Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedures

Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen

(semaglutide)

Product Licence Numbers: PLGB 04668/0429-0433

Novo Nordisk A/S

LAY SUMMARY

Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen

(semaglutide)

This is a summary of the Public Assessment Report (PAR) for Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg, solution for injection in pre-filled pen. It explains how these products were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Wegovy in this lay summary for ease of reading.

For practical information about using Wegovy, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Wegovy and what is it used for?
These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Wegovy is used for weight loss and weight maintenance in addition to diet and physical activity in adults, who have
• a Body Mass Index (BMI), a measure of weight in relation to height, of 30 kg/m² or greater (with obesity) or
• a BMI of 27 kg/m² and less than 30 kg/m² (overweight) and weight-related health problems.

How does Wegovy work?
Wegovy is a medicine for weight loss and weight maintenance that contains the active substance semaglutide. It is similar to a natural hormone called glucagon-like peptide-1 (GLP-1) that is released from the intestine after a meal. Wegovy works by acting on receptors in the brain that controls the appetite, causing patients to feel fuller and less hungry and experience less craving for food. This will help patients eat less food and reduce the body weight. Wegovy should be used with a reduced calorie meal plan and increased physical activity.

How is Wegovy used?
The pharmaceutical form of this medicine is a solution for injection in pre-filled pen and the route of administration is as an injection under the skin (subcutaneous injection). Wegovy should not be injected into a vein or muscle. This medicine should be used once a week and if possible, on the same day each week. Patients can inject themselves at any time of the day regardless of meals.

The best places to give the injection are the front of the waist (abdomen), the thigh, or the upper arm. Before patients use the pen for the first time, they should ask a doctor or nurse how to use it.

The treatment will start at a low dose which will be gradually increased over 16 weeks of treatment.

When patients first start using Wegovy, the starting dose is 0.25 mg once weekly. A doctor will instruct patients to gradually increase a dose every 4 weeks until they reach the recommended dose of 2.4 mg once weekly.

Once patients reach the recommended dose of 2.4 mg, they should not increase this dose further.

Patients will be told to follow the table below.

Dose escalation	Weekly dose
Week 1-4	0.25 mg
Week 5-8	0.5 mg
Week 9-12	1 mg
Week 13-16	1.7 mg
From week 17	2.4 mg

A doctor will assess the treatment on a regular basis.

People with diabetes
Patients should tell a doctor if they have diabetes. A doctor may adjust the dose of diabetes medicines to prevent patients from getting low blood sugar.

Wegovy should not be mixed up with other medicines that patients inject (e.g. insulins).

Wegovy should not be used in combination with other medicines that contain GLP-1 receptor agonists (such as liraglutide, dulaglutide, exenatide or lixisenatide).

For further information on how Wegovy is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Wegovy have been shown in studies?
Several studies have been done in obese or overweight patients, patients injecting semaglutide once a week lost significantly more weight at the end of the studies than patients given placebo (dummy injection).

All patients were on a reduced calorie meal plan and took regular exercise. In patients who were diabetic the average weight loss was around 6 kg more than the placebo group. In other patients the average weight loss was around 10 to 13 kg more than in the placebo group. The amount of weight loss varied between patients, so in an individual the effect may be better or worse than this average amount.

Some benefits were also shown in reducing waist size and blood pressure, and in control of blood sugar.

What are the possible side effects of Wegovy?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Wegovy approved?
It was concluded that Wegovy has been shown to be effective in the treatment of weight loss and weight maintenance in addition to diet and physical activity in adults. Furthermore, the side effects observed with use of these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

What measures are being taken to ensure the safe and effective use of Wegovy?
A Risk Management Plan (RMP) has been developed to ensure that Wegovy is used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Wegovy
Marketing Authorisations for Wegovy were granted in Great Britain (GB), consisting of England, Scotland and Wales) on 24 September 2021.

The full PAR for Wegovy follows this summary.

This summary was last updated in November 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Wegovy 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen (PLGB 04668/0429-0433) could be approved.

The products are 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/m2 (obesity), or
• ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity.

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.

Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem, and direct and indirect effects on areas involved in hedonic regulation of food intake, including the septum, thalamus and amygdala.

In addition, in clinical studies semaglutide has shown to reduce blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

These applications were approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), full-dossier applications. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 08 April 2021 and from Chemistry Pharmacy and Standards Expert Advisory Group (CPS EAG) on 06 April 2021 to consider the clinical aspects. At the meeting on 03 August 2021 (CPS) and 05 August 202 (CHM) considered that the issues were resolved and approval of the Marketing Authorisations was recommended.

National marketing authorisations were granted in Great Britain (GB, consisting of England, Scotland and Wales) on 24 September 2021.

II QUALITY ASPECTS

II.1 Introduction

These products consist of solution for injection in pre-filled pen. Each pre-filled pen contains 0.25 mg, 0.5 mg, 1.0 mg, semaglutide* in 0.5 mL and 1.7 mg and 2.4 mg semaglutide* in 0.75 mL, as an active substance.

In addition to semaglutide, these products also contain the excipients disodium phosphate, dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

The finished products are packaged in type I glass syringe with attached stainless-steel needle, rigid needle shield (type II/polyisoprene) and a rubber plunger (type I/chlorobutyl). The syringe is assembled into a disposable pre-filled pen made of stainless steel, polyoxymethylene and acrylonitrile butadiene styrene.

The solution is filled in a 1 ml prefilled syringe, with a filling volume of 0.5 ml (0.25 mg, 0.5 mg or 1 mg) or 0.75 ml (1.7 mg or 2.4 mg) and assembled in a single dose pen-injector.

The pack sizes are 4 pre-filled pens.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

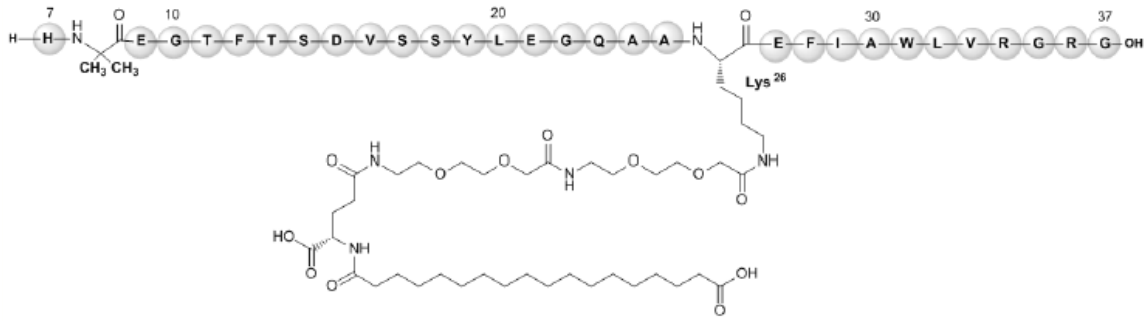
II.2 ACTIVE SUBSTANCE

rINN: Semaglutide

Chemical Name: $N^{\epsilon 26}$[(22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl)][Aib^{8},Arg^{34}]GLP-1-(7-37)peptide

Molecular Formula: $C_{187}H_{291}N_{45}O_{59}$

Chemical Structure:



Molecular Weight: 4113.6 g/mol

Appearance: White or almost white powder.

Solubility: Very slightly soluble in ethanol.

The active substance, semaglutide, is neither covered by a Certificate of Suitability nor a Drug Master File (DMF). Full information was provided in the dossier.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions “Store in a refrigerator (2°C to 8°C), Keep away from the cooling element, and Do not freeze and do not use Wegovy if it has been frozen” is approved. The pen should be stored in the original carton in order to protect from light.

Wegovy may be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
To support the applications, the applicant has provided a full nonclinical safety package (also submitted for Ozempic) supplemented by 2 new pharmacodynamic studies and a literature review for the weight management indication. All studies were conducted in accordance with current Good Laboratory Practice (GLP).

III.2 Pharmacology
New pharmacological (pharmacodynamic (PD)) data including bibliographic summaries and two new studies support the rationale for the development of the product to treat weight-management (WM) as proposed. Rodent PD studies indicated that semaglutide has direct and indirect effects on areas in the brain involved in homeostatic regulation of food intake in the

hypothalamus and the brainstem; and the hedonic reward system (septum, thalamus and amygdala). Through activation of these sites, semaglutide orchestrates the homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice.

No new secondary or safety pharmacology or pharmacokinetic (PK) studies were performed with semaglutide for the WM indication. These data were fully assessed in the previous application for Ozempic.

III.3 Pharmacokinetics

Previously, semaglutide exposures were compared with the human steady state exposure at the maximum recommended human dose (MRHD) of 1 mg/week (T2D indication). The human exposure was based on pharmacokinetic data obtained in subjects with T2D in trial 3635. For the proposed indication the MRHD is 2.4 mg/week; Animal:Human exposure ratios in pivotal toxicology studies were calculated based on human exposure derived by population pharmacokinetic modelling on data from obese subjects in the STEP 1 phase III trial (trial 4373).

In line with the linear PK profiles previously reported across species, the calculated exposure ratios have generally halved for the WM posology versus the reported Animal:Human safety margins (T2D). Notably, the exposure multiple for the juvenile toxicity study (study 214479) has reduced from x22 (T2D) to x8 (WM). Of note, in juvenile studies semaglutide caused reduced food consumption, and reduced body weight gain to an extent beyond the effect of reduced food consumption alone. Moreover, semaglutide further caused a delay in sexual maturation in both males and females, and body weight at attainment of sexual maturation was higher than in the pair-fed control group.

III.4 Toxicology

There are no new toxicology data. Originally, in all pivotal studies, exposure of the treated animals was confirmed, and formation of anti-semaglutide antibodies was observed in few animals and did not affect exposure. Semaglutide was generally well-tolerated and the toxicology programme demonstrated effects mainly considered to be pharmacologically mediated via GLP-1R activation, either directly or secondary to the effects on food consumption and body weight.

In carcinogenicity studies in mice and rats, thyroid C-cell adenomas and carcinomas were observed at all dose levels. This is an expected result also seen with other GLP-1 agonists and was considered a class effect. No other tumours were found. Other non-neoplastic effects were secondary to the decreased body weight gain related to the pharmacological action of semaglutide. The relevance for humans is low but cannot be completely excluded. No genotoxicity was reported.

Reproductive toxicology studies revealed toxicities at exposure multiples lower than that expected at the MHRD and hence ‘Women of childbearing potential are recommended to use contraception when treated with semaglutide’; ‘semaglutide should not be used during pregnancy’ and ‘Semaglutide should not be used during breast-feeding’. This is accepted. Treatment-related effects on fertility were ruled out in the original assessment. Furthermore, this is in line with recommendations for the currently marketed GLP-1R agonists, which generally are not recommended for use during pregnancy due to observations of reproductive toxicity in animal studies.

The applicant's rationale for not conducting specific local tolerance studies is accepted. The new formulation consists of pharmacopeial grade excipients and considered to be well-tolerated when used subcutaneously (s.c.). Regarding the active, concentrations up to 10 mg/ml has been evaluated in pigs without any safety concerns (3.2 mg/ml is now proposed).The impurities in the semaglutide drug product have been tested in non-clinical studies and are considered to have been adequately safety qualified.

III.5 Ecotoxicity/Environmental Risk Assessment

According to European Medicines Agency's guideline "Guideline on the environment risk assessment of medical products for human use" ERA studies are not required for substances like amino acids, peptides, proteins, carbohydrates and lipids since they are unlikely to result in significant risk to the environment.

On this basis it is concluded that the use of semaglutide is unlikely to result in significant risk to the environment and consequently, is exempt from submitting ERA studies according to the EMA guideline on environmental risk assessment of medicinal products for human use.

III.6 Discussion on the non-clinical aspects

In conclusion, the updated pharmacodynamic data; the clinical margins of exposure and the proposed product information support the new indication and proposed MRHD for the weight management indication from a non-clinical perspective. No additional safety concerns are anticipated.

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In support of the applications, the applicant has provided 8 new completed clinical trials:

- 3 clinical pharmacology studies (two bioequivalence studies and a new interaction study trial)
- 1 phase II dose-finding study
- 4 phase IIIA therapeutic confirmatory trials (STEP trials)

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

The pharmacokinetic (PK) properties of semaglutide and other GLP-1 agonists have been extensively studied. The applicant referenced the original Ozempic dossier, supporting this with new bridging bioequivalence studies, a new interaction study and a new phase II clinical trial. Population PK and exposure-response analyses were also provided, based on sparse sampling in two phase III trials.

Study 4590

Bioequivalence of 1 and 2.4 mg product

This study was a 21 week, randomised open label trial to demonstrate bioequivalence between the final 2.4 mg product proposed for marketing (single dose pen injector, 3.2 mg/mL) and the 2.4 mg product used in the weight management phase IIIA studies (PDS290 multiple-dose pen injector, 3 mg/mL), in overweight/obese adults, at steady state.

Bioequivalence was demonstrated for $AUC_{0\text{-}168h}$ and C_{max} at 2.4 mg, with the same median T_{max} between formulations. Half-way through the study when the subjects had been titrated to 1 mg of either device, the pharmacokinetic (PK) profile was also comparable between formulations. AUC and C_{max} were dose-proportional between the 1 mg and 2.4 mg doses. Based on study 4590, there are adequate bioequivalence data to bridge the 1, 1.7 and 2.4 mg formulations used in the phase IIIA weight loss program to those proposed for marketing.

Study 4588

Bioequivalence of 0.25 mg product

This study was a 7-week, randomised, open-label trial to demonstrate bioequivalence between semaglutide formulations in overweight/obese adults

This study dosed up to 1 mg only, and compared the steady state PK following 2 different formulations, the original Ozempic formulation (1.34 mg/ml, in multidose injector) to the proposed marketing presentations in the single-dose pen-Injector for the 1.0 mg and 0.25 mg doses.

Study 4588 did not show bioequivalence at the 1 mg strength, between the current Ozempic formulation and the product proposed for marketing. However, bioequivalence at 1 mg was shown for the more relevant comparison in study 4590.

The applicant has not shown bioequivalence for the 0.25 mg and 0.5 mg products used in phase IIIA studies, compared to the products proposed for marketing. These are not intended as maintenance doses, and are given for 4 weeks each in the dose escalation phase of treatment. Therefore, small differences would not be expected to contribute to efficacy in the maintenance phase. Based on previous data, no clinically relevant difference in C_{max} is expected based on the concentration of semaglutide administered.

New interaction data

In the PD study 4455, the effect of semaglutide on gastric emptying in obese subjects was compared to placebo. Semaglutide was titrated to 2.4 mg weekly, with matching placebo, then at 20 weeks both groups were given 1.5 mg paracetamol with a standard breakfast. An increase in paracetamol $AUC_{0\text{-}5h}$ of 8% was observed with semaglutide 2.4 mg compared to placebo, with no change in C_{max}, $AUC_{0\text{-}1h}$ or median T_{max}. No significant difference was observed in $AUC_{0\text{-}5h}$ between semaglutide 2.4 mg and placebo, in a *post-hoc* analysis adjusting for weight loss.

New population PK analysis

Population PK and exposure-response analyses were provided, based on sparse sampling for semaglutide concentration in 2 of the phase III trials, STEP 1 and 2.

