in the intended-to-market tablets when considering formulation effects.

Covariate effects included in the final model were body weight, sex, age, Asian race, ethnicity, renal function, T2D, upper GI disease using a full model approach. All covariate effects were added on bioavailability along with separate effects for each trial included. Effect of body weight was also included on disposition parameters. Several other adjustment factors were included to account for differences in bioavailability dependent of formulation type and dose, a factor for "higher initial exposure" and a Box-Cox transformation parameter for description of BSV. It is clear that bioavailability depends on route of administration and that oral sema also depends on formulation and health status.

Body weight had most profound effect on exposure. The effect of body weight was fixed from a previous model. A Forest plot investigated the effect across 70-141 kg. The reference subject was a female with body weight of 100 kg which is above the mean body weight of the data pool (93.2 kg) that also includes data from male subjects. The body weight range in the data pool was 40.2-211.8 kg.

Sensitivity analyses were conducted excluding BLQ values, outliers (CWRES>6), including only OASIS data or applying a linear model on log(Cavg). Structural parameters seemed fixed. No great differences were observed on the remaining parameter estimates compared to the final model.

Exposure levels for oral and s.c. semaglutide were calculated as Cavg for each participant using the individual parameter estimates obtained using the five final population PK models developed for OASIS, PIONEER and PIONEER PLUS; for SUSTAIN; for STEP 1 +2; for STEP 6 and for SUSTAIN FORTE.

5.2.2.3. Absorption

Semaglutide absorption was investigated for all strengths applied for. Absorption was low, however increased when taken with a limited amount of water. Information was provided om absorption of the initially registered semaglutide 3, 7 and 14 mg. These strengths were shown to be bioequivalent with the new 1.5, 4 and 9 mg. The bioavailability of oral semaglutide in the intended-to-be marketed oral semaglutide tablets 1.5, 4, 9, and 25 mg is approximately 1% to 2%. Bioavailability of oral semaglutide is markedly reduced in the presence of food. Exposure of semaglutide was approximately 40% lower after a single dose when administered with 240 mL of water compared to 120 mL. Further, exposure of semaglutide increased as the time between dosing and the first meal after dosing increased. Semaglutide $AUC_{0\text{-}24h}$ and C_{max} was 34% and 32% lower, respectively, when oral semaglutide was co-administered with 5 oral placebo tablets compared to when administered alone. If

a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

5.2.2.4. Distribution

The semaglutide Vd is 8.9l, and plasma protein binding was >99%. The Vd indicates that semaglutide is primarily distributed in the blood corresponding to the high binding to plasma proteins.

5.2.2.5. Metabolism and elimination

Clearance of semaglutide was 0.041 L/h, the geometric mean $t_{1/2}$ of oral semaglutide was found to be approximately 1 week.

Being a polypeptide conjugated with a fatty acid chain, metabolism of semaglutide occurs via both proteolytic cleavage of the peptide backbone and sequential β-oxidation of the fatty acid sidechain. As generally known for polypeptides, metabolism does not appear to be confined to specific organs.

5.2.2.6. Dose proportionality and time dependency

Dose-proportionality. The dose-proportionality assessment showed that concentration levels were close to dose proportional across the 3–50 mg dose range (for 3, 7, and 14 mg in the initially approved formulation for Rybelsus and for 25 and 50 mg in Formulation C), with exposure of semaglutide increasing in a dose-proportional manner within formulations range (i.e. between 7 mg and 14 mg, and between 25 mg and 50 mg), with higher bioavailability for the 25 and 50 mg strengths. Since comparable bioavailability has been demonstrated for initially and currently available strengths (1.5 vs 3, 4 vs 7, 9 vs 14 mg), this implies that dose-proportionality is also the case for the new semaglutide D 1.5, 4, 9 mg formulation. Further, for the dose range 1.5, 4, 9, 25 and 50 mg, systemic exposure of semaglutide increases in a dose-proportional manner over the complete range of strengths.

Time dependency. Semaglutide concentrations in the OASIS studies were reasonably stable over time, with slightly higher exposure levels seen during the first 6 months than at the end of the studies.

Intra- and inter-individual variability. The variability of the exposure of single and multiple doses up to 10 mg of oral semaglutide was high, with an estimated total variability of AUC of oral semaglutide of 166% after a single dose and 68% at steady state. The within-participant variability in exposure was 137% after a single dose and 33% at steady state.

5.2.2.7. Pharmacokinetics in the target population

With respect to PK in the target population, body weight was the most influential covariate, resulting in lower semaglutide exposure with higher body weight (e.g. in case of obese or overweight patients) and vice versa. Exposure levels of 25 mg and 50 mg doses were higher in the healthy subject clinical pharmacology Study NN9924-4633 than in the phase 3 study (PIONEER PLUS).

5.2.2.8. Special populations

Impaired renal function. Based on the presented results of Study NN4429-4079 and the Phase 3 popPK analysis it appears that renal impairment does not affect the pharmacokinetics of semaglutide in a consistent manner. These results are in line with previous findings of studies with the semaglutide s.c. formulation. The total number of subjects in the renal impairment Study NN4429-4079 is relatively low

when taking into account the high (90%) variability of the absorption. Therefore, the study is underpowered to detect small differences between populations. Further, semaglutide was dosed only 10 days and semaglutide steady state is usually observed after 4 to 5 weeks, therefore the maximum impact of renal impairment is difficult to assess from this study. Therefore, the results of the Phase 3 popPK study and previous studies with the semaglutide s.c. formulation are relevant to assess the impact of renal impairment. In this Phase 3 popPK model, lack of a relevant effect of renal impairment was shown in patients with overweight or obesity.

Impaired hepatic function. In the hepatic impairment study NN9924-4082 it was shown that the total exposure ($AUC_{0\text{-}24h}$) of semaglutide and its C_{max} is comparable between subjects with mild, moderate, and severe hepatic impairment (classified as Child-Pugh A,B, or C) and healthy matched controls. These results are in line with previously collected data on the semaglutide 0.5 mg s.c. formulation observed in Study NN9935-3651 for the Ozempic MAA. Overall it is concluded that hepatic impairment does not have any impact on the exposure of oral semaglutide.

Upper gastrointestinal disease. In the upper gastrointestinal disease study 9924-4267 it was shown that the total exposure ($AUC_{0\text{-}24h}$) of semaglutide and its C_{max} is comparable in patients with or without gastrointestinal disease. This was confirmed in the Phase 3 popPK analysis, where 90% CI of the mean C_{avg} in participants with upper GI disease relative to participants without upper GI disease were within the (0.80-1.25)-limits. Overall it is concluded that upper gastrointestinal disease did not have any impact on the exposure of oral semaglutide.

Lactation. In the upper gastrointestinal disease Study 9924-4267 no semaglutide was detected in breast milk after a 10-days dosing regimen up to semaglutide 7 mg (old oral formulation, comparable to 4 mg of current formulation). Since SNAC and SNAC metabolites E494, E506 and E1247 were detected in breastmilk of lactating women, a potential risk to a breastfed infant cannot be excluded.

Gender and weight. Gender and weight were found not to impact oral semaglutide exposure to a relevant extend.

Ethnic factors. Race (White, Black or African American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) were found not to impact oral semaglutide exposure to a relevant extend.

Elderly. Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3 trials including patients 18–92 years of age.

Overall, no new covariates were identified with inclusion of Phase 3 Studies 4737 (OASIS 1), 4738 (OASIS 2) and 4954 (OASIS 4) as compared to the already existing Phase 3a PopPK model, as provided in support of the Rybelsus MAA. As concluded for the already registered 1.5, 4, 9, 25 and 50 mg semaglutide strengths (Rybelsus), no dose adjustment is considered necessary in relation to age, gender, body weight, race, ethnicity, upper gastrointestinal disease, renal function or hepatic function.

5.2.2.9. Pharmacokinetic interaction studies

5.2.2.9.1. PK drug-drug interactions

In vitro. Semaglutide is not expected to cause any clinically relevant drug-drug-interactions based on in vitro studies evaluating the major drug-metabolizing CYP enzymes in liver, CYP3A4/5 in intestine, and drug transporters.

In vivo. Based on the results of the *in vivo* DDI trials, no dose adjustment for drugs taken with oral semaglutide is required. These trials also demonstrated that co-formulation with SNAC (i.e.

formulation in the same tablet) is required for the absorption-enhancing effect of SNAC to take place. The minor effects on the exposures of some victim drugs observed when dosed with oral semaglutide may instead be attributed to delayed gastric emptying associated with treatment with semaglutide. Further, no dose adjustment of oral semaglutide is required for subjects being treated with drugs that increase gastric pH, demonstrating the absorption enhancing capabilities of SNAC on semaglutide are preserved under conditions with increased gastric pH. Results from Study NN9924-4873 support no further delay in gastric emptying with oral semaglutide 50 mg as compared oral semaglutide at lower doses.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Semaglutide is a GLP-1 analogue, classified as a GLP-1 RA, with 94% homology to human GLP- 1. GLP-1 is an incretin hormone with multiple physiological actions, including stimulation of insulin secretion and inhibition of glucagon secretion in a glucose-dependent manner. The blood glucose-lowering effect of GLP-1 can provide glycaemic control. GLP-1 is a naturally occurring regulator of appetite and induces feelings of satiety and fullness and reduces the feeling of hunger via GLP-1 receptors in the brain. The effect is reduced energy intake that results in weight loss.

Semaglutide has shown unique therapeutic effect in chronic weight management, including weight loss and weight maintenance, due to its combined effects on body weight and glucose metabolism, mediated through specific activation of the GLP-1 receptor. Studies with semaglutide have shown reduced energy intake during an *ad libitum* meal, improved control of eating, less food cravings (for dairy and savoury foods), less desire for sweet food and less preference for high fat food compared to placebo.[6] GLP-1 receptors are also expressed in the pancreas, heart, blood vessels, and kidneys and can thus mediate glucose lowering, cardiovascular and microvascular effects.

For oral administration, semaglutide has been co-formulated with SNAC in a tablet. SNAC transiently increases the transcellular permeability of the gastric epithelium to semaglutide and increases pH locally around the tablet, facilitating the semaglutide molecule absorption, which mainly occurs in the stomach after oral administration. The systemic effects of semaglutide are independent of the route of administration.

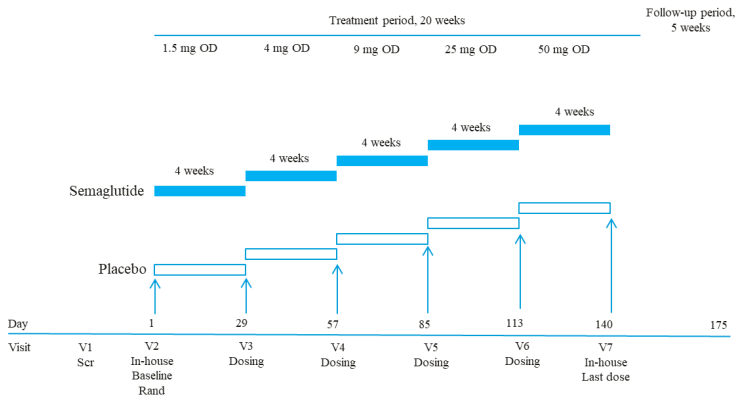
5.2.3.2. Primary and secondary pharmacology

Study NN9932-4873

Study design

This was an interventional, single-centre, randomised, parallel group, multiple-dose, double-blind, placebo-controlled study investigating pharmacodynamic effects and pharmacokinetics at steady state of oral semaglutide 50 mg once-daily in participants with obesity. The study consisted of up to 4 weeks of screening period, a 20-week intervention period and 5 week follow up period. A total of 61 healthy adults living with obesity were randomised to once daily oral semaglutide or placebo (1.5 mg, 4 mg, 9 mg, 25 mg and 50 mg for 4 weeks on each dose, respectively; Figure 4).

Figure 2: NN9932-4873 – Study design



Treatment period is 20 weeks from first to last dose. Follow-up period is 5 weeks after last dose. Randomisation 1:1. OD: once-daily

Adult male and female patients were included with a BMI between 30.0 and 45.0 kg/m^2. Patients with presence or history of any clinically relevant respiratory, metabolic, renal, hepatic, gastrointestinal, or endocrinological conditions were excluded.

The primary endpoint was the relative change from baseline to day 140 in energy intake during ad libitum lunch (%). The supportive secondary endpoints were, among others, change in body weight (%).

Results

Baseline characteristics were listed in Table 13.

Table 3: Demographics and baseline characteristics - summary - safety analysis set

	oral sema 50 mg N (%)	placebo N (%)	Total N (%)
Number of participants	30	31	61
Sex			
Female	12 (40.0)	9 (29.0)	21 (34.4)
Male	18 (60.0)	22 (71.0)	40 (65.6)
Ethnicity			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	30 (100.0)	31 (100.0)	61 (100.0)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	1 (3.2)	1 (1.6)
Native Hawaiian or Other Pacific Islander	0	0	0
White	30 (100.0)	30 (96.8)	60 (98.4)
Other	0	0	0

N: Number of participants, %: Percentage of participants

The relative change in energy intake during ad libitum lunch at day 140 was 39.2%-point lower with oral semaglutide 50 mg vs. placebo (-33.0% vs. 6.2%). The mean weight loss at day 141 was - 9.8% with oral semaglutide 50 mg and 1.5% with placebo. Oral semaglutide 50 mg reduced appetite, improved control of eating with less food cravings compared to placebo. No statistically significant effect on gastric emptying was observed with oral semaglutide 50 mg vs. placebo.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

N/A.

5.2.3.4. Genetic differences in PD response

N/A.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Relationship between plasma concentration and effect and safety. Exposure-response relationship for the change from baseline in body weight indicates increasing reductions in body weight with increasing exposure of both oral and s.c. semaglutide after 64-68 weeks of treatment in a range of studies.

Exposure-response relationships for the proportion of participants reporting nausea or vomiting indicate increasing gastrointestinal AEs with increasing exposure of semaglutide. The relationships appear to plateau with the exposure range associated with oral semaglutide 25 mg, indicating limited additional gastrointestinal AEs for participants with the highest exposure levels.

Exposure-response relationship for the proportion of patients reporting dysaesthesia in OASIS studies indicated that these AEs increased with increasing semaglutide exposure during the first 26 weeks of treatment, with increased reporting with the 25 mg dose.

Evaluation and qualification of PK/PD models. Exposure-response relationships were reasonably well described by the pre-specified models, and adequate for predictive purposes. It was assumed that all relevant confounding factors had been identified and taken into account as covariates in the E/R analyses. The E-R models were sufficiently evaluated by goodness-of-fit plots.

Due to differences in visit schedule across studies, the 6-month timepoint could not be conducted using the exact same time point. It is acceptable to assume that efficacy response was sufficiently stable from week 26 to week 30, so that differences in response at these timepoints could be compared across studies with oral and s.c. semaglutide.

5.2.5. Dose selection and therapeutic window

The recommended oral dose of Wegovy in the weight management indication (25 mg) is the same as one of the doses approved for Rybelsus in the T2D indication. Exposure obtained with oral Wegovy is comparable to that obtained with the semaglutide s.c. administration and semaglutide Rybelsus oral administration.

A comparison of the systemic exposure levels of s.c. semaglutide 2.4 mg in STEP 1 and STEP 2 with the systemic exposure levels in participants with T2D and a BMI ≥ 27 kg/m^2 included in PIONEER PLUS treated with 25 mg and 50 mg oral semaglutide is provided in Table 14, Table 15.

The majority of the participants in PIONEER PLUS, in both dose groups of oral semaglutide 25 mg and 50 mg, were within the STEP 2 exposure range (32–164 nmol/L), with 67% on 25 mg and 72% on 50 mg. Exposure above the STEP 2 range (>164 nmol/L) was observed in 2.3% of participants on oral semaglutide 25 mg; a higher proportion (17.8%) were on oral semaglutide 50 mg. Notably, a markedly higher proportion of subjects on 50 mg (65.6%) exceeded the typical STEP 2 exposure (>68 nmol/L) compared with 25 mg (27.9) (Table 15).

A higher proportion of participants on 25 mg (75.5%) than 50 mg (66.7%) obtained exposure levels within the exposure range in STEP 1 (27-147 nmol/L). Exposure above the STEP 1 range (>147 nmol/L) was observed in 2.6% of participants on oral semaglutide 25 mg compared to 25.1% on oral semaglutide 50 mg. Similar to the trend seen in STEP 2, a markedly higher proportion of subjects on 50 mg (60.1%) exceeded the typical STEP 1 exposure (>75 nmol/L) compared with 25 mg (23%) (Table 14).

Table 4 Exposure of oral semaglutide 25 and 50 mg (PIONEER PLUS – BMI ⩾ 27) in comparison to s.c. semaglutide 2.4 mg (STEP 1)

Exposure range	**PIONEER PLUS (25 mg) proportion of subjects (%)**	**PIONEER PLUS (50 mg) proportion of subjects (%)**
Within STEP 1 exposure range (27-147 nM)	75.5	66.7
Above the exposure levels (range) in STEP 1 (above 147 nM)	2.6	25.1
Below the exposure levels (range) in STEP 1 (below 27 nM)	21.9	8.3
Above the average STEP 1 exposure (above 75 nM)	23	60.1

Table 5 Exposure of oral semaglutide 25 and 50 mg (PIONEER PLUS – BMI ⩾ 27) in comparison to s.c. semaglutide 2.4 mg in T2D (STEP 2)

Exposure range	**PIONEER PLUS (25 mg) proportion of subjects (%)**	**PIONEER PLUS (50 mg) proportion of subjects (%)**
Within STEP 2 exposure range (32-164 nM)	67	72
Above the exposure levels (range) in STEP 2 (above 164 nM)	2.3	17.8
Below the exposure levels (range) in STEP 2 (below 32 nM)	30.6	10.2
Above the average STEP 2 exposure (above 68 nM)	27.9	65.6

The data demonstrate that, in the T2D population, there was generally comparable exposure overlap with 25 mg and 50 mg oral semaglutide in PIONEER PLUS compared to s.c. semaglutide 2.4 mg in STEP 2, while a greater overlap was observed for 25 mg when compared to STEP 1. The totality of evidence supports that oral semaglutide 25 mg provides clinically meaningful improvements in body weight and other cardiometabolic health parameters in individuals with T2D in line with the effects observed with s.c. semaglutide 2.4 mg.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The MAH is seeking approval of Wegovy oral tablets 1.5 mg, 4 mg, 9 mg and 25 mg. Tablets 1.5, 4 and 9 mg are formulation D (=100 mg SNAC) while the 25 mg tablet is formulation C (=300 mg SNAC). In an earlier submission, bioequivalence was established between semaglutide formulations: Rybelsus formulation (= similar to formulation C but includes also microcrystalline cellulose and povidone K) and formulation D on the 3 lower dose formulations: 14 mg vs 9 mg, 7 mg vs 4 mg and

3 mg vs 1.5 mg (Study 4799 Rybelsus II-38). For the lowere doses ≤ 14 mg Rybelsus formulation, bioavailability was increased and thus exposure increased by about 40% when switching to formulation D, therefore the doses were reduced accordingly to 1.5, 4 and 9 mg.

The majority of studies in the OASIS program performed in support of oral Wegovy for weight-loss were using the original semaglutide formulation with 3, 7 and 14 mg doses, except the PD study NN9932-4873 where the new formulation D doses 1.5, 4 and 9 mg doses were used.

Despite the fact that the pivotal studies in the OASIS program were performed with the original oral semaglutide 3, 7 and 14 mg formulation, it is the new lower 1.5, 4 and 9 mg doses in formulation D, which will be marketed. As these doses are already documented to be bioequivalent to the original formulation and marketed for Rybelsus, this is accepted. The marketed formulation for the final dose level of 25 mg will be the same as used in the pivotal clinical study OASIS 4.

ADME of semaglutide in the proposed oral Wegovy formulation was discussed, for a large part based on PK data already provided in support of the Rybelsus dossier.

Bioanalysis

A large number of validation reports relating to bioanalysis of semaglutide, SNAC and/or metabolites thereof in plasma and urine and immunogenicity were re-submitted in support of this variation. Moreover, some validation reports concerned co-administered drugs in DDI studies. Overall, the bioanalytical program appears to have been developed over time as especially the PK method for semaglutide was validated after change of platform from LOCI to LC-MS/SM, when changing from without to with stable labelled internal standard and again when applying the protein precipitation sample preparation method to robotics.

Six studies are considered important for this application. All six studies conducted a successful incurred sample reproducibility test for semaglutide and the pass rate of batches in general was high. All study samples were analysed within established long-term stability at -20°C. Hence, the bioanalytical program for semaglutide appear in good control.

The reports supporting the bioanalytical validation program for SNAC were resubmitted in this variation application. The bioanalytical methods for plasma SNAC have been used extensively in the Rybelsus development program. Therefore, it is anticipated that validations still hold, hence validation reports will not be assessed here.

Validation of immunogenicity methods was performed before 2019. Hence validation reports are anticipated to have been assessed in previous submissions. Anti-semaglutide antibody development and hypersensitivity markers was investigated in subject with suspected hypersensitivity reactions in OASIS 2 (50 mg), but not in the phase 3 study OASIS 4 (25 mg). Here samples were collected but not analysed as no hypersensitivity reactions occurred. Hence, classical ADA screening in all subjects was not performed. This is acceptable, since semaglutide is well-characterised and has already been administered to a vast number of patients.

In conclusion, the bioanalytical program is vast but well-established. All bioanalytical methods and reports assessed showed acceptable performance of batch pass rate and ISR.

Pharmacokinetic modelling

A prior 2-compartment popPK model based on oral PIONEER data in T2D was extended to describe the sparse OASIS trial data collected following treatment with 25 or 50 mg oral sema C. The pop PK population consisted of only sparse sampled data. Disposition parameters, ka and T2D factor and effects of body weight on disposition parameters were kept fixed from previous models. Disposition

parameters originated from a 1-compartment popPK model based on sparse data from the STEP programme. ka was fixed to 2.64 h-1 for the lower doses (Rybelsus formulation) and to 3.05 h-1 for the 25 and 50 mg data (formulation C).

The original Rybelsus formulation and the oral semaglutide C formulation, SNAC content 300 mg, were applied in the OASIS, PIONEER and PIONEER PLUS oral programmes contributing data to the current oral popPK model. No data from oral semaglutide 1.5 mg, 4 mg and 9 mg formulation D with 500 mg SNAC was included. This is accepted as bioequivalence was established to oral semaglutide 3 mg, 7 mg and 14 mg original Rybelsus formulation.

Covariate effects included in the final Pop PK model were body weight, sex, age, Asian race, ethnicity, renal function, T2D, upper GI disease using a full model approach.

Exposure levels for oral and s.c. semaglutide were calculated as Cavg for each participant using the individual parameter estimates obtained using the five final population PK models developed for OASIS, PIONEER and PIONEER PLUS; for SUSTAIN; for STEP 1 +2; for STEP 6 and for SUSTAIN FORTE.

A bridging strategy via virtual studies was used to predict the efficacy response for treatments not included in the trials. The validity of these simulations is difficult to assess and the outcome should be interpreted with caution.

