Australian Government
Department of Health
Therapeutic Goods Administration

Delegate's Summary and Request for ACM advice

Active substance: semaglutide (rys)

Product Name: WEGOVY

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

4 January 2022

TGA Health Safety Regulation

Contents

1. Summary of overview

1.1. Submission information

Submission number	PM-2021-00612-1-5 e005802 (0000, 0001, 0002, 0003)
Active ingredients	Semaglutide (rys)
Product name	WEGOVY
Strengths/dose form	0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle
Sponsor	Novo Nordisk Pharmaceutical Pty Ltd
Description of the submission and proposed indication	This is a Category 1, Type C (extension of indication) application for WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle. The application is to extend the indications for semaglutide to include management of obesity. The new indication is intended to be registered with a new trade name (WEGOVY), new strengths and a new dosage delivery system (a single use prefilled pen with pre-assembled needle). The currently approved indication for OZEMPIC (semaglutide) is: *Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:* • *as monotherapy when metformin is not tolerated or contraindicated.* • *in addition to other medicinal products for the treatment of type 2 diabetes.* The proposed additional new indication is: *WEGOVY is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of* • *≥30 kg/m² (obesity), or* • *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight related comorbidity*
Summary of data	Pharmacology: section 2.4.1 Efficacy: section 2.4.2 Safety: section 2.4.3

Preliminary view

While a decision is yet to be made, at this stage I am inclined to approve the registration of the product for the following additional indication:

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

- *≥30 kg/m² (obesity); or*
- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity.*

1.2. Questions for the sponsor

No questions.

1.3. Request for independent expert advice

Not applicable.

1.4. Request for ACM advice

ACM meeting number: 31 **Date (of meeting): 4 February 2022**

Summary of issues for advice and advice sought

The committee is requested to provide advice on the following specific issues:

Q1: Sufficient data for registration (including long term data and the potential for rebound)

The Phase 3a studies provided a large amount of data supporting the proposed indication. Long-term data beyond 2 years and data regarding potential rebound are limited.

- Can the ACM comment on whether the provided data are sufficient to support registration for the proposed indication?

Q2: General

- The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Pre ACM preliminary assessment

☑ I have no reason to say, at this time, that the application for WEGOVY should not be approved for registration for the proposed indication.

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Delegate of the Secretary under regulation 35A of the Therapeutic Goods Regulations 1990

4 January 2022

Date

2. Body of overview

2.1. Background

This is a Category 1, Type C (extension of indication) application for WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle.

The application is to extend the indications for semaglutide to include management of obesity. The new indication is intended to be registered with a new trade name (WEGOVY), new strengths and a new dosage delivery system (a single use prefilled pen with pre-assembled needle).

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with a 94% homology to human GLP-1. Both native GLP-1 and GLP-1 RAs reduce body weight by lowering energy intake via inducing feelings of satiety and fullness, and lowering feelings of hunger.

2.1.1. Background on condition being treated

Obesity is a common condition with high associated morbidity and mortality. Body Mass Index (BMI) is used as a surrogate measure of being overweight and obese:

- 25.0 to 29.9 kg/m^2 is classified as overweight but not obese
- ≥30.0 kg/m^2 is classified as obese.
- >35.0 kg/m^2 is classified as severely obese.

These definitions may not apply to a highly muscled individual or to children and adolescents. Interpretation of BMI may vary between ethnic groups. Waist circumference in adults may be a better measure of adiposity and a better measure of obesity-related morbidity.

In 2021, the AIHW reports that in 2017–18, an estimated 2 in 3 (67%) Australians aged 18 and over were overweight or obese, 36% were overweight but not obese, and 31% were obese. This equates to approximately 12.5 million adults in Australia. The prevalence of overweight and obesity was higher in males compared to females (75% vs. 60%) and also the prevalence of obesity was higher in males (33% vs. 30%). Obesity is more prevalent in older age groups.

Obesity is associated with cardiovascular disease, hypertension, type 2 diabetes mellitus (T2DM) and metabolic syndrome, non-alcoholic fatty liver disease, cholelithiasis, cancer, and sleep apnoea.

2.1.2. Proposed indication

The proposed additional new indication is:

> *WEGOVY is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of*
>
> - *≥30 kg/m^2 (obesity), or*
> - *≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight related comorbidity*

2.1.3. Current treatment options

Current treatment options include:

- **Lifestyle modification:** diet and exercise with or without psychological support
- **Pharmacological treatments:**

  - Orlistat: a selective inhibitor of pancreatic lipase, resulting in decreased absorption of fat. Orlistat is a Schedule 3 drug in Australia and is available over the counter.
  - Liraglutide: a GLP-1 agonist
  - Phentermine: sympathomimetic agent with anorectic actions.
  - Naltrexone/bupropion is approved for the following indication in Australia:
- **Pharmacological treatments not approved in Australia:**
  - Phentermine/topiramate: is approved in the US for weight control. Topiramate is associated with weight loss due to an unknown mechanism (approved in the US).
  - Lorcaserin: an appetite suppressant through activation of hypothalamic 5-HT_{2C} receptors (approved in the US).
- **Bariatric surgery:** usually reserved for patients with severe obesity with considerable peri-operative and post-operative morbidity.

2.1.4. Australian Regulatory Status

OZEMPIC (semaglutide) solution for injection (intended for subcutaneous administration) was approved in Australia on 28 August 2019 for the identical indication of:

> *Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:*
>
> - *as monotherapy when metformin is not tolerated or contraindicated.*
> - *in addition to other medicinal products for the treatment of type 2 diabetes.*

RYBELSUS (in its semaglutide (rys) tablet form for oral administration) is currently under evaluation for management of Type 2 diabetes.

A comparison of WEGOVY with the currently registered OZEMPIC solution is shown in Table 7. In addition the amounts, differences in the composition of the new formulation *cf.* the old formulation includes the use of sodium chloride as a tonicity agent instead of propylene glycol, and the removal of phenol (preservative).

2.1.5. International Regulatory Status

Similar applications have been submitted and are under consideration in the EU (4 January 2021), the US (4 December 2020), Canada (8 December 2020) and the UK (5 January 2021). Similar applications have not been made in New Zealand, Singapore or Switzerland. A similar application has not been refused market approval or withdrawn.

The US FDA registered WEGOVY on 4 June 2021 for the following indication:

> *WEGOVY is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of*
>
> *• 30 kg/m2 or greater (obesity) or*
>
> *• 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).*

2.2. Manufacturing and quality control (Module 3) data evaluation

Quality (Module 3) Summary (Biological Medicines) (D21-3363118)

2.2.1. Summary

There are no objections on quality grounds to the approval of WEGOVY.

2.2.2. Proposed conditions of registration

Condition(s) of registration resulting from primary evaluation/secondary evaluations

None specified.

Laboratory testing & compliance with Certified Product Details (CPD)

i. All batches of WEGOVY supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

ii. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

2.3. Non-clinical (Module 4) data evaluation

Module 4 Nonclinical Evaluation Report (Round 2) (D21-2820164)

2.3.1. Summary

Conclusions and recommendations

Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indications for semaglutide to be used as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of ≥30 kg/m^2 (obesity), or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. For the new indication, the Sponsor is proposing a new trade name (WEGOVY®), new strengths (up to 3.2 mg/mL), an increase in the maximum dose (from 1 mg/week, SC to 2.4 mg/week, SC) and a new dosage delivery system.

The submitted Module 4 dossier was generally acceptable. No major deficiencies were identified.

Two primary pharmacology studies were submitted. Semaglutide is a GLP-1 receptor agonist, which is a physiological regulator of appetite and caloric intake. The GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies showed that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake, and therefore support the new indication.

There are no new safety concerns associated with the higher systemic exposures expected with the higher strength formulation of semaglutide (as WEGOVY®), and overall no nonclinical objections to registration.

The draft Product Information should be amended as directed on pages 10-14 in the NCER.

2.3.2. Proposed conditions of registration

None specified.

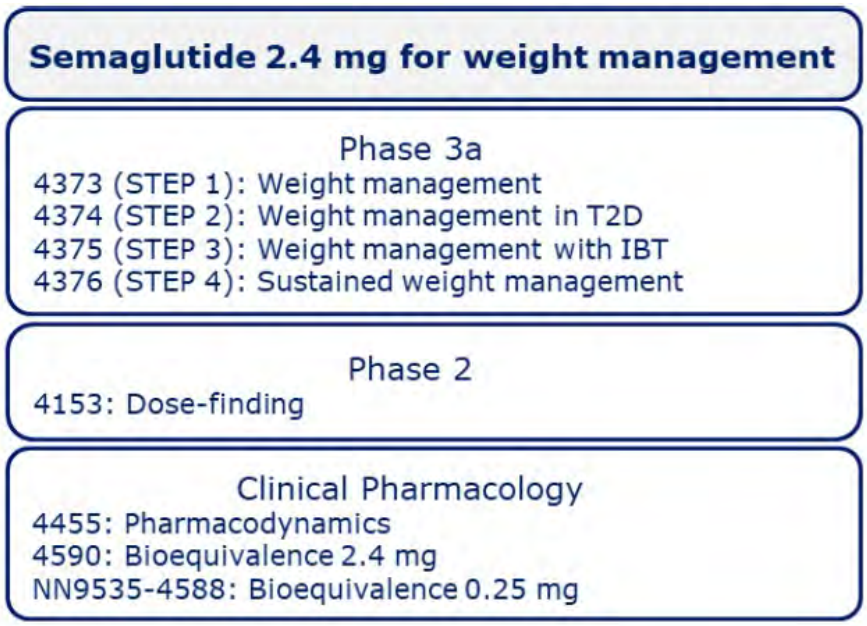
2.4. Clinical (Module 5) data evaluation

Module 5 Clinical Evaluation Report Round 2 (D21-3227089)

The dossier contains data the following studies that have not previously been submitted to the TGA for evaluation:

- 3 clinical pharmacology trials (2 of which are bioequivalence trials): Studies NN9536-4590, NN9535-4588, and NN9536-4455
- 1 Phase 2 dose-finding trial: Study NN9536-4153
- 2 PKPD modelling reports (based on Phase 2 data, and STEP 1 and 2 studies)
- 4 Phase 3a therapeutic confirmatory trials (STEP trials): Studies NN9536-4373 (STEP 1), NN9536-4374 (STEP 2), NN9536-4375 (STEP 3), and NN9536-4376 (STEP 4)

Table 1. Overview of the WEGOVY clinical trial program studies.



2.4.1. Pharmacology

2.4.1.1. Pharmacokinetics (PK)

WEGOVY (semaglutide) is intended for subcutaneous administration. Semaglutide formulation D with the single-dose pen-injector (DV3396) appears to be the formulation intended for marketing. The pharmacokinetic studies were performed in populations typical of those intended for marketing in Australia.

Absorption

Absolute bioavailability was 89% (**NN9535-3687**).

Mean T_{max} (SD) was 21.3 (14.90) h for formulation D and 64.5 (16.84) h for Formulation B (NN9535-4588). In **NN9536-4590**, median (range) Tmax was 24 (3 to 48) h for Formulation D.

Distribution

A volume of distribution of 9.8 L indicates limited tissue distribution for semaglutide. The unbound fraction assessed with *in vitro* assay was less than 0.5% for all subjects (**NN9535-3651**). The geometric mean (CV%) Vss/F was 9.8 (23.4) L (Formulation D in **NN9536-4590**).

Metabolism

Prior to elimination, semaglutide is extensively metabolised to multiple metabolites that appear to be inactive. Semaglutide is a peptide, and would be expected to have similar metabolism to other endogenous and exogenous peptides.

In plasma, semaglutide was the primary component circulating at all timepoints. 6 metabolites were detected in plasma, each accounting for 0.4–7.7% of the semaglutide-related material based on AUC. In urine, 22 components were detected in urine and 7 minor metabolites in faeces.

Excretion

The CV% for CL/F was 20.7, indicating inter-individual variability to be typical for a peptide drug.

3.1% of semaglutide was excreted unchanged in urine. The total recovery (measured as the total excretion) of [$_3$H]-semaglutide related material was 75.1% of the administered dose: 53.0% in urine, 18.6% in faeces and 3.2% in expired air (**NN9535-3789**).

CL, t½, Tmax and Vss were similar for both B and D formulations at the 2.4 mg dose level (**NN9536-4590**). For Formulation D, geometric mean (CV%) CL/F was 0.040 (22.6) L/h, t½ was 155 (9.8) h, and Vss/F was 9.8 (23.4) L. Median (range) T_{max} was 24 (3 to 48) h.

The geometric mean terminal t½ of s.c. semaglutide (range 143–152 hours) and i.v. semaglutide were comparable (137 hours) (**NN9535-3687**).

Bioequivalence

At a dose of 0.8 mg semaglutide, equivalence between semaglutide 1 mg/mL, 3 mg/mL and 10 mg/mL was demonstrated for $AUC_{0-\infty}$. but not for C_{max}.

Synthetic vs. recombinant: Bioequivalence has been demonstrated between synthetic semaglutide and recombinant semaglutide at a concentration of 1.34 mg/mL and dose of 0.5 mg (**NN9535-4010**).

Formulation B and D: Study **NN9536-4590** compared the semaglutide Formulation D with the DV3396 pen-injector with Formulation B with the PDS290 pen-injector. The two formulations were:

- bioequivalent at the 2.4 mg dose level for AUC but not for C_{max}. The ratio (90% CI) Formulation D/B for AUC_{0-168h} was 1.0539 (1.0003 to 1.1104). The ratio (90% CI) Formulation D/B for C_{max} was 1.1556 (1.0800 to 1.2365). The Formulation D resulted in slightly higher exposure.
- bioequivalent at the 1 mg dose level for AUC and C_{max}, but Formulation D also resulted in slightly higher exposure.

Similar results were found in Study **NN9535-4588**.

Dose proportionality

There was dose proportionality between the 1 mg and 2.4 mg dose levels: ratio (95% CI) (2.4 mg/1 mg) was 2.57 (2.49 to 2.65) for AUC and 2.57 (2.42 to 2.73) for C_{max} (**NN9536-4590**).

The Sponsor has examined dose-proportionality for the intended dose range in the titration phase. This indicates dose-proportionality for overall exposure (AUC) but not for peak exposure (C_{max}). However, this would not be expected to result in any differences in effect during the titration phase.

Pharmacokinetics in special populations

Pharmacokinetic properties and exposure of semaglutide was not affected by hepatic impairment (**NN9535-3651**).

For subjects with impaired renal function, the 'no-effect' criterion was met for all renal impairment groups, except for the severe renal impairment group ($AUC_{0-\infty}$ approx. 22% higher) (**NN9535-3616**). Based on these results, a dose adjustment of semaglutide may not be warranted in subjects with renal impairment.

There were no differences in PK properties between Caucasian and Japanese subjects with comparable steady state exposure and maximum concentration (**NN9535-3633**).

Drug-drug interactions (DDIs)

Semaglutide did not have a clinically significant effect on exposure to ethinylestradiol (11% increase) and levonorgestrel (20% increase) (**NN9535-3819**).

Semaglutide had no significant effect on exposure to digoxin, metformin, warfarin, or atorvastatin (**NN9535-3817 and NN9535-3818**).

2.4.1.2. Population PK data (popPK)

Modelling Report for Data from Phase 2 Study NN9536-4153

The covariate analysis indicated body weight was the most important covariate influencing exposure (Table 8). The concentration response relationship was described by the model (Figure 2).

Modelling Report for Data from Phase 3a STEP 1 and STEP 2 studies

For a typical participant, CL/F was estimated as 0.0475 L/h and V/F as 12.4 L. Dose proportionality was demonstrated in the dose range 0.25 to 2.4 mg. Interindividual variability in CL/F in the final model was 18.7%. Body weight had a significant effect on exposure (Table 2). The presence of antibodies did not affect the PK of semaglutide.

Table 2. PopPK modelling based on Phase 3a STEP 1 and STEP 2 studies. Forest plot of covariate effects for semaglutide exposure.

Covariate	Test category	Reference category	Relative Exposure (C_{avg})	Ratio [90% CI]
Sex	Male	Female		0.93 [0.91;0.94]
Age group	65-<75 years	18-<65 years		0.99 [0.97;1.01]
	>=75 years			0.94 [0.87;1.02]
Race	Black or African American	White (other)		1.07 [1.04;1.11]
	Asian			0.97 [0.95;0.99]
	American Indian or Alaska Native			0.98 [0.93;1.04]
Ethnicity	Hispanic or Latino	Non-Hispanic or Latino		0.97 [0.94;1.00]
Body weight	74 kg	110 kg		1.40 [1.38;1.43]
	143 kg			0.80 [0.79;0.81]
Renal function	Mild	Normal		1.04 [1.02;1.06]
	Moderate			1.06 [1.02;1.11]
Injection site	Thigh	Abdomen		0.99 [0.96;1.01]
	Upper arm			0.99 [0.95;1.03]
Glycaemic status	Prediabetes (STEP 1)	Normoglycaemia (STEP 1)		0.96 [0.94;0.98]
	Diabetes (STEP 2)			0.85 [0.83;0.87]

Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino, normoglycaemic (STEP 1) white female aged 18-<65 years, with a body weight of 110 kg and normal renal function, who injected in the abdomen). The forest plot and the column to the right show means and 90% CI for the relative exposures. Body weight test categories (74 and 143 kg) represent the 5% and 95% percentiles, respectively in the data set. There was 1 subject with severe renal impairment included in the moderate group. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80;1.25).

2.4.1.3. Pharmacodynamics (PD)

Individual study results are shown in CER section 5.2.

The pharmacodynamics of WYGOVY (semaglutide) have been adequately characterised. Semaglutide has a dose-dependent effect on weight loss. Semaglutide decreases appetite, decrease food intake and decreased food cravings. An E_{max} relationship between concentration and the proportion of responders has been demonstrated.

Semaglutide has a beneficial effect on β-cell function. The improvement in glycaemic and weight control has been previously documents in patients with T2DM.

Semaglutide did not have adverse effects on gastric emptying or cardiac repolarisation.

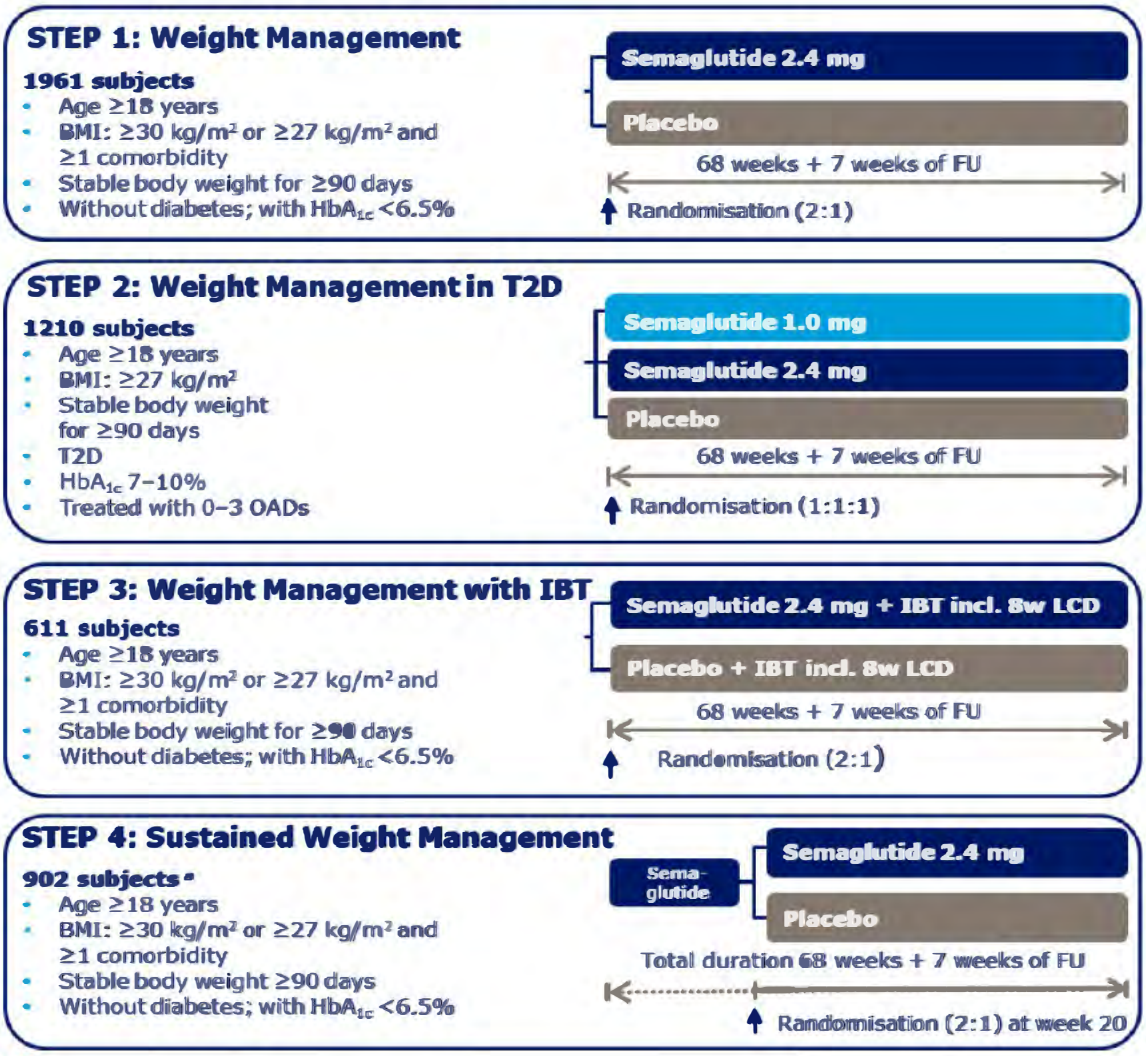
2.4.1.4. Dose-finding

The Sponsor has obtained adequate data to inform the dosage selection. The optimal dosing was defined using E_{max} models, and by balancing efficacy against tolerability. The proposed dose-titration, with initiation of treatment, is also supported by these data.

2.4.2. Efficacy

There were 4 pivotal Phase 3a efficacy studies: NN9536-4373 (STEP 1), NN9536-4374 (STEP 2), NN9536-4375 (STEP 3), and NN9536-4376 (STEP 4). An overview is at Table 3.

Table 3. Overview of STEP efficacy trials.



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

The main secondary objectives of STEP 1–4 were to compare the effect of semaglutide s.c. 2.4 mg once weekly on other factors related to body weight, cardiovascular risk factors, glucose metabolism, and clinical outcome assessments including patient-reported outcomes.

2.4.2.1. Pivotal STEP trials (Pivotal STEP 1, 2, 3, and 4)

Design

The pivotal STEP trials (STEP 1, 2, 3, and 4) were Phase 3a, randomised, double-blind, multi-centre, parallel-group, controlled studies to assess the efficacy and safety of semaglutide. 4585 adult subjects were randomised in STEP 1–4: 2652 to semaglutide 2.4 mg, 1530 to placebo, and 403 to semaglutide 1.0 mg.

STEP 1, 3, and 4 were two-armed trials with 2:1 randomisation (semaglutide 2.4 mg : placebo) and STEP 2 was a 3-arm, double-blind, double-dummy trial with 1:1:1 randomisation (semaglutide 1.0 mg : semaglutide 2.4 mg : placebo). Dose escalation occurred in STEP 1–3, but not in STEP 4.

The primary endpoint was the identical in all 4 phase 3a trials: change from baseline to week 68 in body weight (%). Furthermore, STEP 1–3 included a co-primary endpoint: subjects achieving (y/n) ≥5% body weight reduction at week 68. An overview of endpoints is at Table 9.

Trial population and study design are summarised in Table 3. Inclusion criteria and key exclusion criteria are summarised in Table 10, and Table 11, respectively.

Subject disposition, baseline demographic characteristics, and co-morbidities at screening are summarised in Table 12, Table 13, and Table 14, respectively.

Treatment effects were estimated using a treatment policy estimand method (primary estimand; disregarding product adherence or use of other anti-obesity therapies), and a hypothetical estimand method (without the potentially confounding effects of discontinuation or use of other anti-obesity therapies). The analyses of the confirmatory endpoints were controlled for multiplicity only for the treatment policy estimand, and all superiority claims were based on conclusions from the treatment policy estimand.

Magnitude of the treatment effect and its clinical significance

An overview of primary endpoint results is at Table 4. The treatment effect was well in excess of a clinically significant 5% weight loss. The effect size was consistent across the four studies. The effect persisted in a patient group undergoing IBT.

STEP 1 (NN9536-4373) (patients without diabetes) main findings (Table 15):

The mean (SD) change in body weight (%) from baseline to Week 68 was -15.1 (10.1) % for semaglutide and -2.8 (6.5) % for placebo; treatment difference (95% CI), semaglutide – placebo, -12.44 (-13.37 to -11.51) %, p <0.0001.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. There were improvements in glycaemic control. There were significant improvements in quality of life and physical functioning. There were improvements in fatty liver index.

The DEXA sub-study demonstrated that the losses in weight, waist circumference and BMI were due to a decrease in adipose, and not to loss of another body component (such as water or muscle).

STEP 2 (NN9536-4374) (patients with T2DM) main findings (Table 16):

In patients with T2DM, the mean (SD) change in body weight (%) from baseline to Week 68 was -7.2 (6.6) % for semaglutide 1.0 mg, -9.9 (8.0) % for semaglutide 2.4 mg and -3.3 (5.5) % for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -6.21 (-7.28 to -5.15) %, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -2.65 (-3.66 to -1.64) %, p <0.0001.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period compared with both placebo and semaglutide 1.0 mg groups. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure in both semaglutide groups. There were improvements in glycaemic control in both semaglutide groups, with no significant differences between the dose levels. There were significant improvements in quality of life and physical functioning, that were greater in the semaglutide 2.4 mg group compared with both semaglutide 1.0 mg and placebo.

STEP 3 (NN9536-4375) (patients without diabetes with IBT background treatment) main findings (Table 17):

With background treatment with IBT, the mean (SD) change in body weight from baseline to Week 68 was -16.5 (10.1) % for semaglutide and -5.8 (7.7) % for placebo; treatment difference (95% CI), semaglutide – placebo, -10.27 (-11.97 to -8.57) %, p <0.0001.

The background treatments included those in the proposed indication: diet and exercise. However, an additional background treatment was IBT.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period in patients who were also having IBT. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. There were improvements in glycaemic control.

However, there were improvements in quality of life and physical functioning in both treatment groups, with no significant differences between the treatment groups.

STEP 4 (NN9536-4376) main findings (Table 18):

The mean (SD) change in body weight from Week 20 to Week 68 was -8.8 (7.8) % for semaglutide and 6.1 (7.7) % for placebo; treatment difference (95% CI), semaglutide – placebo, -14.75 (-16.00 to -13.50) %, p <0.0001.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. There were improvements in glycaemic control. There were significant improvements in quality of life and physical functioning.

There were significant improvements in the semaglutide group both for the randomisation phase, and the treatment period. However, the placebo group had loss of benefit following the titration phase. The initial gains in this group were lost over the remainder of the study. This indicates that the benefits that occur during treatment may be lost after treatment is ceased. Semaglutide is likely to be a long-term treatment for obesity.

Table 4. Pivotal STEP trials. Inclusion criteria. Primary endpoint results.

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

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

2.4.3. Safety

2.4.3.1. Summary of safety

Exposure

14,520 patients (7,432 males and 6,721 females) in 21 trials were exposed in all Phase 3 clinical trials (oral and s.c. semaglutide for T2D; and semaglutide s.c. 2.4 mg for weight management) 9.925 patients were exposed for ≥12 months and 1,266 for ≥24 months.

In completed Phase 3a trials for weight management (STEP 1–4), 402 patients have been exposed to semaglutide 1.0 mg and 3,018 to 2.4 mg. Exposure to semaglutide 1.0 mg was 361 patients for 12 months and semaglutide 2.4 mg was 2.389 patients for 12 months (Table 5). There were 930 males and 2,123 females. There were 311 patients aged 65 to 74 years, 27 aged 75 to 84 years and one aged ≥85 years. There were 2,234 White patients, 410 Asian and 283 Black/African American.

Additionally, the sponsor made reference to 7 supportive trials from the Ozempic program (including the SUSTAIN 6 CVOT) and the clinical pharmacology trials investigating drug-drug interactions, populations with renal or hepatic impairment, and potential impact on cardiac electrophysiology (QTc).

Table 5. Pivotal STEP trials. Summary of exposure to semaglutide s.c. 2.4 mg for weight management.

Semaglutide s.c. 1.0 mg		Semaglutide s.c. 2.4 mg		All semaglutide s.c.		Placebo	
N	SYE	N	SYE	N	SYE	N	SYE
402	530	3,018	3,651	3,420	4,181	1,529	1,885

[a]Exposure from the STEP trials included in Table 2-6.

Abbreviations: N = number of subjects; s.c. = subcutaneous(-ly); SYE= subject-years of exposure.