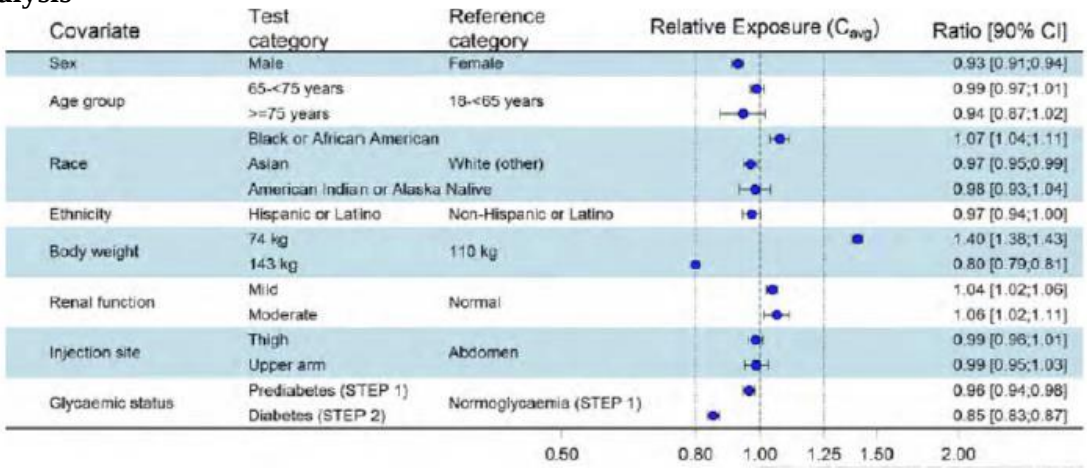
Blood samples for plasma semaglutide concentration measurements were taken on 6–7 occasions; at week 2 (STEP 1 only), during dose-escalation at weeks 4, 8 and 12 (respectively at 0.25 mg, 0.50 mg and 1.0 mg) in the maintenance period (weeks 28 and 52, both at 2.4 mg) at end of treatment (week 68) and at end of trial (week 75). Based on data from these two trials, the effects of various prespecified covariates on semaglutide exposure were assessed in a population PK analysis, using a one-compartment model with first-order absorption and elimination. Ka was fixed, based on previous modelling.

The final population PK dataset comprised 11,827 PK observations from 2077 subjects. The steady-state PK profile based on the pop PK analysis and the phase II dose-response study

was as expected from the prior data, with an elimination half-life (t½) of approximately one week, supporting the proposed once-weekly dose regimen. Exposure of semaglutide increased dose-proportionally up to 2.4 mg once weekly.

Body weight was the most important covariate resulting in lower exposure with higher body weight and vice versa. Other investigated covariates (sex, age, race, ethnicity, renal function, injection site and glycaemic status) had a minor or no influence on semaglutide exposure.

Figure 1. Forest plot of covariate effects for semaglutide exposure. Population PK analysis

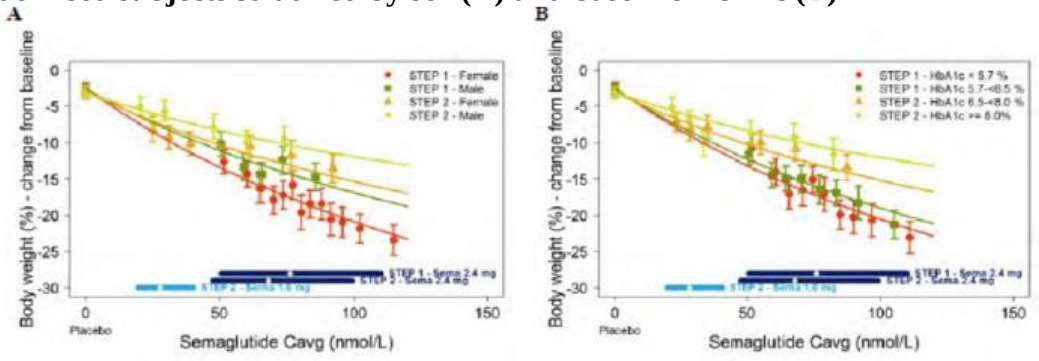


New exposure-response analysis

Exposure-response assessments including again the STEP 1 and STEP 2 trials showed that the desired effect on body weight increased with increasing semaglutide exposure, which was duplicated across subgroups.

The exposure-response relationship for weight loss was explored for various covariate effects, to adjust for confounding factors and to identify subgroups relevant for further exposure- response evaluation. Baseline body weight, sex, race, trial and baseline HbA1c levels were retained covariates and were included in the model, the weight response was larger in females compared to males. Covariates of sex and baseline HbA1c levels were compared across trials in the same plots, indicating that the weight loss increased in an exposure-dependent manner within all subgroups.

Figure 2: Body weight change from baseline by trial versus semaglutide exposure for all randomised subjects stratified by sex (A) and baseline HbA1c (B)



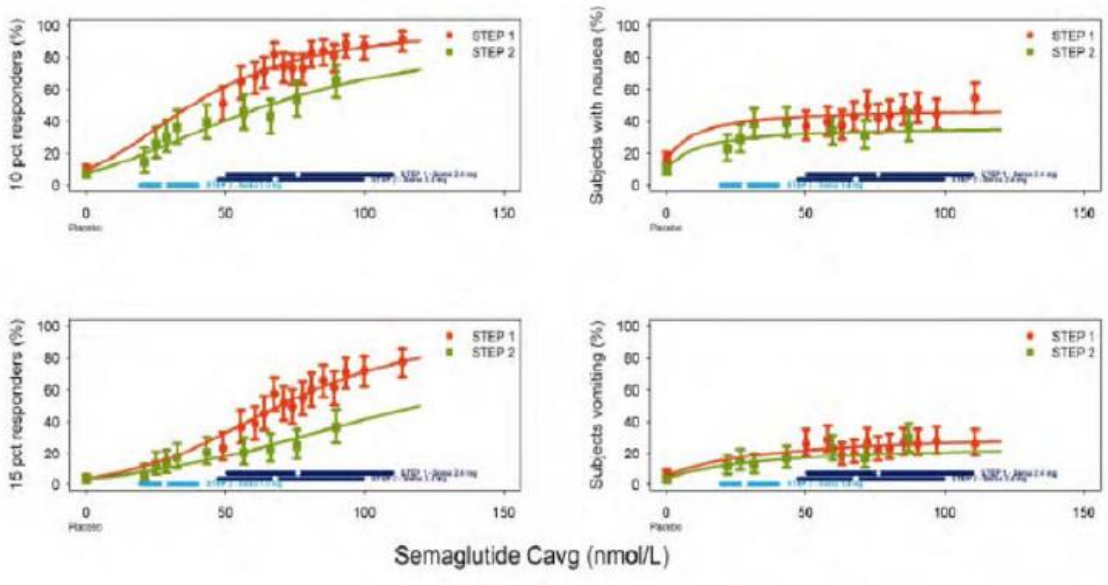
Responder analyses were done for the proportions of subjects reaching at least 5%, 10%, 15% and 20% weight loss. The proportions of subjects reaching each of these targets were all

related to semaglutide exposure, with larger proportions of subjects reaching targets at higher exposure levels. In accordance with the exposure-response analysis for weight loss, larger proportions reaching the specified targets at a given exposure were seen in STEP 1 than in STEP 2.

The proportion of subjects reporting gastrointestinal adverse events, in particular nausea or vomiting, increased to a minor extent with increasing semaglutide exposure and appeared to plateau so that it was almost constant over the studied exposure range for semaglutide 2.4 mg. Furthermore, an adequate exposure was observed across the concentration range associated with semaglutide 2.4 mg. Based on these data the proposed maintenance dose of semaglutide 2.4 mg is acceptable in all patients.

Some selected responder analyses by exposure are given in the figure below.

Figure 3: Response versus semaglutide exposure – 10 and 15% efficacy response, nausea, vomiting



There is an exposure-response for both efficacy and safety, however the data are considered limited to allow an E_{max} model to be fitted. While it is appreciated that the objective function value (OFV) for a linear relationship for efficacy was higher, the data do not support the determination of an EC_{50} and E_{max} with confidence. The EC_{50} for efficacy (222 nM) is higher than any measured data and higher than that determined in the phase 2 study (54.6 nM) which utilised once daily dosing. This suggested that changes in exposure can have a significant effect on efficacy.

There are a number of important covariates (e.g. weight on exposure, and gender/baseline HbA1c levels on efficacy). This would give rise to a different response in different subgroups, and has not been fully presented. More consistent efficacy might be achieved with dosing on a mg/kg basis. However, the population used in the phase III studies is representative of the whole population, and the proposed dose and dosing scheme demonstrate a favourable benefit-risk profile.

IV.3 Pharmacodynamics

The pharmacodynamic properties of multiple GLP-1 agonists have been extensively studied, including the effect on weight, appetite, satiety and energy intake. For semaglutide the

properties have been previously studied in patients with T2DM, at a dose up to 1 mg s.c once weekly. The highest dose in the previous thorough QT study was 1.5 mg, lower than the 2.4 mg highest dose than proposed. However, the previous study did not indicate any clinically relevant effects of semaglutide on QT, and this was fully in line with the non-clinical findings at very high concentrations. Given the lack of new clinical trial safety findings in the proposed population at the new 2.4 mg weekly dose, a new QT study is not considered necessary. The absence of a new formal QT study at the new dose has been adequately justified.

The applicant submitted a single new clinical pharmacodynamic trial.

Study 4455
This study was a randomised double-blind placebo-controlled parallel group study in obese subjects. The active treatment arm was semaglutide 2.4 mg s.c once weekly, for 20 weeks (steady state). In an *ad libitum* lunch at week 20, energy intake was nearly a third lower with semaglutide 2.4 mg than with placebo (1736 kJ vs 2676 kJ) and there were indications of reduced appetite, greater satiety and fewer food cravings in subjective rating scales.

IV.4 Clinical efficacy

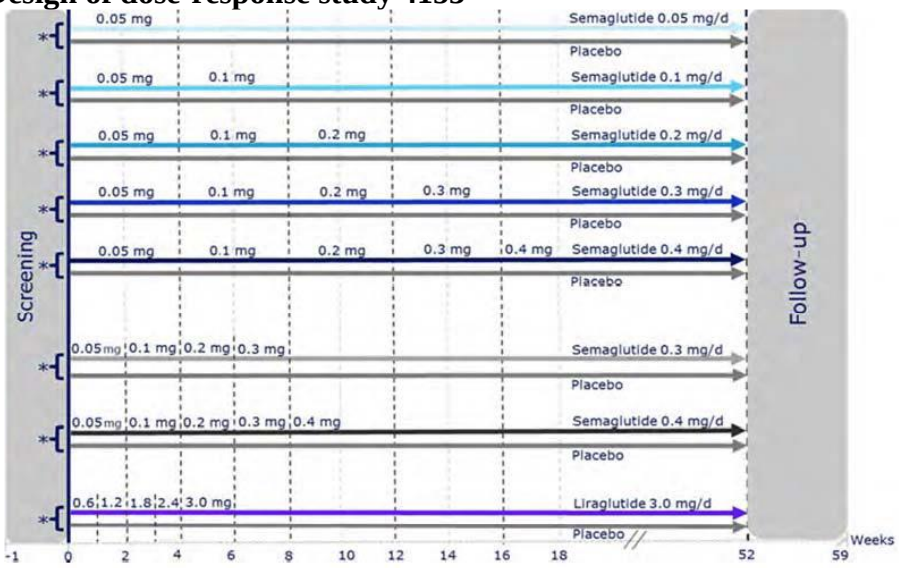
In support of the applications, the applicant has submitted a dose response study and 4 completed phase IIIA studies, referred to as the STEP trials (Semaglutide Treatment Effect in People with obesity)

Dose Response Study (Study 4153)
This study was a randomised, double-blind, placebo and active controlled 52-week dose-finding study in 957 obese subjects without diabetes, as an adjunct to a reduced-calorie diet and increased physical activity. The study compared 5 different doses of daily s.c. semaglutide (0·05 mg to 0·4 mg) versus liraglutide (3 mg) and matched placebo. The trial included a 1-week screening period, followed by a 52-week treatment period and a follow-up visit after 59 weeks. The primary endpoint was percentage weight loss at week 52.

At the time the initial phase 2 trials were designed, daily semaglutide administration was implemented because it was thought a flatter PK profile would cause fewer adverse events compared with weekly dosing. Later on, the chosen daily dose was modelled to the weekly dose regime used in the phase IIIA studies.

As an exploratory objective, 2 further groups with matched placebo controls were added, in which escalation to 0.3 and 0.4 mg was done every 2 weeks, instead of every 4 weeks. This gives a total of 16 randomised treatment arms, as shown in the figure below. Each active treatment arm was blinded versus placebo with matching injection volumes, but not towards the other arms. No down-titration was permitted, although dose escalation could be postponed for up to 1 week, or for up to 4 days in the fast escalating groups.

Figure 4: Design of dose-response study 4153



The study included two parts (A & B). Part A was concerned with identifying the optimal dose and Part B was concerned with identifying the optimal dose escalation regime. The sample size calculation for Part A was based on the relative change after 52 weeks treatment in the primary endpoint, assuming pooling of placebo groups and no correlation between body weight change after 52 weeks and placebo injected volume. The justification for the sample size is considered adequate.

The primary endpoint was the relative change from baseline in body weight (%) at 52 weeks. Two estimands were defined:

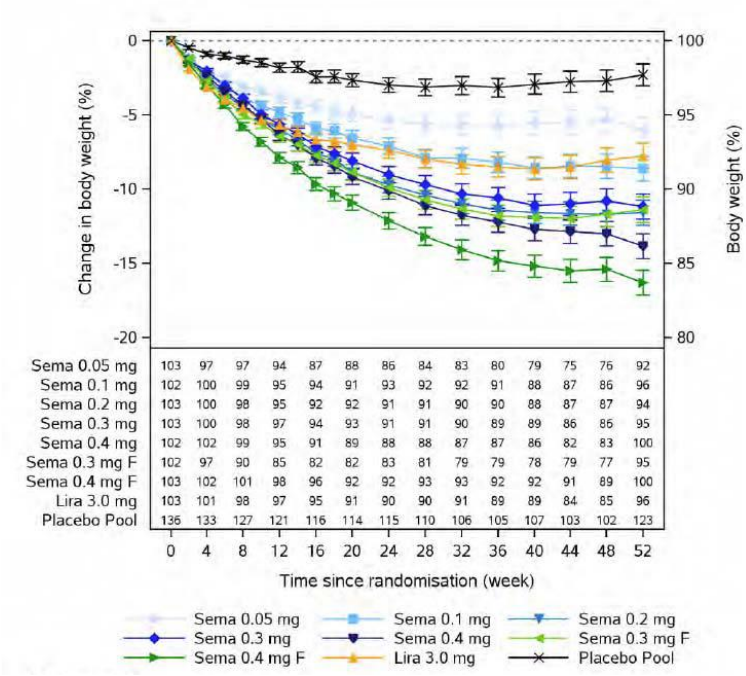
1) Effectiveness estimand: the average treatment effect of once-daily semaglutide relative to placebo and liraglutide 3.0 mg after 52 weeks, as add-on to nutritional and physical activity counselling, in all randomised subjects regardless of adherence to treatment (Primary). The primary analysis was based on ANCOVA model with missing data imputed using a 'jump-to reference' multiple imputation approach.

2) Efficacy estimand: the average treatment effect of once-daily semaglutide relative to placebo and liraglutide 3.0 mg after 52 weeks, as add-on to nutritional and physical activity counselling, if all randomised subjects had adhered to the assigned treatment regimen for the entire planned duration of the trial. Analysis was based on mixed model for repeated measurements (MMRM) comparing the change from baseline in body weight (%) at 52 weeks between treatments.

For both analysis the ANCOVA model included region, sex and baseline weight. Data from the placebo arms was pooled. Various sensitivity analyses were performed to assess the impact of missing data on the primary analysis.

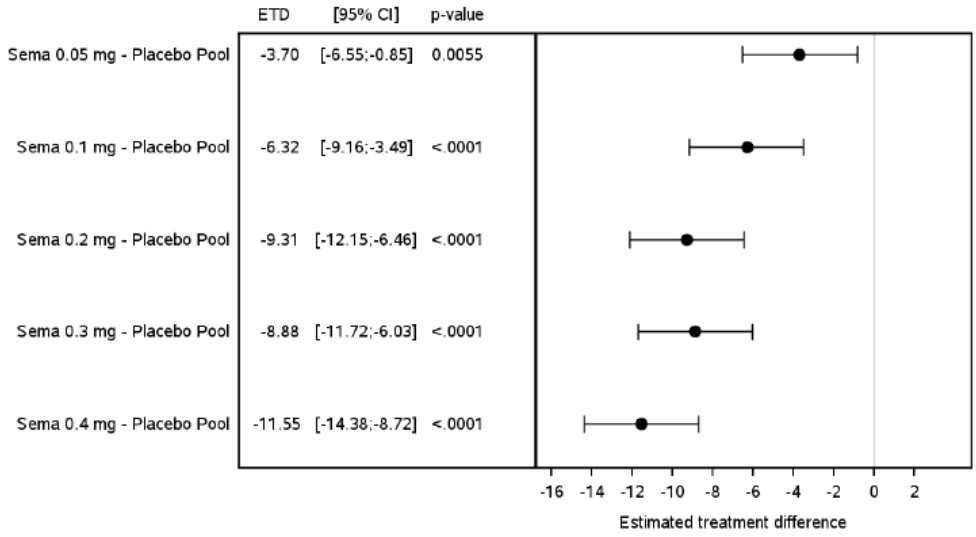
The mean weight at baseline was around 112 kg, which was comparable between groups. The change in body weight over time is shown below for all treatment arms. The 2 fast escalation arms are labelled "0.3mg F" and "0.4 mg F".