The Applicant claims exposure levels observed in OASIS 1, 2, and 4 are overlapping with levels observed in thorough QTc study NN9535-3652 and concludes this support that no QTc prolongation is expected from treatment with oral semaglutide 25 mg in patients with obesity or overweight. This is not agreed. Based on Cavg, the healthy participants in the thorough QTc study (NN9535-3652) experienced exposure levels up to 100 nmol/L whereas obese patients receiving 25 mg oral sema experience exposures up to 500 nmol/L. This is 5-fold higher Cavg. In addition, the evaluation is based on Cavg and should in principle be based on Cmax values. Therefore Study 3652 is not considered acceptable for coverage of potential QTc prolongation following 25 mg oral semaglutide. However, there is a large amount of data supporting the preventing effect for MACE. In addition, 50 mg oral semaglutide was approved for T2D (Rybelsus), thus the issue will not be further pursued.

Absorption

Absorption was low, decreased when taken with food, and increased when taken with a limited amount of water. Further, exposure of semaglutide increased as the time between dosing and the first meal after dosing increased. In the posology section of the SmPC it is rightfully stated that Wegovy should be taken on an empty stomach after a recommended fasting period of at least 8 hours. Further, in the posology section of the SmPC it is stated that the tablet should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 ml). Finally, it is stated in the SmPC that patients should wait at least 30 minutes before eating, drinking or taking other oral medicinal products. This advice is in line with the advice for the Rybelsus formulation. Semaglutide $AUC_{0\text{-}24h}$ and C_{max} was 34% and 32% lower, respectively, when oral semaglutide was co-administered with 5 oral placebo tablets compared to when administered alone. Oral semaglutide should therefore be dosed alone, and if other oral medication is taken, it is to be taken at least 30 minutes after dosing with oral semaglutide. This is sufficiently indicated in the SmPC. If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day. This is sufficiently indicated in the SmPC.

The wording in section 5.2 of the SmPC on average concentration obtained with oral Wegovy is presented similar to Rybelsus and reads as follow: *Average predicted concentration was*

approximately 77 nmol/L with 90% of subjects treated with semaglutide 25 mg having an average concentration between 27 and 186 nmol/L.

Distribution

Information is provided in the SmPC on the semaglutide absolute Vd of 8.9l, and plasma protein binding of >99%. The Vd indicates that semaglutide is primarily distributed in the blood corresponding to the high binding to plasma proteins. The absolute Vd reported is slightly higher than for Rybelsus PO (8L) and lower than for Wegovy s.c (12.4 L).

Metabolism and elimination

Semaglutide is a low clearance drug, with clearance being 0.041 L/h and a t1/2 of oral semaglutide of approximately 1 week. The wording on Elimination in section 5.2 of the SmPC for oral Wegovy is mostly similar to the wording for Rybelsus and Wegovy s.c. but the absolute Cl is 0.04 L/h for oral Wegovy while apparent clearance is 0.05 L/h for s.c. Wegovy.

Being a polypeptide conjugated with a fatty acid chain, metabolism of semaglutide occurs via both proteolytic cleavage of the peptide backbone and sequential β-oxidation of the fatty acid sidechain. As generally known for polypeptides, metabolism does not appear to be confined to specific organs. The wording in the SmPC is identical to the wording for Wegovy Sc. This is acceptable.

Dose proportionality and time dependency

Dose-proportionality. For the dose range 1.5, 4, 9, 25 and 50 mg, systemic exposure of semaglutide increases in a dose-proportional manner over the complete range of strengths.

Time dependency. Semaglutide concentrations in the OASIS studies were reasonably stable over time, with slightly higher exposure levels seen during the first 6 months than at the end of the studies. The slightly reduced exposure in time is considered not to be clinically relevant.

Intra- and inter-individual variability. The variability of the exposure of single and multiple doses up to 10 mg of oral semaglutide was high, with an estimated total variability of AUC of oral semaglutide of 166% after a single dose and 68% at steady state. The within-participant variability in exposure was 137% after a single dose and 33% at steady state. This variability is indicated in the SmPC section 5.2.

Pharmacokinetics in the target population. With respect to PK in the target population, body weight was the most influential covariate, resulting in lower semaglutide exposure with higher body weight (e.g. in case of obese or overweight patients) and vice versa. As indicated in Table 3-4 of the Summary of Clinical Pharmacology and Table 6-4 of the Phase 3 Modelling Report, the maximum exposure for the 25 mg oral semaglutide in the obese population exceeds both the exposure range from the PIONEER and the STEP trials. There are 12.4% of participants exposed to 25 mg oral semaglutide with higher exposure than seen in the STEP 1 trial conducted with 2.4 mg SC semaglutide. In OASIS 4, 0.5 % of subjects exhibited exposure above the exposure range in PIONEER PLUS (25 mg), while no subjects had exposure below 3 nmol/L. In addition, 81.7% of subjects achieved exposure levels above the typical PIONEER PLUS exposure (>44 nmol/L).

Special populations

Overall, no new covariates were identified with inclusion of Phase 3 Studies 4737 (OASIS 1), 4738 (OASIS 2) and 4954 (OASIS 4) as compared to the already existing Phase 3a PopPK model, as provided in support of the Rybelsus MAA. As concluded for the already registered 1.5, 4, 9, 25 and 50 mg semaglutide strengths (Rybelsus), no dose adjustment is considered necessary in relation to

age, gender, body weight, race, ethnicity, upper gastrointestinal disease, renal function or hepatic function.

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3 trials including patients 18–92 years of age.

As indicated in Table 3-4 of the Summary of Clinical Pharmacology and Table 6-4 of the Phase 3 Modelling Report, the maintenance C_{avg} of oral semaglutide is 1.7 times higher in the obese population in OASIS 4 than in the diabetic population in the PIONEER PLUS trial (77 v. 44 nmol/L). These data may suggest a clinically meaningful decrease in exposure, especially taking into account the high variability of semaglutide with oral dosing and the reliance on strict patient compliance. Furthermore, the comorbidity prescription requirement for patients in the BMI range of 27>30 includes diabetes which could lead to lower exposure in these particular patients and thereby decreased efficacy. This potential under-exposure may be increased by the fact that the maximum dose for obesity treatment is 25 mg and not 50 mg as for oral Rybelsus. Therefore, information on the treatment response is included in section 4.4 of the SmPC as is included in the Rybelsus SmPC, informing on the potential lower exposure in patients with concomitant diabetes:

Compliance with the dosing regimen is recommended for the optimal effect of semaglutide. If the treatment response with semaglutide is lower than expected, the treating physician should be aware that the absorption of semaglutide is highly variable and may be minimal, and that the absolute bioavailability of semaglutide is low. Furthermore, patients with diabetes have been predicted to have lower drug exposure than patients without diabetes.

The applicant has modified the text about bodyweight in 5.2 in the SmPC. The final text reads as follows: *Subcutaneous and oral administration of semaglutide has provided clinically efficacious exposures over the body weight range of 54.4−245.6 kg in clinical trials*. *Also f*or all other intrinsic factors potentially affecting PK, the wording in section 5.2 of the SmPC is accepted.

PK drug-drug interactions

In vitro. Semaglutide is not expected to cause any clinically relevant drug-drug-interactions based on *in vitro* studies evaluating the major drug-metabolizing CYP enzymes in liver, CYP3A4/5 in intestine, and drug transporters.

In vivo. Based on the results of the *in vivo* DDI trials, no dose adjustment for drugs taken with oral semaglutide is required. These trials also demonstrated that co-formulation with SNAC (i.e. formulation in the same tablet) is required for the absorption-enhancing effect of SNAC to take place. The minor effects on the exposures of some victim drugs observed when dosed with oral semaglutide may instead be attributed to delayed gastric emptying associated with treatment with semaglutide. Further, no dose adjustment of oral semaglutide is required for subjects being treated with drugs that increase gastric pH, demonstrating the absorption enhancing capabilities of SNAC on semaglutide are preserved under conditions with increased gastric pH. Results from Study NN9924-4873 support no further delay in gastric emptying with oral semaglutide 50 mg as compared oral semaglutide at lower doses. This is sufficiently worded in the SmPC

Pharmacodynamics

Pharmacokinetics/pharmacodynamics (PK/PD). Relationship between plasma concentration and effect and safety. Exposure-response relations were described by E_{max} models for efficacy end-points and logistic E_{max} models for safety end-points. The efficacy endpoint was body-weight under various conditions. All efficacy models had parameter estimates with reasonable precision and valid 95% CIs. When multiple covariates of administration route were included the effect of oral was estimated

with low precision. The safety endpoints evaluated were nausea, vomiting and skin sensation after 6 months of treatment. For the 3 safety models, model parameters were estimated with reasonable precision except for several covariate effects which also had invalid %95 CIs. This was observed in all 3 safety models and these uninformative covariate factors should have been removed. Sensitivity analyses were conducted on the exposure-response relationship for change in body weight at week 64-68 with varying impact on parameter estimates but limited impact on the exposure-response relationship.

Exposure-response relationship for the change from baseline in body weight indicates increasing reductions in body weight with increasing exposure of both oral and s.c. semaglutide after 64-68 weeks of treatment in a range of studies.

Exposure-response relationships for the proportion of participants reporting nausea or vomiting indicate increasing gastrointestinal AEs with increasing exposure of semaglutide. The relationships appear to plateau with the exposure range associated with oral semaglutide 25 mg, indicating limited additional gastrointestinal AEs for participants with the highest exposure levels.

Exposure-response relationship for the proportion of patients reporting dysaesthesia in OASIS studies indicated that these AEs increased with increasing semaglutide exposure during the first 26 weeks of treatment, with increased reporting with the 25 mg dose.

Evaluation and qualification of PK/PD models. Exposure-response relationships were reasonably well described by the pre-specified models, and adequate for predictive purposes. It was assumed that all relevant confounding factors had been identified and taken into account as covariates in the E/R analyses. The E-R models were sufficiently evaluated by goodness-of-fit plots.

Overall, exposure-effect results support the proposed dosing regimen for Wegovy.

Dose selection and therapeutic window. The recommended oral dose of Wegovy in the weight management indication is the same as approved for Rybelsus in the T2D indication, except the highest dose is 25 mg for Wegovy and 50 mg for Rybelsus. The data demonstrate that, in the T2D population, there was generally comparable exposure overlap with 25 mg and 50 mg oral semaglutide in PIONEER PLUS compared to s.c. semaglutide 2.4 mg in STEP 2 (weight management in T2D), while a greater overlap was observed for 25 mg when compared to STEP 1 (weight management).

5.2.6.2. Conclusions

The pharmacokinetics of oral semaglutide was generally well characterised. Oral semaglutide has a very low bioavailability and highly variable absorption, with the absorption of semaglutide affected by drug intake conditions. Food, administration with large amounts of water and concomitant administration of other tablets decreases bioavailability.

Overall, the PDs of oral semaglutide for weight management are considered adequately characterised.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

Clinical studies with oral semaglutide conducted prior to the OASIS program have demonstrated dose-dependent reductions in body weight, at dose levels up to a well-tolerated and safe dose of 40 mg

(Study NN9924-3790, a phase 2 study for T2D). Similarly, dose-dependent effects on body weight reduction were seen for once daily semaglutide s.c.

In the OASIS programme, oral semaglutide was evaluated at doses ranging from 25 mg to 50 mg. According to the Applicant, results from the OASIS 4 study confirmed that exposure levels for oral semaglutide 25 mg were comparable to those observed with semaglutide s.c. 2.4 mg. Additional details regarding exposure modelling can be found in the Phase 3 (OASIS) Modelling Report. The efficacy and safety profile of oral semaglutide 25 mg was, according to the Applicant, demonstrated to be consistent with that of semaglutide s.c. 2.4 mg.

Based on prior experience with semaglutide and other GLP-1 RAs, a low starting dose and gradual dose escalation of oral semaglutide is, according to the Applicant, expected to mitigate the risk of developing GI AEs. In OASIS 4, participants were initiated at a once-daily dose of 3 mg and followed a fixed-dose escalation regimen, with dose increases every 4 weeks to doses of 7 mg, 14 mg and 25 mg, until the target dose of 25 mg/day was reached after 12 weeks.

The proposed dosing of oral semaglutide 25 mg for weight management will include dose escalation doses of 1.5 mg, 4 mg and 9 mg from the recently approved formulation for Rybelsus (oral semaglutide D), with 25 mg oral semaglutide to be used as the maintenance dose. The study NN9924-4799 confirmed bioequivalence between the 1.5 mg, 4 mg and 9 mg dose level of oral semaglutide D and 3 mg, 7 mg and 14 mg dose level of oral semaglutide, respectively.

5.3.2. Main study(ies)

5.3.2.1. OASIS 4 (NN9932-4954)

5.3.2.1.1. OASIS 4: Efficacy and safety of oral semaglutide 25 mg once daily in adults with overweight or obesity (NN9932-4954)

5.3.2.1.2. Study design

5.3.2.1.2.1. General design

OASIS 4 was an interventional 64 week, randomised, phase III b, placebo-controlled, double-blind two-armed, multi-centre, multinational clinical study comparing the efficacy of once daily 25 mg oral semaglutide versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with overweight and weight-related comorbidities, or with obesity.

In total, approximately 300 participants were to be randomised in a 2:1 ratio to receive either:

- oral semaglutide 25 mg once daily
- oral semaglutide placebo once daily

as an adjunct to a reduced-calorie diet and increased physical activity. The study consisted of a 1-week screening period to assess the participant's eligibility followed by a randomisation visit and a 64-week treatment period. The treatment period was divided into a dose escalation period of 12 weeks and a maintenance period of 52 weeks. After the end-of-treatment visit, all participants were to enter a follow-up period of 7 weeks, ended by a follow-up visit (end-of-study). The planned total study duration for the individual participant was approximately 72 weeks (including screening) (Figure 5).

Figure 3: Study schema

5.3.2.1.2.2. Treatment

Gastrointestinal AEs are the most common adverse reactions reported with GLP-1 RAs. To mitigate the risk of gastrointestinal adverse events, both studies included an initial dose escalation period of 12 weeks during which the dose was gradually increased to the maintenance dose of oral semaglutide 25 mg.

Dose escalation should take place during the first 12 weeks after randomisation as illustrated in Table 16. All participants should aim at reaching the recommended maintenance dose of 25 mg semaglutide once daily or the corresponding placebo.

Table 6: Dose escalation and maintenance of oral semaglutide/ semaglutide placebo

		Dose escalation			Maintenance	Follow-up
Study periods	**Screening**	**Randomisation/ Treatment-period 1**	**Treatment-period 2**	**Treatment-period 3**	**Treatment-period 4**	**End-of-treatment**
Duration of each period	2 weeks	4 weeks	4 weeks	4 weeks	52 weeks	7 weeks
Treatment arm						
Oral semaglutide 25 mg	Screening	Oral semaglutide 3 mg Dose pack	Oral semaglutide 7 mg Dose pack	Oral semaglutide 14 mg Dose pack	Oral semaglutide C 25 mg HDPE bottle	Follow-up
Semaglutide placebo	Screening	Placebo Dose pack	Placebo Dose pack	Placebo Dose pack	Placebo HDPE bottle	Follow-up

If a participant did not tolerate the current dose during dose escalation, the participant was allowed to prolong the dose escalation phase. If a participant did not tolerate the recommended maintenance dose of 25 mg, the participant was allowed to stay at a lower dose level as per the investigator's discretion. However, it was recommended that the participant makes at least one attempt to re-escalate or stay at the recommended maintenance dose of 25 mg. Deviations from the planned dose regimen were only allowed if randomised treatment would otherwise be discontinued.

5.3.2.1.2.3. Randomisation

OASIS 4 was a randomised, double-blind, placebo-controlled, multi-centre, multinational clinical study, with 2 study arms with 2:1 randomisation (oral semaglutide 25 mg: placebo). Participants, care providers, investigators and outcome assessors were blinded to IMP allocation.

All participants will be screened and centrally randomised using the RTSM/IWRS and assigned to the next available treatment according to the randomisation schedule. IMP will be dispensed/allocated at the study visits. At screening, each participant will be assigned a unique 6-digit subject number which will remain the same throughout the study. Each site is assigned a 3-digit number and all subject numbers will start with the site number.

5.3.2.1.2.4. Blinding

Placebo tablets are visually identical to oral semaglutide tablets and will be available in identical primary and secondary packaging. Consequently, investigators and site staff will remain blinded throughout the study.

The RTSM/IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's IMP is warranted. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a participant's IMP unless this could delay emergency treatment of the participant.

5.3.2.1.2.5. Patient population

Inclusion criteria

Patients were eligible to be included in the trial only if all the following inclusion criteria apply: Male or female, age ≥ 18 years at the time of signing informed consent; body mass index (BMI) of ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or CV disease, OR BMI ≥ 30.0 kg/m^2, and a history of at least one self-reported unsuccessful dietary effort to lose body weight.

Exclusion criteria

Subjects were excluded from the trial if any of the following relevant criteria applied (in addition to standard exclusion criteria):

Obesity related
A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records; treatment with any medication indicated for weight management within 90 days prior to screening; Previous or planned (during the study period) obesity treatment with surgery or a weight loss device However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year prior to screening, (2) lap banding, if the band has been removed >1 year prior to screening, (3) intragastric balloon, if the balloon has been removed >1 year prior to screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year prior to screening; uncontrolled thyroid disease per investigator's discretion.

Glycaemia-related
HbA1c ≥ 6.5% (48 mmol/mol) as measured by the central laboratory at screening; history of type 1 or type 2 diabetes; treatment with glucose-lowering agent(s) within 90 days prior to screening.

Mental health
History of major depressive disorder within 2 years prior to screening; diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder); Patient Health Questionnaire-9 (PHQ-9) score ≥ 15 at screening; lifetime history of suicidal attempt; suicidal behaviour within 30 days prior to screening; suicidal ideation.

General Safety
Presence of acute pancreatitis within 180 days prior to screening ;history or presence of chronic pancreatitis; personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; renal impairment (eGFR <15); history of major surgical procedures involving the stomach potentially affecting absorption of drugs and/or nutrients, as judged by the investigator; presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to screening; myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within 60 days prior to screening; New York Heart Association (NYHA) Class IV; surgery scheduled for the duration of the study, except for minor surgical procedures, in the opinion of the investigator; known or suspected abuse of alcohol or recreational drugs; any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol.

Countries
The study was conducted at 22 sites that enrolled participants in 4 countries (Canada, Germany, Poland, and the USA).

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objective

Primary objective: To confirm superior efficacy on body weight reduction from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.

Coprimary endpoints:

- Relative change in body weight; from baseline (week 0) to end of treatment (week 64) (%)
- Achievement of body weight reduction ≥ 5% (Yes/No); at end of treatment (week 64) (count of participants)

5.3.2.1.3.2. Estimands for the primary objective

Table 7: Estimands for primary objective

Population	Adults with overweight (defined as BMI ≥27 kg/m^2 and <30 kg/m^2), with at least one weight-related comorbidity, or with obesity (defined as BMI ≥30 kg/m^2), with or without weight-related comorbidities
Treatment condition<s>	Oral semaglutide 25 mg once daily versus placebo regardless of discontinuation or dose reduction of randomised treatment, and regardless of initiating other anti-obesity therapies

Endpoint (variable)	1) Relative change from baseline to week 64 in body weight and 2) body weight reduction ≥5% (yes/no) at week 64
Population-level summary	1) difference in mean changes and 2) odds ratio between treatment conditions
Intercurrent events and strategy to handle them	
discontinuation or dose reduction of randomised trial product	Treatment policy: captured by the treatment condition attribute
initiating other anti-obesity therapies (weight management drugs or bariatric surgery)	Treatment policy: captured by the treatment condition attribute

The primary clinical question of interest in OASIS 4 was: What is the treatment effect of oral semaglutide 25 mg once daily versus placebo as adjunct to a reduced-calorie diet and increased physical activity on body weight in adults with overweight or obesity, measured by relative change from baseline (week 0) to end of treatment (week 64) in body weight, and participants achieving a body weight reduction of ≥5% at end of treatment (week 64), regardless of discontinuation or dose reduction of randomised trial product, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery)?

Additionally, the same clinical question was analysed, had patients remained on their randomised treatment for the entire planned duration of the study and not initiated any other anti-obesity therapies (weight management drugs or bariatric surgery)?

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

The FAS comprised all randomised participants. Participants contributed to a treatment group based on the trial product they were randomised to receive. The FAS was used for all efficacy evaluations.

Two different observation periods were defined for the efficacy evaluations in OASIS 4:

- The in-study period, defined as the uninterrupted time interval from date of randomisation to date of last contact with study site.
- The on-treatment period, defined as the interval from the date of first trial product administration to the date of last trial product administration plus a 3-day ascertainment window and excluding any off-treatment time intervals. For the evaluation of AEs, the lag time for each on-treatment interval was 7 weeks.

For the efficacy endpoints, the treatment policy strategy was based on data from the full in-study period and the hypothetical strategy on data from the on-treatment period.

Analysis of continues primary and secondary endpoints

The analysis model for percentage weight change was a linear regression (ANCOVA) with randomised treatment as a factor and the baseline value of the endpoint as covariate. The estimated treatment contrast between semaglutide and placebo were reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

The additional estimands for continuous endpoints were assessed using an MMRM for efficacy (using on-treatment data). The MMRM was fitted using the endpoint as response and the same factors and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same participant was employed, assuming measurements for different participants are independent.

Analysis of binary primary and secondary endpoints

The analysis model for the binary (responder) endpoints was a logistic regression using randomised treatment as a factor and the baseline value of the endpoint as covariate. The estimated odds ratio (OR) between semaglutide and placebo were reported together with the associated two-sided 95% CI and corresponding p-value.

In addition to the estimated OR the estimated treatment differences (ETDs) were provided by calculating the responder probabilities and treatment differences between responder probabilities based on the logistic regression model, with confidence intervals for treatment differences obtained using the delta method.

The additional estimands for binary (responder) endpoints were assessed using the same MMRM for efficacy except that the week 64 assessment of the endpoint was used as response variable in the model.

Missing data

All available data at end of trial (EOT) (AT and AD) were used and missing values (MT and MD) at EOT were imputed and the endpoints derived from the imputed values. A primary imputation approach was used to address the co-primary and secondary estimand (treatment policy strategy) and sensitivity analyses were used to assess the robustness of the primary analysis results. The primary imputation approach was a multiple imputation approach using retrieved participants (RD-MI).

Sensitivity analyses investigated how assumptions on body weight development after discontinuation of randomised treatment impacted the estimated treatment contrasts between semaglutide and placebo. The sensitivity analyses consisted of jump to reference multiple imputation approach (J2R-MI), tipping-point multiple imputation analysis (TP-MI), and mixed model for repeated measurements (MMRM). For binary responder endpoints an analysis using non-retrieved participants as non-responders in the logistic regressions was done.

The evaluation of efficacy in subgroups in OASIS 4 was based on the co-primary endpoints and included descriptive statistics and estimated treatment differences/OR with 95% CI (oral semaglutide 25 mg versus placebo). The subgroup analyses were performed for sex, age, race, ethnicity, region, baseline body weight, baseline BMI, baseline renal function, baseline glycaemic status and upper gastrointestinal disease at baseline.

