EMADOC-1700519818-2317237
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMA/VR/0000284664

Invented name: Wegovy

International non-proprietary name: Semaglutide

Marketing authorisation holder (MAH): Novo Nordisk A/S

Table of contents

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 02 July 2025 an application for group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.13	C.I.13 Submission of additional clinical and non-clinical studies, including BE-studies.	Variation type II

A grouped application consisting of: C.I.4: Update of sections 4.2, 4.8 and 5.1 of the SmPC based on two pivotal phase 3b clinical studies, NN9536-4999 and NN9536-7545. The Package Leaflet is updated accordingly. C.I.13: Submission of the final report from study NN9932-4737 (OASIS 1). This is a Phase 3a study to investigate the Efficacy and Safety of Oral semaglutide 50 mg Once Daily in Subjects with Overweight or Obesity.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

Semaglutide is approved globally for weight management as a once weekly 2.4 mg subcutaneous (s.c.) injection (Wegovy) as an adjunct to reduced-calorie diet and increased physical activity in adults living with obesity (body mass index (BMI) ≥30.0 kg/m^2) or overweight (BMI ≥27.0 kg/m^2) with at least one weight-related comorbidity (such as high blood pressure, type 2 diabetes (T2D), or high cholesterol).

This application aims at updating the Wegovy Product Information (PI) to support the use of a higher dose (semaglutide 7.2 mg) as maintenance dose based on the results from Study NN9536-4999 (STEP UP) and Study NN9536-7545 (STEP UP T2D) by demonstrating a greater weight loss effect with semaglutide 7.2 mg following 72 weeks of treatment compared to semaglutide 2.4 mg and placebo.

Design

STEP UP and STEP UP T2D studies were designed to evaluate the efficacy and safety of semaglutide 7.2 mg once weekly versus placebo once-weekly as an adjunct to reduced-calorie diet and increased physical activity in adults living with obesity (STEP UP) or obesity and T2D (STEP UP T2D). In addition, both trials also included a semaglutide 2.4 mg once-weekly arm.

Both studies were randomised, double-blind, placebo-controlled, multi-national, multi-centre, three-armed, parallel-group studies consisting of a 1-week screening period, a 20-week dose escalation period, a 52-week maintenance period, and a 9-week follow-up period.

Participants were randomised 5:1:1 (STEP UP) or 3:1:1 (STEP UP T2D) to receive either semaglutide 7.2 mg, semaglutide 2.4 mg, or placebo once-weekly, as an adjunct to reduced-calorie diet and increased physical activity. In STEP UP, a sub-population of 55 randomised participants had their body composition assessed by MRI at the beginning and at the end of the treatment to investigate the effect on body composition.

Objectives

The co-primary objectives for both the STEP UP and the STEP UP T2D study were to demonstrate superiority of semaglutide 7.2 mg once-weekly versus placebo as an adjunct to reduced-calorie diet and increased physical activity with respect to relative change in body weight and achieving body weight reduction of ≥ 5% after 72 weeks in the respective study populations.

However, for the proposed higher dose of 7.2 mg, a comparison with the already marketed dose of 2.4 mg is considered more relevant.

Participants

The study population was chosen to consist of adults with BMI ≥30.0 kg/ m^2 with or without weight-related (except T2D) comorbidities (STEP UP) and adults living with obesity (BMI ≥30.0 kg/m) and T2D (STEP UP T2D). The BMI cut off value is different from that in the current indication. The current indication includes not only patients BMI ≥30.0 kg/ m^2, but also patients with BMI ≥27.0 kg/ m^2 with comorbidities. For the high dose of 7.2 mg, patients with BMI between 27 and 30 have not been investigated. This is now clearly stated in the SmPC section 4.2.

Efficacy

Body weight change

In STEP UP, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was: -18.71% for semaglutide 7.2 mg, -15.61% for semaglutide 2.4 mg and -3.90% for placebo treatment. The estimated treatment difference (ETD) between semaglutide 7.2 mg versus placebo was: -14.81% points (p-value <0.0001). The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg was only -3.10% points.

In STEP UP T2D, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was: -13.18% for semaglutide 7.2 mg, -10.36% for semaglutide 2.4 mg and -3.86% for placebo treatment. The ETD between semaglutide 7.2 mg versus placebo was: 9.33% points (p-value <0.0001). The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg for relative change in body weight was only: -2.80% points.

In both studies, the effects of the 2.4 mg and the 7.2 mg dose on body weight are clinically relevant. However, the difference between the 2.4 and 7.2 mg is small and of its clinical relevance is considered uncertain (-3.1% and -2.8% points body weight). Compared to the 2.4 mg dose, the efficacy response to semaglutide 7.2 mg was similarly low across sub-populations. Specifically, there were no relevant differences in efficacy between body weight subgroups.

The magnitude of the weight loss in participants with T2D (STEP UP T2D) was smaller than in participants without T2D (STEP UP), an observation that has been well documented in previous weight management studies with semaglutide.

Proportion of participants achieving body weight reduction ≥5%

In STEP UP, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was: 88.47% with semaglutide 7.2 mg, 86.61% with semaglutide 2.4 mg, and 38.83% with placebo.

In STEP UP T2D, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was: 84.23% with semaglutide 7.2 mg, 73.93% with semaglutide 2.4 mg and 34.76% with placebo.

These data show that in both studies both doses of semaglutide resulted in more weight loss than placebo. The effects of semaglutide are clinically relevant. However, the differences between the 2 doses are small. In STEP UP only 1.9% more patients achieved the body weight reduction of ≥5% with the 7.2 mg dose compared to the 2.4 mg dose. In STEP UP T2D, only 10.3% more patients achieved this reduction with the higher dose.

Waist and body composition

The ETD between semaglutide 7.2 mg versus placebo for waist circumference from baseline (week 0) to end of treatment (week 72) was: -11.66 in STEP UP and -6.55 cm in STEP T2D. However, the decrease in waist with the 7.2 mg dose was only 2.9 cm (STEP UP) and 1.5 cm (STEP UP T2D) higher than with the 2.4 mg dose. The clinical relevance of these differences is considered uncertain.

Treatment with semaglutide resulted in improvements in MRI estimates of total fat (-24%), visceral fat (-25%), and lean body (-7%). However, these differences reflect the differences between both semaglutide doses on the one hand and placebo on the other. The differences between the 7.2 and the 2.4 dose are difficult to assess as only 6 patients were treated with the 2.4 mg dose in the MRI substudy.

Other CV risk factors

Both doses of semaglutide were associated with a reduction in systolic blood pressure (SBP). However, the differences between the doses were very small and not clinically relevant (<2 mmHg). Similarly, the differences between the doses in diastolic blood pressure (DBP) were also very small (<2 mmHg).

Small improvements in several serum lipids could be detected with semaglutide 2.4 and 7.2 mg (approximate changes compared to placebo for total cholesterol -0.1 mmol/L, LDL -0.2 mmol/L, HDL -0.2 mmol/L). However, the differences between the 2 doses were negligible.

Similarly, CRP improved somewhat with semaglutide 2.4 and 7.2 mg (approximately 0.5 mg/L), but there were no differences between the doses.

In STEP UP T2D, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in HbA1c (mmol/mol) from baseline (week 0) to end of treatment (week 72) was: -16.5 (p-value <0.0001). HbA1c reduction was also seen in STEP UP, although to a smaller extent than for STEP UP T2D. In STEP UP, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo was: -3.28 (p-value <0.0001). In both studies, the differences between the 7.2 and the 2.4 doses were negligible.

Safety

The safety of semaglutide 7.2 mg was evaluated by a pooled data set consisting of data from both studies STEP UP and STEP UP T2D. The exposure to semaglutide 7.2 mg was 1311 participants, 1004 in the STEP UP trial and 307 in STEP UP T2D corresponding to a total of 1915 PYE exposure.

Overall adverse events (AE) rate

In the pooled analysis (STEP UP Pool), the overall AE rate was higher for semaglutide 7.2 mg compared to 2.4 mg and placebo. (85.1% (7.2 mg) vs. 81.1% (2.4 mg) and 76% (placebo). Most reported events were gastrointestinal disorders, nervous system disorders, and skin and subcutaneous disorders. Of the PTs, dysaesthesia and alopecia were mostly reported.

For details on the risk of dysaesthesia, see below.

A greater proportion of participants in the semaglutide 7.2 mg group reported AEs compared to both the semaglutide 2.4 mg and placebo groups within the PTs Alopecia (5.8% versus 3.3% versus 1.0%). The

events of Alopecia were associated with weight loss, as a higher proportion and rate of events related to Alopecia were reported in participants with ≥20% weight loss, with a more pronounced difference in the semaglutide 7.2 mg group (≥20% weight loss: 9.0%, 6.0 events per 100 PYE versus. <20% weight loss: 4.1% and 2.9 events per 100 PYE) compared to the semaglutide 2.4 mg group (≥20% weight loss: 4.2%, 2.8 events per 100 PYE versus <20% weight loss: 3.4%, 2.3 events per 100 PYE).

Serious AEs

Overall, serious AEs were mostly reported in the 2.4 mg group and were comparable between 7.2 mg group, the 2.4 mg group and placebo (7.5%, 10.2% and 6.6% respectively).

In the 2.4 mg semaglutide group, one patient reported 21 SAEs including one fatal event.

Safety focus areas

Dysaesthesia

Dysaesthesia AEs were reported more frequently with semaglutide 7.2 mg (22%) than with semaglutide 2.4 mg (5.6%) and placebo (0.3%). Especially the PT's sensitive skin, hyperaesthesia and dysaesthesia were more reported in the 7.2 mg semaglutide group. All AEs related to dysaesthesia were non-serious, and the majority were mild in severity and reported as recovered. Nevertheless, in 5% of patients dysaesthesia was reported as not recovered. Overall, the data suggest an increased frequency of AEs related to dysaesthesia with semaglutide 7.2 mg compared to semaglutide 2.4 mg and placebo. The risk is much higher than previously observed with higher doses of oral semaglutide. In PIONEER PLUS, the proportion of patients reporting AEs related to a clinical picture of dysaesthesia were 5.2% (5.7 events per 100 PYE) with oral semaglutide 50 mg, 2.1% (1.7 events per 100 PYE) with oral semaglutide 25 mg and 1.1% (1.2 events per 100 PYE) with oral semaglutide 14 mg.

Gastrointestinal AEs

Gastrointestinal AEs were reported more frequently with semaglutide 7.2 mg (70.8%) than with semaglutide 2.4 mg (61.2%) and placebo (vs 42.8%). The most frequently reported gastrointestinal AEs were nausea, vomiting and diarrhoea. Most of the gastrointestinal AEs were non-serious and mild or moderate in severity. The proportion of participants with serious or severe gastrointestinal AEs were similar across the semaglutide treatment groups. As expected, most gastrointestinal AEs were reported during dose escalation. These types of AEs are well-known for semaglutide and for the GLP-1 receptor agonist (GLP-1 RA) class in general and can usually be managed.

Pancreatitis

AEs of pancreatitis were reported by a comparable proportion of participants and rate of events in the semaglutide 7.2 mg (0.2%, 0.1 events per 100 PYE) and semaglutide 2.4 mg (0.3%, 0.2 events per 100 PYE) groups. In the placebo group, no AEs of pancreatitis were reported.

Gallbladder-related disorders

AEs related to gallbladder-related disorders were reported by a higher proportion of participants and reporting rates in the semaglutide 7.2 mg (2.4%, 1.9 events per 100 PYE) and semaglutide 2.4 mg (2.3%, 1.6 events per 100 PYE) groups compared to the placebo group (only 0.3% gallbladder-related disorders).

Psychiatric disorders

AEs related to psychiatric disorders were reported by a comparable proportion and at a comparable rate in the semaglutide 7.2 mg (6.2%, 5.5 events per 100 PYE), semaglutide 2.4 mg (7.0%, 5.9 events per 100 PYE), and placebo (6.0%, 5.2 events per 100 PYE) groups.

Hepatic disorders

AEs related to hepatic disorders were reported by a lower proportion of participants, and at a lower rate, in semaglutide 7.2 mg (2.7%, 2.6 events per 100 PYE) compared to the semaglutide 2.4 mg group (3.3%, 3.1 events per 100 PYE). The proportions and rates in placebo were lower (1.0%, 1.0 events per 100 PYE).

Immunogenicity

AEs related to Allergic reactions were reported by a similar proportion of participants, and at a similar rate, in both the s.c semaglutide 7.2 mg (4.6%, 3.8 events per 100 PYE) and semaglutide 2.4 mg (4.7%, 3.2 events per 100 PYE) groups, and lower in placebo (3.3%, 2.5 events per 100 PYE).

The presence of anti-semaglutide antibodies did not appear to impact exposure, efficacy, or safety of semaglutide in either semaglutide treatment group.

Cardiovascular disorders

AEs related to cardiovascular disorders were reported by a similar proportion of participants, and at a similar rate, in the semaglutide 7.2 mg (8.7%, 9.8 events per 100 PYE) and placebo (8.9%, 9.1 events per 100 PYE) groups, with a higher proportion and rate in the semaglutide 2.4 mg group (10.9%).

Neoplasm events

The proportion of participants and rate of neoplasm events were similar among the semaglutide 7.2 mg (6.4%, 4.8 events per 100 PYE, 93 AEs in 81 participants), semaglutide 2.4 mg (5.9%, 5.6 events per 100 PYE, 26 AEs in 18 participants), and placebo (5.0%, 4.5 events per 100 PYE, 20 AEs in 15 participants) groups.

Kidney disorders

The proportion of participants with AEs related to Kidney disorders and the rate of such events were lower in the semaglutide 7.2 mg (0.3%, 0.2 events per 100 PYE) than in the semaglutide 2.4 mg (0.7%, 0.7 events per 100 PYE) and placebo (0.7%, 0.5 events per 100 PYE. Creatinine and eGFR values were stable over time and comparable across treatment groups.

Aspiration and intestinal obstruction

No events related to aspiration in association with anaesthesia or deep sedation were reported. The search for events of Intestinal obstruction captured one AE (PT Oesophageal stenosis) in the semaglutide 7.2 mg group.

Hypoglycaemia

In STEP UP T2D, there were no imbalances in level 2 hypoglycaemic episodes across treatment groups, with 2.0% in semaglutide 7.2 mg, 1.9% in semaglutide 2.4 mg, and 2.9% in placebo. Overall, the data do not suggest an important effect on risk of hypoglycaemic episodes with semaglutide 7.2 mg compared to semaglutide 2.4 mg in patients with diabetes.

In STEP UP in patients without diabetes, there was higher risk in both semaglutide groups compared to the placebo group. 3 AEs were reported in 3 participants in the semaglutide 7.2 mg group (0.3%, 0.2 events per 100 PYE), 3 AEs were reported in 2 participants in the semaglutide 2.4 mg group (1.0%, 1.0 events per 100 PYE), and none were reported in the placebo group. 4 AEs were reported as recovered, but 2 (1 in each semaglutide treatment group) were reported as not recovered. However, the CHMP concluded that, in people with obesity and without diabetes, the risk of hypoglycaemia with semaglutide 2.4 mg and 7.2 mg is very low.

Diabetic retinopathy

The proportion and rate of AEs of Diabetic retinopathy were lower but comparable in semaglutide 7.2 mg (1.3%, 0.9 events per 100 PYE) followed by semaglutide 2.4 mg (1.9%, 1.9 events per 100 PYE) and placebo (3.9%, 2.6 events per 100 PYE). Retinal disorders are a known risk of Wegovy in the T2D population. The data do not suggest an increased risk of retinal disorders with semaglutide 7.2 mg compared to semaglutide 2.4 mg in the T2D population, but the trial duration of 52 weeks may be relatively short to detect this event

Subgroups

The evaluation of the subgroups investigated did not reveal any new safety concerns or markedly different AE profiles for semaglutide 7.2 mg relative to placebo and semaglutide 2.4 mg for any subgroups.

Conclusions and benefit/risk balance

Both 7.2 mg and 2.4 mg of semaglutide were associated with clinically relevant reductions in body weight in obese individuals with and without diabetes. However, the differences between the new 7.2 mg dose compared to the already marketed 2.4 mg dose were very small and their clinical relevance was not considered established: *a 3 times higher dose of semaglutide was associated with only 3% points more weight loss*. The uncertainty about the clinical relevance of the proposed higher dose is supported by the fact that there were also no relevant differences between the 7.2 and 2.4 mg dose with respect to CV risk factors, such as waist, body composition, blood pressure, serum lipids, CRP and HbA1c. The company argues that the 3% additional weight loss with the high dose should be viewed in the context of the proportions of participants in STEP UP who achieved several clinically significant treatment targets for weight loss and key cardiometabolic risk factors. The additional benefit with the higher dose may be clinically relevant for some patients (7-15% of the total population), but not for the majority of patients (85-93%). The Applicant did not identify a subgroup of patients that may have substantially improved benefit-risk balance with the higher dose. Additionally, the 3 times higher dose is associated with an increased risk of adverse events. Therefore, the benefit-risk profile for the 7.2 mg dose level is negative for most patients.

The CHMP considered the benefit-risk of the 7.2 mg dose only positive in patients who need additional weight loss. In case of side effects, the dose may be titrated back. In addition, if a clinical improvement in body weight has not been achieved with the 7.2 mg dose, the dose should be titrated back to 2.4 mg in order to prevent risks with the high dose. This is now clearly stated in the posology section of the SmPC**.** The BMI cut off value in the two submitted studies is different from that in the current indication. The current indication includes not only patients BMI ≥30.0 kg/ m^2, but also patients with BMI ≥27.0 kg/m^2 with comorbidities. For the high dose of 7.2 mg, patients with BMI between 27 and 30 have not been investigated. These relatively low weight patients should not be treated with the high dose of 7.2 mg semaglutide. This is now also clearly stated in the posology section of the SmPC.

The safety and tolerability profile for semaglutide 7.2 mg was overall consistent with the safety profile for semaglutide and the GLP-1 RA class. Gastrointestinal AEs were reported more frequently with semaglutide 7.2 mg than with semaglutide 2.4 mg and placebo, but these types of AEs are well-known for semaglutide and for the GLP-1 RA class in general and can usually be managed. However, AEs related to dysaesthesia were reported by a higher proportion of participants and at a higher rate in the semaglutide 7.2 mg group (22%). The risk is much higher than previously observed with higher doses of oral semaglutide. The CHMP agrees with the company that the reported symptoms and location of the affected areas are diverse and do not indicate an anatomical pattern, which is typical for a neuropathy. However, the underlying mechanism for dysaesthesia remains unknown. This is considered a problem as

risks with unknown underlying mechanisms are unpredictable and difficult to avoid or mitigate. Long term effects of the 3 times higher dose on dysaesthesia are unknown.

Across the STEP UP studies, 66 (15%) of the 434 events identified by the dysaesthesia MedDRA search had not recovered in the semaglutide 7.2 mg group. For the events that recovered in the semaglutide 7.2 mg group, 191 events (44% of all reported events) only recovered after changes in the dose of the trial product.

The CHMP therefore considered it important that the high risk of dysaesthesia and other possible long-term risks are taken into account when dosing semaglutide.

In conclusion, the benefit/risk ratio is considered acceptable in a small subpopulation of patients who need additional weight loss and for whom the higher dose allows to achieve a clinically relevant amount of weight loss. If efficacy of the high dose is not sufficient in a patient, the dose should be titrated back to avoid unnecessary risks. This issue has been mitigated by adding to section 4.2 of the SmPC that the 7.2 mg dose should be titrated back to 2.4 mg if a clinical improvement in body weight has not been achieved with the 7.2 mg dose. In addition, the Applicant is requested to continue monitoring dysaesthesia through routine post-marketing pharmacovigilance activities. Clinical studies with semaglutide should collect additionally detailed data to enhance the characterisation of any reported dysaesthesia events.

The benefit-risk balance of Wegovy remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.13	C.I.13 Submission of additional clinical and non-clinical studies, including BE-studies.	Variation type II

A grouped application consisting of: C.I.4: Update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC based on two pivotal phase 3b clinical studies, NN9536-4999 and NN9536-7545. The Package Leaflet is updated accordingly. C.I.13: Submission of the final report from study NN9932-4737 (OASIS 1). This is a Phase 3a study to investigate the Efficacy and Safety of Oral semaglutide 50 mg Once Daily in Subjects with Overweight or Obesity.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es)I, IIIB are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Wegovy-H-C-5422-II-EMA/VR/0000284664'

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

1. Introduction

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

Semaglutide is approved globally for weight management as a once weekly 2.4 mg s.c. injection (Wegovy®) as an adjunct to reduced-calorie diet and increased physical activity in adults living with obesity (BMI ≥30.0 kg/m^2) or overweight (BMI ≥27.0 kg/m^2) with at least one weight-related comorbidity (such as high blood pressure, T2D, or high cholesterol).

The phase 3a weight management study NN9536-4373 (STEP 1) evaluated weight loss in participants with BMI ≥ 27.0 kg/m^2 with comorbidities (except for T2D). Of the participants with a baseline BMI ≥ 35.0 kg/m^2, 11% reached a BMI < 27.0 kg/m^2 after 68 weeks of treatment with semaglutide 2.4 mg. For the group with baseline BMI ≥ 30.0 kg/m^2, 30% reached a BMI < 27 kg/m^2 after 68 weeks of treatment with semaglutide 2.4 mg. Thus, although most participants achieved a clinically relevant weight loss in this study, further weight loss would still be beneficial.

To fully utilize data from the semaglutide weight management development programme, a *post-hoc* longitudinal exposure-response analysis was undertaken, developing a model that is suited for simulation of the time-course of weight loss across different dose regimens and time points. The simulations show that substantial weight loss benefits could be realised with semaglutide 7.2 mg once weekly. Modelling of data based on expected exposure levels suggest that a dose of 7.2 mg semaglutide could be an effective treatment option without jeopardising the safety of the individuals.

To address this unmet medical need for treatment intensification in adults living with obesity with and without T2D, and to ensure meaningful additional weight loss, Novo Nordisk has investigated an additional maintenance dose level of semaglutide, semaglutide 7.2 mg. STEP UP and STEP UP T2D were designed to evaluate the efficacy and safety of semaglutide 7.2 mg once weekly versus placebo once-weekly as an adjunct to reduced-calorie diet and increased physical activity in adults living with obesity (STEP UP) or obesity and T2D (STEP UP T2D). Additionally, STEP UP evaluated the efficacy of semaglutide 7.2 mg versus semaglutide 2.4 mg once weekly.

This application aims at extending the current Wegovy® label to support the use of semaglutide 7.2 mg as maintenance dose based on the results from STEP UP and STEP UP T2D by demonstrating a greater weight loss effect with semaglutide 7.2 mg following 72 weeks of treatment compared to current treatment options.

2. Clinical Pharmacology aspects

2.1. Effect of semaglutide 7.2 mg s.c. on the rate of gastric emptying

No studies are conducted investigating the dose of 7.2 mg semaglutide s.c. once weekly on gastric emptying. The applicant, however, indicated that the following studies are relevant due to similar exposure:

NN9932-4873: Pharmacodynamic and *pharmacokinetic* phase I study investigating the effect of oral semaglutide 50 mg OD on energy intake, appetite, control of eating and *gastric emptying*.

NN9932-4737 (OASIS 1): Efficacy and safety phase IIIa study of oral semaglutide 50 mg in adults with overweight or obesity (*PK* samples were obtained for 50 mg semaglutide once daily and analysed in a popPK model).

2.1.1. Methods – analysis of data submitted

Study NN9932-4873 is a phase 1, randomised, parallel group, multiple-dose, double-blind, placebo-controlled study in 61 healthy adults with obesity randomised to once daily oral semaglutide (1.5 mg, 4 mg, 9 mg, 25 mg and 50 mg for 4 weeks on each dose, respectively) or placebo. Study subjects had a BMI between 30.0 and 45.0 kg/m2. Use of paracetamol 72 hours prior to Visits 2 and 7 was not allowed.

Gastric emptying was assessed by the paracetamol absorption technique during the standardised breakfast meal at baseline and at day 141 at steady state with oral semaglutide 50 mg compared to placebo (as was performed also for 1 mg and 2.4 mg semaglutide dosing in previous procedures). All gastric emptying related endpoints (mean paracetamol concentration area under the curve from 0 to 5 hours ($AUC_{0-5h,para}$), mean paracetamol concentration area under the curve from 0 to 1 hours ($_{AUC0-1h,para}$), maximum paracetamol concentration ($C_{max,para}$) and time to maximum paracetamol concentration ($t_{max,para}$) were supportive secondary endpoints in this study.

Study NN9932-4737 (OASIS 1) is a phase 3a study included in this dossier to provide additional PK data, which was used for popPK modelling.

2.1.2. Results

Mean paracetamol concentrations peaked after approximately 30 minutes after start of the breakfast meal at baseline and at day 141 during oral semaglutide 50 mg treatment and placebo in study NN9932-4873. Paracetamol concentration-time profiles are indicated in Figure 1 below. Treatment ratios are calculated and reported in Table 1.

Figure 1: Paracetamol concentration v.s. time profiles after 20 weeks of semaglutide treatment

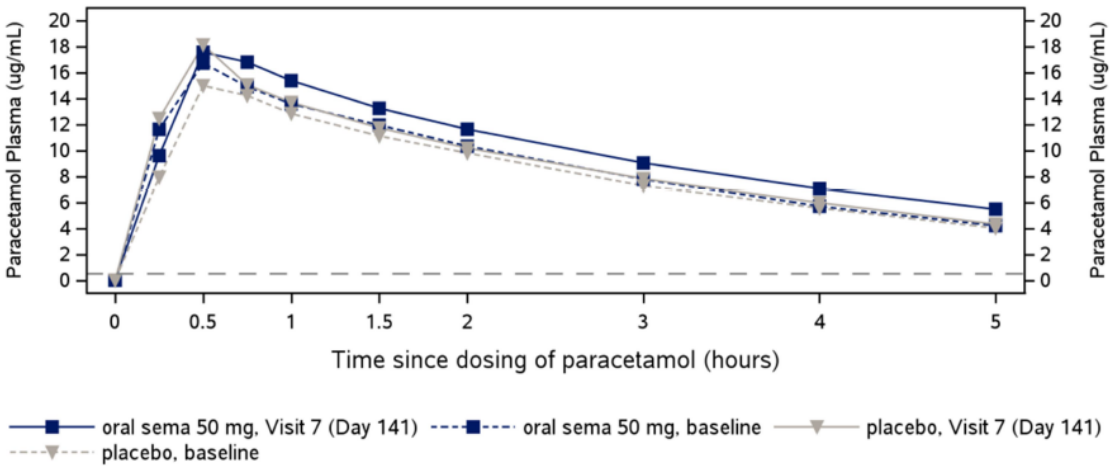


Table 1: AUC and C_{max} ratios oral semaglutide 50 mg v.s. placebo

	Estimate	95% CI	p-value
$AUC_{0\text{-}1h,para}$ (h*µg/mL) Treatment ratio Oral semaglutide 50 mg / placebo	0.92	(0.76; 1.11)	0.36
$AUC_{0\text{-}5h,para}$ (h*µg/mL) Treatment ratio Oral semaglutide 50 mg / placebo	1.06	(0.97; 1.16)	0.17
$C_{max,para}$ (µg/mL) Treatment ratio Oral semaglutide 50 mg / placebo	1.01	(0.88; 1.17)	0.84

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; CI = confidence interval

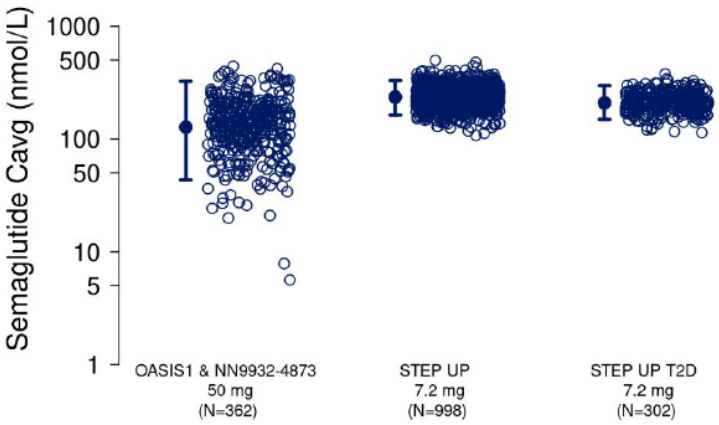
In addition, pharmacokinetic values for the oral semaglutide 50 mg treatment group on day 140 are presented in Table 2 (study NN9932-4873).

Table 2: Semaglutide PK parameter values at day 140

	oral sema 50 mg
Number of participants	30
AUC, 0-24h, semaglutide, SS (h*nmol/L)	
N	28
Mean (SD)	2904 (1360)
Geometric mean (CV)	2547 (60.6)
Median	2866
Min ; Max	656 ; 5331
Cmax semaglutide, SS (nmol/L)	
N	28
Mean (SD)	161.5 (83.1)
Geometric mean (CV)	140.9 (60.0)
Median	161.5
Min ; Max	44.4 ; 419.0

The applicant also provided a comparative plot using oral 50 mg OD semaglutide data from studies NN9932-4873 and NN9932-4737 (OASIS 1) combined, and s.c. 7.2 mg once weekly semaglutide (from the popPK model described in section 6.2 below in subjects with and without type 2 diabetes) in Figure 2.

Figure 2: Individual semaglutide exposure (C_{avg}) after 50 mg oral and 7.2 mg s.c. administration



Pharmacokinetic data are from STEP UP and STEP UP T2D (week 72), NN9932-4873 (week 20), and OASIS 1 (week 68). Average individual steady-state semaglutide concentrations (C_{avg}) were obtained from the final population PK model. The number of participants contributing with PK data is shown in parenthesis. Error bars are geometric mean with 5th and 95th percentiles.

2.2. Population PK of semaglutide 7.2 mg s.c

The report submitted in support of this extension describes the population PK and exposure-response (see section 6.3. Exposure-response of semaglutide 7.2 mg s.c) analyses to support regulatory evaluation of semaglutide 7.2 mg for weight management in adults with obesity (BMI ≥30.0 kg/m2). The main PK questions were to identify the exposure levels following administration of a semaglutide s.c. dose of 7.2 mg using one single injection (drug product strength of 9.6 mg/mL) compared to administration using three injections of 2.4 mg (drug product strength of 3.2 mg/mL) and the exposure levels for semaglutide s.c. 7.2 mg compared to oral semaglutide 50 mg.

2.2.1. Methods – analysis of data submitted

The population PK and exposure-response analyses are based on semaglutide s.c. 2.4 and 7.2 mg once-weekly investigated in the phase 3b studies STEP UP (NN9536-4999) and STEP UP T2D (NN9536-7545), semaglutide s.c. 2.4 mg once-weekly investigated in the phase 3a studies STEP 1 (NN9536-4373) and STEP 2 (NN9536-4374) and the semaglutide s.c. 1.0 mg once-weekly investigated in STEP 2. All studies were placebo controlled. The analyses of the STEP UP and STEP UP T2D data builds on the existing analyses of the previous STEP studies.

The population PK analyses were carried out in NONMEM (version 7.5 or above) and Perl-speaks-NONMEM (University of Uppsala) (version 5.0.0 or above), using first-order conditional estimation with interaction (FOCE+i). The full model was used to illustrate covariate effects. The final population PK model was used to predict individual C_{avg} estimates used in the exposure-response models. The simulation model was developed to facilitate predictions of PK for most populations, e.g. based on published demographic information from other studies.

A one-compartment model with first-order absorption and elimination was used to describe the semaglutide PK. Between-subject variability was included for CL/F, V/F, and ka, with assuming the individual effects on ka to be independent from the individual effects on CL/F, V/F, and applying a

bivariate log-normal distribution. Within-subject variability (residual) was described by a proportional error model.

Dose proportionality was evaluated by a plot of the geometric mean C_{avg} with 95% CI vs dose together with the estimated trend line and 90 % CI from a linear model including the same covariates as in the final PK model. The estimated mean and 90 % CI for exposure versus dose of this dose-dependent model was compared to the 80–125 % range of exposures from a model following exact dose-proportionality.

Covariate effects investigated on CL/F are presented in Table 5-1, where baseline body weight was modelled as a continuous covariate, and all other included covariates as categorical. Covariates were prespecified based on clinical interest in the patient population of interest. In addition, the method of administration of the 7.2 mg dose, that is 3 x 2.4 mg doses vs 1 x 7.2 mg dose, was implemented as a time-varying covariate on apparent clearance. Covariate effects applied on V/F and ka are also shown in the table. In the full model all covariate effects on CL/F were estimated simultaneously relative to a reference participant profile. A covariate is considered to not have a clinically relevant impact on exposure when its relative effect on exposure and 90% CI, fall within the acceptance interval for bioequivalence [0.80–1.25]. The final model only included statistically significant covariates, based on backwards elimination with a significance level of $p<0.001$ (equivalent to $\Delta OFV>10.8$) from the full model.

Assessor's comments

Population pharmacokinetic (PK) modelling was conducted using a standard approach. A one-compartment model was used to describe the PK behavior of semaglutide with between-subject variability added to all three PK parameters and proportional error model to describe the within subject variability.

The covariate analysis focused solely on clearance because the sparse PK sampling design limited the ability to reliably estimate other individual parameters, making CL/F the only parameter with robust individual estimates. We agree with the applicant that this is a limitation of the modelling exercise. Only statistically significant covariates (backwards elimination criteria $\Delta OFV>10.8$) were kept in the final model which is an adequate approach.

Using the final covariate model dose proportionality was assessed by comparing observed exposure trends to those expected under ideal dose-proportional conditions which is deemed appropriate.

2.2.2. Results

The final PK dataset comprised 25,105 observations from 3,676 participants from four phase 3 studies. The final model was a PK model with only statistically significant covariates included. Following the backward elimination of covariates, only effects of body weight on CL/F and on V/F and effects of sex, race, body weight, renal function and glycaemic status on CL/F were retained in the final model. In general, body weights were distributed with large overlaps between other covariate subgroups and hence, signs of co-linearities were limited for all covariates except for BMI. Therefore, BMI was not included in the PK models. The geometric mean concentration profiles, overall and by study were adequately captured by the model (Figure 3).

With regards to the covariate analysis as expected, the exposures appeared to be inversely related to body weight with lower exposures at higher body weights. Furthermore, exposures were higher in females than in males mainly due to a difference in baseline body weight. Exposures appeared independent of age, race, ethnicity and renal impairment.

The VPC was stratified on study and doses (Figure 4) showing that the reduced model was able to reproduce the geometric mean and the 5th and 95th percentiles of the observed concentrations and hence, is suitable for simulating semaglutide concentrations used in the exposure-response analysis.

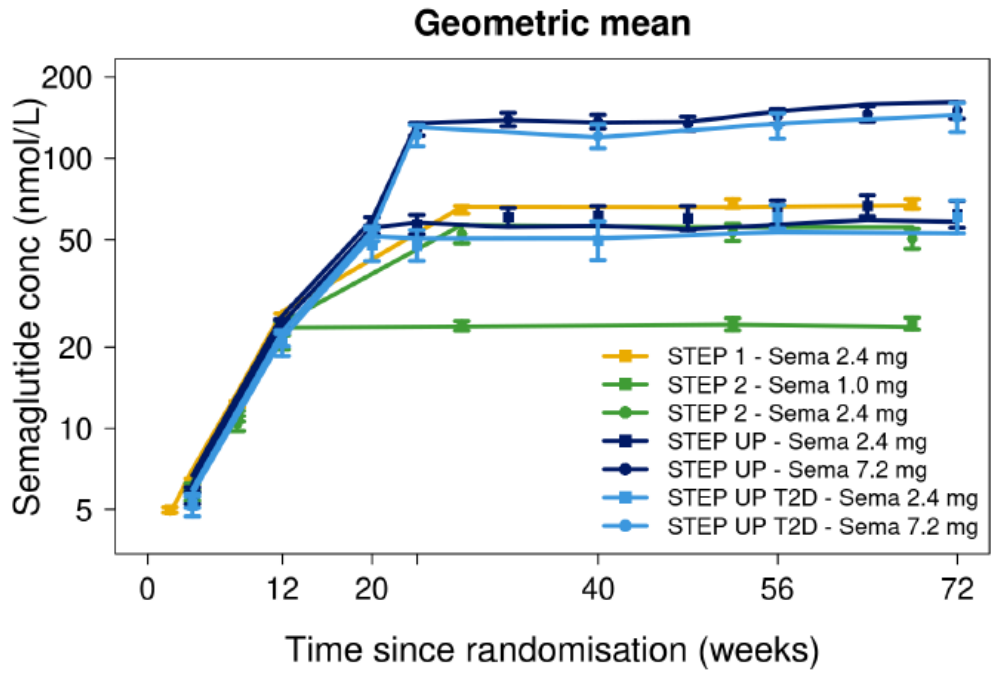


Figure 3: Observed and model-predicted exposure over time from the final model

Note: Symbols with error bars are geometric mean observations with 95% CIs. Lines are geometric mean population predictions for the corresponding observations, obtained from the full population PK model.

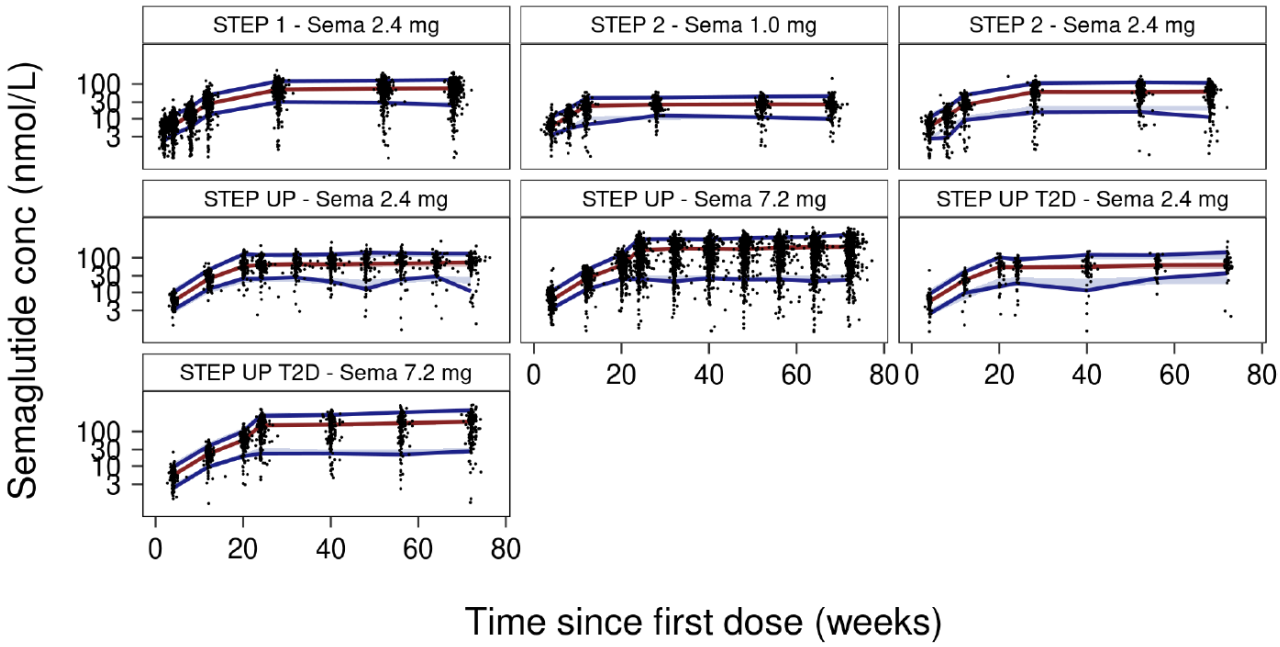


Figure 4: Visual predictive check, stratified by study and dose

Note: Data are observed (lines) and 95% CIs (shaded area, n=500) of simulated medians and 5th and 95th concentration percentiles versus time since first dose.