Number of subjects				
Duration of exposure (at least)	Semaglutide s.c. 1.0 mg	Semaglutide s.c. 2.4 mg	All semaglutide s.c.	Placebo
1 month	400	3,012	3,412	1,524
3 months	389	2,936	3,325	1,499
6 months	373	2,530	2,903	1,438
9 months	369	2,448	2,817	1,377
12 months	361	2,389	2,750	1,305
16 months	353	2,266	2,619	1,006
18 months	–	4	4	2

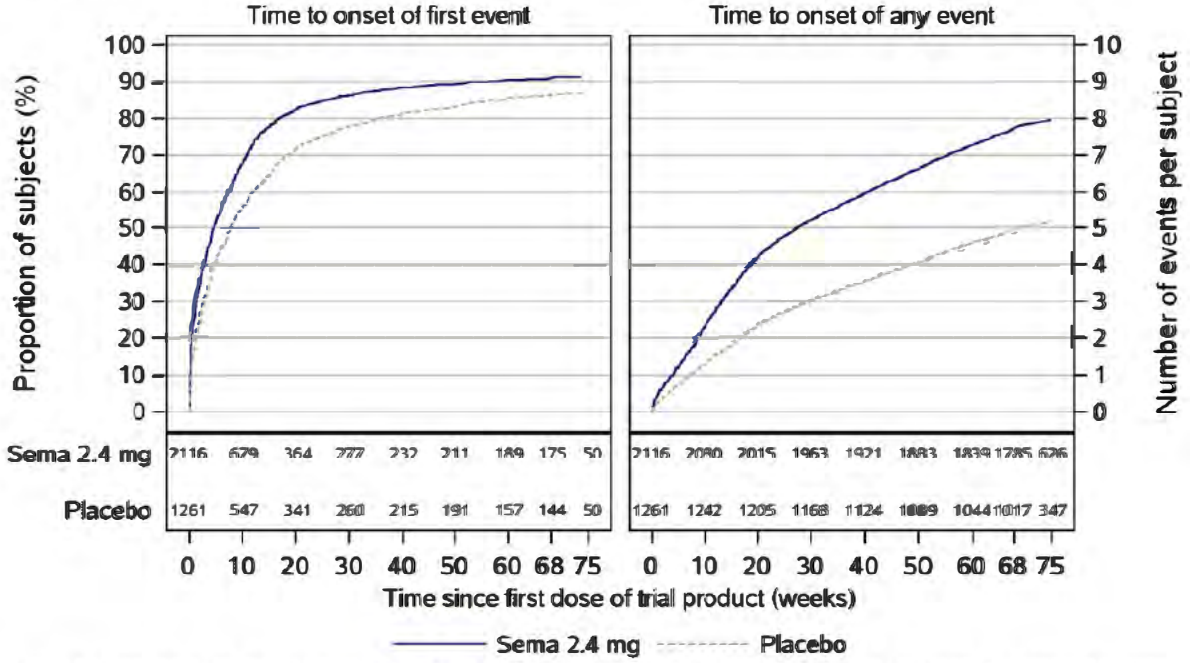
s47

Abbreviations: s.c. = subcutaneous(-ly).

Adverse event overview

Adverse events presented early in treatment (Figure 1). There were increased rates of gastrointestinal disorders and neurological disorders with semaglutide in comparison with placebo (Table 6). The gastrointestinal adverse events that occurred more frequently with semaglutide compared to placebo were: nausea, diarrhoea, vomiting, constipation, abdominal pain, decreased appetite, dyspepsia, eructation and abdominal distension. The neurological disorders that occurred more commonly with semaglutide were headache, fatigue and dizziness. Other AEs that were reported more frequently with semaglutide were alopecia (3.3% patients compared to 1.4% with placebo) and migraine (2.1% patients compared to 1.3% with placebo). In Study NN9536-4153, the Phase II dose-finding study, gastrointestinal adverse effects (vomiting, diarrhoea and constipation) were dose-related.

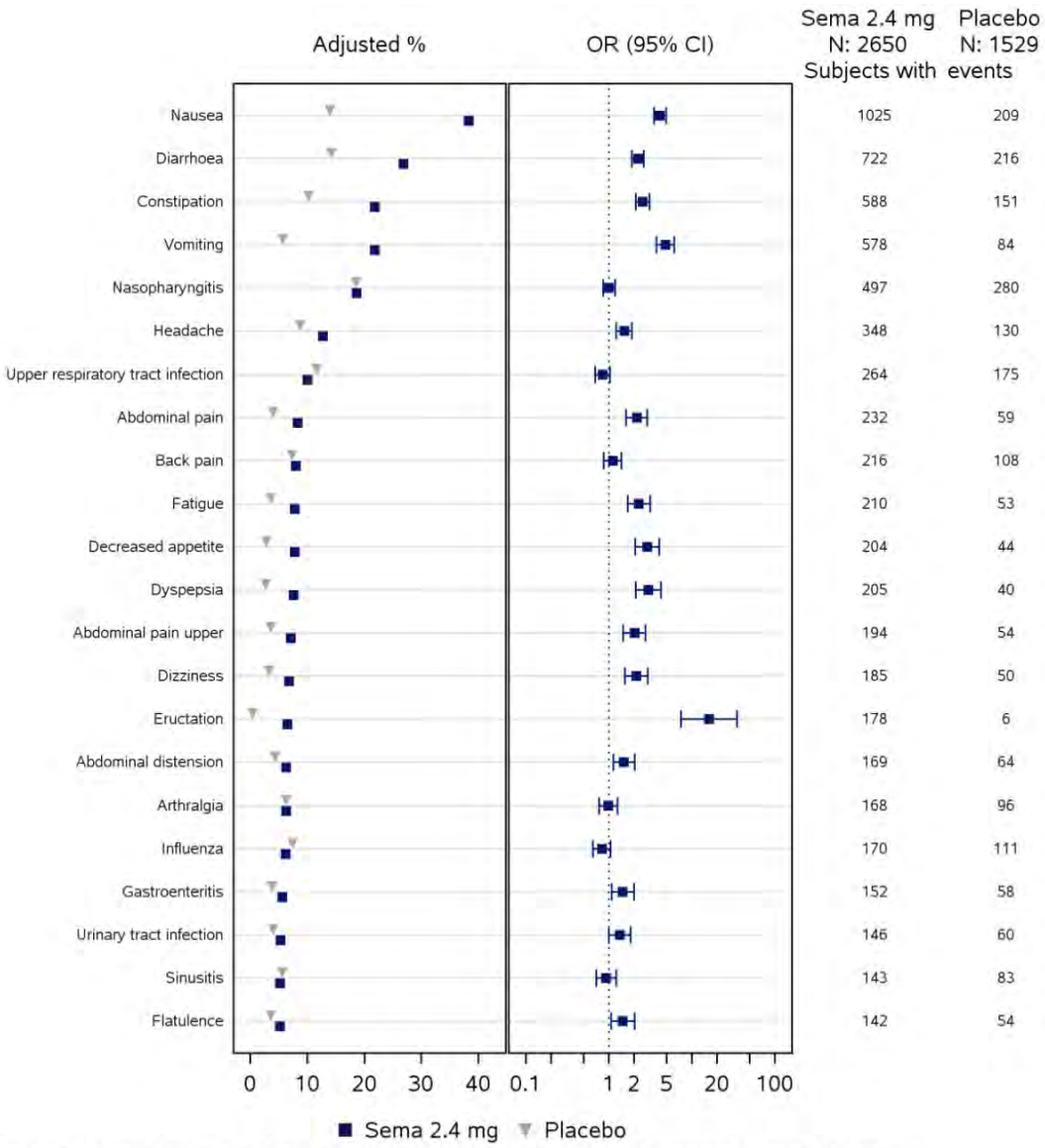
Injection site reactions occurred at a similar frequency with semaglutide 2.4 mg in comparison with placebo.



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Numbers shown in the lower panel are subjects at risk.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

Figure 1. Pivotal STEP 1-3 trials (pooled data). Time to onset of first or to onset of any event.

Table 6. Pivotal STEP trials (pooled data). On-treatment AEs in ≥5% of subjects.



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms.
Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
%: Percentage of subjects experiencing at least one event, OR: Odds ratio, CI: Confidence interval, N: Number of subjects
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 trial as factors.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

Deaths

8 deaths were reported in the completed clinical trials: 7 deaths in the STEP trials and 1 death in the phase 2 trial 4153. There were no deaths in the clinical pharmacology trials.

In the phase 3a pool, there was no difference between semaglutide 2.4 mg and placebo in proportion of subjects who died (3 subjects [0.1%] in the semaglutide 2.4 mg group and 3 subjects [0.2%] in the placebo group). There was one death at the semaglutide 1.0 mg dose level (undetermined cause of death). There was one death in the 0.4 mg fast escalation group in Study NN9536-4153 (malignancy). There were three deaths under placebo treatment, all due to malignancy.

Serious adverse events

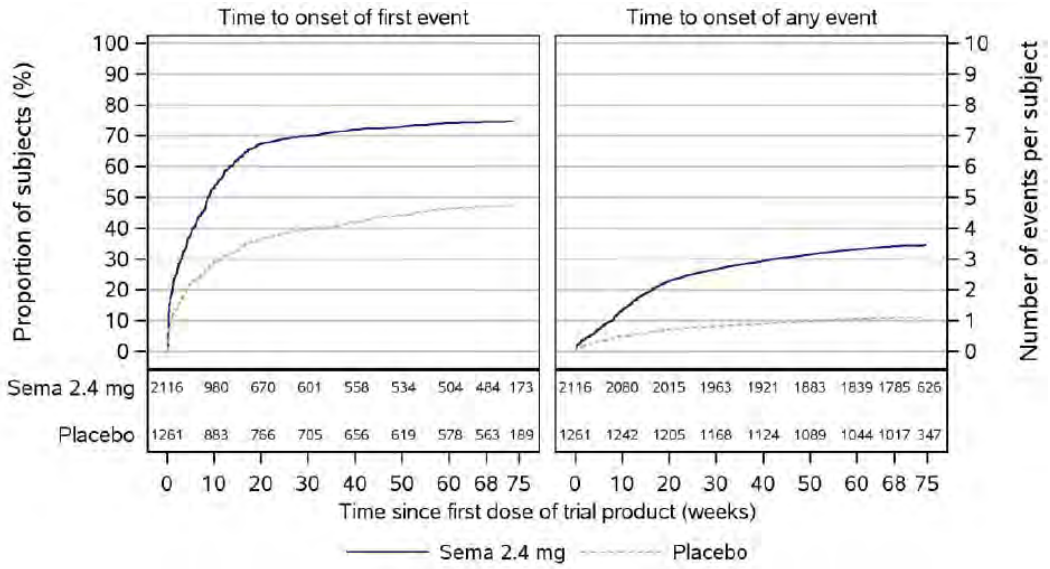
The rate of SAEs was increased relative to placebo. SAEs were reported in 9.3% with semaglutide and in 6.4% with placebo. The rate of SAEs was 10.5/100 person-year with semaglutide and 6.8/100 person-year with placebo. Hepatobiliary SAEs were reported at a rate of 1.2/100 person-year with semaglutide and 0.2/100 person-year with placebo. Gastrointestinal SAEs were reported at a rate of 1.1/100 person-year with semaglutide and 0.6/100 person-year with placebo.

Discontinuations

In the Phase 3a pool, more patients discontinued due to AEs in the semaglutide groups compared to placebo: 149 (5.7%) patients in the semaglutide group and 47 (3.0%) for placebo. This was primarily due to gastrointestinal disorders: nausea, vomiting, diarrhoea, upper abdominal pain, and constipation.

Adverse events of special interest

GI AEs: In the dose escalation group (STEP 1–3: dose-escalation regimen with 4-week increments to reach the 2.4 mg maintenance dose to improve tolerability), GI AEs were reported for 72.9% of subjects on semaglutide 2.4 mg compared to 47.1% of subjects on placebo. The GI AE incidence was highest during the initial 20 weeks of treatment (covering the dose-escalation period), and tapered off subsequently (Figure 2).



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Numbers shown in the lower panel are subjects at risk.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

Figure 2. Pivotal STEP 1-3 trials (pooled data). Time to onset of first or to onset of any GI event.

Hepatobiliary AEs: Hepatobiliary disorders were more frequent with semaglutide 2.4 mg, but elevation of transaminases was not more frequent, and no patients fulfilled the criteria of Hy's law. There were few reports of pancreatitis: four in the semaglutide groups and one for placebo.

In the phase 3a pool, there were more events of gallbladder-related disorders with semaglutide 2.4 mg than with placebo (2.5% vs 1.6%). Most of the events were cholelithiasis (1.6% vs 1.1% for semaglutide 2.4 mg vs placebo) or related complications. The increased risk may be at least partly explained by the larger weight loss.

Renal AEs: The rate of renal dysfunction was not increased with semaglutide 2.4 mg. Plasma calcitonin concentrations were not increased by semaglutide 2.4 mg.

Haematological AEs: Haematology AEs occurred at similar rates to placebo.

CV AEs: Cardiovascular AEs were less frequent with semaglutide than placebo. This supports the improvement in surrogate measures of cardiovascular risk in the pivotal studies. In the pivotal studies, mean pulse rate increased by 2 to 5 bpm, but there was a significant decrease in SBP relative to placebo in the semaglutide groups.

Immunogenicity: In the clinical studies semaglutide 2.4 mg had low immunogenicity. In the two Phase 3 studies that tested for anti-semaglutide antibodies, there were 50 (2.9%) patients with treatment induced anti-semaglutide antibodies; none were neutralising and 28 (1.6%) had antibodies that cross-reacted with GLP-1. The rate of allergic AEs was similar to the placebo group.

Neoplasia: The rates of neoplasia were similar for semaglutide 2.4 mg and placebo.

Hypoglycaemia: Hypoglycaemia was infrequent and was not identified as a safety concern in this population.

Mental health: Mental health scores and suicidality did not differ significantly between semaglutide 2.4 mg and placebo.

Misuse: Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data.

Diabetic retinopathy: In Study NN9536-4374, diabetic retinopathy was reported in 25 (6.2%) patients in the semaglutide 1 mg group, 28 (6.9%) in the semaglutide 2.4 mg and 17 (4.2%) in the placebo.

In the phase 3a without T2D group, there were no PT diabetic retinopathy events reported.

Subgroups: The safety of semaglutide 2.4 mg was evaluated in subgroups of subjects defined based on: intrinsic factors (sex, baseline age, race, ethnic origin, baseline body weight, baseline BMI, baseline renal function [phase 3a pool], and baseline glycaemic status [phase 3a without T2D group]), extrinsic factors (region [phase 3a pool]; anti-diabetic background medication [phase 3a with T2D trial]), and weight loss category (≥20% vs <20%).The evaluation did not reveal any new safety concerns or markedly different AE profiles for any subgroups.

Pregnancy and lactation: 37 pregnancies were reported in the weight management trials: 29 with semaglutide (24 in the phase 3a pool) and 8 with placebo. In all cases, the subject was exposed to trial product for a short time (or not exposed at all) until the pregnancy was discovered and trial product discontinued. One child of a female subject exposed to semaglutide was born with a congenital anomaly of the external ear. Spontaneous abortions were reported in 6 of 29 (21%) pregnancies in the semaglutide 2.4 mg group. In the placebo group, 2 of 8 (25%) pregnancies resulted in a spontaneous abortion or a stillbirth. None of the elective abortions were due to congenital anomalies. There were few AEs related to fertility without significant differences between groups. No AEs related to lactation were reported.

OZEMPIC currently has pregnancy category D. This is also proposed for WEGOVY.

Post-market experience

No data available.

2.5. Risk Management Plan (RMP) evaluation

RMP exemption email (D21-2371267)

2.5.1. Summary

A Risk Management Plan was not requested for this submission. The rationale given by the RMP Evaluation section included:

- No significantly different target population from an RMP perspective.
- Semaglutide is currently approved for use in Type 2 diabetes (Ozempic) as a once weekly SC injection.
- There are currently no additional risk minimisation activities in place for Ozempic.
- Although there is a change in presentation and the inclusion of new strengths, this product is intended to be approved under a new name, with its own PI and CMI so the risk of medication error in relation to other strengths of semaglutide on the market could be expected to be minimal.

However, in the dossier for WEGOVY, the sponsor submitted EU-RMP version 5.0 (26 November 2020; DLP 31 May 2018 (semaglutide s.c), 2 November 2018 (oral semaglutide), and 28 Oct 2020 (semaglutide s.c. 2.4 mg for weight management)) and ASA version 0.1 (28 August 2020) in support of this application.

It is noted that the ASA version 0.1 appears to be only an annex to semaglutide s.c. 2.4 mg for weight management (WYGOVY, but not for OZEMPIC or RYBELSUS).

The sponsor proposes Pregnancy Category D.

The sponsor proposes inclusion in the Black Triangle Scheme (as per PI).

Summary of safety concerns and missing information

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Diabetic retinopathy complications	✓	✓	✓	–
Important potential risks	Neoplasms (malignant and non-malignant)	✓	✓	–	–
	Pancreatic cancer	✓	✓	✓	–
	Medullary thyroid cancer	✓	✓	✓	–
Missing information	Pregnancy and lactation	✓	–	✓	–
	Patients with severe hepatic impairment	✓	–	✓	–

The clinical evaluator commented that misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data. This may be addressed in the risk management plan under off-label use.

2.5.2. Recommended condition/s of registration

To be confirmed.

2.6. Discussion

2.6.1. Pharmacology and formulations

The pharmacokinetics and pharmacodynamics of WEGOVY (semaglutide) have been adequately characterised. This includes bioequivalence studies for the new formulation. Semaglutide has a dose-dependent effect on weight loss. Semaglutide decreases appetite, decrease food intake and decreased food cravings. An E_{max} relationship between concentration and the proportion of responders has been demonstrated. Semaglutide has a beneficial effect on β-cell function. The improvement in glycaemic and weight control has been previously documents in patients with T2DM. Semaglutide did not have adverse effects on gastric emptying or cardiac repolarisation.

The Sponsor has obtained adequate data to inform the dosage selection. The optimal dosing was defined using E_{max} models, and by balancing efficacy against tolerability. The proposed dose-titration, with initiation of treatment, is also supported by these data.

Deficiencies of data

The Sponsor has not examined the PK for all the formulations intended for marketing, and that would be used in the titration phase. These are: 0.25 mg/dose (0.5 mg/mL); 0.5 mg/dose (1.0 mg/mL); 1 mg/dose (2.0 mg/mL); 1.7 mg/dose (2.27 mg/mL); and 2.4 mg/dose (3.2 mg/mL).

However, in Modelling Report 3, dose proportionality was demonstrated for the doses used in the Phase 3a clinical trials. In the opinion of the Clinical Evaluator, dose-proportionality can be extrapolated to the new formulations.

The primary differences between the clinical trial formulations and the to-be-marketed formulations are:

- Composition (Table 7): the to-be-marketed formulations do not contain phenol or propylene glycol
- Concentration (Table 8): the titration formulations and the maintenance dose formulations used in the clinical trials are different concentrations to the to-be-marketed formulations.

The different formulation is unlikely to have an effect on efficacy, especially as bioequivalence has been demonstrated for the maintenance formulations. The different concentrations in the titration formulations are unlikely to have any effect on efficacy, because efficacy is primarily from the maintenance formulations, which have been demonstrated to be bioequivalent.

Table 7. Phase 3a formulation vs. To-be-marketed formulation: Composition differences.

PDS290 pen-injector Phase 3a **Name of ingredient** **Drug substance**	**Single-dose pen-injector** *To-be-marketed* **Name of ingredient** **Drug substance**	**Function**	**Pharmacopoeia**
Semaglutide	Semaglutide	Active pharmaceutical ingredient	Novo Nordisk A/S
Other ingredients	**Other ingredients**		
Disodium hydrogen phosphate, dihydrate	Disodium hydrogen phosphate, dihydrate	Buffering agent	USP/Ph. Eur
Propylene glycol	Sodium chloride	Isotonic agent	USP/JP/Ph. Eur
Phenol	-	Preservative	USP/JP/Ph. Eur
Hydrochloric acid	Hydrochloric acid	pH adjustment	USP/JP/Ph. Eur
Sodium hydroxide	Sodium hydroxide	pH adjustment	USP/JP/Ph. Eur
Water for injection	Water for injection	Solvent	USP/JP/Ph. Eur

Abbreviations: JP: the Japanese Pharmacopoeia; Ph. Eu: European Pharmacopoeia; USP: United States Pharmacopoeia.

Table 8. Phase 3a formulation vs. To-be-marketed formulation: Concentration differences.

Formulation	**Semaglutide** Phase 3a					**Semaglutide** *To-be-marketed*				
Delivery device	PDS290 pen-injector for semaglutide					Single-dose pen-injector for semaglutide				
Type of dose	Escalation				Mainte-nance	Escalation				Mainte-nance
Doses	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg
Injection volume	0.25 mL	0.5 mL	0.34 mL	0.57 mL	0.80 mL	0.5 mL	0.5 mL	0.5 mL	0.75 mL	0.75 mL
Semaglutide concentration	**1.0 mg/mL**		**3.0 mg/mL**			**0.5 mg/mL**	**1.0 mg/mL**	**2.0 mg/mL**	**2.27 mg/mL**	**3.2 mg/mL**

2.6.2. Efficacy

The design and conduct of the Phase 3a studies was appropriate and complied with the Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (EMA/CHMP/311805/2014) 23 June 2016. The primary outcome measure was weight loss, and this was analysed both as % body weight and by mass (kg). The studies were placebo controlled. The predictive value of short-term versus long-term treatment can be determined from the data. Waist circumference and BMI were used as secondary endpoints. DEXA was used to validate that the weight loss was due to loss of adipose and not due to loss of other body constituents. Cardiovascular risk and co-morbidities were also measured as outcomes. A relevant proportion of the study population had coexisting cardiovascular and other co-morbidities.

The patient populations were representative of the target population in Australia.

The background treatments were the same as those in the proposed indication: diet and exercise. The background treatments were applied consistently and were clearly defined in the study protocols.

Bias was controlled through randomisation and blinding. Multiplicity was addressed. The statistical analysis was appropriate. The outcome measures were appropriate and measured different aspects of treatment effect.

The Phase 3a studies demonstrated a statistically and clinically significant weight loss with semaglutide 2.4 mg weekly dosing. The treatment effect was well in excess of a clinically significant 5% weight loss. The effect size was consistent across the four studies. The effect persisted in a patient group undergoing IBT.

The decrease in body weight was matched by decreases in waist circumference and in BMI.

There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. The improvements in plasma lipids were primarily in total cholesterol, LDL-cholesterol and VLDL-cholesterol, with lesser effect on HDL-cholesterol. These improvements are associated with a lessening of cardiovascular risk.

Deficiencies of data

Deficiencies include:

- In STEP 2, there was lack of blinding between the 1.0 mg / placebo groups and the 2.4 mg / placebo groups. However, the outcome measures were objective and the primary comparison was between semaglutide 2.4 mg and placebo.
- In STEP 2, in patients with T2DM the decrease in body weight was not as great as in STEP 1, where T2DM was excluded. However, there was still significant benefit in this patient group.

Clinical issues that have not been addressed by the submitted data are:

Persistence of treatment effect beyond one year of treatment (continuing on treatment): The data indicate that treatment with semaglutide is likely to be required long-term. There was a return to baseline in the placebo group (who received WEGOVY initially) in Study STEP 4.

In the s31 response (Efficacy Question 2), the sponsor presented data that appears to demonstrate a persistence of the treatment effect beyond one year: STEP 5 (NN9536-4378, data publicly available in 2022), a phase 3b trial, showed that weight loss obtained after approximately one year of semaglutide 2.4 mg treatment, persisted up until end of treatment of semaglutide 2.4 mg (week 104) (Figure 3).

However, no data beyond 2 years is available.

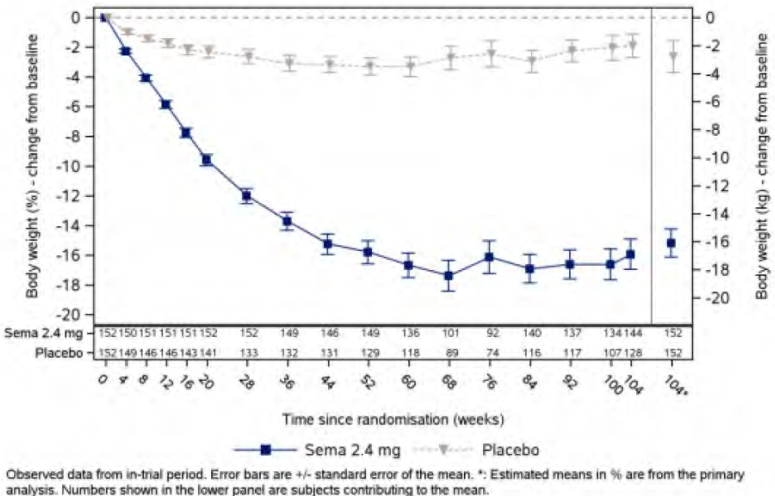


Figure 3. STEP 5 (not provided in the dossier). Body weight change (%) from baseline.

Potential for rebound in weight once treatment is stopped (not continuing on treatment): While the results of Study STEP 4 suggest this is unlikely, a rebound in weight might occur over the long term in patients who cease semaglutide treatment.

s47 the sponsor presented data from the STEP 1 extension study regarding the effect after semaglutide cessation at Week 68: The trajectory of weight gain after treatment cessation indicates a return towards baseline, but not rebound (i.e. weight gain in excess of baseline weight) with the extension study period (Figure 4).

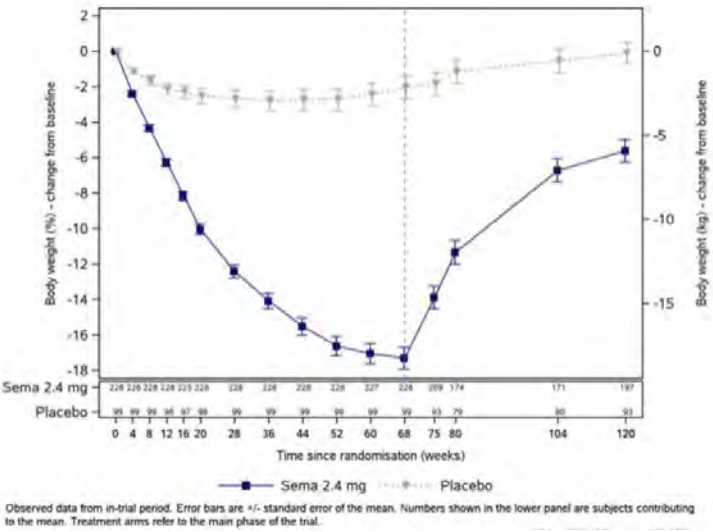


Figure 4. STEP 1 Extension (not in dossier). Body weight change (%) from baseline.

Paediatric data: This application is for an adult indication. For weight management in the adolescent and paediatric populations, two clinical trials are planned:

- A trial in adolescents (12 to <18 years) with overweight or obesity (NN9536-4451, STEP TEENS) is currently ongoing.
- A trial in children and adolescents (6 to <18 years of age) will be conducted (first patient first visit planned for Q3 2023) (NN9536-4512, STEP YOUNG).

2.6.3. Safety

There were increased rates of gastrointestinal disorders and neurological disorders with semaglutide in comparison with placebo. These events were predominantly non-serious and were of limited duration and without long-term sequelae.

The gastrointestinal adverse events that occurred more frequently with semaglutide compared to placebo were: nausea, diarrhoea, vomiting, constipation, abdominal pain, decreased appetite, dyspepsia, eructation and abdominal distension. The neurological disorders that occurred more commonly with semaglutide were headache, fatigue and dizziness.

In the pivotal studies the rate of SAEs was 10.5 /100 person-year with semaglutide and 6.8 /100 person-year with placebo. Hepatobiliary SAEs were reported at a rate of 1.2 /100 person-year with semaglutide and 0.2 /100 person-year with placebo. Gastrointestinal SAEs were reported at a rate of 1.1 /100 person-year with semaglutide and 0.6 /100 person-year with placebo.

Discontinuation due to AE occurred at a higher rate in the semaglutide groups compared to placebo. In the Phase IIIa pool there were 149 (5.7%) patients in the semaglutide group and 47 (3.0%) in the placebo discontinuing because of AEs. This was primarily due to gastrointestinal disorders: nausea, vomiting, diarrhoea, upper abdominal pain and constipation

Cardiovascular AEs were less frequent with semaglutide than placebo.

Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data.

2.6.4. Conclusion and remaining issues

The Clinical Evaluator has no objection to the approval of WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle, for the proposed indication:

> *WEGOVY is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of:*
>
> - *≥30 kg/m^2 (obesity); or*
> - *≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight related comorbidity.*

2.6.5. Questions to the ACM

Q1: Sufficient data for registration (including long term data and the potential for rebound): The Phase 3a studies provided a large amount of data supporting the proposed indication. Long-term data beyond 2 years and data regarding potential rebound are limited.

> Can the ACM comment on whether the provided data are sufficient to support registration for the proposed indication?

Q2: General: The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

3. References/attachments for ACM

No.	Document name	Location/ID	ACM attachment
A1	Delegate's summary and request for ACM advice	D22-5010494	☒
A1a	Proposed PI	e005802 (0003-) - Product information – annotated	☒
A1b	TGA-adopted EMA guideline	EMA/CHMP/311805/2014	☒
A2	Sponsor's application letter	e005802 (0003-) - Cover Letter - Initial Application	☒
M3	Pharmaceutical chemistry summary	Quality (Module 3) Summary (Biological Medicines) (D21-3363118)	☒
M4	Nonclinical summary	Module 4 Nonclinical Evaluation Report (Round 2) (D21-2820164)	☒
M5	CER	Module 5 Clinical Evaluation Report Round 2 (D21-3227089)	☒
M5a	Clinical Overview	e005802 (0003-) - Clinical Overview e005802 (0003-) - Summary of Clinical Pharmacology Studies e005802 (0003-) - Summary of Clinical Efficacy e005802 (0003-) - Summary of Clinical Safety	☒
M5b	Sponsor S31 Response	e005802 (0003-) - Response to request for information - clinical	☒
R1	RMP evaluation report	N/A	☒
R1a	RMP ASA	e005802 (0003-) - Risk management plan e005802 (0003-) - Risk Management Plan - Australian Specific Annex	☒

4. Appendices

Appendix 1: Review of the Product Information

PI change requests are not included in this section, but will be sent to the sponsor post-ACM.

Appendix 2: Additional tables and figures

Table 9. Product formulation of WEGOVY compared to OZEMPIC (from NCER, p.15).