Figure 5: Primary endpoint- dose-response study 4153



The primary analysis excluded the fast escalation arms and corrected for multiple comparisons. The decrease in body weight at week 52 was statistically greater for all semaglutide arms versus pooled placebo, with a placebo-corrected difference ranging from -3.7-11.5%. The results between 0.2 and 0.3 mg were similar. Semaglutide doses ≥0.2 mg per day were statistically superior to liraglutide.

Figure 6: Dose-response study: Statistical analysis of primary endpoint between each dose and placebo



The proportion of subjects achieving a weight loss of ≥5% at week 52 showed a more consistent response to dose, ranging from 53.50% (0.05 mg) to 82.52% (semaglutide 0.4 mg). Likewise, the proportion of subjects achieving a weight loss of ≥10% at week 52 increased with dose, ranging respectively from 18.94% to 64.61%.

Titrating up to 0.3 mg semaglutide every 2 weeks made no difference to the primary endpoint, compared to escalating every 4 weeks. There was a small efficacy benefit to a

quicker escalation when comparing the 0.4 mg groups (around 2.5% weight difference) although each 0.4 mg group showed a clinically significant weight loss at the end of the study.

There was a small trend for increased adverse events (AEs) with dose, but the majority of AEs were non-serious, mild or moderate in severity and assessed as unlikely related to trial product by the investigators. AEs considered related to trial product were most frequently gastrointestinal (GI), as expected.

Table 1. Dose-response study : Total and GI adverse events

	Sema 0.05 mg				Sema 0.1 mg				Sema 0.2 mg				Sema 0.3 mg				Sema 0.4 mg			
System organ class	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	103				102				103				103				102			
Adverse events	93	(90.3)	539	5412	94	(92.2)	729	6856	96	(93.2)	732	6948	93	(90.3)	582	5514	98	(96.1)	766	7427
Gastrointestinal disorders	64	(62.1)	152	1526	72	(70.6)	249	2342	72	(69.9)	311	2952	72	(69.9)	263	2492	84	(82.4)	343	3325

In the same data set, the proportion of subjects discontinuing trial prematurely due to AEs was highest (14.7%) in the 0.4 mg arm, although there was no clear dose-response between the lower doses. The most common reason for premature discontinuation was because of gastrointestinal events, with more in the 0.4 mg group than in the 0.3 mg group.

Table 2. Dose-response study : Total and GI adverse events leading to premature discontinuation

System organ class High level group term Preferred term	Sema 0.05 mg				Sema 0.1 mg				Sema 0.2 mg				Sema 0.3 mg				Sema 0.4 mg			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	103				102				103				103				102			
Observation time (years)	99.6				106.3				105.4				105.5				103.1			
Events	8	(7.8)	25	251.0	8	(7.8)	8	75.2	5	(4.9)	8	75.9	4	(3.9)	4	37.9	15	(14.7)	21	203.6
Gastrointestinal disorders	6	(5.8)	9	90.4	5	(4.9)	5	47.0	3	(2.9)	6	57.0	4	(3.9)	4	37.9	13	(12.7)	18	174.5

The proportion of subjects reporting serious adverse effects (SAEs) showed no dose-dependency.

With the 0.3 mg arms, there were numerically more subjects in the 2-week escalation group versus the 4-week escalation group who discontinued prematurely due to AEs, and because of gastrointestinal AEs. However, this was not seen when comparing the two 0.4 mg escalation approaches.

Semaglutide was statistically superior to placebo at all doses in the dose-response study. No difference was seen in the primary endpoint between the groups titrated to 0.3 and 0.4 mg/day, although the higher dose subjects did slightly better in *post-hoc* responder analyses and some other endpoints.

There were no serious dose-related safety issues, and the majority of AEs were non-serious and mild/moderate in severity. There was an increase in AEs – including AEs leading to

premature treatment discontinuation - between the 0.3 and 0.4 mg doses. The group sizes are fairly small and obviously the dose-response can only be estimated for the most common AEs. Also, although each active treatment arm was blinded towards placebo with matching injection volumes, there was no blinding to the assigned dose, due to differences in dose escalation and volume delivered. This could have introduced bias into the AE reporting.

Dose-escalation is well established for GLP-1 receptor agonists, predominately to mitigate gastrointestinal side effects. For the semaglutide T2DM indication, the 3 doses are titrated up every 4 weeks, so it was reasonable to study this approach with higher doses. A more rapid escalation made little difference, so the more conservative escalation every 4 weeks was reasonable to take into phase IIIA, and likely easier from a practical point of view. A slower escalation than this has not been discussed by the applicant. Arguably, if the dose escalation is too slow, the motivational benefit of seeing an early response might be lost.

The phase IIIA maintenance dose of 2.4 mg once weekly was not directly assessed in the dose finding study. However, the population pharmacokinetic modelling showed that the C_{max} at steady state following 2·4 mg once-weekly s.c. semaglutide did not exceed the level following 0·4 mg once daily.

Only a single maintenance dose was taken into the phase IIIA weight management program, except for STEP 2, which was only in subjects with T2DM. Statistical superiority for 2.4 mg versus 1 mg was seen in STEP 2 for the primary and confirmatory secondary endpoints.

Pivotal Efficacy studies
In the 4 pivotal studies (STEP 1-4), 2652 subjects were randomised to semaglutide 2.4 mg, 1530 to placebo, and 403 to semaglutide 1.0 mg.

STEP studies
Trial 4373 (STEP 1) weight management:
This is a 68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly versus placebo, as an adjunct to lifestyle intervention, in adults with overweight or obesity.

Trial 4374 (STEP 2) weight management in T2D
This is a 68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly versus placebo, as an adjunct to lifestyle intervention, in adults with overweight or obesity and T2D.

Trial 4375 (STEP 3) weight management with intensive behavioural therapy (IBT)
This is a 68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly versus placebo, as an add-on to IBT, in adults with overweight or obesity.

Trial 4376 (STEP 4) sustained weight management
This is a 68-week, randomised, double-blind, placebo-controlled trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly versus placebo in adults with overweight or obesity who had reached the maintenance dose of semaglutide (2.4 mg) during a 20-week run in period.

Objectives

The primary objectives of the four phase IIIa trials (STEP 1-4) was to compare the effect of semaglutide s.c. 2.4 mg once weekly versus placebo in subjects with overweight or obesity (and T2D in STEP 2) on body weight, either as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or to IBT (STEP 3).

The main secondary objective of STEP 1-4 were to compare the effect of semaglutide s.c. 2.4 mg once weekly versus placebo in subjects with overweight or obesity (and T2D in STEP 2) on other factors related to body weight, cardiovascular risk factors, clinical outcome assessments including patient-reported outcomes and glucose metabolism.

Study design

The STEP 1-4 studies had many similarities. All were 68 week randomised, double-blind, placebo-controlled studies in obese adults, or in overweight adults (BMI ≥27) who had at least one weight-related comorbidity. All subjects needed to have tried at least once to lose weight with lifestyle intervention alone. There was an additional 7 weeks of follow-up after the end of the treatment periods. All studies included an arm where semaglutide was titrated in 4-week steps to the maintenance dose of semaglutide 2.4 mg s.c., once weekly. Treatment was always given in conjunction with a reduced calorie diet, counselling and increased physical activity.

The key differences between studies were:
STEP 2 was only in T2DM patients, and had an extra arm where the maintenance dose of semaglutide was 1 mg weekly
STEP 3 was on the background of more intensive behavioural intervention, with an initial 8-week very low-calorie diet
STEP 4 was a randomised withdrawal design, in subjects reaching maintenance dose during the 20-week run-in
STEP 1, 2 and 4 were multinational, whilst STEP 3 was done in the US only. STEP 1 and 2 both included 10 UK sites.

Note that for the efficacy analyses, the baseline for STEP 4 was at week 20, when patients were randomised to either continue on semaglutide or switch to placebo.

The overall design of the phase IIIA program is in line with current regulatory guidance for the therapeutic area (CHMP/311805/2014) and has been discussed in previous regulatory advice. The overall number of subjects in STEP 1-4 is adequate for an efficacy evaluation. STEP 1 is especially important, as it was the largest trial and was specifically in non-diabetics. STEP 3 explored the additional benefit of semaglutide when added to more intensive lifestyle interventions. STEP 4 evaluates weight regain when treatment is withdrawn, but in an enriched population who reached the 2.4 mg maintenance dose during run-in.

In STEP 1, 2 and 4, the recommended diet was a 500-kcal deficit per day, relative to the estimated total energy expenditure calculated at randomisation. The target physical activity was 150 minutes per week. Counselling was provided by a dietician or a similar qualified healthcare professional every month, via visits or phone contact. Subjects were instructed to record their food intake and physical activity, to assist and evaluate lifestyle interventions. In STEP 3 lifestyle interventions were more intense. The first 8 weeks after randomisation required a 1000-1200 kcal/day diet, then subjects gradually were transferred to a less strict diet, depending on body weight at randomisation. Behavioural counselling was conducted

from randomisation to end of treatment. The physical activity targets started at 100 minutes per week, increased up to 200 minutes per week.

Outcomes and Estimation
The primary endpoint in all 4 studies was the percentage change in body weight from baseline. STEP 1-3 had a co-primary endpoint, which was the number of subjects with ≥5% body weight reduction from baseline at week 68.

Secondary objectives included other metrics of obesity, cardiovascular risk factors, patient-reported outcomes, and glucose metabolism. Secondary endpoints differed slightly between trials.

Secondary endpoints defined a prior as confirmatory were:
STEP 1-2: IWQOL-Lite-CT (Impact of Weight on Quality of Life-Lite, Clinical Trials version) 5 item physical function score
STEP 2: HbA1c
STEP 1-3: % of subjects with 10% and 15% weight reduction
STEP 1-4: Waist circumference, systolic blood pressure (SBP), short form (SF)-36 physical functioning scores

Estimands
Objectives were assessed with 2 pre-defined estimands:
- Treatment policy (primary) estimand (intention-to-treat): trial population average effect of subjects randomised to treatment regardless of adherence to treatment and regardless of initiation of any other anti-obesity therapies, based on data from the full in-trial period.

- Hypothetical (secondary) estimand: average treatment effect of semaglutide relative to placebo after 68 weeks in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not initiated any other anti-obesity therapies. All randomised subjects contributed with data collected from first dose of trial product to end of treatment or until first discontinuation of randomised treatment or initiation of other anti-obesity therapies.

Treatment policy was the protocol defined primary estimand in all studies, from which superiority claims were based. Analyses of confirmatory endpoints were controlled for multiplicity only for the treatment policy estimand, using a fixed sequence strategy.

All results below are for the treatment-policy estimand, unless otherwise stated. The choice of (co)primary endpoints and key secondary endpoints is in line with current regulatory guidance for the therapeutic area, and are discussed in previous regulatory advice.
As the 1 mg dose is not being pursued, the main analyses of the primary and secondary efficacy endpoints include those randomised to the 2.4 mg maintenance dose only, the 2 active dose arms in STEP 2 are then compared separately.

Cardiovascular outcomes were assessed as a safety endpoint rather than an efficacy one. The applicant does not make any claims for cardiovascular (CV) outcomes in the weight loss indication - referring in the Summary of the Characteristics (SmPC) only to the SUSTAIN 6 data (which relate to the 1 mg weekly dose, in patients with T2DM only).

The choice of treatment-policy estimand as the primary estimand is supported. The secondary estimand based on hypothetical strategy is considered supportive.

In Step 4 the primary treatment-policy-estimand and secondary estimand based on hypothetical strategy quantifies the treatment effect after 48 weeks of treatment. Two additional estimands were defined:

Tertiary estimand: Average treatment effect of semaglutide after 68 weeks, as an adjunct to reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies".

Quaternary estimand: Average treatment effect of semaglutide after 68 weeks, as an adjunct to reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire 68 weeks and not initiated other anti-obesity therapies).

The results based on these estimands are considered supportive.

Randomisation
The applicant provided details of the randomisation scheme. Simple randomisation was used in STEP 1, 2, 3, and 4. STEP 2 used block randomisation with stratification. Randomisation was implemented using Interactive Web Response Systems (IWRS).

Blinding
Step 1, 2 and 3: Treatment allocation remained blinded to the subjects, the investigators and to Novo Nordisk during the entire treatment and follow-up period in the main phase of the trial and until after data base lock (DBL) for the main phase of the trial.

Step 4: Treatment allocation remained blinded to the subjects, the investigators and to Novo Nordisk during the randomised (maintenance) period and follow-up period and until after DBL.

Semaglutide and placebo were identical in appearance and were packed and labelled to fulfil the requirements for double blind procedures.

The blinding procedure is considered adequate.

Sample size
The sample size in all studies has been adequately justified.

Statistical methods
Analysis and imputation method to address the primary and secondary estimands and confirmatory secondary endpoints were provided.

Primary analysis
Primary Estimand
The analysis model for % weight change is a linear regression (ANCOVA) of % weight change with randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated treatment difference between semaglutide 2.4 mg and semaglutide placebo was reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value. The primary imputation approach for the primary estimand was based on a multiple imputation.

Missing body weight measurement at week 68 for non-retrieved subjects were imputed using assessments from retrieved subjects in each randomised treatment arm using assessment retrieved in each treatment group. Missing body weight measurements at week 68 for subjects on randomised treatment were imputed in a similar way by sampling from available measurements at week 68 from subjects on randomised treatment in the relevant randomised treatment arm.

Secondary Estimand
The secondary estimand for % weight change addresses the efficacy of semaglutide 2.4 mg and was assessed using a 'mixed model for repeated measures (MMRM) for efficacy'. The MMRM for efficacy was fitted using percentage weight change and the same factor and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject was employed, assuming that measurements for different subjects are independent.

Sensitivity analyses
The sensitivity analyses for the primary estimand were performed to investigate how assumptions on body weight development after discontinuation of randomised treatment impact the estimated treatment contrasts between semaglutide 2.4 mg and semaglutide placebo (Jump to Reference, Tipping point multiple imputation, and MMRM).

Secondary analyses
All confirmatory secondary endpoints were analysed using the same imputation approach as used for the primary endpoints and to address the primary estimand.
The confirmatory secondary endpoints which relate to the primary objective were analysed to address the secondary estimand using the same MMRM for efficacy described for the primary endpoints.

A logistic regression was used for the analysis of responder endpoint using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratio (OR) between semaglutide 2.4 mg and semaglutide placebo was reported together with the associated two-sided 95% CI and corresponding p-value. Subjects with missing week 68 assessment as were included as non-responders in the analysis.

Continuous outcomes were analyses using MMRM and ANCOVA model. Sensitivity analyses were performed based on multiple imputation using J2R approach.

Multiplicity adjustment
The tests of superiority of semaglutide 2.4 mg to semaglutide placebo for the primary and confirmatory secondary endpoints are performed using the fixed-sequence statistical strategy. This strategy tests the endpoints using a predefined hierarchical order, all at the significance level of 5%.

Similar methodology for the analysis of the primary and secondary endpoints was used in all studies (STEP 1 to 4). Note though in STEP 2, the primary analysis was adjusted for factors used to randomise subjects and this is appropriate.
In all studies, sensitivity analyses were provided to address the primary and secondary estimands as well as key secondary endpoints. The definitions of the primary and secondary estimands were adapted in each study to reflect the study design.
In all cases the primary estimands were based on treatment-policy strategy for handling intercurrent events and the secondary estimands were based on a hypothetical strategy for

handling intercurrent events (e.g. adherence to treatment, initiation of other anti-obesity therapies).