Assessor's comments

Looking at the final model the selected covariates seem appropriate. The fit of the final model is satisfactory based on the comparisons of the geometric mean exposures over time and the visual predictive checks. As described earlier in the method section due to sparse sampling CL/F is the only parameter with robust individual estimates, hence the higher shrinkage for the inter-induvial variability on KA and V/F is as expected. It is noted in the visual predictive checks that the model has some difficulty to adequately capture the lower percentiles, especially for the 2.4 mg dosing regimen. Nevertheless, the overall exposure has been described properly and thus it is agreed with the applicant that the final model is suitable for simulating semaglutide concentrations.

2.3. Exposure-response of semaglutide 7.2 mg s.c

The main exposure-response related questions were to identify the exposure-response relationship between s.c. semaglutide for dose levels up to 7.2 mg and weight loss, gastrointestinal adverse events, QTs prolongation, and dysesthesia. Furthermore, the additional effect of 7.2 mg compared to 2.4 mg, overall and across relevant subgroups was explored with the population PK and subsequent exposure-response analyses.

2.3.1. Methods – analysis of data submitted

Cross-sectional exposure-response analyses were carried out in R and performed to support the benefit-risk evaluation of 7.2 mg semaglutide s.c. The software ran on systems that are qualified according to Novo Nordisk procedures.

Endpoints included change from baseline at week 0 to week 72 in body weight (%), participants who after 72 weeks achieve bodyweight reduction from baseline (yes/no, 5 categories, range ≥ 5-25 %), participants who at any time experience safety endpoints (yes/no, 1) gastro-intestinal adverse events of any severity, according to system organ class, 2) nausea events of any severity, 3) vomiting events of any severity), participants who experience dysesthesia events during the first 26 weeks (yes/no), and change from from baseline at week 0 to week 72 in QTc interval.

The exposure metric applied in the exposure-response models, was the participant individual steady-state average concentration estimate (C_{avg}) derived from the final population PK model. Individual steady-state average concentrations (C_{avg}) were calculated as C_{avg} =dose/(τ*CL/F), based on the individual parameter estimates of CL/F using the final PK model, and where τ is the dosing interval (168 hours). For participants in the exposure-response population on placebo treatment semaglutide exposure was set to zero.

The population used for the exposure-response analyses is the same as used in the population PK model. The starting exposure-response weight model was prespecified based on the substantial knowledge available from the STEP program. Overall, limited model development was pursued. The percent change from baseline in body weight (BW_{CFB}) was described by an Emax model. The model was implemented in the logit domain, ensuring that the prediction of responders was bound between 0 and 100%.

The exposure response models of safety endpoints were based on logistic regression models. Additional covariates, being age, BMI class, race, ethnicity and disease status were explored. Additionally, an evaluation of dysaesthesia events was performed.

Exposure-response models were evaluated based on observed response vs. predicted and residual vs predicted response diagnostic plots.

Assessor's comments

The selected endpoints for the exposure-response analyses seem appropriate and comparable to the clinical exposure related endpoints. The overall methodology for the exposure-response analyses is adequate.

2.3.2. Results

A total of 5,090 participants with 5,081 observations of weight loss contributed with data to the exposure-response analyses. 5,078 observations contributed to the exposure-response analyses of GI AEs, nausea, and vomiting events. 1,152 observations contributed to the analysis of QTc interval change. To enhance the readability of the AR document, only figures deemed relevant by the assessor are included.

Efficacy

The exposure-response analysis showed increasing reduction in body weight compared to baseline with increasing concentrations of semaglutide (Figure 5). Less weight loss was seen in studies with T2D populations compared to studies with a non-T2D population and in participants with higher baseline HbA1c levels. This was in line with previously reported results on treatment with the 2.4 mg dose. Male subjects also showed less weight loss compared to female subject when stratified by sex and study.

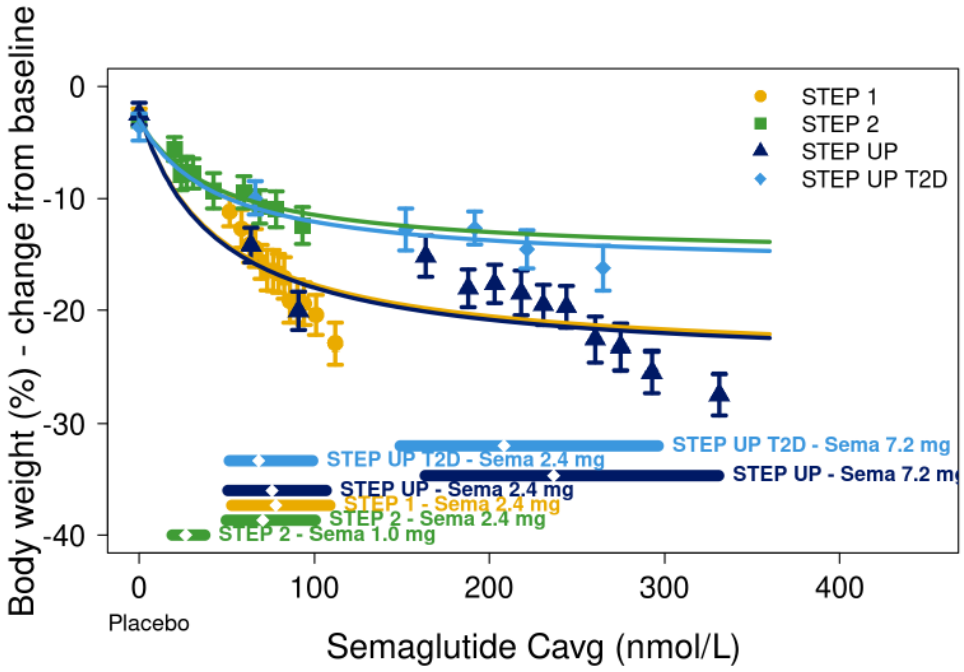


Figure 5: Exposure-response relationship of body weight change from baseline

Note: Data points with error bars are mean body weight changes with 95% CI obtained after 72 weeks (STEP UP and STEP UP T2D) and after 68 weeks (STEP 1 and STEP 2) of treatment versus exposure expressed as quantiles of Cavg (plus placebo at Cavg of 0 nmol/L). Lines through data are covariate-adjusted model-derived exposure-response relations. Horizontal lines with diamonds represent the median and 90% exposure range. Missing data at week 68 and 72 were study wise predicted using a mixed model for repeated measures, using treatment as factor and baseline BW as covariate all nested within visit. Data from studies STEP UP, STEP UP T2D, STEP 1, and STEP 2.

The proportion of participants reaching the weight loss goals of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% weight reduction at week 72 of treatment increased with increasing semaglutide exposure (Figure 6).

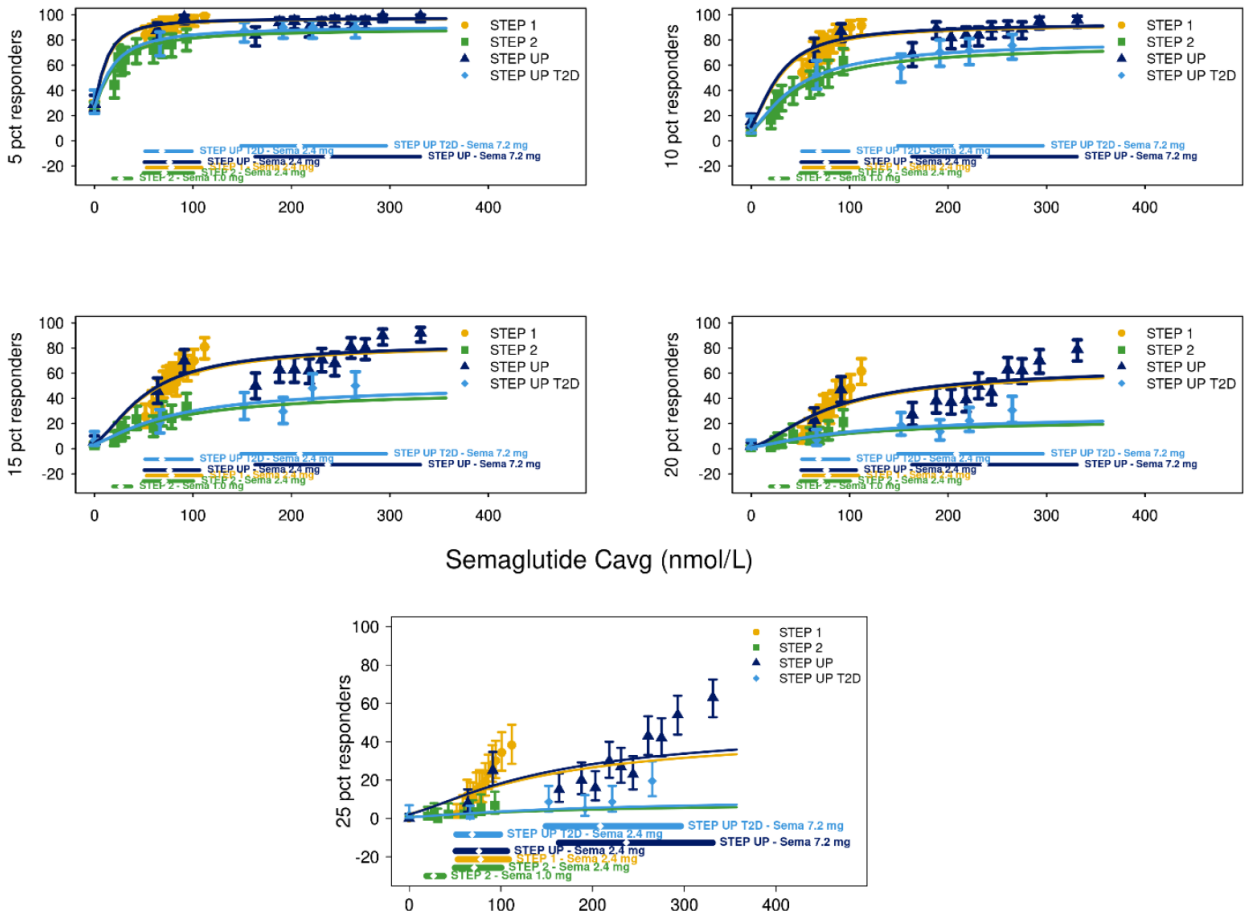


Figure 6: Proportion of participants reaching the weight loss goals of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% weight loss versus semaglutide exposure

Note: Symbols are proportions of participants expressed as quantiles of Cavg values plus placebo (at Cavg of 0 nmol/L) versus exposure, together with 95% CI (vertical bars). Lines through data represent covariate-adjusted model-derived relations using on-treatment data from the safety analysis set. The horizontal lines with diamonds along the x-axes represent medians and 90% exposure ranges. Data are from STEP UP, STEP UP T2D, STEP 1, and STEP 2.

Safety

The proportion of participants reporting at least one GI AE, nausea event, or vomiting event of any kind or severity during treatment increased to a minor extent with semaglutide exposure and plateaued at exposure levels associated with the 2.4 mg and 7.2 mg doses. Exposure-response analysis showed a flat exposure-response profile with regards to QTc change from baseline with increasing concentrations of semaglutide. Hence, semaglutide did not appear to have an effect on the QTc interval at doses up to 7.2 mg. The exposure-response relationship for the proportion of participants reporting AEs related to dysesthesia indicated that these AEs were observed in participants with high exposure levels (turning point C_{avg} >100 nmol/L and plateau around 20% >250 nmol/L, see Figure 7) during the first 26 weeks of treatment.

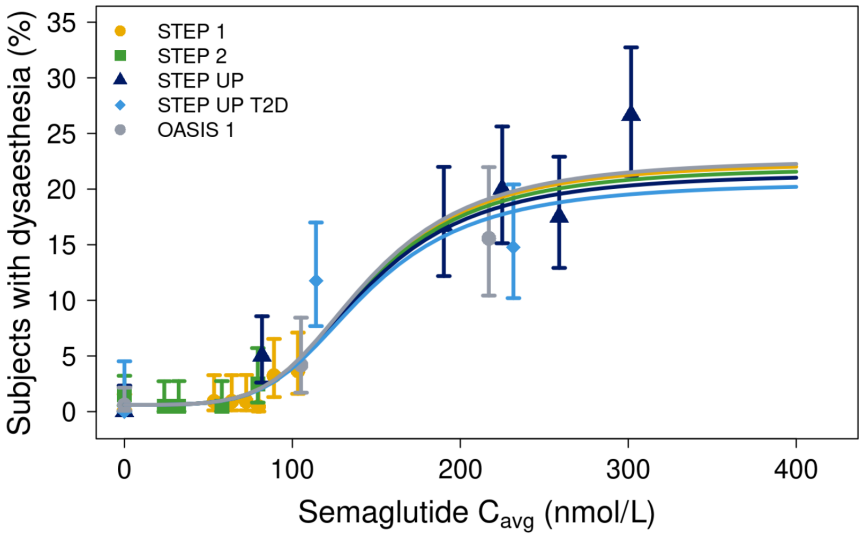


Figure 7: Proportion of participants reporting AEs related to dysaesthesia during the first 26 weeks of treatment versus semaglutide exposure

Assessor's comments

Looking at the overall weight loss in Figure 5, the 90% exposure range is visibly larger with the 7.2 mg dosing regimen compared to the 1 mg and 2.4 mg dosing regimens indicating the variability in exposure increased with increasing dose. The same variability is seen in all other figures included.

With the covariate-adjusted model-derived relations for the proportions of participants reaching the grouped weight loss goals (Figure 6), the 5% and 10% responders seem to match properly with the observations. For the 15%, 20% and 25% responders the plots are difficult to read because of the dense x-axis. Though, it is noteworthy that the model-derived relations seem to present an underprediction of the proportion of responders, especially in the 2.4 mg dosing regimen in STEP 1 trial and 7.2 mg dosing regimen in STEP UP trial. The lines seem to capture the median observations, so this misspecification mainly concerns the variability. A lower percentage of weight reduction is observed in STEP UP around 200 nmol/L compared to the weight reduction observed in Step 1 around 100 nmol/L despite the higher exposure. This issue is not pursued, as substantial weight loss is still observed also at this concentration.

It is agreed with the applicant that the increased occurrence of relevant adverse events (gastro-intestinal related, nausea or vomiting) between the 2.4 mg and 7.2 mg s.c. dosing regimens has a limited clinical impact. It is also agreed that semaglutide does not appear to have an effect on QTc interval at doses up to 7.2 mg. There is a clear relation noticeable for the increased occurrence of dysesthesia during the first 26 weeks of treatment with exposures > 100 nmol/L. Because the mechanisms of dysesthesia are not clear the long term use of high dose semaglutide injections is a potential serious issue (see section *8.3. Clinical Safety aspects – Discussion* for additional assessment and remaining questions).

Overall, the exposure-response model provided an adequate description of the exposure-response relationship.

2.4. Discussion

Effect of semaglutide 7.2 mg s.c. on the rate of gastric emptying

The applicant provided an paracetamol absorption study to assess gastric emptying, in line with a previous study conducted during the original MAA for Wegovy at a s.c. dose of 2.4 mg. In general, it is accepted that paracetamol absorption is a suitable surrogate to study (potential) PD/DDI effects on gastric emptying. It is agreed with the applicant that paracetamol PK profiles in study NN9932-4873 indicated no effect of Wegovy on paracetamol absorption. In this study, however, oral doses of 50 mg daily are administered, which is, according to the applicant, resulting in a similar C_{avg} exposure compared to s.c. 7.2. mg weekly. In theory, it could be accepted that this would make this study relevant also in the current type II variation.

However, the applicant provided PK data from two 50 mg studies in order to describe exposure (in Figure 2). Although it is agreed that this gives a more precise estimate on the expected C_{avg} when using the 50 mg dosing regimen, only in study NN9932-4873 gastric emptying has been studied. Therefore, only in this study an actual exposure-gastric emptying relationship has been evaluated. This is especially of importance as the C_{avg} for study NN9932-4873 is lower compared to the combined data from NN9932-4873 and NN9932-4737 (OASIS 1) (i.e. study NN9932-4873 geometric mean: 106 nmol/L, range: 27 nmol/L - 222 nmol/L, combined 50 mg oral geometric mean 128 nmol/L, range: 6 nmol/L - 442 nmol/L). Potential effect on gastric emptying will therefore be studied in a new paracetamol absorption study with adequate exposure levels. The applicant has committed to this study, which will be conducted post-approval (see section 14). In The applicant discussed the potential differences in the shape of the PK curves between 7.2 mg weekly s.c. administration and 50 mg daily oral intake and substantiated that this likely would not impact gastric emptying.

Population PK of semaglutide 7.2 mg s.c

The PK and PD properties of semaglutide has been characterized previously in a comprehensive clinical pharmacology programme.

The exposure levels achieved following the single injection of 7.2 mg was similar to the exposure levels achieved using three injections of 2.4 mg as the difference between the two delivery solutions was 1.15 (90% CI: 1.14-1.16). Thus the 90% CI did not exceed the bioequivalence limits [0.80;1.25].

The exposure levels following administration of s.c. 7.2 mg were within the exposure levels observed following administration of oral 50 mg. 99.7% and 100% of predicted C_{avg} levels following administration of 7.2 mg s.c. in STEP UP and STEP UP T2D, respectively, overlapped with the C_{avg} levels seen following administration of 50 mg oral in OASIS 1 and NN9932-4873. However, the overlap was mainly at the higher end of the exposure range, with the majority of C_{avg} levels in STEP UP and STEP UP T2D being above the C_{avg} geometric mean observed following administration of oral 50 mg. In addition, the data from study NN9932-4873 appeared lower than the combined/modelling data (see OC above).

Exposure-response of semaglutide 7.2 mg s.c

The population PK and exposure-response analysis supports that administration of 7.2 mg can lead to (slightly) increase weight loss compared to 2.4 mg with only a minor increase in GI AE, vomiting, nausea events. A lower percentage of weight reduction is observed in STEP UP around 200 nmol/L compared to the weight reduction observed in Step 1 around 100 nmol/L despite the higher exposure. This issue is not pursued, as substantial weight loss is still observed also at this concentration.

A higher proportion of participants with dysesthesia events was seen following administration of 7.2 mg compared to 2.4 mg. The body weight loss response was somewhat lower in a population with T2D.

3. Clinical Efficacy aspects

3.1. Methods – analysis of data submitted

Both STEP UP studies were randomised, double-blind, placebo-controlled, multi-national, multi-centre, three-armed, parallel-group studies consisting of a 1-week screening period, a 20-week dose escalation period, a 52-week maintenance period, and a 9-week follow-up period.

A 72-week treatment duration (20 week of dose escalation and 52 weeks on maintenance dose) was chosen to assess weight loss, safety and tolerability of semaglutide 7.2 mg versus semaglutide 2.4 mg once weekly and placebo in accordance with regulatory guidelines. The 9-week follow-up period is included to account for the exposure and long half-life of semaglutide.

The study population was chosen in accordance with regulatory guidelines to consist of adults with BMI ≥30.0 kg/m^2 with or without weight-related (except T2D) comorbidities (STEP UP) and adults living with obesity (BMI ≥30.0 kg/m) and T2D (STEP UP T2D).

Participants were randomised 5:1:1 (STEP UP) or 3:1:1 (STEP UP T2D) to receive either semaglutide 7.2 mg, semaglutide 2.4 mg, or placebo once-weekly, as an adjunct to reduced-calorie diet and increased physical activity. In STEP UP, a sub-population of 55 randomised participants had their body composition assessed by MRI at the beginning and at the end of the treatment to investigate the effect on body composition after 72 weeks of treatment with semaglutide.

Assessor's comments

STEP UP and STEP UP T2D were designed to evaluate the efficacy and safety of semaglutide 7.2 mg once weekly versus placebo once-weekly as an adjunct to reduced-calorie diet and increased physical activity in adults living with obesity (STEP UP) or obesity and T2D (STEP UP T2D). In addition, both trials also included a semaglutide 2.4 mg once weekly arm.

Both STEP UP studies were randomised, double-blind, placebo-controlled, multi-national, multi-centre, three-armed, parallel-group studies consisting of a 1-week screening period, a 20-week dose escalation period, a 52-week maintenance period, and a 9-week follow-up period.

The study population was chosen to consist of adults with BMI ≥30.0 kg/m2 with or without weight-related (except T2D) comorbidities (STEP UP) and adults living with obesity (BMI ≥30.0 kg/m) and T2D (STEP UP T2D). The BMI cut off value in the 2 submitted studies is different from that in the current indication. The current indication includes not only patients BMI ≥30.0 kg/m2, but also patients with BMI ≥27.0 kg/m2 with comorbidities. For the high dose of 7.2 mg, patients with BMI between 27 and 30 have not been investigated. These relatively low weight patients should not be treated with the high dose of 7.2 mg semaglutide. This should be clearly stated in the spc **(MO)**.

Participants were randomised 5:1:1 (STEP UP) or 3:1:1 (STEP UP T2D) to receive either semaglutide 7.2 mg, semaglutide 2.4 mg, or placebo once-weekly, as an adjunct to reduced-calorie diet and increased physical activity. In STEP UP, a sub-population of 55 randomised participants had their body composition assessed by MRI at the beginning and at the end of the treatment to investigate the effect on body composition.

Objectives and endpoints

The co-primary objectives for both the STEP UP and the STEP UP T2D study were to demonstrate superiority of semaglutide 7.2 mg once-weekly versus placebo as an adjunct to reduced-calorie diet and increased physical activity with respect to relative change in body weight and achieving body weight reduction of ≥ 5% after 72 weeks in the respective study populations.

The endpoints in STEP UP and STEP UP T2D that are summarised are listed in Table 4-1.

Table 3-1: Efficacy endpoints presented in addendum – STEP UP and STEP UP T2D

	STEP UP	STEP UP T2D
Change from baseline (week 0) to week 72	**Sema 7.2 mg vs Placebo**	**Sema 7.2 mg vs Placebo**
Body weight-related endpoints		
Change in body weight (%)	**P**	**P**
Change in body weight (kg)	S	S
Change in waist circumference (cm)	**C**	**C**
Change in body-mass index change (kg/m^2)	S	S
Total fat mass, lean body mass and visceral fat mass (%, L)[a]	S	-
Participants who achieve at week 72 (yes/no):		
≥5% body weight reduction from week 0	**P**	**P**
≥10% body weight reduction from week 0	**C**	**C**
≥15% body weight reduction from week 0	**C**	**C**
≥20% body weight reduction from week 0	**C**	**C**
≥25% body weight reduction from week 0	**C**	**-**
Achieving BMI <27.0 kg/m^2	E	E
Change in waist to height ratio	E	E
Achieving waist to height ratio <0.53	E	E
Glycaemic control-related endpoints		
Change in HbA_{1c} (%)	S	**C**
HbA_{1c} < 7.0 % (53 mmol/mol)	-	S
HbA_{1c} ≤ 6.5 % (48 mmol/mol)	-	S
Change in fasting plasma glucose (mg/dL)	S	S
Change in fasting serum insulin (ratio to baseline at week 72)	S	S
Change in glycaemic category (normo-glycaemia, pre-diabetes, T2D)	S	-
Cardiovascular risk-related endpoints		
Change in systolic and diastolic blood pressure (mmHg)	S	S
Lipids ratio to baseline at week 72	S	S
High-sensitivity C-reactive protein (hsCRP) ratio to baseline at week 72	S	S
Change in lipid-lowering treatment	S	E
Change in antihypertensive treatment	S	E
Participant-behaviour endpoints		
Control of Eating Questionnaire (CoEQ): Scores from the 4 domains and 19 individual items[b]	E	E
Three Factor Eating Questionnaire revised 18-items (TFEQ-R18): Scores from 18 items	E	E
Change in concomitant oral antidiabetic drug	-	E
Physical functioning		
Sit-to-stand test	E	E
Body weight-related endpoints	**Sema 7.2 mg vs Sema 2.4 mg**	**Sema 7.2 mg vs Sema 2.4 mg**
Body weight (%, kg)	**C**	-
≥20% body weight reduction (yes/no)	**C**	-
≥25% body weight reduction (yes/no)	**C**	-

[a]Only for the MRI group in STEP UP

[b]The 4 domains are: Craving control, Positive mood, Craving for Savoury and Craving for sweet.

Abbreviations: P: primary endpoint; C: confirmatory secondary endpoint; S: supportive secondary endpoint; E: exploratory endpoint

Assessor's comments

The co-primary objectives for both the STEP UP and the STEP UP T2D study were to demonstrate superiority of semaglutide 7.2 mg once-weekly versus placebo as an adjunct to reduced-calorie diet and increased physical activity with respect to relative change in body weight and achieving body weight reduction of ≥ 5% after 72 weeks in the respective study populations.

However, for a high new dose, a comparison with the older lower dose is considered more relevant.

Estimands and statistical considerations

Pre-specified estimands were used to address the study objectives. The primary estimand addresses the primary clinical question of interest which was: What is the treatment effect of semaglutide 7.2 mg once weekly versus placebo, as an adjunct to reduced-calorie diet and increased physical activity in adults with obesity (STEP UP) and in adults with obesity and T2D (STEP UP T2D), measured by relative change from baseline (week 0) to week 72 in body weight and ≥5% body weight reduction at week 72, regardless of discontinuation or dose reduction of randomised trial product, and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery).

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

Study population

Overall, the study populations in STEP UP and STEP UP T2D were comparable with regards to Key eligibility (inclusion and exclusion) criteria.

The eligibility criteria were selected to ensure a population with obesity considered appropriate for treatment with pharmacotherapy for weight management. Pharmacotherapy is normally an adjunct to dietary and lifestyle interventions and so it was ensured to select a population that had previously been unsuccessful trying to lose weight. Eligibility criteria were also selected to safeguard the participants which is in accordance with the Declaration of Helsinki.[3] In STEP UP T2D the selected range of HbA_{1c} of 7.0% to 10.0% was to ensure that the participants could tolerate a decrease in the HbA_{1c} level during the study. The rationale for the upper limit of HbA_{1c} was to ensure that the participants were not glycaemic unstable.

STEP UP (Study 4999)

The participants were adult males and females who met the following key inclusion criteria and none of the following key exclusion criteria.

Key inclusion criteria

- Male or female.
- Age above or equal to 18 years at the time of signing informed consent.
- BMI ≥30.0 kg/m^2.

- History of at least one self-reported unsuccessful dietary effort to lose body weight.

Key exclusion criteria

- HbA_{1c} ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening.
- History of type 1 or type 2 diabetes.
- Treatment with glucose-lowering agent(s) within 90 days before screening.
- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records.
- Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

STEP UP T2D (study 7545)

The participants were adult males and females who meet the following key inclusion criteria and none of the following key exclusion criteria.

Key inclusion criteria

- Male or female.
- Age above or equal to 18 years at the time of signing informed consent.
- BMI ≥30.0 kg/m^2.
- Diagnosed with T2D ≥180 days prior to the day of screening.
- History of at least one self-reported unsuccessful dietary effort to lose body weight.
- HbA_{1c} 7.0-10.0% (53-86 mmol/mol) (both inclusive) as measured by central laboratory at screening.

Key exclusion criteria

- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records.
- Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
- Renal impairment with estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2 (<45 mL/min/1.73 m^2 in participants treated with SGLT2i) according to CKD-EPI creatinine equation as defined by KDIGO 2012[4] by the central laboratory at screening.
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before screening or in the period between screening and randomisation. Pharmacological pupil-dilation was a requirement unless using a digital fundus photography camera specified for non-dilated examination.

Assessor's comments

Overall, the study populations in STEP UP and STEP UP T2D were comparable with regards to Key eligibility (inclusion and exclusion) criteria.

The eligibility criteria were selected to ensure a population with obesity considered appropriate for treatment with pharmacotherapy for weight management. In STEP UP T2D the selected range of HbA1c of 7.0% to 10.0% was to ensure that the participants could tolerate a decrease in the HbA1c level during the study. The rationale for the upper limit of HbA1c was to ensure that the participants were not glycaemic unstable. In STEP UP, only patients with an HbA1c <6.5% were included.

Dosing

A fixed-dose escalation regimen was followed, with dose escalation every 4 weeks until the target dose was reached. In addition, all participants received diet and exercise counselling by a dietician or similar qualified healthcare professional. Participants started with a onceweekly dose of 0.25 mg and increased the dose every 4 weeks (to 0.5, 1.0, 1.7, 2.4 mg/week). After 20 weeks of treatment, the participants started on their respective maintenance doses of 7.2 mg/week, 2.4 mg/week, or placebo. If a participant did not tolerate the current dose, delaying the dose escalation or reducing the dose was allowed. This was allowed only if the participant would otherwise discontinue trial product completely and if considered safe to continue trial product, as per the investigator's discretion. It was recommended that the participant made at least one attempt to re-escalate. If reescalation was not tolerated participants were to stay at a lower dose level.

For the first part of the studies the maintenance dose of 7.2 mg was administered as 3 injections of semaglutide 2.4 mg. To maintain blinding 3 injections were also administered in the semaglutide 2.4 mg treatment group (1 injection of semaglutide 2.4 mg + 2 injections of placebo) and the placebo arm (3 injections of placebo). From December 2023 (approximately 47 weeks after the studies were initiated in January 2023) all maintenance doses were administered as a single dose of either semaglutide 7.2 mg (using the 7.2 mg semaglutide drug_device combination product).

Assessor's comments

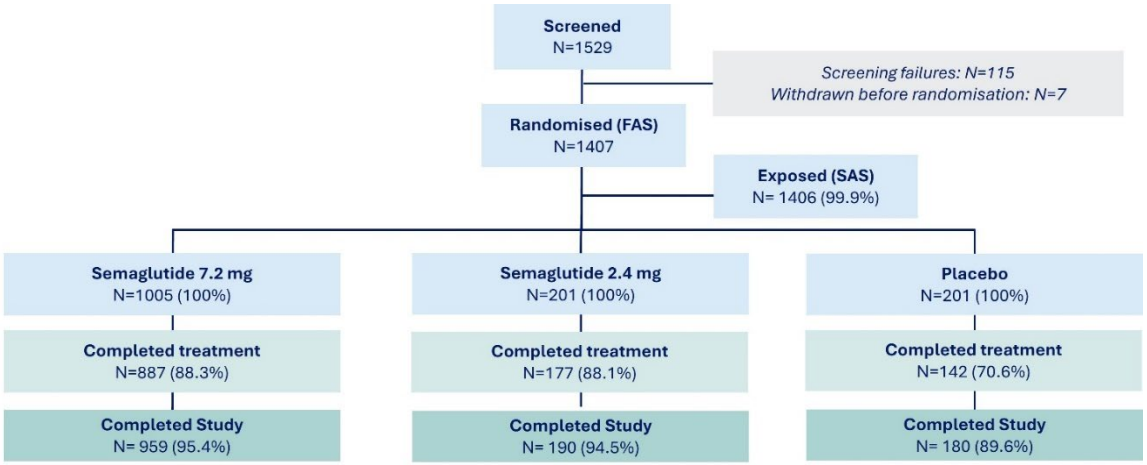
A fixed-dose escalation regimen was followed, with dose escalation every 4 weeks until the target dose was reached. In addition, all participants received diet and exercise counselling by a dietician or similar qualified healthcare professional. Participants started with a once weekly dose of 0.25 mg and increased the dose every 4 weeks (to 0.5, 1.0, 1.7, 2.4 mg/week). After 20 weeks of treatment, the participants started on their respective maintenance doses of 7.2 mg/week, 2.4 mg/week, or placebo.

Participant disposition and demographics

STEP UP (Study 4999)

Of the 1407 randomised participants 1406 were exposed to trial product and 1329 (94.5%) completed the study. Of the randomised participants 1206 (85.7%) completed treatment while 200 (14.2%) permanently discontinued treatment. A summary of participant disposition is provided in Figure 7.

Fifty-five participants were included in the MRI subpopulation, of which, 52 participants completed the study, and 3 participants withdrew from the study. Ten (18.2%) participants in the MRI subpopulation permanently discontinued trial product. The primary reason was adverse events (3 participants; 5.5%).



Abbreviations: %: proportion of participants of full analysis set, FAS: full analysis set, SAS: safety analysis set, MRI: : magnetic resonance imaging

Figure 78: Participant disposition study 4999

Table 5 Demographics and baseline characteristics - summary - full analysis set

+ Add image

	Sema 7.2 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of participants	1005	201	201	1407
Age (years)				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
18-<65	932 (92.7)	188 (93.5)	189 (94.0)	1309 (93.0)
65-<75	69 (6.9)	13 (6.5)	10 (5.0)	92 (6.5)
75-<85	4 (0.4)	0	2 (1.0)	6 (0.4)
>=85	0	0	0	0
Sex				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
Female	753 (74.9)	137 (68.2)	147 (73.1)	1037 (73.7)
Male	252 (25.1)	64 (31.8)	54 (26.9)	370 (26.3)
Country of residence				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
Bulgaria	89 (8.9)	13 (6.5)	16 (8.0)	118 (8.4)
Canada	46 (4.6)	11 (5.5)	11 (5.5)	68 (4.8)
Germany	100 (10.0)	16 (8.0)	23 (11.4)	139 (9.9)
Greece	127 (12.6)	24 (11.9)	22 (10.9)	173 (12.3)
Hungary	61 (6.1)	19 (9.5)	13 (6.5)	93 (6.6)
Norway	33 (3.3)	10 (5.0)	7 (3.5)	50 (3.6)
Poland	88 (8.8)	15 (7.5)	19 (9.5)	122 (8.7)
Portugal	26 (2.6)	5 (2.5)	3 (1.5)	34 (2.4)
Slovakia	72 (7.2)	16 (8.0)	12 (6.0)	100 (7.1)
South Africa	80 (8.0)	8 (4.0)	18 (9.0)	106 (7.5)
United States	283 (28.2)	64 (31.8)	57 (28.4)	404 (28.7)
Ethnic origin				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
Hispanic or Latino	44 (4.4)	12 (6.0)	7 (3.5)	63 (4.5)
Not Hispanic or Latino	961 (95.6)	189 (94.0)	194 (96.5)	1344 (95.5)

N: Number of participants, %: Percentages are based on number of participants, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, RI: Renal impairment. Glycaemic category evaluated at baseline by the investigator based on available relevant information.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

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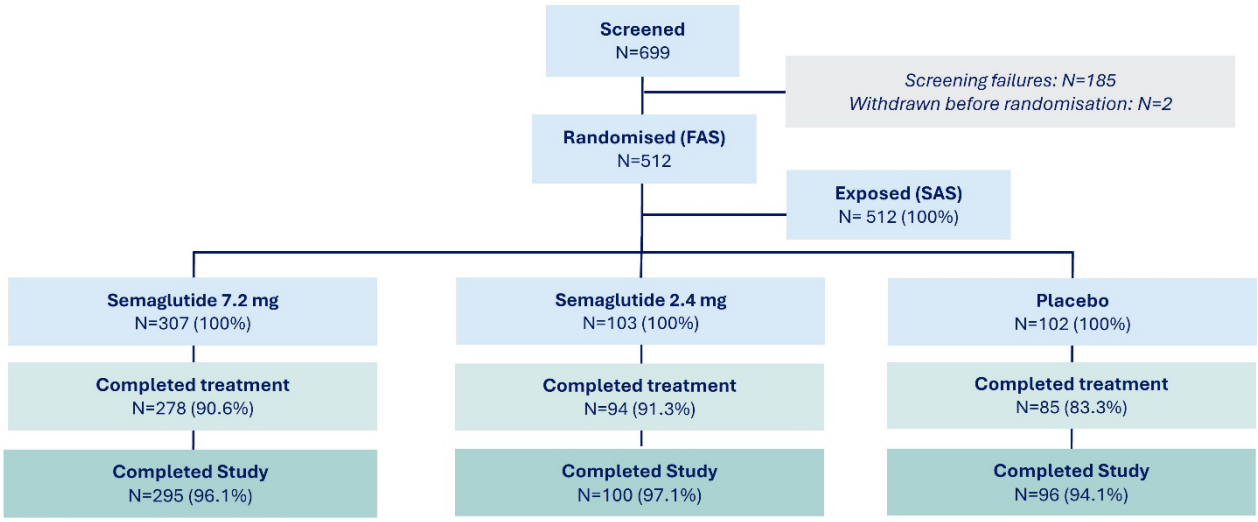
	Sema 7.2 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Race				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
American Indian or Alaska Native	0	0	3 (1.5)	3 (0.2)
Asian	52 (5.2)	4 (2.0)	7 (3.5)	63 (4.5)
Black or African American	82 (8.2)	17 (8.5)	22 (10.9)	121 (8.6)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	2 (1.0)	0	3 (0.2)
White	859 (85.5)	176 (87.6)	168 (83.6)	1203 (85.5)
Multiple	9 (0.9)	1 (0.5)	1 (0.5)	11 (0.8)
Missing	2 (0.2)	1 (0.5)	0	3 (0.2)
BMI (kg/m^2)				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
<30	4 (0.4)	1 (0.5)	0	5 (0.4)
30-<35	280 (27.9)	51 (25.4)	56 (27.9)	387 (27.5)
35-<40	305 (30.3)	58 (28.9)	60 (29.9)	423 (30.1)
>=40	416 (41.4)	91 (45.3)	85 (42.3)	592 (42.1)
Smoking habits				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
Never Smoked	620 (61.7)	126 (62.7)	115 (57.2)	861 (61.2)
Previous Smoker	234 (23.3)	42 (20.9)	52 (25.9)	328 (23.3)
Current Smoker	151 (15.0)	33 (16.4)	34 (16.9)	218 (15.5)
Renal function, eGFR (mL/min/1.73 m^2)				
N	1005 (100)	201 (100)	201 (100)	1407 (100)
Normal (>=90)	676 (67.3)	142 (70.6)	140 (69.7)	958 (68.1)
Mild RI (60-<90)	302 (30.0)	57 (28.4)	55 (27.4)	414 (29.4)
Moderate RI (30-<60)	26 (2.6)	2 (1.0)	6 (3.0)	34 (2.4)
Severe RI (15-<30)	1 (<0.1)	0	0	1 (<0.1)
End-stage renal disease (<15)	0	0	0	0
Glycaemic status at baseline				
N	1005 (100)	201 (100)	200 (99.5)	1406 (99.9)
Normo-glycaemia	627 (62.4)	132 (65.7)	118 (58.7)	877 (62.3)
Pre-diabetes	378 (37.6)	69 (34.3)	82 (40.8)	529 (37.6)

N: Number of participants, %: Percentages are based on number of participants, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, RI: Renal impairment. Glycaemic category evaluated at baseline by the investigator based on available relevant information.