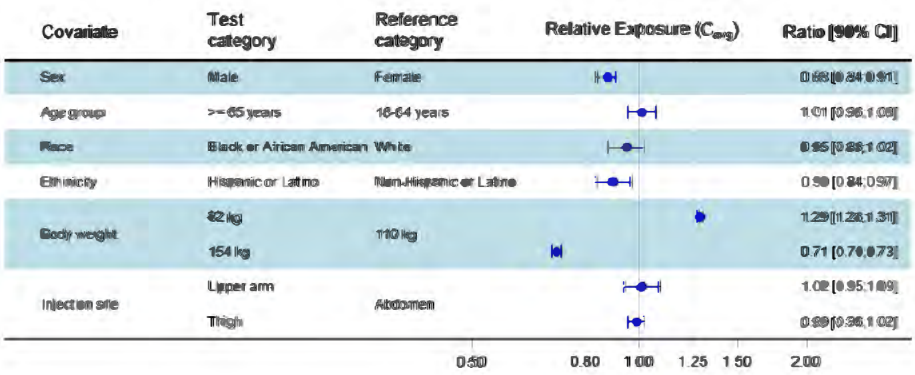
Ingredient	Function	Quantity (mg) per mL		
		WEGOVY®		OZEMPIC®
Semaglutide	Active ingredient	WEGOVY® 0.25 mg [a]	0.5	1.34
		WEGOVY® 0.5 mg [a]	1.0	
		WEGOVY® 1.0 mg [a]	2.0	
		WEGOVY® 1.7 mg [b]	2.27	
		WEGOVY® 2.4 mg [b]	3.2	
Disodium phosphate, dehydrate	Buffer	1.42		1.42
Propylene glycol	Tonicity agent	—		14
Phenol	Preservative	—		5.5
Sodium chloride	Tonicity agent	8.25		—
Hydrochloric acid	pH adjustment	q.s. [c]		
Sodium hydroxide	pH adjustment	q.s. [c]		
Water for injection	Solvent	To make 1.0 mL		

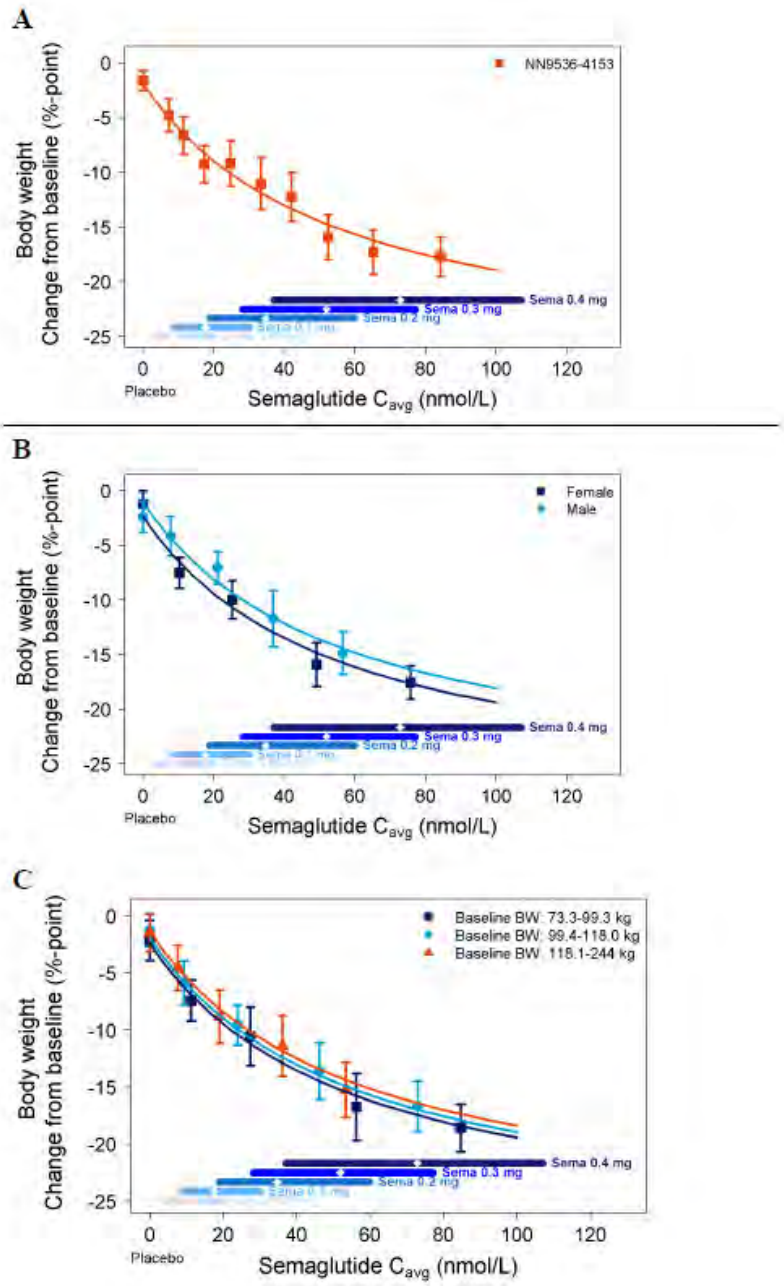
[a] Semaglutide 0.5 mg/mL, 1.0 mg/ml and 2.0 mg/ml in single dose pen-injector for semaglutide supplied as 0.5 mL volume;

[b] Semaglutide 2.27 mg/ml and 3.2 mg/ml in single dose pen-injector for semaglutide supplied as 0.75 mL volume;

[c] To reach pH 7.4

Table 10. PopPK modelling based on NN9536-4153. Forest plot of covariate analysis for semaglutide exposure expressed as steady-state dose-normalised average semaglutide concentrations relative to a reference subject.





Data are mean body weight changes with 95% CI obtained after 52 weeks versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-derived exposure-response relations. Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges. Data from trial 4153 excluding treatment with fast dose escalation.

Figure 5. PopPK modelling based on NN9536-4153. Body weight change from baseline versus exposure of semaglutide for all subjects (A) and shown by sex (B) and body weight quantile (C).

Table 11. Overview of STEP trial endpoints.

	STEP 1 Weight management	STEP 2 Weight management in T2D	STEP 3 Weight management with IBT	STEP 4 Sustained weight management
Body weight-related endpoints				
Change from baseline[a] to week 68 in:				
Body weight (%)	**P**	**P**	**P**	**P**
Body weight (kg)	S	S	S	S
Waist circumference (cm)	**C**	**C**	**C**	**C**
Body-mass index (kg/m^2)	S	S	S	S
Soluble leptin receptor (ng/mL)	S			
Leptin (ng/mL)	S			
Body composition (DEXA)	S			
Change from baseline to week 8 in body weight (%)			S	
Change from week 0 to week 68 in body weight (%)				S
Subjects who achieve at week 68 (y/n):				
≥5% body weight reduction from week 0	**P**	**P**	**P**	S
≥10% body weight reduction from week 0	**C**	**C**	**C**	S
≥15% body weight reduction from week 0	**C**	**C**	**C**	S
≥20% body weight reduction from week 0	S	S	S	S
<0% body weight reduction from week 0				S
<0% body weight reduction from week 20				S
Glucose metabolism-related endpoints				
Change from baseline[a] to week 68 in:				
HbA_{1c} (% and mmol/mol)	S	**C**	S	S
FPG (mmol/L and mg/dL)	S	S	S	S
Fasting serum insulin (pmol/L and mIU/mL)	S	S	S	S
Subjects who achieve at week 68 (y/n):				
HbA_{1c} < 7.0%		S		
HbA_{1c} ≤ 6.5%		S		
Body weight reduction ≥10% and HbA_{1c} <7.0%		S		
Body weight reduction ≥15% and HbA_{1c} <7.0%		S		
Cardiovascular-related endpoints				
Change from baseline[a] to week 68 in:				
Systolic blood pressure (mmHg)	**C**	**C**	**C**	**C**
Diastolic blood pressure (mmHg)	S	S	S	S
Lipids (mmol/L and mg/dL)	S	S	S	S
C-reactive protein (CRP) (mg/L)	S	S	S	
Plasminogen activator inhibitor-1 (PAI-1) activity (AU/mL)	S	S	S	

a. In STEP 4, baseline is at week 20 (randomisation)

P: primary/co-primary endpoint; C: confirmatory secondary endpoint; S: supportive secondary endpoint

Table 12. Pivotal STEP trials. Inclusion criteria.

Inclusion criterion	STEP 1	STEP 2	STEP 3	STEP 4
Informed consent obtained before any trial-related activities	x	x	x	x
Male or female, age ≥18 years at the time of signing informed consent	x	x	x	x
History of at least one self-reported unsuccessful dietary effort to lose body weight	x	x	x	x
BMI ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease	x		x	x
BMI ≥27 kg/m^2		x		
Diagnosed with T2D ≥180 days prior to the day of screening		x		
Subject treated with either diet and exercise alone or stable treatment with metformin, SU, SGLT2i, glitazone as single-agent therapy or up to 3 OADs (metformin, SU, SGLT2i or glitazone) according to local label		x		
HbA_{1c} 7–10% (53–86 mmol/mol) (both inclusive)		x		

Subjects who fulfilled the inclusion criteria were eligible for randomisation (STEP 1–3), or for entering the run-in (STEP 4).

Table 13. Pivotal STEP trials. Key exclusion criteria.

	STEP 1	STEP 2	STEP 3	STEP 4
Body weight-related				
A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records	x	x	x	x
Treatment with any medication for the indication of obesity within the past 90 days before screening	x		x	x
Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening	x	x	x	x
Uncontrolled thyroid disease, defined as TSH >6.0 mIU/L or <0.4 mIU/L as measured by the central laboratory at screening	x	x	x	x
Glycaemia or diabetes-related				
HbA_{1c} ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening	x		x	x
History of type 1 or type 2 diabetes mellitus	x		x	x
Treatment with glucose-lowering agent(s) within 90 days before screening	x		x	x
Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior day of screening		x		
Treatment with a GLP-1 receptor agonist within 180 days before screening	x	x		
Renal impairment measured as eGFR value of <30 mL/min/1.73 m^2 (<60 mL/min/1.73 m^2 in subjects treated with SGLT2i)		x		
Renal impairment measured as eGFR value of <15 mL/min/1.73 m^2	x		x	x

Table 14. Pivotal STEP trials. Study disposition.

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

Treatment completion: Treatment period completion is defined as when the randomised subject has attended the 'end of treatment' visit as planned.
Trial completion: A trial completer is defined as a randomised subject who has completed the final scheduled visit.

Cross-reference: Based on Appendix 6.2, Table 6.2.1

Table 15. Pivotal STEP trials. Baseline demographics - categorical values.

	STEP 1 WM N (%)	STEP 2 WM in T2D N (%)	STEP 3 WM with IBT N (%)	STEP 4 Sustained WM N (%)	Total N (%)
Number of subjects	1961	807	611	803	4182
Age (years)					
<65	1805 (92.0)	633 (78.4)	565 (92.5)	755 (94.0)	3758 (89.9)
65-<75	145 (7.4)	156 (19.3)	43 (7.0)	44 (5.5)	388 (9.3)
>=75	11 (0.6)	18 (2.2)	3 (0.5)	4 (0.5)	36 (0.9)
Sex					
Female	1453 (74.1)	413 (51.2)	495 (81.0)	634 (79.0)	2995 (71.6)
Male	508 (25.9)	394 (48.8)	116 (19.0)	169 (21.0)	1187 (28.4)
Ethnic origin					
Not Hisp./Latino	1669 (85.1)	711 (88.1)	490 (80.2)	740 (92.2)	3610 (86.3)
Hisp./ Latino	236 (12.0)	96 (11.9)	121 (19.8)	63 (7.8)	516 (12.3)
Not Applicable	55 (2.8)	0	0	0	55 (1.3)
Unknown	1 (0.1)	0	0	0	1 (0.0)
Race					
White	1472 (75.1)	479 (59.4)	465 (76.1)	672 (83.7)	3088 (73.8)
Asian	261 (13.3)	220 (27.3)	11 (1.8)	19 (2.4)	511 (12.2)
Black/Afr. American	111 (5.7)	72 (8.9)	116 (19.0)	104 (13.0)	403 (9.6)
Other	62 (3.2)	36 (4.5)	19 (3.1)	8 (1.0)	125 (3.0)
Not Applicable	55 (2.8)	0	0	0	55 (1.3)
Body weight (kg)					
<90	501 (25.5)	289 (35.8)	155 (25.4)	365 (45.5)	1310 (31.3)
90-<100	418 (21.3)	155 (19.2)	138 (22.6)	157 (19.6)	868 (20.8)
100-<115	494 (25.2)	185 (22.9)	154 (25.2)	146 (18.2)	979 (23.4)
>=115	548 (27.9)	178 (22.1)	164 (26.8)	135 (16.8)	1025 (24.5)
BMI (kg/m^2)					
<30	117 (6.0)	145 (18.0)	38 (6.2)	238 (29.6)	538 (12.9)
30-<35	643 (32.8)	275 (34.1)	184 (30.1)	263 (32.8)	1365 (32.6)
35-<40	614 (31.3)	200 (24.8)	212 (34.7)	168 (20.9)	1194 (28.6)
>=40	587 (29.9)	187 (23.2)	177 (29.0)	134 (16.7)	1085 (25.9)
Glycaemic status					
Normo-glycaemia	1105 (56.3)	0	307 (50.2)	427 (53.2)	1839 (44.0)
Pre-diabetes	856 (43.7)	0	304 (49.8)	376 (46.8)	1536 (36.7)

Phase 3a trials: STEP 1-4 data from subjects randomised to sema 2.4 mg or placebo during the controlled periods of the trials. STEP 1-3: Baseline: Randomisation (week 0), STEP 4: Baseline: Randomisation (week 20).
Race: Other includes American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. Ethnic origin and race are recorded as 'Not applicable' for France.
%: Percentages are based on number of subjects., Hisp.: Hispanic; Afr.: African.

Cross-reference: Based on Appendix 6.2, Table 6.2.2

Table 16. Pivotal STEP trials. Comorbidities at screening.

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

STEP 1-4 data from subjects randomised to semaglutide 2.4 mg or placebo during the controlled periods of the trials. Table is sorted by total frequency. In STEP 2 'Impaired glucose tolerance' or 'Impaired fasting glucose' or 'Elevated HbA1c' were not specified on comorbidities form. In STEP 4 'Elevated HbA1c' was not specified on comorbidities form. 'Elevated HbA1c' is defined as 5.7-6.4%.
*Reproductive system summarises answers from female subjects only for all three comorbidities and % is based on number of female subjects. For 'Menstrual disorder' and 'Polycystic ovarian syndrome' only answers from females are shown and % is based on female subjects. For 'Involuntary impaired fertility/infertility' answers from females and males are shown and % is based on number of subjects.

Cross-reference: Based on Appendix 6.2, Table 6.2.4

Table 17. STEP 1 study. Primary and confirmatory secondary endpoint results.

	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoints					
Change from baseline in body weight (%) at week 68					
Sema 2.4 mg – placebo	ETD: -12.44 [-13.37; -11.51]	<0.0001	0.05	Superiority	Confirmed
Subjects who achieve at week 68 (y/n) ≥5% body weight reduction					
Sema 2.4 mg / placebo	OR: 11.22 [8.88; 14.19]	<0.0001	0.05	Superiority	Confirmed
Confirmatory secondary endpoints					
Subjects who achieve at week 68 (y/n) ≥10% body weight reduction					
Sema 2.4 mg / placebo	OR: 14.68 [11.08; 19.44]	<0.0001	0.05	Superiority	Confirmed
Subjects who achieve at week 68 (y/n) ≥15% body weight reduction					
Sema 2.4 mg / placebo	OR: 19.26 [12.89; 28.76]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in waist circumference (cm) at week 68					
Sema 2.4 mg – placebo	ETD: -9.42 [-10.30; -8.53]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in systolic blood pressure (mmHg) at week 68					
Sema 2.4 mg – placebo	ETD: -5.10 [-6.34; -3.87]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in SF-36 Physical Functioning score					
Sema 2.4 mg – placebo	ETD: 1.80 [1.18; 2.42]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in IWQOL-Lite-CT Physical Function score					
Sema 2.4 mg – placebo	ETD: 9.43 [7.50; 11.35]	<0.0001	0.05	Superiority	Confirmed

Table 18. STEP 2 study. Primary and confirmatory secondary endpoint results.

	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoints					
Change from baseline in body weight (%) at week 68					
Sema 2.4 mg – placebo	ETD: -6.21 [-7.28; -5.15]	<0.0001	0.05	Superiority	Confirmed
Subjects who achieve at week 68 (y/n) ≥5% body weight reduction					
Sema 2.4 mg / placebo	OR: 4.88 [3.58; 6.64]	<0.0001	0.05	Superiority	Confirmed
Confirmatory secondary endpoints					
Subjects who achieve at week 68 (y/n) ≥10% body weight reduction					
Sema 2.4 mg / placebo	OR: 7.41 [4.89; 11.24]	<0.0001	0.05	Superiority	Confirmed
Subjects who achieve at week 68 (y/n) ≥15% body weight reduction					
Sema 2.4 mg / placebo	OR: 7.65 [4.11; 14.22]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in waist circumference (cm) at week 68					
Sema 2.4 mg – placebo	ETD: -4.88 [-5.97; -3.79]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in body weight (%) at week 68					
Sema 2.4 mg – sema 1.0 mg	ETD: -2.65 [-3.66; -1.64]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in HbA_{1c} (%) at week 68					
Sema 2.4 mg - placebo	ETD: -1.23 [-1.42; -1.05]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in systolic blood pressure (mmHg) at week 68					
Sema 2.4 mg – placebo	ETD: -3.43 [-5.57; -1.30]	0.0016	0.05	Superiority	Confirmed
Change from baseline in SF-36 Physical Functioning score					
Sema 2.4 mg – placebo	ETD: 1.52 [0.44; 2.61]	0.0061	0.05	Superiority	Confirmed
Change from baseline in IWQOL-Lite-CT Physical Function score					
Sema 2.4 mg – placebo	ETD: 4.83 [1.79; 7.86]	0.0018	0.05	Superiority	Confirmed

Table 19. STEP 3 study. Primary and confirmatory secondary endpoint results.

	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoints					
Change from baseline in body weight (%) at week 68					
Sema 2.4 mg – placebo	ETD: -10.27 [-12.0; -8.57]	<0.0001	0.05	Superiority	Confirmed
Subjects who achieve at week 68 (y/n) ≥5% body weight reduction					
Sema 2.4 mg / placebo	OR: 6.11 [4.04; 9.26]	<0.0001	0.05	Superiority	Confirmed
Confirmatory secondary endpoints					
Subjects who achieve at week 68 (y/n) ≥10% body weight reduction					
Sema 2.4 mg / placebo	OR: 7.36 [4.93; 10.99]	<0.0001	0.05	Superiority	Confirmed
Subjects who achieve at week 68 (y/n) ≥15% body weight reduction					
Sema 2.4 mg / placebo	OR: 7.87 [4.90; 12.63]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in waist circumference (cm) at week 68					
Sema 2.4 mg – placebo	ETD: -8.34 [-10.1; -6.59]	<0.0001	0.05	Superiority	Confirmed
Change from baseline in systolic blood pressure (mmHg) at week 68					
Sema 2.4 mg – placebo	ETD: -3.94 [-6.36; -1.52]	0.0014	0.05	Superiority	Confirmed
Change from baseline in SF-36 Physical Functioning score					
Sema 2.4 mg – placebo	ETD: 0.86 [-0.22; 1.93]	0.1180	0.05	Superiority	Not confirmed

Table 20. STEP 4 study. Primary and confirmatory secondary endpoint results.

	Estimate [95% CI]	p-value	alpha	Hypothesis	Conclusion
Primary endpoint					
Change from baseline[a] in body weight (%) at week 68					
Sema 2.4 mg – Placebo	ETD: -14.75 [-16.0; -13.5]	<0.0001	0.05	Superiority	Confirmed
Confirmatory secondary endpoints					
Change from baseline[a] in waist circumference (cm) at week 68					
Sema 2.4 mg – Placebo	ETD: -9.74 [-10.9; -8.54]	<0.0001	0.05	Superiority	Confirmed
Change from baseline[a] in systolic blood pressure (mmHg) at week 68					
Sema 2.4 mg – Placebo	ETD: -3.92 [-5.82; -2.03]	<0.0001	0.05	Superiority	Confirmed
Change from baseline[a] in SF-36 Physical Functioning score at week 68					
Sema 2.4 mg – Placebo	ETD: 2.46 [1.59; 3.32]	<0.0001	0.05	Superiority	Confirmed

a. Baseline is at randomisation (week 20), after the run-in

Therapeutic Goods Administration

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Document 2

Australian Government
Department of Health
Therapeutic Goods Administration

Delegate's overview

Active ingredient(s): Semaglutide

Proprietary product name: WEGOVY

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Submission number: PM-2022-04980-1-5

eID: e005802

31 October 2023

TGA Health Safety Regulation

Submission information

Submission number	PM-2022-04980-1-5
Active ingredient(s)	Semaglutide
Product name	WEGOVY
Strengths/dose form	0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection.
Sponsor	Novo Nordisk Pharmaceuticals Pty Ltd
Description of the submission/proposed indication	This is a Category 1, Type C (extension of indications) application relating to WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection. The application is to extend the weight management indication to include adolescents from 12 years of age and above. The currently approved indication is: **Adults** Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of • ≥30 kg/m^2 (obesity), or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials). The sponsor proposed new indication is: **Adults** Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of • ≥30 kg/m^2 (obesity), or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Adolescents

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* or
- overweight* and at least one weight-related comorbidity

*Obesity (BMI ≥ 95th percentile) and overweight (BMI ≥ 85th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1 and Figure 1).

Table 1 BMI cut-off points for obesity (≥95th percentile) and overweight (≥85th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 85th Percentile		BMI (kg/m2) at 95th Percentile	
	Males	Females	Males	Females
12	21	21.7	24.2	25.2
12.5	21.4	22.1	24.7	25.7
13	21.8	22.5	25.1	26.3
13.5	22.2	22.9	25.6	26.8
14	22.6	23.3	26.0	27.2
14.5	23.1	23.7	26.4	27.7
15	23.4	24.0	26.8	28.1
15.5	23.8	24.3	27.2	28.5
16	24.2	24.6	27.5	28.9
16.5	24.6	24.9	27.9	29.3
17	24.9	25.2	28.2	29.6
17.5	25.3	25.4	28.6	30.0

Figure 1 BMI cut-off points for obesity (≥95th percentile) and overweight (≥85th percentile)

Summary of data	The dossier contained data from one population pharmacokinetic study (NN9536-4451 Modelling Report) and a s47 [redacted] in adolescents: • Study NN9536-4451 (STEP TEENS): weight management in adolescents with overweight or obesity And three Phase III studies in adults: • Study NN9536-4378 (STEP 5): extended treatment • Study NN9536-4376 (STEP 8): comparison with liraglutide • Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide
Preliminary view	While a decision is yet to be made, at this stage I am inclined to approve the registration of the product with an amended indication. The overall final decision will be made following the ACM discussion. The proposed Conditions for Registration is in Appendix 2.
Outstanding issues	None

Request for ACM advice

ACM meeting number:42 **Date (of meeting): 1 December 2023**

Summary of issue/s for advice	1. Considering there was only one subject within the 'overweight (BMI ≥ 85th percentile) with comorbidities' category included in the pivotal adolescent study at baseline, it is not possible to establish a positive benefit risk profile in this indication for the adolescents. 2. Although the benefit of Wegovy on body weight and BMI management in adolescents from Study NN9536-4451 was significant, and appears clinically relevant, 27.5% of the patients treated with Wegovy still had a body weight loss of less than 5% even at week 68. Almost 10% of the patients on Wegovy did not have a decrease in BMI or an increase. Inclusion of a stopping and re-evaluating rule for adolescents would prevent unnecessary long-term treatment. 3. Inclusion of a Table with BMI cut-off points in the indication is considered sufficient. The graph with BMI cut-off points included in the PI causes duplicity, hard to decipher, don't add any value and could be removed. 4. All the adolescent subjects included in the pivotal STEP TEENS study were with a body weight >60 kg. The treatment experience with Wegovy in only in the individuals with a body weight >60 kg. In the EU both Wegovy and Saxenda are only indicated for adolescents with a body weight above 60 kg.
Advice sought	The ACV is requested to provide advice on the following specific questions: 1. Please advice on the sponsor proposal to extend Wegovy (semaglutide) weight management indication in adolescents considering the above listed issues and Delegate proposed (amended) therapeutic indication, ***"Adolescents*** *Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with* • *obesity** *Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.*

Obesity (BMI ≥ 95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1)

Table 1 BMI cut-off points for obesity (≥95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 95th Percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

2. Should a lower bound of body weight be included in the indication of Wegovy restricting it for adolescents with a body weight above 60 kg?

s22 [redacted]

Delegate of the Secretary under regulation 35A of the Therapeutic Goods Regulations 1990

31 Oct 2023

Date

Body of overview

Background

Condition

Adult population:

Obesity is a common condition with high associated morbidity and mortality.

Body mass Index (BMI) is used as a measure of being overweight and obese. The definitions for obesity and overweight used by the Australian Institute of Health and Welfare (AIHW) are:

- A BMI of 25.0 to 29.9 kg/m^2 is classified as overweight but not obese
- A BMI of ≥30.0 kg/m^2 is classified as obese.
- A BMI of >35.0 kg/m^2 is classified as severely obese.

These definitions of obesity and overweight align with the World Health Organisation definitions.

BMI is a composite measure of weight and height:

$$BMI = \frac{body\ weight\ (kg)}{(height\ [cm])^2}$$

Hence, this measure is not a direct measure of adiposity, but is a surrogate measure. Hence, these definitions may not apply to a highly muscled individual or to children and adolescents. Interpretation of BMI may vary between ethnic groups. Waist circumference in adults may be a better measure of adiposity and a better measure of obesity-related morbidity.

The AIHW (AIHW 2021) reports that in 2017–18, an estimated 2 in 3 (67%) Australians aged 18 and over were overweight or obese, 36% were overweight but not obese, and 31% were obese. This equates to approximately 12.5 million adults in Australia. The prevalence of overweight and obesity was higher in males (75% compared to 60% in females) and also the prevalence of obesity was higher in males (33% compared to 30% in females). Obesity is more prevalent in older age groups: 16% of adults aged 18–24 compared with 41% of adults aged 65 to 74 years.

Obesity is associated with increased prevalence of cardiovascular disease, hypertension, type 2 diabetes mellitus (T2DM) and metabolic syndrome, non-alcoholic fatty liver disease, cholelithiasis, cancer, sleep apnoea, osteoarthritis and reduced psychosocial function (Bray 2004). Overall, obesity is associated with increased mortality, increased morbidity and decreased quality of life.

It has been estimated that in 2015 high BMI accounted for 4.0 million deaths globally, representing 7.1% of deaths from any cause, and 120 million disability-adjusted life-years, representing 4.9% of disability adjusted life-years (Afshin 2017). More than two thirds of deaths related to high BMI were due to cardiovascular disease.

Adolescent population:

Measuring obesity in the paediatric and adolescent population differs from the adult in that normal body proportions change with development. Hence, particularly in younger children, the normal ranges of BMI are different in paediatric populations compared to adults. It may be more appropriate in the paediatric population to refer to age appropriate Z-scores (number of SDs from the mean, also referred to by the sponsor as Standard Deviation Score [SDS]) which indicate the degree of variation from the average. A higher Z-score represents a greater BMI in relation to the age group. Response to treatment would therefore be best expressed as a decrease in the Z-score.

The AIHW has prepared a report on the prevalence of obesity and overweight in children and adolescents in Australia (AIHW 2020). When interpreting this report, it is important to recognise that the age bands used differ from those used in medicines regulation. In particular, the age band used for adolescents is 15 to <20 years, and not 12 to <18 years. The key findings of the report are:

- One quarter (25%) of Australian children and adolescents aged 2 to 17 were overweight or obese in 2017 to 2018, and 8.2% were obese.
- The obesity rate in the lowest socioeconomic areas (11%) was more than twice as high as the rate in the highest areas (4.4%).
- The proportion of Aboriginal and Torres Strait Islander children and adolescents aged 2 to 17 who were overweight or obese increased from 31% in 2012 to 2013 to 38% in 2018 to 2019. The biggest increase was for those aged 5 to 9 years (from 27% to 36%).
- The prevalence of overweight and obesity, and obesity alone, increased for 5 to 17 year old Australians between 1995 and 2007 to 2008, but has been relatively stable since.
- When measuring the same children every 2 years in the Longitudinal Study of Australian Children, overweight and obesity generally increased with age. Over 4 in 10 were overweight or obese at least once but only a small proportion of children were overweight or obese every time they were measured.
- Adolescents and young people aged 15 to 24 years in 2017 to 2018 were more likely to be overweight or obese compared with people at the same age 10 and 22 years earlier.

The consequences of obesity in adolescents and children are abnormal serum lipids, hypertension, non-alcoholic fatty liver disease, polycystic ovarian syndrome, obstructive sleep apnoea, insulin resistance and type 2 diabetes, gastrointestinal, musculoskeletal and orthopaedic complications, asthma, gallstones, and heartburn (Kelsey 2014, CDC 2023). These consequences translate to both short- and long-term poorer health outcomes.

Hence, obesity in adolescents is common, has a high disease burden and disproportionately affects disadvantaged sections of the Australian community.

Current treatment options

Currently there are limited treatment options for adolescents with obesity or who are overweight. The NHMRC guideline (2013) recommends weight maintenance rather than weight loss in most children and many adolescents, with the anticipation that with linear growth weight maintenance will result in improvement in BMI and waist circumference measurements. However, particularly in adolescents, weight maintenance may be insufficient to result in significant benefit.

In adults, a 5% decrease in body weight, in patients with obesity, is associated with significant improvements in cardiovascular risk factors, such as hypertension and lipid profile (Look 2010). Hence, this has become the target for measuring treatment effectiveness, and treatments should achieve at least a 5% sustained reduction in body weight. However, in children the effectiveness of an intervention should take into account linear growth, therefore changes in indexes, such as BMI or waist circumference, may be better measures of efficacy.