Multiplicity

Confirmatory hypotheses of superiority were tested for the co-primary and secondary estimands. The type I error was controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This was based on priority ordering of the null hypotheses and testing them in this order using the 2-sided 95% confidence interval approach until an insignificant result appeared. Consequently, all previous hypotheses were to be rejected in order to proceed to the next hypothesis test thereby preserving the type I error rate. The test hierarchy was:

1. Change from baseline to EOT in body weight (%)
2. Participants who achieve (y/n) $\geqslant$5% body weight reduction

3. Participants who achieve (y/n) ⩾10% body weight reduction
4. Participants who achieve (y/n) ⩾15% body weight reduction
5. Participants who achieve (y/n) ⩾20% body weight reduction
6. Change from baseline in IWQOL-Lite-CT PF score

Sample size

The sample size has been determined to ensure adequate statistical power to confirm superiority of oral semaglutide 25 mg once daily to placebo with respect to the co-primary endpoints as well as to enable evaluation of safety, tolerability and ensure sufficient exposure. The sample size calculation assumed 5% significance level, 2:1 randomisation and findings from STEP 1 and from the SCALE, SUSTAIN and PIONEER projects. When accounting for 20% discontinuation the expected treatment difference is 6.5 with standard deviation of 21.1. Given these assumptions, a sample size of 300 participants (200 randomised to 25 mg semaglutide and 100 randomised to placebo), provides more than 99% power for confirming superiority for both co-primary endpoints, and 71% power for confirming superiority for all confirmatory endpoints.

5.3.2.1.3.3. Secondary objectives

The secondary objectives are as follows:

- To confirm superior efficacy on physical function from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.
- To estimate the efficacy on cardio-metabolic parameters from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.
- To compare the safety and tolerability from baseline (week 0) to end-of-study (week 71) of oral semaglutide once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.

5.3.2.1.3.4. Estimands for the secondary objectives

The secondary estimands with confirmatory and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. The secondary estimands with continuous endpoints for secondary objectives are similar to the co-primary estimand for relative weight change, with the exception of endpoints with units of ratio to baseline, for which the population-level summary is the ratio between treatment conditions. The secondary estimands with binary endpoints for secondary objectives are similar to the co-primary estimand for body weight reduction ≥5%.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

See statistical methods for the primary objective.

5.3.2.1.3.5. Exploratory objective

The exploratory objective was: To estimate the efficacy on clinical outcome assessments from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity.

5.3.2.1.4. Results

5.3.2.1.4.1. Participant flow and numbers analysed

Participant disposition is summarised below (Table 18).

Table 8: OASIS 4 - Participant disposition

	Oral Sema 25 mg N (%)	Placebo N (%)	Total N (%)
Screened			346
Screening failures			37
Withdrawn before randomisation			2
Randomised	205 (100)	102 (100)	307 (100)
Exposed	204 (99.5)	102 (100)	306 (99.7)
Analysis sets			
Full analysis set	205 (100)	102 (100)	307 (100)
Safety analysis set	204 (99.5)	102 (100)	306 (99.7)
Treatment completion			
On-treatment at week 64 (treatment completers)	167 (81.5)	76 (74.5)	243 (79.2)
After at least one temporary interruption	51 (24.9)	16 (15.7)	67 (21.8)
Attended end-of-treatment visit without permanent discontinuation of trial product	167 (81.5)	75 (73.5)	242 (78.8)
Trial product permanently discontinued	37 (18.0)	26 (25.5)	63 (20.5)
Primary reason for permanent discontinuation of trial product			
Adverse event	14 (6.8)	6 (5.9)	20 (6.5)
Protocol violation	3 (1.5)	2 (2.0)	5 (1.6)
Included in the study in violation of the inclusion and/or exclusion criteria	0	0	0
Intention of becoming pregnant	2 (1.0)	0	2 (0.7)
Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study	0	0	0
Safety concern as judged by the investigator	0	0	0
Other	1 (0.5)	2 (2.0)	3 (1.0)
Lost to follow-up	6 (2.9)	6 (5.9)	12 (3.9)
Pregnancy	0	1 (1.0)	1 (0.3)
At the discretion of the investigator	0	0	0
Site closure	0	0	0
Epi/Pandemic	0	0	0
Other	14 (6.8)	11 (10.8)	25 (8.1)
Withdrawal of consent	1 (0.5)	1 (1.0)	2 (0.7)
Other	13 (6.3)	10 (9.8)	23 (7.5)
Attended end-of-treatment visit after permanent discontinuation of trial product	29 (14.1)	20 (19.6)	49 (16.0)
Study completion			
Attended end-of-study visit (study completers)	196 (95.6)	94 (92.2)	290 (94.5)
Attended end-of-study visit and end-of-treatment visit without permanent discontinuation of trial product	166 (81.0)	73 (71.6)	239 (77.9)
Withdrawn from study	9 (4.4)	8 (7.8)	17 (5.5)
Primary reason for study withdrawal			
Withdrawal by subject	1 (0.5)	1 (1.0)	2 (0.7)
Lost to follow-up	7 (3.4)	7 (6.9)	14 (4.6)
Investigator decision	1 (0.5)	0	1 (0.3)
Site closure	0	0	0
Epi/Pandemic	0	0	0
Death	0	0	0
Withdrawn from study before week 64	7 (3.4)	2 (2.0)	9 (2.9)
Withdrawn from study without prior permanent discontinuation of trial product	1 (0.5)	1 (1.0)	2 (0.7)

N: Number of participants, %: Percentages are based on randomised participants.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 3 days. Permanent discontinuation is when a participant stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 64). Temporary interruption is when a participant missed more than 3 consecutive doses of trial product and resumed treatment before end of treatment period (week 64).

5.3.2.1.4.2. Deviations from study plan

Protocol deviations were summarised in Table 19.

Table 9: OASIS 4 – Protocol deviations

		Participant level PDs				
Protocol deviation category	Site level PDs N	Oral Sema 25 mg N	Placebo N	Not allocated N	Total N	Total site and participant level PDs N
Total	5	45	26	1	72	77
Informed consent	0	3	2	1	6	6
Inclusion/exclusion criteria	0	2	2	0	4	4
Treatment administration	0	10	5	0	15	15
Study procedures/assessments	5	27	17	0	44	49
AE and other safety procedures	0	0	0	0	0	0
Concomitant medication/medical intervention	0	0	0	0	0	0
Subject visit schedule	0	0	0	0	0	0
Privacy and data protection	0	0	0	0	0	0
Participant contact schedule	0	3	0	0	3	3
Other	0	0	0	0	0	0

N: Number of PDs within category and subcategory, Not allocated: PDs for screening failures and participants not allocated treatment. PD: Protocol deviation, SAE: Serious adverse event.

5.3.2.1.4.3. Baseline data

The demographic and baseline characteristics are summarised in Table 20, and relevant comorbidities are summarised in Table 21.

Table 10: OASIS 4 - Demographics and baseline characteristics – summary – full analysis set

	Oral Sema 25 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	205		102		307	
Age (years)						
N	205	(100)	102	(100)	307	(100)
18-<65	184	(89.8)	94	(92.2)	278	(90.6)
65-<75	16	(7.8)	6	(5.9)	22	(7.2)
75-<85	5	(2.4)	2	(2.0)	7	(2.3)
>=85	0	(0.0)	0	(0.0)	0	(0.0)
Sex						
N	205	(100)	102	(100)	307	(100)
Female	155	(75.6)	87	(85.3)	242	(78.8)
Male	50	(24.4)	15	(14.7)	65	(21.2)
Country						
N	205	(100)	102	(100)	307	(100)
Canada	19	(9.3)	13	(12.7)	32	(10.4)
Germany	57	(27.8)	24	(23.5)	81	(26.4)
Poland	51	(24.9)	29	(28.4)	80	(26.1)
United States	78	(38.0)	36	(35.3)	114	(37.1)
Ethnicity						
N	205	(100)	102	(100)	307	(100)
Hispanic or Latino	17	(8.3)	7	(6.9)	24	(7.8)
Not Hispanic or Latino	188	(91.7)	95	(93.1)	283	(92.2)
Not Reported	0	(0.0)	0	(0.0)	0	(0.0)
Race						
N	205	(100)	102	(100)	307	(100)
American Indian or Alaska Native	0	(0.0)	0	(0.0)	0	(0.0)
Asian	1	(0.5)	1	(1.0)	2	(0.7)
Black or African American	13	(6.3)	9	(8.8)	22	(7.2)
Native Hawaiian or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)
White	190	(92.7)	91	(89.2)	281	(91.5)
Other	1	(0.5)	1	(1.0)	2	(0.7)
Not Reported	0	(0.0)	0	(0.0)	0	(0.0)
BMI (kg/m^2)						
N	205	(100)	102	(100)	307	(100)
<30	13	(6.3)	5	(4.9)	18	(5.9)
30-<35	73	(35.6)	39	(38.2)	112	(36.5)
35-<40	64	(31.2)	22	(21.6)	86	(28.0)
>=40	55	(26.8)	36	(35.3)	91	(29.6)
Smoking habits						
N	205	(100)	102	(100)	307	(100)
Never smoked	119	(58.0)	65	(63.7)	184	(59.9)
Previous smoker	56	(27.3)	22	(21.6)	78	(25.4)
Current smoker	30	(14.6)	15	(14.7)	45	(14.7)
Region						
N	205	(100)	102	(100)	307	(100)
Europe	108	(52.7)	53	(52.0)	161	(52.4)
North America	97	(47.3)	49	(48.0)	146	(47.6)
Renal function, eGFR (mL/min/1.73 m^2)						
N	205	(100)	102	(100)	307	(100)
Normal (>=90)	128	(62.4)	69	(67.6)	197	(64.2)
Mild RI (60-<90)	70	(34.1)	31	(30.4)	101	(32.9)
Moderate RI (30-<60)	7	(3.4)	2	(2.0)	9	(2.9)
Severe RI (15-<30)	0	(0.0)	0	(0.0)	0	(0.0)
End-stage renal disease (<15)	0	(0.0)	0	(0.0)	0	(0.0)
Glycaemic status at randomisation*						
N	205	(100)	102	(100)	307	(100)
Normo-glycaemia	105	(51.2)	53	(52.0)	158	(51.5)
Pre-diabetes	97	(47.3)	47	(46.1)	144	(46.9)
Diabetes	3	(1.5)	2	(2.0)	5	(1.6)

N: Number of participants, %: Percentages are based on number of participants, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, RI: Renal impairment. Normo-glycaemia: HbA1c < 5.7%, Pre-diabetes: 5.7% <= HbA1c < 6.5%, Diabetes: HbA1c >= 6.5%. *, No participants had HbA1c >= 6.5% at screening. The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 11: OASIS 4 – Comorbidities at screening – summary – full analysis set

	Oral Sema 25 mg	Placebo	Total
	N (%)	N (%)	N (%)
Number of participants	205	102	307
Comorbidities			
Asthma	19 (9.3)	9 (8.8)	28 (9.1)
Coronary artery disease	3 (1.5)	2 (2.0)	5 (1.6)
Dyslipidaemia	64 (31.2)	29 (28.4)	93 (30.3)
Glucose metabolism disorder	22 (10.7)	10 (9.8)	32 (10.4)
Gout	3 (1.5)	1 (1.0)	4 (1.3)
Hypertension	91 (44.4)	42 (41.2)	133 (43.3)
Kidney disease	2 (1.0)	1 (1.0)	3 (1.0)
Knee or hip osteoarthritis	14 (6.8)	10 (9.8)	24 (7.8)
Liver disease	8 (3.9)	5 (4.9)	13 (4.2)
Obstructive sleep apnoea	15 (7.3)	12 (11.8)	27 (8.8)
Reproductive system	8 (3.9)	3 (2.9)	11 (3.6)
Thyroid disorder	34 (16.6)	14 (13.7)	48 (15.6)

5.3.2.1.4.4. Outcomes and estimation

Primary and confirmatory secondary endpoints

The primary and confirmatory secondary endpoints are summarised in Table 22.

Relative change in body weight – treatment policy estimand

At week 0 (baseline), the observed mean (SD) body weight was 106.4 (23.5) kg for participants in the oral semaglutide 25 mg treatment group and 104.8 (19.7) kg for participants in the placebo treatment group. At week 64 (end of treatment), the estimated mean change in body weight for the treatment policy estimand was -13.61% for participants in the oral semaglutide 25 mg treatment group and -2.18% for participants in the placebo treatment group (ETD -11.43% [-13.88; -8.98]95% CI; p-value <0.0001)

Achievement of body weight reduction ≥ 5% (Yes/No) – treatment policy estimand

At week 64 (end of treatment), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy estimand was 76.3% for participants in the oral semaglutide 25 mg treatment group and 30.5% for participants in the placebo treatment group (EOR 7.34 [4.22;12.76]95% CI; p-value <0.0001).

Achievement of body weight reduction ≥10%, ≥15%, ≥20% (Yes/No) – treatment policy estimand

The proportion of patients achieving a body weight reduction of ≥10%, ≥15% and ≥20% are depicted in Figure 6. The corresponding EORs are listed in Table 22.

Figure 4: OASIS 4 - Proportion of participants achieving body weight loss response criteria since baseline at week 64 - bar plot - in-trial - full analysis set – treatment policy estimand

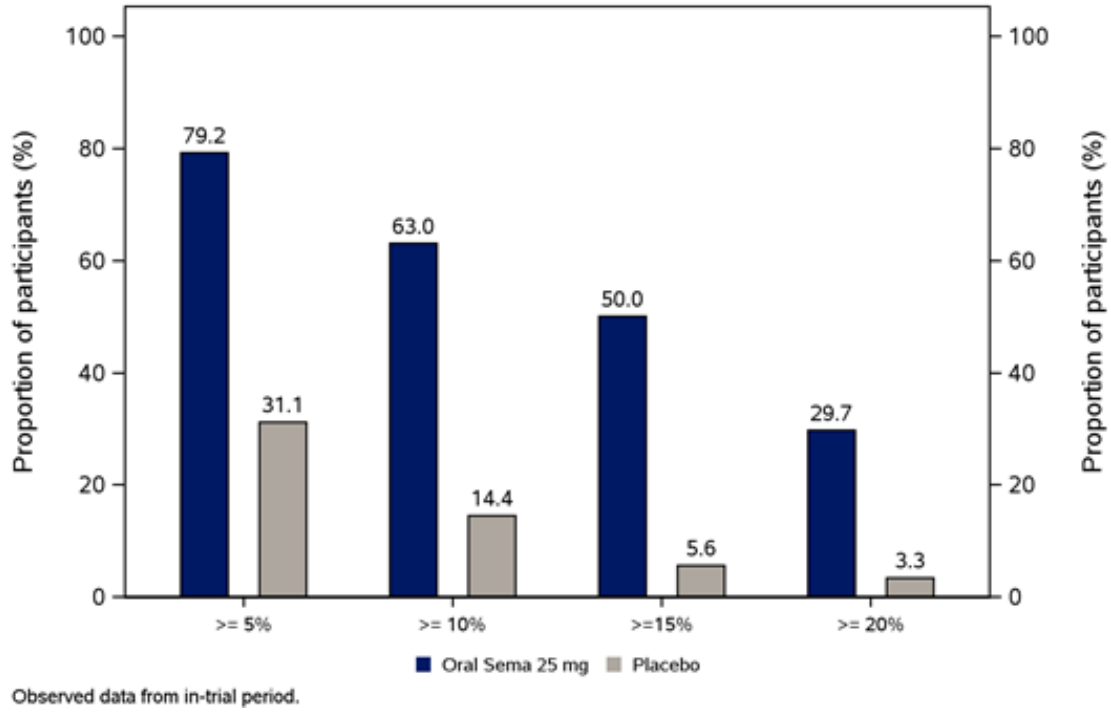


Table 12: OASIS 4- Key efficacy results

		Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Co-primary endpoints						
Change from baseline in body weight (%) at week 64						
Treatment policy estimand	**Oral sema 25 mg – placebo**	**ETD: -11.43 [-13.88; -8.98]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Additional (hypothetical) estimand		**ETD: -13.87% [-16.53; -11.21]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Participants who achieve ≥5% body weight reduction at week 64 (y/n)						
Treatment policy estimand	**Oral sema 25 mg / placebo**	**OR: 7.34 [4.22; 12.76]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Additional (hypothetical) estimand		**OR: 25.23 [13.24; 48.07]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Confirmatory secondary endpoints						
Participants who achieve ≥10% body weight reduction at week 64 (y/n)						
Treatment policy estimand	**Oral sema 25 mg / placebo**	**OR: 9.06 [4.74; 17.29]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Additional (hypothetical) estimand		**OR: 18.84 [9.89; 35.89]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Participants who achieve ≥15% body weight reduction at week 64 (y/n)						
Treatment policy estimand	**Oral sema 25 mg / placebo**	**OR: 15.74 [6.16; 40.24]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Additional (hypothetical) estimand		**OR: 26.19 [10.78; 63.65]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Participants who achieve ≥20% body weight reduction at week 64 (y/n)						
Treatment policy estimand	**Oral sema 25 mg / placebo**	**OR: 12.24 [3.72; 40.26]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Additional (hypothetical) estimand		**OR: 12.45 [4.35; 35.62]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**
Change from baseline in IWQOL-Lite-CT Physical Function score						
Treatment policy estimand	**Oral sema 25 mg – placebo**	**ETD: 7.73 [3.30;12.16]**	**0.0006**	**0.05**	**Superiority**	**Confirmed**
Additional (hypothetical) estimand		**ETD: 10.40 [5.30;15.50]**	**<0.0001**	**0.05**	**Superiority**	**Confirmed**

Change in Physical function domain (5-items) score (IWQOL-Lite-CT) – treatment policy estimand
At week 0 (baseline), the observed mean (SD) IWQOL-Lite-CT Physical Function score was 56.8 (22.9) for participants in the oral semaglutide 25 mg treatment group and 56.9 (22.8) for participants in the placebo treatment group. At week 64 (end of treatment), the estimated mean change in IWQOL-Lite-CT Physical Function score for the treatment policy estimand was 16.18 for participants in the oral semaglutide 25 mg treatment group and 8.45 for participants in the placebo treatment group (ETD 7.73 [3.30;12.16]95% CI; p-value = 0.0006).

Supportive secondary endpoints (treatment policy estimand)

Change in IWQOL-Lite-CT PFD score ≥14.6 (Yes/No)

At week 64 (baseline), the estimated proportion of participants achieving IWQOL-Lite-CT meaningful within patient change of ≥14.6 points for the treatment policy estimand was 54.6% for participants in the oral semaglutide 25 mg treatment group and 33.7% for participants in the placebo treatment group.

Change in body weight (kg)

At 0 (baseline), the observed mean (SD) body weight was 106.4 (23.5) kg for participants in the oral semaglutide 25 mg treatment group and 104.8 (19.7) kg for participants in the placebo treatment group. At 64 (end of treatment), the estimated mean change in body weight was -14.20 kg for participants in the oral semaglutide 25 mg treatment group and -2.16 kg for participants in the placebo treatment group (ETD: -12.04 kg [-14.64; - 9.45]95% CI; p-value <0.0001).

Change in body mass index (BMI)

At week 0 (baseline), the observed mean (SD) body mass index was 37.5 (6.7) kg/m^2 for participants in the oral semaglutide 25 mg treatment group and 37.8 (6.1) kg/m^2 for participants in the placebo treatment group. At week 64 (end of treatment), the estimated mean change in body mass index was -5.06 kg/m^2 for participants in the oral semaglutide 25 mg treatment group and -0.77 kg/m^2 for participants in the placebo treatment group (ETD: 4.28 kg/ m^2 [-5.20;-3.36]95% CI; p-value <0.0001).

Change in waist circumference

At week 0 (baseline), the observed mean (SD) waist circumference was 114.0 (15.8) cm for participants in the oral semaglutide 25 mg treatment group and 113.6 (14.7) cm for participants in the placebo treatment group. At week 64 (end of treatment), the estimated mean change in waist circumference was -12.24 cm for participants in the oral semaglutide 25 mg treatment group and -2.76 cm for participants in the placebo treatment group (ETD -9.48 cm [-12.41;-6.55]95% CI; p-value <0.0001).

Change in systolic and diastolic blood pressure

At week 0 (baseline), the observed mean (SD) systolic blood pressure was 131 (16) mmHg for participants in the oral semaglutide 25 mg treatment group and 131 (18) mmHg for participants in the placebo treatment group. At week 64 (end of treatment), the estimated mean change in systolic blood pressure was -6.75 mmHg for participants in the oral semaglutide 25 mg treatment group and -5.36 mmHg for participants in the placebo treatment group (ETD -1.39 mmHg [-4.59;1.81]95% CI; p-value =0.3960).

At week 0 (baseline), the observed mean (SD) diastolic blood pressure was 83 (10) mmHg for participants in the oral semaglutide 25 mg treatment group and 83 (10) mmHg for participants in the placebo treatment group. At week 64 (end of treatment), the estimated mean change in diastolic blood pressure was -2.72 mmHg for participants in the oral semaglutide 25 mg treatment group and -2.07 mmHg for participants in the placebo treatment group (ETD -0.65 mmHg [-2.80;1.49] 95% CI; p-value = 0.5500).

Change in glyceamic parameters

Changes in glycaemic parameters are summarised in Table 23.

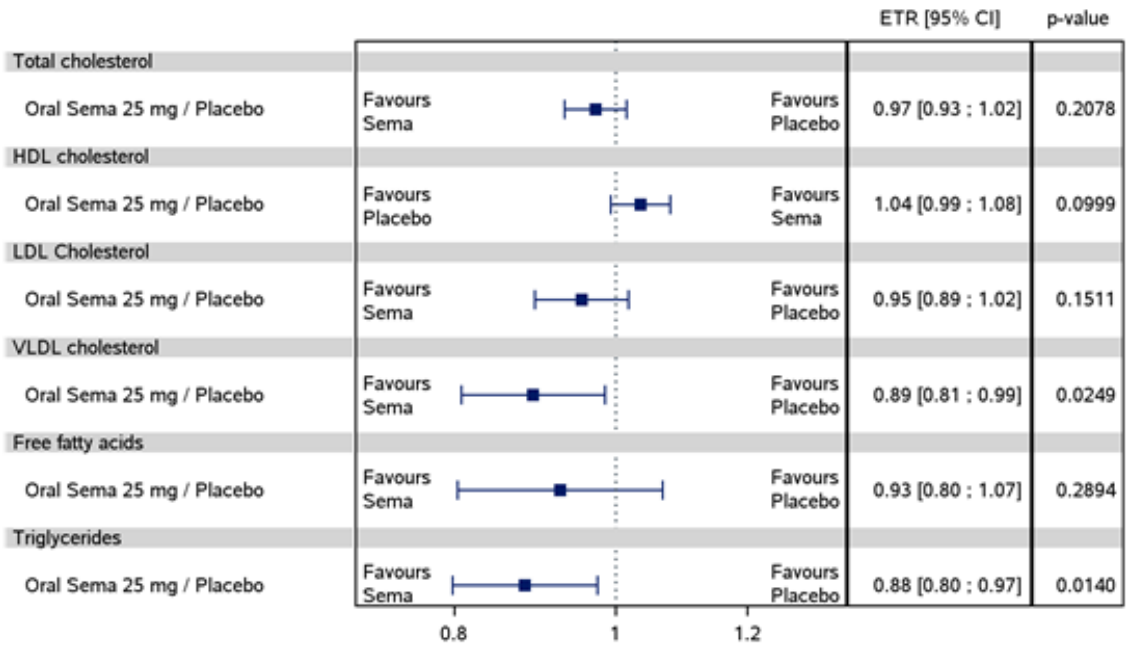
Table 13: OASIS 4 - HbA1c and fasting plasma glucose

Study	HbA_{1c} Mean estimates and treatment differences					
	(%-points)			(mmol/mol)		
	Sema	Placebo	ETD [95% CI]	Sema	Placebo	ETD [95% CI]
OASIS 4	-0.29	-0.06	-0.23 (-0.31; -0.15)	-3.22	-0.70	-2.52 (-3.43; -1.60)
Fasting plasma glucose						
	(mmol/L)			(mg/dL)		
	Sema	Placebo	ETD [95% CI]	Sema	Placebo	ETD [95% CI]
OASIS 4	-0.36	0.02	-0.39 (-0.62; -0.15)	-6.56	0.42	-6.98 (-11.19; -2.77)

Change in lipids

Changes in lipids (total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids and triglycerides) are presented in Figure 7.