STEP UP T2D (study 7545)

Of the 512 randomised participants all 512 were exposed to trial product and 491 (95.9%) completed the study. Of the randomised participants 457 (89.3%) completed treatment while 55 (10.7%) permanently discontinued treatment. A summary of participant disposition is provided in Figure 8.



%: proportion of participants of full analysis set, FAS: full analysis set, SAS: safety analysis set

Figure 89: Participant disposition study 7545

Table 7 - Demographics and baseline characteristics - summary - full analysis set

	Sema 7.2 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of participants	307	103	102	512
Age (years)				
N	307 (100)	103 (100)	102 (100)	512 (100)
18-<65	237 (77.2)	73 (70.9)	81 (79.4)	391 (76.4)
65-<75	63 (20.5)	26 (25.2)	21 (20.6)	110 (21.5)
75-<85	7 (2.3)	4 (3.9)	0	11 (2.1)
>=85	0	0	0	0
Sex				
N	307 (100)	103 (100)	102 (100)	512 (100)
Female	166 (54.1)	47 (45.6)	52 (51.0)	265 (51.8)
Male	141 (45.9)	56 (54.4)	50 (49.0)	247 (48.2)
Country of residence				
N	307 (100)	103 (100)	102 (100)	512 (100)
Bulgaria	44 (14.3)	18 (17.5)	18 (17.6)	80 (15.6)
Canada	19 (6.2)	5 (4.9)	8 (7.8)	32 (6.3)
Hungary	41 (13.4)	22 (21.4)	13 (12.7)	76 (14.8)
Poland	50 (16.3)	16 (15.5)	8 (7.8)	74 (14.5)
Portugal	5 (1.6)	3 (2.9)	2 (2.0)	10 (2.0)
Slovakia	40 (13.0)	7 (6.8)	14 (13.7)	61 (11.9)
South Africa	32 (10.4)	9 (8.7)	13 (12.7)	54 (10.5)
United States	76 (24.8)	23 (22.3)	26 (25.5)	125 (24.4)
Ethnic origin				
N	307 (100)	103 (100)	102 (100)	512 (100)
Hispanic or Latino	16 (5.2)	5 (4.9)	8 (7.8)	29 (5.7)
Not Hispanic or Latino	291 (94.8)	98 (95.1)	94 (92.2)	483 (94.3)

N: Number of participants, %: Percentages are based on number of participants, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, RI: Renal impairment.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

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	Sema 7.2 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Race				
N	307 (100)	103 (100)	102 (100)	512 (100)
American Indian or Alaska Native	1 (0.3)	0	0	1 (0.2)
Asian	19 (6.2)	7 (6.8)	6 (5.9)	32 (6.3)
Black or African American	22 (7.2)	13 (12.6)	9 (8.8)	44 (8.6)
Multiple	2 (0.7)	0	0	2 (0.4)
Native Hawaiian or Other Pacific Islander	5 (1.6)	0	0	5 (1.0)
White	258 (84.0)	83 (80.6)	87 (85.3)	428 (83.6)
Missing	0	0	0	0
BMI (kg/m^2)				
N	307 (100)	103 (100)	102 (100)	512 (100)
<30	1 (0.3)	0	2 (2.0)	3 (0.6)
30-<35	109 (35.5)	40 (38.8)	32 (31.4)	181 (35.4)
35-<40	90 (29.3)	34 (33.0)	33 (32.4)	157 (30.7)
>=40	107 (34.9)	29 (28.2)	35 (34.3)	171 (33.4)
Smoking habits				
N	307 (100)	103 (100)	102 (100)	512 (100)
Never Smoked	182 (59.3)	54 (52.4)	50 (49.0)	286 (55.9)
Previous Smoker	87 (28.3)	29 (28.2)	32 (31.4)	148 (28.9)
Current Smoker	38 (12.4)	20 (19.4)	20 (19.6)	78 (15.2)
Renal function, eGFR (mL/min/1.73 m^2)				
N	307 (100)	103 (100)	102 (100)	512 (100)
Normal (>=90)	202 (65.8)	63 (61.2)	69 (67.6)	334 (65.2)
Mild RI (60-<90)	91 (29.6)	34 (33.0)	25 (24.5)	150 (29.3)
Moderate RI (30-<60)	14 (4.6)	6 (5.8)	8 (7.8)	28 (5.5)
Severe RI (15-<30)	0	0	0	0
End-stage renal disease (<15)	0	0	0	0

N: Number of participants, %: Percentages are based on number of participants, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, RI: Renal impairment.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 8 - Demographics and baseline characteristics - descriptive statistics - full analysis set

	Sema 7.2 mg	Sema 2.4 mg	Placebo	Total
Number of participants	307	103	102	512
Age (years)				
N	307	103	102	512
Mean (SD)	57 (10)	58 (10)	55 (10)	56 (10)
Median	57	58	56	57
P5 ; P95	41 ; 73	39 ; 72	39 ; 69	40 ; 72
Min ; Max	19 ; 79	30 ; 76	30 ; 73	19 ; 79
Height (m)				
N	307	103	102	512
Mean (SD)	1.69 (0.10)	1.68 (0.10)	1.70 (0.11)	1.69 (0.10)
Median	1.68	1.68	1.68	1.68
P5 ; P95	1.53 ; 1.85	1.52 ; 1.83	1.55 ; 1.88	1.53 ; 1.85
Min ; Max	1.45 ; 1.96	1.47 ; 1.93	1.47 ; 1.93	1.45 ; 1.96
Body weight (kg)				
N	307	103	102	512
Mean (SD)	110.5 (22.9)	107.0 (23.0)	112.1 (22.9)	110.1 (22.9)
Median	106.8	105.2	109.9	106.8
P5 ; P95	81.0 ; 150.7	79.2 ; 138.4	80.3 ; 157.1	79.6 ; 150.6
Min ; Max	71.5 ; 199.7	71.5 ; 231.2	74.2 ; 185.8	71.5 ; 231.2
BMI (kg/m^2)				
N	307	103	102	512
Mean (SD)	38.7 (7.1)	37.7 (6.4)	39.0 (7.6)	38.6 (7.1)
Median	36.5	36.7	37.1	36.7
P5 ; P95	30.9 ; 52.1	30.7 ; 47.1	30.9 ; 51.9	30.8 ; 51.7
Min ; Max	29.8 ; 74.6	30.2 ; 67.6	29.4 ; 69.9	29.4 ; 74.6
Waist circumference (cm)				
N	307	103	102	512
Mean (SD)	121.8 (15.2)	119.1 (13.2)	123.9 (15.5)	121.7 (14.9)
Median	120.0	118.0	120.0	120.0
P5 ; P95	101.0 ; 149.0	101.0 ; 139.0	101.0 ; 158.0	101.0 ; 148.0
Min ; Max	88.0 ; 183.0	91.0 ; 174.0	95.0 ; 168.0	88.0 ; 183.0
HbA1c (%)				
N	307	103	102	512
Mean (SD)	8.0 (0.8)	8.1 (0.9)	8.2 (0.9)	8.1 (0.9)
Median	7.9	8.0	8.1	7.9
P5 ; P95	7.0 ; 9.6	7.0 ; 9.6	6.9 ; 9.8	7.0 ; 9.6
Min ; Max	6.1 ; 10.4	6.3 ; 10.2	6.6 ; 10.3	6.1 ; 10.4
HbA1c (mmol/mol)				
N	307	103	102	512
Mean (SD)	64.4 (9.2)	65.0 (9.4)	65.9 (9.8)	64.8 (9.3)
Median	62.8	63.9	65.0	62.8
P5 ; P95	53.0 ; 81.4	53.0 ; 81.4	51.9 ; 83.6	53.0 ; 81.4
Min ; Max	43.2 ; 90.2	45.4 ; 88.0	48.6 ; 89.1	43.2 ; 90.2

N: Number of participants, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile. CV: Coefficient of variation
BMI: Body mass index, eGFR: Estimated glomerular filtration rate, HbA1c: Haemoglobin A1c.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

	Sema 7.2 mg	Sema 2.4 mg	Placebo	Total
Fasting plasma glucose (mg/dL)				
N	302	101	101	504
Mean (SD)	173.1 (42.9)	175.4 (43.0)	177.4 (54.4)	174.4 (45.4)
Median	170.2	172.3	171.7	170.9
P5 ; P95	115.9 ; 252.1	115.5 ; 251.6	104.7 ; 272.6	112.6 ; 259.1
Min ; Max	72.8 ; 328.0	93.2 ; 289.9	98.0 ; 404.9	72.8 ; 404.9
Fasting plasma glucose (mmol/L)				
N	302	101	101	504
Mean (SD)	9.6 (2.4)	9.7 (2.4)	9.8 (3.0)	9.7 (2.5)
Median	9.4	9.6	9.5	9.5
P5 ; P95	6.4 ; 14.0	6.4 ; 14.0	5.8 ; 15.1	6.3 ; 14.4
Min ; Max	4.0 ; 18.2	5.2 ; 16.1	5.4 ; 22.5	4.0 ; 22.5
eGFR (mL/min/1.73m^2)				
N	307	103	102	512
Geometric mean (CV)	92.47 (21.3)	91.46 (22.3)	92.59 (25.6)	92.29 (22.4)
Median	95.99	95.79	100.23	96.82
P5 ; P95	61.58 ; 120.66	59.23 ; 118.69	56.71 ; 120.58	58.45 ; 120.58
Min ; Max	31.43 ; 146.42	43.34 ; 135.22	37.95 ; 137.38	31.43 ; 146.42
Duration of diabetes (years)				
N	307	103	102	512
Mean (SD)	8.4 (6.5)	8.4 (6.5)	8.2 (5.9)	8.4 (6.4)
Median	7.2	7.0	7.3	7.2
P5 ; P95	0.9 ; 21.2	0.8 ; 21.3	1.0 ; 20.4	0.9 ; 21.3
Min ; Max	0.6 ; 41.3	0.6 ; 30.2	0.6 ; 27.3	0.6 ; 41.3

N: Number of participants, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile. CV: Coefficient of variation
BMI: Body mass index, eGFR: Estimated glomerular filtration rate, HbA1c: Haemoglobin A1c.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

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In both studies, ~60% of the populations were from countries within the EU.

Assessor's comments

Of the 1407 randomised participants 1406 were exposed to trial product and 1329 (94.5%) completed the STEP UP study. Of the randomised participants 1206 (85.7%) completed treatment while 200 (14.2%) permanently discontinued treatment.

Fifty-five participants were included in the MRI subpopulation, of which, 52 participants completed the study, and 3 participants withdrew from the study. Ten (18.2%) participants in the MRI subpopulation permanently discontinued trial product. The primary reason was adverse events (3 participants; 5.5%).

Of the 512 randomised participants all 512 were exposed to trial product and 491 (95.9%) completed the STEP UP T2D study. Of the randomised participants 457 (89.3%) completed treatment while 55 (10.7%) permanently discontinued treatment.

For the full study population from both studies, the median age was 48 years (range: 18 to 80 years). The majority of participants were female (73.7%) and of white race (85.5%). The mean (SD) body weight at baseline was 113.0 (24.1) kg and the mean (SD) BMI 39.9 (7.1) mg/kg2. There were 67% of the participants who had at least one weight-related comorbidity. Hypertension was the most frequently reported comorbidity (41.6%) followed by dyslipidaemia (27.9%).

3.2. Results

Body weight – change from baseline

Superiority of semaglutide 7.2 mg versus placebo was confirmed in both studies for the primary endpoint change from baseline (week 0) to week 72 in body weight (%) (Table 2-1 and Table 2-2).

The baseline mean (SD) body weight (kg) was comparable across treatment groups in each study, with no significant differences noted in baseline mean (SD) body weight (kg) between the studies.

- In STEP UP, at baseline (week 0), the observed mean (SD) body weight was:

112.4 (23.8) kg for participants in the semaglutide 7.2 mg treatment group
116.5 (26.2) kg for participants in the semaglutide 2.4 mg treatment group
112.4 (22.8) kg for participants in the placebo treatment group

- In STEP UP T2D, at baseline (week 0), the observed mean (SD) body weight was:

110.5 (22.9) kg for participants in the semaglutide 7.2 mg treatment group
107.0 (23.0) kg for participants in the semaglutide 2.4 mg treatment group
112.1 (22.9) kg for participants in the placebo treatment group

Across the studies, both semaglutide treatment groups experienced a significantly greater weight loss compared with the placebo treatment group; however, the reduction was more pronounced in participants receiving semaglutide 7.2 mg. The effect on relative change in body weight of semaglutide 7.2 mg versus semaglutide 2.4 mg was superior.

Mean body weight (%) change from baseline by week is presented in Figure 3-1 and Figure 3-2, respectively for studies STEP UP and STEP UP T2D.

- In STEP UP, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was :

-18.71% for participants in the semaglutide 7.2 mg treatment group
-15.61% for participants in the semaglutide 2.4 mg treatment group
-3.90% for participants in the placebo treatment group

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: -14.81%-points $[-16.21; -13.41]_{95\% CI}$; p-value <0.0001 (Figure 3-3). The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: -3.10%-points $[-4.66; -1.55]_{95\% CI}$; p-value <0.0001.

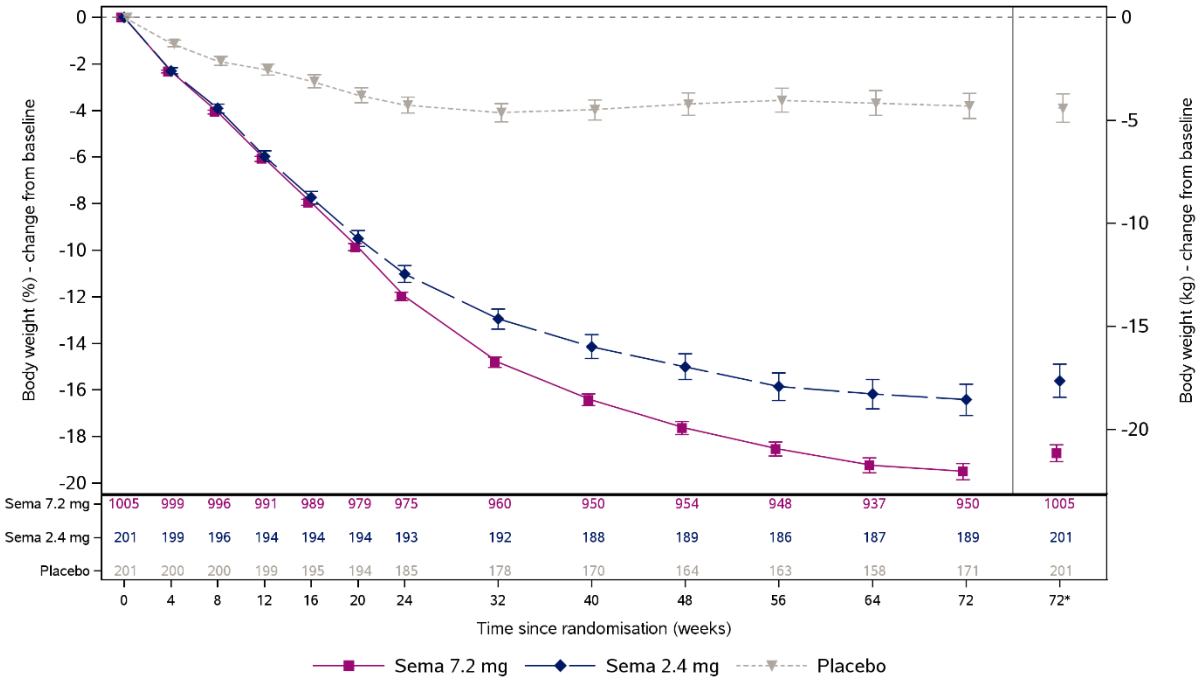
- In STEP UP T2D, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was:

-13.18% for participants in the semaglutide 7.2 mg treatment group
-10.36% for participants in the semaglutide 2.4 mg treatment group
-3.86% for participants in the placebo treatment group

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: -9.33%-points $[-10.95; -7.71]_{95\% CI}$; p-value <0.0001. The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg for relative change in body weight from baseline (week 0) to end of treatment (week 72) was only: -2.80% points

The magnitude of the weight loss in participants with T2D (STEP UP T2D) was smaller than in participants without T2D (STEP UP), an observation that has been well documented in previous weight management studies with semaglutide.

Figure 3-1 Body weight (%, kg) change from baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP)



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are participants contributing to the mean.

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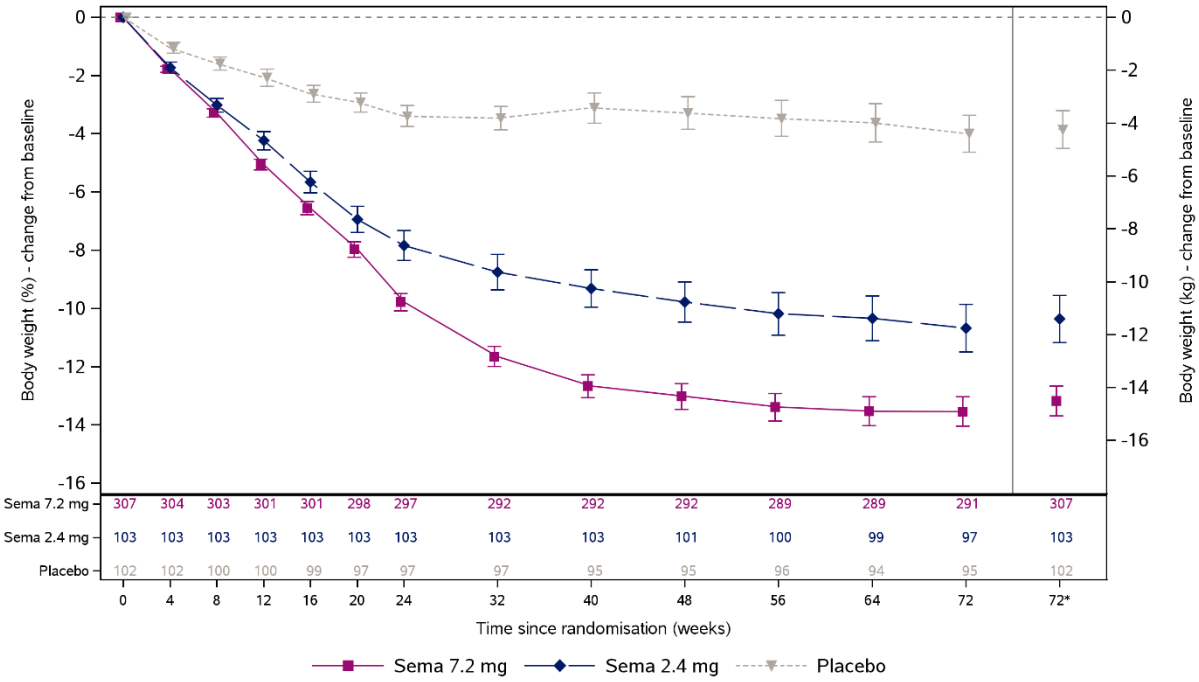
Figure 3-10 Body weight (%, kg) change from baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP T2D)



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are participants contributing to the mean.

nn9536/nn9536-7545/csr_20250526_er
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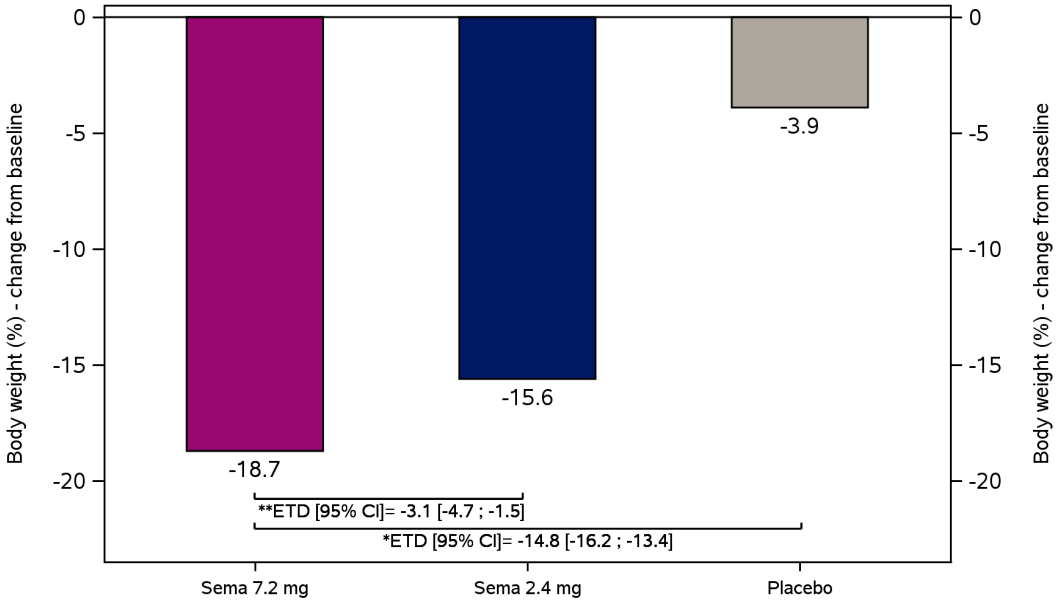
Figure 3-11 Body weight (%) change from baseline to week 72 - bar plot - treatment policy strategy - full analysis set (STEP UP)



ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment difference and corresponding confidence interval are from the primary analysis(*) and confirmatory secondary analysis(**).

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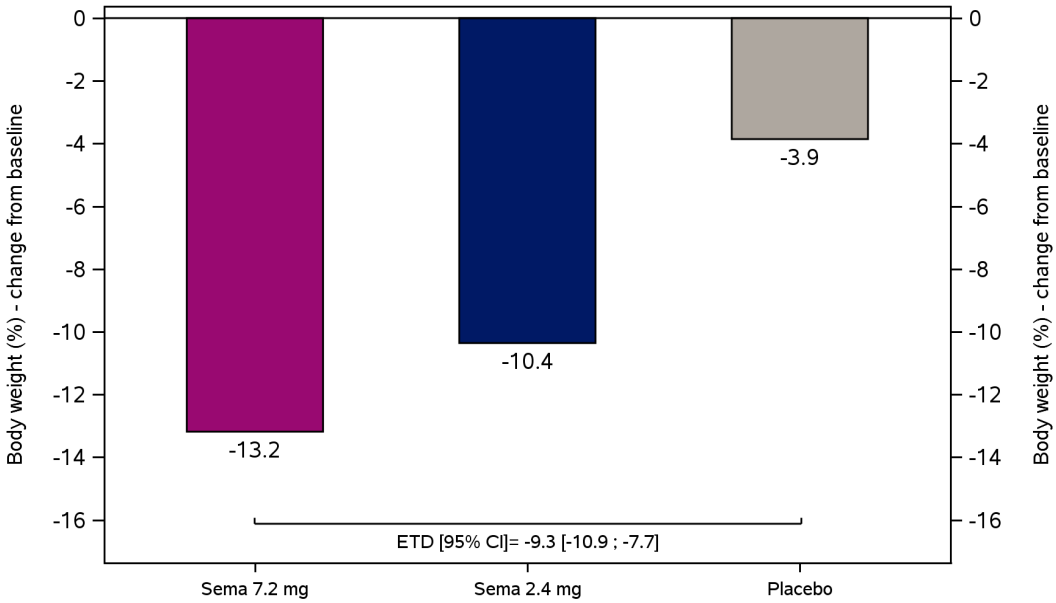
Figure 3-12 Body weight (%) change from baseline to week 72 - bar plot - treatment policy strategy - full analysis set (STEP UP T2D)



ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment difference and corresponding confidence interval are from the primary analysis(*).

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An ANCOVA - J2R-MI sensitivity analysis supported the robustness of the conclusions for the superiority of semaglutide 7.2 mg in both studies (Table 3-4 and Table 3-5).

The sensitivity analysis of the imputed data (TP_MI) for semaglutide 7.2 mg demonstrated a definitive tipping point that confirms its superiority over placebo in both studies (Figure 3-5).

Assessor's comments

In STEP UP, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was :

-18.71% for participants in the semaglutide 7.2 mg treatment group

-15.61% for participants in the semaglutide 2.4 mg treatment group

-3.90% for participants in the placebo treatment group

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: -14.81% points [16.21; -13.41]95% CI; p-value <0.0001 (Figure 3 3). The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg for relative change in body weight from baseline (week 0) to end of treatment (week 72) was only: -3.10% points [4.66; 1.55]95% CI; p-value <0.0001. The effects of the 2.4 mg and the 7.2 mg dose on body weight are clinically relevant. However, the difference between the 2.4 and 7.2 mg is small and of doubtful clinical relevance (3.1% points body weight).

In STEP UP T2D, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was:

-13.18% for participants in the semaglutide 7.2 mg treatment group

-10.36% for participants in the semaglutide 2.4 mg treatment group

-3.86% for participants in the placebo treatment group

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: 9.33%points [-10.95; -7.71]$_{95\% CI}$; p-value <0.0001. The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg for relative change in body weight from baseline (week 0) to end of treatment (week 72) was only: -2.80% points. The effects of the 2.4 mg and the 7.2 mg dose on body weight are clinically relevant. However, the difference between the 2.4 and 7.2 mg is small and of doubtful clinical relevance (2.8% points body weight).

The magnitude of the weight loss in participants with T2D (STEP UP T2D) was smaller than in participants without T2D (STEP UP), an observation that has been well documented in previous weight management studies with semaglutide.

Body weight – categorical response

Superiority of semaglutide 7.2 mg over placebo was demonstrated for the primary endpoint of proportion of participants who achieve ≥5% weight loss from baseline to week 72 in both studies (Table 2-1 and Table 2-2). The proportion of participants achieving at least 5% baseline body weight loss at week 72 is presented in Figure 3-13 and Figure 3-14, respectively, for STEP UP and STEP UP T2D.

In STEP UP, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was (Table 3-6):

88.47% of participants in the semaglutide 7.2 mg treatment group

86.61% of participants in the semaglutide 2.4 mg treatment group

38.83% of participants in the placebo treatment group

For the treatment policy strategy estimand, the estimated OR between semaglutide 7.2 mg and placebo for ≥5% body weight reduction from baseline (week 0) to end of treatment (week 72) was: 12.10 [8.32; 17.61]$_{95\% CI}$; p-value <0.0001 (Table 3-6)

For the hypothetical strategy estimand, the estimated OR between semaglutide 7.2 mg and placebo for ≥5% body weight reduction from baseline (week 0) to end of treatment (week 72) was: 37.89 [25.37; 56.60]$_{95\% CI}$; p-value <0.0001

- In STEP UP T2D, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was (Table 3-7):

84.23% of participants in the semaglutide 7.2 mg treatment group
73.93% of participants in the semaglutide 2.4 mg treatment group
34.76% of participants in the placebo treatment group

For the treatment policy strategy estimand, the estimated OR between semaglutide 7.2 mg and placebo for ≥5% body weight reduction from baseline (week 0) to end of treatment (week 72) was: 10.03 [5.96; 16.87]$_{95\% CI}$; p-value <0.0001 (Table 3-7)

For the hypothetical strategy estimand, the estimated OR between semaglutide 7.2 mg and placebo for ≥5% body weight reduction from baseline (week 0) to end of treatment (week 72) was: 19.81 [11.34; 34.61]$_{95\% CI}$; p-value <0.0001

Figure 3-13 Proportion of participants achieving at least 5% baseline body weight loss at week 72 - bar plot - in-trial - full analysis set (STEP UP)

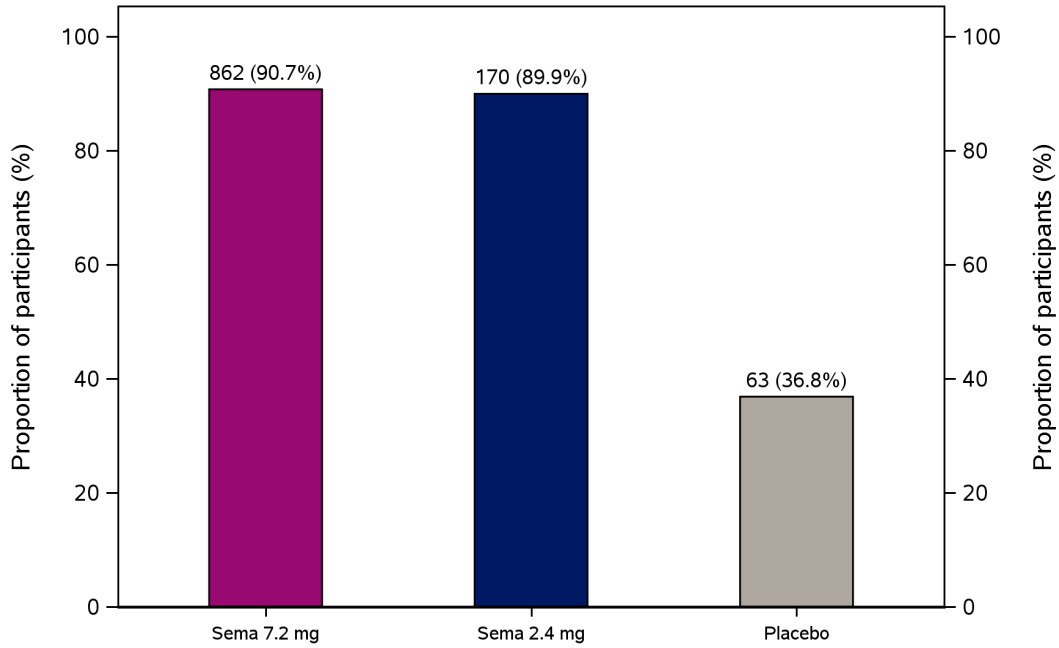


Table 3-4 Achieving at least 5% baseline body weight loss at week 72 - co-primary endpoint - treatment policy strategy - full analysis set (STEP UP)

	FAS	N	Estimate	95% CI	p-value
Body weight loss >= 5%					
LR marginal method - RD-MI					
Odds at Visit 22 (week 72)					
Sema 7.2 mg	1005	950	7.68		
Sema 2.4 mg	201	189	6.47		
Placebo	201	171	0.63		
Treatment odds ratio					
Sema 7.2 mg / Placebo			12.10	[8.32; 17.61]	<0.0001
Estimated percentage at Visit 22 (week 72)					
Sema 7.2 mg	1005	950	88.47		
Sema 2.4 mg	201	189	86.61		
Placebo	201	171	38.83		
Treatment difference (%-points)					
Sema 7.2 mg - Placebo			49.64	[41.89; 57.39]	

FAS: Full analysis set, N: Number of participants with an observation at the visit, CI: Confidence interval. p-value: Unadjusted two-sided p-value for test of no difference. Analysis of data from in-trial period.
LR: Week 72 responses were analysed using a binary regression model with randomized treatment as factor and baseline value as covariate. Estimation was done with marginal method where predicted probabilities of response for each participant on assigned treatment and respective counterfactual

probabilities - had they been assigned to one of the alternative treatments - were used to estimate odds, odds ratios, percentages, and treatment differences. RD-MI: Missing observations were multiple (x1000) imputed from retrieved participants of the same randomised treatment arm.

Figure 3-14 Proportion of participants achieving at least 5% baseline body weight loss at week 72 - bar plot - in-trial - full analysis set (STEP UP T2D)

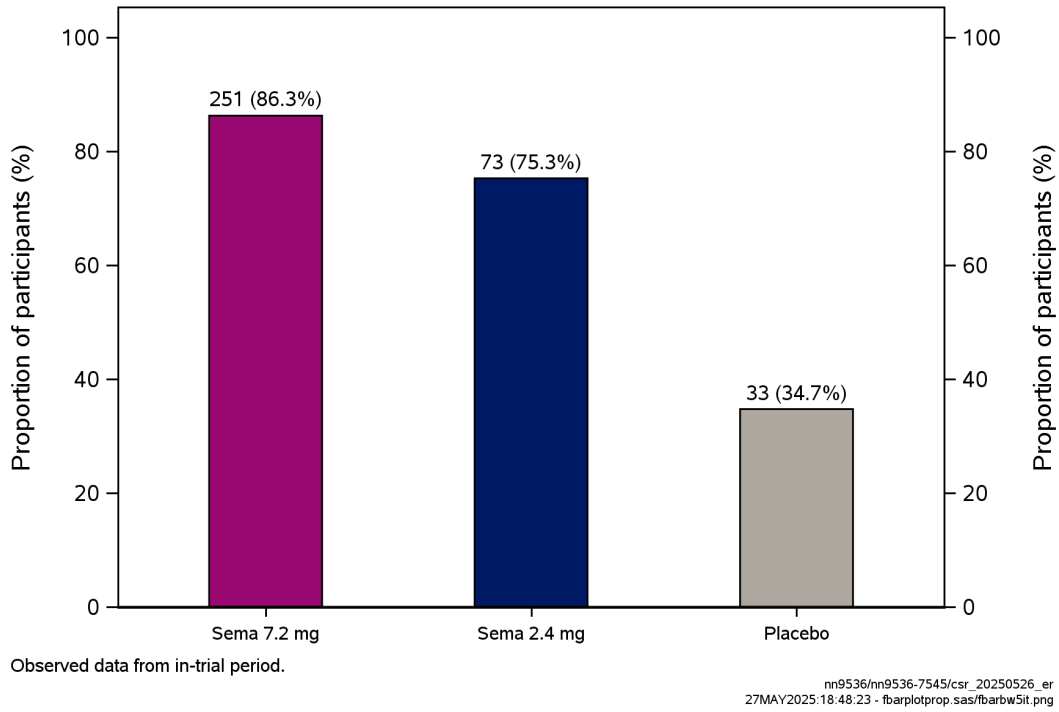


Table 3-5 Achieving at least 5% baseline body weight loss at week 72 - co-primary endpoint - treatment policy strategy - full analysis set (STEP UP T2D)

FAS	N	Estimate	95% CI	p-value
Body weight loss >= 5%				
LR marginal method - RD-MI				
Odds at Visit 22 (week 72)				
Sema 7.2 mg	307	291	5.34	
Sema 2.4 mg	103	97	2.84	
Placebo	102	95	0.53	
Treatment odds ratio				
Sema 7.2 mg / Placebo			10.03	[5.96; 16.87] <0.0001
Estimated percentage at Visit 22 (week 72)				
Sema 7.2 mg	307	291	84.23	
Sema 2.4 mg	103	97	73.93	
Placebo	102	95	34.76	
Treatment difference (%-points)				
Sema 7.2 mg - Placebo			49.46	[39.22; 59.71]

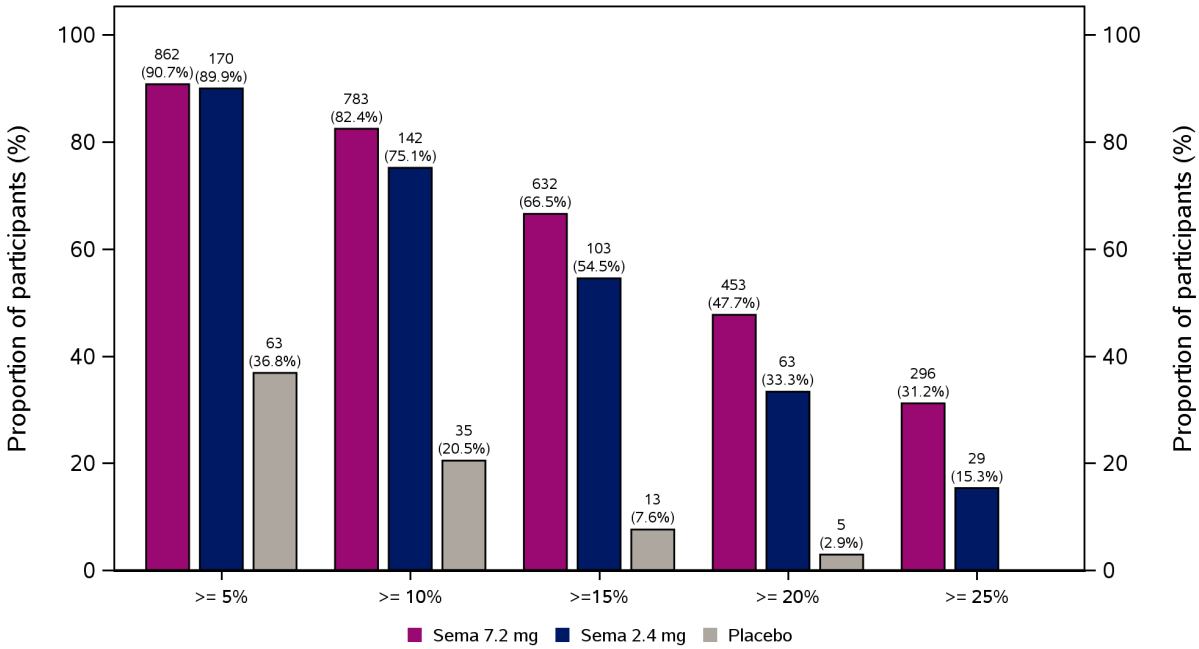
FAS: Full analysis set, N: Number of participants with an observation at the visit, CI: Confidence

interval. p-value: Unadjusted two-sided p-value for test of no difference. Analysis of data from in-trial period.
LR: Week 72 responses were analysed using a binary regression model with randomized treatment as factor and baseline value as covariate. Estimation was done with marginal method where predicted probabilities of response for each participant on assigned treatment and respective counterfactual probabilities - had they been assigned to one of the alternative treatments - were used to estimate odds, odds ratios, percentages, and treatment differences. RD-MI: Missing observations were multiple (x1000) imputed from retrieved participants regardless of randomised treatment arm.

In both studies, treatment with semaglutide 7.2 mg also resulted in greater proportions of participants achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to week 72 compared with semaglutide 2.4 mg and placebo (Figure 3-15 and Figure 3-16). These results were statistically significant for the confirmatory secondary endpoints regarding the proportion of participants achieving these levels of weight loss, as demonstrated by the ETDs (Table 3-8). Hence, superiority of semaglutide 7.2 mg to placebo and semaglutide 2.4 mg was demonstrated (Table 2-1 and Table 2-2).

Additionally, in STEP UP, proportions of participants achieving ≥25% body weight reduction from baseline to week 72 was greater in the semaglutide 7.2 mg treatment group as compared with placebo treatment group. In addition, semaglutide 7.2 mg proved to be superior to semaglutide 2.4 mg for confirmatory secondary endpoints on body weight loss of ≥25% (Table 38).

Figure 3-15 Proportion of participants achieving body weight loss response criteria since baseline at week 72 – bar plot – observed in-study data (STEP UP)



Observed data from in-trial period.