The choice of primary and secondary analyses are supported. The Applicant has performed a number of sensitivity analyses to assess the robustness of the primary and secondary estimands as well as key secondary endpoints under different strategies for handling missing data. This approach is in line with the principles set out in the ICH E9 (R1) addendum.

In STEP 2, responders based on 5% threshold was co-primary. The use of hierarchical approach for controlling the Type I error at 5% two-sided significance level when testing key secondary endpoints is acceptable.

Study Participants
Inclusion and Exclusion criteria for STEP 1-4 were provided.

STEP 2 was restricted to patients with T2DM (on diet alone, or up to 3 Oral Anti-Diabetic Drugs) and included patients with BMI between ≥27 kg/m^2. The other trials excluded those with HbA1c ≥ 6.5% at screening (or with a history of T2DM) and were done in subjects with BMI ≥30.0 kg/m^2 or ≥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 cardiovascular disease.

Subjects with just 1 unsuccessful dietary attempt to lose weight were eligible to join the trials – in practice, the barriers to pharmacological treatment could be higher. The inclusion and exclusion criteria were as expected for a GLP-1 agonist and trials of this nature.

Baseline data
Important baseline demographic and comorbid findings are summarised in the tables below. For STEP 2, only the subjects randomised to the 2.4 mg dose are included in the table.

Table 3: Baseline data, STEP 1-4

	STEP 1 Weight management	**STEP 2** Weight management in T2D	**STEP 3** Weight management with IBT	**STEP 4** Sustained weight management
Number of subjects	1961	807	611	803
Age, years (SD)	46 (13)	55 (11)	46 (13)	46 (12)
Sex, % (female/male subjects)	74.1/25.9	51.2/48.8	81.0/19.0	79.0/21.0
Race, % (White/Asian/Black or African American)	75.1/13.3/5.7	59.4/27.3/8.9	76.1/1.8/19.0	83.7/2.4/13.0
Ethnicity, % (not Hispanic or Latino/Hispanic or Latino)	85.1/12.0	88.1/11.9	80.2/19.8	92.9/7.8
Body weight, kg (SD)	105.3 (21.9)	100.2 (21.7)	105.8 (22.9)	96.1 (22.6)
BMI, kg/m^2 (SD)	37.9 (6.7)	35.9 (6.5)	38.0 (6.7)	34.4 (7.0)
Waist circumference, cm (SD)	114.7 (14.6)	115.0 (14.1)	113.0 (15.5)	105.3 (16.2)
HbA_{1c}, % (SD)	5.7 (0.3)	8.1 (0.8)	5.7 (0.3)	5.4 (0.3)
HbA_{1c}, mmol/mol (SD)	39.0 (3.5)	65.3 (8.8)	39.3 (3.7)	35.2 (3.1)
Fasting plasma glucose, mmol/L (SD)	5.3 (0.6)	8.6 (2.3)	5.2 (0.5)	4.9 (0.4)
Fasting plasma glucose, mg/dL (SD)	95.2 (10.6)	155.3 (41.3)	94.0 (9.4)	87.6 (7.7)
eGFR, mL/min/1.73 m^2 (CV)	96.14 (18.6)	93.28 (22.8)	96.55 (21.1)	92.23 (21.0)
Diabetes duration, years (SD)	N/A	8.2 (6.2)	N/A	N/A

Table 4: Baseline comorbidities at screening, STEP 1-4

	STEP 1 WM N (%)	STEP 2 WM in T2D N (%)	STEP 3 WM with IBT N (%)	STEP 4 Sustained WM N (%)	Total N (%)
Number of subjects	1961	807	611	803	4182
Number of female subjects	1453	413	495	634	2995
Hypertension	706 (36.0)	563 (69.8)	212 (34.7)	298 (37.1)	1779 (42.5)
Dyslipidaemia	725 (37.0)	549 (68.0)	212 (34.7)	288 (35.9)	1774 (42.4)
Impaired glucose metabolism	457 (23.3)		185 (30.3)	88 (11.0)	730 (17.5)
Elevated HbA1c	351 (17.9)		155 (25.4)		506 (12.1)
Impaired fasting glucose	151 (7.7)		65 (10.6)	61 (7.6)	277 (6.6)
Impaired glucose tolerance	67 (3.4)		30 (4.9)	42 (5.2)	139 (3.3)
Osteoarthritis	311 (15.9)	158 (19.6)	114 (18.7)	107 (13.3)	690 (16.5)
Symptomatic osteoarthritis of the knee	275 (14.0)	140 (17.3)	107 (17.5)	99 (12.3)	621 (14.8)
Symptomatic osteoarthritis of the hip	86 (4.4)	46 (5.7)	25 (4.1)	23 (2.9)	180 (4.3)
Reproductive system*	245 (16.9)	49 (11.9)	103 (20.8)	95 (15.0)	492 (16.4)
Menstrual disorder	163 (11.2)	36 (8.7)	73 (14.7)	76 (12.0)	348 (11.6)
Polycystic ovarian syndrome	96 (6.6)	17 (4.1)	27 (5.5)	25 (3.9)	165 (5.5)
Involuntary impaired fertility/infertility	62 (3.2)	22 (2.7)	26 (4.3)	29 (3.6)	139 (3.3)
Obstructive sleep apnoea	230 (11.7)	122 (15.1)	77 (12.6)	94 (11.7)	523 (12.5)
Asthma/chronic obstructive pulmonary disease	227 (11.6)	68 (8.4)	92 (15.1)	92 (11.5)	479 (11.5)
Liver diseases	168 (8.6)	182 (22.6)	37 (6.1)	59 (7.3)	446 (10.7)
Non-alcoholic fatty liver disease	163 (8.3)	179 (22.2)	35 (5.7)	55 (6.8)	432 (10.3)
Non-alcoholic steatohepatitis	7 (0.4)	5 (0.6)	2 (0.3)	8 (1.0)	22 (0.5)
Hyperuricaemia/gout	116 (5.9)	79 (9.8)	13 (2.1)	35 (4.4)	243 (5.8)
Kidney diseases	40 (2.0)	76 (9.4)	22 (3.6)	20 (2.5)	158 (3.8)
Kidney disease	39 (2.0)	71 (8.8)	22 (3.6)	20 (2.5)	152 (3.6)
Obesity-related kidney disease	1 (<0.1)	9 (1.1)	1 (0.2)	1 (0.1)	12 (0.3)
Coronary artery disease	49 (2.5)	59 (7.3)	10 (1.6)	7 (0.9)	125 (3.0)
Cerebrovascular disease	19 (1.0)	26 (3.2)	6 (1.0)	17 (2.1)	68 (1.6)

At baseline, the majority of subjects were female (apart from the T2DM study) and white, however there are an adequate number of subjects in other groups. Another trial specifically in east Asian subjects (STEP 6) is ongoing (completed) . STEP 3 was conducted only in the US. The other studies were global, including subjects from Europe. Sex, race and geographic region were included in the pre-defined subgroup analyses.

BMI and related indices were lower in STEP 4 at baseline, understandable as this was taken after 20 weeks of treatment, before the randomised withdrawal. These measures were comparable between STEP 1-3. Excluding STEP 4, only 538 (12.9%) subjects had BMI <30, mean baseline BMI was over 35 (grade II obesity) and the mean baseline waist circumference in all studies reflected a significant cardiometabolic risk.

Again, excluding STEP 2 and 4, many subjects met the criteria for “pre-diabetes” at baseline (43.7 and 49.8% respectively).

Participant flow

The proportions of trial completers ranged from 93% in STEP 3 to 98% in STEP 4. The proportion of subjects completing treatment ranged from 81% to 92%, again highest in STEP 4.

For treatment completers in the active treatment arms (excluding the subjects on the 1 mg arm in STEP 2) 82% to 89.6% of subjects were on the maintenance dose of 2.4 mg semaglutide, 4.0% to 7.4% were on 1.7 mg, and between 2.8% and 10.6% were on lower

doses than 1.7 mg at completion. Further details are given in the table below:

Table 5: Subject disposition, STEP 1-4

Trial / Subjects	STEP 1 Weight management	STEP 2 Weight management in T2D	STEP 3 Weight management with IBT	STEP 4 Sustained weight management	Total STEP 1–4
	Total Sema 2.4 mg / placebo	Total Sema 2.4 mg / placebo	Total Sema 2.4 mg / placebo	Total Sema 2.4 mg / placebo	Total Sema 2.4 mg / placebo
FAS	**1961** 1306 / 655	**807** 404 / 403	**611** 407 / 204	**803** 535 / 268	**4182** 2652 / 1530
Treatment completion after randomisation					
Treatment completers (%)	**81.1** 82.9 / 77.6	**87.2** 88.4 / 86.1	**82.7** 83.3 / 81.4	**92.3** 94.2 / 88.4	**84.7** 86.1 / 82.2
Trial product permanently discontinued (%)	**18.9** 17.1 / 22.4	**12.8** 11.6 / 13.9	**17.3** 16.7 / 18.6	**7.7** 5.8 / 11.6	**15.3** 13.9 / 17.8
- primary reason: AE (%)	**5.7** 7.0 / 3.2	**4.8** 6.4 / 3.2	**5.2** 6.4 / 2.9	**2.4** 2.4 / 2.2	**4.8** 5.9 / 3.0
Trial completion after randomisation					
Trial completers (%)	**94.3** 94.9 / 93.0	**95.9** 96.8 / 95.0	**92.8** 92.4 / 93.6	**98.0** 98.5 / 97.0	**95.1** 95.6 / 94.3
Withdrawn from trial (%)	**5.7** 5.1 / 7.0	**4.1** 3.2 / 5.0	**7.2** 7.6 / 6.4	**2.0** 1.5 / 3.0	**4.9** 4.4 / 5.7

The full analysis set (FAS) includes all randomised subjects according to the intention-to-treat principle. Subjects in the FAS will contribute to evaluation “as randomised”. This definition was used consistently across all study. This definition is considered acceptable. Trial completion rates were generally high in all studies (range 92.8% to 98%) and generally comparable across the placebo and treatment groups in all studies.

Treatment discontinuations were in the range of 7.7% to 18.9%. In all studies, treatment discontinuations were higher in the placebo (range 11.6% to 22.4%) groups compared to the treatment group (range 5.8% to 17.1%). Withdrawal from the trials were generally low (range 2.0% to 7.2%) but more common in the placebo group compared to the treatment group in all studies.

Results

Primary endpoints

Statistical superiority of semaglutide 2.4 mg versus placebo was demonstrated for the (co)primary endpoints in all 4 trials, as shown in the table below:

Table 6: (co)Primary endpoints, STEP 1-4

	STEP 1 Weight management		STEP 2 Weight management in T2D		STEP 3 Weight management with IBT		STEP 4 Sustained weight management	
	Sema[b] N=1306	Placebo N=655	Sema[b] N=404	Placebo N=403	Sema[b] N=407	Placebo N=204	Sema[b] N=535	Placebo N=268
Change from baseline[a] to week 68 in body weight (%)								
Change from baseline (%)	-14.85	-2.41	-9.64	-3.42	-15.97	-5.70	-7.88	6.87
ETD (%) [95% CI]	-12.44 [-13.37;-11.51]		-6.21 [-7.28; -5.15]		-10.27 [-11.97; -8.57]		-14.75 [-16.00; -13.50]	
Subjects who achieved ≥5% body weight reduction from week 0 to week 68[c]								
OR [95% CI]	11.22 [8.88; 14.19]		4.88 [3.58; 6.64]		6.11 [4.04; 9.26]			
ETD (%) [95% CI]	52.41 [48.06; 56.75]		37.25 [30.68; 43.81]		37.04 [28.90; 45.19]			
Observed proportion (%)[d]	N=1212	N=577	N=388	N=375	N=373	N=189		
	86.5	31.5	68.8	28.5	86.6	47.6		

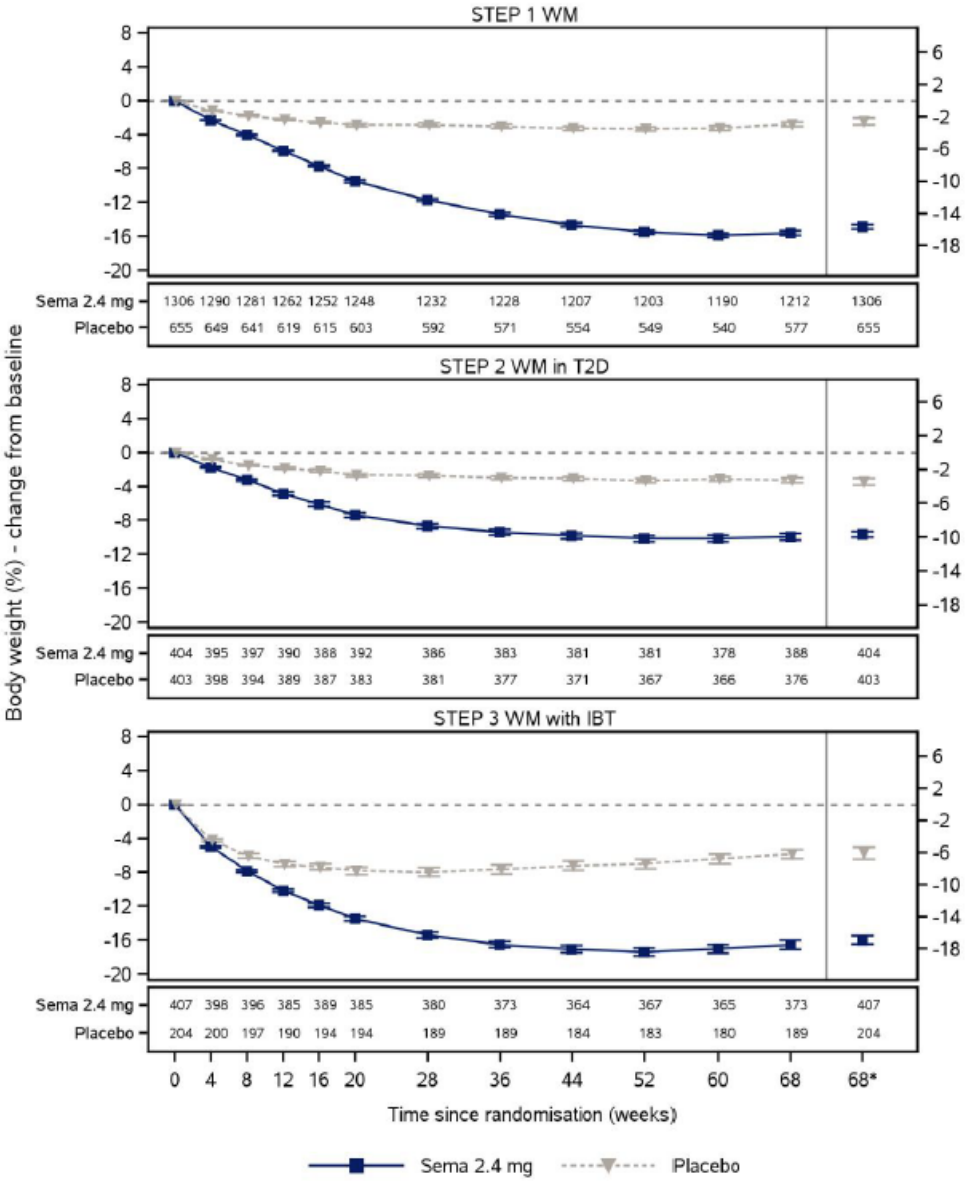
[a] Baseline for STEP 4 was defined as the start of the randomisation period at week 20. [b] Semaglutide 2.4 mg. [c] Primary endpoint for STEP 1−3 only. [d] Observed data from in-trial period. N=subjects with an observation at the visit.