Lifestyle modification: diet and exercise with or without psychological support. In adolescents these interventions may be family interventions in preference to individual.

Pharmacological treatments approved for adults:

- Orlistat: a selective inhibitor of pancreatic lipase, resulting in decreased absorption of fat. Orlistat is a Schedule 3 drug in Australia and is available over the counter. However, the Product Information for Xenical (orlistat) contains the warning: "The safety and efficacy of XENICAL in children have not been established."

- Liraglutide: a GLP-1 agonist, is approved in Australia for the indication:

  SAXENDA is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of
  - ≥30 kg/m^2 (obese) or
  - ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.

  Treatment with SAXENDA should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

  However, the Product Information for SAXENDA (liraglutide) states: "The safety and efficacy of SAXENDA in children and adolescents below 18 years of age have not been established [see section 5.1 Pharmacodynamic Properties]. No data are available. SAXENDA is not indicated for use in paediatric patients."

- Phentermine: sympathomimetic agent with anorectic actions. Phentermine is approved for adolescents aged over 12 years, but has cardiovascular and CNS adverse effects that may discourage use in the adolescent age group.

- Naltrexone/bupropion is approved for the following indication in Australia:

  CONTRAVE is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of
  - ≥ 30 kg/m^2 (obese), or
  - ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)

  Treatment with CONTRAVE should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

Pharmacological treatments not approved in Australia:

- Phentermine/topiramate: is approved in the US for weight control. Topiramate is associated with weight loss due to an unknown mechanism (approved in the US).
- Lorcaserin: an appetite suppressant through activation of hypothalamic 5-HT^{2C} receptors (approved in the US)

Pharmacological treatments in development:

Products in development include GLP-1 agonists (such as semaglutide), dual GLP-1/GIP receptor antagonists and GLP-1/GIP/glucagon triple agonists (Williams 2020). SGLT-2 inhibitors are also under development as potential weight control agents. Amylin mimetics, leptin analogues and ghrelin vaccines and antagonists, neuropeptide Y inhibitors and melanocortin-4 receptor antagonists are potential therapeutic agents for this indication (Williams 2020).

Bariatric surgery:

Bariatric surgery is available for adolescents and is usually reserved for patients with severe obesity: a BMI ≥40 kg/m^2 or >35 kg/m^2 with obesity-related co-morbidity (Williams 2020, NHMRC 2013). Surgical interventions include devices (e.g., intragastric balloon, endoscopic sleeve gastroplasty, vagal nerve blockade, hydrogels) and surgery [e.g., laparoscopic adjustable gastric banding (LAGB), roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD-DS)]. These surgical interventions have considerable peri-operative and post-operative morbidity.

Australian regulatory status

WEGOVY (semaglutide) was approved in Australia for the adult population on 1st September 2022.

Semaglutide 1.34 mg/mL is currently also approved with the trade name Ozempic® (initial application number PM-2018-02748-1-5) for use in type 2 diabetes mellitus (T2DM). The current application does not propose any changes to the Ozempic indications, dosage information or other registered details.

International regulatory status

EMA:

Approved therapeutic indications:

Adults

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

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

Adolescents (≥12 years)

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* and
- body weight above 60 kg.

Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

*Obesity (BMI ≥95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1).

Table 1 BMI cut-off points for obesity (≥95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 95th Percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7

Age (years)	BMI (kg/m2) at 95th Percentile	
	Males	Females
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

FDA:

Approved Indications and Usage:

WEGOVY is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in:

- adults with an initial body mass index (BMI) of *[see Dosage and Administration (2.1)]*:
  - 30 kg/m^2 or greater (obesity) or
  - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)
- pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater standardized for age and sex (obesity) *[see Dosage and Administration (2.1)]*

Similar applications have not been submitted in Canada, New Zealand, Singapore, or Switzerland.

Manufacturing and quality control (Module 3) data evaluation

Not applicable- No module 3 data

Non-clinical (Module 4) data evaluation

The Module 4 evaluation report is saved in TRIM ref. D23-2843074

The evaluator has confirmed that no nonclinical PI changes are proposed, and none are necessary. Overall, there are no nonclinical objections to registration of Wegovy for the proposed indication in adolescence.

Clinical (Module 5) data evaluation

The full details of clinical evaluation can be found in the Clinical Evaluation Report (CER)- D23-3264808

The following regulatory guidance applies to the present application:

- Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (EMA/CHMP/311805/2014) 23 June 2016
- Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control (CPMP/EWP/281/96 Rev. 1) Addendum on Weight Control in Children
- Reflection Paper on Investigation of Pharmacokinetics and Pharmacodynamics in the Obese Population - draft (EMA/CHMP/535116/2016) 25 January 2018
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses. (CHMP/EWP/185990/06) 21 June 2007.

Pharmacology

Pharmacokinetics (PK)

Semaglutide is a human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in a Saccharomyces cerevisiae strain followed by purification.

The dossier contained PK data from one population pharmacokinetic study (NN9536-4451 Modelling Report) to support the proposed dosing for semaglutide in adolescents (aged 12 to <18 years).

Population PK data (popPK)

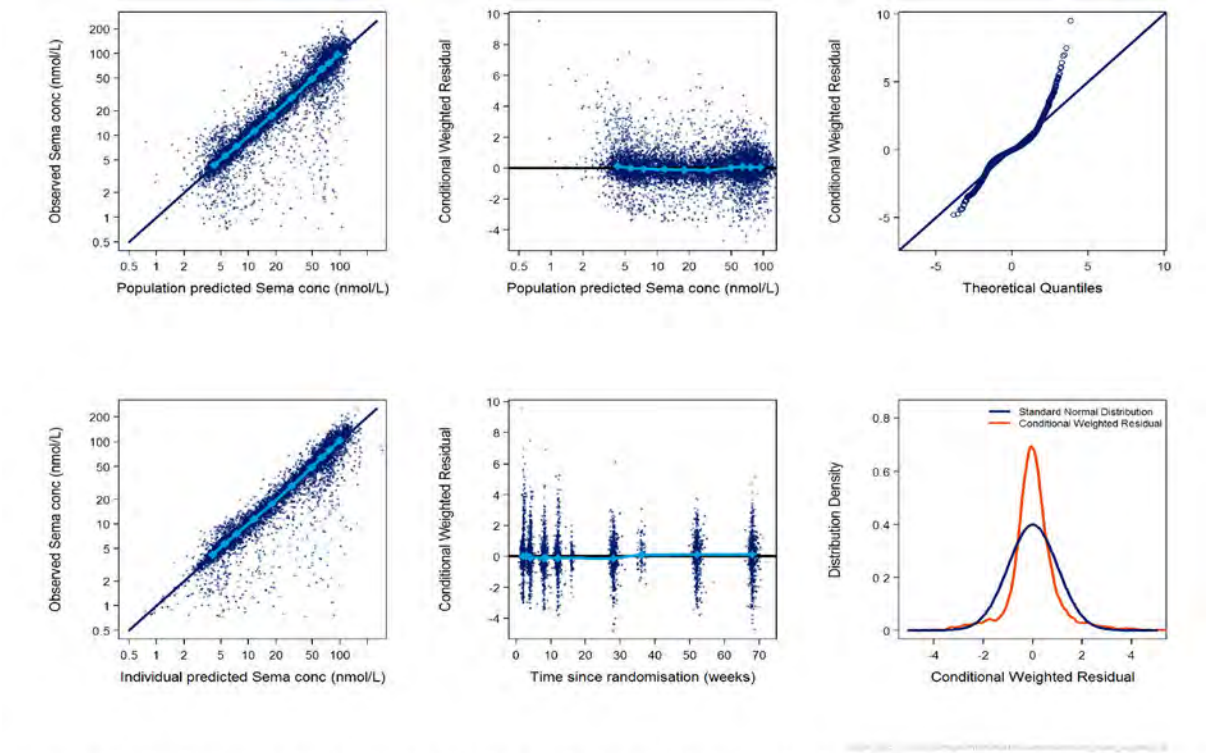
Study NN9536-4451 Modelling Report

Objective: The objective of the analysis was to support the dose selection in the target adolescent population (12 to <18 years), and in the STEP Young trial in children (6 to <12 years).

The Study NN9536-4451 Modelling Report (refer to the CER for full details) conducted a population PK analysis of plasma concentration and covariate data from STEP TEEN (a randomised placebo-controlled study of semaglutide 2.4 mg in overweight or obese adolescents) and STEP1 (a Phase IIIa study conducted in adults). A one-compartment model with first-order absorption and elimination was used to describe the semaglutide PK in adults and adolescents.

The diagnostic plots showed a good fit for the model (figure below)

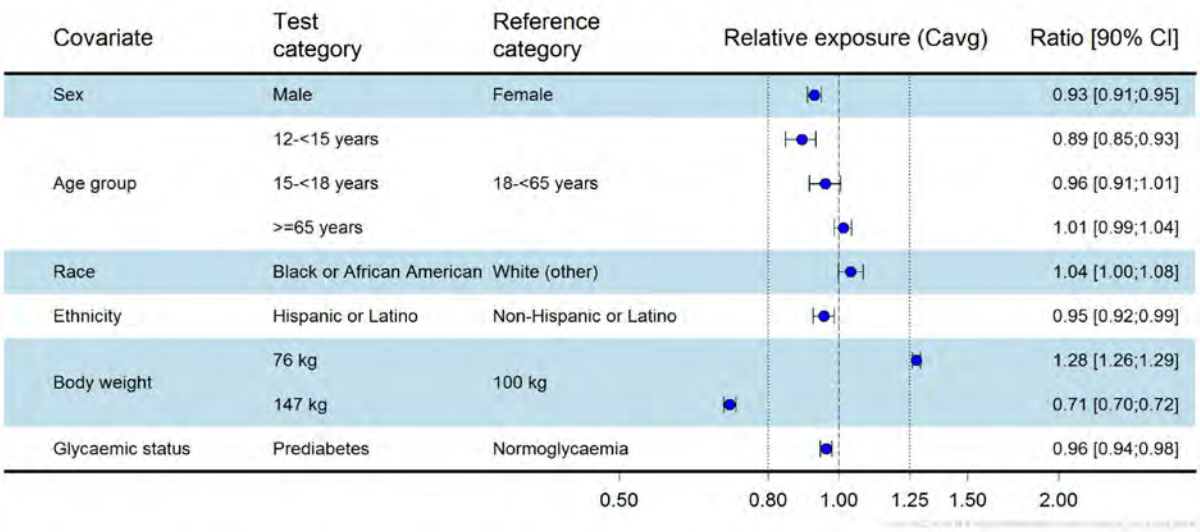
Figure: Standard goodness-of-fit plot for the full PK model including all the covariates (copied from Figure 9-4, Study NN9536-4451 Modelling Report)



Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Light blue lines are median values for quantiles of concentration or time.

In the analysis, the only clinically significant covariate for exposure was body weight, with decreased semaglutide exposure with increasing body weight. From the model, in the adolescent population geometric mean(CV%) C_{avg} was 74 nmol/L (26%), $AUC_{0\text{-}168h}$ was 12366 nmol•h/L (26%) and CL/F was 0.047 L/h (26%). The modelling study demonstrates increased exposure to semaglutide in subjects with lower body weight. Given a median weight of 100 kg, the increase in exposure for a subject of 76 kg was approximately 25% and the decrease in exposure in a subject of 147 kg was approximately 25% (figure below). This range of variation appears unlikely to be clinically important. There were no other significant covariate effects on exposure, which appears acceptable. Hence, the PK data support the proposed dosing regimen for the 12 to <18 years population.

Figure: Forest plot of covariate effects for semaglutide exposure (copied from Figure 6-2, Study NN9536-4451 Modelling Report)



Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino, normoglycaemic white female aged 18-<65 years (STEP 1) and with a body weight of 100 kg). The forest plot and the column to the right show means and 90% CI for the relative exposures. Body weight test categories (76 and 147 kg) represent the 5% and 95% percentiles, respectively in the data set. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80;1.25).

Using the model, CL/F and C_{avg} were simulated for a semaglutide 2.4 mg dose, for a population with body weight from 47.2 to 114.1 kg, representing a population with overweight or obesity aged 6 to <18 years. The starting dose of 0.25 mg in the paediatric population did not result in greater exposure than the 0.5 mg dose in the adult population.

Pharmacodynamics (PD)

Semaglutide acts as a GLP-1 receptor agonist (GLP-1 RA) that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

The dossier contained PD data from the population pharmacokinetic study (NN9536-4451 Modelling Report) to support the proposed dosing for semaglutide in adolescents (aged 12 to <18 years).

In the Study NN9536-4451 Modelling Report there was a linear relationship between exposure and decrease in BMI with decreasing BMI with increasing exposure. There was poor precision for the estimate of baseline BMI effect, but the remaining parameters were estimated with adequate precision. There was no clear relationship between either nausea or vomiting and exposure in these analyses. There was poor precision of the estimates in the linear models and the plots of exposure vs % subjects effected did not have a slope significantly different to 0.

Efficacy

There was one pivotal efficacy study, in adolescents, submitted to support the extension of indications to include weight management in adolescents with overweight or obesity: Study NN9536-4451 (STEP TEENS).

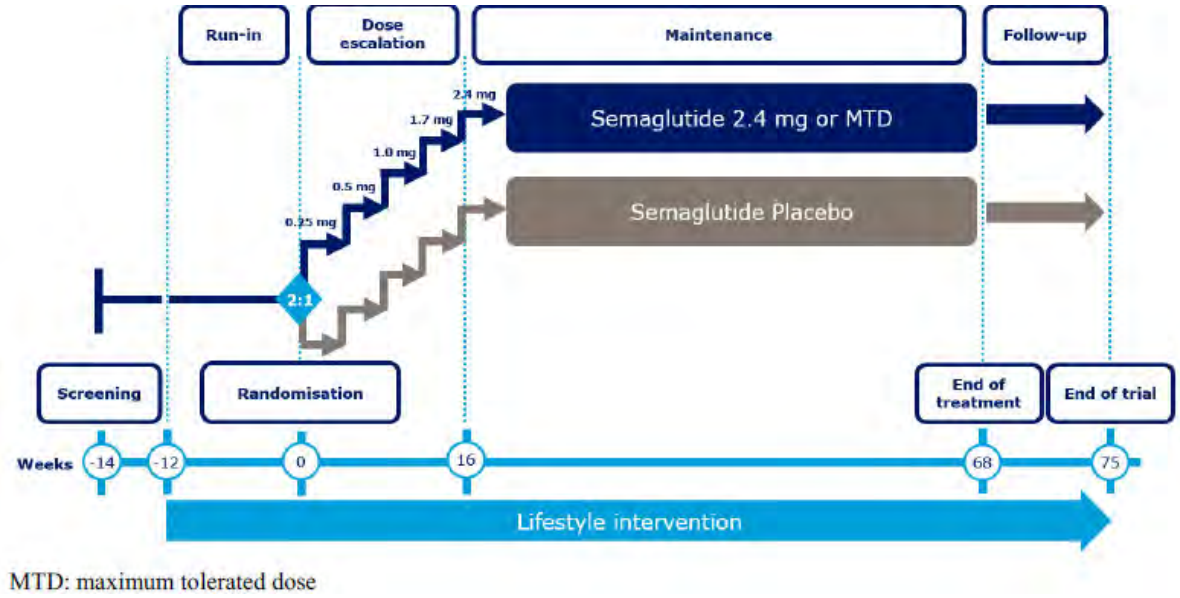
There were three other efficacy studies submitted were in adults and to support changes to the Product Information:

- Study NN9536-4378 (STEP 5): extended treatment
- Study NN9536-4376 (STEP 8): comparison with liraglutide
- Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide.

Study NN9536-4451 (STEP TEENS)

This was a Phase IIIa, randomised, parallel group, placebo-controlled study of the effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity. The study duration was 68 weeks. The study was conducted from October 2019 to March 2022, at 37 sites in eight countries.

Trial design



MTD: maximum tolerated dose

Inclusion criteria:

- Male or female, aged 12 to <18 years
- BMI ≥95th percentile, or ≥85th percentile (on gender and age-specific CDC growth charts) with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or type 2 diabetes
- History of at least one self-reported unsuccessful dietary effort to lose weight
- For subjects with T2DM, HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening; and: subject treated with either diet and exercise alone or stable treatment for at least 90 days prior to screening with metformin

Key exclusion criteria:

- Prepubertal subjects (Tanner stage 1)
- History of type 1 diabetes (T1DM)
- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records
- Subjects with secondary causes of obesity (i.e., hypothalamic, monogenic or endocrine causes)

The study treatments were:

1. Semaglutide: initially 0.25 mg once weekly and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week).
2. Placebo

The treatments were administered by s.c. injection once weekly, in the thigh, abdomen or upper arm at any time of day irrespective of meals. The device used for injections was a 3 mL PDS290 pre-filled pen-injector. If a subject did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose level, if the subject would otherwise discontinue trial product completely and if it was considered safe to continue on trial product.

Primary efficacy outcome:

The primary efficacy outcome measure was the % change in body mass index (BMI) from baseline (week 0) to week 68.

The confirmatory secondary efficacy outcome measure was the proportion of subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68.

The safety outcome measures were AEs, pulse rate, amylase, lipase, and calcitonin.

Statistical methods:

For the primary endpoint, % change in BMI, a linear regression (ANCOVA) on randomised treatment, using the stratification groups (gender and Tanner stage group) and the interaction between gender and Tanner stage as factors, and baseline BMI (kg/m^2) as a covariate. Secondary binary endpoints were tested using logistic regression. Missing data were imputed using multiple imputation using retrieved subjects.

There were 229 subjects screened and 201 were randomised to treatment: 134 to semaglutide and 67 to placebo. All randomised subjects were included in the efficacy analysis. There were 133 (99.3%) subjects in the semaglutide group and 67 (100%) in the placebo who were exposed to treatment. All exposed subjects were included in the safety analysis. There were 120 (89.6%) subjects in the semaglutide group and 60 (89.6%) in the placebo who completed treatment. The most frequent reason for discontinuing treatment was AE: six (4.5%) subjects in the semaglutide group and four (6.0%) in the placebo. There were no protocol deviations that were considered to have a significant impact on the accuracy and reliability of the study data.

Results:

There was only one subject within the overweight (BMI ≥ 85th percentile) with comorbidities category included at baseline (refer the table below).

Demographics and other baseline characteristics

Table: Demographics and baseline characteristics – summary – full analysis set (Source: CTR Synopsis)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	134	67	201
Age (years)			
N	134 (100)	67 (100)	201 (100)
12-<15	47 (35.1)	25 (37.3)	72 (35.8)
15-<18	87 (64.9)	42 (62.7)	129 (64.2)
Sex			
N	134 (100)	67 (100)	201 (100)
Female	84 (62.7)	41 (61.2)	125 (62.2)
Male	50 (37.3)	26 (38.8)	76 (37.8)
Country			
N	134 (100)	67 (100)	201 (100)
Austria	4 (3.0)	7 (10.4)	11 (5.5)
Belgium	15 (11.2)	9 (13.4)	24 (11.9)
Croatia	12 (9.0)	4 (6.0)	16 (8.0)
Ireland	3 (2.2)	1 (1.5)	4 (2.0)
Mexico	13 (9.7)	5 (7.5)	18 (9.0)
Russian Federation	37 (27.6)	18 (26.9)	55 (27.4)
United Kingdom	15 (11.2)	7 (10.4)	22 (10.9)
United States	35 (26.1)	16 (23.9)	51 (25.4)
Race			
N	134 (100)	67 (100)	201 (100)
White	104 (77.6)	55 (82.1)	159 (79.1)
Other	14 (10.4)	6 (9.0)	20 (10.0)
Black or African American	11 (8.2)	5 (7.5)	16 (8.0)
Asian	3 (2.2)	1 (1.5)	4 (2.0)
American Indian or Alaska Native	2 (1.5)	0	2 (1.0)
Native Hawaiian or Other Pacific Islander	0	0	0
Glycaemic category			
N	134 (100)	67 (100)	201 (100)
Normo glycaemia	110 (82.1)	56 (83.6)	166 (82.6)
Pre diabetes	19 (14.2)	8 (11.9)	27 (13.4)
Diagnosed with type 2 diabetes	5 (3.7)	3 (4.5)	8 (4.0)
Weight category CDC			
N	134 (100)	67 (100)	201 (100)
Overweight	1 (0.7)	0	1 (0.5)
Obesity class	133 (99.3)	67 (100)	200 (99.5)
Obesity class I	42 (31.3)	27 (40.3)	69 (34.3)
Obesity class II	44 (32.8)	25 (37.3)	69 (34.3)
Obesity class III	47 (35.1)	15 (22.4)	62 (30.8)

CDC: Centers for Disease Control and Prevention.
N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index. Overall Tanner Stage for each subject is calculated as maximum Tanner Stage combining all the categorical questions per visit.
The last available and eligible observation at or prior to the randomisation visit was selected for summary except for age where date of informed consent was used. Weight categories according to CDC are based on BMI growth charts: Normal weight: BMI <85th percentile; Overweight: BMI >=85th - <95th percentile; Obesity class I: BMI >=95th - <120% of the 95th percentile; Obesity class II: BMI >=120% of the 95th percentile - <140% of the 95th percentile; Obesity class III: BMI >=140% of the 95th percentile.

All the adolescent subjects included in the study were with a body weight >60 kg. The treatment experience with Wegovy in only in the individuals with a body weight >60 kg (see table below).

Table: Demographics and baseline characteristics for continuous variables (Source: CTR Synopsis)

	Sema 2.4 mg	Placebo	Total
Number of subjects	134	67	201
Age (years)			
N	134	67	201
Mean (SD)	15.5 (1.5)	15.3 (1.6)	15.4 (1.6)
Median	15.8	15.4	15.7
P5 ; P95	13 ; 18	12 ; 18	13 ; 18
Min ; Max	12 ; 18	12 ; 18	12 ; 18
Body weight (kg)			
N	134	67	201
Mean (SD)	109.9 (25.2)	102.6 (22.3)	107.5 (24.5)
Median	106.4	97.8	104.3
P5 ; P95	75.7 ; 156.8	73.5 ; 140.7	75.1 ; 151.8
Min ; Max	61.6 ; 211.9	61.0 ; 147.4	61.0 ; 211.9
BMI (kg/m^2)			
N	134	67	201
Mean (SD)	37.7 (6.7)	35.7 (5.4)	37.0 (6.4)
Median	36.7	34.9	36.2
P5 ; P95	28.7 ; 49.8	28.0 ; 45.7	28.5 ; 49.4
Min ; Max	26.8 ; 60.0	26.6 ; 49.9	26.6 ; 60.0
BMI CDC % of 95th percentile			
N	134	67	201
Mean (SD)	133.8 (22.7)	127.8 (17.6)	131.8 (21.2)
Median	130.0	125.1	128.0
P5 ; P95	104.4 ; 174.3	104.9 ; 162.8	104.9 ; 167.0
Min ; Max	99.5 ; 206.4	101.7 ; 166.2	99.5 ; 206.4
Waist circumference (cm)			
N	134	67	201
Mean (SD)	111.9 (16.9)	107.3 (13.4)	110.4 (16.0)
Median	110.0	107.5	110.0
P5 ; P95	87.5 ; 141.0	87.0 ; 131.0	87.5 ; 138.5
Min ; Max	79.0 ; 163.0	84.5 ; 140.0	79.0 ; 163.0
HbA1c (%)			
N	134	67	201
Mean (SD)	5.5 (0.4)	5.5 (0.4)	5.5 (0.4)
Median	5.5	5.4	5.5
P5 ; P95	5.0 ; 6.0	4.9 ; 6.1	5.0 ; 6.0
Min ; Max	4.8 ; 9.0	4.8 ; 7.0	4.8 ; 9.0
Fasting plasma glucose (mmol/L)			
N	134	67	201
Mean (SD)	5.0 (0.7)	5.0 (0.7)	5.0 (0.7)
Median	5.0	4.9	4.9
P5 ; P95	4.3 ; 6.0	4.2 ; 6.3	4.3 ; 6.0
Min ; Max	4.1 ; 9.6	4.0 ; 8.3	4.0 ; 9.6

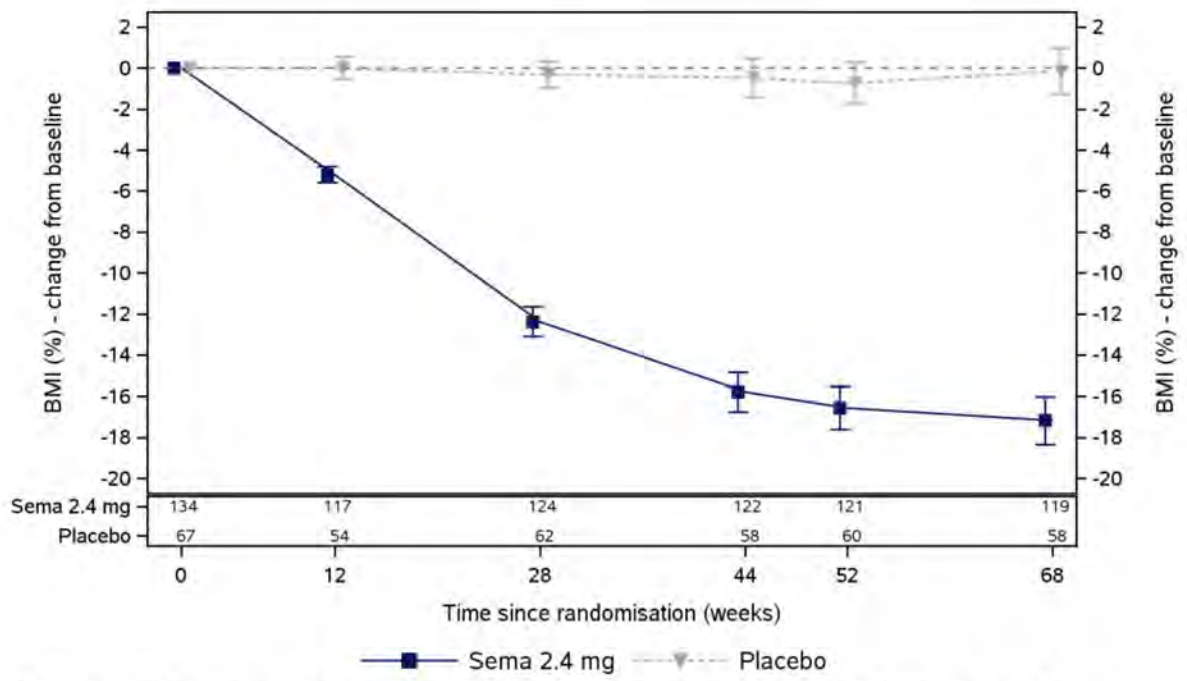
N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, SDS: Standard Deviation Score (reference WHO 2007), HbA1c: Haemoglobin A1c. BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) (%). CDC: Centers for Disease Control and Prevention.
The last available and eligible observation at or prior to the randomisation visit was selected for summary except for age where date of informed consent was used.

There were 125 (62.2%) females and 76 (37.8%) males. There were 159 (79.1%) White subjects and 16 (8.0%) Black or African American. The treatment groups were similar in weight and pubertal staging. The age range was 12 to 18 years. The BMI range was 26.6 to 60.0 kg/m^2 and the BMI SDS score ranged from 2.0 to 6.6. The treatment groups were similar in anthropomorphic measures. There were 25 (18.7%) subjects in the semaglutide group and eight (11.9%) in the placebo with pre-existing hepatic disorders (predominantly hepatic steatosis). The incidence of comorbidity was dyslipidaemia 18.4%; hypertension 13.4%, T2DM 4.0%; and obstructive sleep apnoea 1.5%. There were 29 (21.6%) subjects in the semaglutide group and 13 (19.4%) in the placebo treated with biguanides at baseline. There were eight (6.0%) subjects in the semaglutide group and four (6.0%) in the placebo treated with thyroid hormones at baseline.

Primary efficacy analyses

The mean (SD)% change in BMI from baseline to Week 68 was -16.2 (12.9) % in the semaglutide group and -0.1 (8.6) % in the placebo, difference (95% CI) -16.75 (-20.27 to -13.23) %; p <0.0001. The rate of weight loss was greatest in the first 44 weeks of treatment.

Figure: BMI (%) change from baseline by week - mean plot - on-treatment - full analysis set (copied from 14.2.18, Study NN9536-4451)

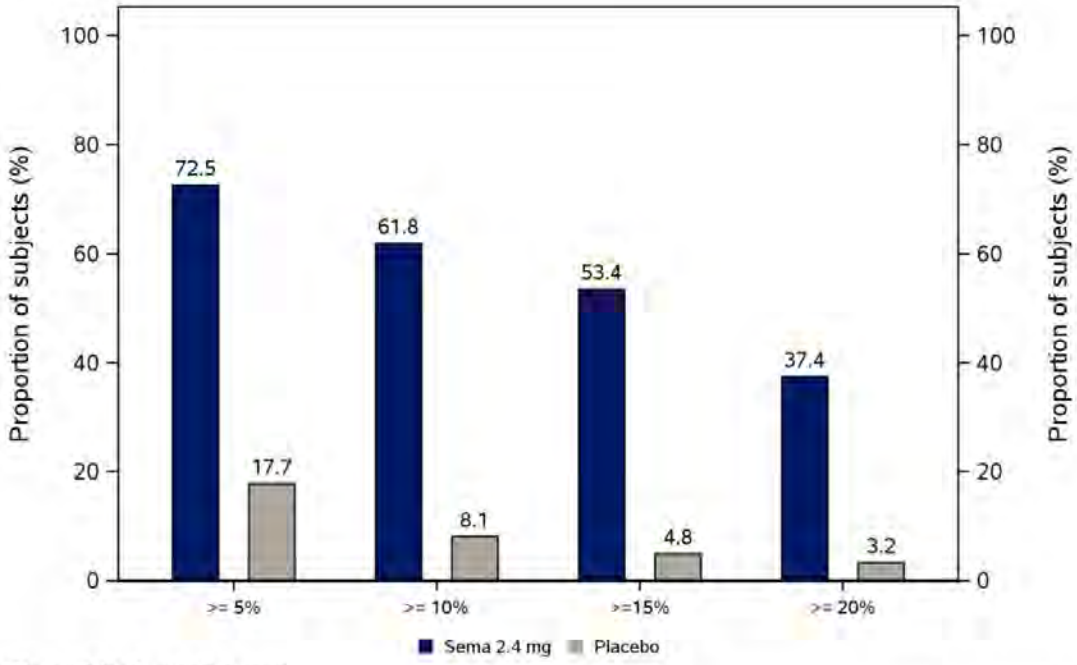


Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Confirmatory secondary efficacy analyses

The proportion of subjects in the semaglutide group with body weight loss ≥5% at week 68 was 72.5% and in the placebo group was 17.7%, OR (95% CI) 14.02 (6.34 to 31.02), p <0.001.