Figure 5: OASIS 4 - Lipids ratio to baseline at week 64 - forest plot - treatment policy strategy – full analysis set



ETR: Estimated treatment ratio. CI: Confidence interval. HDL: High density lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Change in hsCRP

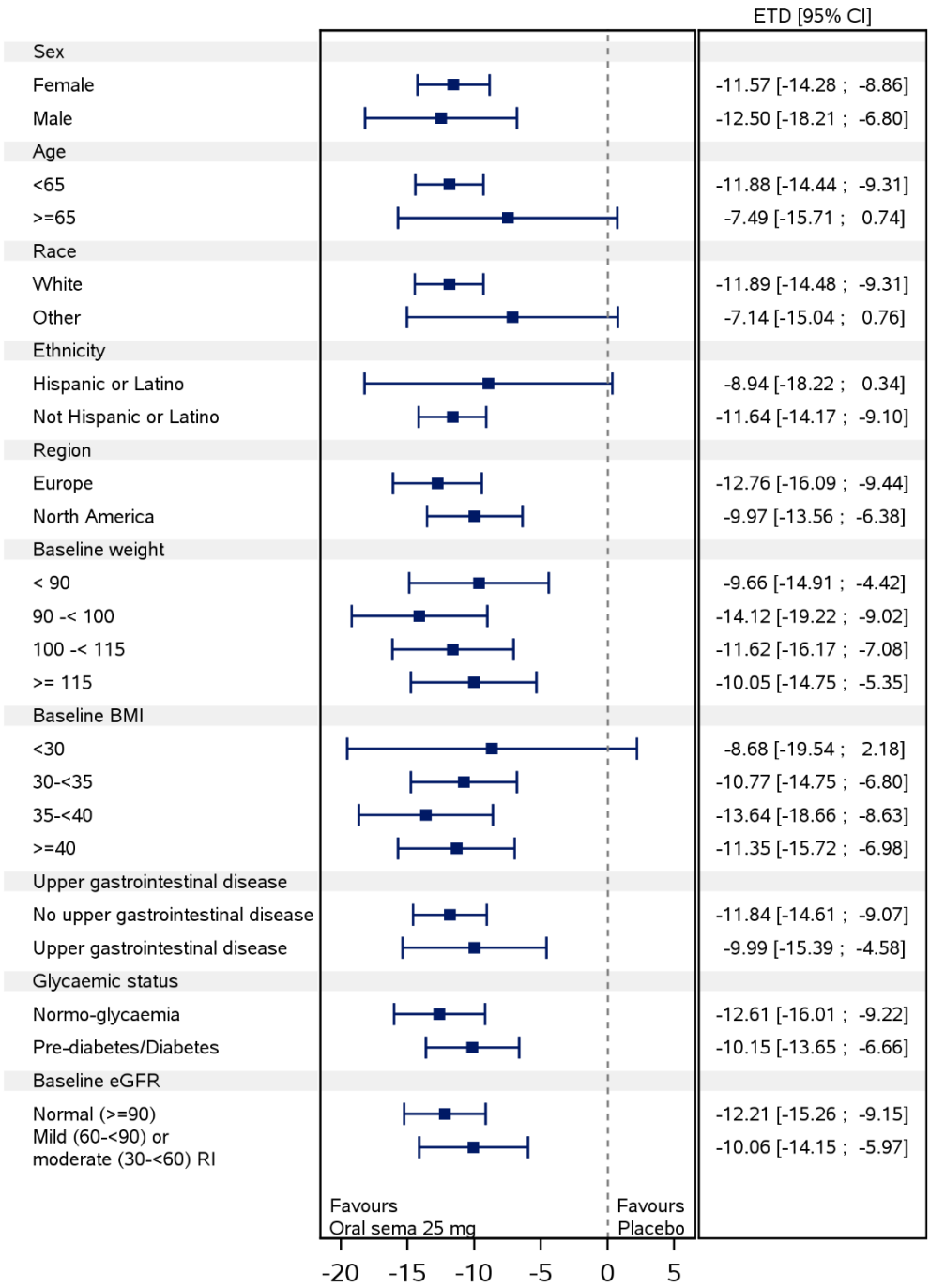
At week 0 (baseline), the observed geometric mean (CV) high sensitivity C-Reactive Protein was 3.59 (140.2) mg/L for participants in the oral semaglutide 25 mg treatment group and 3.84 (120.4) mg/L for participants in the placebo treatment group. At week 64 (end of treatment), the estimated ratio of high sensitivity C-Reactive Protein to baseline was 0.54 in the oral semaglutide 25 mg treatment group and 0.96 in the placebo treatment group (EOR 0.56 [0.42; 0.74]95% CI; p-value < 0.0001).

5.3.2.1.4.5. Pre-defined and post-hoc subgroup analyses

To investigate whether there were differences in the efficacy response to oral semaglutide 25 mg in pre-specified subgroups of participants from OASIS 4, subgroup analyses of body weight (%) change from baseline to week 64 and ≥5% body weight loss responders at week 64 were conducted In OASIS 4, 10 predefined subgroups were analysed for efficacy evaluation, including sex, age (<65/ ≥65 years), race, ethnicity, region, baseline body weight, baseline BMI, baseline renal function, baseline glycaemic status and upper GI disease at baseline.

The efficacy response (% body weight change) to oral semaglutide 25 mg compared to placebo is shown in Table 24.

Table 14: OASIS 4 - Body weight (%) change from baseline by subgroups- estimated treatment difference - forest plot - treatment policy strategy - full analysis set



BMI: body mass index GI: Gastrointestinal, eGFR: Estimated glomerular fikltration rate, RI: Renal impairment, ETD: Estimated treatment difference, CI: Confidence interval.

Analysis of data from in-trial period.

5.3.3. Clinical studies in special populations

To investigate whether there were differences in the efficacy response to oral semaglutide 25 mg in pre-specified subgroups of participants from OASIS 4, subgroup analyses of body weight (%) change

from baseline to week 64 and ≥5% body weight loss responders at week 64 were conducted In OASIS 4, 10 predefined subgroups were analysed for efficacy evaluation, see Table 25.

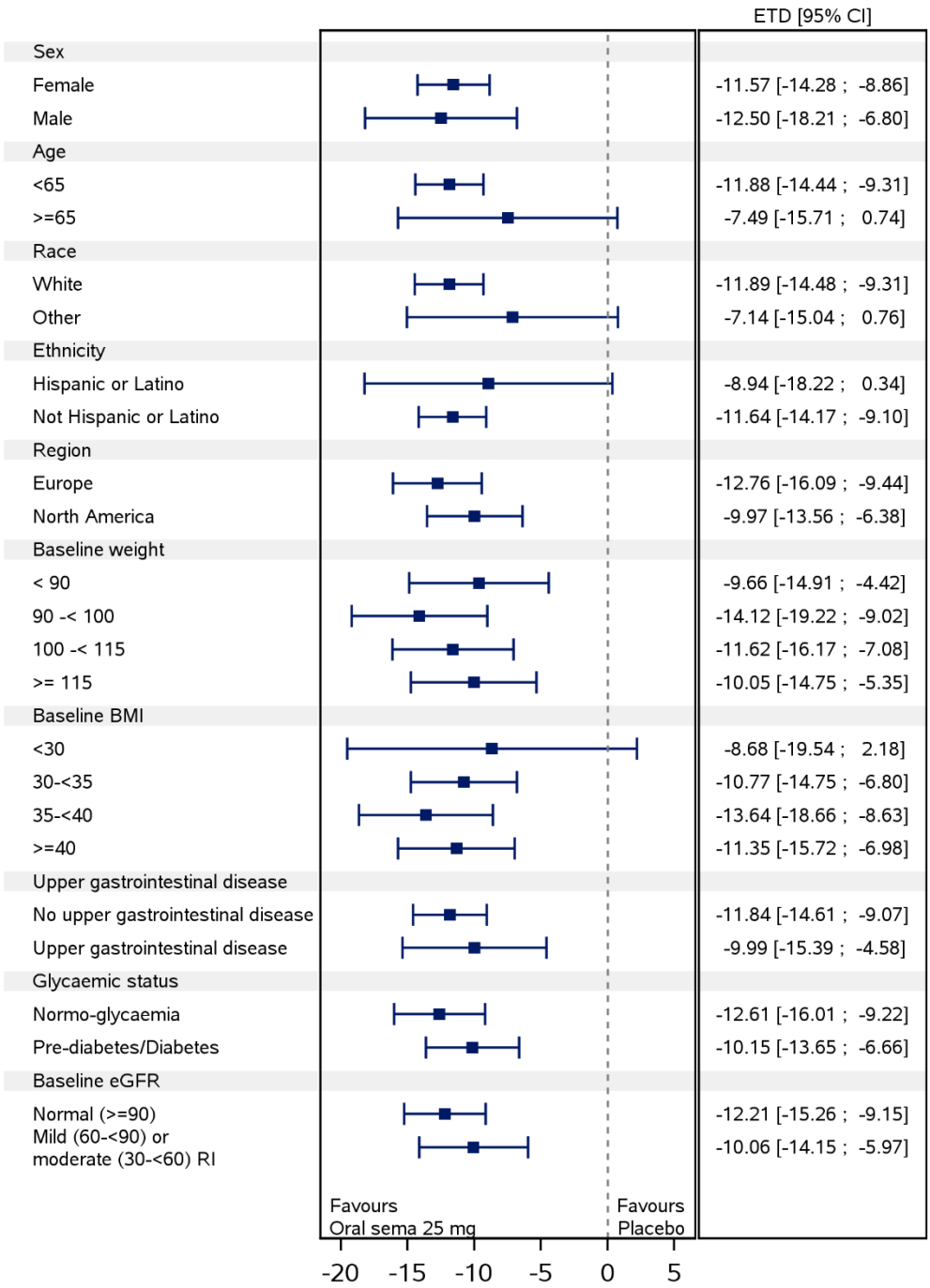
Table 15: OASIS 4 – subgroup for evaluation of efficacy data

Subgroup	Categories	Comments
Sex	Male Female	
Age (years)	<65 ≥65	
Race [a]	White Black/African American Asian Other	Other includes Native Hawaiian, Pacific Islander and race not reported.
Ethnicity [a]	Hispanic/Latino Not Hispanic/Latino Not reported	
Region	Europe North America	Europe includes Germany and Poland North America includes United States and Canada.
Baseline body weight (kg)	<90 90 ≤ to < 100 100 ≤ to < 115 115 ≤	The cut-off has been prespecified to achieve approximately equal numbers of participants in the different groups
Baseline BMI (kg/m^2)	<30 (overweight) 30≤ to < 35 (class I obesity) 35≤ to < 40 (class II obesity) ≥40 (class III obesity)	
Baseline renal function (eGFR, mL/min/1.73 m^2)	Normal (≥90) Mild RI (60 ≤ to < 90) or moderate RI (≥30 to <60)	
Baseline glycaemic status	Normo-glycaemia Pre-diabetes/diabetes	Derived based on HbA_{1c} at randomisation: Normo-glycaemia: HbA_{1c} <5.7% Pre-diabetes/diabetes HbA_{1c} ≥5.7%
Upper gastrointestinal disease at baseline	No upper gastrointestinal disease Upper gastrointestinal disease	Upper gastrointestinal disease is defined as a concomitant illness of gastroesophageal reflux disease, chronic gastritis, gastric ulcer, acid peptic disease, dyspepsia, gastritis, gastritis erosive, peptic ulcer or reflux gastritis

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate (CKD-EPI); HbA_{1c}: glycosylated hemoglobin; RI: renal impairment. [a]In a few countries, the law prohibits collection of data on race and ethnicity; the data are recorded as not applicable.

The efficacy response (% body weight change) to oral semaglutide 25 mg compared to placebo is shown in Table 26.

Table 16: OASIS 4 - Body weight (%) change from baseline by subgroups- estimated treatment difference - forest plot - treatment policy strategy - full analysis set



BMI: body mass index GI: Gastrointestinal, eGFR: Estimated glomerular fikltration rate, RI: Renal impairment, ETD: Estimated treatment difference, CI: Confidence interval.

Analysis of data from in-trial period.

Overall, results were fairly consistent across all subgroups. For some subgroups, confidence intervals were large and included 0, hence no statistically significant effect. However, this is considered to be due to a limited number of patients included in that subgroup (e.g. only 24 Hispanic/ Latino patients were included in the study) and does not raise concerns (with the exception of patients with BMI<30 kg/m^2).

5.3.4. In vitro biomarker test for patient selection for efficacy

N/A.

5.3.5. Supportive study(ies)

PIONEER PLUS - Body weight change in T2D populations
PIONEER PLUS was a 68-week, randomised, active-controlled, double-blinded, three-armed, multicentre, multinational clinical study comparing the efficacy, safety and tolerability of once-daily oral semaglutide 14 mg, 25 mg and 50 mg in participants with T2D, on stable doses of 1-3 oral anti-diabetic drugs (OADs) (metformin, sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors). The 68 weeks of treatment with oral semaglutide included dose escalation in 4-weeks intervals starting at 3 mg (i.e., 12 weeks dose escalation for the oral semaglutide 25 mg group). Primary endpoint was change in HbA1c (%) from baseline to week 52, confirmatory secondary endpoint was change in body weight (kg) from baseline to week 52. Supportive secondary endpoints included glycaemic endpoints, weight-loss endpoints (relative change in body weight, change in BMI, change in waist circumference, achievement of ≥5%; ≥10% weight loss) and lipid-related endpoints.

STEP 2 was a 68-week, randomised, double-blind, double dummy, placebo-controlled, multi-centre, multinational study investigating efficacy and safety of semaglutide s.c. 2.4 mg, once weekly in participants with T2D. In addition to comparing semaglutide s.c. 2.4 mg once weekly with placebo, a treatment arm with semaglutide s.c. 1.0 mg once weekly was included to enable comparison with the semaglutide s.c. T2D development programme (Ozempic) and a comparison of the effect on body weight between the two semaglutide doses (1.0 and 2.4 mg, only data from the semaglutide s.c. 2.4 mg group and placebo will be presented). The 68 weeks of treatment with semaglutide s.c. 2.4 mg included 16 weeks of dose escalation and 52 weeks on maintenance dose, followed by a 7-week follow-up period off treatment. In STEP 2 participants with a BMI ≥27 kg/m^2 and T2D were included.

In PIONEER PLUS participants with a BMI ≥25 kg/m^2 and T2D were included. Of the 535 participants in the oral semaglutide 25 mg group, 479 had a BMI ≥27 kg/m^2. Baseline characteristics of the patients included in STEP 2 and PIONEER PLUS are depicted in Table 27.

Body weight change (treatment policy strategy) from baseline to week 68 was -9.64% (-9.67 kg) in the STEP 2 semaglutide s.c. 2.4 mg group and -3.42% (-3.54 kg) in the STEP 2 placebo group. The relative body weight change from baseline to week 68 was -6.8% (-6.6 kg) in the PIONEER PLUS oral semaglutide 25 mg group.

Table 17: STEP 2 and PIONEER PLUS – Baseline characteristics

	STEP 2		PIONEER PLUS
Treatment group	Semaglutide s.c. 2.4 mg	Placebo	Oral semaglutide 25 mg
Number of participants (FAS)	404	403	535
Age, years (SD)	55 (11)	55 (11)	59 (11)
Sex			
Female (%)	55.2	47.1	43.2
Male (%)	44.8	52.9	56.8
Body weight, kg (SD)	99.9 (22.5)	100.5 (20.9)	96.6 (21.2)
BMI, kg/m^2 (SD)	35.9 (6.4)	35.9 (6.5)	34.1 (6.5)
Waist circumference, cm (SD)	115 (14)	116 (14)	113 (14)
HbA_{1c}, % (SD)	8.1 (0.8)	8.1 (0.8)	9.0 (0.8)

Abbreviations: BMI: body mass index; FAS: full analysis set; HbA_{1c}: glycosylated haemoglobin; s.c.: subcutaneous; SD: standard deviation.

The observed proportion of participants with a body weight loss ≥5% in STEP 2 was 68.8% and 28.5% for the semaglutide s.c. 2.4 mg group and placebo group, respectively. In PIONEER PLUS, the

proportion of participants with a weight loss ≥5% was 58.5% in the oral semaglutide 25 mg group at week 68.

STEP 1

This study investigated the efficacy and safety of semaglutide s.c. 2.4 mg once weekly for weight management as an adjunct to a reduced-calorie diet and increased physical activity in participants with obesity (BMI ≥30 kg/m^2), or participants with overweight (BMI ≥27 to <30 kg/m^2) with at least one weight related- comorbidity. In total, 1961 participants were randomised and exposed in a 2:1 ratio to either semaglutide s.c. 2.4 mg or placebo. Semaglutide s.c. 2.4 mg is the maintenance dose evaluated for weight management in STEP phase 3a programme. The objectives of STEP 1 were similar to OASIS 4. Primary endpoints were also similar between OASIS 4 and STEP 1. Secondary endpoints were merely similar, with some exceptions in categorisation of confirmatory or supportive secondary endpoint.

Comparison between OASIS 4 and STEP 1

Study populations

In OASIS 4, 205 of the 307 participants were randomised to oral semaglutide 25 mg and in STEP 1, 1306 of the 1961 participants were randomised to semaglutide s.c. 2.4 mg. In OASIS 4, 95.6% of sema and 92.2% of placebo patients completed the study, versus 94.9% of sema and 93.0% of placebo patients in STEP 1. Gastrointestinal disorders were the most frequent AEs leading to permanent treatment discontinuation with semaglutide regardless of route of administration.

Baseline characteristics were listed in Table 28.

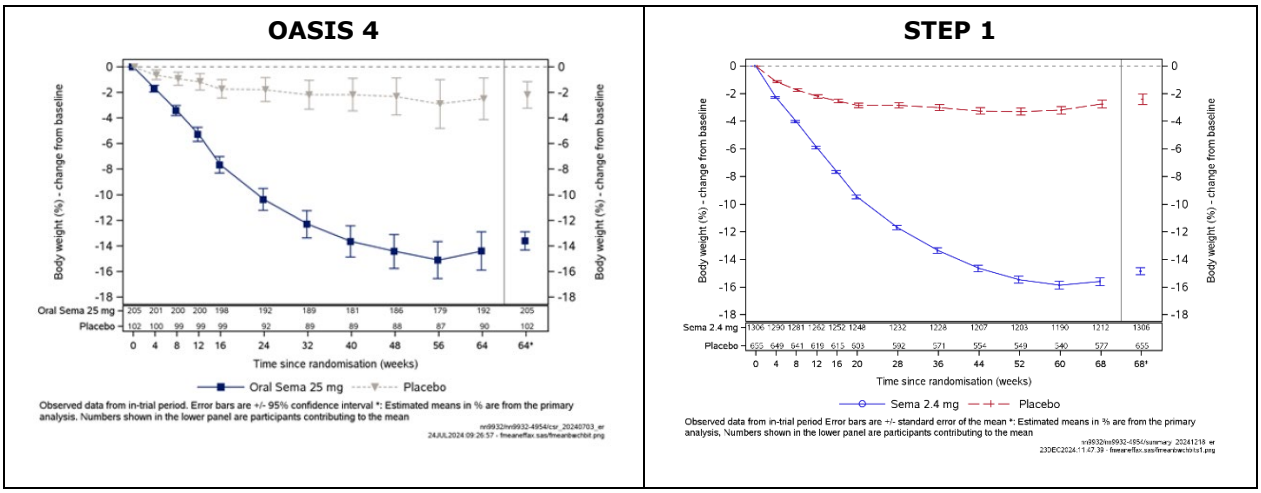
Table 18: OASIS 4 and STEP 1 – Demographics and baseline characteristics

	OASIS 4	**STEP 1**
Number of participants (FAS)	307	1961
Age, years (SD)	48 (13)	46 (13)
Sex		
Female, %	78.8	74.1
Male, %	21.2	25.9
Body weight, kg (SD)	105.9 (22.3)	105.3 (21.9)
BMI, kg/m^2 (SD)	37.6 (6.5)	37.9 (6.7)
Waist circumference, cm (SD)	113.9 (15.4)	114.7 (14.6)
HbA_{1c}, % (SD)	5.7 (0.3)	5.7 (0.3)
HbA_{1c}, mmol/mol (SD)	38.3 (3.7)	39.0 (3.5)

Efficacy – body weight

Change in body weight is depicted in Figure 8. In OASIS 4, participants treated with oral semaglutide 25 mg had a mean change in body weight from baseline to week 64 of -13.61% (-16.0 kg) compared to -2.18% (-2.2 kg) in participants treated with placebo. The estimated treatment differences (ETD [95% CI]) for change in mean body weight (%) at EOT was -11.43% [-13.88; -8.98]. Likewise, in STEP 1, participants treated with semaglutide s.c. 2.4 mg had a mean change in body weight from baseline to week 68 of -14.85% (-15.3 kg) compared to -2.41%(-2.6 kg) in participants treated with placebo. The ETD for change in mean body weight (%) at EOT was -12.44% [-13.37; -11.51].

Figure 6: OASIS 4 and STEP 1 - Body weight change from baseline (%) by week – mean plot – treatment policy strategy



The proportion of patients achieving weight loss response criteria are depicted in Table 29. In OASIS 4, the observed proportion of participants treated with oral semaglutide 25 mg who achieved ≥5% weight loss was 76.3% compared to 30.5% of participants treated with placebo. In STEP 1, 86.4% of participants treated with semaglutide s.c. 2.4 mg achieved ≥5% weight loss compared with 31.5% of participants treated with placebo.

Table 19: OASIS 4 and STEP 1 - Estimated proportion of participants (%) and treatment difference for categorical responses from baseline to EOT – treatment policy strategy

	OASIS 4		STEP 1	
	Oral sema 25 mg N=205	Placebo N=102	Sema s.c. 2.4 mg N=1306	Placebo N=655
Estimated % of participants achieving weight loss ≥5%	76.3	30.5	83.5	31.1
Estimated treatment difference [95% CI]	45.8 [34.6; 56.9]		52.4 [48.1; 56.8]	
Estimated % of participants achieving weight loss ≥10%	59.8	14.1	66.1	12.0
Estimated treatment difference [95% CI]	45.7 [35.9; 55.5]		54.1 [50.4; 57.9]	
Estimated % of participants achieving weight loss ≥15%	47.0	5.4	47.9	4.8
Estimated treatment difference [95% CI]	41.6 [33.4; 49.9]		43.1 [39.8; 46.3]	
Estimated % of participants achieving weight loss ≥20%[a]	27.5	3.0	30.2	1.7
Estimated treatment difference [95% CI]	24.5 [17.4; 31.5]		28.6 [25.9; 31.3]	

Abbreviations: CI: confidence interval; ETD: estimated treatment difference; N: number of participants; s.c.: subcutaneous.