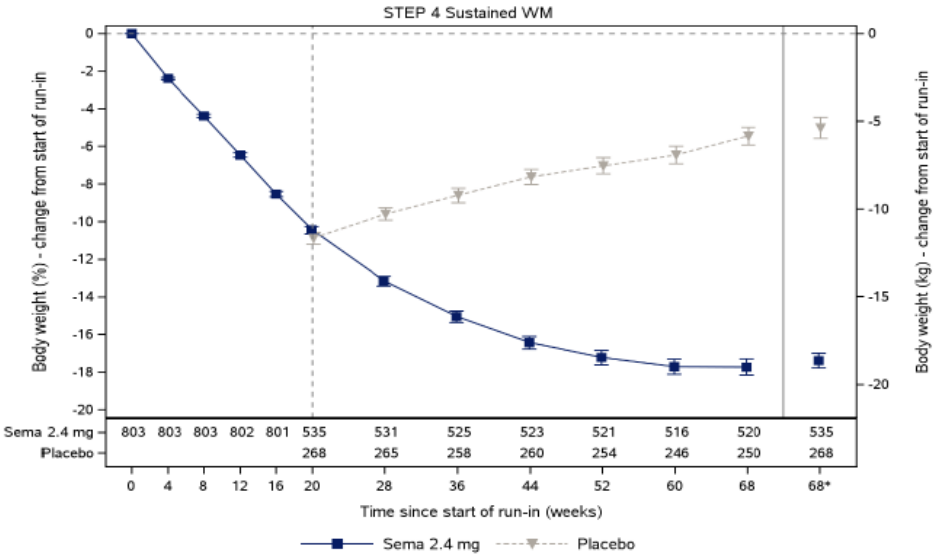
Comparing to STEP 1 (-12.44%), the relative improvement versus placebo (estimated treatment difference, ETD) was lower in patients with T2DM (-6.21%, STEP 2) and against a background of more intensive lifestyle intervention (-10.27, STEP 3).

In STEP 4, all subjects received semaglutide 2.4 mg for the first 20 weeks and had a mean weight loss of 10.6% during this period. Subjects randomised to continue semaglutide treatment at week 20 had a further mean weight loss of 7.9%, plateauing at week 60. In contrast, subjects randomised to placebo regained most of the weight, although not returning to baseline within the limited duration of follow-up.

The mean changes in body weight compared to baseline are shown below for STEP 1-4, for the treatment policy estimand:

Figure 7: % body weight change versus time, STEP 1-4





Statistical superiority of semaglutide 2.4 mg versus placebo was demonstrated for the primary endpoints in all 4 trials. The effect size is of clear clinical relevance, and was preserved out to 68 weeks of treatment. The effect was also preserved against a background of more intensive behavioural therapy, and the randomised withdrawal study supports the need for continued dosing.

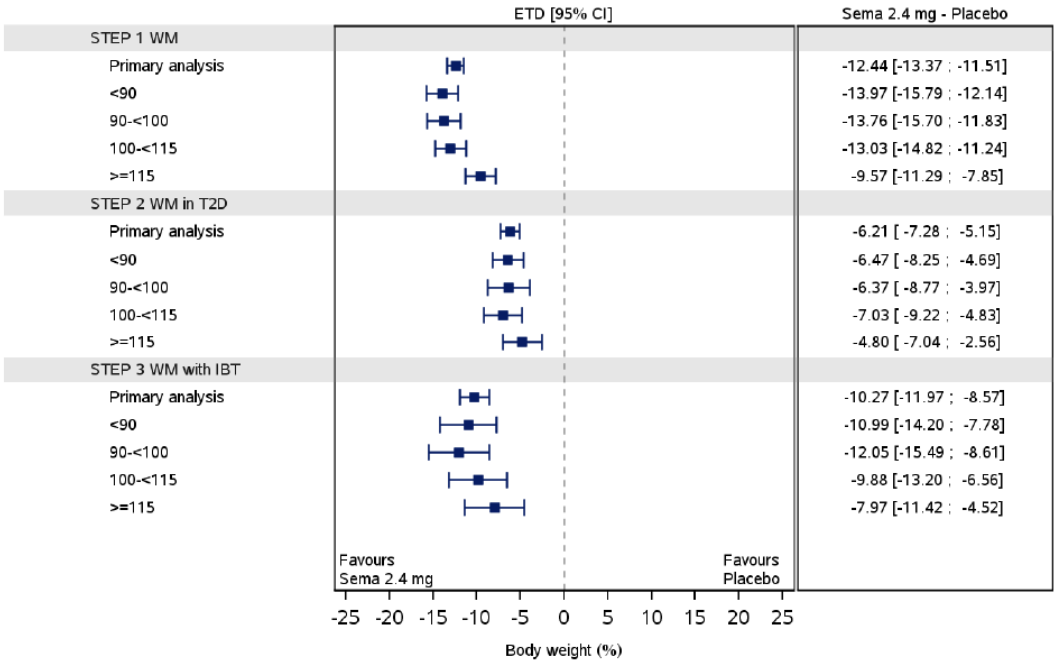
The treatment effects based on the primary estimand are generally consistent across the studies. The proportion of responders (key secondary endpoint in STEP 1 to 3 only) is also consistently higher in the treatment group (range 68.8% to 86.6%) compared to the placebo group (range 28.5% to 47.6%). The sensitivity analyses are generally supportive including those based on secondary estimands.

The applicant has shown that the weight loss is not due to gastrointestinal AEs, based on analyses in populations with and without these. Also, DEXA scans done in a subset of STEP 1 suggested that weight reduction benefits are due to an improvement in body composition rather than lean body mass. It is not clear whether the early weight loss in STEP 3 includes some lean weight (because of the initial hypocaloric diet). However, there was a decrease in waist circumference in both groups during the first 8 weeks.

In line with the high retention rates and the high proportions of subjects who stayed on treatment without initiating other anti-obesity therapies, the results were consistent across the two estimands.

Primary endpoints in subgroups
The predefined subgroups were sex, age, race, ethnicity, region, and baseline body weight/BMI/renal function/glycaemic status. An effect of sex (STEP 1, 2, 4) and baseline body weight (STEP 1 and STEP 4) was seen, with a treatment effect of baseline BMI in STEP 3 and 4 – this is shown in the figures below:

Figure 8: Body weight (%) change from baseline by baseline body weight (kg) –- STEP 1-4



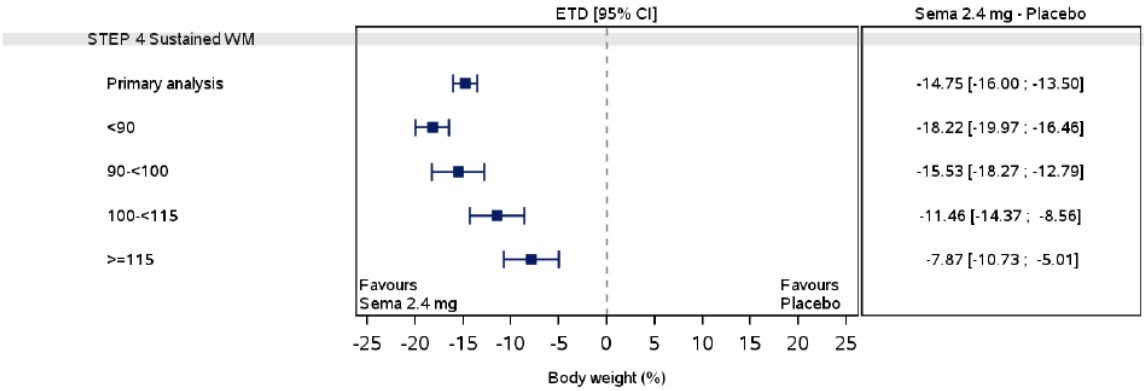
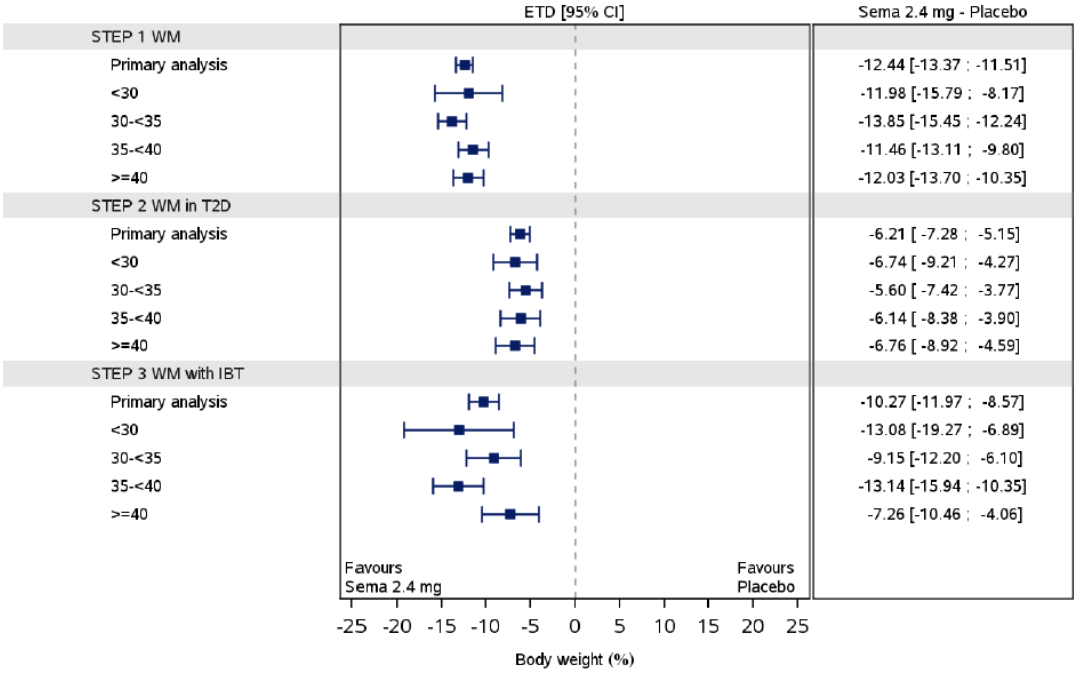
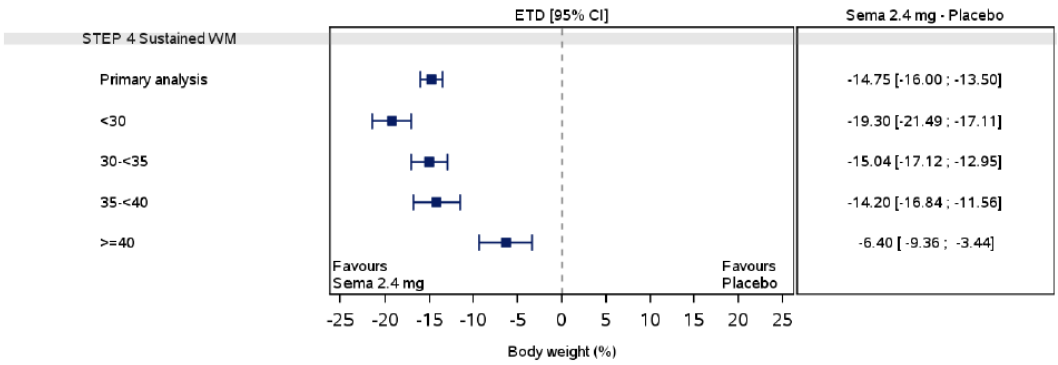


Figure 9: Body weight (%) change from baseline by baseline BMI –- STEP 1-4





Autoantibodies

Autoantibodies were evaluated in STEP 1 and 2. In both studies the rate of formation was low (2.9% of subjects randomised to 2.4 mg semaglutide, versus 1-2% overall in the Ozempic trials) with low titres, and in the subgroup with these it did not impact the primary weight endpoint.

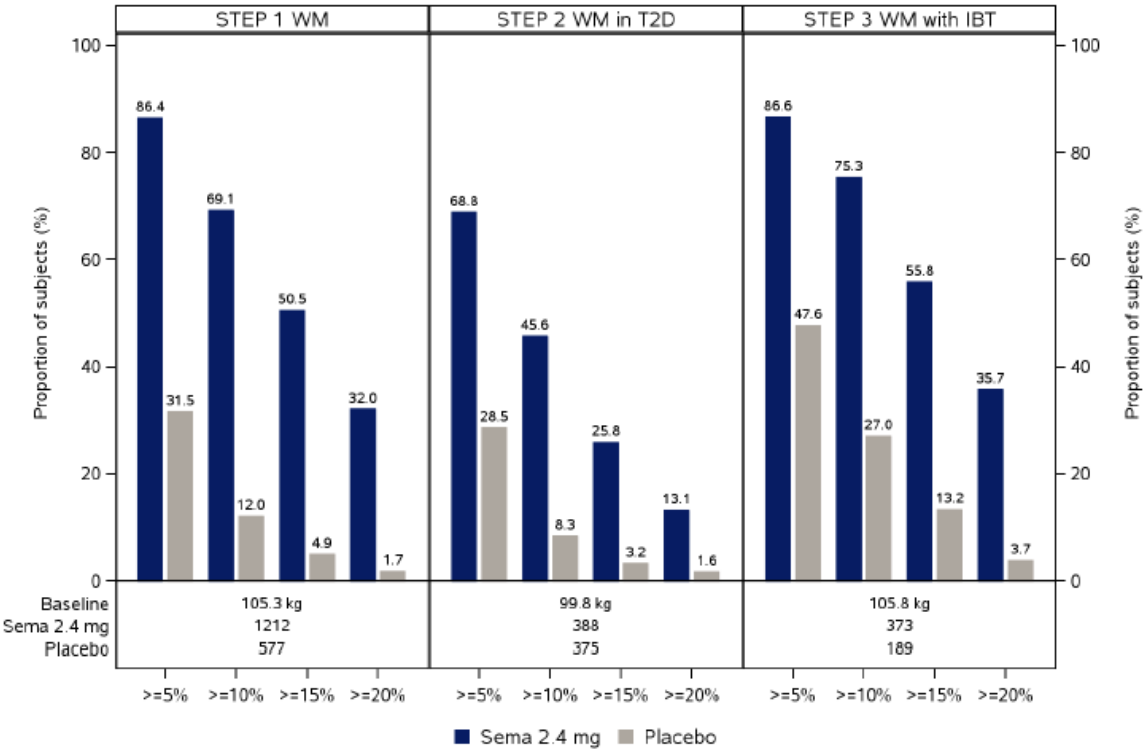
The response to semaglutide 2.4 mg was fairly consistent across sub-populations, other than for sex (females responded better) and baseline body weight/BMI (subjects with lower values

responded better) in some studies. These findings relate mostly to the predicted exposure and are consistent with results in the SUSTAIN program. Efficacy was maintained in subjects with autoantibodies, although this was a small subgroup. The level of weight loss was lower in patients with T2DM than those without. This is not fully explained, although in the Population PK analysis there is a modest reduction in exposure compared to those without T2DM, and also the modest weight reducing effect of concomitant metformin or SGLT2 inhibitors may be relevant.

Results – other responder analyses for weight loss

In these secondary analyses, treatment with semaglutide 2.4 mg also resulted in greater proportions of subjects achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to week 68. This was statistically significant for the proportions of subjects achieving ≥10% and ≥15% weight loss in STEP 1-3, where it was a pre-defined confirmatory secondary endpoint. As seen below, around 70% of subjects lost ≥10% of body weight, around half lost ≥15%.

Figure 10: Responder analyses for % body weight change vs time, STEP 1-3



Results - Other Secondary endpoints

In STEP 1–3, treatment with semaglutide 2.4 mg resulted in mean reductions in waist circumference from baseline to week 68 of 9.40–14.61 cm compared with 4.13–6.27 cm reduction for placebo.

In STEP 2 (subjects all had T2DM, mean baseline HbA1c 8.1%) there was a reduction in HbA1c of 1.60% with semaglutide 2.4 mg, 1.45% in the 1 mg arm, and 0.37% with placebo.

In non-diabetics, higher proportions who had pre-diabetes at baseline shifted to normoglycaemia by week 68 to the category of normo-glycaemia by week 68 with semaglutide 2.4 mg (84.1%–89.5%) compared to placebo (47.8%–55.0%).

There were modest reductions in SBP in semaglutide-treated subjects, greater than for those on placebo, and likewise small improvements in lipid profile. These findings were reflected in the use of concomitant medication.

Semaglutide 2.4 mg was also superior to placebo in all confirmatory secondary endpoints except SF-36 physical functioning score in STEP 3, where no statistically significant treatment difference was observed.

In STEP 1, physical functioning was improved with semaglutide 2.4 mg, reflected by an increase from baseline in SF-36 PF score of 2.21 versus 0.41 for placebo, and increase from baseline in IWQOL-Lite-CT PF score of 14.67 versus 5.25. Similar results in patient reported outcomes were reported in STEP 2.