Figure: Proportion of subjects achieving body weight loss response criteria since baseline at week 68 - bar plot - in-trial - full analysis set (copied from Figure 11-7, Study NN9536-4451)



Observed data from in-trial period.

Supportive secondary efficacy outcome measures were:

- From baseline to week 68, BMI was reduced in approximately 90% of subjects on semaglutide 2.4 mg compared to approximately 50% of subjects on placebo (CTR).
- There was a significant decrease in body weight in the semaglutide group relative to placebo at Week 68; treatment difference (95% CI) semaglutide – placebo: -17.73 (-21.76 to -13.70) kg.
- There was a significant decrease in % in body weight in the semaglutide group relative to placebo; treatment difference (95% CI) semaglutide – placebo: -17.42 (21.08 to 13.75) (%).
- The proportion of subjects in the semaglutide group with body weight loss ≥10% at week 68 was 61.8% and in the placebo group was 8.1%, OR (95% CI) 23.04 (8.34 to 63.67), p <0.001.
- The proportion of subjects in the semaglutide group with body weight loss ≥15% at week 68 was 53.4% and in the placebo group was 4.8%, OR (95% CI) 25.78 (7.55 to 88.01), p <0.001.
- The proportion of subjects in the semaglutide group with body weight loss ≥20% at week 68 was 37.4% and in the placebo group was 3.2%, OR (95% CI) 19.99 (4.63 to 86.30), p <0.001.
- **The estimated mean change in BMI percentage of the 95th percentile** on gender and age-specific growth charts (CDC.gov) from baseline to Week 68 was -24.58 %-points with semaglutide and -4.18 %-points with placebo; estimated mean treatment difference (95% CI) -20.40 (-25.01 to -15.79) %-points**.**
- Improvement in weight category was recorded for 71.8% subjects in the semaglutide group compared with 21.0% in the placebo.
- **The mean change in BMI standard deviation score** was -1.22 in the semaglutide group and -0.05 in the placebo: estimated mean treatment difference (95% CI) -1.17 (-1.41 to -0.93) p <0.0001.
- The estimated mean change in BMI from baseline to Week 68 was -5.85 kg/m^2 in the semaglutide group and 0.11 kg/m^2 in the placebo: estimated treatment difference (95% CI) -5.96 (-7.29 to -4.62) kg/m^2.
- **The mean change in waist circumference** from baseline to Week 68 was -12.69 cm in the semaglutide group and -0.55 cm in the placebo; estimated on-trial mean treatment difference (95% CI) -12.14 (-15.59 to -8.69) cm, p <0.0001.
- The proportion of subjects achieving ≥5% reduction of BMI was 77.1% in the semaglutide group and 19.7% in the placebo; OR (95% CI), semaglutide/placebo, 13.76 (6.31 to 30.02).

Exploratory secondary efficacy endpoints demonstrated improvements in serum lipids (a cardiovascular risk factor) and in glycaemic indices (HbA1c in subjects with T2DM, and FPG in subjects without T2DM.

Other efficacy studies (submitted in support of changes to the PI)

Study NN9536-4378 (STEP 5): extended treatment

Study NN9536-4378 was a randomised, double-blind, placebo-controlled, two-armed, parallel group, clinical trial comparing semaglutide 2.4 mg once weekly with semaglutide placebo in subjects with overweight or obesity. The objective of the study was to examine the efficacy and safety of semaglutide 2.4 mg over a 2-year period. The study was conducted at 41 sites in five countries: Canada (9 sites), Hungary (6), Italy (5), Spain (6) and the US (15). The study was conducted from October 2018 to March 2021.

The study included males and females, aged ≥18 years, with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease; and a history of at least one self-reported unsuccessful dietary effort to lose body weight. The study excluded subjects with HbA_{1c} ≥48 mmol/mol (6.5%); or a self-reported change in body weight >5 kg (11 lbs) within 90 days before screening.

The study treatments were:

1. Semaglutide 2.4 mg weekly
2. Placebo

Semaglutide was administered using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL (depending on dose level). Dose escalation was to take place during the first 16 weeks after randomisation with dose increase every 4 weeks (from 0.25 mg/week to doses of 0.5, 1.0, 1.7 and 2.4 mg/week). If a subject could not tolerate the recommended dose of semaglutide 2.4 mg, the subject could stay at a lower dose level.

The primary efficacy outcome measures were:

- Change from baseline (week 0) to week 104 in body weight (%)
- Proportion of subjects with body weight reduction ≥5% from baseline at 104 weeks

The secondary efficacy outcome measures were:

- Proportion of subjects who at Week 104 achieved body weight reduction from baseline ≥10%, ≥15% and ≥ 20%
- Change from baseline to Week 104 in: waist circumference (cm), body weight (kg) and BMI (kg/m^2)
- Cardiovascular endpoints: Change from baseline to Week 104 in: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), serum lipids and CRP
- Glucose metabolism endpoints: Change from baseline to Week 104 in HbA1c, FPG and fasting serum insulin

One-year endpoints were:

- Change from baseline to Week 52 in body weight, BMI and waist circumference
- Proportion of subjects who after 52 weeks achieved body weight reduction ≥5%, ≥10%, ≥15% and ≥20%

The safety outcome measures were AEs, vital signs, amylase, lipase, and calcitonin.

The Full Analysis Set (FAS) included all randomised subjects and the Safety Analysis Set (SAS) included all randomised subjects exposed to at least one dose of randomised treatment. Continuous outcome measures were tested using ANOVA models and dichotomous outcome measures were tested using logistic regression models. Hypothesis testing was hierarchical, using a decision criteria of $p < 0.05$. The sample size estimation was based on a power of 43% for the first six endpoints, and was for 150 subjects in each group.

There were 347 subjects screened, and 304 were randomised to treatment: 152 to semaglutide and 152 to placebo. All were included in both the FAS and SAS. There were 148 (97.4%) subjects in the semaglutide group and 134 (88.2%) in the placebo who completed the trial. There were 132 (86.8%) subjects in the semaglutide group and 111 (73.0%) in the placebo who completed treatment.

There were 236 (77.6%) females, 68 (22.4%) males and the age range was 21 to 78 years. The range for BMI was 27.6 to 82.7 kg/m^2. The range for waist circumference was 83.0 to 193.4 cm. The treatment groups were similar in demographic and baseline characteristics.

Semaglutide was superior to placebo for both primary endpoints. The mean (SD) -change in body weight from baseline to Week 104 was -17.3 (11.9) % in the semaglutide group and -2.0 (8.6%) in the placebo: treatment difference (95% CI) -12.55 (-15.33 to -9.77) %, p <0.0001. There was weight loss to Week 68 of treatment, after which the weight loss was maintained to Week 104. The proportion of subjects with body weight reduction ≥5% from baseline at 104 weeks was 77.1% in the semaglutide group and 34.4% in the placebo: OR (95% CI) 4.99 (2.95 to 8.42) p <0.0001.

For the secondary efficacy endpoints:

- The proportion of subjects with body weight reduction ≥10% from baseline at 104 weeks was 61.8% in the semaglutide group and 13.3% in the placebo: OR (95% CI) 7.23 (3.95 to 13.23) p <0.0001.
- The proportion of subjects with body weight reduction ≥15% from baseline at 104 weeks was 52.1% in the semaglutide group and 7.0% in the placebo: OR (95% CI) 9.40 (4.41 to 20.04) p <0.0001.
- The proportion of subjects with body weight reduction ≥20% from baseline at 104 weeks was 36.1% in the semaglutide group and 2.3% in the placebo: OR (95% CI) 12.84 (3.94 to 41.88) p <0.0001.
- The mean (SD) change from baseline to Week 104 in waist circumference was -16.4 (12.2) cm in the semaglutide group and -4.4 (9.2) cm in the placebo: treatment difference (95% CI), semaglutide – placebo, -9.17 (-12.17 to -6.17) cm, p <0.0001. There was a decrease in mean waist circumference in the semaglutide group to Week 60, and after that the improvement was maintained to Week 104.
- The mean (SD) change from baseline to Week 104 in body weight was -18.3 (13.7) kg in the semaglutide group and -2.2 (9.5) kg in the placebo: treatment difference (95% CI) -12.91 (-16.05 to -9.77) kg, p <0.0001. The decrease in weight was to Week 68, after which time weight stabilised to Week 104.
- The mean (SD) change from baseline to Week 104 in BMI was -6.8 (5.2) kg/m2 in the semaglutide group and -0.8 (3.4) kg/m2 in the placebo: treatment difference, semaglutide – placebo, -4.30 (-5.73 to -2.87), p <0.0001. The decrease in BMI was to Week 68, after which time BMI stabilised to Week 104.
- There was a decrease in SBP and DBP in the semaglutide group from baseline to Week 20, which was then maintained throughout the treatment period. The proportion of subjects who had a decrease or stopped taking antihypertensive medication was higher with semaglutide 2.4 mg (32%) compared to placebo (16%) and a lower proportion of subjects had an increase with semaglutide 2.4 mg (6%) compared to placebo (23%).
- There was a decrease in total cholesterol, VLDL cholesterol and triglycerides in the semaglutide group relative to the placebo from baseline to Week 104.
- For CRP, the estimated ratio to baseline at Week 104 was 0.43 for semaglutide, and 0.92 for placebo: estimated treatment ratio (95% CI) 0.47 (0.37 to 0.60).
- HBA1c decreased in the semaglutide group relative to placebo: for the treatment policy estimand, the estimated mean change in HbA1c from baseline to Week 104 was −0.43%-points with semaglutide and −0.10 %-points with placebo: ETD (95% CI) −0.33 (−0.41 to −0.25) %-points.
- FPG decreased in the semaglutide group relative to placebo: for the treatment policy estimand, the estimated mean change in FPG from baseline to Week 104 was −0.42 for semaglutide and 0.09 mmol/L for placebo; ETD (95% CI) −0.51 (−0.66 to −0.36) mmol/L.
- Fasting serum insulin decreased in the semaglutide group relative to placebo: estimated mean ratio to baseline at Week 104 was 0.67 for semaglutide and 0.93 for placebo: treatment ratio (95% CI) 0.73 (0.61 to 0.87).
- Of the subjects who had pre-diabetes at baseline, 80% treated with semaglutide switched to being normo-glycaemic by Week 104 and 20% remained having pre-diabetes. None of the subjects treated with semaglutide switched to having diabetes.

For subjects treated with placebo, a lower proportion of subjects switched from having pre-diabetes to being normo-glycaemic (37%), while higher proportions of subjects remained having pre-diabetes (59%) and 4% switched to having diabetes. The Control of Eating Questionnaire indicated better control for semaglutide compared to placebo.

Study NN9536-4376 (STEP 8): comparison with liraglutide

Study NN9536-4376 was a randomised, open-label, pairwise placebo-controlled, efficacy and safety study comparing semaglutide with liraglutide. The objective of the study was to compare the efficacy and safety of semaglutide with liraglutide. The study was conducted over a 68 week period. The study was conducted at 19 sites in the US from 11th September 2019 to 11th May 2021.

The inclusion criteria included:

- Male or female, age ≥18 years at the time of signing informed consent.
- Body mass index (BMI) ≥30.0 kg/m2 or ≥27.0 kg/m2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.
- History of at least one self-reported unsuccessful dietary effort to lose body weight.

The exclusion criteria included:

- HbA1c ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening.
- History of Type 1 or Type 2 diabetes mellitus.
- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.

The study treatments were:

1. Semaglutide: dose escalation of semaglutide was to take place during the first 16 weeks after randomisation with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg once weekly after 16 weeks. If a subject did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose of 1.7 mg semaglutide once weekly.
2. Placebo for semaglutide.
3. Liraglutide: Dose escalation of liraglutide was to take place during the first 4 weeks after randomisation with dose increases every week (to doses of 1.2, 1.8, 2.4 and 3.0 mg), aiming at reaching the maintenance dose of 3.0 mg once daily after 4 weeks.
4. Placebo for liraglutide.

Semaglutide was administered using a PDS290 pre-filled pen-injector up to Week 44, then subsequently a DV3396 single-dose pen-injector. Liraglutide was administered using aPDS290 pre-filled pen-injector.

The primary efficacy outcome measures were:

- Change from baseline (week 0) to Week 68 in body weight (%)

The secondary efficacy outcome measures were:

- Proportion of subjects who at Week 68 achieved body weight reduction from baseline ≥10%, ≥15% and ≥ 20%
- Change from baseline to Week 68 in: waist circumference (cm) and body weight (kg)
- Cardiovascular endpoints: Change from baseline to Week 68 in: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), serum lipids and hsCRP
- Glucose metabolism endpoints: Change from baseline to Week 68 in HbA1c, FPG, fasting serum insulin, and glycaemic category.

The exploratory endpoint was:

- Proportion of subjects with body weight reduction ≥5% from baseline at 68 weeks.

The safety outcome measures were AEs and vital signs.

Randomisation was in the ratio 3:1:3:1 for semaglutide: placebo: liraglutide: placebo.

There were 387 subjects screened and 338 were randomised, all of whom were treated: 126 in the semaglutide group, 127 in the liraglutide and 85 in the placebo. There were 109 (86.5%) in the semaglutide group, 92 (72.4%) in the liraglutide and 70 (82.4%) in the placebo who completed treatment.

There were 265 (78.4%) females and 73 (21.6%) males. The age range was 18 to 79 years, and the BMI range was 26.5 to 81.0 kg/m^2. The treatment groups were similar in demographic and baseline variables.

Semaglutide was superior to liraglutide for the primary and confirmatory secondary efficacy outcome measures. The mean (SD) change in body weight % at Week 68 was -16.4 (10.5) % for semaglutide, -6.4 (7.7) % for liraglutide and -1.6 (8.6) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -9.38 (-11.97 to -6.80) %, p <0.0001.

For the secondary efficacy outcome measures:

- The % subjects with change in body weight ≥10% at Week 68 was 70.9% for semaglutide, 25.6% for liraglutide and 15.4% for placebo: OR (95% CI), semaglutide / liraglutide, 6.28 (3.53 to 11.18) %, p <0.0001.
- The % subjects with change in body weight ≥15% at Week 68 was 55.6% for semaglutide, 12.0% for liraglutide and 6.4% for placebo: OR (95% CI), semaglutide / liraglutide, 7.90 (4.06 to 15.38) %, p <0.0001.
- The % subjects with change in body weight ≥20% at Week 68 was 38.5% for semaglutide, 6.0% for liraglutide and 2.6% for placebo: OR (95% CI), semaglutide / liraglutide, 8.19 (3.51 to 19.13) %, p <0.0001.
- The mean (SD) change in body weight (kg) at Week 68 was -15.8 (10.2) kg for semaglutide, -6.8 (9.5) kg for liraglutide and -1.4 (9.6) kg for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -8.49 (-11.24 to -5.74) kg, p <0.0001; semaglutide – placebo, estimand (95% CI) -13.79 (-16.83 to -10.74) kg, p<0.0001; and liraglutide – placebo, estimand (95% CI) -5.30 (-8.30 to -2.29) kg, p = 0.0006
- The mean (SD) change in waist circumference (cm) at Week 68 was -13.6 (10.0) cm for semaglutide, -6.8 (8.4) cm for liraglutide and -2.0 (7.2) kg for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -6.61 (-9.06 to -4.16) cm, p <0.0001.
- SBP decreased to a similar extent in the semaglutide and liraglutide groups relative to placebo.
- For the majority of the treatment period there was no significant difference in DBP between the study groups.
- Between baseline and week 68, the proportion of subjects who had a decrease or stopped taking antihypertensive medication was higher with semaglutide 2.4 mg (29.2%) compared to liraglutide 3.0 mg (16.3%) and pooled placebo (9.7%) and a lower proportion of subjects had an increase in antihypertensive medication with semaglutide 2.4 mg (20.8%) compared to liraglutide 3.0 mg (23.3%) and pooled placebo (22.6%).
- The semaglutide group had a decrease in total serum cholesterol, VLDL cholesterol and triglycerides relative to liraglutide.
- The ratio of hsCRP at Week 68 to baseline was 0.5 for semaglutide, 0.8 for liraglutide and 0.8 for placebo; estimated treatment ratio (95% CI) semaglutide / liraglutide, 0.6 (0.5 to 0.8).

- The mean (SD) change in HbA1c at Week 68 was -0.3 (0.2) % for semaglutide, -0.1 (0.2) % for liraglutide and 0.1 (0.2) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -0.16 (-0.22 to -0.09) cm, p <0.0001.
- The mean (SD) change in FPG at Week 68 was -0.5 (0.5) mmol/L for semaglutide, -0.3 (0.6) mmol/L for liraglutide and 0.1 (0.6) mmol/L for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -0.22 (-0.40 to -0.04) mmol/L, p = 0.0174
- The geometric mean ratio (CV%) for fasting serum insulin at Week 68 / baseline was 0.73 (57.3) semaglutide, 0.85 (47.5) for liraglutide and 0.98 (56.8): treatment ratio (95% CI), semaglutide / liraglutide 0.85 (0.73 to 1.00) p = 0.0540
- Of subjects who were normoglycaemic at baseline, the proportion who shifted to pre-diabetes at Week 68 was 2.8% for semaglutide, 12.2% for liraglutide and 27.7% for placebo. Of subjects who were pre-diabetic at baseline, the proportion who shifted to normoglycaemic at Week 68 was 89.5% for semaglutide, 64.9% for liraglutide and 13.3% for placebo.
- The % subjects with change in body weight ≥5% at Week 68 was 87.2% for semaglutide, 58.1% for liraglutide and 129.5% for placebo (hypothesis not tested as was exploratory endpoint).

Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide

Study NN9536-4373 (STEP 1) was randomised, double-blind, two-armed, parallel group, placebo-controlled study of the effect on body weight of semaglutide as an adjunct to reduced-calorie diet and increased physical activity. The results of the 68-week main phase have previously been submitted and the results of the 52-week off-treatment extension phase were included in the present submission. The extension study was conducted at 37 sites in five countries: Canada (6), Germany (13), Japan (3), United Kingdom (10) and US (5). The trial was commenced in June 2018 and the extension phase was completed in March 2021.

The trial included Males and females, aged ≥18 years; with BMI ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease; and a history of at least one self-reported unsuccessful dietary effort to lose body weight.

There was no intervention treatment for the extension phase.

There were 333 patients included in the extension study, 232 from the semaglutide group and 101 from the placebo. There were 216 (93.1%) subjects in the semaglutide group and 96 (95.0%) in the placebo who completed the extension phase. There were 228 (98.3%) subjects in the semaglutide group and 99 (98.0%) in the placebo who were included in the extension analysis set. There were 219 (67.0%) females and 108 (33.0%) males and the age range was 18 to 83 years.

In the semaglutide group there was weight loss through to Week 68 when on treatment with semaglutide, but when treatment was ceased weight was regained through to Week 120. At Week 68, in the semaglutide group the mean (SD) body weight was 87.5 (21.4) kg and at Week 120 it was 99.0 (22.5) kg; mean (SD) increase 12.0 (8.4) kg. This was a mean (SD) increase of 14.8 (10.7) % in the semaglutide group. At Week 68, in the placebo group the mean (SD) body weight was 103.2 (25.6) kg and at Week 120 it was 105.5 (26.2) kg; mean (SD) increase 2.0 (4.8) kg. This was a mean (SD) increase of 2.1 (4.9) % in the placebo group.

In the semaglutide group there was decrease in BMI through to Week 68 when on treatment with semaglutide, but when treatment was ceased BMI increased through to Week 120, but with some preservation of treatment effect over the year without treatment. At Week 68, in the semaglutide group the mean (SD) BMI was 31.2 (7.2) kg/m^2 and at Week 120 it was 35.0 (7.1) kg/m^2; mean (SD) increase 4.3 (2.9) kg/m^2. At Week 68, in the placebo group the mean (SD) BMI was 36.9 (8.0) kg/m^2 and at Week 120 it was 37.6 (8.2) kg/m^2; mean (SD) increase 0.7 (1.7) kg/m^2.

In the semaglutide group there was an increase in HbA_{1c} after treatment was ceased, predominantly in the first 12 weeks, and by one year off treatment was not significantly different to the placebo group. At Week 68, in the semaglutide group the mean (SD) HbA_{1c} was 33.6 (3.1) mmol/mol and at Week 120 it was 37.5 (3.8) mmol/mol; mean (SD) increase 3.9 (2.9) mmol/mol. At Week 68, in the placebo group the mean (SD) HbA_{1c} was 37.1 (4.2) mmol/mol and at Week 120 it was 38.4 (5.6) mmol/mol; mean (SD) increase 1.4 (2.9) mmol/mol.

The benefits in decreased blood pressure with semaglutide treatment were lost within 12 weeks of ceasing treatment.

Total cholesterol and LDL cholesterol were decreased during semaglutide treatment and returned to the same concentrations as placebo within 12 weeks of ceasing treatment. However, HDL cholesterol increased with semaglutide treatment, and remained elevated after treatment was ceased. Higher concentrations of HDL cholesterol are associated with decreased cardiovascular risk.

CRP concentrations decreased with semaglutide treatment, and increased following ceasing treatment, but were still less than those of the placebo group after one year off treatment.

Safety

In the pivotal study (*Study NN9536-4451-STEP TEENS)* the safety outcome measures were AEs, pulse rate, amylase, lipase, and calcitonin. There were 133 adolescents exposed to semaglutide and 67 to placebo.

In Study *NN9536-4376* (126 subjects exposed to semaglutide group, 127 to liraglutide and 85 to placebo) and Study *NN9536-4378* (152 subjects exposed to semaglutide and placebo) the safety outcome measures were AEs, vital signs, clinical laboratory tests (including lipase, amylase and calcitonin) and ECGs.

In Study *NN9536-4373* Extension (232 from the semaglutide group and 101 from the placebo) AEs were not systematically collected. There were no reports of deaths, SAEs or withdrawals due to AE. Clinical laboratory tests were not performed routinely. Vital signs were recorded as part of the efficacy assessment.

Study NN9536-4451-STEP TEENS

In Study NN9536-4451 there were 812 TEAEs reported in 106 (79.7%) subjects in the semaglutide group and 333 in 56 (83.6%) in the placebo. Gastrointestinal disorders were the most frequently reported group of disorders and were more frequent in the semaglutide group: 82 (61.7%) subjects compared with 28 (41.8%) in the placebo. There was a higher incidence of nausea with semaglutide (56 [42.1%] subjects compared with 12 [17.9%] in the placebo) and vomiting (48 [36.1%] subjects compared with seven [10.4%] in the placebo). The prevalence of gastrointestinal adverse events in the semaglutide group was constant over the period of treatment.

In Study NN9536-4451 there were 396 possible or probable treatment related TEAEs reported in 77 (57.9%) subjects in the semaglutide group and 98 in 26 (38.8%) in the placebo. There was a higher incidence of nausea attributed to treatment with semaglutide (52 [39.1%] subjects compared with 12 [17.9%] in the placebo), vomiting (40 [30.1%] subjects compared with four [6.0%] in the placebo), abdominal pain (17 [12.8%] subjects compared with two [3.0%] in the placebo) and headache (13 [9.8%] subjects compared with two [3.0%] in the placebo). Injection site AEs were recorded for four (3.0%) subjects in the semaglutide group and three (4.5%) in the placebo.

In Study NN9536-4451 there were no deaths. There were 17 SAEs reported in 15 (11.3%) subjects in the semaglutide group and seven in six (9.0%) in the placebo.

There were four (3.0%) subjects with hepatobiliary disorders and two (1.5%) with appendicitis in the semaglutide group and none with either of these conditions in the placebo. There were six SUSARs in the semaglutide group and two in the placebo. These were predominantly

gastrointestinal. there was one subject in each treatment group with elevated lipase, and one subject in the placebo group with elevated calcitonin.

In Study NN9536-4451 the incidence of hepatic AEs was higher in the semaglutide group: 13 events in 10 (7.5%) subjects, compared with one in one (1.5%) in the placebo. There were three (2.3%) subjects with increased ALT in the semaglutide group. There were no clinically significant abnormalities in haematology parameters.

In Study NN9536-4451 there were 13 cardiovascular AEs in 10 (7.5%) subjects in the semaglutide group and seven in seven (10.4%) in the placebo. There were no clinically significant abnormalities in ECGs. mean pulse rate was similar for the two treatment groups. There were no significant differences in vital signs or physical examination findings between the treatment groups.

In Study NN9536-4451 there were 14 allergic AEs in 12 (9.0%) subjects in the semaglutide group and four in four (6.0%) in the placebo. In the semaglutide group these were predominantly dermatological. One subject in the semaglutide group was positive for anti-semaglutide antibodies at Week 68, but negative at Week 75.

In Study NN9536-4451 there was no significant difference between the treatment groups in growth parameters. The mean (SD) change from baseline in height was 1.3 (2.1) cm for semaglutide and 2.1 (2.6) cm for placebo. The mean (SD) change from baseline in height SDS was -0.076 (0.252) for semaglutide and -0.048 (0.249) for placebo. The mean (SD) change from baseline in bone age was 1.3 (0.8) years for semaglutide and 1.5 (0.9) years for placebo. There were no significant differences between the treatment groups in bone metabolism biomarkers. There were no significant differences between the treatment groups in the shifts in pubertal status from baseline to Week 68. There were no clinically significant differences between the treatment groups in the serum concentrations of TSH, FT_4, dehydroepiandrosterone sulphate, estradiol, FSH, IGF-1, LH, or prolactin.

Other studies

Study NN9536-4378

There were 1606 adverse events reported in 146 (96.1%) patients in the semaglutide group and 1004 in 136 (89.5%) in the placebo. The most frequently reported TEAEs, which were also more frequent in the semaglutide group, were nausea, diarrhoea, constipation and vomiting. Most TEAEs were reported in the first 20 weeks of treatment. There were 696 gastrointestinal AEs reported in 125 (82.2%) subjects in the semaglutide group and 252 in 82 (53.9%) in the placebo. There were four (2.6%) subjects with hepatobiliary disorders in the semaglutide group and two (1.3%) in the placebo. There were 734 adverse events possibly or probably related to study drug reported in 123 (80.9%) patients in the semaglutide group and 267 in 77 (50.7%) in the placebo.

There was one death in the semaglutide group (acute myocardial infarction). There were 18 SAEs reported in 12 (7.9%) patients in the semaglutide group and 20 in 18 (11.8%) in the placebo. There was no apparent pattern to the SAEs.

There were three (2.0%) subjects with hepatic AEs in the semaglutide group and three (2.0%) in the placebo. Two subjects in each group had elevated ALT. There were no significant differences between the treatment group in mean haematology parameters. There were no treatment emergent cases of pancreatitis. Mean amylase and lipase concentrations increased in the semaglutide group but not to abnormal levels. There were no elevations of amylase or lipase >3xULN. There was no increase in mean calcitonin concentrations. There were no calcitonin concentrations >100 ng/L during the on-treatment period. there were 24 reports of neoplastic events in 19 (12.5%) subjects in the semaglutide group and 23 in 19 (12.5%) in the placebo. There were two reports of malignant neoplastic events in two (1.3%) subjects in the semaglutide group and four in four (2.6%) in the placebo. No events related to malignant neoplasms were reported.

There were fewer cardiovascular AEs in the semaglutide group (19 events in 17 [11.2%] subjects) than in the placebo group (41 events in 30 [19.7%) subjects). There were three subjects in the semaglutide group and two in the placebo with post-baseline clinically significant ECG abnormalities. There was an increase in pulse rate in the semaglutide group relative to placebo: estimated EOT treatment difference (95% CI) 4.14 (2.05 to 6.24) bpm. There was a decrease in SBP and DBP in the semaglutide group from baseline to Week 20, which was then maintained throughout the treatment period.

There were 36 allergic reaction AEs in 23 (15.1%) subjects in the semaglutide group and nine in eight (5.3%) in the placebo. The excess in reactions in the semaglutide group was due to more dermatological reactions, including urticaria and contact dermatitis.

Study NN9536-4376

There were 904 TEAEs reported in 120 (95.2%) subjects in the semaglutide group, 823 in 122 (96.1%) in the liraglutide and 522 in 81 (95.3%) in the placebo. Gastrointestinal AEs were more frequent with semaglutide and liraglutide than placebo, particularly nausea, with no clear differences between semaglutide and liraglutide. There were 483 AEs possibly or probably related to study treatment reported in 107 (84.9%) subjects in the semaglutide group, 350 in 106 (83.5%) in the liraglutide and 141 in 49 (57.6%) in the placebo.

There were no deaths. There were 14 SAEs reported in 10 (7.9%) subjects in the semaglutide group, 18 in 14 (11.0%) in the liraglutide and nine in six (7.1%) in the placebo. There was no apparent pattern to the SAEs.