Efficacy – cardiovascular

Blood pressure

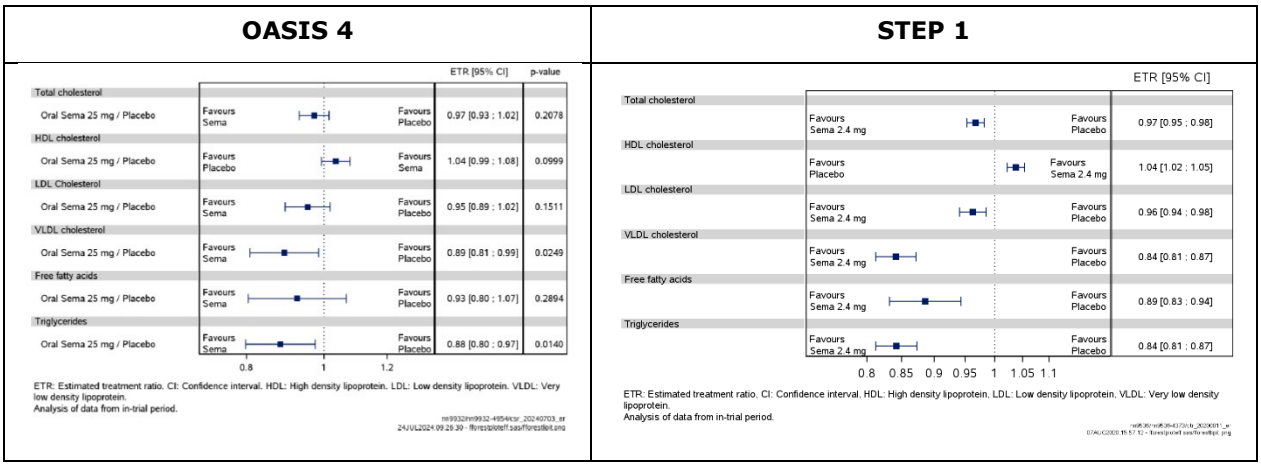
In OASIS 4, estimated mean change in SBP from baseline to EOT was -6.75 mmHg with oral semaglutide 25 mg treatment and -5.36 mmHg in the placebo group, ETD -1.39 mmHg [-4.59; 1.81] $_{95\%\ CI}$. In STEP 1, semaglutide s.c. 2.4 mg treatment resulted in a mean change of -6.16 mmHg and -1.06 mmHg with placebo, ETD -5.1 mmHg [-6.3; -3.9] $_{95\%\ CI}$.

In OASIS 4, estimated mean change in DBP from baseline to EOT was -2.72 mmHg with oral semaglutide 25 mg treatment and -2.07 mmHg in the placebo group (ETD: -0.65 mmHg [-2.80; 1.49]$_{95\%\ CI}$. In STEP 1, semaglutide s.c. 2.4 mg treatment resulted in a mean change of -2.83 mmHg and -0.42 mmHg with placebo (ETD: -2.41 mmHg [-3.25; -1.57]$_{95\%\ CI}$

Lipids

Lipid ratios are depicted in Figure 9: Lipids ratio to baseline at week 64 (OASIS 4) and at week 68 (STEP 1) - forest plot - treatment policy strategy - full analysis set for both studies.

Figure 7: Lipids ratio to baseline at week 64 (OASIS 4) and at week 68 (STEP 1) - forest plot - treatment policy strategy - full analysis set



CRP

Mean CRP levels decreased from baseline to EOT and the decrease was greater with semaglutide versus placebo in both studies. Estimated treatment ratios (ETRs) (semaglutide / placebo) were 0.56 [0.42; 0.74]$_{95\%\ CI}$ in OASIS 4 and 0.56 [0.51; 0.61]$_{95\%\ CI}$ in STEP 1.

Glycaemic efficacy

In OASIS 4, treatment with oral semaglutide 25 mg improved glucose metabolism with reductions in HbA_{1c} and FPG, consistent with those in STEP 1.

Study	HbA_{1c} Mean estimates and treatment differences					
	(%-points)			(mmol/mol)		
	Sema	Placebo	ETD [95% CI]	Sema	Placebo	ETD [95% CI]
OASIS 4	-0.29	-0.06	-0.23 (-0.31; -0.15)	-3.22	-0.70	-2.52 (-3.43; -1.60)
STEP 1	-0.45	-0.15	-0.29 (-0.32; -0.26)	-4.89	-1.69	-3.20 (-3.53; -2.87)
Fasting plasma glucose						
	(mmol/L)			(mg/dL)		
	Sema	Placebo	ETD [95% CI]	Sema	Placebo	ETD [95% CI]
OASIS 4	-0.36	0.02	-0.39 (-0.62; -0.15)	-6.56	0.42	-6.98 (-11.19; -2.77)
STEP 1	-0.46	-0.03	-0.44 (-0.50; -0.37)	-8.35	-0.48	-7.87 (-9.04; -6.70)

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

N/A.

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

Dose finding

No dedicated dose-response studies were performed for oral semaglutide for weight management indication. The dose selection was primarily based on previous extensive experience with semaglutide and modelling, and a PD study was performed.

In the PD study, the pharmacodynamic effects and pharmacokinetics at steady state of oral semaglutide 50 mg once-daily in participants with obesity were investigated. The relative change in energy intake during ad libitum lunch at day 140 was 39.2%-point lower with oral semaglutide 50 mg vs. placebo (-33.0% vs. 6.2%). The mean weight loss at day 141 was - 9.8% with oral semaglutide 50 mg and 1.5% with placebo. The study was performed with oral semaglutide 50 mg. However, the 25 mg dose was selected for weight managementand to support the dose choice, a comparison of the systemic exposure levels of semaglutide s.c. 2.4 mg in STEP 1 and 2, with the systemic exposure levels in patients with T2D and a BMI $\geq$ 27 kg/ m^2 included in PIONEER PLUS treated with 25 mg and 50 mg oral semaglutide, were presented. The results showed a generally comparable exposure overlap with 2.4 mg s.c. semaglutide in STEP 1 and 2 with the exposure levels of oral semaglutide 25 mg and 50 mg in the PIONEER PLUS study (65%-75%). The 50 mg dose resulted in a larger proportion of patients with systemic exposure levels above the exposure level (range) in STEP 1 and 2 compared to the 25 mg dose (18-25% vs 2-3%). The decision of choosing the 25 mg dose in patients with T2D is considered acceptable.

Clinical studies

Study design and population

The efficacy of oral semaglutide was studied in OASIS 4, accompanied with data from s.c. semaglutide and from oral semaglutide in T2DM population (Rybelsus). OASIS 4 was an

interventional 64 week, randomised, phase III b, placebo-controlled, double-blind two-armed, multi-centre, multinational clinical study comparing the efficacy of once daily 25 mg oral semaglutide versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with overweight and weight-related comorbidities, or with obesity. OASIS 4 had a 12-week dose escalation phase for patients to build up to semaglutide 25 mg (or placebo), followed by a 52-week treatment phase. This is considered appropriate for studies in weight management (EMA/CHMP/311805/2014).

Inclusion and exclusion criteria were generally considered appropriate and were previously agreed upon in the Scientific Advice (EMA/SA/0000051734). Patients with renal impairment (eGFR <15 ml/min/1.73 m^2) were excluded, which is in line with the recommendations for semaglutide (Rybelsus). Patients with diabetes mellitus were excluded, although type 2 diabetes is listed as a weight-related comorbidity in the indication. The co-primary endpoints and secondary endpoints were acceptable and in line with EMA guidance and SA. Patients were randomised in a 2:1 (oral semaglutide 25 mg: placebo) ratio. Randomisation was not stratified according to baseline characteristics such as baseline BMI.

The primary estimand attributes are agreed. Two intercurrent events were defined, discontinuation of trial medication and initiation of anti-obesity therapy, both handled by a treatment policy strategy. This results in a clinically relevant question, is appropriate for decision-making and is acceptable.

The definition of the analysis sets and observation periods are considered standard and acceptable. Continues endpoints were analysed using ANCOVA with baseline measurement as covariate. For binary endpoints, the analysis was performed using logistic regression with baseline measurement as covariate. This is considered standard and acceptable. Missing data was handled using retrieved drop-out imputation, which is aligned with the primary estimand and acceptable as well. Sensitivity analyses using jump to reference, tipping point and MMRM are adequate to test the assumptions of missing data handling. Multiplicity for the co-primary and confirmatory secondary endpoints was handled using fixed sequence hierarchical testing, which controls the overall type I error.

The sample size calculation is based on reasonable assumptions derived from earlier semaglutide studies and can be followed.

Results

The percentage of patients who completed the treatment was higher in the semaglutide group (81.5% versus 74.5% in the placebo group), which is reassuring. There were no apparent differences in patient disposition between the semaglutide group and the placebo group that raised concern on semaglutide. However, although the number of discontinuations or lost to follow-up were not large, patients that discontinued might differ from those who completed the study. Characteristics of patients that discontinued treatment did not differ from treatment completers

In total, 307 patients were included in OASIS 4 (205 in the semaglutide and 102 in the placebo group), which means that the sample size was met. The study population in OASIS 4 included an overrepresentation of females, which was also the case in the STEP program for s.c. semaglutide for weight management indication. However, no differences were seen in the efficacy in females versus males (see below). Therefore, no issue is raised on the overrepresentation of females (and, consequently, underrepresentation of male patients).

Subgroups

Patients with high BMI are well-represented. However, there are limited data in OASIS 4 on patients with BMI $\geq$ 27 kg/m^2 to <30 kg/m^2 and a weight-related comorbidity, n=18, of which only 13 were

treated with oral semaglutide 25 mg and 5 with placebo. However, weight loss in those participants was in line with that in participants with higher BMI' s (-8.66 vs -11.57 kg; p for interaction 0.6081). In addition, no clinically meaningful heterogeneity of treatment effect was identified in this sub-population across other trials.

A total of 9 patients with moderate renal impairment were included, which is considered low. The number of patients with comorbidities was large, but percentage and type of comorbidities were well-balanced between groups and do not raise concern. About half of included patients were prediabetic, which is expected in the target population.

Primary endpoints

The co-primary endpoints were met. Compared with placebo, mean body weight change was -11.43% for oral semaglutide 25mg (ETD -11.43% [-13.88; -8.98]95% CI; p-value <0.0001). This effect is also considered clinically relevant. For patients receiving semaglutide, body weight reduction started briefly after initiation of treatment and continued to reduce until approximately 40 weeks of treatment, with the steepest decline in the first 24 weeks. Body weight reduction was maintained until the end of treatment (week 64).

Other endpoints

Also, significantly more patients in the oral semaglutide 25mg group (76.3%) achieved a body weight reduction of ≥5%, versus 30.5% in the placebo group. These results were confirmed in the other weight loss categories (≥10%, ≥15%, ≥20%), and the other supportive secondary endpoints that assess change in weight/ BMI, and a decrease in waist circumference.

Patients receiving oral semaglutide 25mg achieved a mean change of 16.18 in IWQOL-Lite-CT Physical Function, versus 8.45 in patients receiving placebo (confirmatory secondary endpoint), with an ETD of 7.73 [3.30;12.16]95%CI. The clinical meaning of this change was however questioned. The meaningful within-patient change was defined as 14.6 score points. IWQOL-Lite-CT results are not included in the SmPC, therefore, this issue was not pursued.

Semaglutide for weight management in T2DM patients (PIONEER PLUS)

Patients with T2DM were excluded from OASIS 4. Data for supporting the use of oral semaglutide 25 mg for weight management indication in patients with BMI 27 – 30 kg/m^2 came from PIONEER PLUS, which was agreed upon in the SA.

Patients in PIONEER PLUS were older (mean age 59[SD 11]) compared with those in OASIS 4 (mean age 48 [SD 13]) and had a lower mean BMI (34.1 versus 37.6 in OASIS 4), which is likely because patients with BMI ≥25 kg/m^2 were included in PIONEER PLUS. Mean HbA1c was higher in PIONEER PLUS (9.0% versus 5.7%), which is logical for a study in T2DM population.

The relative change in body weight was -6.8% compared to baseline and the proportion of participants with a weight loss ≥5% was 58.5% (data from PIONEER PLUS), compared with a body weight change of -13.6% and 76.3% of patients achieving ≥5% weight loss in OASIS 4. The effects on body weight in patients with obesity/overweight and T2DM is considered clinically relevant since even modest weight loss can improve glycemia, blood pressure, lipids and, in general, help reduce obesity-associated health risks.

In STEP 2, the relative change in body weight was -6.22% compared with placebo. As STEP 2 is performed with s.c. semaglutide and in patients with T2DM and BMI ≥27 kg/m^2, these results are considered mildly supportive for the current application.

Supportive studies and comparison with s.c. semaglutide

STEP 1 was previously assessed for the MAA of Wegovy s.c. In the context of Wegovy tablets, the

most important and/ or relevant characteristics of the study were assessed. It must be noted that results from studies performed with s.c. semaglutide cannot be extrapolated to oral semaglutide. Due to the large variability in exposure, it remains uncertain if the exposure obtained with oral semaglutide is sufficient for the entire population to exhibit the effects of s.c. semaglutide. However, while some patients have not achieved the same exposure with oral semaglutide 25 mg and subcutaneous semaglutide 2.4 mg, data from the following trials with the subcutaneous formulation are considered informative for the oral formulation and have therefore been accepted in section 5.1 for the tablet formulation.

In OASIS 4, change in body weight was -11.43% (95%CI -13.88;-8.98) compared with placebo, which is similar to that in STEP 1 (-12.44[95%CI -13.37; -11.51]),

Blood pressure was not statistically significantly reduced in OASIS 4 (SBP -1.39 mmHg[-4.59; 1.81] $_{95\% CI}$; DBP -0.65mmHg [-2.80; 1.49]$_{95\% CI}$ compared with placebo), while in STEP 1 SBP (-5.1 mmHg [-6.3; -3.9] $_{95\% CI}$) and DPB (-2.41 mmHg [-3.25; -1.57]$_{95\% CI}$) were statistically significantly and clinically relevantly reduced. Changes in lipid profile were more favourable in STEP 1; total, LDL and VLDL cholesterol, free fatty acids and triglycerides were reduced, HDL cholesterol was increased in STEP 1. Change in hsCRP was similar in OASIS 4 as in STEP 1.

Product information

The proposed indication in section 4.1 in the SmPC initially included the statement

"*For trial results with respect to cardiovascular risk reduction, obesity-related heart failure, and populations studied, see section 5.1*."

The studies included on cardiovascular risk reduction and obesity-related heart failure are SELECT, SUSTAIN and STEP-HFpEF. All these studies are performed with s.c. semaglutide and inclusion of studies performed with s.c. administered semaglutide was not considered acceptable in the SmPC of oral semaglutide. Bridging of efficacy data from s.c. to oral is not considered possible. Due to the large variability in exposure, it remains uncertain if the exposure obtained with oral semaglutide is sufficient for the entire population to exhibit the effects of s.c. semaglutide and the effect size, if any, cannot be estimated. The applicant was therefore requested to remove these studies from the SmPC. In the first round, SUSTAIN and STEP-HFpEF were removed by the applicant. However, the SELECT trial was not removed from section 5.1, and the applicant proposed to maintain the statement cited above (SmPC section 4.1). Even if there are overlaps between the exposure of semaglutide and the study populations, it is uncertain if treatment with Wegovy tablets will have the same cardioprotective effect as was indicated by the results of the SELECT trial. However, the experience from the CV outcomes trial performed with subcutaneous semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results in section 5.1 for Wegovy tablets. However, the reference in section 4.1 with respect to effect on CV events is not supported by the data and has been deleted.

5.3.7.2. Conclusions on the clinical efficacy

In the pivotal study OASIS 4, oral semaglutide demonstrated statistically significant and clinically relevant beneficial effects on the co-primary endpoints mean change in body weight (ETD -11.43% [-13.88; -8.98]95% CI) and the observed proportion of participants who achieved ≥5% weight loss (79.2% for those receiving oral semaglutide 25 mg and 31.1% for those receiving placebo). These beneficial effects found in those treated with oral semaglutide were supported by beneficial outcomes on other weight-related secondary endpoints, and reduction in waist circumference.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety evaluation is primarily based on results from the pivotal phase 3 confirmatory study OASIS 4. In OASIS 4, a total of 307 participants with obesity (BMI ≥30 kg/m^2) or with overweight (BMI ≥27 kg/m^2) and at least one weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease) were randomised 2:1 to once-daily treatment with oral semaglutide 25 mg or placebo.

The safety evaluation is based on standard assessments with in-depth evaluation of a range of safety focus areas predefined based on experience with the GLP-1 RA drug class and on regulatory advice and requirements. Additional data collection on event specific forms was done for acute gallstone disorder, acute pancreatitis, malignant neoplasms, hepatic disorders, medication error, abuse and misuse. These data were intended as a supplement to the data collected on the standard AE forms.

Supportive data from PIONEER PLUS and STEP

Although treatment with oral semaglutide 25 mg in OASIS 4 resulted in exposure levels that were on average on par with exposure levels of s.c. semaglutide 2.4 mg in STEP 1, there also was a significant part of the population that did not show overlap in exposure levels. In addition, there was greater variability in exposure with oral semaglutide treatment compared to s.c. semaglutide treatment, and at the same dose level and route of administration, lower exposure was seen in participants with T2D (STEP 2, PIONEER PLUS) versus participants without T2D (STEP 1, OASIS 1, OASIS 2, and OASIS 4). Therefore, the use of safety data from the PIONEER PLUS study with oral semaglutide 25 mg as well as from the STEP programme (STEP 1−4) with s.c. semaglutide at a dose of 2.4 mg in the overall safety evaluation of oral semaglutide 25 mg for weight management is only considered supportive. The PIONEER and STEP studies have been assessed previously, and data have been added to the SmPC of Rybelsus and subcutaneous Wegovy. A direct comparison between studies is not possible.

5.4.2. Patient exposure

In OASIS 4, a total of 306 participants were exposed to treatment, including 204 participants who were exposed in the oral semaglutide 25 mg group. The total duration of exposure to trial product was 251.1 PYE in the oral semaglutide 25 mg treatment group.

5.4.3. Adverse events

The proportions of participants with AEs and event rates were slightly higher with oral semaglutide 25 mg than with placebo (93.1% versus 85.3%; 493.5 versus 355.9 events per 100 PYE). The relative distribution of AEs with respect to seriousness, severity, and outcome were similar across both groups.

The proportion of participants with AEs leading to permanent treatment discontinuation was slightly higher with oral semaglutide 25 mg than with placebo (6.9% versus 5.9%). AEs leading to permanent discontinuation were distributed across multiple SOCs, with the majority being reported within the SOC Gastrointestinal disorders.

Adverse events - overview - safety analysis set: OASIS 4

	Oral Sema 25 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of participants	204				102			
Patient years of exposure (PYE)	251.1				121.4			
Adverse Events (OT)	190	(93.1)	1239	493.5	87	(85.3)	432	355.9
Serious								
Yes (OT)	8	(3.9)	17	6.8	9	(8.8)	13	10.7
Severity								
Severe (OT)	10	(4.9)	16	6.4	10	(9.8)	17	14.0
Relationship to trial product								
Probable (OT)	110	(53.9)	309	123.1	16	(15.7)	22	18.1
Possible (OT)	113	(55.4)	363	144.6	34	(33.3)	83	68.4
Outcome								
Fatal (IT)	0				0			
Leading to								
Permanent treatment discontinuation (OT)	14	(6.9)	14	5.6	6	(5.9)	6	4.9

N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 years. PYE: The duration of the on-treatment period in years. OT: On-treatment. IT: In-trial.
On-treatment adverse events have onset date during on-treatment period. A time-point is considered
as on-treatment if any dose of trial product has been administered within the prior 49 days.

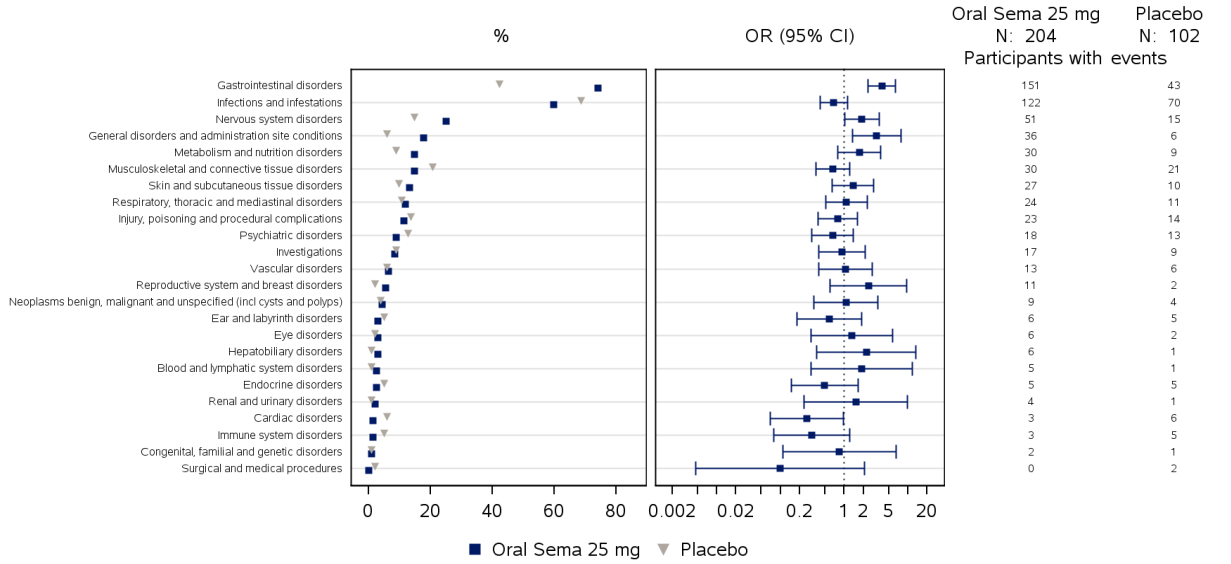
As expected for the GLP-1 RA drug class, the most frequent AEs were reported in the SOC Gastrointestinal disorders, with a higher frequency for oral semaglutide 25 mg (74.0%) versus placebo (42.2%). The common PTs related to gastrointestinal disorders observed more frequently with oral semaglutide 25 mg than with placebo included: Nausea, Vomiting, Constipation, Dyspepsia, Diarrhoea, Eructation, and Abdominal pain upper.

Besides gastrointestinal disorders, the proportion of participants and event rates were higher in the oral semaglutide 25 mg group (25.0%) compared to the placebo group (14.7%) for the Nervous

system disorders (mainly driven by events of Headache and Dizziness), and General disorders and administration site conditions (mainly driven by events of Fatigue).

Less common PTs observed more frequently with oral semaglutide 25 mg than with placebo included events related to a clinical picture of dysaesthesia (PTs Dysaesthesia, Hyperaesthesia, Paraesthesia, Skin burning sensation, Burning sensation, Pain of skin, Sensitive skin, Skin discomfort, Skin sensitization, Allodynia, and hyperpathia). In the oral semaglutide 25 mg group, 4.9% of participants reported events of dysaesthesia, at an event rate of 5.2 events per 100 PYE, as compared to no events in placebo group. All events were non-serious, and majority of events were mild in severity and reported as recovered. None of the events led to permanent treatment discontinuation.