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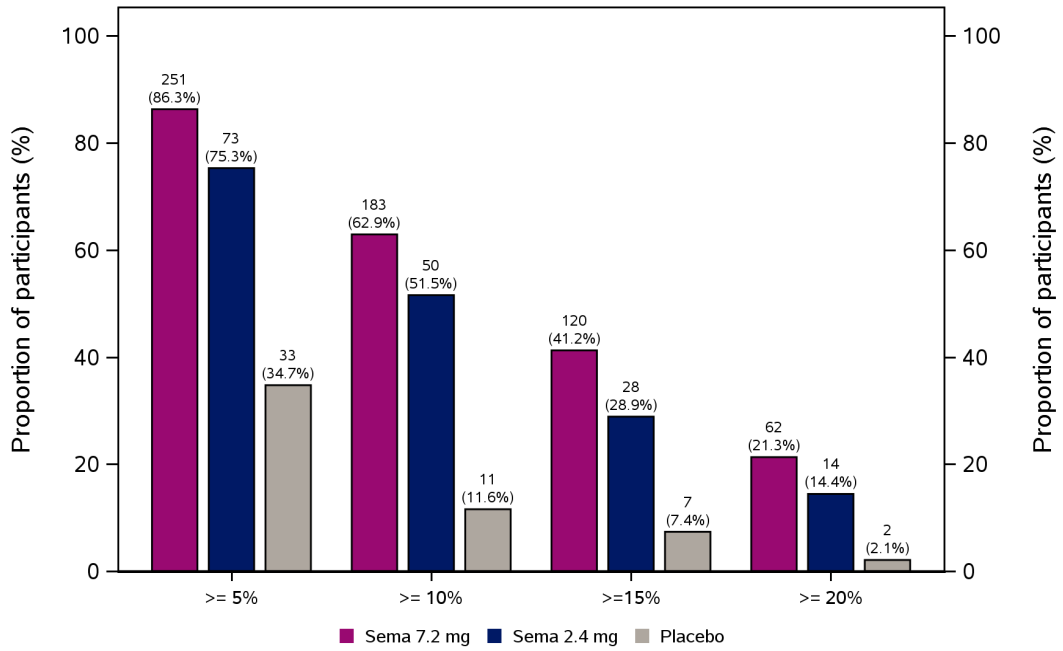
Figure 3-16 Proportion of participants achieving body weight loss response criteria since baseline at week 72 – bar plot – observed in-study data (STEP UP T2D)



Observed data from in-trial period.

nn9536/nn9536-7545/csr_20250526_er
27MAY2025:18:48:37 - fbarplotpropcat.sas/fbarbwcatit.png

Table 3-6 Body weight (%) change from baseline to week 72 - sensitivity analysis - treatment policy strategy - full analysis set (STEP UP)

	FAS	N	Estimate	95% CI	p-value
Body weight (%)					
ANCOVA - J2R-MI					
Change from baseline (%) to Visit 22 (week 72)					
Sema 7.2 mg		1005	950	-18.63	
Sema 2.4 mg		201	189	-15.76	
Placebo		201	171	-3.77	
Treatment difference (%-points)					
Primary comparison					
Sema 7.2 mg - Placebo				-14.86 [-16.14;-13.58]	<0.0001
Confirmatory secondary comparison					
Sema 7.2 mg - Sema 2.4 mg				-2.87 [-4.39; -1.35]	0.0002

FAS: Full analysis set, N: Number of participants with an observation at the visit, CI: Confidence interval. p-value: Unadjusted two-sided p-value for test of no difference.
Analysis of data from in-trial period. ANCOVA: Week 72 responses were analysed using an analysis of covariance model with randomised treatment as factor and baseline body weight as covariate. J2R-MI: Missing observations multiple (x1000) imputed from placebo participants based on a jump to reference approach.

Table 3-7 Body weight (%) change from baseline to week 72 - sensitivity analysis - treatment policy strategy - full analysis set (STEP UP T2D)

	FAS	N	Estimate	95% CI	p-value
Body weight (%)					
ANCOVA - J2R-MI					
Change from baseline (%) to Visit 22 (week 72)					
Sema 7.2 mg		307	291	-13.04	
Sema 2.4 mg		103	97	-10.29	
Placebo		102	95	-4.00	
Treatment difference (%-points)					
Sema 7.2 mg - Placebo				-9.04 [-10.64; -7.44]	<0.0001

FAS: Full analysis set, N: Number of participants with an observation at the visit, CI: Confidence interval. p-value: Unadjusted two-sided p-value for test of no difference.
Analysis of data from in-trial period. ANCOVA: Week 72 responses were analysed using an analysis of covariance model with randomised treatment as factor and baseline body weight as covariate. J2R-MI: Missing observations multiple (x1000) imputed from placebo participants based on a jump to reference approach.

In STEP UP, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was (Table 3 6):

- 88.47% of participants in the semaglutide 7.2 mg treatment group

- 86.61% of participants in the semaglutide 2.4 mg treatment group
- 38.83% of participants in the placebo treatment group

In STEP UP T2D, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was (Table 3 7):

- 84.23% of participants in the semaglutide 7.2 mg treatment group
- 73.93% of participants in the semaglutide 2.4 mg treatment group
- 34.76% of participants in the placebo treatment group

These data show that in both studies both doses of semaglutide resulted in more weight loss than placebo. The effects of semaglutide are clinically relevant. However, the differences between the 2 doses are small. In STEP UP only 1.9% more patients achieved the body weight reduction of ≥5% with the 7.2 mg dose compared to the 2.4 mg dose. In STEP UP T2D, only 10.3% more patients achieved this reduction with the higher dose.

Waist circumference

The baseline mean (SD) waist circumference (cm) was comparable across treatment groups in each study, with no significant differences noted between the studies.

Change from baseline (week 0) to week 72 in waist circumference (cm) was a confirmatory endpoint in both studies. Participants treated with semaglutide had a statistically significant decrease in waist circumference from baseline to end of treatment, whereas the placebo-treated participants only had a minor change in waist circumference.

- In STEP UP, at end of treatment (week 72), the estimated change from baseline (week 0) in waist circumference for the treatment policy strategy estimand was:

-17.50 cm for participants in the semaglutide 7.2 mg treatment group
-14.58 cm for participants in the semaglutide 2.4 mg treatment group
-5.85 cm for participants in the placebo treatment group

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for waist circumference from baseline (week 0) to end of treatment (week 72) was: -11.66 [-12.95; -10.37]$_{95\% CI}$; p-value <0.0001.

- In STEP UP T2D, at end of treatment (week 72), the estimated change from baseline (week 0) in waist circumference for the treatment policy strategy estimand was:

-12.31 cm for participants in the semaglutide 7.2 mg treatment group
-10.66 cm for participants in the semaglutide 2.4 mg treatment group
-5.77 cm for participants in the placebo treatment group

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for change in waist circumference from baseline (week 0) to end of treatment (week 72) was: -6.55 cm [-9.00; -4.09]$_{95\% CI}$; p-value <0.0001.

Assessor's comments

The ETD between semaglutide 7.2 mg versus placebo for waist circumference from baseline (week 0) to end of treatment (week 72) was: -11.66 in STEP UP and -6.55 cm in STEP T2D. However, the

decrease in waist with the 7.2 mg dose was only 2.9 cm (STEP UP) and 1.5 cm (STEP UP T2D) higher than with the 2.4 mg dose. The clinical relevance of these differences is doubtful.

Body mass index

The baseline mean (SD) BMI (kg/m^2) was comparable across treatment groups in each study, with no significant differences noted between the studies.

Reductions in BMI in the two studies showed a similar pattern too and reflected the weight loss. BMI change from baseline to week 72 for the treatment policy strategy estimand is shown in Table 3-9 and Table 3-10, respectively for STEP UP and STEP UP T2D.

Table 3-8 BMI change from baseline to week 72 - supportive secondary endpoint - treatment policy strategy - full analysis set (STEP UP)

	FAS	N	Estimate	95% CI	p-value
BMI (kg/m^2)					
ANCOVA - RD-MI					
Mean at Visit 22 (week 72)					
Sema 7.2 mg		1005	950	32.42	
Sema 2.4 mg		201	189	33.74	
Placebo		201	171	38.23	
Change from baseline to Visit 22 (week 72)					
Sema 7.2 mg		1005	950	-7.45	
Sema 2.4 mg		201	189	-6.13	
Placebo		201	171	-1.64	
Treatment difference					
Sema 7.2 mg - Placebo				-5.81	[-6.36; -5.26] <0.0001

FAS: Full analysis set, N: Number of participants with an observation at the visit, BMI: Body mass index. CI: Confidence interval. p-value: Unadjusted two-sided p-value for test of no difference. Analysis of data from in-trial period.
ANCOVA: Week 72 responses were analysed using an analysis of covariance model with randomised treatment as factor and baseline BMI as covariate. RD-MI: Missing observations were multiple (x1000) imputed from retrieved participants of the same randomised treatment arm.

Table 3-9 BMI change from baseline to week 72 - supportive secondary endpoint - treatment policy strategy - full analysis set (STEP UP T2D)

	FAS	N	Estimate	95% CI	p-value
BMI (kg/m^2)					
ANCOVA - RD-MI					
Mean at Visit 22 (week 72)					
Sema 7.2 mg		307	291	33.40	
Sema 2.4 mg		103	97	34.48	
Placebo		102	95	37.09	
Change from baseline to Visit 22 (week 72)					
Sema 7.2 mg		307	291	-5.17	
Sema 2.4 mg		103	97	-4.09	
Placebo		102	95	-1.48	
Treatment difference					
Sema 7.2 mg - Placebo				-3.69	[-4.35; -3.03] <0.0001

FAS: Full analysis set, N: Number of participants with an observation at the visit, CI: Confidence interval. BMI: Body mass index. p-value: Unadjusted two-sided p-value for test of no difference. Analysis of data from in-trial period.
ANCOVA: Week 72 responses were analysed using an analysis of covariance model with randomised treatment as factor and baseline BMI as covariate. RD-MI: Missing observations were multiple (x1000) imputed from retrieved participants regardless of randomised treatment arm.3

Body composition (only STEP UP)

Changes in body composition (total fat, total lean body, and visceral fat volume) from baseline to week 72 were included as a supportive secondary endpoint for MRI sub-study population of 55 participants in STEP UP.

To be able to analyse endpoints related to body composition based on MRI scans and the endpoints of change in body weight (%, L), the two active treatment groups (semaglutide 7.2 mg and semaglutide 2.4 mg) were pooled and compared against placebo. There were 49 participants in the pooled semaglutide treatment group and 6 participants in the placebo treatment group.

In this subpopulation, baseline mean body composition (%, L) was comparable between semaglutide and placebo. At baseline (week 0), the observed mean (SD) body composition by MRI was:

Total fat volume was:
- 42.9 (9.6) L for participants in the pooled semaglutide treatment group
- 47.1 (10.1) L for participants in the placebo treatment group

Lean body volume was:
- 23.8 (5.6) L for participants in the pooled semaglutide treatment group
- 24.5 (6.0) L for participants in the placebo treatment group

Visceral fat volume by MRI was:
- 5.4 (1.7) L for participants in the pooled semaglutide treatment group
- 5.1 (2.5) L for participants in the placebo treatment group

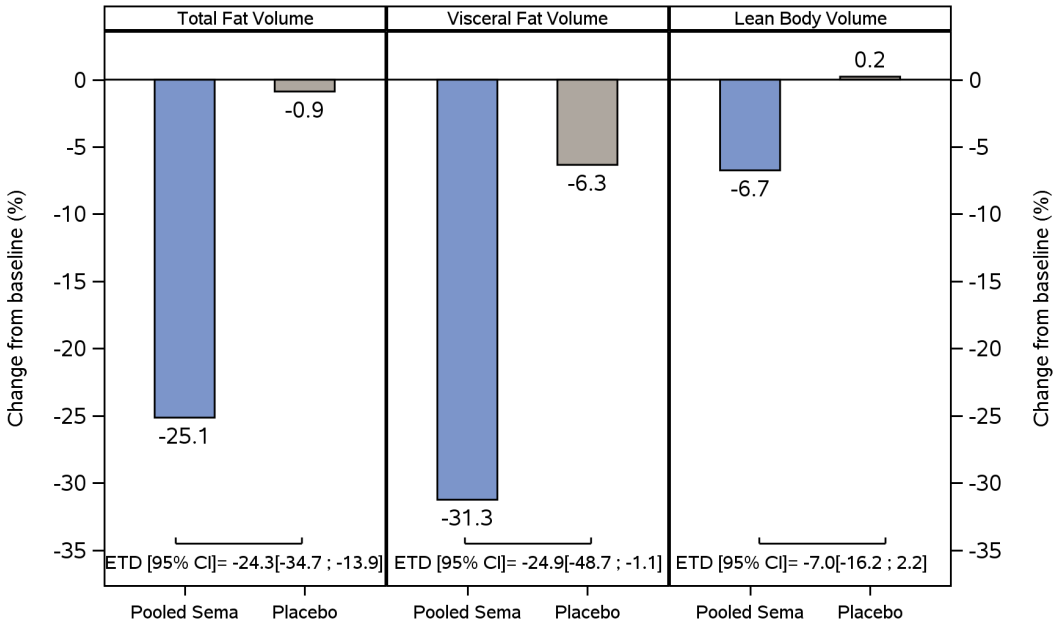
Body weight was:
- 109.9 (19.3) kg for participants in the pooled semaglutide treatment group
- 117.9 (23.1) kg for participants in the placebo treatment group

Treatment with semaglutide resulted in improvements (% and L) in total fat, visceral fat, and lean body. Body weight also reduced (%, kg) after treatment with semaglutide.

- At end of treatment (week 72), the estimated change from baseline (week 0) in body composition for the treatment policy strategy estimand was:

Total fat volume: ETD: -24.26%-points $[-34.66; -13.86]_{95\% CI}$; p-value <0.0001/-11.10 L $[-16.53; -5.68]_{95\% CI}$; p-value <0.0001
Visceral fat volume: ETD: -24.91%-points $[-48.71; -1.11]_{95\% CI}$; p-value = 0.0402/-1.49 L $[-2.93; -0.05]_{95\% CI}$; p-value = 0.0420
Lean body volume: ETD: -6.97%-points $[-16.19; 2.25]_{95\% CI}$; p-value = 0.1384/-1.65 L $[-3.98; 0.68]_{95\% CI}$; p-value = 0.1641
Body weight: ETD: -16.53%-points $[-26.30; -6.76]_{95\% CI}$; p-value = 0.0009/-19.13 kg $[-32.06; -6.20]_{95\% CI}$; p-value =0.0037

Figure 3-17 Body composition (MRI) (%) change from baseline to week 72 - bar plot - treatment policy strategy - MRI subpopulation



ETD: Estimated treatment difference. CI: Confidence interval. MRI: Magnetic resonance imaging.
Analysis of data from in-trial period.

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27MAY2025:21:22:18 - fbarplotmrieff.sas/fbarmriitpct.png

Assessor's comments

Treatment with semaglutide resulted in improvements in total fat (-24%), visceral fat (-25%), and lean body (-7%). However, these differences reflect the differences between both semaglutide doses on the one hand and placebo on the other. The differences between the 7.2 and the 2.4 dose are difficult to assess as only 6 patients were treated with the 2.4 mg dose in the MRI substudy.

Blood pressure

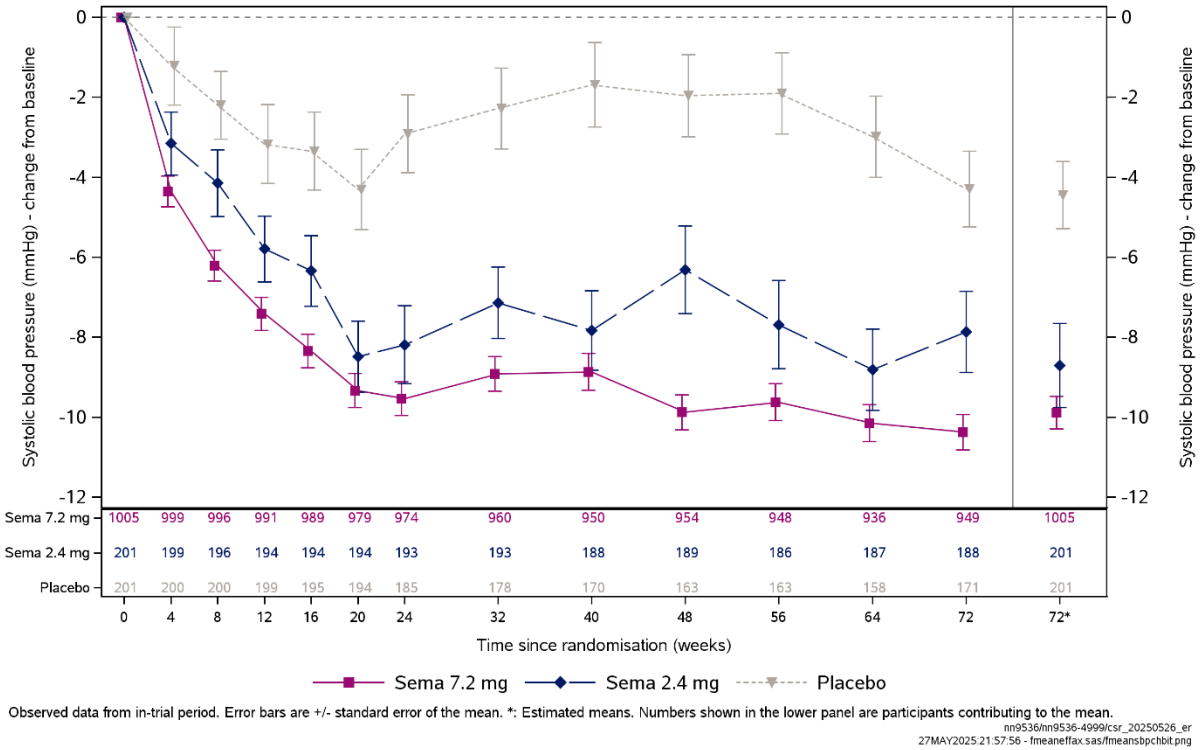
Systolic blood pressure

In both studies, mean SBP decreased over time with semaglutide 7.2 mg and 2.4 mg treatment, and nadir was reached by week 24, whereas with placebo, SBP remained largely unchanged. In STEP UP T2D, a higher proportion of participants used antihypertensive medication between week 0 and week 72, consistent with the higher proportion of participants with hypertension at screening in the study (Appendix 6.2, TFL 6.2.4).

In STEP UP, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in systolic blood pressure from baseline (week 0) to end of treatment (week 72) was: -5.44 mmHg [-7.27; -3.61]$_{95\% \text{ CI}}$; p-value <0.0001

In STEP UP T2D, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in systolic blood pressure from baseline (week 0) to end of treatment (week 72) was: -3.95 mmHg [-6.69; -1.22]$_{95\% \text{ CI}}$; p-value = 0.0046

Figure 3-18 Systolic blood pressure change from baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP)



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means. Numbers shown in the lower panel are participants contributing to the mean.

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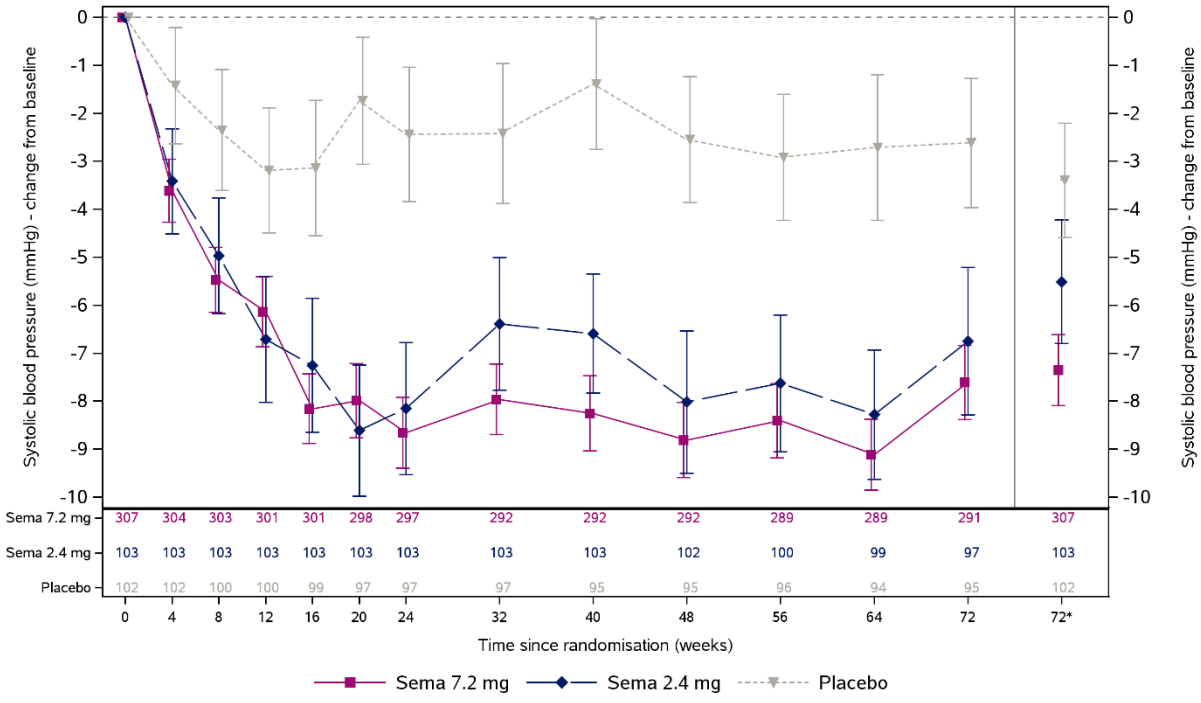
27MAY2025:21:57:56 - fmeaneffax.sas/fmeansbpchbit.png

Figure 3-19 Systolic blood pressure change from baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP T2D)

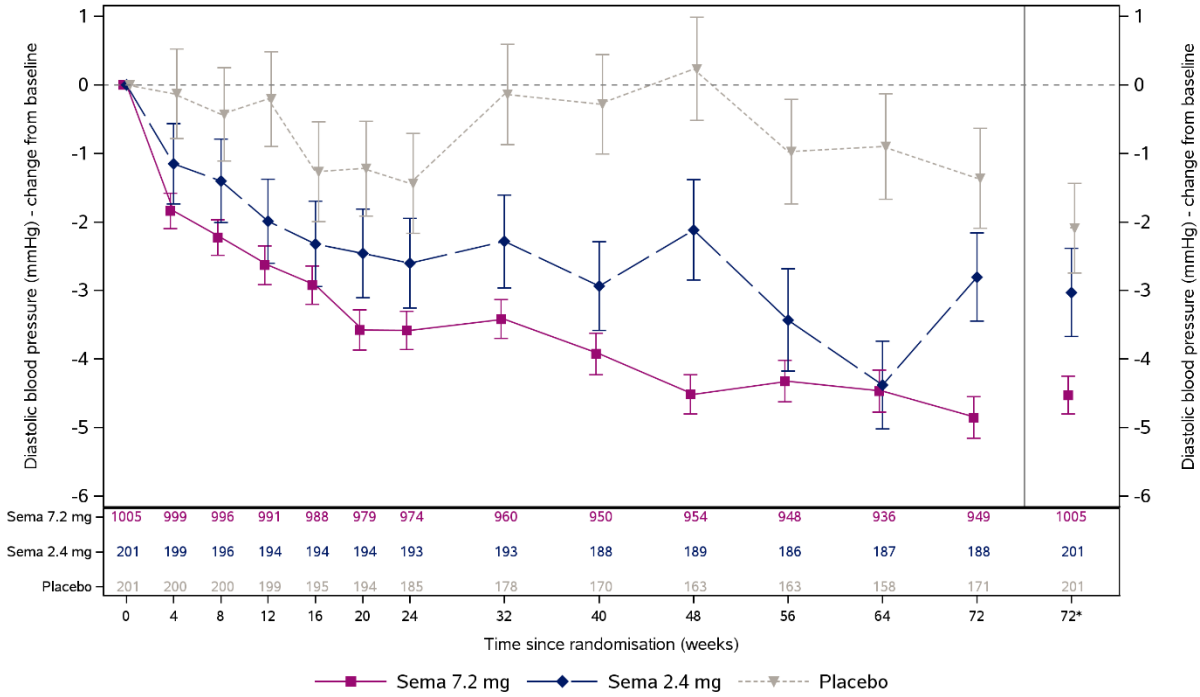


Diastolic blood pressure

In STEP UP, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in diastolic blood pressure from baseline (week 0) to end of treatment (week 72) was: -2.44 mmHg [-3.83; -1.05]$_{95\% \text{ CI}}$; p-value = 0.0006. In this study, DBP decreased over time with semaglutide 7.2 mg and 2.4 mg treatment, whereas with placebo, DBP remained largely unchanged (Figure 3-24).

In STEP UP T2D, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in diastolic blood pressure from baseline (week 0) to end of treatment (week 72) was: -0.27 mmHg [-2.00; 1.46]$_{95\% \text{ CI}}$; p-value = 0.7595. In this study, DBP decreased over time with both semaglutide and placebo (Figure 3-25).

Figure 3-20 Diastolic blood pressure change from baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP)



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means. Numbers shown in the lower panel are participants contributing to the mean.

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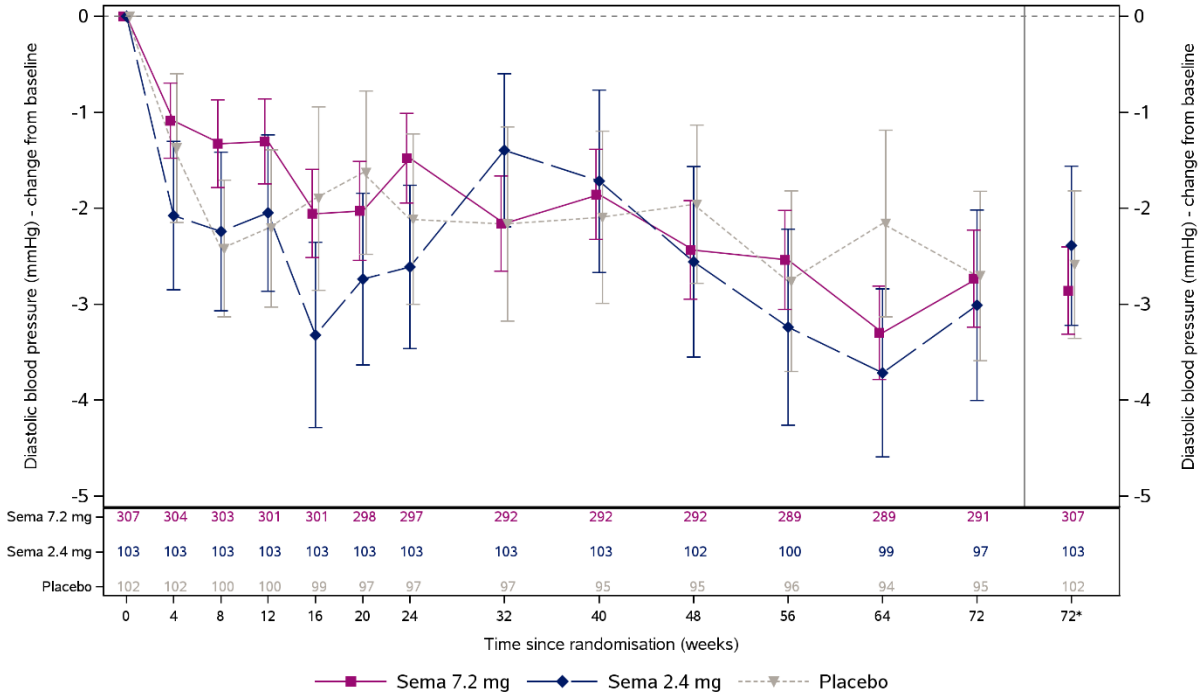
27MAY2025:21:58:02 - fmeaneffax.sas/fmeandbpchb.png

Figure 3-21 Diastolic blood pressure change from baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP T2D)



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means. Numbers shown in the lower panel are participants contributing to the mean.

nn9536/nn9536-7545/csr_20250526_er
27MAY2025:19:01:31 - fmeaneffax.sas/fmeandbpchb.png

Assessor's comments

Both doses of semaglutide were associated with a reduction in SBP. However, the differences between the doses were very small and not clinicaly relevant (<2 mmHg). Similarly, the differences between the doses in DBP were also very small (<2 mmHg).

Lipids

The baseline observed geometric mean (CV) of the respective lipid parameters is provided in Table 3-12. In STEP UP T2D (conducted in participants with T2D), a lower LDL cholesterol level at baseline was observed compared to STEP UP. In STEP UP, significant and beneficial effects were seen for LDL, VLDL and triglycerides while in STEP UP T2D, significant and beneficial effects were seen for VLDL, free fatty acids and triglycerides.

Table 3-10 Lipids - change from baseline at week 72 - treatment policy strategy estimand – STEP UP and STEP UP T2D

Lipids	**STEP UP**			**STEP UP T2D**		
	Sema 7.2 mg N =1005	Sema 2.4 mg N = 201	Placebo N = 201	Sema 7.2 mg N = 307	Sema 2.4 mg N = 103	Placebo N = 102
• Total cholesterol (n)	998	201	200	304	101	102
Baseline Geometric mean (CV) (mmol/L)	5.01 (20.3)	4.93 (19.6)	5.01 (19.9)	4.54 (23.8)	4.47 (27.3)	4.58 (28.7)
Baseline Geometric mean (CV) (mg/dL)	193.6 (20.3)	190.4 (19.6)	193.4 (19.9)	175.2 (23.8)	172.6 (27.3)	176.8 (28.7)
Est. change from baseline	-4.96	-4.64	-0.01	-2.76	-3.49	-0.60
Est treatment difference (Sema 7.2 mg vs. Placebo)	-4.95 [-9.80; 0.15]			-2.18 [-7.43; 3.38]		
• HDL cholesterol (n)	984	200	198	304	101	102
Baseline Geometric mean (CV) (mmol/L)	1.3 (22.7)	1.2 (22.3)	1.3 (23.8)	1.1 (25.5)	1.1 (23.5)	1.1 (23.0)
Baseline Geometric mean (CV) (mg/dL)	48.8 (22.7)	48.2 (22.3)	48.9 (23.8)	42.6 (25.5)	41.9 (23.5)	42.5 (23.0)
Est. change from baseline	8.26	5.65	1.86	9.29	4.88	6.10
Est treatment difference (Sema 7.2 mg vs. Placebo)	6.29 [-3.72; 17.33]			3.01 [-0.87; 7.05]		
• LDL cholesterol (n)	984	200	198	304	101	102
Baseline Geometric mean (CV) (mmol/L)	3.0 (29.6)	3.0 (27.9)	3.0 (29.3)	2.4 (44.5)	2.4 (41.9)	2.4 (41.3)
Baseline Geometric mean (CV) (mg/dL)	115.77 (29.6)	114.37 (27.9)	116.44 (29.3)	91.51 (44.5)	93.76 (41.9)	93.52 (41.3)
Est. change from baseline	-6.84	-6.79	-1.44	0.12	-3.05	-0.62
Est treatment difference (Sema 7.2 mg vs. Placebo)	-5.48 [-10.58; -0.08]			0.74 [-7.43; 9.62]		
• VLDL cholesterol (n)	994	201	198	304	101	102

Lipids	**STEP UP**			**STEP UP T2D**		
Baseline Geometric mean (CV) (mmol/L)	0.62 (46.2)	0.61 (45.4)	0.61 (46.9)	0.87 (47.5)	0.81 (50.0)	0.87 (55.7)
Baseline Geometric mean (CV) (mg/dL)	24.1 (46.2)	23.7 (45.4)	23.7 (46.9)	33.5 (47.5)	31.1 (50.0)	33.4 (55.7)
Est. change from baseline	-22.67	-15.24	-0.55	-25.75	-20.23	-7.76
Est treatment difference (Sema 7.2 mg vs. Placebo)	-22.25 [-28.17; -15.84]			-19.51 [-26.63; -11.69]		
• Triglycerides (n)	996	201	198-	304	101	102
Baseline Geometric mean (CV) (mmol/L)	1.40 (47.9)	1.37 (46.1)	1.37 (48.6)	1.97 (52.5)	1.81 (52.7)	2.03 (69.2)
Baseline Geometric mean (CV) (mg/dL)	124.18 (47.9)	121.59 (46.1)	121.93 (48.6)	175.49 (52.5)	161.13 (52.7)	180.46 (69.2)
Est. change from baseline	-22.89	-15.83	-0.86	-26.89	-22.02	-9.02
Est treatment difference (Sema 7.2 mg vs. Placebo)	-22.22 [-28.32; -15.61]			-19.64 [-27.28; -11.19]		

[a]Free fatty acids were not measured at visit 2 (week 0) for STEP UP.

Abbreviations: CI = Confidence interval; CV = coefficient of variation in %; FAS = full analysis set; HDL = high density lipoprotein; LDL = low density lipoprotein; N = Total number of participants; n = number of participants with an observation at the baseline visit; p-value = unadjusted two-sided p-value for test of no difference; VLDL = very low-density lipoprotein.

Table 3-11 Lipids change from baseline at week 72 treatment policy strategy estimand – STEP UP and STEP UP T2D

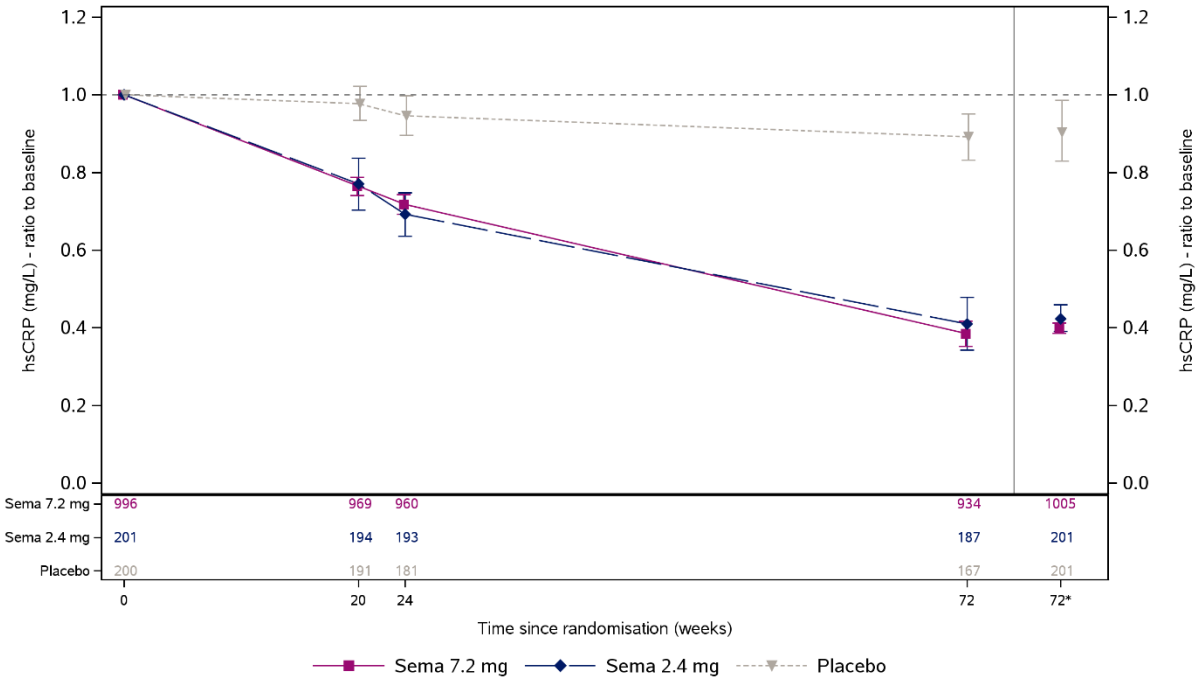
Lipids	**STEP UP**			**STEP UP T2D**		
	Sema 7.2 mg N =1005	Sema 2.4 mg N = 201	Placebo N = 201	Sema 7.2 mg N = 307	Sema 2.4 mg N = 103	Placebo N = 102
• Total cholesterol (n)	998	201	200	304	101	102
Baseline Geometric mean (CV) (mmol/L)	5.01 (20.3)	4.93 (19.6)	5.01 (19.9)	4.54 (23.8)	4.47 (27.3)	4.58 (28.7)
Baseline Geometric mean (CV) (mg/dL)	193.6 (20.3)	190.4 (19.6)	193.4 (19.9)	175.2 (23.8)	172.6 (27.3)	176.8 (28.7)
Est. change from baseline	-4.96	-4.64	-0.01	-2.76	-3.49	-0.60
Est treatment difference (Sema 7.2 mg vs. Placebo)	-4.95 [-9.80; 0.15]			-2.18 [-7.43; 3.38]		
• HDL cholesterol (n)	984	200	198	304	101	102
Baseline Geometric mean (CV) (mmol/L)	1.3 (22.7)	1.2 (22.3)	1.3 (23.8)	1.1 (25.5)	1.1 (23.5)	1.1 (23.0)
Baseline Geometric mean (CV) (mg/dL)	48.8 (22.7)	48.2 (22.3)	48.9 (23.8)	42.6 (25.5)	41.9 (23.5)	42.5 (23.0)
Est. change from baseline	8.26	5.65	1.86	9.29	4.88	6.10
Est treatment difference (Sema 7.2 mg vs. Placebo)	6.29 [-3.72; 17.33]			3.01 [-0.87; 7.05]		
• LDL cholesterol (n)	984	200	198	304	101	102
Baseline Geometric mean (CV) (mmol/L)	3.0 (29.6)	3.0 (27.9)	3.0 (29.3)	2.4 (44.5)	2.4 (41.9)	2.4 (41.3)
Baseline Geometric mean (CV) (mg/dL)	115.77 (29.6)	114.37 (27.9)	116.44 (29.3)	91.51 (44.5)	93.76 (41.9)	93.52 (41.3)
Est. change from baseline	-6.84	-6.79	-1.44	0.12	-3.05	-0.62
Est treatment difference (Sema 7.2 mg vs. Placebo)	-5.48 [-10.58; -0.08]			0.74 [-7.43; 9.62]		
• VLDL cholesterol (n)	994	201	198	304	101	102

Lipids	**STEP UP**			**STEP UP T2D**		
Baseline Geometric mean (CV) (mmol/L)	0.62 (46.2)	0.61 (45.4)	0.61 (46.9)	0.87 (47.5)	0.81 (50.0)	0.87 (55.7)
Baseline Geometric mean (CV) (mg/dL)	24.1 (46.2)	23.7 (45.4)	23.7 (46.9)	33.5 (47.5)	31.1 (50.0)	33.4 (55.7)
Est. change from baseline	-22.67	-15.24	-0.55	-25.75	-20.23	-7.76
Est treatment difference (Sema 7.2 mg vs. Placebo)	-22.25 [-28.17; -15.84]			-19.51 [-26.63; -11.69]		
• Triglycerides (n)	996	201	198-	304	101	102
Baseline Geometric mean (CV) (mmol/L)	1.40 (47.9)	1.37 (46.1)	1.37 (48.6)	1.97 (52.5)	1.81 (52.7)	2.03 (69.2)
Baseline Geometric mean (CV) (mg/dL)	124.18 (47.9)	121.59 (46.1)	121.93 (48.6)	175.49 (52.5)	161.13 (52.7)	180.46 (69.2)
Est. change from baseline	-22.89	-15.83	-0.86	-26.89	-22.02	-9.02
Est treatment difference (Sema 7.2 mg vs. Placebo)	-22.22 [-28.32; -15.61]			-19.64 [-27.28; -11.19]		

[a]Free fatty acids were not measured at visit 2 (week 0) for STEP UP.