There was one (0.8%) subject in the semaglutide group with elevated ALT. There were no significant differences between the treatment group in mean haematology parameters. there was one subject with acute pancreatitis in the liraglutide group and none in the semaglutide or placebo groups. At Week 68, there were eight (7.7%) subjects in the semaglutide group, seven (7.9%) in the liraglutide and one (1.5%) in the placebo with elevated serum lipase. At Week 68, there were three (2.9%) subjects in the semaglutide group, four (4.5%) in the liraglutide and one (1.5%) in the placebo with elevated serum amylase. there were 16 reports of neoplastic events in 13 (10.3%) subjects in the semaglutide group, 24 in 17 (13.4%) in the liraglutide and 16 in 12 (14.1%) in the placebo. There were three malignant neoplasms reported in the semaglutide group, three in the liraglutide and one in the placebo.

At Week 68, there were seven (6.7%) subjects in the semaglutide group, one (1.1%) in the liraglutide and two (3.0%) in the placebo with elevated calcitonin. There were no cases of medullary thyroid carcinoma (MTC).

Cardiovascular AEs were reported in 16 (12.7%) subjects in the semaglutide group, 18 (14.2%) in the liraglutide and nine (10.6%) in the placebo. There were no clinically significant changes in ECG findings. An increase in pulse rate was recorded on-treatment for both the semaglutide and liraglutide treatment groups. SBP decreased to a similar extent in the semaglutide and liraglutide groups relative to placebo. For the majority of the treatment period there was no significant difference in DBP between the study groups.

There were 13 allergic reactions in nine (7.1%) subjects in the semaglutide group, 12 in 11 (8.7%) in the liraglutide and 13 in 10 (11.8%) in the placebo. The majority of these events were dermatological.

Risk Management Plan (RMP) evaluation

The RMP evaluation report is saved in TRIM ref: D23-3434894

In support of the extended indications, the sponsor has submitted EU-RMP version 7.1 (dated 26 April 2022; DLP 31 May 2021) and updated ASA version 1.5 (dated 15 September 2023).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies as listed in the ASA, are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Diabetic retinopathy complications (only for patients with type 2 diabetes)	✓	✓*	✓	–
Important potential risks	Pancreatic cancer	✓	✓*	✓	–
	Medullary thyroid cancer	✓	✓*	✓	–
	Pregnancy and lactation	✓	–	✓	–
Missing information	Patients with severe hepatic impairment	✓	–	✓	–

*Post authorisation safety study (PASS)

The evaluator has confirmed that there is nothing outstanding from an RMP perspective.

- The summary of safety concerns mostly aligns with the updated EU-RMP. In its Milestone 5 response, sponsor re-categorised the risk of 'pregnancy and lactation' from missing information to important potential risk as requested in Round 2 and based on its Pregnancy Category D classification. The summary of safety concerns is acceptable from an RMP perspective.

- Routine pharmacovigilance activities for all safety concerns have been proposed. Additional pharmacovigilance activities for the risks of pancreatic cancer, medullary thyroid cancer and long-term effects on diabetic retinopathy in subjects with type 2 diabetes in the form of post authorisation safety studies, have been proposed. The pharmacovigilance plan aligns with the EU-RMP and is acceptable as no new safety concerns have been identified as a result of the proposed extension of indication.

- The sponsor has proposed routine risk minimisation activities for all safety concerns. The sponsor has proposed no additional risk minimisation activities. This is considered acceptable. The proposed changes to the PI and CMI relate to the proposed extension of the indication to the adolescent population. The warning of pregnancy in the CMI has been strengthened in accordance with the warning in the PI.

  The sponsor has provided an assurance that the CMI and Instruction for Use will be included as a package insert.

RMP evaluator recommendations regarding condition/s of registration

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Wegovy EU-Risk Management Plan (RMP) (version 7.1, dated 26 April 2022, data lock point 31 May 2021), with Australian Specific Annex (version 1.5, dated 15 September 2023), included with submission PM-2022-04980-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As the indication for WEGOVY is being extended into a significantly different population it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

WEGOVY (Semaglutide) is to be included in the Black Triangle Scheme. The PI and CMI for WEGOVY must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

Discussion

Efficacy:

The population pharmacokinetic study (NN9536-4451 Modelling Report) analysed the PK and PD data from Study NN9536-4451 (STEP TEENS) in comparison with an adult population from Study NN9536-4373 (STEP 1). The population PK analysis showed that exposure was inversely correlated with body weight. Age caused no clinically relevant change in semaglutide exposure. Other covariates such as sex, race, ethnicity, and glycaemic status had no or only minor effects on exposure. The estimates for apparent clearance and exposure (CL/F and Cavg) were comparable between adolescent and adult subjects with obesity. As expected, CL/F increased with baseline BW, whereas the CL/F appeared to be independent of age. It indicated that the only significant covariate effect on semaglutide exposure was body weight. The PK data support the proposed dosing regimen for the 12 to <18 years population.

Efficacy in the adolescent population (age range 12 to ≤18 years)*- Study NN9536-4451 (STEP TEENS)*

Primary efficacy analyses: The mean (SD)% change in BMI from baseline to Week 68 was -16.2 (12.9) % in the semaglutide group and -0.1 (8.6) % in the placebo, difference (95% CI) -16.75 (-20.27 to -13.23) %; p <0.0001.

Confirmatory efficacy analyses: The proportion of subjects in the semaglutide group with body weight loss ≥5% at week 68 was 72.5% and in the placebo group was 17.7%, OR (95% CI) 14.02 (6.34 to 31.02), p <0.001.

The primary and confirmatory efficacy analyses demonstrated superiority for semaglutide. Although this semaglutide benefit has statistical superiority and appears clinically relevant, 27.5% of the patients treated with semaglutide still had a body weight loss of less than 5% even at week 68. From baseline to week 68, BMI was reduced in approximately 90% of subjects on semaglutide 2.4 mg compared to approximately 50% of subjects on placebo (CTR). Almost 10% of the patients on Wegovy (semaglutide) did not have a decrease in BMI or an increase. This raises **the first issue for discussion** and concern about a knowledge gap of the length of treatment needed with semaglutide. The delegate considers inclusion, in the indication, of a stopping and re-evaluating rule for adolescents who haven't reduced their BMI by at least 5% after 12 weeks of treatment with Wegovy 2.4mg or maximum tolerated dose, would prevent unnecessary long-term treatment in them, similar to the EU SmPC.

"Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose."

The second issue for discussion is about the two patient categories (obesity or overweight with ≥1 weight related comorbidity) included in the Adolescents therapeutic indication proposed by the sponsor in this submission which are based on the STEP TEENS Study Inclusion criteria ie,

- BMI ≥95th percentile, or
- BMI ≥85th percentile (on gender and age-specific CDC growth charts) with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or type 2 diabetes.

4.1 THERAPEUTIC INDICATIONS

Adolescents

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* or
- overweight* and at least one weight-related comorbidity

*Obesity (BMI ≥ 95th percentile) and overweight (BMI ≥ 85th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1 and Figure 1).

However, there was only one subject within the 'overweight (BMI ≥ 85th percentile) with comorbidities' category included in the study at baseline. It is not possible to assess and establish a positive benefit risk profile of Wegovy in this patient category of overweight (BMI ≥85th percentile) and at least one-weight-related comorbidity. Therefore, the delegate doesn't support Wegovy indication in overweight adolescents with comorbidity.

The third issue for discussion is the inclusion of the graph (with BMI cut-off points) in the indication/PI. Considering the therapeutic indication now includes the Table with BMI cut-off points, the delegate believes that the graph with BMI cut-off points included in the PI causes duplicity, hard to decipher and don't add any value. The delegate believes that this graph can be removed from the PI (therapeutic indication).

The fourth issue for discussion is the fact that all the adolescent subjects included in the pivotal STEP TEENS study were with a body weight >60 kg. The treatment experience with Wegovy in only in the individuals with a body weight >60 kg. In the EU both Wegovy and Saxenda are only indicated for adolescents with a body weight above 60 kg.

Supportive studies in adult population (aged ≥18 years)

In the supportive Study NN9536-4378 (STEP 5), for a two-year treatment duration, in adults (aged ≥18 years) there was weight loss for the first year, and preservation of weight loss for the second year, with weekly semaglutide 2.4 mg. The treatment difference (95% CI), semaglutide – placebo, in % body weight was -12.55 (-15.33 to -9.77) %, p <0.0001 (i.e., treatment effect size). There was weight loss to Week 68 of treatment, after which the weight loss was maintained to Week 104. The improvements in cardiovascular risk factors and glycaemic indices were also preserved during the second year of treatment.

Study NN9536-4376 (STEP 8) reported superiority for semaglutide in comparison with liraglutide in adults (age ≥18 years). The mean (SD) change in body weight % at Week 68 was -16.4 (10.5) % for semaglutide, -6.4 (7.7) % for liraglutide and -1.6 (8.6) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -9.38 (-11.97 to -6.80) %, p <0.0001. The dosing regimen for both treatments was the same as recommended in their respective Product Information.

Study NN9536-4373 (STEP 1), in adults (age ≥18 years), demonstrated that the weight loss following one year of semaglutide treatment is not preserved when the treatment is ceased. There was some preservation of weight loss after one year off treatment, but this was despite a

clinically significant increase in weight in the semaglutide group after cessation of treatment. There was also loss of the benefits of glycaemic control and blood pressure. However, the semaglutide group retained the benefits of an increase in HDL cholesterol and a decrease in CRP.

Safety:

The profile of adverse effects in the adolescent population is similar to the adult population. There were more adverse effects with semaglutide than with placebo, primarily due to an increase in gastrointestinal AEs, as expected. However, although a large proportion of the Wegovy (semaglutide) treated patients experienced gastrointestinal AEs there were relatively few SAEs. There were double the number of SAEs in the Wegovy (semaglutide) group compared with placebo, also due to an excess of gastrointestinal SAEs. There were few discontinuations due to AEs. There were dose reductions in 12% of adolescent subjects, primary related to GI disturbance. Hence, the majority of gastrointestinal AEs were tolerable, with or without dose reduction. There were no clinically significant abnormalities in ECGs. mean pulse rate was similar for the two treatment groups. There were no significant differences in vital signs or physical examination findings between the treatment groups. Mental health questionnaires (the PHQ-9 and C-SSRS) showed no relevant differences between semaglutide and placebo.

Wegovy (semaglutide) did not interfere with growth, development, or puberty in the adolescent population. There were no malignancies reported in the adolescent population. There was one subject treated with semaglutide with elevated lipase, and no reports of pancreatitis. There were no subjects in the semaglutide group with elevated calcitonin.

With extended treatment, over a two-year period, most TEAEs were reported in the first 20 weeks of treatment. These were predominantly gastrointestinal in the Wegovy (semaglutide) treatment group and did not increase over time. The rate of SAEs in the semaglutide population was similar to that in the placebo. There was one death in the semaglutide group that was not attributed to study treatment. Over a two-year period, the incidence of neoplasia in the semaglutide group was that same as the placebo group. The incidence of cardiovascular AEs was approximately half that of the placebo group.

The profile of adverse effects was similar for Wegovy (semaglutide) and liraglutide. Both treatments had increased incidences of gastrointestinal AEs compared to placebo. There were more AEs leading to discontinuation in the liraglutide group, and more leading to dose reductions in the semaglutide. Hence, semaglutide may have better tolerability than liraglutide.

With discontinuation of semaglutide, there was weight gain and other losses of treatment effect. However, there were no reports of AEs related to withdrawal and no rebound effects.

Conclusions

Population PK analysis in adolescents was aligned with the adult data, it showed that exposure was inversely correlated with body weight. There were no clear differences observed between adolescents and adults based on the presented exposure-response data (BMI) or exposure-safety data (nausea and vomiting).

In general, the benefit of Wegovy on body weight and BMI management in adolescents, seen in Study NN9536-4451 (STEP TEENS), was significant and appears clinically relevant. The safety data presented in the dossier confirm the known adverse event profile of Wegovy (semaglutide) and no new safety concerns were identified. In general, the safety and tolerability data in adolescents (from Study STEP Teens) are comparable with the safety profile established in the adult clinical development programmes with semaglutide 2.4 mg.

The Delegate considers the benefit risk of Wegovy in adolescents with obesity as positive. However, considering there was only one subject within the 'overweight (BMI ≥ 85th

percentile) with comorbidities' category included in the study at baseline, it is not possible to establish a positive benefit risk profile and the delegate doesn't support this indication.

Considering the other issues discussed above, the delegate proposed (amended) therapeutic indication for discussion at the ACM:

"Adolescents

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

• *obesity**

Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

**Obesity (BMI ≥ 95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1)*

Table 1 BMI cut-off points for obesity (≥95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 95th Percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

References/attachments for ACM

Number	Document name	Location/ID	ACM attachment
1	Module 4 evaluation report	D23-2843074	☒
2	Clinical Evaluation Report (CER)	D23-3264808	☒
3	RMP report	D23-3434894	☒

Appendix 1: Review of the Product Information

Product information (PI) negotiation will be done after the ACM meeting.

Appendix 2: Conditions for Provisional Registration

Terms and conditions were imposed upon the authorisation with respect to quality, clinical, labelling, and Risk Management Plan requirements:

Quality conditions:

N/A

Clinical conditions:

N/A

RMP conditions:

Discussed above and in the RMP report D23-3434894

Therapeutic Goods Administration

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https://www.tga.gov.au

Document 3

Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: Semaglutide

Product name: WEGOVY®

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Submission number: PM-2021-00612-1-5

eSubmission number: e005802

First round evaluator:
Date of first round report: 6th July 2021
TRIM reference: E21-358491
Second round evaluator:
Date of second round report: 9th October 2021
TRIM reference: E21-358491

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
ACS	Acute coronary syndrome
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CK	Creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	Clinical laboratory adverse event
CL/F	Apparent clearance
C_{max}	Maximum concentration
COEQ	Control of Eating Questionnaire
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia Suicidality Severity Rating Scale
CT	Computerised axial tomography
CV	Cardiovascular / Coefficient of variability
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trial

Abbreviation	Meaning
DBP	Diastolic blood pressure
DEXA	Dual-energy X-ray absorptiometry
DPP-4	Dipeptidyl peptidase-4
DXA	DEXA analysis set
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
ETD	Estimated treatment difference
ETR	Estimated treatment ratio
FAS	Full analysis set
FDA	US Food and Drug Administration
FFA	Free Fatty Acids
FPG	Fasting plasma glucose
FSFV	First subject first visit
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1 RA	Glucagon-like peptide-1 receptor antagonist
HbA_{1c}	Glycosylated haemoglobin
HDL	High-density lipoprotein
HLGT	High-level group term
hsCRP	High-sensitivity C-reactive protein
IBT	Intensive behavioural therapy.
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form

Abbreviation	Meaning
IgE	Immunoglobulin E
INR	International normalised ratio
ITT	Intention to treat
IVGTT	Intravenous glucose tolerance test
IWQoL-Lite	Impact of Weight on Quality of Life Lite
IWRS	Interactive web response system
KDIGO	Kidney Disease: Improving Global Outcomes
LAO	Last available observation
LAO-OT	Last available observation on randomised treatment
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	Multiple endocrine neoplasia type 2
MESI	Medical event of special interest
MI	Myocardial infarction
MTC	Medullary thyroid carcinoma
MMRM	Mixed model for repeated measurements
MRI	Magnetic resonance imaging
NA	Not applicable
NASH	Non-alcoholic steatohepatitis
NRS	Numeric rating scale
OAD	Oral antidiabetic drug
OAS	Overall appetite score
OR	Odds ratio

Abbreviation	Meaning
PAI-1	Plasminogen activator inhibitor-1
PD	Pharmacodynamics
PGI-C	Patient's Global Impression of Change
PGI-S	Patient's Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetics
PRO	Patient-reported outcome
PT	Preferred term
PTQ	Preferred terms query
PYE	Patient-years of exposure
PYO	Patient-years of observation
QoL	Quality of life
RD-MI	Multiple imputation using retrieved subjects
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SBP	Systolic blood pressure
s.c.	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36
SGLT-2	Sodium/glucose co-transporter 2
SOC	System organ class
SPS-6	Stanford Presenteeism Scale
STEP	Semaglutide Treatment Effect in People with obesity

Abbreviation	Meaning
SUSAR	Suspected unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TEE	Total energy expenditure
T_{max}	Time to maximum concentration
TP-MI	Tipping-point multiple imputation
TSH	Thyroid stimulating hormone
UNR	Upper normal range
VLDL	Very-low-density lipoprotein
VLCAD	Very long-chain acyl-CoA dehydrogenase
V_{ss}/F	Apparent volume of distribution at steady state
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire – Specific Health Problem
WRSSM	Weight Related Sign and Symptom Measure

1. Submission details

1.1. Identifying information

Submission number	PM-2021-00612-1-5
eSubmission number	e005802
eSubmission sequences covered in this report	0000
Sponsor	Novo Nordisk Pharmaceuticals Pty Ltd
Trade name	WEGOVY®
Active substance	Semaglutide

1.2. Submission type

This is a Category 1, Type C (extension of indication) application for TRADENAME (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle. The application is to extend the indications for semaglutide to include management of obesity.

The new indication is intended to be registered with a new trade name (to be confirmed), new strengths and a new dosage delivery system (a single use prefilled pen with pre-assembled needle).

1.3. Drug class and therapeutic indication

Semaglutide is a glucagon-like peptide-1 analogue (GLP-1 RA) with a high degree of homology to human GLP-1. Semaglutide is a potent and selective agonist on the GLP-1 receptor (GLP-1R), displaying the known pharmacological effects of the GLP-1 RA class, i.e. lowering of blood glucose and reduction of body weight. Both native GLP-1 and GLP-1 RAs reduce body weight by lowering energy intake via inducing feelings of satiety and fullness, and lowering feelings of hunger.

Semaglutide has a 94% homology to human GLP-1. Compared to native GLP-1, the semaglutide molecule has the following structural modifications in order to obtain a longer half-life:

- Substituting the alanine in position 8 of the peptide backbone to 2-aminoisobutyric acid to increase stability against the DPP-4 enzyme
- Substituting the lysine in position 34 to arginine to prevent acylation in this position
- Addition of a hydrophilic spacer between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached
- Addition of a C18 fatty di-acid with a terminal acidic group

The spacer and the fatty acid both contribute to increased albumin binding which slows the degradation of semaglutide in plasma and decreases the renal clearance, which combined with the increased stability against the DPP-4 enzyme, prolong the half-life of semaglutide to approximately 1 week, thus enabling once weekly s.c. administration.

Semaglutide is produced in *Saccharomyces cerevisiae* by recombinant DNA technology followed by protein purification.

The currently approved indication for OZEMPIC (semaglutide) is:

Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- *as monotherapy when metformin is not tolerated or contraindicated.*
- *in addition to other medicinal products for the treatment of type 2 diabetes.*

The proposed additional new indication is:

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

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

1.4. Dosage forms and strengths

The following proposed new strengths included in this application are:

- TRADENAME (semaglutide) 0.25 mg/dose (0.5 mg/mL)
- TRADENAME (semaglutide) 0.5 mg/dose (1.0 mg/mL)
- TRADENAME (semaglutide) 1 mg/dose (2.0 mg/mL)
- TRADENAME (semaglutide) 1.7 mg/dose (2.27 mg/mL)
- TRADENAME (semaglutide) 2.4 mg/dose (3.2 mg/mL)

1.5. Dosage and administration

The proposed dosing recommendations are:

"The maintenance dose of 2.4 mg once-weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 1). In case of significant gastrointestinal symptoms, consider delaying dose escalation until symptoms have improved. If patients do not tolerate the 2.4 mg dose, the dose can be temporarily decreased to 1.7 mg weekly. Patients should re-escalate to the therapeutic/ maintenance 2.4 mg dose.

Table 1: Dose escalation schedule

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

Method of administration

[Trade Name] is administered once weekly at any time of the day, with or without meals.

[Trade Name] is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. [Trade Name] should not be administered intravenously or intramuscularly. [Trade Name] pen is for use by one person only.

The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

When administering semaglutide, the pen should be pressed firmly against the skin until the yellow bar has stopped moving. The injection takes about 5-10 seconds.

Patients should be advised to read the instruction for use included in the package leaflet carefully before administering [Trade Name].

Missed Dose

If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day of the week. In each case, patients can then resume their regular once weekly dosing schedule. If more doses are missed, reducing the starting dose for re-initiation should be considered.

Special Populations

Patients with Type 2 diabetes:

[Trade Name] should not be used in combination with other GLP-1 receptor agonist products.

When initiating [Trade Name], consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia.

Elderly patients (≥ 65 years old)

No dose adjustment is required based on age.

Gender

No dose adjustment is required based on gender.

Race and Ethnicity

No dose adjustment is required based on race and ethnicity.

Patients with renal impairment

No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with end-stage renal disease.

Patients with hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2 Pharmacokinetic properties). Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide.

Children and adolescents

Safety and efficacy of [Trade Name] in children and adolescents below 18 years have not been studied."

1.6. Proposed changes to the product documentation

The TRADENAME product information is separate to the OZEMPIC product information, and it is original to the present application. However, some sections of the TRADENAME product information appear to be based on the OZEMPIC product information, e.g. drug interactions, pharmacokinetics. The sections on adverse events and clinical trials are based on the data for TRADENAME.

2. Background

2.1. Information on the condition being treated

Obesity is a common condition with high associated morbidity and mortality.

Body mass Index (BMI) is used as a measure of being overweight and obese. The definitions for obesity and overweight used by the Australian Institute of Health and Welfare (AIHW) are:

- A BMI of 25.0 to 29.9 kg/m^2 is classified as overweight but not obese
- A BMI of ≥30.0 kg/m^2 is classified as obese.
- A BMI of >35.0 kg/m^2 is classified as severely obese.

These definitions of obesity and overweight align with the World Health Organisation definitions.

BMI is a composite measure of weight and height:

$$BMI = \frac{body\ weight\ (kg)}{(height\ [cm])^2}$$

Hence, this measure is not a direct measure of adiposity, but is a surrogate measure. Hence, these definitions may not apply to a highly muscled individual or to children and adolescents. Interpretation of BMI may vary between ethnic groups. Waist circumference in adults may be a better measure of adiposity and a better measure of obesity-related morbidity.

The AIHW (AIHW 2021) reports that in 2017–18, an estimated 2 in 3 (67%) Australians aged 18 and over were overweight or obese, 36% were overweight but not obese, and 31% were obese. This equates to approximately 12.5 million adults in Australia. The prevalence of overweight and obesity was higher in males (75% compared to 60% in females) and also the prevalence of obesity was higher in males (33% compared to 30% in females). Obesity is more prevalent in older age groups: 16% of adults aged 18–24 compared with 41% of adults aged 65 to 74 years.

Obesity is associated with increased prevalence of cardiovascular disease, hypertension, type 2 diabetes mellitus (T2DM) and metabolic syndrome, non-alcoholic fatty liver disease, cholelithiasis, cancer, sleep apnoea, osteoarthritis and reduced psychosocial function (Bray 2004). Overall, obesity is associated with increased mortality, increased morbidity and decreased quality of life.

It has been estimated that in 2015 high BMI accounted for 4.0 million deaths globally, representing 7.1% of deaths from any cause, and 120 million disability-adjusted life-years, representing 4.9% of disability adjusted life-years (Afshin 2017). More than two thirds of deaths related to high BMI were due to cardiovascular disease.

2.2. Current treatment options

A 5% decrease in body weight, in patients with obesity, is associated with significant improvements in cardiovascular risk factors, such as hypertension and lipid profile (Look 2010). Hence, this has become the target for measuring treatment effectiveness, and treatments should achieve at least a 5% sustained reduction in body weight.

The following treatment options are available for patients who are overweight or obese:

Lifestyle modification: diet and exercise with or without psychological support

Pharmacological treatments:

- Orlistat: a selective inhibitor of pancreatic lipase, resulting in decreased absorption of fat. Orlistat is a Schedule 3 drug in Australia and is available over the counter.
- Liraglutide: a GLP-1 agonist, is approved in Australia for the indication:

SAXENDA (liraglutide) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of

- *≥30 kg/m² (obese) or*
- *≥27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.*

Treatment with SAXENDA should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

- Phentermine: sympathomimetic agent with anorectic actions.
- Naltrexone/bupropion is approved for the following indication in Australia:

CONTRAVE is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of

- *≥ 30 kg/m² (obese), or*
- *≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of one or more weight-related comorbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)*

Treatment with CONTRAVE should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

Pharmacological treatments not approved in Australia:

- Phentermine/topiramate: is approved in the US for weight control. Topiramate is associated with weight loss due to an unknown mechanism (approved in the US).
- Lorcaserin: an appetite suppressant through activation of hypothalamic 5-HT^{2C} receptors (approved in the US)

Pharmacological treatments in development:

Products in development include GLP-1 agonists (such as semaglutide), dual GLP-1/GIP receptor antagonists and GLP-1/GIP/glucagon triple agonists (Williams 2020). SGLT-2 inhibitors are also under development as potential weight control agents. Amylin mimetics, leptin analogues and ghrelin vaccines and antagonists, neuropeptide Y inhibitors and melanocortin-4 receptor antagonists are potential therapeutic agents for this indication (Williams 2020).

Bariatric surgery:

Bariatric surgery is usually reserved for patients with severe obesity: a BMI ≥40 kg/m² or >35 kg/m² with obesity-related co-morbidity (Williams 2020). Surgical interventions include devices (e.g., intragastric balloon, endoscopic sleeve gastroplasty, vagal nerve blockade, hydrogels) and surgery [e.g., laparoscopic adjustable gastric banding (LAGB), roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD-DS)]. These surgical interventions have considerable peri-operative and post-operative morbidity.

NHMRC Statement on Management of Overweight and Obesity

The NHMRC guidance (NHMRC 2013) is to use treatments sequentially, commencing with a very low energy diet, then using pharmacological interventions to counter the hormonal changes and hunger following the initial weight loss, and to reserve bariatric surgery for when:

- other interventions have not been successful
- other interventions are contraindicated, or
- a person's BMI is >50 kg/m²

The relative effectiveness of treatments available in Australia is summarised in Table 2.2.1 (NHMRC 2013).

2.3. Clinical rationale

The clinical rationale for developing semaglutide for weight control is stated by the Sponsor as:

"For people with obesity there is a lack of safe and efficacious treatment options that can provide a reduction in body weight approaching what can be obtained by surgical procedures, and at the same time enables the patient to maintain the weight loss. Pharmacotherapy may serve as a valuable alternative to bariatric surgery as a supplement to lifestyle intervention to achieve and sustain a clinically relevant weight loss. Currently, only a very limited number of pharmacological options are approved for weight management. Furthermore, some are only indicated for short term use whereas others are associated with significant adverse effects.

Collectively, there is a clear unmet medical need for a convenient, efficacious and safe weight lowering drug with beneficial effects on obesity-related comorbidities. The GLP-1 RA drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors as well as glucose metabolism."

2.4. Formulation

2.4.1. Formulation development

The Sponsor has developed dose sizes and formulations for the new indication. OZEMPIC® has 1.34 mg/mL semaglutide and contains phenol and propylene glycol as excipients.

2.4.2. Excipients

TRADENAME 0.5 mg/mL contains the active ingredient semaglutide 0.5 mg/mL and the following excipient ingredients:

- dibasic sodium phosphate dihydrate, 1.42 mg/mL
- sodium chloride, 8.25 mg/mL
- hydrochloric acid, as required to adjust pH
- sodium hydroxide, as required to adjust pH
- Water for injections, to 1.0 mL

TRADENAME 1.0 mg/mL contains the active ingredient semaglutide 1.0 mg/mL and the following excipient ingredients:

- dibasic sodium phosphate dihydrate, 1.42 mg/mL
- sodium chloride, 8.25 mg/mL
- hydrochloric acid, as required to adjust pH
- sodium hydroxide, as required to adjust pH
- Water for injections, to 1.0 mL

TRADENAME 2.0 mg/mL contains the active ingredient semaglutide 2.0 mg/mL and the following excipient ingredients:

- dibasic sodium phosphate dihydrate, 1.42 mg/mL
- sodium chloride, 8.25 mg/mL
- hydrochloric acid, as required to adjust pH
- sodium hydroxide, as required to adjust pH
- Water for injections, to 1.0 mL

TRADENAME 2.27 mg/mL contains the active ingredient semaglutide 2.27 mg/mL and the following excipient ingredients:

- dibasic sodium phosphate dihydrate, 1.42 mg/mL
- sodium chloride, 8.25 mg/mL
- hydrochloric acid, as required to adjust pH
- sodium hydroxide, as required to adjust pH
- Water for injections, to 1.0 mL

TRADENAME 3.2 mg/mL contains the active ingredient semaglutide 3.2 mg/mL and the following excipient ingredients:

- dibasic sodium phosphate dihydrate, 1.42 mg/mL
- sodium chloride, 8.25 mg/mL
- hydrochloric acid, as required to adjust pH
- sodium hydroxide, as required to adjust pH
- Water for injections, to 1.0 mL

2.5. Regulatory history

2.5.1. Australian regulatory history

Semaglutide 1.34 mg/mL is currently approved with the trade name Ozempic® (initial application number PM-2018-02748-1-5) for use in type 2 diabetes mellitus (T2DM). The current application does not propose any changes to the Ozempic indications, dosage information or other registered details.

2.5.2. Orphan drug designation

Orphan Drug Designation does not apply to the present application.

2.5.3. Related submissions

There are no related submissions.

2.5.4. Overseas regulatory history

Similar applications have been submitted and are under consideration in the EU (4th January 2021), the US (4th December 2020), Canada (8th December 2020) and the UK (5th January 2021). Similar applications have not been made in New Zealand, Singapore or Switzerland. A similar application has not been refused market approval or withdrawn.

The Australian submission is based on the dossier submitted in the EU and which is currently under evaluation. Minor changes to the dossier include updates to Module 3 for example, additional stability data temperature cycling studies have been incorporated.