In general, benefits were seen across key secondary endpoints representing weight related morbidity and patient reported outcomes. For the key secondary endpoint responders (5%, 10%, and 15%) were tested first followed by WC (STEP 1 to Step 3). SF-36 (STEP 1 to STEP 4) and IWQOL-Lite-CT PF were tested last (Step 1 and Step 2).

Additional dose response data
In STEP 2, statistical superiority of semaglutide 2.4 mg versus semaglutide 1 mg was confirmed for the two primary endpoints and then all secondary confirmatory endpoints, using the pre-defined statistical strategy. Further results are given in the figure and table below.

Figure 11: Mean Body weight change by week and maintenance dose, STEP 2 study

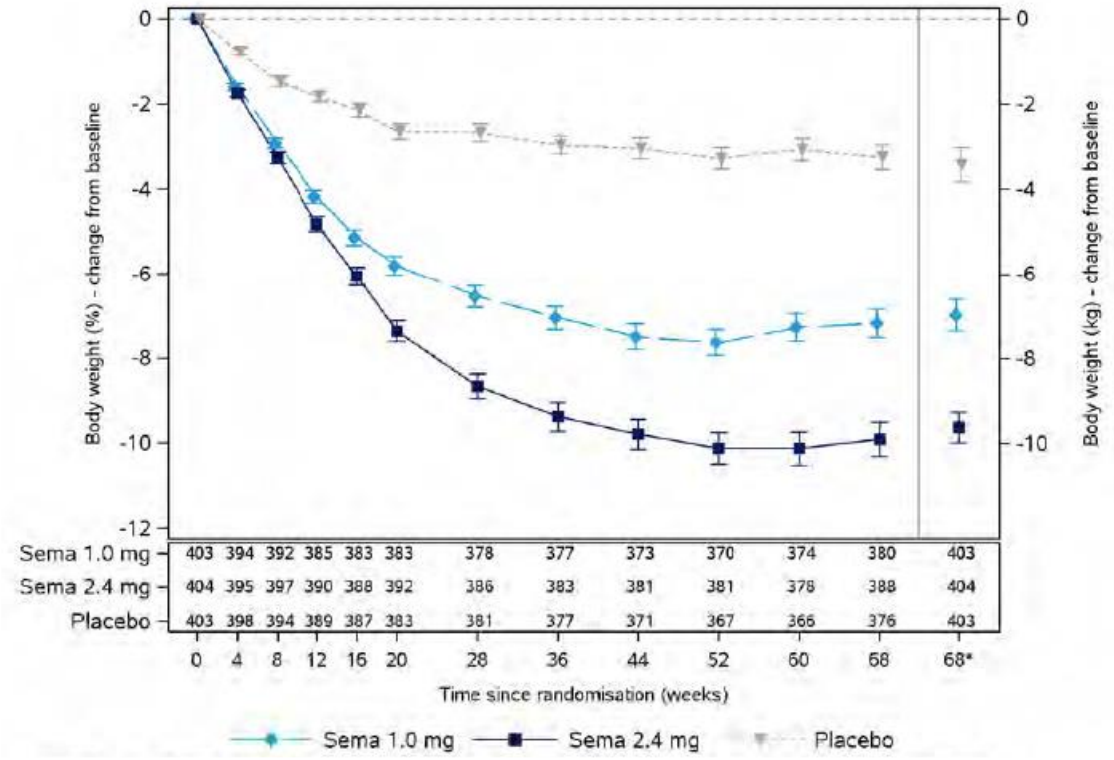


Table 7: Selected week 68 endpoints by maintenance dose, STEP 2

	Placebo	1 mg	2.4 mg
Change in body weight	-3.42%	-7.00%	-9.64%
Proportion subjects with ≥ 5% weight loss	28.5%	57.1%	68.8%
Proportion subjects with ≥ 10% weight loss	8.2%	28.7%	45.6%
Proportion subjects with ≥ 15% weight loss	3.2%	13.7%	25.8%
Proportion subjects with ≥ 20% weight loss	1.6%	4.7%	13.1%
HbA1c reduction	-0.4%	-1.5%	-1.6%
Proportion subjects with HbA1C <7%	26.5%	72.3%	78.5%
Proportion subjects with HbA1C ≤6.5%	15.5%	60.1%	67.5%

The weight and glycaemic control reduction endpoints in the 1 mg arm of STEP 2 are quite similar to the previously assessed SUSTAIN studies, which supported the use of semaglutide up to 1 mg/week in the treatment of T2DM.

An additional weight reduction benefit of the 2.4 mg maintenance dose in STEP 2 was seen compared to the 1 mg maintenance dose, although the difference was modest and this did not translate into meaningful differences in glycaemic control.

However, in the 4 STEP studies assessed there was scope for individual subjects to stay on a lower dose of semaglutide than the planned escalation, for tolerability reasons. This did happen in a small number of subjects. The SmPC allows prescribers to reduce dose until GI symptoms improve.

Analysis of early efficacy as a predictor of response
An analysis of 68-week response according to response at week 20 was done. As predefined, the primary analysis of this was in STEP 4, with the other studies providing supportive data.

In STEP 4, 89.5% of subjects responded (≥5% weight loss) by week 20, About half the subjects who were non-responders at 20 weeks went on to respond after a further 48 weeks of semaglutide.

Using the same 5% criterion of non-response, in STEP 1, 85.3% in the semaglutide 2.4 mg group were week 20 responders, and 57.7% of week 20 (5%) non-responders with semaglutide 2.4 mg achieved a clinically relevant weight loss ≥5% at week 68.

Likewise, in STEP 2, 70.2% subjects in the semaglutide 2.4 mg group were week 20 responders, and 37.3% of week 20 non-responders achieved a clinically relevant weight loss ≥5% at week 68.

A stopping rule has been applied in the SmPC to avoid patients unresponsive to therapy being exposed to the potential risks of treatment.
If patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient.

IV.5 Clinical safety

The primary safety analysis pool derives from the STEP 1-4 phase III studies, omitting the 1 mg arm from STEP 2 and the non-randomised run-in period from STEP 4. In this group, 2650 subjects were exposed, for 3309 patient year equivalents..

Table 8: Summary of exposure by duration for safety evaluation, phase IIIA pool

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	2650	1529	4179
Duration of exposure (months)			
>=0	2650 (100)	1529 (100)	4179 (100)
>=1	2646 (99.8)	1524 (99.7)	4170 (99.8)
>=2	2623 (99.0)	1513 (99.0)	4136 (99.0)
>=3	2586 (97.6)	1499 (98.0)	4085 (97.8)
>=4	2548 (96.2)	1479 (96.7)	4027 (96.4)
>=5	2533 (95.6)	1456 (95.2)	3989 (95.5)
>=6	2499 (94.3)	1438 (94.0)	3937 (94.2)
>=7	2476 (93.4)	1414 (92.5)	3890 (93.1)
>=8	2455 (92.6)	1391 (91.0)	3846 (92.0)
>=9	2436 (91.9)	1377 (90.1)	3813 (91.2)
>=10	2409 (90.9)	1349 (88.2)	3758 (89.9)
>=11	2395 (90.4)	1334 (87.2)	3729 (89.2)
>=12	2370 (89.4)	1305 (85.3)	3675 (87.9)
>=13	1863 (70.3)	1055 (69.0)	2918 (69.8)
>=14	1830 (69.1)	1042 (68.1)	2872 (68.7)
>=15	1809 (68.3)	1026 (67.1)	2835 (67.8)
>=16	1762 (66.5)	1008 (65.9)	2770 (66.3)
>=17	1636 (61.7)	945 (61.8)	2581 (61.8)
>=18	2 (0.1)	2 (0.1)	4 (0.1)

Table 9: Summary of subgroup exposure for safety evaluation, phase IIIA pool

	Sema 2.4 mg N	Sema 2.4 mg PYE	Placebo N	Placebo PYE	Total N	Total PYE
Number of subjects	2650		1529		4179	
Age group (years)						
N	2650	3309	1529	1885	4179	5195
<65	2394	2987	1362	1676	3756	4663
65-<75	233	297	154	192	387	489
>=75	23	26	13	17	36	43
Sex						
N	2650	3309	1529	1885	4179	5195
Female	1920	2381	1073	1312	2993	3693
Male	730	928	456	574	1186	1502
Race						
N	2650	3309	1529	1885	4179	5195
White	1962	2439	1124	1378	3086	3816
Black or African American	255	311	147	166	402	477
Asian	313	409	198	266	511	675
Other	57	70	28	35	85	105
Not applicable	38	48	17	24	55	71
Region						
N	2650	3309	1529	1885	4179	5195
Europe	890	1088	516	624	1406	1713
North America	1304	1628	719	872	2023	2500
South America	103	141	66	88	169	229
Africa	57	62	38	46	95	108
East Asia	135	187	89	125	224	312
Asia (excluding East Asia)	161	203	101	130	262	333

The safety population is adequate in terms of overall numbers exposed and length of exposure. There are no concerns related to the definition of safety analysis populations, the pooling strategy or the analyses of safety submitted.
Semaglutide s.c. 2.4 mg once weekly for weight management is not yet marketed, so there are no post-marketing data to include. Nothing additional of concern is revealed in late

breaking reports submitted after the database cut-off, or in the subjects exposed to semaglutide in the phase II studies.

Summary of adverse events

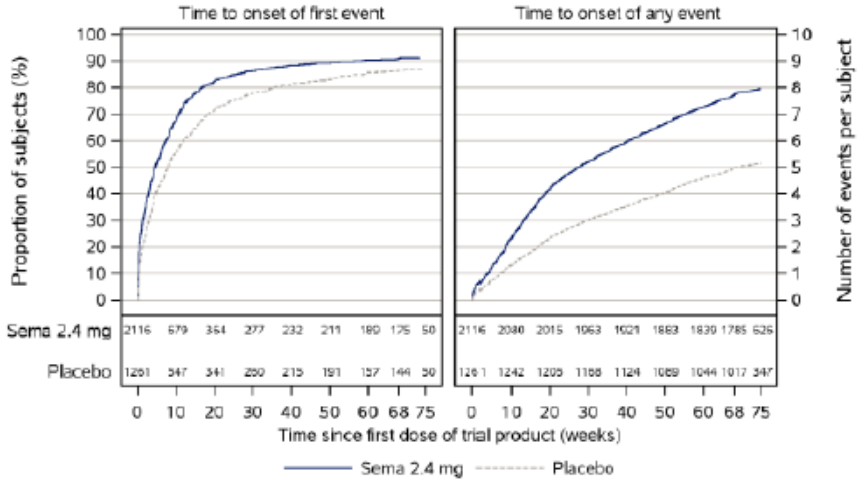
The most frequent terms reported by ≥5% of subjects and more frequently with semaglutide than with placebo are tabulated below:

Table 10: Most frequent AEs (≥5%) on-treatment, phase IIIA pool

	Semaglutide 2.4 mg	Placebo
Nausea	38.3%	14.0%
Diarrhoea	26.8%	14.3%
Constipation	21.8%	10.2%
Vomiting	21.8%	5.7%
Headache	12.8%	8.7%
Abdominal pain	8.4%	4.0%
Fatigue	7.9%	3.6%
Decreased appetite	7.8%	2.8%
Dyspepsia	7.6%	2.7%
Abdominal pain upper	7.1%	3.6%
Dizziness	6.8%	3.3%
Eructation (belching)	6.5%	0.4%
Abdominal distension	6.3%	4.3%
Gastroenteritis	5.6%	3.8%
Flatulence	5.3%	3.7%

The reporting of the first event mainly occurred during the first 20 weeks of treatment, in the dose escalation period; this is shown in the plots below:

Figure 12: Timing of AEs



Terms reported for ≥2 to <5% of subjects that occurred more frequently with semaglutide were gastroesophageal reflux disease (4.6% versus 2.1%), abdominal discomfort (3.4% versus 1.3%) and gastritis (2.7% versus 1.2%), viral gastroenteritis (3.7% versus 2.5%) Alopecia (3.3% versus 1.4%) and Migraine (2.1% versus 1.3%)

In the phase IIIA pool, there were 3 deaths in each treatment groups. The deaths in the semaglutide group were classified as cardiovascular deaths, while the 3 deaths in the placebo

group were classified as death due to malignancy. All deaths were subject to an external adjudication committee. More subjects on semaglutide (9.3%) versus placebo (6.4%) reported serious AEs, mainly driven by gastrointestinal AEs and gallbladder-related disorders (primarily seen in STEP 3).

The proportion of subjects (5.7% versus 3.0%) and the overall rate of AEs leading to permanent treatment discontinuation were higher with semaglutide than placebo, driven by gastrointestinal disorders, mainly nausea, vomiting, diarrhoea, upper abdominal pain and constipation. The proportion of subjects with serious AEs that led to permanent treatment discontinuation was similar between groups, and those occurring with semaglutide mostly occurred within the escalation period at the time of increment.
In STEP 2 and the phase 2 dose-finding trial there was some dose-response in the overall reporting of AEs, and in the reporting of AEs leading to permanent treatment discontinuation, again driven by a dose response in the reporting of gastrointestinal AEs. This is supported by the exposure-response analyses performed on data from STEP 1 and 2. In STEP 2, a dose-response was also seen for reporting of AEs of fatigue and decreased appetite (although the latter is obviously a desired therapeutic effect).

Overall, the nature, frequency and severity of adverse events is quite similar comparable to existing data with semaglutide and others in the class – including the type of events in patients established on the 2.4 mg dose. The case narratives for the small numbers of death in the semaglutide group were reviewed, no particular conclusion can be drawn.
There was some dose-response in overall AEs, and AEs leading to permanent treatment discontinuation, driven by gastrointestinal AEs. Obviously, the data do not allow evaluation of dose-response for rarer events, hence the need for close follow-up of ongoing studies and post-marketing reports.

Of these 3 events, hair loss is proposed to be added to the SmPC – this is agreed. Subjects obtaining a weight loss of ≥20% with semaglutide 2.4 mg reported hair loss events more often. Hair loss (including telogen effluvium) is mentioned in literature as a consequence of weight loss.
More than half of the migraine reports were graded as “mild” (although, this might question whether it was a migraine) and the majority of events were assessed unlikely related to trial product. 2 events led to permanent discontinuation. There is some biological plausibility, given that GLP-1 RAs may have vasoactive effects, but the link for now is not clear, and headache is already labelled as an AE. The Applicant will monitor events of migraine in the PSUR and will provide an assessment of
this after 2 years of marketing.

Safety areas of particular interest
There are a number of adverse events associated with semaglutide or GLP-1 receptor agonists as a whole, under particular scrutiny. Of these, an independent and blinded external adjudication committee considered CV events and acute pancreatitis.

GI tolerability
These adverse events (in particular nausea, diarrhoea, vomiting and constipation) were reported in 72.9% of semaglutide treated subjects versus 47.1% for placebo. The percentages leading to permanent discontinuation were 4.3% versus 0.7% of subjects respectively, although a larger number required temporary interruption of trial product or a dose reduction. In both treatment groups the majority of the first gastrointestinal AEs occurred during the initial 20 weeks of the trial.

Table 11: Gastrointestinal disorder AEs, on-treatment – phase IIIa dose escalation group

	Sema 2.4 mg N	(Adj.%)	E	Adj.R	Placebo N	(Adj.%)	E	Adj.R
Number of subjects	2116				1261			
Patient years of exposure (PYE)	2765.3				1619.3			
All AEs	1562	(72.9)	6993	246.3	581	(47.1)	1334	85.5
SAEs	26	(1.3)	34	1.2	5	(0.4)	6	0.3
Severe AEs	91	(4.1)	135	4.7	11	(0.9)	16	1.0
Leading to permanent treatment discontinuation	90	(4.3)	122	4.4	9	(0.7)	11	0.6
Severity								
Severe	91	(4.1)	135	4.7	11	(0.9)	16	1.0
Moderate	711	(32.7)	1838	64.4	173	(14.3)	268	17.4
Mild	1409	(65.7)	5020	177.2	501	(40.6)	1050	67.1
Outcome								
Fatal	0				0			
Recovered	1496	(69.8)	6576	231.5	534	(43.4)	1189	76.4
Recovering	32	(1.5)	41	1.4	11	(0.9)	11	0.7
Recovered With Sequelae	7	(0.3)	8	0.3	1	(<0.1)	1	<0.1
Not Recovered	278	(12.9)	363	12.9	104	(8.4)	132	8.3
Unknown	3	(0.2)	5	0.2	1	(<0.1)	1	<0.1
Missing	0				0			

GI adverse events are very common with all GLP-1 receptor agonists. The rate of discontinuation for subjects experiencing GI adverse events is slightly higher to that seen in the Ozempic dossier, and as already noted there is some dose-response pattern. However, the number of severe GI events and events leading to discontinuation is acceptably low if the treatment benefits are accepted.