Abbreviations: CI = Confidence interval; CV = coefficient of variation in %; FAS = full analysis set; HDL = high density lipoprotein; LDL = low density lipoprotein; N = Total number of participants; n = number of participants with an observation at the baseline visit; p-value = unadjusted two-sided p-value for test of no difference; VLDL = very low-density lipoprotein.

Figure 3-22 hsCRP ratio to baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP)



hsCRP: High sensitivity C-reactive protein. Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means. Numbers shown in the lower panel are participants contributing to the mean.

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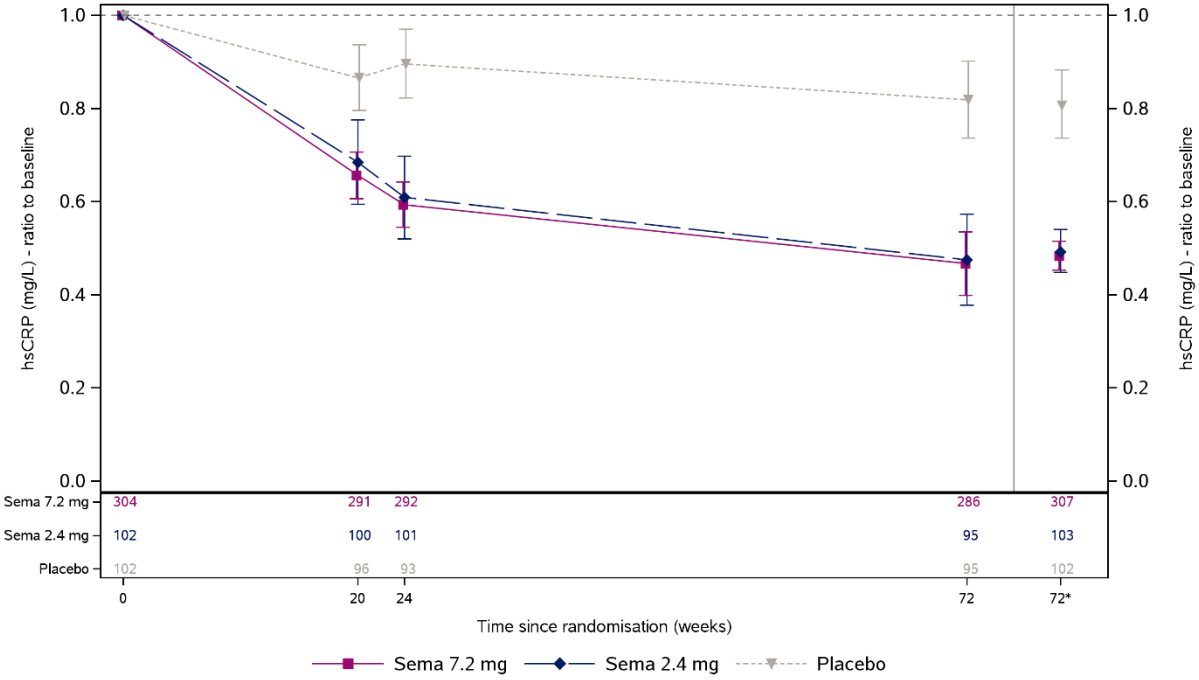
Figure 3-23 hsCRP ratio to baseline by week - mean plot - treatment policy strategy - full analysis set (STEP UP T2D)



hsCRP: High sensitivity C-reactive protein. Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means. Numbers shown in the lower panel are participants contributing to the mean.

nn9536/nn9536-7545/csr_20250526_er
27MAY2025:19:01:50 - fmeaneffax.sas/fmeanhscrpr2bit.png

Assessor's comments

Small improvements in several serum lipids could be detected with semaglutide 2.4 and 7.2 mg (approximate changes compared to placebo for total cholesterol -0.1 mmol/L, LDL -0.2 mmol/L, HDL -0.2 mmol/L). However, the differences between the 2 doses were negligible. Similarly, CRP improved somewhat with semaglutide 2.4 and 7.2 mg (approximately 0.5 mg/L), but there were no differences between the doses.

HbA_{1c}

Change in HbA_{1c} from baseline to week 72 was a confirmatory and supportive endpoint in STEP UP T2D and STEP UP, respectively. Superiority of semaglutide 7.2 mg versus placebo was confirmed in STEP UP T2D for the confirmatory endpoint of change from baseline (week 0) to week 72 in HbA_{1c} (%) (Table 2-2).

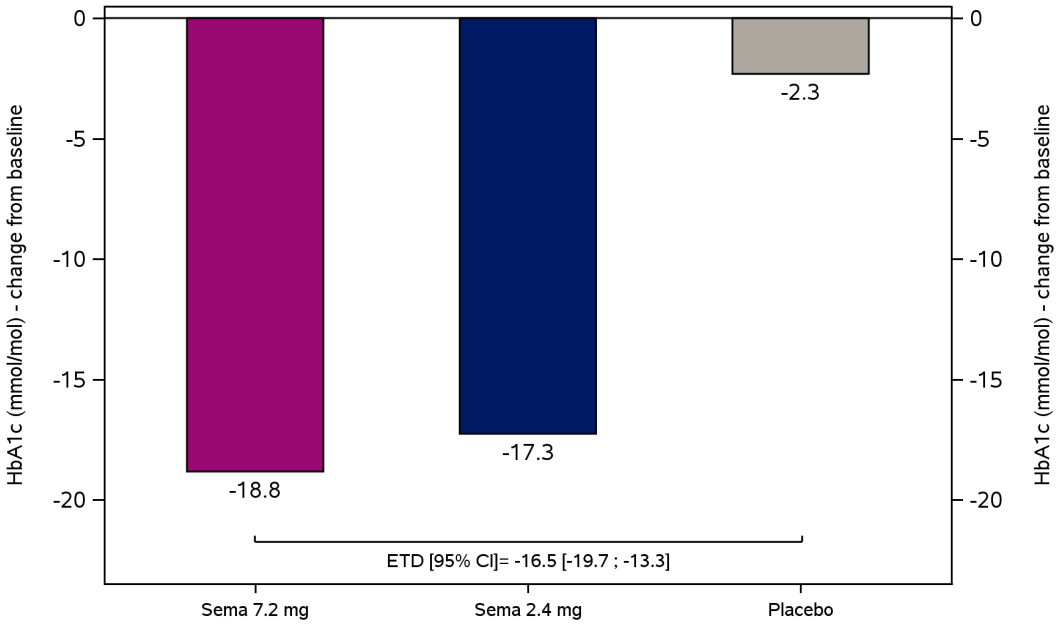
Baseline mean HbA_{1c} was comparable between treatment groups in each study but varied between studies: as expected, participants with T2D (STEP UP T2D) had a higher baseline HbA_{1c} (8.1% [64.8 mmol/mol] than participants without T2D in STEP UP (5.7% [38.4 mmol/mol]).

In STEP UP T2D, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in HbA_{1c} (mmol/mol) from baseline (week 0) to end of treatment (week 72) was: -16.5 $[-19.7; -13.3]_{95\% CI}$; p-value <0.0001 (Figure 3-30).

In STEP UP T2D, a larger proportion of participants achieved the HbA_{1c} targets of <7.0% (53.0 mmol/mol) and ≤6.5% (48 mmol/mol) with semaglutide 7.2 mg compared with placebo (Figure 3-31).

HbA_{1c} reduction was also seen in STEP UP, although to a smaller extent than for STEP UP T2D. In STEP UP, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in HbA1c (mmol/mol) from baseline (week 0) to end of treatment (week 72) was: -3.28 $[-3.98; -2.57]_{95\% CI}$; p-value <0.0001 (Figure 3-32).

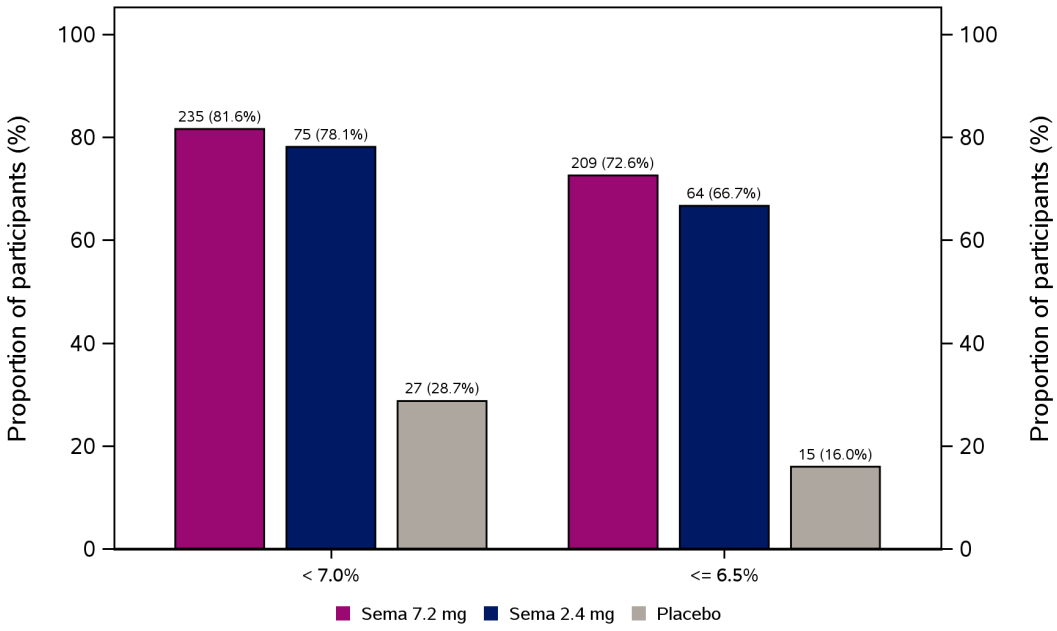
Figure 3-24 HbA1c change from baseline to week 72 (mmol/mol) - bar plot - treatment policy strategy - full analysis set (STEP UP T2D)



ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-7545/csr_20250526_er
27MAY2025:18:48:04 - fbarploteff.sas/fbarhbait.png

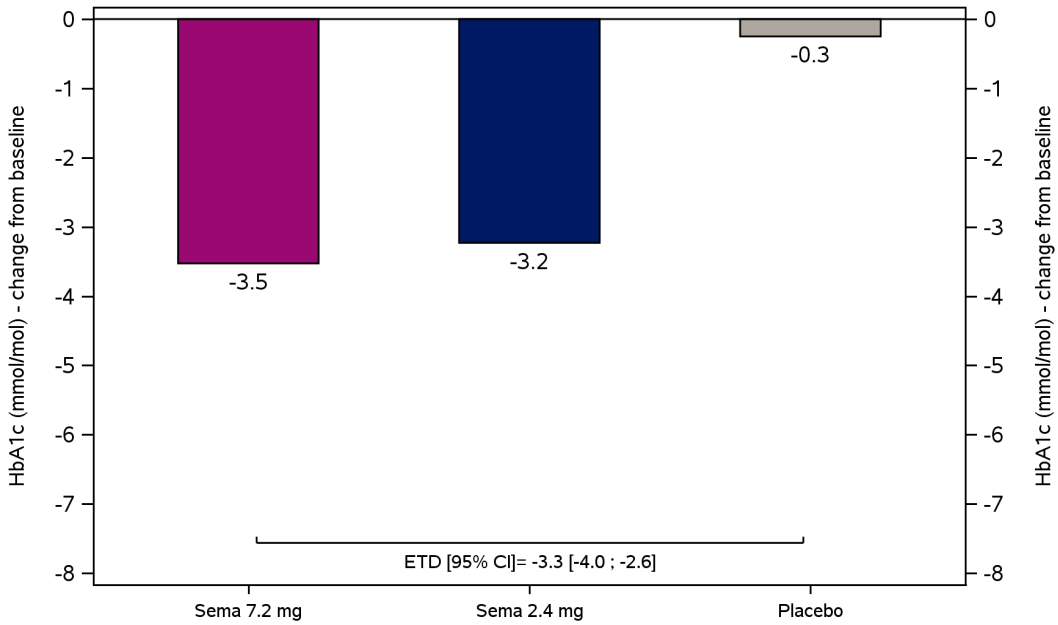
Figure 3-25 Proportion of participants achieving less than or equal to 6.5% or less than 7.0% HbA1c at week 72 (%) - bar plot - in-trial - full analysis set (STEP UP T2D)



HbA1c: Haemoglobin A1c.
Observed data from in-trial period.

nn9536/nn9536-7545/csr_20250526_er
27MAY2025:18:48:51 - fbarplotpropcat.sas/fbar53hbait.png

Figure 3-26 HbA1c change from baseline to week 72 (mmol/mol) - bar plot - treatment policy strategy - full analysis set (STEP UP)



ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-4999/csr_20250526_er
27MAY2025:21:22:10 - fbarploteff.sas/fbarhbait.png

Assessor's comments

In STEP UP T2D, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in HbA1c (mmol/mol) from baseline (week 0) to end of treatment (week 72) was: -16.5 [-19.7; -13.3]95% CI; p-value <0.0001.

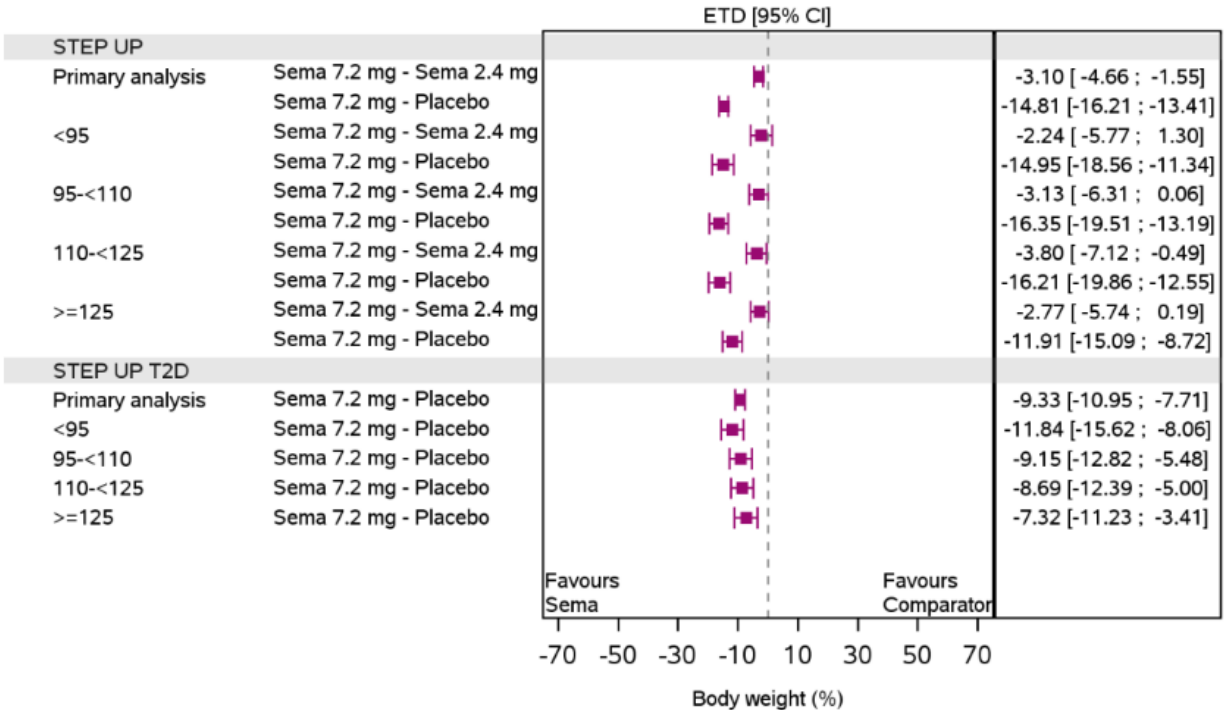
HbA1c reduction was also seen in STEP UP, although to a smaller extent than for STEP UP T2D. In STEP UP, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in HbA1c (mmol/mol) from baseline (week 0) to end of treatment (week 72) was: -3.28 [-3.98; -2.57]95% CI; p-value <0.0001.

In both studies, the differences between the 7.2 and the 2.4 doses were negligible.

Subgroup analyses

Compared to the 2.4 mg dose, the efficacy response to semaglutide 7.2 mg was similarly low across sub-populations (see Appendix Summary of clinical efficacy 6.3.2 to 6.3.88). Specifically, there were no relevant differences in efficacy between body weight subgroups (see Table).

Table. Body weight (%) change from baseline by baseline body weight - estimated treatment difference- forest plot - treatment policy estimand - full analysis set - STEP UP and STEP UP T2D



Assessor's comments

Compared to the 2.4 mg dose, the efficacy response to semaglutide 7.2 mg was similarly low across sub-populations. Specifically, there were no relevant differences in efficacy between body weight subgroups.

3.3. Discussion

Methods – analysis of data submitted

Design

STEP UP and STEP UP T2D were designed to evaluate the efficacy and safety of semaglutide 7.2 mg once weekly versus placebo once-weekly as an adjunct to reduced-calorie diet and increased physical activity in adults living with obesity (STEP UP) or obesity and T2D (STEP UP T2D). In addition, both trials also included a semaglutide 2.4 mg once weekly arm.

Both STEP UP studies were randomised, double-blind, placebo-controlled, multi-national, multi-centre, three-armed, parallel-group studies consisting of a 1-week screening period, a 20-week dose escalation period, a 52-week maintenance period, and a 9-week follow-up period.

Participants were randomised 5:1:1 (STEP UP) or 3:1:1 (STEP UP T2D) to receive either semaglutide 7.2 mg, semaglutide 2.4 mg, or placebo once-weekly, as an adjunct to reduced-calorie diet and increased physical activity. In STEP UP, a sub-population of 55 randomised participants had their body composition

assessed by MRI at the beginning and at the end of the treatment to investigate the effect on body composition.

Objectives

The co-primary objectives for both the STEP UP and the STEP UP T2D study were to demonstrate superiority of semaglutide 7.2 mg once-weekly versus placebo as an adjunct to reduced-calorie diet and increased physical activity with respect to relative change in body weight and achieving body weight reduction of ≥ 5% after 72 weeks in the respective study populations.

However, for a proposed higher dose (7.2 mg), a comparison with the already marketed lower dose (2.4 mg) is considered more relevant.

Participants

The study population was chosen to consist of adults with BMI ≥30.0 kg/m2 with or without weight-related (except T2D) comorbidities (STEP UP) and adults living with obesity (BMI ≥30.0 kg/m) and T2D (STEP UP T2D).

The eligibility criteria were selected to ensure a population with obesity considered appropriate for treatment with pharmacotherapy for weight management. In STEP UP T2D the selected range of HbA1c of 7.0% to 10.0%. In STEP UP, only patients with an HbA1c <6.5% were included.

Overall, the study populations in STEP UP and STEP UP T2D were comparable with regards to Key eligibility (inclusion and exclusion) criteria. For the full study population from both studies, the median age was 48 years (range: 18 to 80 years). The majority of participants were female (73.7%) and of white race (85.5%). The mean (SD) body weight at baseline was 113.0 (24.1) kg and the mean (SD) BMI 39.9 (7.1) mg/kg2. There were 67% of the participants who had at least one weight-related comorbidity. Hypertension was the most frequently reported comorbidity (41.6%) followed by dyslipidaemia (27.9%).

Dose escalation

A fixed-dose escalation regimen was followed, with dose escalation every 4 weeks until the target dose was reached. Participants started with a once weekly dose of 0.25 mg and increased the dose every 4 weeks (to 0.5, 1.0, 1.7, 2.4 mg/week). After 20 weeks of treatment, the participants started on their respective maintenance doses of 7.2 mg/week, 2.4 mg/week, or placebo.

Disposition

Of the 1407 randomised participants 1406 were exposed to trial product and 1329 (94.5%) completed the STEP UP study. Of the randomised participants 1206 (85.7%) completed treatment while 200 (14.2%) permanently discontinued treatment.

Fifty-five participants were included in the MRI subpopulation, of which, 52 participants completed the study, and 3 participants withdrew from the study. Ten (18.2%) participants in the MRI subpopulation permanently discontinued trial product. The primary reason was adverse events (3 participants; 5.5%).

Of the 512 randomised participants all 512 were exposed to trial product and 491 (95.9%) completed the STEP UP T2D study. Of the randomised participants 457 (89.3%) completed treatment while 55 (10.7%) permanently discontinued treatment.

Results

Body weight change

In STEP UP, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was : -18.71% for semaglutide 7.2 mg, -15.61% for semaglutide 2.4 mg and -3.90% for placebo treatment.

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: -14.81% points (p-value <0.0001). The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg was only -3.10% points.

In STEP UP T2D, at end of treatment (week 72), the estimated change from baseline (week 0) in body weight for the treatment policy strategy estimand was: -13.18% for semaglutide 7.2 mg, -10.36% for semaglutide 2.4 mg and -3.86% for placebo treatment.

For the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg versus placebo for relative change in body weight from baseline (week 0) to end of treatment (week 72) was: 9.33%points (p-value <0.0001). The ETD between semaglutide 7.2 mg versus semaglutide 2.4 mg for relative change in body weight was only: -2.80% points.

In both studies, the effects of the 2.4 mg and the 7.2 mg dose on body weight are clinically relevant. However, the difference between the 2.4 and 7.2 mg is small and of doubtful clinical relevance (-3.1% and -2.8% points body weight).

The magnitude of the weight loss in participants with T2D (STEP UP T2D) was smaller than in participants without T2D (STEP UP), an observation that has been well documented in previous weight management studies with semaglutide.

Proportion of participants achieving body weight reduction ≥5%

In STEP UP, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was: 88.47% with semaglutide 7.2 mg, 86.61% with semaglutide 2.4 mg, and 38.83% with placebo.

In STEP UP T2D, at end of treatment (week 72), the estimated proportion of participants achieving body weight reduction ≥5% for the treatment policy strategy estimand was: 84.23% with semaglutide 7.2 mg, 73.93% with semaglutide 2.4 mg and 34.76% with placebo.

These data show that in both studies both doses of semaglutide resulted in more weight loss than placebo. The effects of semaglutide are clinically relevant. However, the differences between the 2 doses are small. In STEP UP only 1.9% more patients achieved the body weight reduction of ≥5% with the 7.2 mg dose compared to the 2.4 mg dose.. In STEP UP T2D, only 10.3% more patients achieved this reduction with the higher dose.

Waist and body composition

The ETD between semaglutide 7.2 mg versus placebo for waist circumference from baseline (week 0) to end of treatment (week 72) was: -11.66 in STEP UP and -6.55 cm in STEP T2D. However, the decrease in waist with the 7.2 mg dose was only 2.9 cm (STEP UP) and 1.5 cm (STEP UP T2D) higher than with the 2.4 mg dose. The clinical relevance of these differences is doubtful.

Treatment with semaglutide resulted in improvements in MRI estimates of total fat (-24%), visceral fat (-25%), and lean body (-7%). However, these differences reflect the differences between both semaglutide doses on the one hand and placebo on the other. The differences between the 7.2 and the 2.4 dose are difficult to assess as only 6 patients were treated with the 2.4 mg dose in the MRI substudy.

Other Cv risk factors

Both doses of semaglutide were associated with a reduction in SBP. However, the differences between the doses were very small and not clinically relevant (<2 mmHg). Similarly, the differences between the doses in DBP were also very small (<2 mmHg).

Small improvements in several serum lipids could be detected with semaglutide 2.4 and 7.2 mg (approximate changes compared to placebo for total cholesterol -0.1 mmol/L, LDL -0.2 mmol/L, HDL -0.2 mmol/L). However, the differences between the 2 doses were negligible.

Similarly, CRP improved somewhat with semaglutide 2.4 and 7.2 mg (approximately 0.5 mg/L), but there were no differences between the doses.

In STEP UP T2D, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo for change in HbA1c (mmol/mol) from baseline (week 0) to end of treatment (week 72) was: -16.5 (p-value <0.0001). HbA1c reduction was also seen in STEP UP, although to a smaller extent than for STEP UP T2D. In STEP UP, for the treatment policy strategy estimand, the ETD between semaglutide 7.2 mg and placebo was: -3.28 (p-value <0.0001). In both studies, the differences between the 7.2 and the 2.4 doses were negligible.

Subgroups

Compared to the 2.4 mg dose, the efficacy response to semaglutide 7.2 mg was similarly low across sub-populations. Specifically, there were no relevant differences in efficacy between body weight subgroups.

Conclusion efficacy

Both doses of semaglutide were associated with clinically relevant reductions in body weight in obese individuals with and without diabetes. However, the differences between the new 7.2 mg dose compared to the already marketed 2.4 mg dose were very small and not clinically relevant: a 3 times higher dose of semaglutide was associated with only 3% points more weight loss. The doubt about the clinical relevance of the proposed higher dose is supported by the fact that there were also no relevant differences between the 7.2 and 2.4 mg dose with respect to CV risk factors, such as waist, body composition, blood pressure, serum lipids, CRP and HbA1c. The company argues that the 3% additional weight loss with the high dose should be viewed in the context of the proportions of participants in STEP UP (study 4999) who achieved several clinically significant treatment targets for weight loss and key cardiometabolic risk factors. The additional benefit with the higher dose may be clinically relevant for some patients (7-15% of the total population), but not for the majority of patients (85-93%). The company did not identify a subgroup of patients that may have substantially improved benefit-risk balance with the higher dose. Unfortunately, the 3 times higher dose is associated with an increased risk of adverse events. Therefore, the benefit-risk profile for the 7.2 mg dose level is negative for most patients.

We consider the 7.2 mg dose only indicated in patients that need additional weight loss. In case of side effects, the dose may be titrated back. In addition, if a clinical improvement in body weight has not been achieved with the 7.2 mg dose, the dose should be titrated back to 2.4 mg in order to prevent risks with the high dose. This should is now clearly stated in the posology section of the SmPC.

4. Clinical Safety aspects

4.1. Methods – analysis of data submitted

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

To support an aggregated evaluation of the safety and tolerability of semaglutide 7.2 mg and increase the likelihood of detecting potential safety signals, data from the two studies (STEP UP and STEP UP T2D) were pooled (STEP UP pool). The STEP UP pool served as the primary foundation for the safety evaluation. Safety of once weekly semaglutide 7.2 mg versus semaglutide 2.4 mg and placebo were evaluated to support bridging of the safety profile to that observed in previous studies.

A dose-escalation regimen, with dose escalations every 4 weeks until the target dose was reached, was followed. Participants started with a once-weekly dose of 0.25 mg and increased the dose every 4 weeks (to 0.5, 1.0, 1.7, 2.4, 7.2 mg). The low starting dose and dose escalation regimen were expected to mitigate the risk of developing gastrointestinal AEs according to the current label.[22] After 20 weeks, participants started on their respective maintenance doses of 7.2 mg, 2.4 mg, or placebo. To increase gastrointestinal tolerability, dose level reductions and extensions of dose escalation periods were allowed based on clinical evaluation made by the investigator.

Assessor's comments:

The safety of semaglutide 7.2 mg was evaluated by a pooled data set consisting of data from both studies STEP UP and STEP UP T2D. A dose-escalation regimen was applied where participants started with 0.25 mg semaglutide, increasing the dose every 4 weeks: 20 weeks of dose-escalation, 52 weeks of maintenance.

Exposure

Exposure was defined as the length of the on-treatment observation period including the 9-week follow-up period.

An overview of the number of participants exposed to semaglutide is provided in Table 5-1.

Table 5-12 Total exposure – on-treatment – safety analysis set – by pool and study

	Sema 7.2 mg		Sema 2.4 mg		Placebo	
	N	PYE	N	PYE	N	PYE
Pool	1311	1915	304	443	303	409
STEP UP	1004	1467	201	291	201	266
STEP UP T2D	307	448	103	152	102	143

N: Number of participants. PYE: Participants years of exposure. T2D: Type 2 Diabetes.
Participants are considered as on-treatment if any dose of trial product has been administered within the prior 63 days.

=

1311 participants were exposed to semaglutide 7.2 mg during the on-treatment period in STEP UP and STEP UP T2D, for a total of 1915 PYE.

Assessor's comments:

The exposure to semaglutide 7.2 mg was 1311 participants, 1004 in the STEP UP trial and 307 in STEP UP T2D corresponding to a total of 1915 PYE exposure.

4.2. Results

Overview of adverse events

Both the proportion of participants with AEs and the event rate were higher in semaglutide 7.2 mg (85.1%, 406 events per 100 PYE) compared to semaglutide 2.4 mg (81.1%, 365 events per 100 PYE) and placebo (76.0%, 233 events per 100 PYE) in the STEP UP Pool. Across all 3 groups, most AEs were non-serious, of mild or moderate severity, and reported as recovered Figure 5-1.

The higher rate and proportion of AEs in the semaglutide 7.2 mg group were driven primarily by AEs in the system organ classes (SOCs) gastrointestinal disorders, Nervous system disorders, and Skin and subcutaneous disorders (Figure 5-2). From the SOCs Nervous system disorders and Skin and subcutaneous disorders, 11 PTs were combined into a grouped term "dysesthesia", and these PTs were reported with a higher rate and frequency with semaglutide 7.2 mg. Both dysaesthesia and gastrointestinal disorders were pre-defined safety focus areas and are well-known side effects of semaglutide treatment as described in details in Sections 5.6.1 and 5.6.2.

A higher proportion of AEs was considered probably or possibly related to trial product in the semaglutide 7.2 mg group (55.6%, 48.8%) compared with semaglutide 2.4 mg (48.8%, 38.0%) and placebo (23.5%, 25.8%), which was driven by AEs related to gastrointestinal disorders, and events included in the grouped terms dysaesthesia and alopecia (for details on alopecia, see Section 5.3.1).

A similar proportion of participants either temporarily interrupted treatment or permanently discontinued treatment due to AEs in semaglutide 7.2 mg (9.8% with temporarily interruption, and 5.4%, permanently discontinued) and semaglutide 2.4 mg (9.5% and 4.6%) groups, with a lower proportion in placebo (3.3% and 1.6%). A higher proportion of participants reduced their dose due to AEs in the semaglutide 7.2 mg group (19.1%) compared to semaglutide 2.4 mg (12.8%) and placebo (1.0%) groups. This was driven by AEs related to gastrointestinal disorders and events included in the grouped terms dysaesthesia and alopecia (see Section 5.3)

The proportion of participants with serious adverse events (SAEs) and the rates were comparable between the semaglutide 7.2 mg (7.5%, 6.8 events per 100 PYE) and placebo groups (6.6%, 7.9 events per 100 PYE) and higher in the semaglutide 2.4 mg group (10.2% and 13.8 events per 100 PYE). Notably, one participant in the semaglutide 2.4 mg group reported 21 SAEs, including one fatal event. The SAEs were distributed among different SOCs and PTs, without any clustering of events, both within and between treatment groups.

For both semaglutide treatment groups, the incidence rate of AEs was highest during dose escalation with rates flattening out for all treatment groups over the remainder of the studies (Figure 5-3). The increase was more pronounced in the semaglutide 7.2 mg group around the timepoint of dose escalation to maintenance dose (week 20) and then continued at a similar rate as the other treatment groups.

Assessor's comments:

In the pooled analysis (STEP UP Pool), the overall AE rate was higher for semaglutide 7.2 mg compared to 2.4 mg and placebo. (85.1% (7.2 mg) vs. 81.1% (2.4 mg) and 76% (placebo). Most reported events were gastrointestinal disorders, nervous system disorders, and skin and subcutaneous disorders. Of the PTs, dysaesthesia and alopecia were mostly reported.

Due to AEs, semaglutide treatment was temporarily interrupted or permanently discontinued:

- temporarily discontinued: 9.8% (7.2 mg) vs. 9.5% (2.4 mg) and 3.3% (placebo)

- permanently discontinued: 5.4% (7.2 mg) vs. 4.6% (2.4 mg) and 1.6% (placebo) -

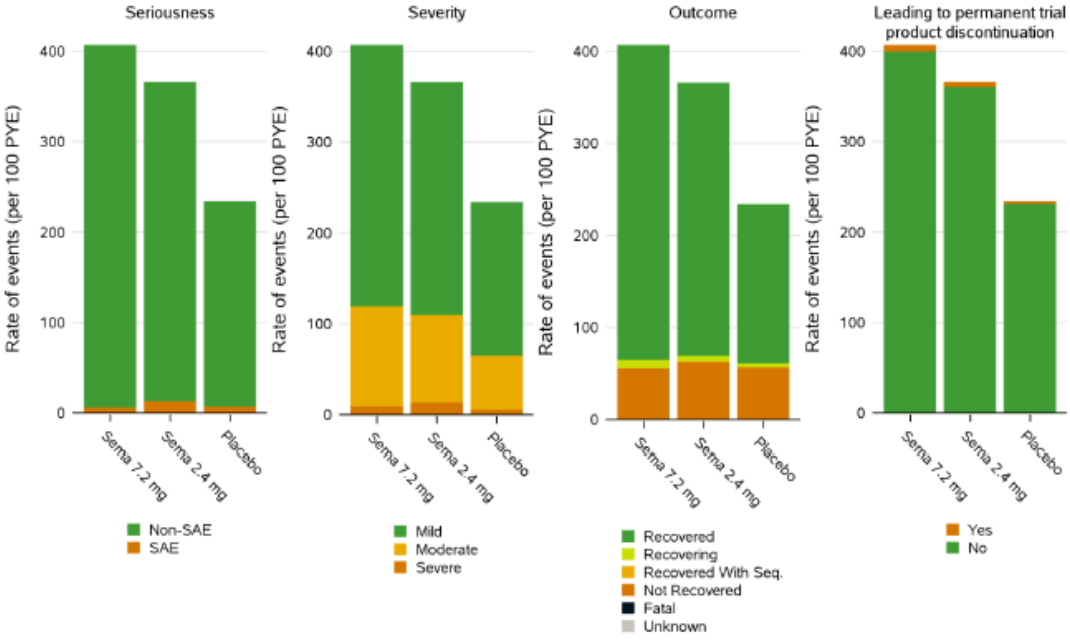
- dose reduction: 19.1 (7.2 mg) vs. 12.8% (2.4 mg) and 1.0% (placebo).

Overall, serious AEs were mostly reported in the 2.4 mg group and were comparable between 7.2 mg group and placebo (7.5% (7.2 mg) vs. 10.2 (2.4 mg) and 6.6% (placebo)

In the 2,4 semaglutide group, one patients reported 21 SAEs including one fatal event. A short narrative of the events should be provided (OC).

It must be noted that due to a clinical supply breach, a total of 99 patients in the 7.2 mg semaglutide group received a lower semaglutide dose of 1.7 mg or less for ~ two months. A lower semaglutide dose may lead to an underestimation of the risks of the proposed new dose. Considering the study duration of 17 months and the total exposure group of 1212 participants, a lower dose for 2 months in 99 patients is likely to have only a modest effect. To evaluate whether this has affected the safety profile of semaglutide 7.2 mg, the company performed an additional analysis after exclusion of the 99 participants. The results showed no or minimal differences in the proportion and rate of evaluated events compared to the total safety population.

Figure 5-27 Adverse events by seriousness, severity, outcome and relationship to trial product - overview - on-treatment - safety analysis set



Adverse events with onset prior to randomisation are not included.
PYE: Patients years of exposure. SAE: Serious Adverse Events.
The rate of events is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
Participants are considered as on-treatment if any dose of trial product has been administered within the prior 63 days.

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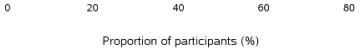
Figure 5-28 Adverse events by system organ class - on-treatment - safety analysis set

System organ class	Sema 7.2 mg N	%	R	Sema 2.4 mg N	%	R	Placebo N	%	R
Gastrointestinal disorders	874	(66.7)	191.5	176	(57.9)	155.4	112	(37.0)	66.9
Infections and infestations	486	(37.1)	46.9	122	(40.1)	50.1	102	(33.7)	45.0
Nervous system disorders	384	(29.3)	36.8	56	(18.4)	24.1	35	(11.6)	12.7
Skin and subcutaneous tissue disorders	268	(20.4)	21.0	40	(13.2)	11.1	17	(5.6)	4.9
General disorders and administration site conditions	246	(18.8)	24.2	55	(18.1)	18.5	30	(9.9)	12.7
Musculoskeletal and connective tissue disorders	226	(17.2)	17.7	61	(20.1)	19.6	47	(15.5)	14.2
Metabolism and nutrition disorders	166	(12.7)	11.5	38	(12.5)	12.2	46	(15.2)	13.7
Injury, poisoning and procedural complications	127	(9.7)	10.0	39	(12.8)	12.9	28	(9.2)	8.6
Investigations	117	(8.9)	9.0	31	(10.2)	9.9	28	(9.2)	8.8
Respiratory, thoracic and mediastinal disorders	91	(6.9)	7.0	23	(7.6)	8.3	21	(6.9)	6.1
Psychiatric disorders	84	(6.4)	5.7	21	(6.9)	5.9	18	(5.9)	5.1
Vascular disorders	73	(5.6)	4.9	24	(7.9)	6.5	22	(7.3)	7.3
Eye disorders	55	(4.2)	3.8	16	(5.3)	6.8	17	(5.6)	5.1
Cardiac disorders	53	(4.0)	5.1	15	(4.9)	4.7	13	(4.3)	4.6
Reproductive system and breast disorders	49	(3.7)	3.3	13	(4.3)	3.2	7	(2.3)	2.2
Hepatobiliary disorders	47	(3.6)	3.1	9	(3.0)	2.5	3	(1.0)	0.7
Renal and urinary disorders	46	(3.5)	3.0	11	(3.6)	3.2	10	(3.3)	2.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	39	(3.0)	2.3	12	(3.9)	2.9	8	(2.6)	2.2
Ear and labyrinth disorders	35	(2.7)	2.2	4	(1.3)	1.1	10	(3.3)	2.7
Blood and lymphatic system disorders	29	(2.2)	1.8	8	(2.6)	1.8	8	(2.6)	2.0
Endocrine disorders	23	(1.8)	1.4	11	(3.6)	2.5	7	(2.3)	1.7
Immune system disorders	16	(1.2)	1.1	2	(0.7)	0.5	1	(0.3)	0.2
Congenital, familial and genetic disorders	5	(0.4)	0.3	1	(0.3)	0.2	0		
Social circumstances	5	(0.4)	0.3	1	(0.3)	0.2	1	(0.3)	0.2
Pregnancy, puerperium and perinatal conditions	1	(0.1)	0.1	0			0		
Product issues	1	(0.1)	0.1	0			0		
Surgical and medical procedures	1	(0.1)	0.1	0			0		



N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, R: Event rate per 100 years. SOC: System organ class.
Adverse events with onset date during on-treatment period: A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 63 days. Sorted in descending order by system organ class based on the proportion of participants in the Sema 7.2 mg arm experiencing at least one event.
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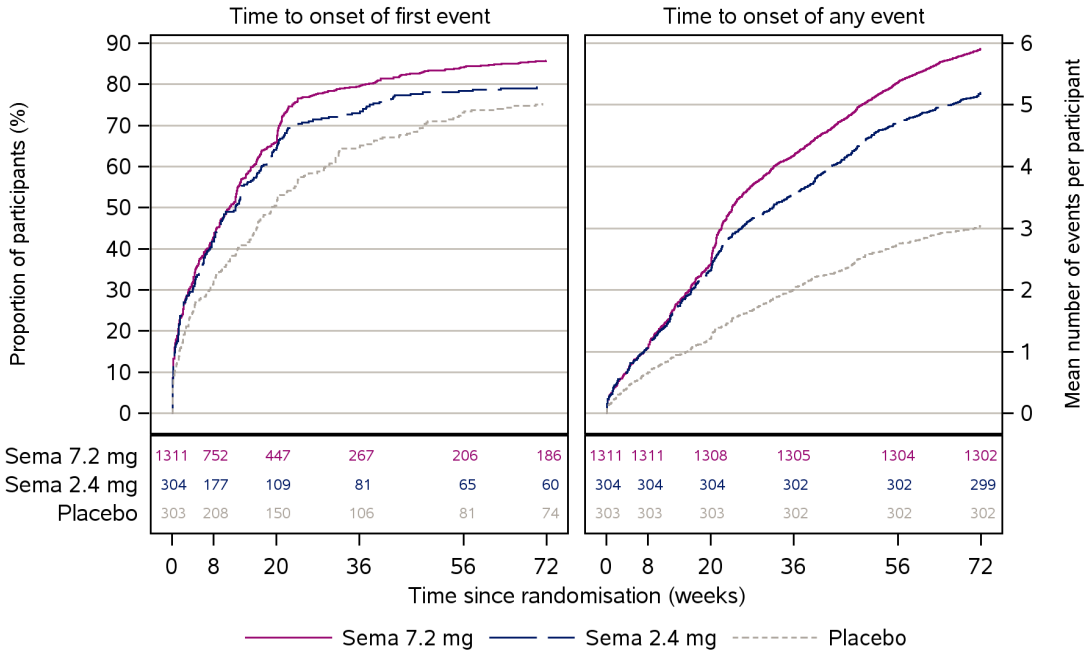
Figure 5-29 Adverse events - plot over time - on-treatment - safety analysis set - pool



Numbers shown in the lower panel are participants at risk.
Participants are considered as on-treatment if any dose of trial product has been administered within the prior 63 days.