Adverse events - statistical analysis by system organ class - forest plot - on-treatment - safety analysis set: OASIS 4



Adverse events with onset prior to randomisation are not included.
Sorted in descending order by system organ class based on the proportion of participants in the oral semaglutide 25 mg arm experiencing at least one event.
N: Number of participants. %: Percentage of participants experiencing at least one event, OR: Odds ratio, CI: Confidence interval dis.: disorders, cond.: conditions, adm.: administration, comp.: complications. Neoplasms include benign, malignant and unspecified (incl cysts and polyps).
Each of the groupings of adverse events were analysed using a binary logistic regression model with randomised treatment as factor.
Participants are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 27.0.

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5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

5.4.4.1. Deaths and other serious events

In OASIS 4, no fatal events were reported in the study.

The proportion of participants reporting one or more SAEs during the on-treatment period was 3.9% in the oral semaglutide 25 mg group and 8.8% in the placebo group. SAEs were distributed on multiple SOCs and PTs with no clustering in the treatment groups.

Serious adverse events by system organ class and preferred term - summary – on-treatment - safety analysis set: OASIS 4

System organ class	Oral Sema 25 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of participants	204				102			
PYE	251.08				121.38			
Events	8	(3.9)	17	6.8	9	(8.8)	13	10.7
Nervous system disorders	2	(1.0)	5	2.0	0			
Metabolism and nutrition disorders	1	(0.5)	2	0.8	1	(1.0)	1	0.8
Musculoskeletal and connective tissue disorders	1	(0.5)	2	0.8	1	(1.0)	1	0.8
Blood and lymphatic system disorders	1	(0.5)	1	0.4	0			
Cardiac disorders	1	(0.5)	1	0.4	0			
Hepatobiliary disorders	1	(0.5)	1	0.4	0			
Infections and infestations	1	(0.5)	1	0.4	2	(2.0)	2	1.6
Injury, poisoning and procedural complications	1	(0.5)	1	0.4	1	(1.0)	1	0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.5)	1	0.4	1	(1.0)	1	0.8
Reproductive system and breast disorders	1	(0.5)	1	0.4	1	(1.0)	1	0.8
Vascular disorders	1	(0.5)	1	0.4	1	(1.0)	1	0.8
Gastrointestinal disorders	0				1	(1.0)	1	0.8
Psychiatric disorders	0				1	(1.0)	2	1.6
Renal and urinary disorders	0				1	(1.0)	1	0.8
Surgical and medical procedures	0				1	(1.0)	1	0.8

N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration
of the on-treatment period in years.
Adverse events with onset date during on-treatment period: A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in
descending order by system organ class and preferred term based, respectively, on the percentage of
participants in the Sema 25 mg arm experiencing at least one event.
MedDRA version 27.0

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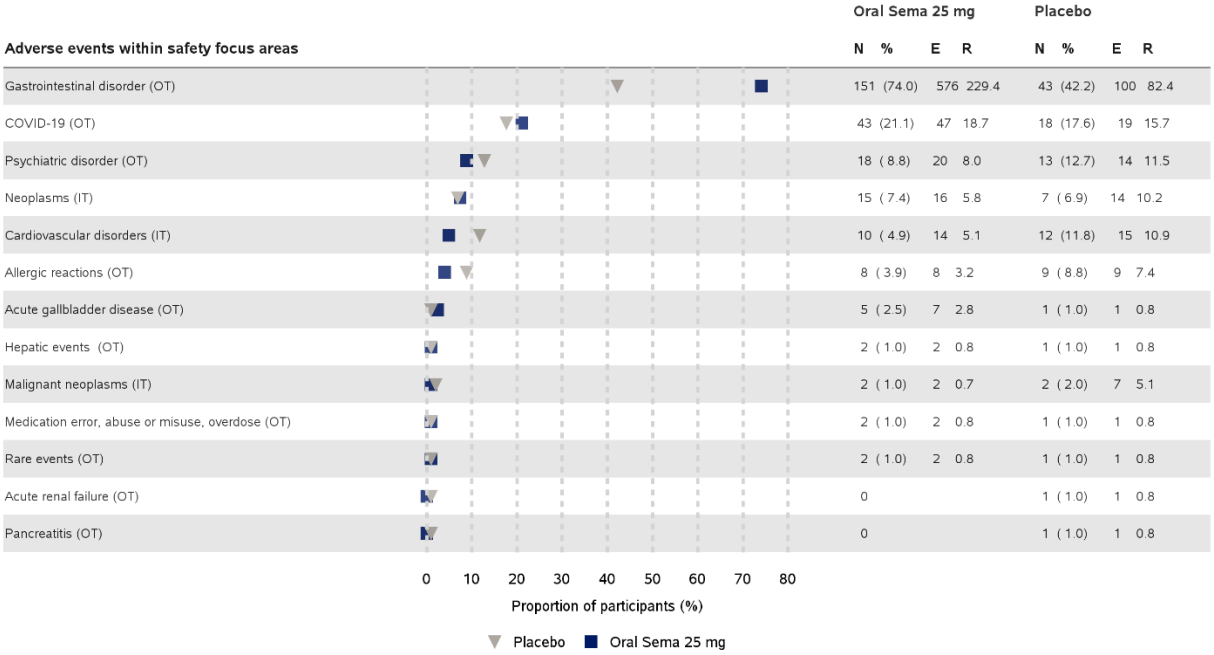
5.4.4.2. Safety focus areas

A number of safety focus areas were predefined as being of special interest in the evaluation of the safety of oral semaglutide 25 mg based on the nonclinical and clinical data with semaglutide, the GLP-1 RA drug class in general, and regulatory feedback and requirements.

An overview of the results for the safety focus areas is provided below.

Overview of safety focus areas from OASIS 4



N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 years . OT: On-treatment. IT: In-trial. Adverse events with onset date during on-treatment period: A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days.
Only safety focus areas with reported events included. Sorted in descending order by preferred term based on the percentage of participants in the Oral Sema 25 mg arm experiencing at least one event.
MedDRA version 27.0

nn9932/nn9932-4954/csr_20240703_er
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Gastrointestinal events

As described above, gastrointestinal AEs were more frequently reported with oral semaglutide 25 mg (74.0% of participants) compared to placebo (42.2% of participants). The majority of gastrointestinal AEs were non-serious, mild or moderate in severity, and reported as recovered.

Cholelithiasis

The proportion of participants reporting events of Cholelithiasis in the oral semaglutide 25 mg group in OASIS 4 was 2.5% vs 1.0% in placebo group.

Pancreatitis

One (1) AE of pancreatitis was reported in OASIS 4 and this event was a mild SAE reported in the placebo group.

Cardiovascular disorders

The proportion of participants reporting AEs related to cardiovascular disorders were lower in the oral semaglutide 25 mg group (4.9%) compared to the placebo group (11.8%). One (1) SAE of cardiovascular disorder (PT Ischaemic stroke) in the oral semaglutide 25 mg group led to permanent treatment discontinuation. The proportion of participants with SAEs related to cardiovascular disorders was similar in the oral semaglutide 25 mg group (1.0%, 1.1 events per 100 PYO) compared to placebo (1.0%, 0.7 events per 100 PYO).

The change in heart rate from baseline to week 64 was 2 beats/min for oral semaglutide 25 mg versus 1 beat/min for placebo, and the treatment difference between oral semaglutide 25 mg and placebo was not statistically significant (0.33 beats/min [2.28; 2.93]95% CI)

Neoplasms (benign and malignant)

AEs related to neoplasms (benign and malignant) were reported by a similar proportion of participants across treatment groups, though at a lower event rate with oral semaglutide 25 mg (7.4%, 5.8 events per PYO) compared to placebo (6.9%, 10.2 events per PYO). There was no clear clustering on SOC and PT levels in the tissue or organ of origin in which the event of neoplasms occurred.

The proportion of participants reporting AEs of malignant neoplasms was low across treatment groups, though with a lower event rate in the oral semaglutide 25 mg group (1.0%, 0.7 events per PYO) compared to the placebo group (2.0%, 5.1 events per PYO).

Hepatic disorders

In OASIS 4, 3 AEs related to hepatic disorders were reported (2 AEs in oral semaglutide 25 mg group and 1 AE in placebo group), with a similar proportion of participants reporting AEs with oral semaglutide 25 mg and placebo (1.0% versus 1.0%).

At week 64, the ratio to baseline of ALT, AST and ALP had decreased in both treatment groups, but to a greater extent with oral semaglutide 25 mg compared to placebo. Conversely, a slight increase of total bilirubin was seen in both treatment groups at week 64, with a greater elevation seen in the oral semaglutide 25 mg group compared to placebo (24% vs 12%).

Renal events

In OASIS 4, participants with severe renal impairment or end-stage renal disease were excluded from the study. No events related to acute renal failure were reported with oral semaglutide 25 mg. One (1) SAE of PT Acute kidney injury was reported in the placebo group, which was severe and was recovered but led to temporary interruption of trial product. Geometric mean ratios of eGFR at week 64 compared with baseline were stable across both treatment groups One (1) non-serious AE related to eGFR (glomerular filtration rate decreased) was reported with oral semaglutide 25 mg, which was moderate in severity, resolved by end of study.

There were no relevant changes in renal function parameters eGFR and creatinine in the OASIS 4 study.

Hypoglycaemia

Hypoglycaemia was not a predefined safety focus area in OASIS 4 study, since the study did not include participants with T2D. No AEs of Hypoglycaemia were reported in both the treatment groups.

Retinal disorders

Retinal disorders was not a predefined safety focus area in OASIS 4 study, since the study did not include participants with T2D. No adverse events of diabetic retinopathy were reported.

Psychiatric disorders

In OASIS 4, AEs related to psychiatric disorders were reported by a lower proportion of participants and lower event rates with oral semaglutide 25 mg (8.8%, 8.0 events per 100 PYE) than with placebo (12.7%, 11.5 events per 100 PYE). In both treatment groups, the events were distributed across a broad range of PTs.

Post baseline, no participants reported suicidal behaviour. Suicidal ideation as assessed by C-SSRS was reported by 1 participant in the oral semaglutide 25 mg group and no participants in the placebo group.

Post baseline, 5 participants in the oral semaglutide 25 mg group had a total maximum score of ≥15 corresponding to moderately severe depression (15–19) or severe depression (≥20) on the PHQ-9 depression questionnaire. No participants in the placebo group had a total maximum score of ≥15

post-baseline. In PIONEER PLUS, psychiatric disorders were not assessed as a predefined safety focus area.

Intestinal obstruction and aspiration

Overall, no AEs were captured by the MedDRA search for intestinal obstruction in the OASIS 4. In addition, there were no AEs reported with oral semaglutide 25 mg in relation to PTs of Aspiration, Pneumonia aspiration, or Anaesthetic complication pulmonary in the OASIS 4.

Rare events

In OASIS 4, rare events were reported by the similar proportion of participants in both treatment groups (2 AEs with oral semaglutide 25 mg and 1 AE with placebo).

Other significant effects

Hair loss (alopecia) was reported in 6.4% of adults using semaglutide and 2% using placebo.

5.4.5. Discontinuation due to adverse events

In OASIS 4, the proportions of participants with AEs leading to permanent treatment discontinuation and the rate of AEs leading to permanent treatment discontinuation were slightly higher with oral semaglutide 25 mg (6.9%; 5.6 events per 100 PYE) than with placebo (5.9%; 4.9 events per 100 PYE).

5.4.6. Safety in special populations

In the OASIS 4 study, the potential impact of various intrinsic and extrinsic factors on the safety profile of oral semaglutide 25 mg versus placebo was evaluated. The prespecified intrinsic and extrinsic factors evaluated were: Sex, Baseline age, Race, Ethnic origin, Baseline body weight, Baseline BMI, Baseline renal function, Presence of upper gastrointestinal disease at baseline, Baseline glycaemic status, Hepatic impairment at baseline, Extrinsic factors, Region, and Anti-diabetic background medication.

While minor differences between some subgroups were observed, no unexpected clinically relevant interactions between oral semaglutide 25 mg and any intrinsic or extrinsic factors were identified. For the subgroup analyses with respect to age, only 21 patients >=65 years were treated. For the subgroup analyses with respect to race, only 13 Black or African American and 1 Asian were treated.

The populations in OASIS 4 were evaluated based on subgroups of body weight loss at the end of treatment. Overall, the treatment differences for all AEs, SAEs, severe AEs and AEs leading to permanent treatment discontinuation in the oral semaglutide 25 mg group were similar between the weight loss subgroups, with no indication of a higher frequency of such events with a greater weight loss. Higher frequencies of AE reporting for participants losing ≥20% versus <20% of their baseline body weight with oral semaglutide 25 mg were seen for the SOC Gastrointestinal disorders.

5.4.7. Immunological events

In OASIS 4, the proportion of participants reporting AEs within the MedDRA searches of allergic reactions and corresponding event rates were higher with placebo (8.8%, 7.4 events per 100 PYE) compared to oral semaglutide 25 mg (3.9%, 3.2 events per 100 PYE).

The company did not report whether the safety profile of semaglutide was impacted by the presence of anti-semaglutide antibodies in OASIS 4.

5.4.8. Vital signs and laboratory findings

In the OASIS 4 study, the estimated mean change in SBP from baseline was 6.75 mmHg with oral semaglutide 25 mg, which was greater than with placebo (-5.36). The estimated mean change in DBP from baseline was -2.72 mmHg with oral semaglutide 25 mg, which was greater than with placebo (-2.07).

In the OASIS 4 study, 5 AEs of Hypotension were reported, 3 in 3 participants in the oral semaglutide 25 mg group and 2 in 2 participants in the placebo group

No notable changes were observed in any of the haematology parameters in the OASIS 4. In the OASIS 4 study, the ratios to baseline at the end of the treatment period (week 64) were also comparable between the oral semaglutide 25 mg and placebo treatment groups for potassium, sodium and TSH.

5.4.9. Overall discussion and conclusions on clinical safety

5.4.9.1. Discussion

In OASIS 4, a total of 307 participants with obesity (BMI ≥30 kg/m^2) or with overweight (BMI ≥27 kg/m^2) and at least one weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease) were randomised 2:1 to once-daily treatment with oral semaglutide 25 mg or placebo. A total of 306 participants were exposed to treatment, including 204 participants who were exposed in the oral semaglutide 25 mg group. In combination with knowledge from semaglutide in other studies, this is considered sufficient for the evaluation of safety and tolerability of oral semaglutide 25 mg for weight management.

Supportive data from PIONEER PLUS and STEP

Although treatment with oral semaglutide 25 mg in OASIS 4 resulted in exposure levels that were on average on par with exposure levels of s.c. semaglutide 2.4 mg in STEP 1, there also was a significant part of the population that did not show overlap in exposure levels. In addition, there was greater variability in exposure with oral semaglutide treatment compared to s.c. semaglutide treatment, and at the same dose level and route of administration, lower exposure was seen in participants with T2D (STEP 2, PIONEER PLUS) versus participants without T2D (STEP 1, OASIS 1, OASIS 2, and OASIS 4). Therefore, the use of safety data from the PIONEER PLUS study with oral semaglutide 25 mg as well as from the STEP programme (STEP 1−4) with s.c. semaglutide at a dose of 2.4 mg in the overall safety evaluation of oral semaglutide 25 mg for weight management is only considered supportive for the currently proposed indication. Study results can be compared, but results from PIONEER and STEP cannot be directly extrapolated to the effects of oral semaglutide in the obese population. The PIONEER and STEP studies have been assessed previously, and data have been added to the SmPC of Rybelsus and subcutaneous Wegovy.

At data-cut-off date of 01 July 2025, 740 subjects were exposed to the 25 mg oral semaglutide maintenance dose. This included 204 subjects in the pivotal OASIS 4 trial with a total of 251.1 patient-years of exposure (PYE) and 534 participants in PIONEER PLUS with a total of 647.1 PYE. In total, 603

subjects were exposed to oral semaglutide 25 mg for ≥ 1 year (N = 174 and N = 429 in OASIS 4 and PIONEER PLUS, respectively). Across the PIONEER PLUS and OASIS 1-3 studies, a total of 1380 subjects were exposed to 50 mg oral semaglutide. In STEP 1-4, 2650 subjects were exposed to weekly semaglutide s.c. 2.4 mg with a total duration of exposure of 3309 patient-years.

Study completement and permanent discontinuations

Of the participants on oral semaglutide 25 mg in OASIS 4 study, 95.6% completed the study, 81.5% completed treatment with the trial product and 66.3% were uptitrated to the intended 25 mg maintenance dose. The proportion of participants who permanently discontinued trial product was lower with oral semaglutide 25 mg (18.0%) than with placebo (25.5%). The majority of participants in the oral semaglutide 25 mg arm, discontinued the treatment due to AEs (6.8%) (mainly driven by gastrointestinal AE), and 'Other' reasons (6.8%). For participants in the placebo group, the primary reason for not completing treatment was 'Other'.

Adverse events

The proportion of participants with AEs and event rates were slightly higher with oral semaglutide 25 mg than with placebo (93.1% versus 85.3%; 493.5 versus 355.9 events per 100 PYE). AEs were reported by a similar proportion of participants with oral semaglutide 25 mg and placebo within most SOCs. For the following SOCs, higher proportions of participants or higher rates were observed with oral semaglutide 25 mg compared to placebo: Gastrointestinal disorders, Nervous system disorders, General disorders and administration site conditions

Gastrointestinal disorders: The most frequent types of reported AEs with oral semaglutide 25 mg compared to placebo were in the SOC Gastrointestinal disorders. The following PTs were reported by ≥5% of participants and more often with oral semaglutide 25 mg compared to placebo: Nausea (46.6% versus 18.6%), Vomiting (30.9% versus 5.9%), Constipation (20.1% versus 9.8%), Dyspepsia (18.1% versus 8.8%), Diarrhoea (17.6% versus 8.8%), Eructation (10.3% versus 2.0%), and Abdominal pain upper (8.8% versus 2.0%). These side effects are already well known.

Nervous system disorders: The imbalance was primarily driven by the PTs Headache (11.8% versus 8.8%) and Dizziness (5.4% versus 1.0%) Headache and dizzyness are already stated in the SmPC.

General disorders and administration site conditions: The imbalance was driven by the PT Fatigue (7.4% versus 1.0%) The development of fatigue is in line with previous findings and already described in the SmPC.

Dysesthesia

Less common PTs reported more frequently with oral semaglutide 25 mg than with placebo included events related to a clinical picture of dysaesthesia (PTs Dysaesthesia, Hyperaesthesia, Paraesthesia, Skin burning sensation, Burning sensation, Pain of skin, Sensitive skin, Skin discomfort, Skin sensitization, Allodynia and Hyperpathia). In total, 13 AEs were reported, and all were reported in the oral semaglutide 25 mg group (4.9% of participants at an event rate of 5.2 events per 100 PYE). Events related to dysaesthesia are known to be associated with semaglutide, and dysaesthesia is included in the text of the SmPC. However, the 4.9% risk is higher than that observed in the oral semaglutide 25 mg group in PIONEER PLUS (2.1% (1.7 events per 100 PYE). Dysaestehsia will be carefully monitored through routine post-marketing pharmacovigilance activities.

Deaths and SAEs

No fatal events were reported in OASIS 4.

The proportion of participants reporting one or more SAEs during the on-treatment period was 3.9% in the oral semaglutide 25 mg group and 8.8% in the placebo group. The proportion of participants with AEs leading to permanent treatment discontinuation and the overall rate of AEs leading to permanent treatment discontinuation were slightly higher with oral semaglutide 25 mg (6.9%; 5.6 events per 100 PYE) than with placebo (5.9%; 4.9 events per 100 PYE). AEs leading to permanent discontinuation were distributed across multiple SOCs, with the majority being reported within SOC of Gastrointestinal disorders.

Focus areas

Gastrointestinal

As described above, gastrointestinal AEs were more frequently reported with oral semaglutide 25 mg (74.0% of participants) compared to placebo (42.2% of participants). The majority of gastrointestinal AEs were non-serious, mild or moderate in severity, and reported as recovered.

Cholelithiasis

The proportion of participants reporting events of Cholelithiasis in the oral semaglutide 25 mg group in OASIS 4 was 2.5% vs 1.0% in placebo group. This was slightly higher than the risk in the STEP trials (1.6% in the semaglutide s.c. 2.4 mg arm vs 1.1% in the placebo arm) and PIONEER PLUS (0.4% vs 0.6% vs 0.6% for 14 mg, 25 mg, and 50 mg treatment groups respectively). However, the observed proportion of subjects with cholelithiasis was not higher than what could be expected based on the magnitude of weight loss observed.

Pancreatitis

One (1) AE of pancreatitis was reported in OASIS 4 and this event was a mild SAE reported in the placebo group. Data are reassuring and in line with those reported in the STEP phase 3a programme and PIONEER PLUS.

Cardiovascular disorders

The proportion of participants reporting AEs related to cardiovascular disorders were lower in the oral semaglutide 25 mg group (4.9%) compared to the placebo group (11.8%). One (1) SAE of cardiovascular disorder (PT Ischaemic stroke) in the oral semaglutide 25 mg group led to permanent treatment discontinuation. The proportion of participants with SAEs related to cardiovascular disorders was similar in the oral semaglutide 25 mg group (1.0%, 1.1 events per 100 PYO) compared to placebo (1.0%, 0.7 events per 100 PYO).

The change in heart rate from baseline to week 64 was 2 beats/min for oral semaglutide 25 mg versus 1 beat/min for placebo, and the treatment difference between oral semaglutide 25 mg and placebo was not statistically significant (0.33 beats/min [2.28; 2.93]95% CI)

The evaluation of data from OASIS 4 did not indicate an increased risk of cardiovascular events with oral semaglutide 25 mg.

Neoplasms (benign and malignant)

AEs related to neoplasms (benign and malignant) were reported by a similar proportion of participants across treatment groups, though at a lower event rate with oral semaglutide 25 mg (7.4%, 5.8 events per PYO) compared to placebo (6.9%, 10.2 events per PYO). There was no clear clustering on SOC and PT levels in the tissue or organ of origin in which the event of neoplasms occurred.

The proportion of participants reporting AEs of malignant neoplasms was low across treatment groups, though with a lower event rate in the oral semaglutide 25 mg group (1.0%, 0.7 events per PYO) compared to the placebo group (2.0%, 5.1 events per PYO).

Data from OASIS 4 did not indicate a causal relationship between oral semaglutide 25 mg and any type of neoplasm. This is consistent with the findings from PIONEER PLUS and STEP.

Hepatic disorders

In OASIS 4, 3 AEs related to hepatic disorders were reported (2 AEs in oral semaglutide 25 mg group and 1 AE in placebo group), with a similar proportion of participants reporting AEs with oral semaglutide 25 mg and placebo (1.0% versus 1.0%).

At week 64, the ratio to baseline of ALT, AST and ALP had decreased in both treatment groups, but to a greater extent with oral semaglutide 25 mg compared to placebo. Conversely, a slight increase of total bilirubin was seen in both treatment groups at week 64, with a greater elevation seen in the oral semaglutide 25 mg group compared to placebo (24% vs 12%). This is consistent with previously known effects of weight loss and does not suggest a safety concern for oral semaglutide with respect to bilirubin metabolism.