As is well known for the class, GI events tend to occur during the initial phase. In these data the early peak was most pronounced for nausea, there was a more continuous separation of groups for diarrhoea/vomiting/constipation. The median duration for individual events of nausea, vomiting and diarrhoea was around a week or less, but the median duration was over a month for constipation.

Hypoglycaemia

Hypoglycaemic episodes were summarised using the ADA 2018/IHSG 2017 classification. In this scale, level 1 is a value < 3.9 mmol/l, level 2 is < 3 mmol/L and level 3 denotes severe cognitive impairment requiring external assistance for recovery. In subjects with T2DM, the proportion of subjects with level 2 episodes of hypoglycaemia was higher in the semaglutide group (6.2% versus 2.5%). More than half of the episodes occurred when semaglutide 2.4 mg was used in combination with a SU.

In subjects without T2DM, the proportion with AEs of hypoglycaemia was low and similar between semaglutide 2.4 mg (0.6%) and placebo (0.7%). All events were non-serious and none were severe.

Immunogenicity

There was no signal for an excess of allergic reactions (including injection site reactions). The proportion of subjects testing positive for anti-semaglutide antibodies (assessed in STEP 1 and 2 only) post baseline was 2.9%, and transient in 21 out of the 50 subjects testing positive. Antibodies cross-reacting with endogenous GLP-1 were detected in 28 subjects

(1.6%) randomised to semaglutide 2.4 mg. No subjects had anti-semaglutide antibodies with *in vitro* neutralising effect against semaglutide or endogenous GLP-1, and there was no indication that formation of anti-semaglutide antibodies influenced AE reporting.

Cardiovascular events

Overall, cardiovascular disorder AEs were reported by a lower proportion of subjects on semaglutide versus placebo (8.7% versus 10.9%). EAC-confirmed cardiovascular events occurred in 0.6% versus 0.7% of subjects respectively.

An exploratory time to first event analysis was performed for the MACE composite endpoint, which comprised EAC-confirmed events of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. Undetermined cause of death was included as cardiovascular death. The estimated hazard ratio for time to first EAC-confirmed MACE was 0.991 [95% CI 0.400; 2.456] for semaglutide 2.4 mg relative to placebo.

As previously assessed in the Ozempic dossier, SUSTAIN 6 was a 104-week cardiovascular disease outcomes study. 3,297 patients with T2DM at high cardiovascular risk were randomised to either semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly or corresponding placebo in addition to standard of care, and followed for 2 years. The mean BMI at baseline was 33 kg/m2. Treatment with semaglutide resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.

SUSTAIN 6 used a maintenance dose of 1 mg rather than 2.4 mg, and was specifically in T2DM patients. Because of the low number of CV events in the weight loss studies assessed, it is not possible to conclude non-inferiority of semaglutide 2.4 mg vs placebo, or conclude that this high dose confers a benefit. Taken as a whole though, the new data do not indicate an excess CV risk or any apparent dose-related cardiovascular toxicity.

Across STEP 1–4, the increase in pulse with semaglutide 2.4 mg corrected for baseline and placebo was 1-4 bpm. Overall, during the study escalation phase, 26 % of subjects in the semaglutide 2.4 mg group had an increase from baseline ≥20 beats/min at one or more timepoints during the on-treatment period, compared to 15.6% in placebo group. SBP and DBP decreased with semaglutide 2.4 mg compared to placebo. There were no relevant changes in interpretation of ECGs from baseline to end of treatment in any of the treatment groups, and no signals in the cardiac disorder SOC or cardiac arrythmia HLGT.

In STEP 2, there is a mean increase in HR with dose, although the effect was small and the 1 and 2.4 mg groups were similar in terms of the numbers with pulse increase ≥ 20 bpm. This is supported by the HR findings in the dose-finding study.

Diabetic retinopathy

In the STEP 2 trial, eye examinations were done at baseline and at weeks 52 and 68. In total, 85 AEs of "retinal disorder" were identified by the pre-defined MedDRA search. These events were reported by a larger proportion of subjects with semaglutide 2.4 mg and 1.0 mg compared to placebo (6.9%, 6.2% and 4.2%, respectively).

Most AEs were reported under the term "diabetic retinopathy", i.e. new onset or worsening of existing disease. Diabetic retinopathy related events were again reported in a higher proportion of those taking semaglutide, but more notable in the 2.4 mg dose group - 4%, 2.7% and 2.7% respectively for 2.4 mg, 1 mg and placebo. All events were non-serious, and the majority of the events were mild. The events were identified at eye examination and were

not based on the emergence of eye-related symptoms. For the majority of events, no treatment was deemed necessary. The proportion of subjects with a history of diabetic retinopathy at baseline was larger in subjects with events, compared to those without, for semaglutide 2.4 mg (26.3% versus 10.4%) semaglutide 1.0 mg (58.3% vs 8.7%) and placebo (27.3% versus 8.7%). There was no clear pattern for the remaining risk factors (diabetes duration, baseline HbA1c, extent of HbA1c reduction).

Table 12: risk factors in subjects with or without AEs of new onset/ worsening of diabetic retinopathy. STEP 2 trial

	Subjects with events			Subjects without events		
	Sema 1.0 mg	Sema 2.4 mg	Placebo	Sema 1.0 mg	Sema 2.4 mg	Placebo
Number of subjects	12	19	11	390	384	391
History of diabetic retinopathy						
No, N (%)	5 (41.7)	14 (73.7)	8 (72.7)	356 (91.3)	344 (89.6)	357 (91.3)
Yes, N (%)	7 (58.3)	5 (26.3)	3 (27.3)	34 (8.7)	40 (10.4)	34 (8.7)
Age (years)						
Mean (SD)	53 (12)	55 (11)	57 (7)	56 (10)	55 (11)	55 (11)
Median	53	55	54	56	56	56
Min ; Max	35 ; 71	32 ; 74	50 ; 72	20 ; 81	19 ; 84	20 ; 82
Diabetes duration (years)						
Mean (SD)	8.8 (5.7)	7.1 (5.6)	10.3 (7.8)	7.7 (5.9)	8.3 (6.2)	8.1 (6.1)
Median	7.6	4.6	8.8	6.5	6.9	6.7
Min ; Max	1.9 ; 23.4	0.5 ; 17.6	0.6 ; 29.9	0.5 ; 34.7	0.5 ; 37.7	0.6 ; 29.6
HbA1c (%) at baseline						
Mean (SD)	8.4 (0.8)	8.3 (1.0)	8.2 (1.0)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Median	8.5	7.7	8.4	8.0	8.0	8.0
Min ; Max	7.2 ; 9.4	7.2 ; 10.4	6.6 ; 9.7	5.8 ; 10.2	6.7 ; 10.6	5.7 ; 10.3
HbA1c (%) change at Visit 24 (Week 68)						
N	12	19	10	363	362	363
Mean (SD)	-1.3 (1.8)	-2.0 (1.2)	-0.2 (1.3)	-1.6 (1.1)	-1.7 (1.2)	-0.3 (1.3)
Median	-1.6	-2.0	-0.2	-1.7	-1.7	-0.3
Min ; Max	-3.7 ; 3.5	-4.5 ; 1.1	-2.1 ; 1.6	-4.7 ; 2.8	-4.9 ; 5.4	-3.8 ; 6.1

The ADR of retinopathy is already labelled for Ozempic. The following warning has been implemented in the Wegovy SmPC:

Diabetic retinopathy in patients with type 2 diabetes: Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy.
Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to local clinical guidelines.

The numbers are rather small. However, the excess in the semaglutide 2.4 mg arm is noted and there are some reasons to postulate other mechanisms at work, not just a link to initial glycaemic control. There were few significant differences between the 1 mg and 2.4 mg/week arms in glycaemic control overall, and the extent of HbA1c reduction did not correlate with the risk of complications related to diabetic retinopathy. Further, in the SUSTAIN 6 CVOT, the incidence of retinopathy events still increased compared to placebo after the first year after initiation of treatment, well after the initial drop in HbA1c. Further, STEP 2 (and all the phase IIIA trials in the Ozempic dossier) excluded diabetics with uncontrolled or and potentially unstable diabetic retinopathy.

Over the longer-term in patients with T2DM who are also obese/overweight and taking semaglutide 2.4 mg weekly, improvements in glycaemic control and other risk factors related to weight loss may counteract this excess incidence of retinopathy complications, or translate into a net benefit. However, at present this is not known, and mechanisms other than glucose reduction cannot be excluded.

A 5 year study in 1500 patients with T2DM is under way (FOCUS study, planned to report in 2025) to formally evaluate the risks of retinopathy, the primary endpoint is the number of subjects with at least 3 steps of progression in the Early Treatment Diabetic Retinopathy Study evaluation. However, this is only with the 1 mg/week maintenance dose of semaglutide. Further, the ongoing SELECT cardiovascular outcomes trial with the 2.4 mg maintenance dose excludes diabetics.

Malignancies
There was no signal of increased risk for neoplasms, including pancreatic and medullary thyroid cancers. A calcitonin level ≥50 ng/L was detected in one subject, at the baseline visit only.

Hepatic adverse events
There was no increased risk of hepatic disorders with semaglutide 2.4 mg based on the reporting of AEs between semaglutide 2.4 mg and placebo (2.3% vs 2.7%) and biochemical markers.

Pancreatitis
5 EAC-confirmed events of acute pancreatitis were reported in 4 subjects taking semaglutide 2.4 mg (0.2%) versus 1 event (<0.1%) in a placebo treated subject. For the semaglutide events, 2 subjects had co-reported events of gallstones and 1 subject had a history of acute pancreatitis. 3 of the 5 events were SAEs, with 2 rated as moderately severe using the 2012 Atlanta classification. Mean levels of lipase and amylase increased with semaglutide, but were not predictive of acute pancreatitis.

Gallbladder disease
Gallbladder-related disorders were reported more frequently with semaglutide versus placebo, driven by cholelithiasis (1.6% versus 1.1%) and its complications. Specific events of acute cholecystitis or biliary colic were more common in the semaglutide group, although the numbers involved were small. AEs of Cholelithiasis were reported with a higher frequency among subjects with a weight loss of ≥20% compared to subjects with a weight loss of <20%.

Gallbladder issues are known for the class - in large part related to weight loss. The study population had a high baseline risk. Across all treatment groups at screening, 15.3% of subject had a medical history of gallbladder disease and 13.4% had a history of cholecystectomy.

Renal
The few relevant AEs reported (mainly from STEP 2) were similarly distributed between semaglutide 2.4 mg and placebo (0.4% vs 0.3%). There was no association between AEs of vomiting or diarrhoea and AEs of acute renal failure. Estimated GFR and creatinine did not change over time for either of the treatment groups, while UACR levels (assessed in STEP 2) improved with semaglutide 2.4 mg as opposed to an overall deterioration with placebo.

In STEP 2 - where the majority of events were seen - eGFR <30 was a general exclusion criterion, and patients treated with SGLT2i were excluded if baseline eGFR was less than 60. There is a risk of dehydration with SGLT2i, which would be exacerbated if semaglutide led to diarrhoea or vomiting, and in any case the effectiveness of SGLT2i declines in parallel with reducing renal function. Only 18 subjects with moderate renal impairment were

randomised to semaglutide 2.4 mg in STEP 2 (63 overall in the phase IIIa safety pool). A renal outcomes study is ongoing , although only with the 1 mg/week semaglutide dose.

Psychiatric disorders
Psychiatric disorders were reported at a similar frequency between semaglutide and placebo treated subjects. There were no post-baseline differences of note between treatment groups in the Patient Health Questionnaire-9 or Columbia Suicide Severity Rating Scale.

This area is of interest as semaglutide given 2.4 mg weekly is suggested to predominantly act centrally, and because of the history with other weight-loss agents. No adverse signal for psychiatric disorders is apparent. Any imbalance more generally under the "CNS disorder" SOC disfavouring semaglutide was driven by headache and dizziness. A few subjects reported increased appetite after stopping semaglutide, but no other withdrawal effects were seen. However, given the regulatory background, mechanism of action, the vulnerability of the indicated population and the entry criteria of STEP 1-4 (excluded subjects with many pre-existing psychiatric conditions) the company has been asked to include the use in patients with depression and other psychiatric disorders as "missing information" in the risk management plan.

Adverse events in subgroups
The SmPC notes limited experience with those >75 years, severe renal impairment, and severe hepatic impairment. It also advises that there is no experience in patients with severe heart failure. The prespecified intrinsic factors evaluated in the STEP studies at were sex, race, ethnic origin and at baseline age, weight, BMI, renal function and (excluding STEP 2) glycaemic status. There were more AEs in those with the lowest weight category at baseline, and more in females.
Gastrointestinal AEs were reported more often by females, subjects with age 65 to <75 years and subjects with moderate renal impairment at baseline. There were no significantly different AE profiles in other subgroups.

233 subjects in the phase IIIa pool randomised to the semaglutide 2.4 mg arms were aged 65-75. Corresponding total numbers were 63 for those with moderate renal failure, 255 Black/African American race and 313 Asian race.

Overall, the proposed SmPC warnings related to experience in subgroups are considered adequate, and there are no new signals.

Other events
Medication error events were rare. There were no reports featuring accidental or intentional overdose of semaglutide. When used in the bioequivalence study, no product defect related events were reported, for the proposed single dose pen injector.
User testing of the new device in a total of 91 individuals (comprising HCPs, caregivers, pharmacists, patients with experience of pen injectors and patients without this experience) did not identify any critical issues related to device use or the label/packaging differentiation. There were no other reports of misuse or abuse related to study medication or AEs of drug interaction.

Despite the exclusion criteria and requirements in place to avoid pregnancies, 37 pregnancies were reported within the weight management program, including 29 in semaglutide-treated subjects. In all cases, subjects were exposed to trial product for a short period of time and it was discontinued. One child was born with a congenital anomaly of the external ear. None of

the elective abortions in female subjects treated with semaglutide were reported to be due to congenital anomalies. Spontaneous abortions were reported in 6 of 29 pregnancies with semaglutide (21%). In the placebo group, 2 of 8 pregnancies resulted in a spontaneous abortion or a stillbirth (25%).

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended.

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:
A targeted follow-up questionnaire targeting the important potential risk of diabetic retinopathy and complications in patients being treated with semaglutide 2.4 mg for weight management.

A follow-up form to capture information on the missing information in pregnancy and lactation in patients being treated with semaglutide 2.4 mg for weight management.
A follow-up questionnaire targeting fertility-related adverse events in patients being treated with semaglutide 2.4mg for weight management.

Additional pharmacovigilance activities

In addition to routine pharmacovigilance and risk minimisation measures, a number of additional safety measures have been proposed. Three PASS which are ongoing will further evaluate safety concerns for semaglutide and will be relevant for semaglutide 2.4 mg for weight management. These include NN9535-4352 (FOCUS) for the important identified risk of diabetic retinopathy complications, NN9535-4447 for the important potential risk of pancreatic cancer, and the MTC registry (MTC-22341) for the important potential risk of medullary thyroid carcinoma. The important potential risk of neoplasms will be monitored in EX9536-4388 (SELECT), a semaglutide cardiovascular outcomes trial in patients with overweight or obesity.

As an additional pharmacovigilance activity for the missing information 'pregnancy and lactation' for semaglutide s.c. 2.4 mg for weight management in the UK population, UK patients are to be added to the planned US pregnancy registry or pregnancy database study.