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Assessor's comments:

The rate of AEs per 100 PYEs was highest in the 7.2 mg group. The severity (mild, moderate, severe) and outcome (not recovered, recovering and recovered) of the AEs were considered comparable between all groups. Most AEs were moderately severe. Most outcomes were recovered. More participants discontinued in the 7.2 mg group compared to 2.4 mg and placebo. **(Fig 5-1)**

Adverse events in the system organ classes (SOCs) gastrointestinal disorders, nervous system disorders and skin and subcutaneous tissue disorders were more reported in the 7.2 mg semaglutide group compared to 2.4 mg and placebo.

- Gastrointestinal disorders: 66.7% (7.2 mg) vs. 57.9% (2.4 mg) and 37.0% (placebo)

- Nervous system disorders: 29.3% (7.2 mg) vs. 18.4% (2.4 mg) and 11.6% (placebo)

- Skin and subcutaneous tissue disorders: 20.4% (7.2 mg) vs. 13.2% (2.4 mg) and 5.6% (placebo)

- Infections and infestations were more reported in the 2.4 mg group: 37.1% (7.2 mg) vs. 40.1% (2.4 mg) and 33.7% (placebo)

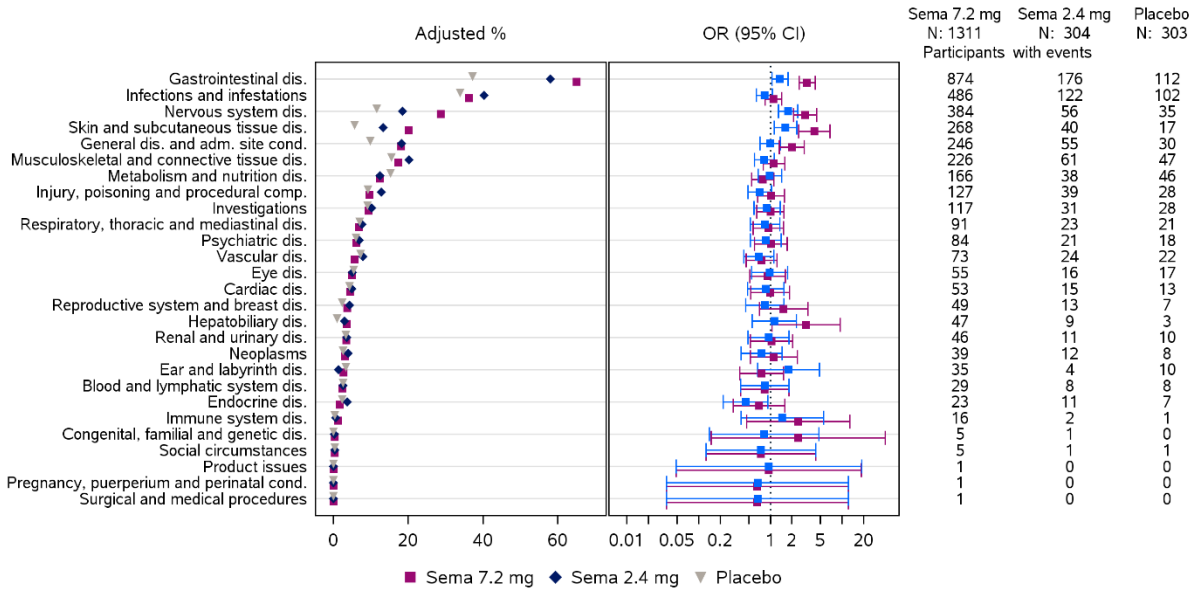
The number of events in other SOCs were comparable. **(Fig 5-2)**

Incidence of AEs were highest during the dose escalation phase (20 wks) of the studies, which is a well-known phenomenon. During the maintenance phase (52 wks), the AE incidence was similar between treatment groups (mean number of events per participant at wk 72 was 6 for 7.2 mg semaglutide and 5 for 2.4 semaglutide). Time to onset of first events was higher for 7.2 mg semaglutide **(Fig 5-3)**

Common adverse events reported by ≥5% of participants by SOC and PT

Forest plots including the proportion of participants with events, number of participants with events and odds ratios for semaglutide 7.2 mg compared to semaglutide 2.4 mg and placebo (with 95% CIs) are presented by SOC in Figure 5-4, and by PT (for AEs reported by ≥5% of participants in any treatment group) in Figure 2-7. Most of the common AEs were non-serious, of mild or moderate severity, and reported as recovered (Figure 5-1). In the STEP UP pool, AEs were overall reported by a slightly higher proportion of participants with semaglutide 7.2 mg (73.0%) compared to semaglutide 2.4 mg (67.5%), with the lowest proportion in placebo (51.7%). For the following SOCs, higher proportions of participants or higher rates were observed with semaglutide 7.2 mg compared to semaglutide 2.4 mg and placebo: Gastrointestinal disorders, Nervous system disorders, and Skin and subcutaneous. These SOCs will be summarised below.

Figure 5-30 Adverse events – statistical analysis by system organ class – forest plot – on-treatment – safety analysis set – pool



OR with 95% CIs for treatment comparisons sema 7.2 mg vs placebo shown in magenta color and sema 7.2 mg vs sema 2.4 mg shown in light blue color. Adverse events with onset prior to randomisation are not included.
Sorted in descending order by system organ class based on the proportion of participants in the Sema 7.2 mg arm experiencing at least one event.
%: Percentage of participants experiencing at least one event. OR: Odds Ratio. Confidence interval. N: Number of participants. dis. :disorders. cond.: conditions. adm.: administration. comp.: complications. Neoplasms include benign, malignant.
The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
Each of the groupings of adverse events were analysed using a binary logistic regression model with randomised treatment and trials as factors.
Participants are considered as on-treatment if any dose of trial product has been administered within the prior 63 days.
MedDRA version 27.1.

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Gastrointestinal disorders: A greater proportion of participants in the semaglutide groups reported AEs related to gastrointestinal disorders than in the placebo group. These types of AEs are well-known for semaglutide and for the GLP-1 RA class in general. GI AEs are addressed in details in Section 5.6.1.

Nervous system disorders: A greater proportion of participants reported AEs in the semaglutide 7.2 mg group compared to both the semaglutide 2.4 mg and placebo groups within the PT Hyperaesthesia (5.3% versus 0.7% versus 0.0%). Hyperaesthesia is evaluated as part of dysesthesia.

Skin and subcutaneous tissue disorders: A greater proportion of participants in the semaglutide 7.2 mg group reported AEs compared to both the semaglutide 2.4 mg and placebo groups within the PTs Sensitive skin (6.7% versus 0.6% versus 0.0%) and Alopecia (5.8% versus 3.3% versus 1.0%. Most of the events related to Alopecia were reported as the lower-level term Hair loss (5.3% versus 2.4% versus 1.0%). The events of Alopecia were associated with weight loss, as a higher proportion and rate of events

related to Alopecia were reported in participants with ≥20% weight loss, with a more pronounced difference in the semaglutide 7.2 mg group (≥20% weight loss: 9.0%, 6.0 events per 100 PYE versus. <20% weight loss: 4.1% and 2.9 events per 100 PYE) compared to the semaglutide 2.4 mg group (≥20% weight loss: 4.2%, 2.8 events per 100 PYE versus <20% weight loss: 3.4%, 2.3 events per 100 PYE). All AEs related to Alopecia were non-serious, and most were mild in severity and reported as recovered. In the semaglutide 7.2 mg group, 1 AE related to Alopecia led to permanent treatment discontinuation, 1 AE led to temporary interruption of trial product, and 5 AEs led to dose reduction. No AEs related to Alopecia led to changes in trial product administration in the semaglutide 2.4 mg or placebo groups.

Assessor's comments:

The reported AEs are comparable with the known safety profile of semaglutide. Most PTs were in the 7.2 mg semaglutide group.

Gastrointestinal disorders

The most frequently reported PTs were nausea, diarrhoea, vomiting, constipation and dyspepsia.

- Nausea: 40.3% (7.2 mg) vs. 34.9% (2.4 mg) and 12.5% (placebo)

- Diarrhoea: 25.0% (7.2 mg) vs. 25.3% (2.4 mg) and 11.6% (placebo)

- Vomiting: 22.9% (7.2 mg) vs. 15.5% (2.4 mg) and 5.6% (placebo)

- Constipation: 21.2% (7.2 mg) vs. 19.1% (2.4 mg) and 7.6% (placebo)

- Dyspepsia: 9.8% (7.2 mg) vs. 5.3% (2.4 mg) and 3.0% (placebo)

Overall, most of these events were mild to moderate in severity, possibly or probably related to trial product, and reported as recovered.

Nervous system disorders and Skin and subcutaneous tissue disorders

The most frequently reported PTs were Hyperaesthesia, Dizziness, Headache, sensitive skin and alopecia.

- Hyperaesthesia: 5.3% (7.2 mg) vs. 0.7% (2.4 mg) and 0.0% (placebo)

- Dizziness: 5.3% (7.2 mg) vs. 5.3% (2.4 mg) and 1.0% (placebo)

- Headache: 8.9% (7.2 mg) vs. 7.9% (2.4 mg) and 6.7% (placebo)

- Sensitive skin 6.7% (7.2 mg) vs. 0.6% (2.4 mg) and 0.0% (placebo)

- Alopecia 5.8% (7.2 mg) vs. 3.3% (2.4 mg) and 1.0% (placebo). Most of the events related to Alopecia were reported as the lower-level term Hair loss (5.3% vs 2.4% vs 1.0%)

Dysaesthesia

Adverse events related to dysaesthesia were evaluated by PTs in a summary plot.

Dysaesthesia: 22% (7,2 mg), 5.6% (2.4 mg) 0.3% (placebo).

Especially the PT's sensitive skin, hyperaesthesia and dysaesthesia were more reported in the 7.2 mg semaglutide group. All AEs related to dysaesthesia were non-serious, and the majority were mild in severity and reported as recovered. Nevertheless, in 5% of patients dysaesthesia was reported as not recovered.

Deaths and other serious adverse events

6 deaths were reported during the STEP UP T2D study. No deaths were reported during the STEP UP study. The deaths were distributed with 4 participants (1.3%) in the semaglutide 7.2 mg group, 1 participant (1.0%) in the semaglutide 2.4 mg group, and 1 participant (1.0%) in the placebo group.

There was no pattern in the cases of death or associated PTs. Five AEs were judged by the investigator as unlikely related to trial product. One AE was judged by the investigator as possibly related to trial product, under the SOC/PT Cardiac disorders/Arrhythmia (Case #1090345). The case of arrhythmia was judged by the sponsor as unlikely related to trial product; the participant's underlying conditions of severe obesity, hypertension and hypercholesterolaemia likely contributed to the event, and the trial product so far has not been associated with malignant cardiac arrhythmia.

SAEs were reported by similar proportions of participants and with comparable event rates in the semaglutide 7.2 mg and placebo groups, and higher in the semaglutide 2.4 mg group. SAEs were distributed across multiple SOCs and PTs with no clustering observed in any of the treatment groups.

Assessor's comments:

Overall, 6 deaths were reported in STEP UP T2D study (4 in 7.2 mg, 1 in 2.4 mg and 1 placebo group). No new safety patterns was identified from the cases.

Adverse events leading to permanent treatment discontinuation

The proportion of participants with AEs leading to permanent treatment discontinuation was similar with semaglutide 7.2 mg (5.4%) and semaglutide 2.4 mg (4.0%), and lower with placebo (1.0%). The difference was primarily driven by events of gastrointestinal disorders, with nausea, vomiting and diarrhoea as the most common events. AEs leading to permanent trial product discontinuation was evenly distributed during the treatment period in both STEP UP and STEP UP T2D.

Assessor's comments:

The AEs leading to discontinuation of semaglutide are overall comparable. The AE rate was higher in the semaglutide 7.2 mg group for GI disorders, Nervous system disorders, and Skin and subcutaneous tissue disorders SOCs compared to the semaglutide 2.4 mg group and placebo.

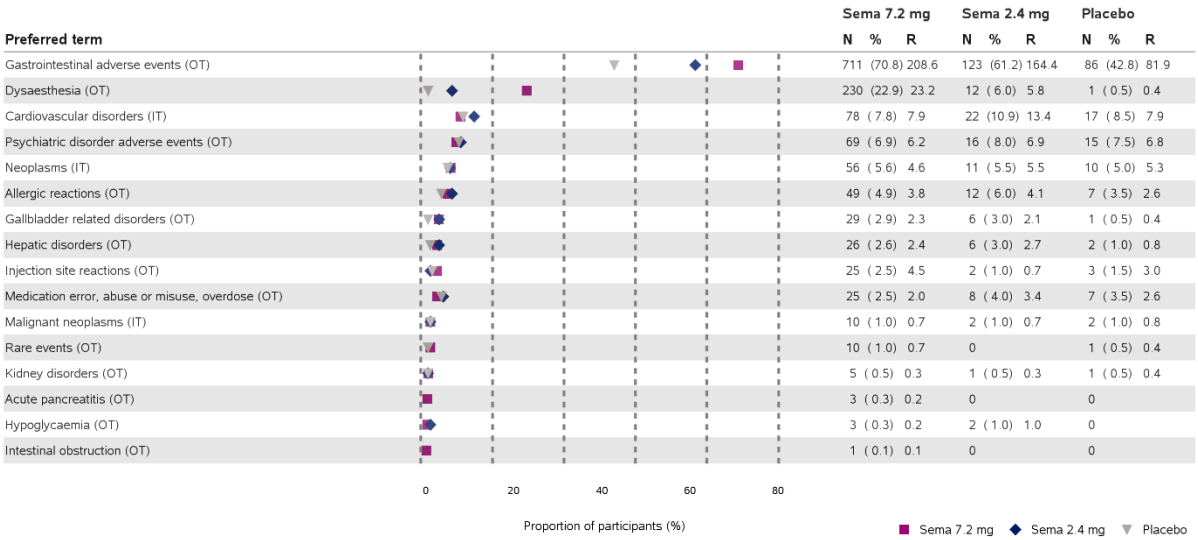
Safety focus areas

Based on the disease, drug class, and regulatory requirements, safety focus areas of special interest were pre-defined for the evaluation of safety with semaglutide 7.2 mg in both STEP UP and STEP UP T2D and comprised:

- Gastrointestinal disorders
- Dysaesthesia
- Cardiovascular disorders
- Psychiatric disorders
- Neoplasms
- Allergic reactions
- Gallbladder-related disorders
- Hepatic disorders
- Injection site reactions
- Medication errors, abuse or misuse, overdose (OT)
- Malignant neoplasms
- Rare events
- Kidney disorders
- Acute pancreatitis
- Hypoglycaemia
- Intestinal obstruction

An overview of the results for the safety focus areas in presented in Figure 5-5.

Figure 5-31 Overview of results for the safety focus areas



N: Number of participants experiencing at least one event. %: Percentage of participants experiencing at least one event. R: Event rate per 100 years. OT: On-treatment. IT: In-trial. Adverse events with onset date during on-treatment period: A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 63 days.
Only safety focus areas with reported events included. Sorted in descending order by preferred term based on the percentage of participants in the Sema 7.2 mg arm experiencing at least one event.
MedDRA version 27.1 .

nn9536/nn9536-4999/csr_20250318_er
20MAR2025:06:19:31 - faesummarysub.sas/faesummfocusot.png

Gastrointestinal disorders

Gastrointestinal AEs were reported more frequently with semaglutide 7.2 mg (70.8%) than with semaglutide 2.4 mg (61.2%) and placebo (vs 42.8%). The most frequently reported gastrointestinal AEs were nausea, vomiting and diarrhoea. Most of the gastrointestinal AEs were non-serious and mild or moderate in severity. The proportion of participants with serious or severe gastrointestinal AEs were similar across the semaglutide treatment groups. As expected, most gastrointestinal AEs were reported during dose escalation and were of short duration with no differences across the semaglutide treatment groups. The proportion of participants with gastrointestinal AEs leading to permanent treatment discontinuation increased with increasing doses of semaglutide, driven by nausea, vomiting and diarrhoea.

Gastrointestinal AEs were reported more frequently with semaglutide 7.2 mg (70.8%) than with semaglutide 2.4 mg (61.2%) and placebo (vs 42.8%). The most frequently reported gastrointestinal AEs were nausea, vomiting and diarrhoea.

Most of the gastrointestinal AEs were non-serious and mild or moderate in severity. The proportion of participants with serious or severe gastrointestinal AEs were similar across the semaglutide treatment groups. As expected, most gastrointestinal AEs were reported during dose escalation.

Dysaesthesia

As described above, AEs related to dysaesthesia were reported by a higher proportion of participants, and at a higher rate, in the semaglutide 7.2 mg group compared to the semaglutide 2.4 mg and placebo

groups. No SAEs related to dysaesthesia were reported, and most events were mild in severity and reported as recovered.

Overall, the data suggest an increased frequency of AEs related to dysaesthesia with semaglutide 7.2 mg compared to semaglutide 2.4 mg and placebo. The increase in reporting of dysaesthesia, was as expected, considering dysaesthesia is observed more frequently with high exposure levels of semaglutide. Dysaesthesia was more frequently reported during the dose escalation phase of semaglutide. Overall, most of the AEs reported were non-serious, mild and recovered. Nevertheless, in 5% of patients dysaesthesia was reported as not recovered.

Other safety focus areas

Pancreatitis

AEs of pancreatitis were reported by a comparable proportion of participants and rate of events in the semaglutide 7.2 mg (0.2%, 0.1 events per 100 PYE) and semaglutide 2.4 mg (0.3%, 0.2 events per 100 PYE) groups. In the placebo group, no AEs of pancreatitis were reported.

The proportion of participants who reported increased pancreatic enzymes and increased levels of serum amylase or lipase were similar or lower in the semaglutide 7.2 mg group compared to the semaglutide 2.4 mg group.

AEs of pancreatitis were reported by a comparable proportion of participants and rate of events in the semaglutide 7.2 mg (0.2%, 0.1 events per 100 PYE) and semaglutide 2.4 mg (0.3%, 0.2 events per 100 PYE) groups. In the placebo group, no AEs of pancreatitis were reported.

Gall bladder

AEs related to gallbladder-related disorders were reported by similar proportion of participants and reporting rates in both the semaglutide 7.2 mg (2.4%, 1.9 events per 100 PYE) and semaglutide 2.4 mg (2.3%, 1.6 events per 100 PYE) groups. In the placebo group, only 0.3% gallbladder-related disorders were reported. The most frequently reported AEs were the PTs Cholelithiasis, Cholecystitis, and Cholecystitis acute. The majority of AEs related to gallbladder-related disorders were non-serious, mild or moderate in severity, and reported as recovered. SAEs were reported by a comparable proportion of participants, and at a comparable rate, in semaglutide 7.2 mg (0.7%, 0.6 events per 100 PYE), semaglutide 2.4 mg (0.7%, 0.5 events per 100 PYE), and placebo (0.7%, 0.5 events per 100 PYE) groups. All SAEs recovered

Thus, the data do suggest an increased risk for gallbladder-related disorders with semaglutide compared to placebo. However, there were no differences between 7.2 mg and 2.4 mg.

AEs related to gallbladder-related disorders were reported by a higher proportion of participants and reporting rates in the semaglutide 7.2 mg (2.4%, 1.9 events per 100 PYE) and semaglutide 2.4 mg (2.3%, 1.6 events per 100 PYE) groups compared to the placebo group (only 0.3% gallbladder-related disorders). The most frequently reported AEs were the PTs Cholelithiasis, Cholecystitis, and Cholecystitis acute.

Psychiatric disorders

AEs related to psychiatric disorders were reported by a comparable proportion and at a comparable rate in the semaglutide 7.2 mg (6.2%, 5.5 events per 100 PYE), semaglutide 2.4 mg (7.0%, 5.9 events per 100 PYE), and placebo (6.0%, 5.2 events per 100 PYE) groups. One SAE was reported (PT Depression) and occurred in the semaglutide 7.2 mg group (Case #1140308). It was classified as severe, unlikely related to the trial product and resolved without changes in the dose of the trial product. One AE of suicidal ideation was reported. The event occurred in the placebo group, and was non-serious, mild in severity, and recovered.

At the post-baseline assessment, few participants overall answered positively to the questions about suicidal ideation and/or behaviour in the C-SSRS, with similar proportions across all groups (semaglutide 7.2 mg: 0.4%, semaglutide 2.4 mg: 0.3%, placebo: 0.7%).

AEs related to psychiatric disorders were reported by a comparable proportion and at a comparable rate in the semaglutide 7.2 mg (6.2%, 5.5 events per 100 PYE), semaglutide 2.4 mg (7.0%, 5.9 events per 100 PYE), and placebo (6.0%, 5.2 events per 100 PYE) groups. At the post-baseline assessment, few participants overall answered positively to the questions about suicidal ideation and/or behaviour in the C-SSRS, with similar proportions across all groups (semaglutide 7.2 mg: 0.4%, semaglutide 2.4 mg: 0.3%, placebo: 0.7%).

Hepatic disorders

AEs related to hepatic disorders were reported by a lower proportion of participants, and at a lower rate, in semaglutide 7.2 mg (2.7%, 2.6 events per 100 PYE) compared to the semaglutide 2.4 mg group (3.3%, 3.1 events per 100 PYE). The proportions and rates in placebo were lower (1.0%, 1.0 events per 100 PYE). The majority of AEs related to hepatic disorders were non-serious, mild or moderate in severity, unlikely related to trial product, not recovered, and none led to permanent treatment discontinuation. In total, 5 SAEs were reported in 3 participants, with 1 SAE in 1 participant in the semaglutide 7.2 mg group (<0.1%, <0.1 events per 100 PYE) and 4 SAEs in 2 participants in the semaglutide 2.4 mg group (0.7%, 0.9 events per 100 PYE;).

There were several events of Hepatic steatosis, with a higher proportion and rate in the semaglutide 7.2 mg (1.0%, 0.7 events per 100 PYE) compared to semaglutide 2.4 mg (0.3%, 0.2 events per 100 PYE) and placebo (0.3%, 0.3 events per 100 PYE).

From baseline to week 72, the mean levels of ALP decreased in the semaglutide 7.2 mg and semaglutide 2.4 mg groups and remained stable in placebo. Mean levels of AST, ALT, and GGT decreased slightly from baseline to week 72 in all treatment groups, with the greatest decrease in semaglutide 7.2 mg, followed by semaglutide 2.4 mg and placebo.

AEs related to hepatic disorders were reported by a lower proportion of participants, and at a lower rate, in semaglutide 7.2 mg (2.7%, 2.6 events per 100 PYE) compared to the semaglutide 2.4 mg group (3.3%, 3.1 events per 100 PYE). The proportions and rates in placebo were lower (1.0%, 1.0 events per 100 PYE). The majority of AEs related to hepatic disorders were non-serious, mild or moderate in severity, unlikely related to trial product, not recovered, and none led to permanent treatment discontinuation. From baseline to week 72, the mean levels of ALP decreased in the semaglutide 7.2 mg and semaglutide 2.4 mg groups and remained stable in placebo.

Immunogenicity

Allergic reactions

AEs related to Allergic reactions were reported by a similar proportion of participants, and at a similar rate, in both the s.c semaglutide 7.2 mg (4.6%, 3.8 events per 100 PYE) and semaglutide 2.4 mg (4.7%, 3.2 events per 100 PYE) groups, and lower in placebo (3.3%, 2.5 events per 100 PYE). The most frequently reported AE in all three treatment groups was under the PT Rash and was reported by a comparable proportion of participants in semaglutide 7.2 mg (1.5%, 1.1 events per 100 PYE), semaglutide 2.4 mg (1.3%, 0.9 events per 100 PYE), and by a higher proportion of participants in placebo (2.0%, 1.5 events per 100 PYE) groups.

Injection site reactions

AEs related to injection site reactions were reported by a slightly higher proportion of participants, and at a slightly higher rate, in the semaglutide 7.2 mg group (2.5%, 3.9 events per 100 PYE), compared to semaglutide 2.4 mg (1.3%, 0.9 events per 100 PYE) and placebo (1.6%, 2.9 events per 100 PYE).

Anti-semaglutide antibodies

Overall, the presence of anti-semaglutide antibodies did not appear to impact exposure, efficacy, or safety of semaglutide in either semaglutide treatment group.

AEs related to allergic reactions were reported by a similar proportion of participants, and at a similar rate, in both the s.c semaglutide 7.2 mg (4.6%, 3.8 events per 100 PYE) and semaglutide 2.4 mg (4.7%, 3.2 events per 100 PYE) groups, and lower in placebo (3.3%, 2.5 events per 100 PYE).

AEs related to injection site reactions were reported by a slightly higher proportion of participants, and at a slightly higher rate, in the semaglutide 7.2 mg group (2.5%, 3.9 events per 100 PYE), compared to semaglutide 2.4 mg (1.3%, 0.9 events per 100 PYE) and placebo (1.6%, 2.9 events per 100 PYE).

Overall, the presence of anti-semaglutide antibodies did not appear to impact exposure, efficacy, or safety of semaglutide in either semaglutide treatment group.

Cardiovascular safety

AEs related to cardiovascular disorders were reported by a similar proportion of participants, and at a similar rate, in the semaglutide 7.2 mg (8.7%, 9.8 events per 100 PYE) and placebo (8.9%, 9.1 events per 100 PYE) groups, with a higher proportion and rate in the semaglutide 2.4 mg group (10.9%).

The most frequently reported AE in the semaglutide 7.2 mg group was Palpitations, which was reported at a higher proportion and rate in the semaglutide 7.2 mg (1.1%, 1.5 events per 100 PYE) group compared to semaglutide 2.4 mg (0.3%, 0.2 events per 100 PYE) and placebo (0.3%, 0.2 events per 100 PYE).

The difference in SAEs between treatment groups was minor; the proportion and rate of SAEs was lowest in the semaglutide 7.2 mg group (2.2%, 1.8 events per 100 PYE), followed by semaglutide 2.4 mg (2.6%, 4.2 events per 100 PYE) and placebo (2.9%, 3.5 events per 100 PYE). 3 SAEs were fatal, with 2 occurring in the semaglutide 7.2 mg group and 1 occurring in the placebo group.

Pulse

The proportion of participants with maximum pulse increase from baseline ≥20 bpm at one or more timepoints was highest in the semaglutide 7.2 mg group (23.8%), followed by semaglutide 2.4 mg (19.8%) and placebo (13.2%) groups (Appendix 7.5, TFL 7.5.2).

At week 72, the mean change from baseline was 1 bpm for the semaglutide 7.2 mg and semaglutide 2.4 mg groups, and -2 bpm for placebo

Blood pressure

The proportion of participants who experienced a reduction in maximum systolic blood pressure of 20 mmHg or more from baseline was highest in the semaglutide 7.2 mg group (52.9%) compared to the semaglutide 2.4 mg (44.9%) and placebo (31.8%) groups (Appendix 7.5, TFL 7.5.8).

At week 72, the mean change in systolic and diastolic blood pressure from baseline was -10 mmHg and -4 mmHg for the semaglutide 7.2 mg group, -7 mmHg and -3 mmHg for the semaglutide 2.4 mg group, and -3 mmHg and -2 mmHg for the placebo group

AEs related to cardiovascular disorders were reported by a similar proportion of participants, and at a similar rate, in the semaglutide 7.2 mg (8.7%, 9.8 events per 100 PYE) and placebo (8.9%, 9.1 events per 100 PYE) groups, with a higher proportion and rate in the semaglutide 2.4 mg group (10.9%).

The difference in SAEs between treatment groups was minor; the proportion and rate of SAEs was lowest in the semaglutide 7.2 mg group (2.2%, 1.8 events per 100 PYE), followed by semaglutide 2.4 mg (2.6%, 4.2 events per 100 PYE) and placebo (2.9%, 3.5 events per 100 PYE). 3 SAEs were fatal, with 2 occurring in the semaglutide 7.2 mg group and 1 occurring in the placebo group.

At week 72, the mean change in pulse from baseline was 1 bpm for the semaglutide 7.2 mg and semaglutide 2.4 mg groups, and -2 bpm for placebo.

At week 72, the mean change in systolic and diastolic blood pressure from baseline was -10 mmHg and -4 mmHg for the semaglutide 7.2 mg group, -7 mmHg and -3 mmHg for the semaglutide 2.4 mg group, and -3 mmHg and -2 mmHg for the placebo group.

Neoplasms

The proportion of participants and rate of events were similar among the semaglutide 7.2 mg (6.4%, 4.8 events per 100 PYE, 93 AEs in 81 participants), semaglutide 2.4 mg (5.9%, 5.6 events per 100 PYE, 26 AEs in 18 participants), and placebo (5.0%, 4.5 events per 100 PYE, 20 AEs in 15 participants) groups. The AEs were distributed across PTsA total of 31 SAEs were reported; there were no notable differences among treatment groups, with a similar proportion of participants reporting SAEs in semaglutide 7.2 mg (1.7%, 1.1 events per 100 PYE), semaglutide 2.4 mg (2.0%, 1.3 events per 100 PYE), and placebo (1.3%, 0.9 events per 100 PYE).

AEs of Blood calcitonin increased were reported by a similar proportion of participants and at a similar rate in all treatment groups, with 0.9% (0.6 events per 100 PYE) in the semaglutide 7.2 mg group, 1.0% (0.9 events per 100 PYE) in the semaglutide 2.4 mg group, and 1.3% (0.9 events per 100 PYE) in the placebo group. Mean levels of calcitonin decreased slightly in each treatment group from week 20 to week 72

The proportion of participants and rate of neoplasm events were similar among the semaglutide 7.2 mg (6.4%, 4.8 events per 100 PYE, 93 AEs in 81 participants), semaglutide 2.4 mg (5.9%, 5.6 events per

100 PYE, 26 AEs in 18 participants), and placebo (5.0%, 4.5 events per 100 PYE, 20 AEs in 15 participants) groups.

AEs of blood calcitonin increased were reported by a similar proportion of participants and at a similar rate in all treatment groups.

Kidney function

The proportion of participants with AEs related to Kidney disorders and the rate of such events were lower in the semaglutide 7.2 mg (0.3%, 0.2 events per 100 PYE) than in the semaglutide 2.4 mg (0.7%, 0.7 events per 100 PYE) and placebo (0.7%, 0.5 events per 100 PYE. In total, 5 SAEs were reported in 4 participants, all of which occurred in the semaglutide 2.4 mg or placebo groups

Creatinine and eGFR values were stable over time and comparable across treatment groups. A higher proportion of participants had creatinine levels >1.5x baseline in the semaglutide 7.2 mg group (1.8%) compared to semaglutide 2.4 mg (1.3%) and placebo (0.3%).

The proportion of participants with AEs related to kidney disorders and the rate of such events were lower in the semaglutide 7.2 mg (0.3%, 0.2 events per 100 PYE) than in the semaglutide 2.4 mg (0.7%, 0.7 events per 100 PYE) and placebo (0.7%, 0.5 events per 100 PYE. Creatinine and eGFR values were stable over time and comparable across treatment groups.

Aspiration

No events related to aspiration in association with anesthesia or deep sedation were reported.

Intestinal obstruction

The search for events of Intestinal obstruction captured one AE (PT Oesophageal stenosis) in the semaglutide 7.2 mg group. The event was non-serious, moderate in severity, judged by the investigator as unlikely related to trial product, and reported as recovering. 1 severe SAE was identified under the reported term of "fecal impaction (intestinal obstruction)" and is therefore included here; the event was not captured by the predefined MedDRA search because it was reported under the PT Faecaloma. The event occurred in the semaglutide 7.2 mg group, led to permanent treatment discontinuation, and the participant recovered.

Assessor's comments:

No events related to aspiration in association with anesthesia or deep sedation were reported. The search for events of Intestinal obstruction captured one AE (PT Oesophageal stenosis) in the semaglutide 7.2 mg group.

Hypoglycaemia

AEs related to hypoglycaemia in STEP UP

In STEP UP, very few AEs related to Hypoglycaemia were reported; 3 AEs were reported in 3 participants in the semaglutide 7.2 mg group (0.3%, 0.2 events per 100 PYE), 3 AEs were reported in 2 participants in the semaglutide 2.4 mg group (1.0%, 1.0 events per 100 PYE), and none were reported in the placebo group. All reported AEs were non-serious, mild in severity. 4 AEs were reported as recovered, and 2 (1 in

each semaglutide treatment group) were reported as not recovered. 1 AE in the semaglutide 2.4 mg group led to temporary interruption of trial product.

AEs related to hypoglycaemia in STEP UP T2D

In STEP UP T2D, AEs related to Hypoglycaemia were categorized as level 1-3, with level 2 defined as clinically significant and level 3 defined as severe. There were no imbalances in level 2 hypoglycaemic episodes across treatment groups, with 2.0% in semaglutide 7.2 mg, 1.9% in semaglutide 2.4 mg, and 2.9% in placebo. There was only 1 level 3 hypoglycaemic episode reported, which occurred in the placebo group.

Assessor's comments:

In STEP UP T2D, AEs related to hypoglycaemia were categorized as level 1-3, with level 2 defined as clinically significant and level 3 defined as severe. There were no imbalances in level 2 hypoglycaemic episodes across treatment groups, with 2.0% in semaglutide 7.2 mg, 1.9% in semaglutide 2.4 mg, and 2.9% in placebo. There was only 1 level 3 hypoglycaemic episode reported, which occurred in the placebo group.

Overall, the data do not suggest an important effect on risk of hypoglycaemic episodes with semaglutide 7.2 mg compared to semaglutide 2.4 mg in patients with diabetes.

In STEP UP in patients without diabetes, very few AEs related to Hypoglycaemia were reported. However, there was higher risk in both semaglutide groups compared to the placebo group. 3 AEs were reported in 3 participants in the semaglutide 7.2 mg group (0.3%, 0.2 events per 100 PYE), 3 AEs were reported in 2 participants in the semaglutide 2.4 mg group (1.0%, 1.0 events per 100 PYE), and none were reported in the placebo group. All reported AEs were non-serious, mild in severity. 4 AEs were reported as recovered, but unfortunately 2 (1 in each semaglutide treatment group) were reported as not recovered. This is worrisome. The company should discuss the risk of hypoglycaemia with higher doses of semaglutide in patients without diabetes (OC).

Retinal disorders

In STEP UP, events related to retinal disorders were not assessed and eye examinations were not performed as participants with T2D were excluded from the study.

In STEP UP T2D, retinal disorders were assessed using a predefined MedDRA search using the in-trial period and results from eye examinations. Additional information was collected in the case of new onset or worsening of diabetic retinopathy. The proportion of participants, but not the rate of events, for AEs related to retinal disorders was similar between the semaglutide 7.2 mg (5.9%, 4.1 events per 100 PYE) and semaglutide 2.4 mg (5.8%, 8.8 events per 100 PYE) groups. The placebo group had the highest proportion of participants with AEs of retinal disorders (8.8%, 6.5 events per 100 PYE). Most events were reported as not recovered, but most events were mild or moderate in severity.

1 mild SAE was reported, which occurred in the semaglutide 2.4 mg group, and recovered with no change in trial product administration. The most frequently reported AE by PT was Diabetic retinopathy. The proportion and rate of AEs of Diabetic retinopathy were lowest in semaglutide 7.2 mg (1.3%, 0.9 events per 100 PYE) followed by semaglutide 2.4 mg (1.9%, 1.9 events per 100 PYE) and placebo (3.9%, 2.6 events per 100 PYE).

Assessor's comments:

The proportion and rate of AEs of diabetic retinopathy were lowest in semaglutide 7.2 mg (1.3%, 0.9 events per 100 PYE) followed by semaglutide 2.4 mg (1.9%, 1.9 events per 100 PYE) and placebo (3.9%, 2.6 events per 100 PYE).

Retinal disorders are a known risk of Wegovy in the T2D population. Overall, the data do not suggest an increased risk of retinal disorders with semaglutide 7.2 mg compared to semaglutide 2.4 mg in the T2D population.

Rare events

Overall, few events were captured by the rare event search. The majority of the AEs across the treatment groups were non-serious, mild in severity, unlikely related to trial product, and reported as recovered. No AEs led to permanent treatment discontinuation, temporary interruption of trial product, or dose reduction of trial product in any of the treatment groups.

Safety in subgroups

The safety of semaglutide 7.2 mg was evaluated in subgroups defined by sex, age, race, ethnicity, region, baseline body weight, baseline BMI, baseline renal function and glycaemic status.

The evaluation of the subgroups investigated did not reveal any new safety concerns or markedly different AE profiles for semaglutide 7.2 mg relative to placebo and semaglutide 2.4 mg for any subgroups. Based on the data, no dose adjustment is warranted in any of the subgroups investigated.

Assessor's comments:

The evaluation of the subgroups investigated did not reveal any new safety concerns or markedly different AE profiles for semaglutide 7.2 mg relative to placebo and semaglutide 2.4 mg for any subgroups.