Renal events

In OASIS 4, participants with severe renal impairment or end-stage renal disease were excluded from the study. No events related to acute renal failure were reported with oral semaglutide 25 mg. One (1) SAE of PT Acute kidney injury was reported in the placebo group, which was severe and was recovered but led to temporary interruption of trial product. Geometric mean ratios of eGFR at week 64 compared with baseline were stable across both treatment groups One (1) non-serious AE related to eGFR (glomerular filtration rate decreased) was reported with oral semaglutide 25 mg, which was moderate in severity, resolved by end of study.

There were no relevant changes in renal function parameters eGFR and creatinine in the OASIS 4 study. However, gastrointestinal side effects may, in rare cases, lead to dehydration and thus affect renal function.

Hypoglycaemia

Hypoglycaemia was not a predefined safety focus area in OASIS 4, since the study did not include participants with T2D. No AEs of Hypoglycaemia were reported in both the treatment groups.

In PIONEER PLUS, alert value (level 1) hypoglycaemic episodes were reported by a slightly higher proportion of participants with oral semaglutide 25 mg and 50 mg compared to oral semaglutide 14 mg, but with similar event rates across treatment groups. The risk of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes was low in all three semaglutide groups.

Retinal disorders

Retinal disorders was not a predefined safety focus area in OASIS 4, since the study did not include participants with T2D. No adverse events of diabetic retinopathy were reported.

Based on other findings with semaglutide, the SmPC includes a warning about the risk of diabetic retinopathy complications. This is in line with the SmPC of Rybelsus and sc Wegovy. A specific retinopathy trial with subcutaneous semaglutide is ongoing.

Allergic reactions and antibodies

In OASIS 4, the proportion of participants reporting AEs within the MedDRA searches of allergic reactions and corresponding event rates were higher with placebo (8.8%, 7.4 events per 100 PYE) compared to oral semaglutide 25 mg (3.9%, 3.2 events per 100 PYE).

The company did not report whether the safety profile of semaglutide was impacted by the presence of anti-semaglutide antibodies in OASIS 4. ADA testing was not performed as no protocol-defined triggers occurred. This is acceptable.

Psychiatric disorders

In OASIS 4, AEs related to psychiatric disorders were reported by a lower proportion of participants and lower event rates with oral semaglutide 25 mg (8.8%, 8.0 events per 100 PYE) than with placebo (12.7%, 11.5 events per 100 PYE). In both treatment groups, the events were distributed across a broad range of PTs.

Post baseline, no participants reported suicidal behaviour. Suicidal ideation as assessed by C-SSRS was reported by 1 participant in the oral semaglutide 25 mg group and no participants in the placebo group.

Post baseline, 5 participants in the oral semaglutide 25 mg group had a total maximum score of ≥15 corresponding to moderately severe depression (15–19) or severe depression (≥20) on the PHQ-9 depression questionnaire. No participants in the placebo group had a total maximum score of ≥15 post-baseline. In PIONEER PLUS, psychiatric disorders were not assessed as a predefined safety focus area.

However, the PHQ-9 is only a screening instrument. An evaluation of psychiatric adverse events did not indicate an increased risk associated with oral semaglutide 25 mg in OASIS 4. This is in line with a recent EMA PSUR. Based on the totality of available data included from clinical development programmes including OASIS studies, it was concluded that there was insufficient evidence supporting a causal relationship between semaglutide use and increased risk of depression, suicidal ideation, or self-injurious behaviour.

Intestinal obstruction and aspiration

Overall, no AEs were captured by the MedDRA search for intestinal obstruction in OASIS 4. In addition, there were no AEs reported with oral semaglutide 25 mg in relation to PTs of Aspiration, Pneumonia aspiration, or Anaesthetic complication pulmonary in OASIS 4.

Rare events

In OASIS 4, rare events were reported by the similar proportion of participants in both treatment groups (2 AEs with oral semaglutide 25 mg and 1 AE with placebo).

Clinical laboratory evaluations

No notable changes were observed in any of the haematology parameters in OASIS 4. In the OASIS 4 study, the ratios to baseline at the end of the treatment period (week 64) were also comparable between the oral semaglutide 25 mg and placebo treatment groups for potassium, sodium and TSH.

Vitals signs

In the OASIS 4 study, the estimated mean change in SBP from baseline was -6.75 mmHg with oral semaglutide 25 mg, which was greater than with placebo (-5.36). The estimated mean change in DBP from baseline was -2.72 mmHg with oral semaglutide 25 mg, which was greater than with placebo (-2.07).

In the OASIS 4 study, 5 AEs of Hypotension were reported, 3 in 3 participants in the oral semaglutide 25 mg group and 2 in 2 participants in the placebo group.

Subgroups

In the OASIS 4 study, the potential impact of various intrinsic and extrinsic factors on the safety profile of oral semaglutide 25 mg versus placebo was evaluated. While minor differences between some subgroups were observed, no unexpected clinically relevant interactions between oral semaglutide 25 mg and any intrinsic or extrinsic factors were identified. However, for the subgroup analyses with respect to age, only 21 patients >=65 years were treated. For the subgroup analyses with respect to race, only 13 Black or African American and 1 Asian were treated.

The populations in OASIS 4 were evaluated based on subgroups of body weight loss at the end of treatment. Overall, the treatment differences for all AEs, SAEs, severe AEs and AEs leading to permanent treatment discontinuation in the oral semaglutide 25 mg group were similar between the weight loss subgroups, with no indication of a higher frequency of such events with a greater weight loss. Higher frequencies of AE reporting for participants losing ≥20% versus <20% of their baseline body weight with oral semaglutide 25 mg were seen for the SOC Gastrointestinal disorders.

Safety analysis population

Clinical studies supporting the safety evaluation of oral semaglutide 25 mg for weight management include one pivotal confirmatory study (OASIS 4), primary supportive studies PIONEER PLUS and STEP 1-4 and supportive studies OASIS 1-3. The designs of the OASIS programme, PIONEER PLUS and STEP 1-2 are described in the current AR's section 6.3.10. STEP 3 included subjects with overweight or obesity who received semaglutide 2.4 mg s.c. or placebo as an add-on to intensive behavioural therapy, while STEP 4 enrolled participants with overweight or obesity who had reached the 2.4 mg maintenance dose of s.c. semaglutide during a 20-week run-in period.

Overall, this extent and duration of patient exposure exceeds the basic requirements outlined by the ICH E1 Note for guidance on The Extent of Population Exposure to Assess Clinical Safety and the EMA Guideline on clinical evaluation of medicinal products used in weight management (EMA/CHMP/311805/2014).

Adverse events

In OASIS 4, no new clear apparent AE imbalances were noted between semaglutide and placebo compared to the safety data reported in the STEP 1-4 trials.

The proportion of participants reporting an adverse event and overall rate of AEs was higher with semaglutide 25 mg compared to placebo (93.1% vs. 85.3% and 493.5 vs. 355.9 events per 100 PYE, respectively). In both treatment arms, most AEs occurred during dose escalation. This between-group difference was primarily due to a higher proportion of subjects with AEs related to gastrointestinal disorders, please refer to safety focus area Gastrointestinal disorders below.

Other imbalances in SOCs between semaglutide 25 mg and placebo disfavouring semaglutide included Nervous system disorders and General disorders and administration site conditions, with the between-group differences driven by the PTs headache (11.8% vs. 8.8% for semaglutide and placebo, respectively), dizziness (5.4% vs. 1.0%) and fatigue/asthenia (8.8% vs. 2.0%). In addition, 4.9% of semaglutide-treated subjects in OASIS 4 reported AEs related to a clinical picture of altered skin sensation compared to no (0) such events in the placebo group (and to 2.1% of patients treated with semaglutide 2.4 mg s.c. in the STEP phase 3a trials); all were non-serious and the majority were

reported as recovered. For comparison, AEs of dysaesthesia were reported by 13% of participants with oral semaglutide 50 mg vs. 1% with placebo in the OASIS 1 trial, with results from the PIONEER PLUS study further supporting dose-dependency for events of dysaesthesia (the proportion of subjects reporting such events in PIONEER PLUS being 5.2%, 2.1% and 1.1% for oral semaglutide 50 mg, 25 mg and 14 mg, respectively).

Death and other serious adverse events

No patient died during the OASIS trials. In OASIS 4, SAEs were reported by a lower proportion of subjects with oral semaglutide 25 mg (3.9%) compared to placebo (8.8%); in the semaglutide group, each PT for the SAEs was reported by no more than one subject.

Adverse events leading to treatment discontinuation

In OASIS 4, a slightly higher proportion of subjects experienced AEs leading to permanent treatment discontinuation with oral semaglutide 25 mg (6.9%) than with placebo (5.9%), with the majority of such AEs of gastrointestinal nature. Of the 14 events leading to permanent discontinuation of semaglutide, the majority were of mild or moderate severity (N = 12) and were recovered at the end of the trial (N = 12).

A larger treatment difference disfavouring semaglutide 25 mg was observed for AEs leading to temporary interruption of trial product (22.5% of participants in the semaglutide group compared to 12.7% with placebo) and AEs leading to a dose reduction of trial product (24.5 % vs. 2.0%, respectively). These differences were again primarily driven by events within the gastrointestinal disorders SOC.

Safety focus areas

Gastrointestinal disorders

In the OASIS 4 trial, as expected, the most frequent AEs observed with semaglutide 25 mg and greater than placebo were gastrointestinal events (74.0% vs. 42.2% for semaglutide and placebo, respectively). Gastrointestinal AEs occurring in higher proportions of subjects on semaglutide included nausea (46.6% vs 18.6%), vomiting (30.9% vs 5.9%), constipation (20.1% vs 9.8%), dyspepsia (18.1% vs 8.8%), diarrhoea (17.6% vs 8.8%), eruction (10.3% vs. 2.0%) and abdominal pain upper (8.8% vs 2.0%). Also, a higher proportion of subjects assigned to semaglutide experienced gastrointestinal AEs leading to dose reduction (20.6% vs. 1.0%), temporary interruption of trial product (13.2% vs. 4.9%) or permanent treatment discontinuation (3.4% versus 2.0%). In both treatment groups, the majority of subjects experiencing a gastrointestinal AE reported the first such event during dose-escalation, after which the prevalence decreased.

The large majority of gastrointestinal AEs were categorized as of mild or moderate severity, and the majority of subjects had recovered by the end of the study. The single serious gastrointestinal adverse event in OASIS 4 was a case of acute pancreatitis reported in the placebo group.

While the frequency and severity of gastrointestinal AEs reported in OASIS 4 were overall broadly similar to the data observed in the STEP phase 3a trials, vomiting appeared numerically higher with oral semaglutide: Proportions of subjects reporting vomiting with semaglutide compared to placebo were 30.9% vs. 5.9% in OASIS 4 and 21.8% vs. 5.7% in STEP1-3. In both trial programmes, median duration of vomiting with semaglutide was 2 days.

Gallbladder-related disorders

In OASIS 4, a greater proportion subjects treated with semaglutide experienced events of cholelithiasis compared to patients treated with placebo (2.5% (N=5) vs. 1.0% (N=1)). Cholelithiasis was

associated with increased weight loss, being reported in 7.0% of subjects with a body weight loss ≥20% at Week 64 vs. 0.7% in participants with a body weight loss < 20% at end of treatment. A smaller imbalance was also noted in AEs of cholelithiasis in the STEP phase 3a pool (1.6% and 1.1% with 2.4 mg semaglutide s.c. and placebo, respectively), where cholelithiasis likewise appeared correlated with larger weight loss. A description of cholelithiasis is included in section 4.8 of the current Wegovy SmPC.

Pancreatitis

No event of pancreatitis was reported in the OASIS 4 semaglutide treatment group.

Cardiovascular disorders

In OASIS 4, less subjects on semaglutide versus placebo reported an AE related to cardiovascular disorders (4.9% vs. 11.8%), with the treatment difference not clearly driven by any particular PT.

A non-significant treatment difference in pulse change from baseline to Week 64 of 0.33 beats/min (95% CI: -2.28-2.93) was observed in OASIS 4. A maximum pulse change from baseline ≥ 20 beats/min bpm was observed in 26.5% of semaglutide-treated subjects compared to 20.8% of participants in the placebo group. The latter finding was similar to data from the STEP phase 3a trials. No AEs related to increased heart rate were reported in the OASIS 4 semaglutide group.

Neoplasms

In OASIS 4, the incidence of neoplasms (benign and malign) and of malignancies were similar among groups with no pattern of occurrence in particular organs. (Neoplasms: 7.4%, 5.8 events per PYO vs. 6.9%, 10.2 events per PYO; malignancies: 1.0%, 0.7 events per PYO vs. 2.0%, 5.1 events per PYO for semaglutide and placebo, respectively). No case of medullary thyroid cancer or pancreatic cancer was reported.

Hepatic and renal disorders

Hepatic AEs were reported in 1.0% of participants in both OASIS 4 treatment groups (2 AEs in the oral semaglutide 25 mg group and 1 AE among placebo-treated subjects, all related to transaminase or "hepatic enzyme" elevations). There were no acute renal failure AEs. In OASIS 4, laboratory tests showed no signal of hepato- or renal toxicity.

Allergic reactions

There was no imbalance disfavoring semaglutide in allergic reactions: In OASIS 4, the proportion of participants reporting AEs of allergic reactions was higher with placebo (8.8%) than with oral semaglutide 25 mg (3.9%), again without any notable pattern of clustering at the PT level. No AE led to assessment of anti-semaglutide antibodies.

Psychiatric disorders

There was no increase in AEs of psychiatric disorders or clustering of PTs within such AEs with semaglutide 25 mg oral (8.8%, 8.0 events per 100 PYE) compared to placebo (12.7%, 11.5 events per 100 PYE).

Intestinal obstruction and aspiration in association with general anaesthesia or deep sedation

No AEs of bowel obstruction or events related to aspiration were reported in OASIS 4.

Rare events

AEs of pre-defined rare events were reported by 1.0% of participants in both OASIS 4 treatment groups and did not raise new safety concerns. The two such events observed with semaglutide 25 mg oral included non-serious single PTs of atrial septal defect and Type V mixed hyperlipidaemia.

Clinical laboratory evaluations

There were no relevant changes or between-group imbalances in routine safety laboratory parameters throughout OASIS 4.

Subgroups

In OASIS 4, no notable differences were observed when AEs were analyzed across subgroups of age, sex, race, ethnicity, region, baseline body weight and renal function, presence of upper gastrointestinal disease or by weight loss at Week 64 (≥20% vs. < 20%), although some subgroups had too few subjects to draw firm conclusions regarding potential imbalances.

Among the 12.0% (N=25) of subjects in OASIS 4 with semaglutide C_{avg} exceeding the maximum exposure range of 147 nmol/L from the STEP phase 3a trials, a slightly higher proportion of participants reduced the dose of trial product or discontinued treatment permanently due to AEs compared to subjects with lower semaglutide exposure (28.0% vs. 24.3% and 8.0% vs. 6.8%, respectively). A number of gastrointestinal AEs were reported by a higher proportion of subjects with semaglutide C_{avg} > 147 nmol/L compared to subjects with lower semaglutide exposure (e.g. nausea: 68.0% vs. 44.1%, vomiting: 52.0% vs. 28.2%, constipation: 40.0% vs. 17.5%, and abdominal pain upper: 20.0% vs. 7.3%), with notable imbalances disfavoring the high semaglutide exposure group further observed for the PTs sensitive skin (12.0% vs. 1.1%) and paraesthesia (8.0% vs. 0%) as well as for headache (16.0% vs. 11.3%). Evidence of an exposure-response relationship for gastrointestinal AEs has previously been described for other GLP-1 RAs. It is further noted that the MAH's model-predicted 90% range for average semaglutide exposure levels for OASIS 4 (27-186 nmol/L) offer some level of reassurance when compared to the corresponding range predicted for the oral 50 mg semaglutide treatment arm in PIONEER PLUS (21-265 nmol/L).

5.4.9.2. Conclusions on clinical safety

In general, the overall safety profile for oral semaglutide 25 mg was consistent with the safety profile for semaglutide and the GLP-1 RA drug class. As expected, the most frequent AEs with oral semaglutide 25 mg were gastrointestinal disorders, although vomiting seems to occur more frequently with oral semaglutide. Other expected adverse events included headache, dizziness, fatigue, dysesthesia and cholelithiasis.

6. Risk management plan

An updated RMP (version 9.2) has been submitted. The administrative information in Part I (Product Overview) has been updated to reflect the proposed new indication, dosage, pharmaceutical form and strengths for Wegovy.

6.1. Safety specification

6.1.1. Proposed safety specification

No updates to safety concerns have been proposed.

6.1.2. Discussion on proposed safety specification

The administrative information in Part I has been updated to reflect the proposed new indication, dosage, pharmaceutical form and strengths for Wegovy.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

No updates have been proposed.

6.3. Risk minimisation measures

6.3.1. Proposed risk minimisation measures

No updates have been proposed.

6.4. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.5. Overall conclusion on the Risk Management Plan

The PRAC considers that the updated risk management plan version 9.2 is acceptable.

7. Pharmacovigilance

Pharmacovigilance system

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

7.1. Periodic Safety Update Reports submission requirements

The scientific opinion holder shall submit periodic safety update reports for this product in alignment with the requirements for the centrally authorised product as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The SmPC section 4.1 text of the already authorised subcutaneous pharmaceutical form in the adult population applies to the new pharmaceutical forms of Wegovy tablets, apart from the reference in section 4.1 with respect to cardiovascular risk reduction and obesity-related heart failure, which is not supported by the data and has been deleted.

Wegovy tablets has not been studied in adolescents (≥12 years of age) and is therefore not indicated for this population.

8.1.2. SmPC section 5.1 justification

Considering the results of the SELECT trial (CVOT performed with subcutaneous semaglutide) the applicant claims that these results are also applicable to the tablet formulation of Wegovy. Even if there are overlaps between the exposure of semaglutide and the study populations, it is uncertain if treatment with Wegovy tablets will have the same cardioprotective effect as was indicated by the results of the SELECT trial. However, the experience from the CV outcomes trial performed with subcutaneous semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results of the SELECT trial as well as the STEP 1-4 trials in section 5.1 for Wegovy tablets. However, the reference in section 4.1 with respect to effect on CV events is not supported by the data and has been deleted.

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Wegovy 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg solution for injection in prefilled pen and Rybelsus 3 mg, 7 mg and 14 mg tablets. The bridging report submitted by the MAH has been found acceptable.

9. Benefit-risk assessment

Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

The prevalence of obesity has reached epidemic proportions and continues to increase. Obesity is associated with several health-related complications. Most concerning, obesity increases the risk of developing cardiovascular disease and certain types of cancers, which are some of the leading causes of early death in these patients. In addition, obesity is a well-established risk factor for other serious conditions including, but not limited to, T2D, hypertension, dyslipidaemia, obstructive sleep apnoea, osteoarthritis, urinary incontinence, asthma and non-alcoholic steatohepatitis. Obesity also significantly impacts health-related quality of life by impairing physical health status and imposing limitations on daily activities. Furthermore, stigmatization and discrimination associated with obesity can contribute to impaired mental well-being.

The risk of obesity-related complications and comorbidities increases with increasing BMI, and a weight loss of 5−10% has significant health benefits by improving obesity-related comorbidities, including slowing progression to T2D, and improving physical symptoms and quality of life. Studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in people with obesity, with or without T2D.

The Applicant initially proposed the following indication:

"Wegovy tablets is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight

management, including weight loss and weight maintenance, in adults with an initial Body Mass Index

(BMI) of

- *≥ 30 kg/m^2 (obesity), or*
- *≥ 27 kg/m2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.*

For trial results with respect to cardiovascular risk reduction, obesity-related heart failure, and populations studied, see section 5.1"

9.1.2. Available therapies and unmet medical need

Lifestyle intervention in diet and exercise is first-line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss, most likely due largely to a homeostatic mechanism involving counteractive biological responses. Bariatric surgery offers an effective alternative for some people with severe obesity, but surgery carries a risk connected with the procedure and for complications afterwards and requires close follow-up, which can be cumbersome and costly. For people with obesity, there is a lack of safe and efficacious treatment options that can provide a reduction in body weight approaching what can be obtained by surgical procedures, and at the same time enables the patient to maintain the weight loss. Pharmacotherapy may serve as a valuable alternative to bariatric surgery as a supplement to lifestyle intervention to achieve and sustain

a clinically relevant weight loss. Currently, only a very limited number of pharmacological options are approved for weight management.

The GLP-1 RA drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors, and glucose metabolism.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

The pivotal study, OASIS 4, was an interventional 64 week, randomised, phase III b, placebo-controlled, double-blind two-armed, multi-centre, multinational clinical study comparing the efficacy of once daily 25 mg oral semaglutide versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with overweight (BMI $\geqslant$ 27.0 kg/m^2) and at least one weight-related comorbidity or with obesity (BMI $\geqslant$ 30.0 kg/m^2). The 64 weeks of treatment included 12 weeks of dose escalation and 52 weeks on maintenance dose. The treatment period was followed by a 7-week follow-up period off-treatment. The study included 307 patients.

The primary objective was to confirm superior efficacy on body weight reduction from baseline (week 0) to end-of-treatment (week 64) of oral semaglutide 25 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in adults with overweight or obesity. The main secondary objectives were to compare the efficacy of oral semaglutide 25 mg versus placebo on other factors related to body weight, cardiovascular risk factors, patient-reported outcomes and glucose metabolism.

9.3. Favourable effects

Primary endpoints Oral semaglutide 25 mg had superior efficacy on body weight reduction from baseline (week 0) to end-of-treatment (week 64) compared with placebo. The estimated treatment difference for the co-primary endpoint of change from baseline to week 64 in body weight (%) was -11.43% [-13.88; -8.98]. The estimated percentage of participants who achieved ≥5% weight loss with oral semaglutide 25 mg was 76.3% compared to 30.5% with placebo (ETD: 45.8 [34.6; 56.9]).

Confirmatory secondary endpoints Patients treated with oral semaglutide 25 mg achieved statistically significantly more often a decrease in weight compared with placebo (≥ 10% weight reduction: 59.8% versus 14.1%, ETD: 9.06 [4.74; 17.29]95% CI; p-value <0.0001; ≥ 15% weight reduction: 47.0% versus 5.4%, ETD 15.74 [6.16; 40.24]95% CI; p-value <0.0001; ≥20% weight reduction: 27.5% versus 3.0%, ETD: 12.24 [3.72; 40.26]95% CI; p-value <0.0001).

Treatment with oral semaglutide 25 mg resulted in a mean change in IWQOL-Lite-CT Physical Function score for the treatment policy estimand of 16.18 points versus 8.45 for placebo (ETD: 7.73 [3.30;12.16]95% CI; p-value = 0.0006).

Supportive secondary endpoints Treatment with oral semaglutide 25 mg resulted in statistically significant improved glycaemic parameters; the estimated mean change in HbA1c was -0.29%-points for oral semaglutide 25 mg and- 0.06%-points for placebo (ETD: -0.23%-points [-0.31;-0.15]95% CI; p-value <0.0001).

Patients receiving oral semaglutide 25 mg had a mean change of waist circumference of -12.24 cm versus -2.76 cm for patients receiving placebo (ETD -9.48 cm [-12.41;-6.55]95% CI; p-value <0.0001).

No statistically significant differences were seen in patients receiving oral semaglutide 25 mg compared with those receiving placebo in terms of SBP, DBP and lipids (except for VLDL cholesterol).