2.6. Guidance

The following regulatory guidance applies to the present application:

- Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (EMA/CHMP/311805/2014) 23 June 2016
- Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control (CPMP/EWP/281/96 Rev. 1) Addendum on Weight Control in Children
- Reflection Paper on Investigation of Pharmacokinetics and Pharmacodynamics in the Obese Population - draft (EMA/CHMP/535116/2016) 25 January 2018

2.7. Evaluator's commentary on the background information

The Sponsor has provided sufficient background information and justification for the application. Obesity is a common condition with considerable associated morbidity and mortality, and with limited effective treatment options. This provides sufficient justification for the development of

semaglutide as a therapeutic option for patients with obesity and patients who are overweight and with comorbidity.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier contains data the following studies that have not previously been submitted to the TGA for evaluation:

- Three clinical pharmacology trials (of which two are bioequivalence trials)
  - Study NN9536-4590 (Section 19.1.1.1)
  - Study NN9535-4588 (Section 19.1.1.2)
  - Study NN9536-4455 (Section 19.1.2.1)
- One Phase II dose-finding trial
  - Study NN9536-4153 (Section 6.2)
- There were two PKPD modelling reports:
  - Modelling of data from Study NN9536-4153 (Section 19.1.3.1).
  - Modelling of data from Study NN9536-4373 and Study NN9536-4374 (Section19.1.3.2)
- Four Phase IIIa therapeutic confirmatory trials (referred to as the STEP trials)
  - Study NN9536-4373 (STEP 1) (Section 7.2.1)
  - Study NN9536-4374 (STEP 2) (Section 7.2.2)
  - Study NN9536-4375 (STEP 3) (Section 7.2.3)
  - Study NN9536-4376 (STEP 4) (Section 7.2.4)
- Two analyses of data from more than one study:
  - Integrated Summary of Immunogenicity
  - Integrated Summary of Patient Reported Outcomes

In addition, the application includes blinded safety data from 1 extension trial (extension phase of STEP 1) and 5 other ongoing trials. For data from these trials a cut-off date of 01 September 2020 has been used.

The dossier contains data from the following studies that have previously been submitted to the TGA for evaluation. These studies established the basic pharmacokinetics and pharmacodynamics for the applications for semaglutide for the treatment of T2DM and are resubmitted to support the pharmacokinetics and pharmacodynamics sections of the Product Information document.

- s47 [redacted]
- Study NN9535-4010 (Section 19.1.1.4)
- Study NN9535-3687 (Section 19.1.1.5)
- s47 [redacted]
- Study NN9535-3789 (Section 19.1.1.7)
- Study NN9535-3633 (Section 19.1.1.8)
- s47 [redacted]
- Study NN9535-3616 (Section 19.1.1.10)
- Study NN9535-3651 (Section 19.1.1.11)
- Study NN9535-3819 (Section 19.1.1.12)
- Study NN9535-3817 (Section 19.1.1.13)
- Study NN9535-3818 (Section 19.1.1.14)
- s47 [redacted]

- s47
- s47
- [redacted]

In addition, there were the following studies included in the dossier that support some of the information in the Product Information document:

- DV3396-s47 [redacted]
- Study NN9535-3744 (SUSTAIN 6): a long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes. This study has previously been submitted for evaluation to the TGA.

3.2. Paediatric data

The submission does not include paediatric data.

There is a waiver for Paediatric Investigation Plan in the EU for the product for the paediatric population <10 years age on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset.

There is a waiver from having to submit a Pediatric Assessment in the USA for the paediatric population with T2DM s47 [redacted]

These waivers may relate to the initial application for treatment of T2DM and may not relate to the current proposed indication of weight control.

3.3. Good clinical practice

The clinical studies submitted in the dossier are stated to have been, and appear to have been, conducted according to Good Clinical Practice.

3.4. Evaluator's commentary on the clinical dossier

The data submitted in the dossier represents a full development program for the new indication. Some of the studies have been previously submitted in support of the clinical pharmacology of semaglutide in the applications relating to T2DM. However, the Sponsor has also submitted clinical pharmacology studies for the new dose forms and for the new indication.

The waivers for Paediatric Investigation Plan in the EU and Pediatric Assessment in the USA may relate to the initial application for treatment of T2DM and may not relate to the current proposed indication of weight control.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Synopsis
PK in healthy adults	s47 [redacted]		
		, Study NN9535-3789	Section 19.1.1.7
	- Multi-dose	Study NN9535-3633	Section 19.1.1.8
	Bioequivalence † - Single dose	Study NN9535-4588	Section 19.1.1.2
		s47 [redacted]	
		Study NN9535-3687	Section 19.1.1.5
		Study NN9535-4010	Section 19.1.1.4
	- Multi-dose	Study NN9536-4590	Section 19.1.1.1
PK in special populations	Hepatic impairment	Study NN9535-3651	Section 19.1.1.11
	Renal impairment	Study NN9535-3616	Section 19.1.1.10
	s47 [redacted]		
PK interactions	Oral contraceptive pill	Study NN9535-3819	Section 19.1.1.12
	Metformin / warfarin	Study NN9535-3817	Section 19.1.1.13
	Digoxin / atorvastatin	Study NN9535-3818	Section 19.1.1.14
Population PK		s47 [redacted]	
		Modelling Report 3	Section 19.1.3.2

There were no pharmacokinetic results excluded from consideration.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

Semaglutide is a human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in a Saccharomyces cerevisiae strain followed by purification.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanism of absorption

TRADENAME (semaglutide) is intended for subcutaneous administration.

In Study NN9535-4588 (Section 19.1.1.2) T_{max} was earlier for Formulation D: mean (SD) 21.3 (14.90) h for formulation D and 64.5 (16.84) h for Formulation B. In Study NN9536-4590 (Section 19.1.1.1), for Formulation D, median (range) Tmax was 24 (3 to 48) h.

4.2.2.2. Bioavailability

Absolute bioavailability

In Study NN9535-3687 (Section 19.1.1.5) the absolute bioavailability of s.c. semaglutide was 89%.

Bioavailability relative to an oral solution or micronised suspension

NA.

Bioequivalence of clinical trial and market formulations

The clinical trials appeared to use the formulation intended for marketing in Australia.

Bioequivalence of different dosage forms and strengths

Exposure is similar for different concentrations of semaglutide in the range 1 mg/mL to 10 mg/mL (Study NN9535-3679, Section 19.1.1.3, and Study NN9535-3687 (Section 19.1.1.5)). At a dose of 0.8 mg semaglutide, equivalence between semaglutide 1 mg/mL, 3 mg/mL and 10 mg/mL was demonstrated for $AUC_{0-\infty}$. but not for C_{max}.

Bioequivalence has been demonstrated between synthetic semaglutide and recombinant semaglutide at a concentration of 1.34 mg/mL and dose of 0.5 mg (Study NN9535-4010, Section 19.1.1.4).

Bioequivalence to relevant registered products

Study NN9536-4590 (Section 19.1.1.1) compared the semaglutide Formulation D with the DV3396 pen-injector with Formulation B with the PDS290 pen-injector. The two formulations were bioequivalent at the 2.4 mg dose level for AUC but not for C_{max} (Table 19.1.1.1.1). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}168h}$ was 1.0539 (1.0003 to 1.1104). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.1556 (1.0800 to 1.2365). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.1.1).

The two formulations were bioequivalent at the 1 mg dose level for AUC and C_{max} (Table 19.1.1.1.2). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}168h}$ was 1.0357 (0.9860 to 1.0879). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.1014 (1.0202 to 1.1891). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.1.2).

In Study NN9535-4588 (Section 19.1.1.2), comparing the semaglutide Formulation D for the DV3396 Pen-Injector and the Formulation B for the PDS290 semaglutide Pen-Injector, the two formulations were bioequivalent at the 1 mg dose level for AUC but not for C_{max} (Table 19.1.1.2.1). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}840h}$ was 1.10 (1.04 to 1.17). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.27 (1.20 to 1.34). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.2.1).

The two formulations were bioequivalent at the 0.25 mg dose level for AUC and C_{max} (Table 19.1.1.2.2). The ratio (90% CI) Formulation D/formulation B for AUC_{0-168h} was 1.08 (1.03 to 1.13). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.10 (1.05 to 1.15). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.2.2).

Influence of food

NA.

Dose proportionality

In Study NN9536-4590 (Section 19.1.1.1) there was dose proportionality between the 1 mg and 2.4 mg dose levels: ratio (95% CI), 2.4 mg/ 1 mg, 2.57 (2.49 to 2.65) for AUC and 2.57 (2.42 to 2.73) for C_{max}.

In Study NN9535-1820 (Section 19.1.1.6), a dose escalation trial, dose proportionality was demonstrated in the dose range 10, 15 and 20 µg/kg.

Bioavailability during multiple-dosing

NA.

Effect of administration timing

NA.

4.2.2.3. Distribution

Volume of distribution

Study NN9536-4590 (Section 19.1.1.1) for Formulation D, geometric mean (CV%) Vss/F was 9.8 (23.4) L.

Plasma protein binding

In Study NN9535-3651 (Section 19.1.1.11) fraction unbound assessed with *in vitro* assay was less than 0.5% for all subjects

Erythrocyte distribution

NA.

Tissue distribution

A volume of distribution of 9.8 L indicates limited tissue distribution for semaglutide.

4.2.2.4. Metabolism

Interconversion between enantiomers

NA.

Sites of metabolism and mechanisms / enzyme systems involved

In the mass balance study, Study NN9535-3789 (Section 19.1.1.7), the total recovery (measured as the total excretion) of [$_3$H]-semaglutide related material was 75.1% of the administered dose: 53.0% in urine, 18.6% in faeces and 3.2% in expired air. In plasma, semaglutide was the primary component circulating at all timepoints. Six metabolites were detected in plasma, each accounting for 0.4−7.7% of the semaglutide-related material based on AUC. Semaglutide was extensively metabolised prior to elimination. In urine, 22 components were detected, and one component was considered likely to be semaglutide (3.1% of dose). In faeces, 7 minor metabolites were detected. [$_3$H]-semaglutide related material was primarily distributed in the plasma compartment.

Non-renal clearance

NA.

Metabolites identified in humans: active and other

Semaglutide is metabolised to multiple metabolites that appear to be inactive. Semaglutide is a peptide, and would be expected to have similar metabolism to other endogenous and exogenous peptides.

Pharmacokinetics of metabolites

NA.

Consequences of genetic polymorphism

NA.

4.2.2.5. Excretion

Routes and mechanisms of excretion

In Study NN9536-4590 (Section 19.1.1.1) CL, t½, Tmax and Vss were similar for both formulations at the 2.4 mg dose level (Table 19.1.1.1.3). For Formulation D, geometric mean (CV%) CL/F was 0.040 (22.6) L/h, t½ was 155 (9.8) h, and Vss/F was 9.8 (23.4) L. Median (range) T_{max} was 24 (3 to 48) h. At the 1 mg dose level, for Formulation D, geometric mean (CV%) CL/F was 0.042 (20.7) L/h and median (range) T_{max} was 18 (6 to 42) h. There was dose proportionality between the 1 mg and 2.4 mg dose levels: ratio (95% CI), 2.4 mg/ 1 mg, 2.57 (2.49 to 2.65) for AUC and 2.57 (2.42 to 2.73) for C_{max}.

In Study NN9535-4588 (Section 19.1.1.2), the t½ of semaglutide was similar for the two formulations: mean (SD) 148 (13.82) h for formulation D and 151 (15.58) h for Formulation B (Table 19.1.1.2.3).

In Study NN9535-3687 (Section 19.1.1.5) the geometric mean of terminal t½ of s.c. semaglutide (range 143−152 hours) and i.v. semaglutide was comparable (137 hours).

Mass balance studies

As per Section 4.2.2.4.

Renal clearance

In the mass balance study, 3.1% of the dose was excreted unchanged in urine.

4.2.2.6. Intra and inter individual variability of pharmacokinetics

The CV% for CL/F was 20.7, indicating inter-individual variability to be typical for a peptide drug.

4.2.3. Pharmacokinetics in the target population

The pharmacokinetic studies for TRADENAME (semaglutide) were performed in populations typical of those intended for marketing in Australia.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

In Study NN9535-3651 (Section 19.1.1.11) exposure of semaglutide was not affected by hepatic impairment. Pharmacokinetic properties for the hepatically impaired subjects were similar to those of the subjects with normal hepatic function.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

In Study NN9535-3616 (Section 19.1.1.10) the 'no-effect' criterion was met for all renal impairment groups, except for the severe renal impairment group, as compared to the group with normal renal function. The $AUC_{0-\infty}$ for the group with severe renal impairment was approximately 22% higher than for the group with normal renal function. There was no clinically relevant relationship was found between creatinine clearance (CLCR) and either exposure (AUC_{0-}

$_{\infty}$) or maximum concentration (C_{max}). Based on these results, a dose adjustment of semaglutide may not be warranted in subjects with renal impairment.

4.2.4.3. Pharmacokinetics according to age

NA.

4.2.4.4. Pharmacokinetics related to genetic factors

NA.

4.2.4.5. Pharmacokinetics in other special population / with other population characteristic

There were no differences in pharmacokinetic properties between Caucasian and Japanese subjects (Study NN9535-3633, Section 19.1.1.8). The exposure and maximum concentration of semaglutide at steady state was comparable between Japanese and Caucasian subjects, with an expected dose-dependent increase s47 [redacted]

4.2.5. Population pharmacokinetics

4.2.5.1. Modelling Report for Data from Study NN9536-4153

Modelling of data from Study NN9536-4153 (Section 6.2) was performed (Section 19.1.3.1). The covariate analysis indicated body weight was the most important covariate influencing exposure (Figure 19.1.3.1.1). The concentration response relationship was described by the model (Figure 19.1.3.1.2). An Emax relationship was described for the proportion of patients achieving a 5% weight loss (Figure 19.1.3.1.3). The proportion of patients discontinuing due to AEs increased with exposure to semaglutide (Figure 19.1.3.1.4).

4.2.5.1. Modelling Report for Data from Study NN9536-4373 and Study NN9536-4374

Modelling of data from Study NN9536-4373 (Section 7.2.1) and Study NN9536-4374 (Section 7.2.2) was performed (Section 19.1.3.2). For a typical participant, CL/F was estimated as 0.0475 L/h and V/F as 12.4 L. Dose proportionality was demonstrated in the dose range 0.25 to 2.4 mg (Figure 19.1.3.2.1). Interindividual variability in CL/F in the final model was 18.7 CV%. Body weight had a significant effect on exposure (Figure 19.1.3.2.2). The presence of antibodies did not affect the PK of semaglutide.

4.2.6. Pharmacokinetic interactions

4.2.6.1. Oral Contraceptive pill

Semaglutide increased exposure to ethinylestradiol by 11% and levonorgestrel by 20% (Study NN9535-3819, Section 19.1.1.12). However, this is not considered to be clinically significant.

4.2.6.2. Metformin

Semaglutide had no significant effect on exposure to metformin (Study NN9535-3817, Section 19.1.1.13).

4.2.6.3. Warfarin

Semaglutide had no significant effect on exposure to either *r*-warfarin or *s*-warfarin (Study NN9535-3817, Section 19.1.1.13).

4.2.6.4. Atorvastatin

Semaglutide did not have a significant effect on exposure to atorvastatin (Study NN9535-3818 Section 19.1.1.14).

4.2.6.5. Digoxin

Semaglutide did not have a significant effect on exposure to digoxin (Study NN9535-3818, Section 19.1.1.14).

4.2.7. Clinical implications of *in vitro* findings

NA.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of TRADENAME (semaglutide) have been adequately characterised. This includes bioequivalence studies for the new formulation.

The Sponsor has examined dose-proportionality for the intended dose range in the titration phase. This indicates dose-proportionality for overall exposure (AUC) but not for peak exposure (C_{max}). However, this would not be expected to result in any differences in effect during the titration phase.

The Sponsor has not examined the PK for all the formulations intended for marketing, and that would be used in the titration phase. These are:

- TRADENAME (semaglutide) 0.25 mg/dose (0.5 mg/mL)
- TRADENAME (semaglutide) 0.5 mg/dose (1.0 mg/mL)
- TRADENAME (semaglutide) 1 mg/dose (2.0 mg/mL)
- TRADENAME (semaglutide) 1.7 mg/dose (2.27 mg/mL)
- TRADENAME (semaglutide) 2.4 mg/dose (3.2 mg/mL)

However, in Modelling Report 3, dose proportionality was demonstrated for the doses used in the Phase IIIa clinical trials. In the opinion of the Clinical Evaluator dose-proportionality can be extrapolated to the new formulations.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Table 2. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	Synopsis
Primary Pharmacology	Effect on appetite and food intake	s47	s47
Secondary Pharmacology	Effect on gastric emptying	Study NN9536-4455	Section 19.1.2.1
	s47	s47	s47
	Hypoglycaemia responsiveness	s47	s47
	Effect on cardiac repolarisation	s47	s47
Gender other genetic and Age Related Differences in PD Response	Effect of ethnic characteristic	s47	s47
PD Interactions	Warfarin	Study NN9535-3817,	Section 19.1.1.13

There were no pharmacodynamic results excluded from consideration.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Semaglutide acts as a GLP-1 receptor agonist (GLP-1 RA) that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

In Study NN9536-4455 (Section 19.1.2.1) energy intake at the end of study *ad libitum* lunch was lower in the semaglutide group: treatment difference (95% CI), semaglutide – placebo, -940 (-1364 to -516) p <0.0001. There were no significant differences between semaglutide and placebo in hunger or satiety ratings, but there was a decrease in hunger and increase in satiety in both groups from baseline to end of study (Figure 19.1.2.1.2). The Control of Eating Questionnaire (COEQ) demonstrated improvement in food cravings in the semaglutide group (Figure 19.1.2.1.3). There was a mean decrease in body weight of 9.9% (10.4 kg) in the semaglutide group and 0.4% (0.4 kg) in the placebo.

In Study NN9535-3685 (Section 19.1.2.3), at a dose of 1.0 mg weekly, *ad libitum* energy intake was lower for subjects when treated with semaglutide compared with placebo. Fasting and postprandial appetite sensations were lower for subjects when treated with semaglutide compared with placebo. Postprandial increments of the composite endpoint, overall appetite

score, was however not significantly different between treatments. Control of eating and food cravings was overall improved for subjects when treated with semaglutide compared with placebo. Relative preference for fat food items was lower and relative preference for sweet food items was higher for subjects when treated with semaglutide compared with placebo.

5.2.2.2. Secondary pharmacodynamic effects

In Study NN9536-4455 (Section 19.1.2.1), a study of the effect of semaglutide 2.4 mg once weekly on gastric emptying in participants with obesity, there was no significant effect of on gastric emptying (Figure 19.1.2.1.1). There was no effect on exposure to paracetamol: ratio (95% CI) semaglutide/placebo 1.08 (1.02 to 1.14) for paracetamol $AUC_{0\text{-}5h}$, and 0.94 (0.82 to 1.07) for C_{max}. There was no delay in absorption: mean T_{max} for semaglutide was 0.45 h and for placebo was 0.44 h; ratio (95% CI), semaglutide/placebo, 1.02 (0.88 to 1.19).

In s47 [redacted] at a dose of 1.0 mg weekly, overall gastric emptying was comparable between semaglutide and placebo. Fasting, as well as postprandial, glucose and lipid metabolism were improved for subjects when treated with semaglutide compared with placebo.

In s47 [redacted] in patients with T2DM, semaglutide administered as multiple 1.0 mg s.c. doses improved insulin secretion, and increased the maximal insulin secretory capacity as compared to placebo as measured by the arginine stimulation test. Semaglutide reduced postprandial glucose and glucagon, and increased C-peptide as compared to placebo in the 24-hour profiles. β-cell responsiveness was increased after treatment with semaglutide compared to placebo, and at end-of-treatment it closely resembled that of healthy subjects as measured by the graded glucose infusion test.

In s47 [redacted] semaglutide administered as multiple 1.0 mg s.c. doses, did not alter physiological responses to hypoglycaemia. However, semaglutide lowered the overall hypoglycaemic symptoms score and hypoglycaemic awareness and resulted in a similar decrease in cognitive function. Overall, treatment with semaglutide did not appear to affect the ability to recover from hypoglycaemia compared with placebo treatment.

In s47 [redacted] a thorough QT study, semaglutide did not result in an unacceptable prolongation in cardiac repolarisation compared to placebo

5.2.3. Time course of pharmacodynamic effects

NA.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

A dose response relationship was demonstrated in the Phase II dose-finding study (Study NN9536-4153, Section 6.2). An Emax relationship was described for the proportion of patients achieving a 5% weight loss (Figure 19.1.3.1.3). The proportion of patients discontinuing due to AEs increased with exposure to semaglutide (Figure 19.1.3.1.4).

Modelling of data from Study NN9536-4373 (Section 7.2.1) and Study NN9536-4374 (Section 7.2.2) was performed and also demonstrated concentration response relationship. The exposure-response relationship for weight loss (%) for this concentration range appeared to be linear (Figure 19.1.3.2.3). However, the responder analysis indicated an E_{max} relationship (Figure 19.1.3.2.4). The proportion of patients reporting GI AEs also demonstrated an Emax relationship (Figure 19.1.2.3.5). The report concluded that the benefit of a larger weight loss with 2.4 mg compared to 1.0 mg semaglutide was associated with only marginally increased risk in terms of GI adverse events.

5.2.5. Genetic, gender and age-related differences in pharmacodynamic response

A dose-dependent weight loss was shown for semaglutide at steady state for both Japanese and Caucasian subjects s47 [redacted]

5.2.6. Pharmacodynamic interactions

Semaglutide had no significant effect on exposure, as measured by INR, when co-administered with warfarin (Study NN9535-3817, Section 19.1.1.13).

5.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamics of TRADENAME (semaglutide) have been adequately characterised. Semaglutide has a dose-dependent effect on weight loss. Semaglutide decreases appetite, decrease food intake and decreased food cravings. An E_{max} relationship between concentration and the proportion of responders has been demonstrated.

Semaglutide has a beneficial effect on β-cell function. The improvement in glycaemic and weight control has been previously documents in patients with T2DM.

Semaglutide did not have adverse effects on gastric emptying or cardiac repolarisation.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The pharmacokinetic studies indicate dose-proportional exposure to semaglutide, which supports the proposed titration regimen.

6.2. Phase II dose finding studies

Study NN9536-4153 was a 52-week, randomised, double-blind, placebo-controlled, 16-armed, parallel group, multi-centre, multinational trial in subjects with obesity without diabetes mellitus. The primary objective of the study was to assess and compare the dose-response of five doses of once-daily semaglutide versus placebo in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus. The study was conducted at 71 sites in eight countries: Australia (5 sites), Belgium (5), Canada (9), Germany (6), Israel (7), Russian Federation (10), the UK (8) and the US (21). The study was conducted from October 2015 to April 2017.

The inclusion criteria included:

- Male or female, age ≥18 years at the time of signing informed consent
- BMI ≥30.0 kg/m^2
- Stable body weight i.e. less than 5 kg self-reported change within 90 days before screening
- At least one unsuccessful weight loss attempt per investigator judgement

The exclusion criteria included:

- HbA1c ≥6.5% at screening or diagnosed with type 1 or type 2 diabetes mellitus
- Hypothyroidism/hyperthyroidism defined as TSH >6 mIU/L or <0.4 mIU/L
- Treatment with glucose lowering agent(s) within 90 days before screening
- Screening calcitonin ≥50 ng/L (pg/mL)
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN-2)
- History of pancreatitis (acute or chronic)
- Obesity induced by an endocrinologic disorder (e.g. Cushing Syndrome)
- Treatment with any medication within 90 days before screening that based on investigator's opinion may cause significant weight change
- Diet attempts using herbal supplements or over-the-counter medications within 90 days before screening

- Participation in an organised weight reduction program (e.g. WeightWatchers®) within 90 days before screening
- Treatment with orlistat, zonisamide, topiramate, phentermine, lorcaserin, bupropion, naltrexone, GLP-1 RAs alone or in combination prescribed for weight loss or any other medication that could promote weight loss in the opinion of the investigator within 90 days before screening
- Previous surgical treatment for obesity (liposuction and/or abdominoplasty is allowed if performed >1 year before screening)
- A Patient Health Questionaire-9 (PHQ-9) score of ≥15 at screening or randomisation
- Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg at screening
- History or presence of malignant neoplasms within the last 5 years before screening (except basal and squamous cell skin cancer, polyps and in-situ carcinomas)

The study treatments were:

1. Semaglutide 0.05 mg/day
2. Semaglutide 0.1 mg/day, dose escalation from 0.05 mg after 4 weeks
3. Semaglutide 0.2 mg/day, dose escalation after 4 weeks at each step
4. Semaglutide 0.3 mg/day, dose escalation after 4 weeks at each step
5. Semaglutide 0.4 mg/day, dose escalation after 4 weeks at each step
6. Semaglutide 0.3 mg/day, dose escalation after 2 weeks at each step
7. Semaglutide 0.4 mg/day, dose escalation after 2 weeks at each step
8. Liraglutide 3.0 mg/day, dose escalation each week at each step
9. Matching placebo

The treatment regimens and dose escalations are summarised in Figure 6.2.1. All treatments were administered subcutaneously. There was a 1-week screening period, 52 week treatment period and a 7 week follow-up period. Subjects in all treatment arms received nutritional and physical activity counselling, on a monthly basis, beginning at the randomisation visit.

There were 957 subjects randomised to treatment: 102 or 103 in each active treatment group and 136 in the placebo pool (Table 6.2.1). There were 777 (81.2%) participants who completed the treatment period. There were 65 (6.8%) participants withdrawn from the trial. All the participants were included in the full analysis set and the safety analysis set.

There were 619 (64.7%) females, 338 (35.3%) males, 700 (73.1%) were White, and 61 (6.4%) were Black or African American. The age range was 18 to 86 years and the BMI range was 29.7 to 80.3 kg/m^2.

There was a dose related decrease in body weight, with the greatest decrease in the 0.4 mg/day group (Figure 6.2.2). The decrease in body weight continued over time in the higher dose groups but flattened out in the lower dose groups (Figure 6.2.3). The decrease in body weight was 13.84% in the 0.4 mg/day slow titration group, 16.29% in the 0.4 mg fast titration group and 7.76% in the liraglutide group (Figure 6.2.4). The difference in % change in body weight (95% CI), semaglutide – placebo, was -3.70 (-6.55 to -0.85) %, p = 0.0055, for 0.05 mg/day; -6.32 (-9.16 to -3.49) %, p <0.0001, for 0.1 mg/day; -9.31 (-12.15 to -6.46) %, p <0.001, for 0.2 mg/day; -8.88 (-11.72 to -6.03) %, p <0.001, for 0.3 mg/day; and -11.55 (-14.38 to -8.72) %, p <0.001, for 0.4 mg/day (Figure 6.2.5). There was superiority for the semaglutide ≥0.2 mg/day compared with liraglutide 3.0 mg: the difference in % change in body weight (95% CI), semaglutide – liraglutide, was -3.83 (-6.18 to -1.49) %, p = 0.0013, for 0.2 mg/day; -3.41 (-5.75 to -1.06) %, p = 0.0044, for 0.3 mg/day; and -6.08 (-8.41 to -3.75) %, p <0.001, for 0.4 mg/day.

The dose-response analysis indicated a linear relationship for % body weight loss up to the 0.4 mg/day dose level (Figure 6.2.6). However, the analysis of 5% responder rates demonstrated an E_{max} relationship (Figure 6.2.7). There was a trade-off between discontinuers and responders that would suggest optimising the dose between 0.3 to 0.4 mg/day.

The responder analysis for 5% weight loss indicated superiority for all doses of semaglutide compared with placebo, but no significant difference between the doses, despite increased response rate with increasing dose (Figure 6.2.8). The responder analysis for 10% weight loss indicated superiority for semaglutide compared with placebo at doses ≥0.1 mg/d, and similar responses for 0.2 mg/day, 0.3 mg/day and 0.4 mg/day (Figure 6.2.9).

The change from baseline to Week 52 in waist circumference was similar to the change in % body weight (Figure 6.2.10). There was a significant decrease in waist circumference at all semaglutide dose levels, with an increasing effect with increasing dose (Figure 6.2.11). There was a similar pattern for hip circumference and for BMI. There were decreases in SBP and DBP relative to placebo, but these were not dose-related. There were improvements in the SF-36 physical score in the semaglutide that were not statistically significant. There were decreases in VLDL cholesterol in the semaglutide groups relative to placebo that were not dose-related. Nutritional compliance scores were higher in the higher dose semaglutide groups.

Modelling of data from Study NN9536-4153 (Section 6.2) was performed. The concentration response relationship was described by the model (Figure 19.1.3.1.2). An Emax relationship was described for the proportion of patients achieving a 5% weight loss (Figure 19.1.3.1.3). The proportion of patients discontinuing due to AEs increased with exposure to semaglutide (Figure 19.1.3.1.4).

6.3. Phase III pivotal studies investigating more than one dose regimen

Study NN9536-4374 (Section 7.2.2) compared the 1.0 mg and 2.4 mg weekly dose levels with placebo. There was superior weight loss with the 2.4 mg dose level compared with the 1.0 mg dose level, and placebo.