4.3. Discussion

The safety of semaglutide 7.2 mg was evaluated by a pooled data set consisting of data from both studies STEP UP and STEP UP T2D. The exposure to semaglutide 7.2 mg was 1311 participants, 1004 in the STEP UP trial and 307 in STEP UP T2D corresponding to a total of 1915 PYE exposure.

Overall AE rate

In the pooled analysis (STEP UP Pool), the overall AE rate was higher for semaglutide 7.2 mg compared to 2.4 mg and placebo. (85.1% (7.2 mg) vs. 81.1% (2.4 mg) and 76% (placebo). Most reported events were gastrointestinal disorders, nervous system disorders, and skin and subcutaneous disorders. Of the PTs, dysaesthesia and alopecia were mostly reported.

For details on the risk of dysaesthesia, see below.

A greater proportion of participants in the semaglutide 7.2 mg group reported AEs compared to both the semaglutide 2.4 mg and placebo groups within the PTs Alopecia (5.8% versus 3.3% versus 1.0%). The

events of Alopecia were associated with weight loss, as a higher proportion and rate of events related to Alopecia were reported in participants with ≥20% weight loss, with a more pronounced difference in the semaglutide 7.2 mg group (≥20% weight loss: 9.0%, 6.0 events per 100 PYE versus. <20% weight loss: 4.1% and 2.9 events per 100 PYE) compared to the semaglutide 2.4 mg group (≥20% weight loss: 4.2%, 2.8 events per 100 PYE versus <20% weight loss: 3.4%, 2.3 events per 100 PYE). All AEs related to Alopecia were non-serious, and most were mild in severity and reported as recovered. In the semaglutide 7.2 mg group, 1 AE related to Alopecia led to permanent treatment discontinuation, 1 AE led to temporary interruption of trial product, and 5 AEs led to dose reduction. No AEs related to Alopecia led to changes in trial product administration in the semaglutide 2.4 mg or placebo groups.

Discontinuations

Due to AEs, semaglutide treatment was temporarily interrupted or permanently discontinued:

- temporarily discontinued: 9.8% (7.2 mg) vs. 9.5% (2.4 mg) and 3.3% (placebo)

- permanently discontinued: 5.4% (7.2 mg) vs. 4.6% (2.4 mg) and 1.6% (placebo) -

- dose reduction: 19.1 (7.2 mg) vs. 12.8% (2.4 mg) and 1.0% (placebo).

Serious AEs

Overall, serious AEs were mostly reported in the 2.4 mg group and were comparable between 7.2 mg group, the 2.4 mg group and placebo (7.5%, 10.2% and 6.6% respectively).

In the 2,4 semaglutide group, one patients reported 21 SAEs including one fatal event.

Clinical supply breach

It must be noted that due to a clinical supply breach, a total of 99 patients in the 7.2 mg semaglutide group received a lower semaglutide dose of 1.7 mg or less for ~ two months. A lower semaglutide dose may lead to an underestimation of the risks of the proposed new dose. Considering the study duration of 17 months and the total exposure group of 1212 participants, a lower dose for 2 months in 99 patients is likely to have only a modest effect. To evaluate whether this has affected the safety profile of semaglutide 7.2 mg, the company performed an additional analysis after exclusion of the 99 participants. The results showed no or minimal differences in the proportion and rate of evaluated events compared to the total safety population.

Dose escalation

Incidence of AEs were highest during the dose escalation phase (20 wks) of the studies, which is a well-known phenomenon. During the maintenance phase (52 wks), the AE incidence was similar between treatment groups (mean number of events per participant at wk 72 was 6 for 7.2 mg sematlugide and 5 for 2.4 semaglutide). Time to onset of first events was higher for 7.2 mg semaglutide. The reported AEs are comparable with the known safety profile of semaglutide. Most PTs were in the 7.2 mg semaglutide group.

<u>Safety focus areas</u>

Dysaesthesia

Dysaesthesia AEs were reported more frequently with semaglutide 7.2 mg (22%) than with semaglutide 2.4 mg (5.6%) and placebo (0.3%). Especially the PT's sensitive skin, hyperaesthesia and dysaesthesia were more reported in the 7.2 mg semaglutide group. All AEs related to dysaesthesia were non-serious, and the majority were mild in severity and reported as recovered. Nevertheless, in 5% of patients dysaesthesia was reported as not recovered. Overall, the data suggest a remarkably increased frequency of AEs related to dysaesthesia with semaglutide 7.2 mg compared to semaglutide 2.4 mg and placebo. The risk is much higher than previously observed with higher doses of oral semaglutide. In PIONEER PLUS, the proportion of patients reporting AEs related to a clinical picture of dysaesthesia were 5.2% (5.7 events per 100 PYE) with oral semaglutide 50 mg, 2.1% (1.7 events per 100 PYE) with oral semaglutide 25 mg and 1.1% (1.2 events per 100 PYE) with oral semaglutide 14 mg.

We agree with the company that the reported symptoms and location of the affected areas are diverse and do not indicate an anatomical pattern, which is typical for a neuropathy. However, the underlying mechanism for dysaesthesia remains unknown. This is considered a problem as risks with unknown underlying mechanisms are unpredictable and difficult to avoid or mitigate. Long term effects of the 3 times higher dose on dysaesthesia are unknown.

Across the STEP UP studies, 66 (15%) of the 434 events identified by the dysaesthesia MedDRA search had not recovered in the semaglutide 7.2 mg group. For the events that did recover in the semaglutide 7.2 mg group, 191 events (44% of all reported events) only recovered after changes in the dose of the trial product.

We therefore consider it important that the high risk of dysaesthesia and other possible long term risks are taken into account when dosing semaglutide. The benefit/risk ratio may be acceptable in patient that lost a clinically relevant amount of weight. If efficacy of the high dose is not sufficient in a patient , the dose should be titrated back to avoid unnecessary risks. This issue can be mitigated by adding to the SPC that the 7.2 mg dose should be titrated back to 2.4 mg if a clinical improvement in body weight has not been achieved with the 7.2 mg dose**.** This is now stated in the SPC. In addition, it is important that Novo Nordisk continues to monitor dysaesthesia through routine post-marketing pharmacovigilance activities. Future clinical studies with semaglutide 7.2 mg should collect additionally detailed data to enhance the characterisation of any reported dysaesthesia events.

Gastrointestinal AEs

Gastrointestinal AEs were reported more frequently with semaglutide 7.2 mg (70.8%) than with semaglutide 2.4 mg (61.2%) and placebo (vs 42.8%). The most frequently reported gastrointestinal AEs were nausea, vomiting and diarrhoea. Most of the gastrointestinal AEs were non-serious and mild or moderate in severity. The proportion of participants with serious or severe gastrointestinal AEs were similar across the semaglutide treatment groups. As expected, most gastrointestinal AEs were reported during dose escalation. These types of AEs are well-known for semaglutide and for the GLP-1 RA class in general and can usually be managed.

Pancreatitis

AEs of pancreatitis were reported by a comparable proportion of participants and rate of events in the semaglutide 7.2 mg (0.2%, 0.1 events per 100 PYE) and semaglutide 2.4 mg (0.3%, 0.2 events per 100 PYE) groups. In the placebo group, no AEs of pancreatitis were reported.

Gallbladder-related disorders

AEs related to gallbladder-related disorders were reported by a higher proportion of participants and reporting rates in the semaglutide 7.2 mg (2.4%, 1.9 events per 100 PYE) and semaglutide 2.4 mg (2.3%, 1.6 events per 100 PYE) groups compared to the placebo group (only 0.3% gallbladder-related disorders).

Psychiatric disorders

AEs related to psychiatric disorders were reported by a comparable proportion and at a comparable rate in the semaglutide 7.2 mg (6.2%, 5.5 events per 100 PYE), semaglutide 2.4 mg (7.0%, 5.9 events per 100 PYE), and placebo (6.0%, 5.2 events per 100 PYE) groups.

At the post-baseline assessment, few participants overall answered positively to the questions about suicidal ideation and/or behaviour in the C-SSRS, with similar proportions across all groups (semaglutide 7.2 mg: 0.4%, semaglutide 2.4 mg: 0.3%, placebo: 0.7%).

Hepatic disorders

AEs related to hepatic disorders were reported by a lower proportion of participants, and at a lower rate, in semaglutide 7.2 mg (2.7%, 2.6 events per 100 PYE) compared to the semaglutide 2.4 mg group (3.3%, 3.1 events per 100 PYE). The proportions and rates in placebo were lower (1.0%, 1.0 events per 100 PYE). The majority of AEs related to hepatic disorders were non-serious, mild or moderate in severity, unlikely related to trial product, not recovered, and none led to permanent treatment discontinuation.

From baseline to week 72, the mean levels of ALP decreased in the semaglutide 7.2 mg and semaglutide 2.4 mg groups and remained stable in placebo.

Immunogenicity

AEs related to Allergic reactions were reported by a similar proportion of participants, and at a similar rate, in both the s.c semaglutide 7.2 mg (4.6%, 3.8 events per 100 PYE) and semaglutide 2.4 mg (4.7%, 3.2 events per 100 PYE) groups, and lower in placebo (3.3%, 2.5 events per 100 PYE).

AEs related to injection site reactions were reported by a slightly higher proportion of participants, and at a slightly higher rate, in the semaglutide 7.2 mg group (2.5%, 3.9 events per 100 PYE), compared to semaglutide 2.4 mg (1.3%, 0.9 events per 100 PYE) and placebo (1.6%, 2.9 events per 100 PYE).

The presence of anti-semaglutide antibodies did not appear to impact exposure, efficacy , or safety of semaglutide in either semaglutide treatment group.

Cardiovascular disorders

AEs related to cardiovascular disorders were reported by a similar proportion of participants, and at a similar rate, in the semaglutide 7.2 mg (8.7%, 9.8 events per 100 PYE) and placebo (8.9%, 9.1 events per 100 PYE) groups, with a higher proportion and rate in the semaglutide 2.4 mg group (10.9%).

The difference in cardiovascular SAEs between treatment groups was minor; the proportion and rate of SAEs was lowest in the semaglutide 7.2 mg group (2.2%, 1.8 events per 100 PYE), followed by semaglutide 2.4 mg (2.6%, 4.2 events per 100 PYE) and placebo (2.9%, 3.5 events per 100 PYE). 3 SAEs were fatal, with 2 occurring in the semaglutide 7.2 mg group and 1 occurring in the placebo group.

At week 72, the mean change in pulse from baseline was 1 bpm for the semaglutide 7.2 mg and semaglutide 2.4 mg groups, and -2 bpm for placebo

Neoplasm events

The proportion of participants and rate of neoplasm events were similar among the semaglutide 7.2 mg (6.4%, 4.8 events per 100 PYE, 93 AEs in 81 participants), semaglutide 2.4 mg (5.9%, 5.6 events per 100 PYE, 26 AEs in 18 participants), and placebo (5.0%, 4.5 events per 100 PYE, 20 AEs in 15 participants) groups.

AEs of Blood calcitonin increased were reported by a similar proportion of participants and at a similar rate in all treatment groups.

Kidney disorders

The proportion of participants with AEs related to Kidney disorders and the rate of such events were lower in the semaglutide 7.2 mg (0.3%, 0.2 events per 100 PYE) than in the semaglutide 2.4 mg (0.7%, 0.7 events per 100 PYE) and placebo (0.7%, 0.5 events per 100 PYE. Creatinine and eGFR values were stable over time and comparable across treatment groups.

Aspiration and intestinal obstruction

No events related to aspiration in association with anesthesia or deep sedation were reported. The search for events of Intestinal obstruction captured one AE (PT Oesophageal stenosis) in the semaglutide 7.2 mg group.

Hypoglycaemia

In STEP UP T2D, AEs related to Hypoglycaemia were categorized as level 1-3, with level 2 defined as clinically significant and level 3 defined as severe. There were no imbalances in level 2 hypoglycaemic episodes across treatment groups, with 2.0% in semaglutide 7.2 mg, 1.9% in semaglutide 2.4 mg, and 2.9% in placebo. There was only 1 level 3 hypoglycaemic episode reported, which occurred in the placebo group. Overall, the data do not suggest an important effect on risk of hypoglycaemic episodes with semaglutide 7.2 mg compared to semaglutide 2.4 mg in patients with diabetes.

In STEP UP in patients without diabetes, very few AEs related to Hypoglycaemia were reported. However, there was higher risk in both semaglutide groups compared to the placebo group. 3 AEs were reported in 3 participants in the semaglutide 7.2 mg group (0.3%, 0.2 events per 100 PYE), 3 AEs were reported in 2 participants in the semaglutide 2.4 mg group (1.0%, 1.0 events per 100 PYE), and none were reported in the placebo group. All reported AEs were non-serious, mild in severity. 4 AEs were reported as recovered, but unfortunately 2 (1 in each semaglutide treatment group) were reported as not recovered. This is worrisome. The company should discuss the risk of hypoglycaemia with higher doses of semaglutide in patients without diabetes (OC).

Diabetic retinopathy

The proportion and rate of AEs of Diabetic retinopathy were lowest in semaglutide 7.2 mg (1.3%, 0.9 events per 100 PYE) followed by semaglutide 2.4 mg (1.9%, 1.9 events per 100 PYE) and placebo (3.9%, 2.6 events per 100 PYE). Retinal disorders are a known risk of Wegovy® in the T2D population. The data do not suggest an increased risk of retinal disorders with semaglutide 7.2 mg compared to semaglutide 2.4 mg in the T2D population

Subgroups

The evaluation of the subgroups investigated did not reveal any new safety concerns or markedly different AE profiles for semaglutide 7.2 mg relative to placebo and semaglutide 2.4 mg for any subgroups.

Conclusion safety

The safety and tolerability profile for semaglutide 7.2 mg was overall consistent with the safety profile for semaglutide and the GLP-1 RA class. Gastrointestinal AEs were reported more frequently with semaglutide 7.2 mg than with semaglutide 2.4 mg and placebo, but these types of AEs are well-known for semaglutide and for the GLP-1 RA class in general and can usually be managed.

AEs related to dysaesthesia were reported by a higher proportion of participants and at a higher rate in the semaglutide 7.2 mg group (up to 22%). The risk is much higher than previously observed with higher doses of oral semaglutide. We therefore consider it important that the high risk of dysaesthesia and other possible long term risks are taken into account when dosing semaglutide. The benefit/risk ratio may be acceptable in patient that lost a clinically relevant amount of weight. If efficacy of the high dose is not sufficient in a patient , the dose should be titrated back to avoid unnecessary risks. This issue can be mitigated by adding to the SPC that the 7.2 mg dose should be titrated back to 2.4 mg if a clinical improvement in body weight has not been achieved with the 7.2 mg dose **(OC).**

5. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8 and 5.1 of the SmPC are being updated to include:

Section 4.8:

Table 3 Frequency of adverse reactions of semaglutide: Inclusion of Dysaesthesia[a,d] under system organ class "Nervous system disorders" and addition of reference "d" under table 3.

Furthermore, inclusion of new information under Description of selected adverse reactions about Hair loss, Immunogenicity and Dysaesthesia based on the STEP UP trials.

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

6. Request for supplementary information

6.1. Major objections

Clinical aspects

Question 1

The new proposed 7.2 mg dose can currently not be approved as based on the following:

A) Both doses of semaglutide were associated with clinically relevant reductions in body weight in obese individuals with and without diabetes. However, the differences between the new 7.2 mg dose compared to the already marketed 2.4 mg dose were very small and not clinically relevant: *a 3 times higher dose of semaglutide was associated with only 3% points more weight loss*. The doubt about the clinical relevance of the proposed higher dose is supported by the fact that there were also no relevant differences between the 7.2 and 2.4 mg dose with respect to CV risk factors, such as waist, body composition, blood pressure, serum lipids, CRP and HbA1c. The company should explain:

A1) why they consider the differences between the 7.2 mg and 2.4 mg dose clinically relevant.

A2) The company did not specifically investigate low-responders to the 2.4 mg dose. So it is difficult to identify patients that may benefit most from treatment with the higher dose. According to subgroup analyses, high-weight patients may not stand out. The company should discuss whether any subgroup of patients could be identified that could be treated with semaglutide 7.2 mg based on a substantially improved benefit-risk balance as compared to the standard 2.4 mg dose.

B) For the high dose of 7.2 mg, patients with BMI between 27 and 30 have not been investigated in current studies. These relatively low weight patients should not be treated with the high dose of 7.2 mg semaglutide. This should be clearly stated in section 4.2 of the SmPC.

6.2. Other concerns

Clinical aspects

Clinical pharmacology

Question **2**

The applicant provided a paracetamol absorption study to assess gastric emptying. However, the applicant provided data from two 50 mg studies in order to describe exposure. Although it is agreed that this gives a more precise estimate on the expected Cav when using the 50 mg dosing regimen, only in study NN9932-4873 gastric emptying has been studied. Therefore, only in this study an actual exposure-gastric emptying relationship has been evaluated. This is especially of importance as the Cav for study NN9932-4873 appears lower compared to the combined data from NN9932-4873 and NN9932-4737 (OASIS 1) (i.e. study NN9932-4873 geometric mean: 106 nmol/L, range: 27 nmol/L - 222 nmol/L, combined 50 mg oral geometric mean 128 nmol/L, range: 6 nmol/L - 442 nmol/L). The applicant is therefore requested to compare the semaglutide Cav from study NN9932-4873 (50 mg oral, daily) to the semaglutide Cav of s.c. 7.2. mg weekly in order to exclude an effect of semaglutide on gastric emptying.

Question 3

The applicant is requested to discuss the potential differences in the shape of the PK curves between 7.2 mg weekly s.c. administration and 50 mg daily oral intake and substantiate whether this would impact gastric emptying.

Question 4

the applicant is requested to explain why the semaglutide exposure-response profile does not follow a typical Emax curve. I.e. the applicant should explain why a lower percentage of weight reduction is observed in STEP UP around 200 nmol/L compared to the weight reduction observed in Step 1 around 100 nmol/L despite the higher exposure.

Efficacy/safety

Question 5

AEs related to dysaesthesia were reported by a higher proportion of participants and at a higher rate in the semaglutide 7.2 mg group (22%), of which 5% was reported not recovered. The risk is much higher than previously observed with higher doses of oral semaglutide. The company acknowledged previously

that the mechanisms were not clear, and dysaesthesia may be considered a manifestation of neuropathy. This is a potential serious issue with the long term use of high dose semaglutide injections. The company should discuss how they are going to investigate mechanisms and how they are going to minimize long term risks.

Question 6

A greater proportion of participants in the semaglutide 7.2 mg group reported AEs than in both the semaglutide 2.4 mg and placebo groups in the PT Alopecia. The events of Alopecia were associated with weight loss, as a higher proportion of events related to Alopecia were reported in participants with ≥20% weight loss (up to 9%). Mechanisms and potential long term effects should be discussed.

Question 7

In STEP UP in patients without diabetes, there was a somewhat higher risk of hypoglycaemia in both semaglutide groups compared to the placebo group. The company should discuss the risk of hypoglycaemia with higher doses of semaglutide in patients without diabetes.

Question 8

In the 2,4 semaglutide group, one patients reported 21 SAEs including one fatal event. A short narrative of the events in this patient should be provided.

7. Assessment of the responses to the request for supplementary information

7.1. Major objections

Clinical aspects

Question 1

The new proposed 7.2 mg can currently not be approved as based on the following:

A. Both doses of semaglutide were associated with clinically relevant reductions in body weight in obese individuals with and without diabetes. However, the differences between the new 7.2 mg dose compared to the already marketed 2.4 mg dose were very small and not clinically relevant: a 3 times higher dose of semaglutide was associated with only 3% points more weight loss. The doubt about the clinical relevance of the proposed higher dose is supported by the fact that there were also no relevant differences between the 7.2 and 2.4 mg dose with respect to CV risk factors, such as waist, body composition, blood pressure, serum lipids, CRP and HbA1c. The company should explain:

i. Why they consider the differences between the 7.2 mg and 2.4 mg dose clinically relevant.

ii. The company did not specifically investigate low-responders to the 2.4 mg dose. So it is difficult to identify patients that may benefit most from treatment with the higher dose. According to subgroup

analyses, high-weight patients may not stand out. The company should discuss whether any subgroup of patients could be identified that could be treated with semaglutide 7.2 mg based on a substantially improved benefit-risk balance as compared to the standard 2.4 mg dose.

B. For the high dose of 7.2 mg, patients with BMI between 27 and 30 have not been investigated in current studies. These relatively low weight patients should not be treated with the high dose of 7.2 mg semaglutide. This should be clearly stated in section 4.2 of the SmpC.

Summary of the MAH's response
Response to question 1A,i

Obesity is a complex chronic disease, characterised by heterogenous patient characteristics such as BMI and comorbidities[1-3], and patient responses to treatment are likewise variable[4], making medical needs in obesity management dynamic and broad. The field is evolving from focusing on mean weight-loss outcomes to increased focus on treat-to-target approaches[1, 2], with guidelines and position papers emphasising individualised strategies tailored to disease burden and treatment response[1-6]. To support this, pharmacotherapeutic options with multiple maintenance dose levels are essential for enabling physicians to personalise therapy and help patients reach targets associated with optimal health benefits. These targets may begin with clinically significant weight loss and, where appropriate, extend to higher categorical thresholds (≥10–25%) and cardiometabolic goals such as reduction in BMI, improved waist-to-height ratio, and restoration of normal metabolic parameters[3-10]. Guided by treatment response and tolerability, therapy is intensified when patients are not on track to meet the targets, with regular reassessment to confirm sustained attainment and to guide de-intensification or adjunctive measures as needed[1-6].

Novo Nordisk remains committed to ensure that all patients with obesity can be served according to their specific unmet medical need. Results from the STEP 1 study (study NN9536-4373) with semaglutide 2.4 mg showed that around 70% of those with a baseline BMI ≥30 kg/m^2 did not reach a BMI <27 kg/m^2 after 68 weeks. Therefore, even though most participants in STEP 1 achieved clinically relevant weight reduction, weight loss beyond that achievable with the 2.4 mg dose level would be relevant

Accordingly, Novo Nordisk developed the higher 7.2 mg dose level of s.c. semaglutide to ensure that an additional maintenance dose level is available for treatment intensification based on individual unmet medical needs and treatment responses in line with the evolving approach to obesity management as discussed above. Novo Nordisk is of the opinion that the semaglutide 7.2 mg maintenance dose level can address an important residual unmet medical need in a sizeable and currently underserved segment of the large and still-increasing population of people with obesity, including those with a baseline BMI ≥30 kg/m^2, for whom the benefits are especially clinically relevant.

Whilst it is acknowledged that the semaglutide 7.2 mg dose level is 3 times greater than the 2.4 mg dose level, Novo Nordisk is of the opinion that it should ultimately be the benefit-risk profile for the 7.2 mg dose level that guides the decision about approvability of the dose level. Compared with the 2.4 mg dose level, clinically relevant greater efficacy was observed with the 7.2 mg dose level on key obesity-related outcomes including absolute and categorical body weight targets as summarised below, with the safety profile remaining consistent with the well-established profile for semaglutide s.c.. For example, in STEP UP (study NN9536-4999) the proportion of participants who discontinued treatment permanently due to adverse events was 5.4% and 4.0% in the semaglutide 7.2 mg and 2.4 mg groups, respectively, and 1.0% in the placebo group.

According to the CHMP guideline on medicinal products in weight management[1], even a sustained difference of 3-5 %-points in mean body weight loss compared to placebo is considered clinically meaningful and associated with health benefits such as blood glucose reductions. The observed difference

between semaglutide 2.4 mg and 7.2 mg was around 3 %-points at week 72 in STEP UP, and the weight loss with semaglutide 7.2 mg appeared maintained over time. These observations align with the threshold defined by the CHMP for sustained clinically relevant additional weight loss, as corroborated by the additional categorical benefits on glycaemic control with semaglutide 7.2 mg over 2.4 mg as summarised below.

Novo Nordisk therefore considers the absolute treatment difference of around 3 %-points between semaglutide 7.2 mg and 2.4 mg with respect to weight loss from baseline to week 72 in STEP UP to be clinically relevant.

Moreover, in line with the treatment target-based individualised approach to obesity management discussed earlier, the clinical relevance of the absolute 3 %-points treatment difference should be viewed in the context of the proportions of participants in STEP UP (study 4999) who achieved several clinically significant treatment targets for weight loss and key cardiometabolic risk factors as discussed next.

At week 72 in STEP UP (study 4999), the observed proportions of participants who achieved highly clinically relevant weight-loss targets were substantially greater with semaglutide 7.2 mg than with 2.4 mg (Table 2-1).

Table 2-13 Categorical weight loss - week 72 - STEP UP (study 4999) – observed – in-trial observation period

Weight loss category	Proportion of participants	
	Semaglutide 7.2 mg	Semaglutide 2.4 mg
≥10%	82.4%	75.1%
≥15%	66.5%	54.5%
≥20%	47.7%	33.3%
≥25%	31.2%	15.3%

Data are observed proportions of participants achieving the weight loss category at week 72 in STEP UP (study 4999).

Additional exploratory weight-related categorical outcomes were also achieved by greater proportions of participants with semaglutide 7.2 mg than with 2.4 mg in STEP UP (Table 2-2).

Table 2-14 Exploratory categorical weight-related outcomes - week 72 - STEP UP – hypothetical strategy – on-treatment observation period

Outcome	Proportion of participants		Odds ratio [95%CI]
	Semaglutide 7.2 mg	Semaglutide 2.4 mg	
BMI <25 kg/m^2	17.85%	9.53%	2.06 [1.32, 3.21]
BMI <27 kg/m^2	29.40%	21.67%	1.51 [1.12, 2.01]
BMI <30 kg/m^2	45.06%	37.38%	1.37 [1.08, 1.75]
Waist-to-height ratio <0.53	27.63%	18.28%	1.71 [1.23, 2.37]

Data are estimated proportions of participants achieving the outcome and odds ratios (semaglutide 7.2 mg/semaglutide 2.4 mg) at week 72 in STEP UP (study 4999).

The additional benefits with semaglutide 7.2 mg over 2.4 mg on the above-mentioned weight-related targets were mirrored by favourable shifts from BMI categories 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2 or ≥40 kg/m^2 (i.e., obesity classes I, II and III, respectively) to a BMI <30 kg/m^2 (normal weight or overweight) (Table 2-3). Greater proportions of participants with obesity classes I-III at baseline achieved

a BMI <30 kg/m^2 (normal weight or overweight) at week 72 with semaglutide 7.2 mg than with semaglutide 2.4 mg.

Table 2-15 BMI category at week 72 - shift table - full analysis set– in-trial observation period

	Baseline (Week 0)				
	Normal weight N (%)	Overweight N (%)	Obesity class I N (%)	Obesity class II N (%)	Obesity class III N (%)
Week 72					
Sema 7.2 mg					
Normal weight	0	3 (75.0)	95 (36.4)	41 (14.0)	9 (2.3)
Overweight	0	1 (25.0)	124 (47.5)	107 (36.5)	30 (7.7)
Obesity class I	0	0	40 (15.3)	106 (36.2)	104 (26.5)
Obesity class II	0	0	2 (0.8)	36 (12.3)	131 (33.4)
Obesity class III	0	0	0	3 (1.0)	118 (30.1)
Sema 2.4 mg					
Normal weight	0	0	10 (21.3)	3 (5.3)	1 (1.2)
Overweight	0	0	27 (57.4)	19 (33.3)	7 (8.3)
Obesity class I	0	0	9 (19.1)	27 (47.4)	14 (16.7)
Obesity class II	0	0	1 (2.1)	8 (14.0)	27 (32.1)
Obesity class III	0	0	0	0	35 (41.7)
Placebo					
Normal weight	0	0	0	0	0
Overweight	0	0	13 (28.9)	1 (1.9)	0
Obesity class I	0	0	27 (60.0)	19 (35.2)	5 (6.9)
Obesity class II	0	0	5 (11.1)	32 (59.3)	10 (13.9)
Obesity class III	0	0	0	2 (3.7)	57 (79.2)

N: Number of subjects, %: Percentages in relation to subjects with respective treatment and BMI category at week 0, BMI: Body Mass Index (kg/m^2).
BMI categories: Normal weight: 18.5 - 24.9; Overweight: 25.0 - 29.9; Obesity class I: 30.0 - 34.9; Obesity class II: 35.0 - 39.9; Obesity class III: above 40.
Observed data from in-trial period. Only subjects with observed data in both week 0 and week 72 are included in the analysis.

Whilst the STEP UP study was not powered or designed to compare the treatment effect on cardiometabolic outcomes between semaglutide 7.2 and 2.4 mg, the proportions of participants with low-risk cardiometabolic state at week 72 (blood glucose levels, triglyceride levels and blood pressure at target) were greater with semaglutide 7.2 mg than with 2.4 mg (Table 2-4), although the proportion of participants with at-target values at baseline were greater in the semaglutide 2.4 mg group than in the 7.2 mg group.

Table 2-16 Proportion of participants with low-risk cardiometabolic state – STEP UP – on-treatment

Outcome	Baseline (week 0)		Week 72	
	Semaglutide 7.2 mg	Semaglutide 2.4 mg	Semaglutide 7.2 mg	Semaglutide 2.4 mg
Normoglycaemia [a]	38.2%	42.4%	86.9%	79.1%
Triglycerides [b]	68.4%	72.1%	87.7%	79.2%
Blood pressure [c]	20.7%	26.4%	47.4%	43.7%
HDL cholesterol [d]	57.1%	60.0%	69.7%	73.1%

a. HbA_{1c} <5.7% and fasting plasma glucose <5.5 mmol/L; b. <1.7 mmol/L; c. SBP/DBP <130/80 mmHg;
d. >1.3 mmol/L (female) or >1.0 mmol/L (male). Data are observed proportions of participants in the full analysis set (on-treatment observation period) in study 4999 (STEP UP). HDL = high-density lipoprotein.

Novo Nordisk acknowledges that the proportion of participants who reached HDL cholesterol targets at week 72 in STEP UP was greater with semaglutide 2.4 mg (73.1%) than with 7.2 mg (69.7%) as noted by the CHMP.

Novo Nordisk would like to note that there is regulatory precedent in the EU region for having multiple maintenance doses for weight management drugs available to allow for treatment intensification, despite numerically low treatment differences between the dose levels with respect to weight loss change from baseline. For tirzepatide in weight management (Mounjaro®), the weight loss observed for the highest two recommended maintenance dose levels (10 mg and 15 mg once weekly) in the SURMOUNT-1 study is reported as −21.4% for tirzepatide 10 mg and −22.5% for tirzepatide 15 mg, representing an assumed treatment difference of around −1 %-points[11], lower than the treatment difference between semaglutide 7.2 mg and 2.4 mg (around −3 %-points) and with modest increases in the proportion of patients achieving categorical weight loss targets (e.g. around 5 to 7 %-points for the ≥10%, ≥15% and ≥20% weight loss targets, compared to 7 to 16 %-points between semaglutide 7.2 mg and 2.4 mg). Novo Nordisk agrees to the approach adopted by the CHMP at the time of approval of Mounjaro® and is of the opinion that it also applies to Wegovy®. Of note, Novo Nordisk remains of the opinion that the benefit-risk balance for semaglutide 7.2 mg is favourable with a safety profile consistent with that of semaglutide 2.4 mg.

In conclusion, Novo Nordisk is of the opinion that semaglutide 7.2 mg provides clinically relevant additional benefits beyond those delivered by the 2.4 mg dose level on weight loss and weight-related key outcomes such as cardiometabolic risk. Thus, semaglutide 7.2 mg enables individualised treat-to-target obesity management through an additional maintenance dose level, with the potential to address the unmet medical need of a sizeable segment of patients with chronic obesity, whilst maintaining the well-established safety profile of semaglutide 2.4 mg. Novo Nordisk is of the opinion that the benefit-risk balance for semaglutide 7.2 mg is favourable in patients with a BMI ≥30.0 kg/m^2, as well as in patients with or without diabetes.

Response to Question 1A, ii

In line with the treat-to-target approach to weight management discussed above, the semaglutide 7.2 mg maintenance dose level is introduced to allow patients with a BMI ≥30.0 kg/m² to intensify treatment as required for additional weight loss and other benefits. As discussed, such treatment escalation should be considered by the treating physician based on response to treatment, including tolerability, and be guided by reassessment to confirm sustained attainment and/or the possibility for de-intensification or adjunctive measures. Accordingly, Novo Nordisk did not evaluate efficacy outcomes for subgroups based on baseline characteristics.

Novo Nordisk is of the opinion that the guidance provided in the proposed posology section of the SmPC (see Section 2.1.3) is sufficiently robust to support prescribers in identifying and managing patients who may benefit from dose escalation, including from semaglutide 2.4 mg to 7.2 mg once weekly.

Response to Question 1B

Novo Nordisk acknowledges the comments provided by the CHMP regarding the posology section of the SmPC for Wegovy® and agrees to update the section to reflect that the Wegovy® dose level can be increased to 7.2 mg in adults with a BMI ≥30 kg/m^2 at treatment initiation (see Section 4).

Assessment of the MAH's response

Question 1A, i

The differences between the new 7.2 mg dose compared to the already marketed 2.4 mg dose were very small: a 3 times higher dose of semaglutide was associated with only 3% points more weight loss. There were also no relevant differences between the 7.2 and 2.4 mg dose with respect to CV risk factors.

The company acknowledges that the semaglutide 7.2 mg dose level is 3 times greater than the 2.4 mg dose level, but is of the opinion that it should ultimately be the benefit-risk profile for the 7.2 mg dose level that guides the decision about approvability of the dose level. We agree with the company that the benefit-risk profile should guide the decision. Nevertheless, the additional efficacy of the three times higher dose is very disappointing and we consider it important to keep in mind that such a very high dose may be associated with additional safety issues.

Responders

The company argues that the 3% additional weight loss with the high dose should be viewed in the context of the proportions of participants in STEP UP (study 4999) who achieved several clinically significant treatment targets for weight loss and key cardiometabolic risk factors. At week 72 in STEP UP, the observed proportions of participants who achieved clinically relevant weight-loss targets (≥10%, ≥15%, ≥20% or ≥25%) was 7-15 %-points greater with semaglutide 7.2 mg than with 2.4 mg. For this 7-15% of the patients, the difference between the 2.4 mg and 7.2 mg may be clinically relevant. However, for the majority of patients, there was no difference in the achievement of clinically relevant weight-loss targets.

The additional effects of the high dose semaglutide on CV risk factors were not clinically relevant. When taking into account the proportions of participants in STEP UP who achieved clinically significant treatment targets for cardiometabolic risk factors, there were small improvements in the %-points response with respect to normoglycaemia, triglycerides and blood pressure, but no improvements in HDL cholesterol response.

Comparison with tirzepatide

The company argues that, for tirzepatide in weight management (Mounjaro®), the weight loss differences observed for the highest two recommended maintenance dose levels (10 mg and 15 mg once weekly) are reported as −1 %-points in the SURMOUNT-1 and -2%-points in SURMOUNT-2. It should be emphasized that approval of the highest dose level of tirzepatide was not based on the additional efficacy of the higher tirzepatide dose, but on the total benefit-risk profile. In addition, the posology of tirzepatide clearly states that doses can be increased "if needed". This statement is not included in the proposed posology section in the SPC of semaglutide (Wegovy).

Conclusion question 1A, i

The additional benefit with the higher dose may be clinically relevant for a small subgroup, but not for the majority of patients (85-93%). In addition, approval of the higher dose level should not only be based on the additional clinical relevance of the efficacy of the higher dose, but also on the risk profile.

Question 1A,ii

For only 7-15% of the patients, the difference between the 2.4 mg and 7.2 mg may be clinically relevant. However, for the majority of patients, there was no difference in the achievement of clinically relevant weight-loss targets. The company did not identify a subgroup of patients that may have substantially improved benefit-risk balance with the higher dose as compared to the standard 2.4 mg dose.

Question 1B

Novo Nordisk agrees to update the section to reflect that the Wegovy® dose level can be increased to 7.2 mg only in adults with a BMI ≥30 kg/m2 at treatment initiation.

Conclusion Question 1

Taken together, a 3 times higher dose of semaglutide was associated with only 3% points more weight loss. When looking at responder analyses, the additional benefit with the higher dose may be clinically relevant for some patients (7-15% of the total population), but not for the majority of patients (85-93%). The company did not identify a subgroup of patients that may have substantially improved benefit-risk balance with the higher dose. Unfortunately, the 3 times higher dose is associated with an increased risk of adverse events. Therefore, the benefit-risk profile for the 7.2 mg dose level is negative for most patients.

We consider the 7.2 mg dose only indicated in patients that need additional weight loss. In addition, if a clinical improvement in body weight has not been achieved with the 7.2 mg dose, the dose should be titrated back to 2.4 mg in order to prevent risks with the high dose. This should be clearly stated in the posology section of the SPC **(OC)**.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

7.2. Other concerns

Clinical aspects

Question 2

The applicant provided a paracetamol absorption study to assess gastric emptying. However, the applicant provided data from two 50 mg studies in order to describe exposure. Although it is agreed that this gives a more precise estimate on the expected Cav when using the 50 mg dosing regimen, only in study NN9932-4873 gastric emptying has been studied. Therefore, only in this study an actual exposure-gastric emptying relationship has been evaluated. This is especially of importance as the Cav for study NN9932-4873 appears lower compared to the combined data from NN9932-4873 and NN9932-4737 (OASIS 1) (i.e. study NN9932-4873 geometric mean: 106 nmol/L, range: 27 nmol/L - 222 nmol/L, combined 50 mg oral geometric mean 128 nmol/L, range: 6 nmol/L - 442 nmol/L). The applicant is therefore requested to compare the semaglutide Cav from study NN9932-4873 (50 mg oral, daily) to the semaglutide Cav of s.c. 7.2. mg weekly in order to exclude an effect of semaglutide on gastric emptying.

Summary of the MAH's response

The exposure levels following administration of s.c. semaglutide 7.2 mg overlapped with the exposure levels observed following administration of oral semaglutide 50 mg in NN9932-4873 (Table 3-1 and Figure 3-1). Following administration of semaglutide 7.2 mg in STEP UP and STEP UP T2D, 37.1% and 60.3%, respectively, of the predicted C_{avg} semaglutide levels overlapped with the C_{avg} levels seen following administration of oral semaglutide 50 mg in study 4873. The overlap was at the higher end of the exposure range in study 4873, with the majority of C_{avg} levels in STEP UP and STEP UP T2D being above the C_{avg} geometric mean observed following administration of oral semaglutide 50 mg in study 4873.

The C_{avg} levels following administration of semaglutide 7.2 mg was 235.9 nmol/L (range: 163.7-331.7 nmol/L) in STEP UP and 208.5 nmol/L (range: 148.3-295.7 nmol/L) in STEP UP T2D compared to 106 nmol/L (range: 27 nmol/L - 222 nmol/L) in study 4873 with oral semaglutide 50 mg. Due to the overlap between the C_{avg} levels outlined above, Novo Nordisk considers that the results from study 4873 are valid to exclude an effect on gastric emptying of semaglutide 7.2 mg.