9.3.1. Uncertainties and limitations about favourable effects

There is no placebo-controlled data of oral semaglutide 25 mg for weight management in patients with overweight/obesity and T2D, since these patients were excluded from OASIS 4. Hence, the efficacy of oral semaglutide 25 mg in patients with overweight/obesity and T2D is based on data from the PIONEER PLUS study, the STEP 2 study, and simulation studies. However, the effects on body weight in patients with obesity/overweight and T2DM is considered clinically relevant since even modest weight loss can improve glycemia, blood pressure, lipids and, in general, help reduce obesity-associated health risks.

There are limited data In OASIS 4 on patients with BMI ≥ 27 kg/m^2 to <30 kg/m^2 and a weight-related comorbidity, n=18, of which only 13 were treated with oral semaglutide 25 mg, and 5 with placebo. However, weight loss in those participants was in line with that in participants with higher BMI's (-8.66 vs -11.57 kg; p for interaction 0.6081). In addition, no clinically meaningful heterogeneity of treatment effect was identified in this sub-population across other trials.

No cardiovascular outcome study has been performed with oral semaglutide in the overweight/ obese population. In addition, treatment with oral semaglutide 25 mg had no statistically significant effect on systolic and diastolic blood pressure and on lipids (except for VLDL cholesterol). Therefore, the benefit of oral semaglutide treatment in the overweight/ obese population on cardiovascular outcomes is not yet clear. In the SmPC section 5.1, studies were included on cardiovascular risk reduction and obesity-related heart failure; SELECT, SUSTAIN and STEP-HFpEF. These 3 studies are all performed with s.c. semaglutide and inclusion of studies performed with s.c. administered semaglutide. Bridging of efficacy data from s.c. to oral was not considered possible. Due to the large variability in exposure, it remains uncertain if the exposure obtained with oral semaglutide is sufficient for the entire population to exhibit the effects of s.c. semaglutide. The applicant was therefore requested to remove these studies from the SmPC. Consequently, the reference in section 4.1 to section 5.1 should be removed. In the first round, SUSTAIN and STEP-HFpEF were removed by the applicant. However, the SELECT trial was not removed from section 5.1, and the applicant proposed to maintain the statement cited above (SmPC section 4.1). Even if there are overlaps between the exposure of semaglutide and the study populations, it is uncertain if treatment with Wegovy tablets will have the same cardioprotective effect as was indicated by the results of the SELECT trial. However, the experience from the CV outcomes trial performed with subcutaneous semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results in section 5.1 for Wegovy tablets. However, the reference in section 4.1 with respect to effect on CV events is not supported by the data and has been deleted.

Patients treated with semaglutide had, compared with those on placebo, a statistically significant improvement in IWQOL-Lite-CT PFD, which was considered the most important patient reported outcome. The improvement observed using the IWQOL-Lite-CT has been reflected in section 5.1. Further, results of other PROs were inconclusive, thus the effect of semaglutide treatment on PROs remains unclear.

9.4. Unfavourable effects

In OASIS 4, a total of 306 participants were exposed to treatment, including 204 participants who were exposed in the oral semaglutide 25 mg group.

Of the participants on oral semaglutide 25 mg in OASIS 4 study, 95.6% completed the study and 81.5% completed treatment with the trial product. The proportion of participants who permanently discontinued trial product was lower with oral semaglutide 25 mg (18.0%) than with placebo (25.5%).

Adverse events

The proportion of participants with AEs and event rates were slightly higher with oral semaglutide 25 mg than with placebo (93.1% versus 85.3%; 493.5 versus 355.9 events per 100 PYE). AEs were reported by a similar proportion of participants with oral semaglutide 25 mg and placebo within most SOCs. For the following SOCs, higher proportions of participants or higher rates were observed with oral semaglutide 25 mg compared to placebo:

Gastrointestinal disorders: The most frequent types of reported AEs with oral semaglutide 25 mg compared to placebo were in the SOC Gastrointestinal disorders. These side effects are already well known.

Nervous system disorders: The imbalance was primarily driven by the PTs Headache (11.8% versus 8.8%) and Dizziness (5.4% versus 1.0%) Headache and dizzyness are already stated in the SmPC.

General disorders and administration site conditions: The imbalance was driven by the PT Fatigue (7.4% versus 1.0%) The development of fatigue is in line with previous findings and already described in the SmPC.

Deaths and SAEs

No fatal events were reported in OASIS 4.

The proportion of participants reporting one or more SAEs during the on-treatment period was 3.9% in the oral semaglutide 25 mg group and 8.8% in the placebo group. The proportion of participants with AEs leading to permanent treatment discontinuation and the overall rate of AEs leading to permanent treatment discontinuation were slightly higher with oral semaglutide 25 mg (6.9%; 5.6 events per 100 PYE) than with placebo (5.9%; 4.9 events per 100 PYE).

Focus areas

Gastrointestinal

As described above, gastrointestinal AEs were more frequently reported with oral semaglutide 25 mg (74.0% of participants) compared to placebo (42.2% of participants). The majority of gastrointestinal AEs were non-serious, mild or moderate in severity, and reported as recovered.

Pancreatitis

One (1) AE of pancreatitis was reported in OASIS 4 and this event was a mild SAE reported in the placebo group. Data are reassuring and in line with those reported in the STEP phase 3a programme and PIONEER PLUS.

Cardiovascular disorders

The proportion of participants reporting AEs related to cardiovascular disorders were lower in the oral semaglutide 25 mg group (4.9%) compared to the placebo group (11.8%). One (1) SAE of cardiovascular disorder (PT Ischaemic stroke) in the oral semaglutide 25 mg group led to permanent

treatment discontinuation. The proportion of participants with SAEs related to cardiovascular disorders was similar in the oral semaglutide 25 mg group (1.0%, 1.1 events per 100 PYO) compared to placebo (1.0%, 0.7 events per 100 PYO). The evaluation of data from OASIS 4 did not indicate an increased risk of cardiovascular events with oral semaglutide 25 mg.

Neoplasms (benign and malignant)

AEs related to neoplasms (benign and malignant) were reported by a similar proportion of participants across treatment groups, though at a lower event rate with oral semaglutide 25 mg (7.4%, 5.8 events per PYO) compared to placebo (6.9%, 10.2 events per PYO). There was no clear clustering on SOC and PT levels in the tissue or organ of origin in which the event of neoplasms occurred. The proportion of participants reporting AEs of malignant neoplasms was low across treatment groups, though with a lower event rate in the oral semaglutide 25 mg group (1.0%, 0.7 events per PYO) compared to the placebo group (2.0%, 5.1 events per PYO).

Data from the OASIS 4 do not indicate a causal relationship between oral semaglutide 25 mg and any type of neoplasm. This is consistent with the findings from PIONEER PLUS and STEP.

Hepatic disorders

In OASIS 4, 3 AEs related to hepatic disorders were reported (2 AEs in oral semaglutide 25 mg group and 1 AE in placebo group), with a similar proportion of participants reporting AEs with oral semaglutide 25 mg and placebo (1.0% versus 1.0%).

Renal events

In OASIS 4, participants with severe renal impairment or end-stage renal disease were excluded from the study. No events related to acute renal failure were reported with oral semaglutide 25 mg. One (1) SAE of PT Acute kidney injury was reported in the placebo group, which was severe and was recovered but led to temporary interruption of trial product. Geometric mean ratios of eGFR at week 64 compared with baseline were stable across both treatment groups. However, gastrointestinal side effects may, in rare cases, lead to dehydration and thus affect renal function.

Hypoglycaemia

Hypoglycaemia was not a predefined safety focus area in OASIS 4 study, since the study did not include participants with T2D. No AEs of Hypoglycaemia were reported in both the treatment groups.

In PIONEER PLUS, alert value (level 1) hypoglycaemic episodes were reported by a slightly higher proportion of participants with oral semaglutide 25 mg and 50 mg compared to oral semaglutide 14 mg, but with similar event rates across treatment groups. The risk of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes was low in all three semaglutide groups.

Retinal disorders

Retinal disorders was not a predefined safety focus area in OASIS 4 study, since the study did not include participants with T2D. No adverse events of diabetic retinopathy were reported. Based on other findings with semaglutide, the SmPC includes a warning about the risk of diabetic retinopathy complications. This is in line with the SmPC of Rybelsus and subcutaneous Wegovy. A specific retinopathy trial with subcutaneous semaglutide is ongoing.

Allergic reactions

In OASIS 4, the proportion of participants reporting AEs within the MedDRA searches of allergic reactions and corresponding event rates were higher with placebo (8.8%, 7.4 events per 100 PYE) compared to oral semaglutide 25 mg (3.9%, 3.2 events per 100 PYE).

Intestinal obstruction and aspiration

Overall, no AEs were captured by the MedDRA search for intestinal obstruction in the OASIS 4. In addition, there were no AEs reported with oral semaglutide 25 mg in relation to PTs of Aspiration, Pneumonia aspiration, or Anaesthetic complication pulmonary in the OASIS 4.

Subgroups

In the OASIS 4 study, the potential impact of various intrinsic and extrinsic factors on the safety profile of oral semaglutide 25 mg versus placebo was evaluated. While minor differences between some subgroups were observed, no unexpected clinically relevant interactions between oral semaglutide 25 mg and any intrinsic or extrinsic factors were identified. However, for the subgroup analyses with respect to age, only 21 patients >=65 years were treated. For the subgroup analyses with respect to race, only 13 Black or African American and 1 Asian were treated.

The populations in OASIS 4 were evaluated based on subgroups of body weight loss at the end of treatment. Overall, the treatment differences for all AEs, SAEs, severe AEs and AEs leading to permanent treatment discontinuation in the oral semaglutide 25 mg group were similar between the weight loss subgroups, with no indication of a higher frequency of such events with a greater weight loss. Higher frequencies of AE reporting for participants losing ≥20% versus <20% of their baseline body weight with oral semaglutide 25 mg were seen for the SOC Gastrointestinal disorders.

9.4.1. Uncertainties and limitations about unfavourable effects

The OASIS 4 study is considered sufficient for the evaluation of safety and tolerability of oral semaglutide 25 mg for weight management in individuals with BMI>30 in the target population. However, demographic representation was relatively narrow – the trial population being mostly female and white – and the low number of participants in some subgroups precluded drawing conclusions regarding potential AE imbalances.

Supportive data from PIONEER PLUS and STEP

Although treatment with oral semaglutide 25 mg in OASIS 4 resulted in exposure levels that were on average on par with exposure levels of s.c. semaglutide 2.4 mg in STEP 1, there also was a significant part of the population that did not show overlap in exposure levels. In addition, there was greater variability in exposure with oral semaglutide treatment compared to s.c. semaglutide treatment, and at the same dose level and route of administration, lower exposure was seen in participants with T2D (STEP 2, PIONEER PLUS) versus participants without T2D (STEP 1, OASIS 1, OASIS 2, and OASIS 4). Therefore, the use of safety data from the PIONEER PLUS study with oral semaglutide 25 mg as well as from the STEP programme (STEP 1−4) with s.c. semaglutide at a dose of 2.4 mg in the overall safety evaluation of oral semaglutide 25 mg for weight management is only considered supportive.

Dysesthesia

Less common PTs reported more frequently with oral semaglutide 25 mg than with placebo included events related to a clinical picture of dysaesthesia. In total, 13 AEs were reported, and all were reported in the oral semaglutide 25 mg group (4.9% of participants at an event rate of 5.2 events per 100 PYE). Events related to dysaesthesia are known to be associated with semaglutide, and dysaesthesia is included in the text of the SmPC.

Cholelithiasis

The proportion of participants reporting events of Cholelithiasis in the oral semaglutide 25 mg group in OASIS 4 was 2.5% vs 1.0% in placebo group. This was higher than the risk in the STEP trials (1.6% in

the semaglutide s.c. 2.4 mg arm vs 1.1% in the placebo arm) and PIONEER PLUS (0.4% vs 0.6% vs 0.6% for 14 mg, 25 mg, and 50 mg treatment groups respectively). However, the observed proportion of subjects with cholelithiasis was not higher than what could be expected based on the magnitude of weight loss observed.

At week 64, the ratio to baseline of ALT, AST and ALP had decreased in both treatment groups, but to a greater extent with oral semaglutide 25 mg compared to placebo. Conversely, a slight increase of total bilirubin was seen in both treatment groups at week 64, with a greater elevation seen in the oral semaglutide 25 mg group compared to placebo (24% vs 12%). This is consistent with previously known effects of weight loss and does not suggest a safety concern for oral semaglutide with respect to bilirubin metabolism.

Psychiatric disorders

In OASIS 4, AEs related to psychiatric disorders were reported by a lower proportion of participants and lower event rates with oral semaglutide 25 mg (8.8%, 8.0 events per 100 PYE) than with placebo (12.7%, 11.5 events per 100 PYE).

Post baseline, no participants reported suicidal behaviour. Suicidal ideation as assessed by C-SSRS was reported by 1 participant in the oral semaglutide 25 mg group and no participants in the placebo group. Post baseline, 5 participants in the oral semaglutide 25 mg group had a total maximum score of ≥15 corresponding to moderately severe depression (15–19) or severe depression (≥20) on the PHQ-9 depression questionnaire. No participants in the placebo group had a total maximum score of ≥15 post-baseline. However, the PHQ-9 is only a screening instrument. An evaluation of psychiatric adverse events did not indicate an increased risk associated with oral semaglutide 25 mg in OASIS 4 study. This is in line with a recent EMA PSUR. Based on the totality of available data included from clinical development programmes including OASIS studies, it was concluded that there was insufficient evidence supporting a causal relationship between semaglutide use and increased risk of depression, suicidal ideation, or self-injurious behaviour.

9.5. Effects Table

Table 20: Effects Table for Wegovy tablets

Effect (short description)	Treatment (oral semaglutide 25 mg)	Control (placebo)	Uncertainties/ Strength of evidence	Ref
Favourable Effects				
Change in body weight from baseline to week 64 (%)	-13.61%	-2.18%	**SoE:** Difference is statistically significant (ETD -11.43% [-13.88; -8.98]$_{95\% CI}$). Effect was accompanied by change in other weight loss-related endpoints Consistent across most subgroups **Unc:** In PIONEER PLUS (T2DM) effects were smaller (-6.8%)	OASIS 4 (/ PIONEER PLUS)
Achievement of body weight reduction ≥5% (%)	76.3%	30.5%	**SoE:** Difference is statistically significant (OR: 7.34 [4.22; 12.76] $_{95\% CI}$). Effect was confirmed in other weight loss categories (≥10%, ≥15%, ≥20%) **Unc:** In PIONEER PLUS (T2DM), endpoint was achieved by fewer patients (58.5%)	OASIS 4 (/ PIONEER PLUS)
Unfavourable Effects				

Effect (short description)	Treatment (oral semaglutide 25 mg)	Control (placebo)	Uncertainties/ Strength of evidence	Ref
Total AEs	93.1%	85.3%		OASIS 4
SAEs	3.9%	8.8%	No fatal events were reported	OASIS 4
Gastrointestinal AEs	74.0%	42.2%	Well known side effects	OASIS 4
Cardiovascular AEs	4.9%	11.8%		OASIS 4
Dysaesthesia AEs	4.9%	0%		OASIS 4
Cholelithiasis AEs	2.5%	1.0%		OASIS 4

Abbreviations: AE; adverse event; ETD: estimated treatment differences; OR: odds ratio; Ref: reference; Unc: uncertainties; SoE: strength of evidence.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Oral semaglutide 25 mg has demonstrated a significant and clinically relevant effect on weight loss in OASIS 4 that was persistent after 64-weeks of treatment. The weight loss effect is in line with expectations based on experience with other semaglutide-containing medicinal products (indirect comparison).

Weight loss effect was assessed in multiple endpoints (e.g. weight loss in % and kg; percentage of patients achieving certain thresholds of weight loss; change in BMI), and all showed beneficial effects of semaglutide treatment, indicating robustness of effect.

However, there is no placebo-controlled data of oral semaglutide 25 mg for weight management in patients with overweight/obesity and T2D, since these patients were excluded from OASIS 4. Hence, the efficacy of oral semaglutide 25 mg in patients with overweight/obesity and T2D is based on data from the PIONEER PLUS study, the STEP 2 study, and simulation studies. Compared to patients without T2D, the results showed lower weight loss of oral semaglutide 25 mg However, even modest weight loss can help reduce obesity-associated health risks. However, it is reassuring that there is no clinically meaningful heterogeneity of treatment effect identified in this sub-population in the current trial as well as in other trials.

Weight loss effect was accompanied with improvements in glycaemic parameters (HbA1c, fasting plasma glucose and fasting serum insulin), but not in systolic and diastolic blood pressure and lipids (except for VLDL cholesterol), which is contrary to expectations from previous trials with semaglutide. No cardiovascular outcome trial has been performed with oral semaglutide in the overweight/ obese population. Less cardiovascular AEs were reported in the oral semaglutide group compared with placebo, but proportions of patients who reported cardiovascular SAEs were similar in both groups, thus the size of any beneficial effect of oral semaglutide on cardiovascular outcomes remains uncertain.

Cardiovascular outcome studies in the overweight/ obese population have been performed with s.c. semaglutide. However, bridging of efficacy data from s.c. to oral was not considered possible. Due to the large variability in exposure, it remains uncertain if the exposure obtained with oral semaglutide is sufficient for the entire population to exhibit the effects of s.c. semaglutide. The applicant was therefore requested to remove these studies from the SmPC. Consequently, the reference in section 4.1 to section 5.1 should be removed. In the first round, SUSTAIN and STEP-HFpEF were removed by the applicant. However, the SELECT trial was not removed from section 5.1, and the applicant proposed to maintain the statement cited above (SmPC section 4.1).Even if there are overlaps between the exposure of semaglutide and the study populations, it is uncertain if treatment with Wegovy tablets will have the same cardioprotective effect as was indicated by the results of the SELECT trial. However, the experience from the CV outcomes trial performed with subcutaneous semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results in section 5.1 for Wegovy tablets. However, the reference in section 4.1 with respect to effect on CV events is not supported by the data and has been deleted.

In general, the overall safety profile for oral semaglutide 25 mg was consistent with the safety profile for semaglutide and the GLP-1 RA drug class. As expected, the most frequent AEs with oral semaglutide 25 mg were gastrointestinal disorders, although vomiting seems to occur more frequently with oral semaglutide. Other expected adverse events included headache, dizziness, fatigue and cholelithiasis. The higher risk of dysaesthesia is considered acceptable. Data from multiple long-term studies with both oral and subcutaneous semaglutide have not identified any serious neurological or dermatological disorders potentially related to dysaesthesia. Dysaestesia will be carefully monitored through routine post-marketing pharmacovigilance activities.

9.6.2. Balance of benefits and risks

Obesity is associated with several health-related complications and most patients experience large difficulties with achieving weight loss. Treatment options (non-surgical) leading to clinically relevant weight loss are considered important. The effect of oral semaglutide 25mg on body weight reduction was studied in OASIS 4, and the overall effects found were statistically significant, robust and clinically relevant.

Data for patients with overweight/obesity and T2D and patients with BMI ≥ 27 kg/m^2 to <30 kg/m^2 and a weight-related comorbidity other than T2DM are also considered acceptable.

In general, the overall safety profile for oral semaglutide 25 mg was consistent with the safety profile for semaglutide and the GLP-1 RA drug class. As expected, the most frequent AEs with oral semaglutide 25 mg were gastrointestinal disorders. Other expected adverse events included headache, dizziness, and fatigue, dysesthesia and cholelithiasis).

9.7. Benefit-risk conclusions

The overall benefit /risk balance of oral Wegovy is positive.

10. Appendix

CHMP AR on similarity dated 21 May 2026

11. QRD checklist for the review of user testing results

PRODUCT INFORMATION

Name of the medicinal product:	Wegovy 1.5 mg tablets Wegovy 4 mg tablets Wegovy 9 mg tablets Wegovy 25 mg tablets Wegovy 50 mg tablets
Name and address of the applicant:	Novo Nordisk A/S Novo Allé 2880 Bagsværd Denmark
Name of company which has performed the user testing:	PAINT-Consult Wenigenjenaer-Ufer 12 07749 Jena Germany
Type of Marketing Authorisation Application:	line extension
Active substance:	semaglutide
Pharmaco-therapeutic group **(ATC Code):**	Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues (A10BJ06)
Therapeutic indication(s):	*Wegovy is used together with diet and physical activity for weight loss and to help keep the weight under control. It is used in adults, who have* *• a BMI of 30 kg/m² or greater (obesity) or* *• a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) who have weight-related health problems (such as diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnoea' or a history of heart attack, stroke or blood vessel problems).*
Orphan designation	☐ **yes** ☒ **no**
Rapporteur/CoRapporteur	

- Full user testing report provided	☐ yes	☒no
- Focus test report provided	☐ yes	☒no
- Bridging form provided[1]	☒ yes	☐no
- Is the justification for bridging acceptable?	☒ yes	☐ no
- Is the justification for not submitting a report acceptable?	☒ yes	☐ no

Reasons

- "extensions for the same route of administration (second parent reference), reference to test with same class of medicinal products, same safety issues, and with common design, layout and style of writing"

- The daughter PL is largely in line with the parent PL of Wegovy 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg solution for injection in prefilled pen.

- The daughter PL is largely in line with the parent PL of Rybelsus 3 mg, 7 mg and 14 mg tablets.

- The daughter PL contains a new paragraph compared to the parent PL only in section 3 regarding *How to take Wegovy*.

- The comparison of the PL layout and design shows that the daughter PL is largely similar or identical to the parent PL.

Further details/applicant's conclusion:
"According to the readability and CMDh bridging guidelines [1, 2], further user consultation is not necessary as the Wegovy daughter package leaflet:
- belongs to medicines that contain the identical active substance as the corresponding medicines of the parent package leaflets
- uses the same pharmaceutical form as the medicine of the Rybelsus parent package leaflet
- presents key messages in almost identical wording to that used in the previously tested parent package leaflets
- uses identical layout and design to the Rybelsus parent package leaflet
- builds upon the results of the previous successful user tests of both parent package leaflets, which are transferable to the daughter package leaflet

Therefore, it can be assumed that patients assess the information contained in the Wegovy daughter package leaflet and the previously tested parent
package leaflets equally well, while also being able to comprehend and subsequently act upon the information provided.

To conclude, the Wegovy daughter package leaflet does not necessitate testing, according to the "Guideline on the readability of the labelling"

Rapporteur's conclusion:
-The daughter PL is largely in line with the parent PL.
- The comparison of the PL layout and design shows that the daughter PL is largely similar or identical to the parent PL.
- According to the *Guideline on the readability of the labelling and package leaflet of medicinal products for human use*, a type size of 9 points, as measured in font 'Times New Roman', not

narrowed, with a space between lines of at least 3 mm, should be considered as a minimum. The PL text has main headings: 9.5pt, subheadings: 7.5pt, remaining text: 7.5pt in font type Frutiger. The Applicant is asked to show that a font of 7.5pt is the same as Times New Roman 9pt, since the parent mockups are missing.
- Real size mock-up of 'parent' package leaflet(s) are missing in the attachments.
- EPAR of 'parent' package leaflet(s), including readability test report, is missing in the attachments.
- No conclusion can be drawn yet.

Rapporteur's D150 conclusion:
With the response, Novo Nordisk explains that the used font Frutiger and size corresponds approximately to 9 pt when measured in Times New Roman. Parent mock-up of Rybelsus is included with this response for reference. The used font is accepted. Issue considered **resolved**.

[1] QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]