These studies are summarised below

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
MTC-22341 Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to	Medullary thyroid cancer	Submitted protocol Final report	To be decided

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	identify any increase related to the introduction of semaglutide into the marketplace.			
EX9536-4388 SELECT – Semaglutide cardiovascular outcomes trial in patients with overweight or obesity Ongoing	To monitor and further characterise the neoplasms in subjects treated with semaglutide.	Neoplasms (malignant and non-malignant)	Final report	To be decided
NN9535-4352 FOCUS – Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes Ongoing	The study will assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy	Diabetic retinopathy complications	Adopted protocol Final report	19 Nov 2018 November 2025
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of Ozempic® (semaglutide s.c.) and Rybelsus® (oral semaglutide) in patients with type 2 diabetes Ongoing	The study will evaluate whether exposure to Ozempic® increases the risk of pancreatic cancer in patients with T2D.	Pancreatic cancer	Semaglutide s.c. for T2D Adopted protocol Final report Oral semaglutide for T2D Adopted protocol Final report	20 Sep 2018 September 2025 Pending September 2025
Observational study to collect data on pregnant patients to	To be decided	Pregnancy and lactation	Draft protocol submission: January 2022	To be decided

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
assess the association between semaglutide exposure during pregnancy with pregnancy outcomes and infant outcomes, including major congenital malformations, spontaneous abortions, stillbirths, small for gestational age/preterm births, and postnatal growth and development. Planned				

IV.7 Discussion on the clinical aspects

Pharmacology

Semaglutide is a selective Glucagon Like Peptide-1 (GLP-1) receptor agonist. GLP-1 is a peptide hormone secreted by enteroendocrine L-cells and some neurons within the brain. It inhibits glucagon secretion, promotes insulin secretion, inhibits gastric emptying, and has a direct effect in the brain to modulate appetite and energy intake. As well as their effects on glycaemic control, all GLP-1 receptor agonists have been shown to reduce weight, without causing hypoglycaemia in non-diabetic subjects.

The company cross-referenced the original Ozempic T2DM dossier, supporting this with bridging bioequivalence studies, a new interaction study, and a new phase 2 clinical trial.

Linear PK is preserved up to the maximum dose of 2.4 mg weekly, and overall, the PK profile is consistent to that already observed. There are adequate bioequivalence bridging data to support the 1, 1.7 and 2.4 mg formulations proposed for marketing. There are some gaps in bridging to the lower doses, but these are only given briefly in the titration phase and this is not considered a critical finding. New data suggests that 2.4 mg is unlikely to cause drug interactions via delay of gastric emptying, and it is agreed that no other new drug interaction studies are required.

Population PK and exposure-response analyses were provided based on sparse sampling for semaglutide concentration in 2 of the phase 3 trials, STEP 1 and 2. As in the Ozempic application, body weight is the most important covariate for exposure.

The phase 2 clinical trial in obese non-diabetic subjects shows that a 2.4 mg weekly maintenance dose of semaglutide reduces energy intake, appetite and food cravings, whilst increasing satiety.

Efficacy

The new data included a dose response study and 4 completed phase IIIA studies, the latter referred to as the STEP trials (Semaglutide Treatment Effect in People with obesity). The design and analysis of the studies was generally in line with regulatory guidance and previous regulatory advice, no conduct issues of concern are apparent, and there was a good subject completion rate. The posology taken into phase III was adequately justified.

As a general caveat, the population choosing to enter the trial may have different levels of motivation to patients in practice, and there are compliance benefits of the trial structure. In UK practice, the available non-pharmacological support will vary, and other barriers to pharmacological treatment may result in a more treatment refractory population.

Statistical superiority of semaglutide 2.4 mg versus placebo was consistently demonstrated for the primary endpoints across the 4 trials, and the effect size is considered clinically relevant. In particular there is a meaningful improvement in the percentages of patients achieving a weight loss of 10%, 15% or 20%, compared to placebo. A meaningful benefit of semaglutide versus placebo was also maintained against a background of more intensive lifestyle change, in the STEP 3 trial.

In line with the high retention rates and the high proportions of subjects who stayed on treatment without initiating other anti-obesity therapies, the results were consistent across the two estimands.

The effect was preserved out to 68 weeks of treatment, and the randomised withdrawal study suggested the need for continued dosing.

In general, benefits were seen across key secondary endpoints representing weight related morbidity, some non-cardiovascular sequelae, and patient reported outcomes.
The efficacy response to semaglutide 2.4 mg was fairly consistent across sub-populations, other than a better response in females, and response being somewhat proportional to baseline weight/BMI. This relates to predicted exposure and is consistent with results in the SUSTAIN program. Efficacy was maintained in the small number of subjects with autoantibodies, which is again consistent with the Ozempic data.

Patients with T2DM generally lost less weight. Around 31% of those in the 2.4 mg maintenance arm did not achieve at least a 5% weight loss at week 68. This compared to 9-13% not responding on this measure, in non-diabetics. In the Population PK analysis, there is a modest reduction in exposure compared to those without T2DM, and also the weight reducing effect of concomitant medication may be relevant. Over half of the subjects were taking metformin or another biguanide at baseline, and 23.5% were taking a SGLT2i at baseline. Some additional benefits were seen for the 2.4 mg compared to the 1 mg maintenance dose in patients with T2DM, although the difference in weight was modest, and differences in glycaemic control were even smaller.

In all of the STEP studies there was scope for individual subjects to stay on a lower dose of semaglutide than the planned escalation, for tolerability reasons. The updated SmPC includes options for dose reduction

In future, more information on the long-term efficacy of the 1.7 mg dose would be useful. There are certainly many regulatory examples where doses have been revised downwards post-licencing.

A stopping rule has been applied in the SmPC to avoid patients unresponsive to therapy being exposed to the potential risks of treatment. If patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient.

It is not known presently whether the degree of weight loss seen at 1 year in the STEP studies can be maintained after a second year of treatment. This is being assessed in an ongoing study. It will also be interesting to see if the relatively low drop-out rate in the pivotal studies can be maintained over 2 years. Also ongoing at the time of assessment is a 45-week off-treatment extension phase to STEP 1.

Safety

The safety population is adequate from a regulatory perspective, and the safety analysis including the selected AE categories of special interest was in line with regulatory expectations. The exposure in special populations is judged adequate given the SmPC caveats proposed. The company will add use in patients with a history of major depression or other severe psychiatric disorders in the risk management plan as missing information in the RMP, likewise concomitant use of other weight lowering drugs.

Overall, the nature and severity of adverse events is comparable to existing data with semaglutide and others in the class. No significant new safety signals were revealed, although clearly the dataset is not adequate to assess rare or late events with the 2.4 mg maintenance dose. The exposure response appears shallower for observed adverse events compared to weight loss, the main finding being more gastrointestinal events with the higher dose. Gastrointestinal adverse events including nausea, diarrhoea, vomiting and constipation were reported in 72.9% of semaglutide treated subjects versus 47.1% for placebo, with 4.3% versus 0.7% respectively leading to permanent discontinuation, and a larger number requiring temporary interruption of trial product or a dose reduction. In both treatment groups the majority of the first gastrointestinal AEs occurred during the initial 20 weeks of the trial. The early peak was most pronounced for nausea. The median duration for individual events of nausea, vomiting and diarrhoea was around a week or less, but over a month for constipation. The rate of discontinuation for subjects experiencing GI adverse events is slightly higher to that seen in the Ozempic dossier, however the number of severe events and events leading to treatment discontinuation are judged acceptably low if the treatment benefits are accepted.

There are no issues in the assessment of hypoglycaemia, immunogenicity, malignancies, hepatic AEs, pancreatitis, gallbladder disease , renal events or psychiatric disorders. Cardiovascular AEs were reported by a lower proportion of subjects on semaglutide versus placebo (8.7% versus 10.9%). Independently adjudicated cardiovascular events occurred in 0.6% versus 0.7% of subjects respectively. Because of the low number of CV events in the weight loss studies assessed, it is not possible to conclude non-inferiority of semaglutide 2.4 mg vs placebo, or conclude that this high dose confers a benefit. Taken as a whole though, the new data do not indicate an excess CV risk or any apparent dose-related cardiovascular toxicity.

As seen in the Ozempic dossier, there was a signal for new or worsening events of diabetic retinopathy, compared to placebo. Whilst rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, the data do not exclude a direct effect of semaglutide, and this will also be carefully monitored.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

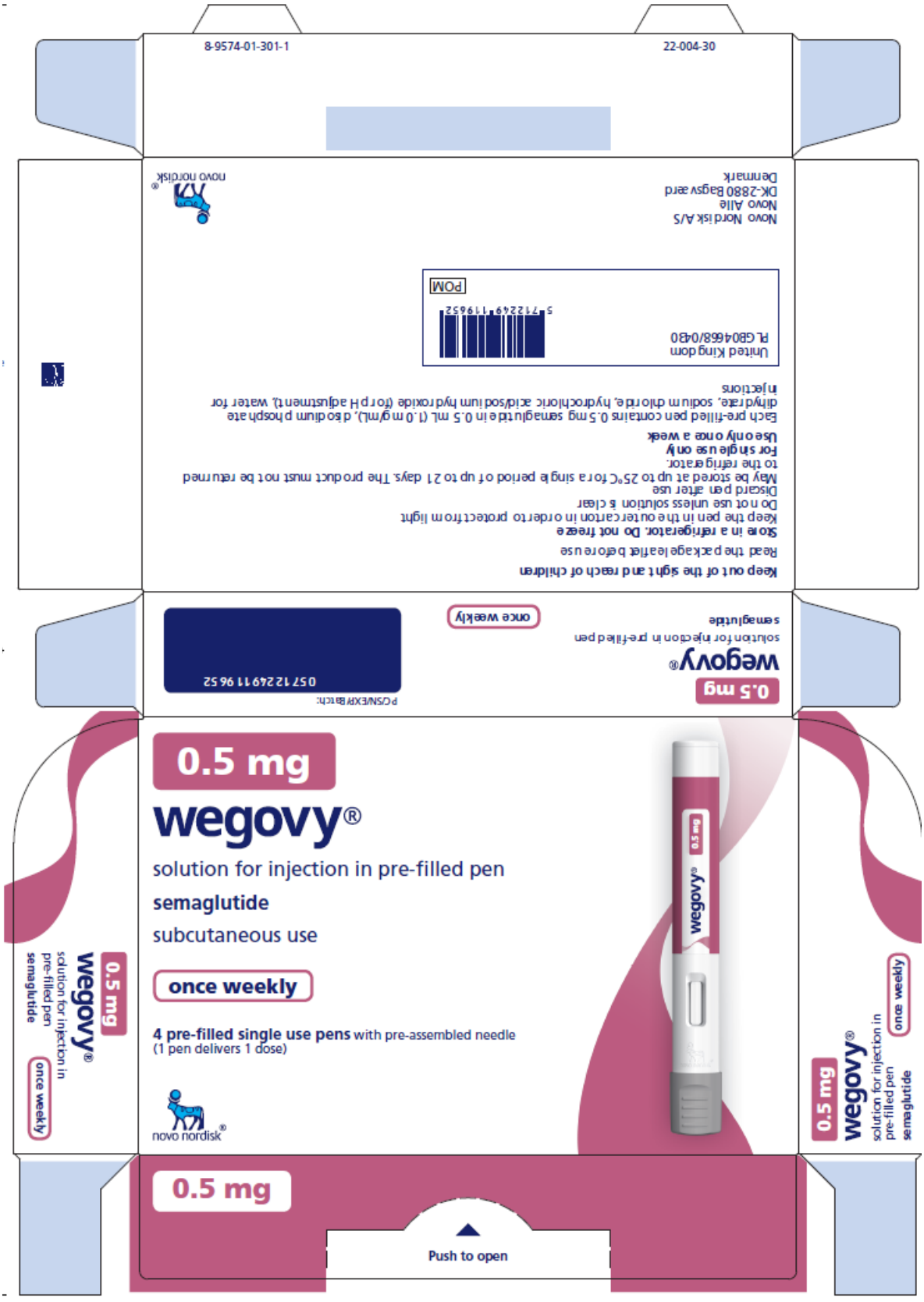
The quality of the products is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of these products as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of ≥30 kg/m2 (obesity), or ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below:


8-9570-01-301-1
22-004-30
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
PLGB04668/0429
POM
Keep out of the sight and reach of children
Read the package leaflet before use
Store in a refrigerator. Do not freeze
Keep the pen in the outer carton in order to protect from light
Do not use unless solution is clear
Discard pen after use
May be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.
For single use only
Use only once a week
Each pre-filled pen contains 0.25 mg semaglutide in 0.5 mL (0.5 mg/mL), disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections
0.25 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
once weekly
0.25 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
subcutaneous use
once weekly
4 pre-filled single use pens with pre-assembled needle
(1 pen delivers 1 dose)
novo nordisk®
Push to open


8-9574-01-301-1
22-004-30
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
PL GB04668/0430
POM
Keep out of the sight and reach of children
Read the package leaflet before use
Store in a refrigerator. Do not freeze
Keep the pen in the outer carton in order to protect from light
Do not use unless solution is clear
Discard pen after use
May be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.
For single use only
Use only once a week
Each pre-filled pen contains 0.5 mg semaglutide in 0.5 mL (1.0 mg/mL), disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections
0.5 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
once weekly
PCSN/EXP Batch:
0.5 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
subcutaneous use
once weekly
4 pre-filled single use pens with pre-assembled needle
(1 pen delivers 1 dose)
novo nordisk®
Push to open


8-9574-01-201-1
EXP/
Batch:
0.5 mg in 0.5 mL
wegovy®
0.5 mg
injection
semaglutide
subcutaneous use
once weekly
Novo Nordisk A/S


1 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
subcutaneous use
once weekly
4 pre-filled single use pens with pre-assembled needle
(1 pen delivers 1 dose)
novo nordisk®
Push to open
Keep out of the sight and reach of children
Read the package leaflet before use
Store in a refrigerator. Do not freeze
Keep the pen in the outer carton in order to protect from light
Do not use unless solution is clear
Discard pen after use
May be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.
For single use only
Use only once a week
Each pre-filled pen contains 1.0 mg semaglutide in 0.5 mL (2.0 mg/mL), disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections
United Kingdom
PLGB 04668/0431
POM
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
novo nordisk®
8-9571-01-301-1
22-004-30


8-9571-01-201-1
EXP/
Batch:
1.0 mg in 0.5 mL
wegovy®
1 mg
injection
semaglutide
subcutaneous use
once weekly
Novo Nordisk A/S


8-9572-01-301-1
22-004-30
novo nordisk
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
POM
United Kingdom
PLGB04668/0432
Each pre-filled pen contains 1.7 mg semaglutide in 0.75 mL (2.27 mg/mL), disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections
Keep out of the sight and reach of children
Read the package leaflet before use
Store in a refrigerator. Do not freeze
Keep the pen in the outer carton in order to protect from light
Do not use unless solution is clear
Discard pen after use
May be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.
For single use only
Use only once a week
1.7 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
once weekly
PC/SN/EXP/Batch:
05712249119676
1.7 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
subcutaneous use
once weekly
4 pre-filled single use pens with pre-assembled needle
(1 pen delivers 1 dose)
novo nordisk
1.7 mg
Push to open
1.7 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
once weekly
1.7 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
once weekly


8-9572-01-201-1
EXP/
Batch:
1.7 mg in 0.75 mL
wegovy®
1.7 mg
injection
semaglutide
subcutaneous use
once weekly
Novo Nordisk A/S


8-9573-01-301-1
22-004-30
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
POM
United Kingdom
PLGB 04668/0433
Keep out of the sight and reach of children
Read the package leaflet before use
Store in a refrigerator. Do not freeze
Keep the pen in the outer carton in order to protect from light
Do not use unless solution is clear
Discard pen after use
May be stored at up to 25°C for a single period of up to 21 days. The product must not be returned to the refrigerator.
For single use only
Use only once a week
Each pre-filled pen contains 2.4 mg semaglutide in 0.75 mL (3.2 mg/mL), disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment), water for injections
2.4 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
once weekly
PC/SN/EXP/Batch:
2.4 mg
wegovy®
solution for injection in pre-filled pen
semaglutide
subcutaneous use
once weekly
4 pre-filled single use pens with pre-assembled needle
(1 pen delivers 1 dose)
novo nordisk®
Push to open


8-9573-01-201-1
EXP/
Batch:
2.4 mg in 0.75 mL
wegovy®
2.4 mg
injection
semaglutide
subcutaneous use
once weekly
Novo Nordisk A/S

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**