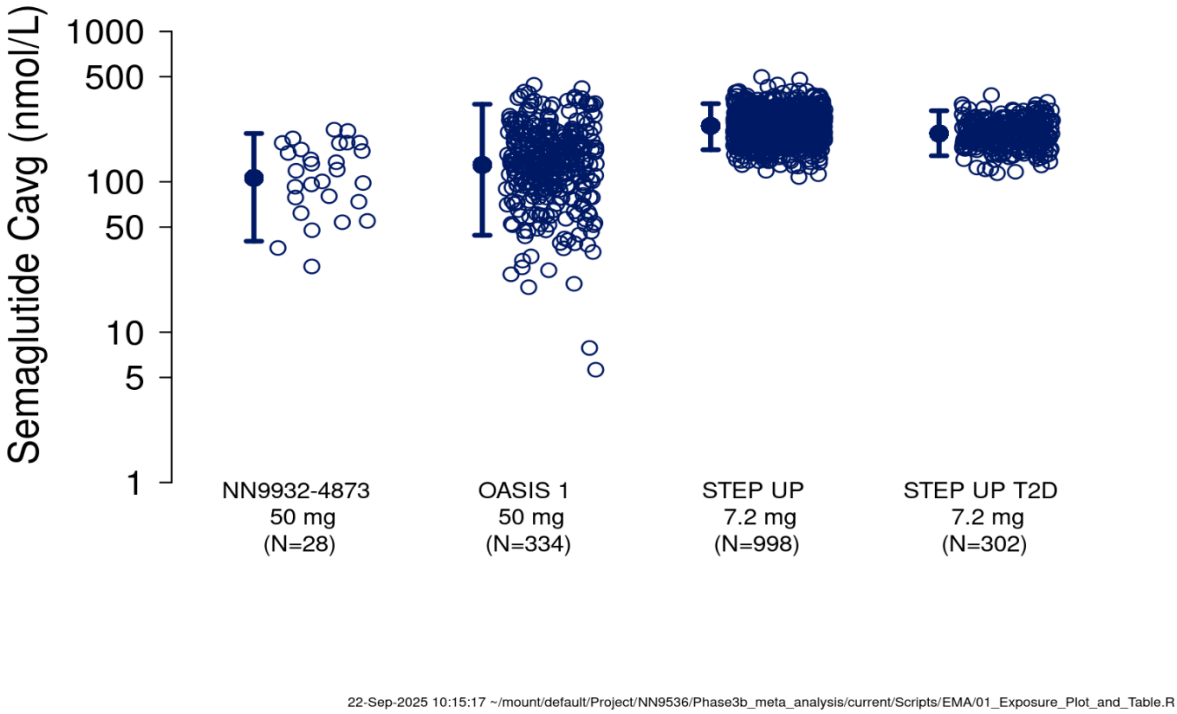
In addition, when comparing the two studies with oral semaglutide 50 mg (OASIS 1 and study 4873), it was found that 81.4% of the C_{avg} levels overlapped and that the range of C_{avg} in study 4873 was within the range of exposures in OASIS 1 (Table 3-1). This shows that study 4873 is representative for an exposure of oral semaglutide 50 mg and the study can support the evaluation of an effect on gastric emptying of semaglutide 7.2 mg because the exposure levels with oral semaglutide 50 mg in OASIS 1 are almost completely (for 99.7%) overlapping with the exposure levels of s.c. semaglutide 7.2 mg.

Table 3-17 Distribution of predicted individual C_{avg} (nmol/L) estimates for s.c. semaglutide 7.2 mg in STEP UP, STEP UP T2D compared to oral semaglutide 50 mg in OASIS 1 and NN9932-4873

		Comparison with OASIS 1				**Comparison with NN9932-4873**			
Study	Total (N)	Within range (6-442nM) (%)	Above range (>442nM) (%)	Above 95-percentile (>328nM) (%)	Above geometric mean (>129nM) (%)	Within range (27-222nM) (%)	Above range (>222nM) (%)	Above 95-percentile (>210nM) (%)	Above geometric mean (>106nM) (%)
STEP UP	998	99.7	0.3	5.6	99.2	37.1	62.9	69.9	100.0
STEP UP T2D	302	100.0	0.0	1.0	98.0	60.3	39.7	48.7	100.0
OASIS 1	334	-	-	-	-	81.4	16.5	20.7	68.6

Data are % overlap in C_{avg} between OASIS 1 and study 4873

Figure 3-32 Predicted individual semaglutide exposure of s.c. semaglutide 7.2 mg and oral semaglutide 50 mg



Assessment of the MAH's response

The data provided is not acceptable. A substantial part of the exposure as observed in study STEP UP (i.e. 62.9%) and STEP UP T2D (i.e. 39.7%) is above the Cavg exposure range observed in study NN9932-4873. Potential effect on gastric emptying should therefore be studied in a new paracetamol absorption study with adequate exposure levels. Especially, given the current unrest regarding unintended pregnancies. The applicant is requested to commit to this study, which could be conducted post-approval. In addition, the applicant should include a statement about potential effects of semaglutide on absorption of other medicines in SmPC section 4.5, at least until results of the gastric emptying study have become available.

Question 3

The applicant is requested to discuss the potential differences in the shape of the PK curves between 7.2 mg weekly s.c. administration and 50 mg daily oral intake and substantiate whether this would impact gastric emptying.

Summary of the MAH's response

As discussed above (Section 3.1.1.1), C_{avg} has been shown to be comparable after weekly dosing of semaglutide s.c. 7.2 mg and daily dosing of oral semaglutide 50 mg.

Novo Nordisk has investigated gastric emptying for s.c. and oral administration of semaglutide in several clinical pharmacology studies across a range of dose levels in participants with obesity and/or T2D. Once-daily or once-weekly dosing regimens were used and the treatment duration was 8, 12, or 20 weeks (Table 3-2).

Across these studies, consistent gastric emptying results were observed. Overall, semaglutide affected gastric emptying by reducing paracetamol exposure (i.e., as assessed by C_{max} or AUC_{0-1h}), when the

gastric emptying was assessed after 8 or 12 weeks of dosing of either once-weekly or once-daily semaglutide s.c. or once-daily oral administration of semaglutide. However, following these treatment periods, semaglutide treatment did not delay gastric emptying 5 hours after meal ingestion (i.e., as assessed by the paracetamol PK parameter of AUC_{0-5h}) indicating no impact on the overall gastric emptying. This observation was consistent and similar across studies. After 20 weeks of dosing, no effect of semaglutide on gastric emptying was observed; i.e., the estimated treatment ratio compared to placebo was approximately 1 for the three paracetamol endpoints (AUC_{0-5h}, AUC_{0-1h}, and $C_{max, 0-5h}$).

Table 3-18 Summary of gastric emptying results in clinical pharmacology studies with semaglutide

Study	Treatment/ duration	ETR [95% CI] per endpoint		
		AUC paracetamol, 0–5h	AUC paracetamol, 0–1h	C_{max} paracetamol, 0-5h
NN9932-4873 (n=54)	Oral OD 50 mg / 20 weeks	1.06 [0.97 ; 1.16]	0.92 [0.76 ; 1.11]	1.01 [0.88 ; 1.17]
NN9924-4248 (n=13)	Oral OD 14 mg / 12 weeks	0.97 [0.79 ; 1.19]	0.69 [0.54 ; 0.87]	0.73 [0.53 ; 1.00]
NN9536-4455 (n=70)	s.c. OW 2.4 mg / 20 weeks	1.08 [1.02 ; 1.14]	0.99 [0.87 ; 1.12]	0.94 [0.82 ; 1.07]
NN9535-3685 (n=28)	s.c. OW 1.0 mg / 12 weeks	0.94 [0.88 ; 1.01]	0.73 [0.61 ; 0.87]	0.77 [0.67 ; 0.88]
	s.c. OW 1.4 mg / 12 weeks	1.01 [0.87 ; 1.17]	0.96 [0.62 ; 1.48]	1.05 [0.87 ; 1.25]
NN9535-4215 (n=108, week 8) (n=106, week 12)	s.c. OD 0.2 mg / 12 weeks	1.05 [0.91 ; 1.21]	0.97 [0.63 ; 1.47]	1.01 [0.85 ; 1.20]
	s.c. OW 0.7 mg / 8 weeks	0.91 [0.77 ; 1.06]	0.66 [0.45 ; 0.97]	0.81 [0.66 ; 0.99]
	s.c. OD 0.1 mg / 8 weeks	0.97 [0.83 ; 1.14]	0.90 [0.62 ; 1.32]	0.88 [0.72 ; 1.07]

In trials NN9536-4455 and NN9932-4873, the endpoints were log transformed and analysed using an ANCOVA with log transformed baseline value of the respective endpoint as covariate and treatment as factor. In trial NN9535-4215, the endpoints were log transformed and analysed using a linear model with treatment as factor. In trial NN9535-3586 a linear mixed model on log-transformed data including treatment, treatment period as fixed effects and subject as random effect. In trial, NN9924-4248 log transformed endpoints were analysed using an ANOVA model with treatment, treatment period and subject as fixed factors. Note: ETR = estimated treatment ratio expressed as semaglutide to placebo, N = number of subjects contributing to the analysis.

In conclusion, consistent gastric emptying results are obtained with s.c. and oral administration of semaglutide. These results show that semaglutide causes a minor delay in early postprandial gastric emptying.

Novo Nordisk is therefore of the opinion that the potential differences in the shape of the PK curves for once-weekly semaglutide 7.2 mg and once-daily oral semaglutide 50 mg do not impact gastric emptying.

Assessment of the MAH's response

The rationale provided by the applicant is acceptable. In principle, similar effect on paracetamol absorption (i.e AUC0-1h, Cmax) were observed between once daily oral dosing and one weekly subcutaneous dosing. Therefore, it has sufficiently been substantiated that the shape of the semaglutide

PK curve likely will not influence the effect gastric emptying. Nevertheless, a study is still needed due to insufficient exposure levels, as discussed below OC 2.

Question 4

The applicant is requested to explain why the semaglutide exposure-response profile does not follow a typical Emax curve. I.e. the applicant should explain why a lower percentage of weight reduction is observed in STEP UP around 200 nmol/L compared to the weight reduction observed in Step 1 around 100 nmol/L despite the higher exposure.

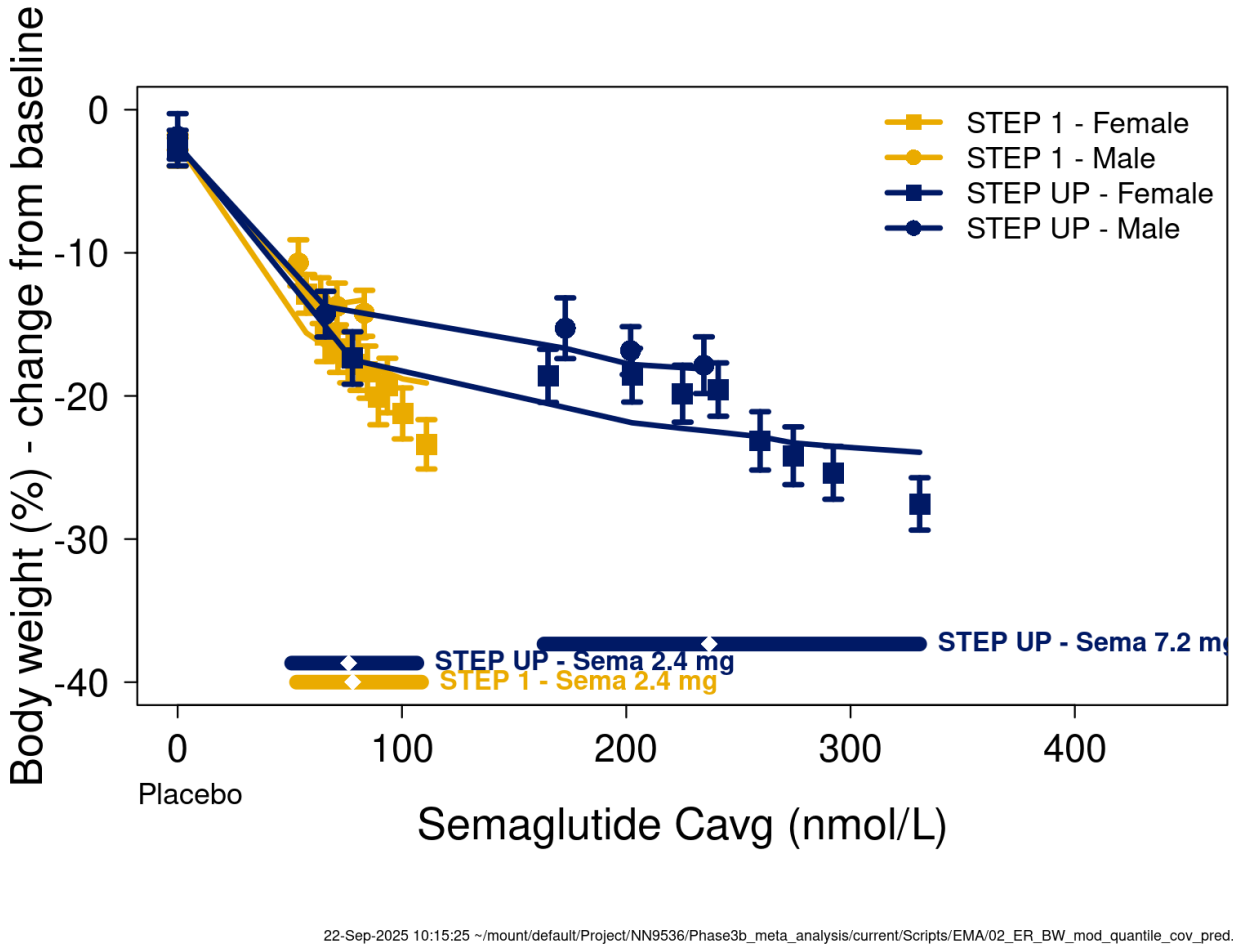
Summary of the MAH's response

A lower percentage of weight reduction is observed in STEP UP around 200 nmol/L compared to the weight reduction observed in STEP 1 around 100 nmol/L because the observed exposure levels within dose groups are confounded by sex. For the semaglutide 7.2 mg dose in the STEP UP study, the C_{avg} quantiles with a value below the geometric mean value of 236 nM contain a relative high number of males as opposed to the C_{avg} quantiles with values above the geometric mean of 236 nM which contain relative few or no males.

On average, females lose more weight than men for the same steady-state C_{avg} value. Therefore, the response values of the semaglutide 7.2 mg C_{avg} quantiles on the left of the geometric mean are pushed slightly upwards (as compared to the model predicted fit), whilst the response values of the semaglutide 7.2 mg C_{avg} quantiles on the right of the geometric mean are pushed slightly downwards (as compared to the model predicted fit). Please note that the model-predicted fit gives the prediction for the mean weight loss over all participants in the semaglutide 7.2 mg arm.

In Figure 3-2, the same information is displayed for the STEP UP and STEP 1 studies as in the figure referenced by the CHMP, but stratified by sex and with prediction lines based on the actual participant covariate set within each of the C_{avg} quantiles. From the exposure-response plot in Figure 3-2 it is seen that male participants on semaglutide 7.2 mg in STEP UP (with C_{avg} values around 200 nM) on average lose more weight than the male participants on semaglutide 2.4 mg in STEP 1 (with C_{avg} values around 70 nM). Further, the female participants on semaglutide 7.2 mg with C_{avg} values above the median of 237 nM on average lose more weight than the female participants on semaglutide 2.4 mg above the median C_{avg} of 78 nM in STEP 1. Additionally, the female participants on semaglutide 7.2 mg with C_{avg} values below the median of 237 nM on average lose more weight than the female participants on semaglutide 2.4 mg below the median C_{avg} of 78 nM in STEP 1.

Figure 3-33 Exposure-response relationship of body weight change from baseline stratified by sex in STEP 1 and STEP UP studies



Assessment of the MAH's response

It is difficult to observe an Emax relationship, when stratified for sex. Especially for female this is not completely the case, as a less pronounced effect is observed for a Cavg between 100 and 200 nmol/L compared to higher and lower concentrations, it is agreed with the applicant that female participants on semaglutide 7.2 mg on average lose more weight than the female participants on semaglutide 2.4 mg (of note, the clinical relevance of the difference in effect for these doses is discussed in MO1). In addition, an effect on bodyweight is also still observed for a Cavg between 100 and 200 nmol/L. The issue is therefore not pursued.

Question 5

AEs related to dysaesthesia were reported by a higher proportion of participants and at a higher rate in the semaglutide 7.2 mg group (22%), of which 5% was reported not recovered. The risk is much higher than previously observed with higher doses of oral semaglutide. The company acknowledged previously that the mechanisms were not clear, and dysaesthesia may be considered a manifestation of neuropathy. This is a potential serious issue with the long term use of high dose semaglutide injections. The company should discuss how they are going to investigate mechanisms and how they are going to minimize long term risks.

Summary of the MAH's response

Novo Nordisk acknowledges that the proportion of participants reporting adverse events (AEs) related to dysaesthesia as identified by a pre-defined MedDRA search was higher in the semaglutide 7.2 mg group than in the semaglutide 2.4 mg and placebo groups as discussed below based on the available data (Table 3-3). In line with previous observations, AEs related to dysaesthesia are reported more frequently in participants with higher exposure.

Dysaesthesia is considered a non-important identified risk for semaglutide s.c. for weight management (Wegovy®) and is described in the SmPC for Wegovy®. Based on the previously provided data and the additional evidence presented below, Novo Nordisk is of the opinion that dysaesthesia is a non-serious AE associated with high-dose semaglutide injections, which, in most of the cases, recovers while on treatment.

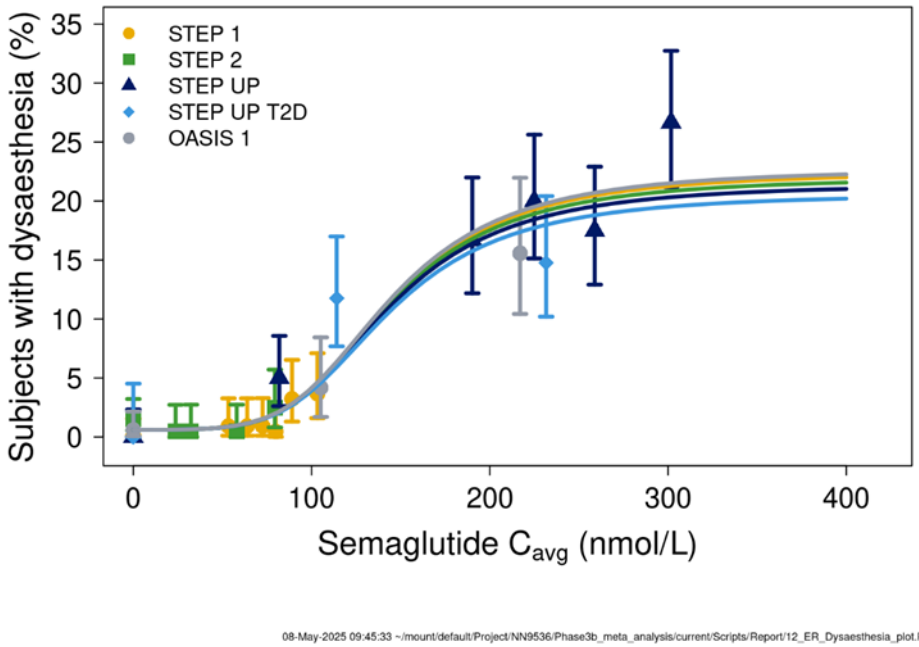
Dysaesthesia is evaluated as a grouped term that includes PTs (Allodynia, Burning sensation, Dysaesthesia, Hyperaesthesia, Hyperpathia, Pain of skin, Paraesthesia, Sensitive skin, Skin burning sensation, Skin discomfort, Skin sensitisation) from two SOCs (Skin and subcutaneous tissue disorders and Nervous system disorder). Pooled data from STEP UP and STEP UP T2D showed that the most frequently reported AEs by PT were Sensitive skin (6.7%), Hyperaesthesia (5.3%) and Dysaesthesia (3.6%). All these AEs were non-serious, and the majority were mild in severity. In the semaglutide 7.2 mg group, 0.4% of participants reported dysaesthesia-related AEs leading to permanent treatment discontinuation (0.3 events per 100 PYE), and 1.7% of participants reported AEs leading to temporary interruption of trial product (1.6 events per 100 PYE); there were no such AEs in the semaglutide 2.4 mg and placebo groups. The proportion and event rate of AEs leading to dose reduction reported in the semaglutide 7.2 mg group were 5.1% and 5.0 events per 100 PYE, respectively, compared with 1.0% and 1.4 events per 100 PYE in the semaglutide 2.4 mg group; there were no such AEs reported for participants in the placebo group.

In some cases, different locations of the same symptom (e.g., "paraesthesia of the left forearm, right forearm and left lower leg", or "paraesthesia of the abdomen skin, back skin, left thigh skin and right thigh skin", etc.,) were reported as 3 or 4 separate events with the same start and end days, which resulted in increased reporting rates.

The reported terms indicate the diversity of the involved locations: scalp, abdomen, back, right and/or left thigh, right and/or left arm, forearms, shoulders, waist, - alone or in combination. In other patients, the symptoms are described as generalised ("discomfort whole skin", "hyperaesthesia" or "hypersensitivity of the skin").

The exposure-response relationship for the participants reporting AEs identified by the MedDRA search for dysaesthesia indicated that these AEs were observed in participants with high semaglutide exposure levels during the first 26 weeks of treatment. A similar pattern for AEs of dysaesthesia was observed with oral semaglutide 50 mg in the OASIS 1 study (Figure 3-3). Furthermore, this observation is consistent with previous exposure-response analyses of dysaesthesia for semaglutide.

Figure 3-34 Proportion of participants reporting AEs related to dysaesthesia during the first 26 weeks of treatment versus semaglutide exposure



Circles with error bars are observed mean proportion of participants reporting altered skin sensation with 95% CI after 26 weeks of treatment versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nmol/L). Line represents covariate-adjusted model-derived exposure-response relations for each study population. Horizontal lines with diamonds along x-axis represent median and 90% exposure range of semaglutide 7.2 mg in STEP UP and STEP UP T2D. Data from OASIS 1, STEP UP, STEP UP T2D, STEP 1, and STEP 2.

Clinical data from both oral semaglutide 50 mg and semaglutide s.c. 7.2 mg studies indicate that dysaesthesia is a transient AE and most of the participants recovered from the event by the end of the study. Across the STEP UP studies, 368 (85%) of the 434 events identified by the dysaesthesia MedDRA search had recovered in the semaglutide 7.2 mg group, and 8 were recovering at the end of the study (Table 3-3).

In the semaglutide 7.2 mg group, 243 events (56% of all reported events) in 187 participants recovered without change in the dose of the trial product, with a median time to recovery of 63 days (Appendix 2, TFL 2.1 to 2.4). In 62 participants in the semaglutide 7.2 mg group who reported 89 events (20% of all reported events), the dose was reduced and the median time to recovery was 30 days. In 21 participants reporting 30 events (7% of all reported events) in the semaglutide 7.2 mg group, the median time to recovery after temporary interruption of the trial product was 18 days. Four participants in the semaglutide 7.2 mg group reporting 4 events (0.9%) discontinued their treatment permanently, with median time to recovery of 47 days.

The underlying mechanism for dysaesthesia remains unknown.[8] Of note, however, the reported symptoms and location of the affected areas (see above) are diverse and do not indicate an anatomical pattern, which is typical for a neuropathy. Furthermore, the majority of the patients recovered within 18 to 63 days (median duration of recovery) after reported onset and most often without change in the assigned dose of semaglutide. Thus, Novo Nordisk assesses that there is a low likelihood that the dysaesthesia is elicited by a neuropathy. Data from several long-term clinical outcome studies with semaglutide (SELECT [EX9536-4388] and SUSTAIN 6 [NN9535-3744] with s.c. semaglutide, and

PIONEER 6 [NN9924-4221] and SOUL [EX9924-4473] with oral semaglutide) with dose levels lower than 7.2 mg have not identified any serious neurological or skin disorders that could be related to dysaesthesia.

In conclusion, Novo Nordisk therefore considers that dysaesthesia is a non-serious AE associated with high-dose semaglutide injections, which, in most of the cases, recovers while on treatment. However, Novo Nordisk will continue to monitor dysaesthesia through routine post-marketing pharmacovigilance activities in alignment with our commitment to patient safety. To further understand any semaglutide-related risks and mechanisms, ongoing and future clinical studies with semaglutide will collect additionally detailed data to enhance the characterisation of any reported dysaesthesia events.

Assessment of the MAH's response

AEs related to dysaesthesia were reported by a higher proportion of participants in the semaglutide 7.2 mg group (22%).

We agree with the company that the reported symptoms and location of the affected areas are diverse and do not indicate an anatomical pattern, which is typical for a neuropathy. However, the underlying mechanism for dysaesthesia remains unknown. This is considered a problem as risks with unknown underlying mechanisms are unpredictable and difficult to avoid or mitigate. Long term effects of the 3 times higher dose on dysaesthesia are unknown.

Across the STEP UP studies, 66 (15%) of the 434 events identified by the dysaesthesia MedDRA search had not recovered in the semaglutide 7.2 mg group. For the events that did recover in the semaglutide 7.2 mg group, 191 events (44% of all reported events) only recovered after changes in the dose of the trial product.

We therefore consider it important that the high risk of dysaesthesia and other possible long term risks are taken into account when dosing semaglutide. If efficacy of the high dose is not sufficient in a patient , the dose should be titrated back to avoid unnecessary risks. In addition, it is important that Novo Nordisk continues to monitor dysaesthesia through routine post-marketing pharmacovigilance activities. Ongoing and future clinical studies with semaglutide should collect additionally detailed data to enhance the characterisation of any reported dysaesthesia events.

Question 6

A greater proportion of participants in the semaglutide 7.2 mg group reported AEs than in both the semaglutide 2.4 mg and placebo groups in the PT Alopecia. The events of Alopecia were associated with weight loss, as a higher proportion of events related to Alopecia were reported in participants with $\geqslant$20% weight loss (up to 9%). Mechanisms and potential long term effects should be discussed.

Summary of the MAH's response

As summarised below, alopecia was reported more frequently with semaglutide 7.2 mg than with semaglutide 2.4 mg and placebo in the STEP UP studies. This observation is considered expected, because of the well-known association between excessive weight loss and hair thinning or transient hair shedding as described in published literature. Hair loss has been observed following weight loss after bariatric surgery and with therapies for weight management.[9-16] Additional details on the mechanisms involved are provided below.

In the STEP UP pool (data from the STEP UP and STEP UP T2D studies), 5.8% of participants reported alopecia in the semaglutide 7.2 mg group vs. 3.3% and 1.0% in the semaglutide 2.4 mg and placebo groups, respectively. Events of hair loss (lowest level term) are described in in the proposed SmPC for

Wegovy®. All events of Alopecia were non-serious and mostly mild or moderate in severity, with the majority resolving spontaneously whilst on treatment. Out of all alopecia events, 1 event (assessed as "mild" and later recovered) led to permanent treatment discontinuation, and 5 events led to dose reduction

In the STEP UP pool, alopecia events were more common in participants with ≥20% weight loss, with a proportion of 9.0% in the semaglutide 7.2 mg group compared to 4.2% in the semaglutide 2.4 mg group. An additional analysis shows that a large proportion of the participants reporting alopecia achieved weight loss of more than 25%. Overall, the majority of the participants with alopecia lost more than 10% of their body weight.

Of the total 76 events of hair loss reported in semaglutide 7.2 mg group, 46 had recovered and 4were recovering and 26 events had not recovered by the end of the study. In semaglutide 2.4 mg, 5 events of hair loss had recovered and 2 had not recovered. In the placebo group, 1 event had recovered and 2 had not recovered

The estimated time to recovery for hair loss amongst participants in the STEP UP studies who received semaglutide 7.2 mg, semaglutide 2.4 mg or placebo is presented in Appendix 2, TFL 2.5 to 2.8. The median time to recovery was 141 days for the 41 participants who recovered with semaglutide 7.2 mg, and 136 days for the 5 participants who recovered with semaglutide 2.4 mg without change in the dose of study drug. The median time to recovery was 142 days for the 4 participants in the semaglutide 7.2 mg group, whose dose level was reduced as a result of the hair loss. There was 1 participant in the semaglutide 7.2 mg group who permanently discontinued treatment and recovered after 279 days.

Overall, the alopecia events observed with semaglutide 7.2 mg in the STEP UP studies were non-serious and mild, most were reversible, and did not require dose level changes.

Mechanisms and potential long-term effects

The hair cycle comprises of sequential phases of growth and rest that each hair follicle undergoes. These phases include the anagen phase (active and growing phase of a hair follicle), the catagen phase (the transitional phase which signals the end of active hair growth) and the telogen phase (the resting phase of a hair follicle). In the normal scalp, 90–95% of the hair follicles are in the anagen phase and the remainder (5–10%) are in the telogen phase with about 100-150 hair being shed daily. Only a few follicles will be in the catagen phase.

Various metabolic alterations or stressful conditions are capable of influencing the biological clock within the hair follicles, and it is possible for an abnormally large number of hair follicles to enter the telogen phase simultaneously. Telogen effluvium (diffuse hair loss) occurs if a significant number of anagen hair follicles are triggered to stop growing prematurely by any stimulus and subsequently enter catagen phase, followed by telogen phase. This leads to excessive hair shedding that starts after about 2−3 months of the initial stimulus and typically resolves within 6 to 9 months after removing the underlying cause.

Telogen effluvium can be caused by various trigger factors including:

1. Physiological stress such as postpartum, difficult labour, surgical trauma, severe febrile illness, serious injuries, major surgery, haemorrhage, starvation, extreme dieting regimens, excessive/ rapid weight loss
2. Drugs like oral retinoids (etretinate and acitretin), oral contraceptives, antithyroid drugs, anticonvulsants, hypolipidemic drugs, beta blockers, captopril, amphetamines
3. Endocrine conditions like hyperthyroidism, hypothyroidism, Polycystic Ovary Syndrome (PCOS)
4. Nutritional causes like iron deficiency anaemia, zinc deficiency, malnutrition

5. Organ dysfunction like renal failure, hepatic failure

A rapid or excessive weight loss is perceived as physiological stress by the body, which in turn can influence the biological clock within hair follicles, pushing an abnormally large number of hair follicles to enter the telogen phase simultaneously leading to diffuse hair loss (telogen effluvium). Further, weight loss may also be associated with restrictive low caloric diets and insufficient intake of micronutrients like essential vitamins and minerals, impacting the metabolically active hair follicle and its growth and further adding to the causes of weight loss induced hair loss.

In conclusion, the mechanisms and long-term aspect of hair loss resulting from weight loss described above appear similar across the known interventions for weight management, including incretin-based therapies and bariatric surgery.

Assessment of the MAH's response

In the STEP UP pool, 5.8% of participants reported alopecia in the semaglutide 7.2 mg group vs. 3.3% and 1.0% in the semaglutide 2.4 mg and placebo groups, respectively

Of the total 76 events of hair loss reported in semaglutide 7.2 mg group, 30 events had not recovered by the end of the study. However, only 1 event (assessed as "mild" and later recovered) led to permanent treatment discontinuation, and 5 events led to dose reduction.

The association between excessive weight loss and hair thinning or transient hair shedding has been described in published literature. With the high dose of semaglutide, hair loss was also related to the amount of weight loss, suggesting that the mechanisms and long-term aspect of hair loss resulting from weight loss appear similar across the known interventions for weight management.

Question 7

In STEP UP in patients without diabetes, there was a somewhat higher risk of hypoglycaemia in both semaglutide groups compared to the placebo group. The company should discuss the risk of hypoglycaemia with higher doses of semaglutide in patients without diabetes.

Summary of the MAH's response

Semaglutide acts through GLP-1 receptor activation, reducing hyperglycaemia in a glucose-dependent manner. Semaglutide rarely causes hypoglycaemia in people without diabetes, unless there are other contributing factors (such as calorie restriction).

In the STEP UP study in participants without diabetes, hypoglycaemia was a pre-defined safety focus area. In the evaluation of the safety focus area, a MedDRA search for events of hypoglycaemia identified very few AEs. Of the 3 AEs of hypoglycaemia reported by 3 participants in the semaglutide 7.2 mg group (0.3%, 0.2 events per 100 PYE), one AE was reported as "suspected hypoglycaemia".

Furthermore, 2 AEs were reported by 1 participant (0.5%, 0.7 events per 100 PYE) in the semaglutide 2.4 mg group, and none were reported in the placebo group. In addition, one event of "blood glucose decreased" was reported in semaglutide 2.4 mg arm. Of note, one event in semaglutide 2.4 mg arm was reported within 9 weeks after permanent treatment discontinuation.

The incidence of hypoglycaemia in the semaglutide 7.2 mg group of the STEP UP study is considered very low. All events were non-serious, mild, and did not require a change in the dose of the study drug. The findings in the semaglutide 2.4 mg group are within the range seen in the phase 3a trials in participants

without diabetes, where the proportion of participants reporting hypoglycaemia was 0.6% and the rate was 0.7 events per 100 PYE.

In conclusion, STEP UP reaffirmed that in people with obesity and without diabetes, the risk of hypoglycaemia with semaglutide 2.4 mg and 7.2 mg is very low.

Assessment of the MAH's response
We agree with the company that in people with obesity and without diabetes, the risk of hypoglycaemia with semaglutide 2.4 mg and 7.2 mg is very low.

Question 8

In the 2,4 semaglutide group, one patients reported 21 SAEs including one fatal event. A short narrative of the events in this patient should be provided.

Summary of the MAH's response
In STEP UP T2D (study 7595), one participant, who was a 71-year-old male, reported 21 SAEs between study days 310 and 352. The SAEs are described in case narratives. The participant was randomised to semaglutide 2.4 mg and had first exposure on study day 1; last exposure to trial product was on study day 339.

Amongst the 21 reported SAEs, 20 SAEs were judged by the investigator as 'unlikely' related to the trial product . The first SAE (orthostatic hypotension) occurred on study day 313 and was judged by the investigator with a causality of 'possible' and the trial product was temporarily discontinued.

The condition of the participant continued to deteriorate, and additional SAEs were reported over the following weeks. Between study days 341 and 352, the participant's renal and liver functions deteriorated, with development of toxic metabolic encephalopathy, respiratory failure and disseminated intravascular coagulation, and multiple osteolytic lesions and a hepatic mass were discovered on study day 352. Eventually, the participant passed away with metabolic acidosis (SAE of metabolic acidosis had a fatal outcome on study day 354).

Table 3-4 summarises information on all AEs reported for this participant in STEP UP T2D. Full narratives, including details about AEs, medical history, concomitant medication, and relevant laboratory parameters are provided in the dossier.

At study day 337, the participant had a single measurement showing an aspartate aminotransferase (AST) value >5xULN, which was predefined as a cut-off value for clinically significant other clinical events. All AST values reported for the participant are summarised in Table 3-5.

Assessment of the MAH's response
As requested, the company provided a detailed narrative of the events in the patient that reported 21 SAEs including one fatal event.

8. Updated 2nd request for supplementary information

8.1. Major objections

None

8.2. Other concerns

Clinical aspects

Clinical pharmacology

Question 1
Potential effect on gastric emptying should be studied in a new paracetamol absorption study with adequate exposure levels. The applicant is requested to commit to this study, which could be conducted post-approval. In addition, the applicant should include a statement about potential effects of semaglutide on absorption of other medicines in SmPC section 4.5, at least until results of the gastric emptying study have become available.

Efficacy/safety

Question 2

The additional benefit with the higher dose may be clinically relevant for some patients (7-15% of the total population), but not for the majority of patients (85-93%). The company did not identify a subgroup of patients that may have substantially improved benefit-risk balance with the higher dose. Unfortunately, the 3 times higher dose is associated with an increased risk of adverse events, especially dysaesthesia. Therefore, the benefit-risk profile for the 7.2 mg dose level is negative for most patients.

We consider the 7.2 mg dose only indicated in patients that need additional weight loss. In case of side effects, the dose may be titrated back. In addition, if a clinical improvement in body weight has not been achieved with the 7.2 mg dose, the dose should be titrated back to 2.4 mg in order to prevent risks with the high dose. This should be clearly stated in the posology section of the SPC.

9. Assessment of the responses to the request for supplementary information

9.1. Other concerns

Clinical aspects

Clinical pharmacology

Question 1
Potential effect on gastric emptying should be studied in a new paracetamol absorption study with adequate exposure levels. The applicant is requested to commit to this study, which could be conducted post-approval. In addition, the applicant should include a statement about potential effects of semaglutide on absorption of other medicines in SmPC section 4.5, at least until results of the gastric emptying study have become available.

Summary of the MAH's response
Novo Nordisk accepts the commitment to conduct a gastric emptying trial post-approval on the 7.2 mg s.c and submit the results by Q2 2027. In addition to this the SmPC section 4.5 has been updated to include the following statement: "The effect of semaglutide 7.2 mg on the rate of gastric emptying has not been investigated".

Proposed study timeline (expected)

- Expected First Patient First Visit (FPFV): July 2026
- Expected Last Patient Last Visit (LPLV): June 2027

These dates are presented as expected timelines to allow for normal operational variability.

Assessment of the MAH's response
The applicant has committed to a post-approval gastric emptying study on the 7.2 mg s.c. administration.

The addition to the SmPC is accepted.

Efficacy/safety

Question 2
The additional benefit with the higher dose may be clinically relevant for some patients (7-15% of the total population), but not for the majority of patients (85-93%). The company did not identify a subgroup of patients that may have substantially improved benefit-risk balance with the higher dose. Unfortunately, the 3 times higher dose is associated with an increased risk of adverse events, especially dysaesthesia. Therefore, the benefit-risk profile for the 7.2 mg dose level is negative for most patients.

We consider the 7.2 mg dose only indicated in patients that need additional weight loss. In case of side effects, the dose may be titrated back. In addition, if a clinical improvement in body weight has not been

achieved with the 7.2 mg dose, the dose should be titrated back to 2.4 mg in order to prevent risks with the high dose. This should be clearly stated in the posology section of the SPC.

Summary of the MAH's response

Novo Nordisk acknowledges the comments provided by the CHMP regarding the SmPC section 4.2 for Wegovy® and agrees to update the section with the following "If no additional clinical improvements in body weight is observed with the 7.2 mg, lower the dose to 2.4 mg once weekly." and "If needed, the dose can be increased to 7.2 mg once weekly after a minimum of 4 weeks on the 2.4 mg dose in adults with BMI ≥ 30 kg/m2 at treatment initiation.".

Assessment of the MAH's response

As requested, the company has updated the section with the following "If no additional clinical improvements in body weight is observed with the 7.2 mg, lower the dose to 2.4 mg once weekly." and "If needed, the dose can be increased to 7.2 mg once weekly after a minimum of 4 weeks on the 2.4 mg dose in adults with BMI ≥ 30 kg/m2 at treatment initiation.".

10. Attachments

1. Product Information (changes highlighted) Wegovy as adopted by the CHMP on 11 December 2025.