Modelling of data from Study NN9536-4373 (Section 7.2.1) and Study NN9536-4374 (Section 7.2.2) was performed. The exposure-response relationship for weight loss (%) for this concentration range appeared to be linear (Figure 19.1.3.2.3). However, the responder analysis demonstrated an E_{max} relationship (Figure 19.1.3.2.4). The proportion of patients reporting GI AEs also demonstrated an E_{max} relationship (Figure 19.1.2.3.5). The report concluded that the benefit of a larger weight loss with 2.4 mg compared to 1.0 mg semaglutide was associated with only marginally increased risk in terms of GI adverse events.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The Sponsor has obtained adequate data to inform the dosage selection. The optimal dosing was defined using E_{max} models, and by balancing efficacy against tolerability. The proposed dose-titration, with initiation of treatment, is also supported by these data.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The dossier contains four Phase IIIa studies in support of efficacy:

- Study NN9536-4373 (STEP 1) (Section 7.2.1)
- Study NN9536-4374 (STEP 2) (Section 7.2.2)
- Study NN9536-4375 (STEP 3) (Section 7.2.3)
- Study NN9536-4376 (STEP 4) (Section 7.2.4)

7.2. Pivotal or main efficacy studies

7.2.1. Study NN9536-4373

7.2.1.1. Study design, objectives, locations and dates

Study NN9536-4373 was randomised, double-blind, two-armed, parallel group, placebo-controlled study of the effect on body weight of semaglutide as an adjunct to reduced-calorie diet and increased physical activity. The study had a 68-week main phase and a 52-week off-treatment extension phase. The study was conducted at 129 sites in 16 countries: Argentina (5 sites), Belgium (5), Bulgaria (5), Canada (7), Denmark (1), Finland (2), France (7), Germany (13), India (13), Japan (5), Mexico (3), Poland (4), Russian Federation (8), Taiwan (1), United Kingdom (10) and US (40). The study was conducted from June 2018 to April 2020.

7.2.1.2. Inclusion and exclusion criteria

The study included:

- Males and females, aged ≥18 years
- BMI ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease
- History of at least one self-reported unsuccessful dietary effort to lose body weight

The exclusion criteria included:

- Glycaemia-related:
  - HbA1c ≥48 mmol/mol (6.5%)
  - History of type 1 or type 2 diabetes mellitus
  - Treatment with glucose-lowering agent(s) within 90 days before screening
  - Treatment with a GLP-1 receptor agonist within 180 days before screening
- Obesity-related:
  - A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening
  - Treatment with any medication for the indication of obesity within the past 90 days
  - Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed > 1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening
  - Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) >6.0 mIU/L or <0.4 mIU/L as measured by the central laboratory at screening
- Mental health:
  - History of major depressive disorder within 2 years before screening
  - Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
  - A Patient Health Questionnaire-9 (PHQ-9) score of ≥15 at screening
  - A lifetime history of a suicidal attempt
  - Suicidal behaviour within 30 days before screening
  - Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening
- General safety:
  - Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 days before screening
  - Presence of acute pancreatitis within the past 180 days prior to the day of screening
  - History or presence of chronic pancreatitis
  - Calcitonin ≥100 ng/L as measured by the central laboratory at screening

- Personal or first-degree relative(s) history of MEN-2 or medullary thyroid carcinoma (MTC)
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <15 ml/min/1.73 m^2 as defined by KDIGO 201268 by the central laboratory at screening
- History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ were allowed
- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening
- Subject presently classified as being in New York Heart Association (NYHA) Class IV
- Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method

7.2.1.3. Study treatments

The study treatments were:

1. Semaglutide: initiated at 0.25 mg and increased every 4 weeks in the steps 0.5, 1.0, 1.7 and 2.4 mg/week. The maintenance dose of 2.4 mg/week was reached after 16 weeks. If 2.4 mg/week was not tolerated, then the dose could be reduced to 1.7 mg/week.
2. Placebo

All patients were also treated with a reduced calorie diet (a 500 kcal deficit/day relative to the estimated Total Energy Expenditure [TEE]) and increased physical activity [150 min per week]).

The treatments were administered with a 3 mL PDS290 pre-filled pen-injector.

7.2.1.4. Efficacy variables and outcomes

The primary efficacy outcome measures were:

- Change from baseline at week 0 to week 68 in body weight (%)
- Patients who after 68 weeks achieve body weight reduction ≥5% from baseline (week 0)

The confirmatory secondary efficacy outcome measures were:

- Patients who after 68 weeks achieve body weight reduction ≥10% from baseline
- Patients who after 68 weeks achieve body weight reduction ≥15% from baseline
- Change from baseline at week 0 to week 68 in SBP (mmHg)
- Change from baseline at week 0 to week 68 in physical functioning score (SF-36)
- Change from baseline at week 0 to week 68 in physical function domain (5-items) score (IWQOL-Lite-CT)
- Waist circumference (cm)

The supportive secondary efficacy outcome measures were:

- Patients who after 68 weeks achieve body weight reduction ≥20% from baseline (week 0)
- Change from baseline at week 0 to week 68 in body weight (kg)
- Change from baseline at week 0 to week 68 in BMI (kg/m^2)
- Change from baseline at week 0 to week 68 in DBP (mmHg)#
- Change from baseline at week 0 to week 68 in lipids (mmol/L and mg/dL): total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids, triglycerides
- Change from baseline at week 0 to week 68 in CRP (mg/L)
- Change from baseline at week 0 to week 68 in PAI-1 activity (AU/mL)
- Change from baseline at week 0 to week 68 in SF-36
- Change from baseline at week 0 to week 68 in IWQOL-Lite-CT

- Responders for SF-36 physical functioning score
- Responders for IWQOL-Lite-CT physical function domain (5-items) score
- Glucose metabolism: HbA1c (% and mmol/mol), FPG (mmol/L and mg/dL) and fasting serum insulin (mIU/L)
- Soluble leptin receptor (ng/mL) and leptin (ng/mL)
- Body composition (as assessed by DEXA in a subset of patients): total fat mass (kg and %); lean body mass (kg and %); and visceral fat mass (kg and %)
- Body weight (kg and %) in the DEXA subset of subjects

The exploratory endpoints were:

- Glycaemic status: normo-glycaemia, pre-diabetes, T2DM
- Use of medication for hypertension and dyslipidaemia
- Work productivity: SPS-6, total score
- Treatment discontinuation and time to treatment discontinuation
- Change from baseline at week 0 to week 68 in fatty liver index score category (<30, ≥30 and <60, ≥60)
- Urinary incontinence: change from baseline at week 0 to week 68 in ICIQ-UI-SF, sum score (assessed in female subjects)
- Diet and physical activity: number of days per week with at least one entry in the food diary from baseline at week 0 to week 68; and number of minutes per week of physical activity from baseline at week 0 to week 68

The safety outcome measures were: AEs, vital signs, clinical laboratory tests including amylase, lipase and calcitonin.

The schedule of study visits is displayed in Table 7.2.1.1.

7.2.1.5. Randomisation and blinding methods

Randomisation was in the ratio 2:1 for semaglutide:placebo, by IWRS. Active and placebo treatments were identical in appearance.

7.2.1.6. Analysis populations

The Full Analysis Set (FAS) included all randomised patients according to the intention-to-treat (ITT) principle.

The safety analysis set (SAS) included all randomised patients exposed to at least one dose of randomised treatment, and patients were analysed according to treatment received.

The DEXA analysis set (DXA) included patients in the sub-population of FAS that had a DEXA scan performed at baseline and where the DEXA scan was found to be of an acceptable quality by the imaging laboratory.

7.2.1.7. Sample size

The sample size calculation was based on all the primary and confirmatory secondary endpoints. The assumptions are summarised in Table 7.2.1.2. The power for all the endpoints was >99% and α was 0.05.

7.2.1.8. Statistical methods

The analysis model for % weight change was a linear regression (ANCOVA) of % weight change with randomised treatment as a factor and baseline body weight (kg) as covariate.

The analysis model for the 5% responder endpoint was a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate.

Missing data were imputed using retrieved subjects from a linear regression model and using multiple imputation (RD-MI).

Multiplicity was addressed using a hierarchical approach to hypothesis testing (Table 7.2.1.2).

7.2.1.9. Participant flow

There were 2303 patients screened and 1961 were randomised and exposed to treatment: 1306 to semaglutide and 655 to placebo (Table 7.2.1.3). All randomised patients were included in the analysis. There were 1083 (82.9%) patients in the semaglutide group and 508 (77.6%) in the placebo who completed 68 weeks of treatment. There were 91 (7.0%) patients in the semaglutide group and 21 (3.2%) in the placebo who discontinued trial product because of AE.

There were 140 patients in the DEXA subpopulation: 95 in the semaglutide group and 45 in the placebo.

7.2.1.10. Major protocol violations/deviations

There were 685 important protocol deviations, but none were considered to have an impact on the data analysis.

7.2.1.11. Baseline data

There were 1453 (74.1%) females and 508 (25.9%) males (Table 7.2.1.4). There were 1472 (75.1%) White patients, 261 (13.3%) Asian and 111 (5.7%) Black or African American. The age range was 18 to 86 years and the BMI range was 26.5 to 83.0 kg/m^2 (Table 7.2.1.5). Comorbidities included dyslipidaemia in 37.0% patients, hypertension in 36.0%, knee osteoarthritis in 14.0%, obstructive sleep apnoea in 11.7%, asthma/chronic obstructive pulmonary disease in 11.6%, non-alcoholic fatty liver disease in 8.3% and polycystic ovarian syndrome in 6.6% of the female subjects. The two treatment populations were similar in demographic characteristics.

There were 106 (75.7%) females and 34 (24.3%) males in the DEXA subpopulation. The age range was 19 to 82 years and the BMI range was 28.1 to 47.0 kg/m^2.

Of the treatment completers, 89.6% of subjects reached the maintenance dose of 2.4 mg semaglutide at their last dose, whereas 98.0% of subject reached an equivalent volume of placebo.

7.2.1.12. Results for the primary efficacy outcome

Semaglutide was superior to placebo for both primary efficacy outcome measures (Table 7.2.1.6). The mean (SD) change in body weight from baseline to Week 68 was -15.1 (10.1) % for semaglutide and -2.8 (6.5) % for placebo; treatment difference (95% CI), semaglutide – placebo, -12.44 (-13.37 to -11.51) %, p <0.0001. Weight loss occurred through to Week 60, and then appeared to stabilise (Figure 7.2.1.1).

There was a higher proportion of patients in the semaglutide group achieving body weight loss ≥5% at Week 68: 978 (92.4%) patients in the semaglutide group and 165 (33.1%) in the placebo; OR (95% CI), semaglutide / placebo, 11.22 (8.88 to 14.19), p <0.0001.

The sensitivity analyses, using alternative methods of imputation, confirmed the primary statistical analysis.

7.2.1.13. Results for other efficacy outcomes

Confirmatory secondary efficacy outcome measures:

- There was a higher proportion of patients in the semaglutide group achieving body weight loss ≥10% at Week 68: 792 (74.8%) patients in the semaglutide group and 59 (11.8%) in the placebo; OR (95% CI), semaglutide / placebo, 14.68 (11.08 to 19.44), p <0.0001.
- There was a higher proportion of patients in the semaglutide group achieving body weight loss ≥15% at Week 68: 580 (54.8%) patients in the semaglutide group and 25 (5.0%) in the placebo; OR (95% CI), semaglutide / placebo, 19.26 (12.89 to 28.76), p <0.0001.
- The mean (SD) change waist circumference from baseline to Week 68 was -15.0 (9.1) cm for semaglutide and -4.8 (6.7) cm for placebo; treatment difference (95% CI), semaglutide –

placebo, -9.42 (-10.30 to -8.53) cm, p <0.0001. Waist circumference decreased through to Week 60, and then appeared to stabilise (Figure 7.2.1.2).

- SBP decreased to a greater extent in the semaglutide group compared to placebo: mean (SD) change from baseline to Week 68 -7 (14) mmHg in the semaglutide group and -1 (13) mmHg in the placebo; treatment difference (95% CI) -5.10 (-6.34 to -3.87), p <0.0001 (Figure 7.2.1.3).
- There was improvement in SF-36 Physical Functioning in the semaglutide group relative to placebo. The mean (SD) change in SF-36 Physical Functioning from baseline to Week 68 was 2.3 (6.8) for semaglutide and 0.4 (7.4) for placebo: treatment difference (95% CI), semaglutide – placebo, 1.80 (1.18 to 2.42), p <0.0001.
- There was improvement in IWQOL-Lite-CT Physical Function in the semaglutide group relative to placebo. The mean (SD) change in SF-36 Physical Functioning from baseline to Week 68 was 15.6 (20.6) for semaglutide and 6.5 (21.1) for placebo: treatment difference (95% CI), semaglutide – placebo, 9.43 (7.50 to 11.35), p <0.0001.

Supportive secondary efficacy outcome measures:

- There was a higher proportion of patients in the semaglutide group achieving body weight loss ≥20% at Week 68: 369 (34.8%) patients in the semaglutide group and 10 (2.0%) in the placebo; OR (95% CI), semaglutide / placebo, 26.89 (14.18 to 50.96).
- The mean (SD) absolute change in body weight from baseline to Week 68 was -13.7 (10.1) kg for semaglutide and -2.5 (7.4) kg for placebo; estimated treatment difference (95% CI), semaglutide – placebo, -12.71 (-13.68 to -11.74) kg, p<0.0001.
- The mean (SD) observed change in BMI from baseline to Week 68 was -6.3 (3.5) kg/m^2 for semaglutide and -1.2 (2.5) kg/m^2 for placebo; estimated treatment difference (95% CI), semaglutide – placebo, -4.61 (-4.96 to -4.27) kg/m^2, p<0.0001. There was sustained decrease in BMI from baseline to Week 60, which then stabilised (Figure 7.2.1.4).
- There was a halving of leptin concentrations in the semaglutide group. The geometric mean (CV) ratio at Week 68 compared to baseline for leptin concentrations was 0.52 (75.9) for semaglutide and 0.87 (52.7) for placebo; and for soluble leptin receptor concentrations was 1.07 (24.9) for semaglutide and 1.02 (22.2) for placebo.
- DBP decreased to a greater extent in the semaglutide group compared to placebo: mean (SD) change from baseline to Week 68 -3 (9) mmHg in the semaglutide group and -1 (9) mmHg in the placebo; treatment difference (95% CI) -2.41 (-3.25 to -1.57), p <0.0001 (Figure 7.2.1.3).
- With semaglutide, relative to placebo, there were statistically significant decreases in total cholesterol, LDL-cholesterol, VLDL-cholesterol, free fatty acids and triglycerides; and an increase in HDL-cholesterol (Figure 7.2.1.5). However, the absolute changes were small and the clinical significance of the changes is uncertain.
- The geometric mean (CV) ratio at Week 68 compared to baseline for hsCRP concentrations was 0.45 (128.2) for semaglutide and 0.84 (102.5) for placebo, estimated treatment ratio (95% CI) semaglutide/placebo, 0.56 (0.51 to 0.61), p <0.0001; and for PAI-1 concentrations was 1.15 (86.5) for semaglutide and 1.53 (77.3) for placebo, estimated treatment ratio (95% CI) semaglutide/placebo, 0.75 (0.71 to 0.79), p <0.0001.
- The number (%) of patients having an increase of 4.3 in SF-36 Physical Functioning from baseline to Week 68 was 278 (26.6%) patients in the semaglutide group and 97 (17.1%) in the placebo; OR (95% CI), semaglutide / placebo, 2.11 (1.53 to 2.91), p <0.0001.
- The individual components, and overall score, of the SF-36 favoured semaglutide over placebo (Figure 7.2.1.6).
- The number (%) of patients having an increase of 20 in IQUOL-Lite-CT Physical Function from baseline to Week 68 was 473 (39.6%) patients in the semaglutide group and 145 (25.6%) in the placebo; OR (95% CI), semaglutide / placebo, 2.46 (1.90 to 3.18), p <0.0001.
- All the components of the IQUOL-Lite-CT favoured semaglutide over placebo (Figure 7.2.1.7).

- The mean (SD) observed change in HbA_{1c} from baseline to Week 68 was -5.5 (3.1) mmol/mol for semaglutide and -1.98 (2.9) mmol/mol for placebo; estimated treatment difference (95% CI), semaglutide – placebo, -3.20 (-3.53 to -2.87) mmol/mol, p<0.0001.
- The mean (SD) observed change in FPG from baseline to Week 68 was -0.6 (0.6) mmol/L for semaglutide and 0.0 (0.7) mmol/L for placebo; estimated treatment difference (95% CI), semaglutide – placebo, -0.44 (-0.50 to -0.37) mmol/L, p<0.0001.
- The geometric mean ratio (CV) observed change in fasting serum insulin from baseline to Week 68 was 0.71 (61.2) for semaglutide and 0.91 (55.5) for placebo; treatment ratio (95% CI), semaglutide / placebo, 0.79 (0.74 to 0.83), p<0.0001.
- In the DEXA subgroup, in the semaglutide group there was a mean (SD) decrease in % total fat mass of 3.9 (5.4) %, an increase in % lean body mass of 3.4 (5.1) % and a decrease in % visceral fat mass of 2.2 (4.4) % (Table 7.2.1.7). There was no significant change in these parameters in the placebo group.

Exploratory endpoints:

- There was a shift towards improvement in Fatty Liver Index in the semaglutide group relative to placebo (Figure 7.2.1.8).
- The number (%) patients ceasing antihypertensive medication by Week 68 was 83 (6.8%) patients in the semaglutide group and 22 (3.8%) in the placebo.
- The number (%) patients ceasing lipid-lowering medication by Week 68 was 39 (3.2%) patients in the semaglutide group and 14 (2.4%) in the placebo (Figure 7.2.1.9).
- There was no difference between the treatments in Stanford Presenteeism Scale-6 (SPS-6).
- There was no difference between the treatments in International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (SPS-6).
- Shifts in glycaemic category favoured semaglutide over placebo (Figure 7.2.1.10).

7.2.1.14. Evaluator commentary

The design and conduct of Study NN9536-4373 was appropriate. The patient population was representative of the target population in Australia, and the results are therefore generalisable.

The titration and dosing regimens were the same as those proposed for marketing in Australia. However, the formulations (specifically concentrations) used in titration were different to those proposed for marketing in Australia.

The background treatments were the same as those in the proposed indication: diet and exercise.

Bias was controlled through randomisation and blinding. Multiplicity was addressed. The statistical analysis was appropriate. The outcome measures were appropriate and measured different aspects of treatment effect.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. There were improvements in glycaemic control. There were significant improvements in quality of life and physical functioning. There were improvements in fatty liver index.

The DEXA sub-study demonstrated that the losses in weight, waist circumference and BMI were due to a decrease in adipose, and not to loss of another body component (such as water or muscle).

7.2.2. Study NN9536-4374

7.2.2.1. Study design, objectives, locations and dates

Study NN9536-4374 was a randomised, double-blind, double dummy, three arm, parallel group, placebo-controlled efficacy and safety trial in overweight or obese patients with T2DM. The study

examined two dose levels of semaglutide: 1 mg or 2.4 mg weekly. The study was conducted at 149 sites in 12 countries: Argentina (5 sites), Canada (10), Germany (9), Greece (6), India (18), Japan (12), Russian Federation (9), South Africa (6), United Arab Emirates (5), UK (10) and US (51). The study was conducted from June 2018 to May 2020.

7.2.2.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, age ≥18 years
- BMI ≥27.0 kg/m^2
- History of at least one self-reported unsuccessful dietary effort to lose body weight
- Diagnosed with T2DM ≥180 days prior to the day of screening
- Patient treated with either:
  - diet and exercise alone or stable treatment with metformin, SU, SGLT2i, glitazone as single agent therapy or
  - up to 3 OADs (metformin, SU, SGLT2i or glitazone) according to local label

  Any approved and marketed metformin, glitazone, SGLT-2 inhibitor or sulfonylurea product or combination products are allowed. Treatment with oral agents should be stable (same drug(s), dose and dosing frequency) for at least 90 days prior to screening.
- HbA_{1c} 7 to 10% (53 to 86 mmol/mol) (both inclusive)

The exclusion criteria included:

- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of <30 mL/min/1.73 m2 (<60 mL/min/1.73 m^2 in subjects treated with SGLT-2 inhibitor) according to CKD-EPI creatinine equation as defined by KDIGO 201285 by the central laboratory at screening
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified health care provider (e.g. optometrist) within the past 90 days prior to screening or in the period between screening and randomisation
- Treatment with a GLP-1 RA within 180 days prior to screening
- Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening
- Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) >6.0 mIU/L or <0.4 mIU/L as measured by central laboratory at screening
- History or presence of chronic pancreatitis
- Calcitonin ≥100 ng/L as measured by the central laboratory at screening
- Personal or first-degree relative(s) history of MEN2 or MTC
- History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ were allowed.
- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening
- Patient classified as being in NYHA Class IV

7.2.2.3. Study treatments

The study treatments were:

1. Semaglutide: initiated at 0.25 mg and increased every 4 weeks in the steps 0.5 and 1.0 mg/week, until the allocated dose of 1 mg was reached. The maintenance dose of 1 mg/week was reached after 8 weeks. If the allocated dose was not tolerated, then the dose could be reduced to the next level. The treatment was presented in a 1.5 mL PDS290 pre-filled pen-injector
2. Placebo 1.5 mL PDS290 pre-filled pen-injector
3. Semaglutide: initiated at 0.25 mg and increased every 4 weeks in the steps 0.5, 1.0, 1.7 and 2.4 mg/week, until the allocated dose of 2.4 mg was reached. The maintenance dose of 2.4 mg/week was reached after 16 weeks. If the allocated dose was not tolerated, then the dose could be reduced to the next level. The treatment was presented in a 3 mL PDS290 pre-filled pen-injector
4. Placebo 3 mL PDS290 pre-filled pen-injector

All patients were also treated with a reduced calorie diet (a 500 kcal deficit/day relative to the estimated Total Energy Expenditure [TEE]) and increased physical activity [150 min per week]).

7.2.2.4. Efficacy variables and outcomes

The primary efficacy outcome measures were:

- Change from baseline at week 0 to week 68 in body weight (%)
- Patients who after 68 weeks achieve body weight reduction ≥5% from baseline (week 0)

The confirmatory secondary efficacy outcome measures were:

- Change from baseline at week 0 to week 68 in waist circumference (cm)
- Patients who after 68 weeks achieve body weight reduction ≥10% from baseline
- Patients who after 68 weeks achieve body weight reduction ≥15% from baseline
- Change from baseline at week 0 to week 68 in HbA_{1c}
- Change from baseline at week 0 to week 68 in SBP
- Change from baseline at week 0 to week 68 in physical functioning score (SF-36)
- Change from baseline at week 0 to week 68 in physical function domain (5-items) score (IWQOL-Lite-CT)

Supportive secondary endpoints

- Change from baseline at week 0 to week 68 in body weight (kg)
- Change from baseline at week 0 to week 68 in BMI (kg/m^2)
- Patients who after 68 weeks achieve body weight reduction ≥20% from baseline
- Change from baseline at week 0 to week 68 in FPG
- Change from baseline at week 0 to week 68 in fasting serum insulin
- Patients who after 68 weeks achieve HbA_{1c} <7.0% (53 mmol/mol)
- Patients who after 68 weeks achieve HbA_{1c} ≤6.5% (48 mmol/mol)
- Patients who after 68 weeks achieve body weight reduction ≥10% and HbA_{1c} <7.0%
- Patients who after 68 weeks achieve body weight reduction ≥15% and HbA_{1c} <7.0%
- Change from baseline at week 0 to week 68 in DBP
- Change from baseline at week 0 to week 68 in serum lipids
- Change from baseline at week 0 to week 68 in CRP
- Change from baseline at week 0 to week 68 in PAI-I activity
- Change from baseline at week 0 to week 68 in SF-36
- Change from baseline at week 0 to week 68 in IWQOL-Lite-CT
- Responders for SF-36 physical functioning score
- Responders for IWQOL-Lite-CT physical function domain (5-items) score

Exploratory secondary outcome measures:

- Change from baseline in antidiabetic drug medication

- Change from baseline in antihypertensives
- Change from baseline in lipid-lowering medication
- Work productivity: Six-minute walking test (6MWT) and Work Productivity and Activity Impairment Questionnaire – Specific Health Problem V2.0 (WPAI-SHP)

The safety outcome measures were: AEs, vital signs, clinical laboratory tests including amylase, lipase and calcitonin, and albuminuria.

The schedule of study procedures is summarised in Table 7.2.2.1.

7.2.2.5. Randomisation and blinding methods

Patients were randomised 1:1:1 to 1 mg, 2.4 mg and placebo by IWRS. The treatments were identical in appearance. However, the titration regimens for the semaglutide 1.0 and 2.4 mg doses were different. Hence it would be possible to determine patients could not be in the 1.0 mg or 2.4 mg treatment groups.

7.2.2.6. Analysis populations

The FAS included all randomised patients and was analysed as ITT.

The SAS included all randomised patients exposed to at least one dose of randomised treatment and was analysed "as treated".

7.2.2.7. Sample size

The sample size was determined for the primary and confirmatory efficacy outcome measures, using the assumptions in Table 7.2.2.2.

7.2.2.8. Statistical methods

For continuous outcome measures, hypothesis tests were performed using ANCOVA models with stratification groups and baseline measures as covariates. Dichotomous variables were analysed using logistic regression models with stratification groups and baseline measures as covariates.

Imputation was performed by RD-MI. The imputation was tested using sensitivity analyses.

Multiplicity was addressed using a hierarchical approach to hypothesis testing.

7.2.2.9. Participant flow

There were 1595 patients screened and 1210 were randomised: 403 to semaglutide 1 mg, 404 to semaglutide 2.4 mg and 403 to placebo (Table 7.2.2.3). One patient in each group was not exposed to study treatment. All randomised patients were included in the FAS and all exposed patients were included in the SAS. There were 354 (87.8%) patients in the semaglutide 1 mg group, 357 (88.4%) in the semaglutide 2.4 mg group and 347 (86.1%) in the placebo who completed treatment. There were 390 (96.8%) patients in the semaglutide 1 mg group, 391 (96.8%) in the semaglutide 2.4 mg group and 383 (95.0%) in the placebo who completed the trial. There were 13 (3.2%) patients in the semaglutide 1 mg group, 13 (3.2%) in the semaglutide 2.4 mg group and 20 (5.0%) in the placebo who withdrew from the trial. There were 19 (4.7%) patients in the semaglutide 1 mg group, 26 (6.4%) in the semaglutide 2.4 mg group and 13 (3.2%) in the placebo who discontinued study treatment because of an AE.

7.2.2.10. Major protocol violations/deviations

There were no major protocol deviations leading to exclusion from analysis or that were considered to impact on the study conclusions. Some of the protocol deviations were dues to on-site visits being converted to phone visits as a result of COVID.

7.2.2.11. Baseline data

There were 616 (50.9%) females and 594 (49.1%) males (Table 7.2.2.4). There were 751 (62.1%) White patients, 317 (26.2%), Asian and 100 (8.3%) Black or African American. The age

range was 19 to 84 years, weight range was 54.4 to 199.2 kg, waist circumference range was 80.0 to 174.0 cm and BMI range was 26.5 to 66.2 kg/m^2 (Table 7.2.2.5). The study groups were similar in demographic, physical and glycaemic characteristics at baseline. At baseline, hypertension was reported by 70.1% patients, dyslipidaemia by 68.3%, obstructive sleep apnoea by 14.5%, coronary artery disease by 8.2%, knee osteoarthritis by 16.2% and non-alcoholic fatty liver disease by 21.6%. Diabetic neuropathy was reported by 20.2% patients, diabetic nephropathy by 12.7% and diabetic retinopathy by 10.2%. OADs were used by 287 (96.0%) patients in the semaglutide 1.0% group, 387 (95.8%) in the semaglutide 2.4 mg and 382 (94.8%) in the placebo. The most frequently used OAD was metformin. Biguanides were used by 90.2% patients, sulfonylurea by 25.1%, SGLT-2 inhibitor by 23.5% and thiazolidinediones by 4.5%.

7.2.2.12. Results for the primary efficacy outcome

Semaglutide 2.4 mg was superior to placebo for the primary efficacy outcome measures. The mean (SD) change in body weight (%) from baseline to Week 68 was -7.2 (6.6) % for semaglutide 1.0 mg, -9.9 (8.0) % for semaglutide 2.4 mg and -3.3 (5.5) % for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -6.21 (-7.28 to -5.15) %, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -2.65 (-3.66 to -1.64) %, p <0.0001. The change in body weight was greater for the semaglutide 2.4 mg group compared to the semaglutide 1 mg group, and body weight decreased to Week 52 and then appeared to stabilise (Figure 7.2.2.1).

The number (%) achieving weight loss ≥5% at Week 68 was 209 (59.2%) in the semaglutide 1 mg group, 257 (73.2%) in the semaglutide 2.4 mg and 94 (27.6%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 4.88 (3.58 to 6.64), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 1.62 (1.21 to 2.18), p = 0.0012.

The sensitivity analyses confirmed the primary analyses.

7.2.2.13. Results for other efficacy outcomes

Confirmatory secondary efficacy outcome measures:

- The number (%) achieving weight loss ≥10% at Week 68 was 105 (29.7%) in the semaglutide 1 mg group, 175 (49.9%) in the semaglutide 2.4 mg and 24 (7.1%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 7.41 (4.89 to 11.24), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 2.07 (1.53 to 2.80), p <0.0001.
- The number (%) achieving weight loss ≥15% at Week 68 was 51 (14.4%) in the semaglutide 1 mg group, 99 (28.2%) in the semaglutide 2.4 mg and nine (2.6%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 7.65 (4.11 to 14.22), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 2.17 (1.50 to 3.15), p <0.0001.
- The mean (SD) change in waist circumference from baseline to Week 68 was -6.9 (6.8) kg for semaglutide 1.0 mg, -9.7 (8.1) kg for semaglutide 2.4 mg and -4.3 (6.5) kg for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -4.88 (-5.97 to -3.79) kg, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -2.69 (-3.72 to -1.65) kg, p <0.0001. The change in waist circumference was greater for the semaglutide 2.4 mg group compared to the semaglutide 1 mg group, and waist circumference decreased to Week 52 and then appeared to stabilise (Figure 7.2.2.2).
- Both semaglutide groups had superior control of HbA_{1c} compared to placebo, but there was no significant difference between the dose levels (Figure 7.2.2.3). The mean (SD) change in HbA_{1c} from baseline to Week 68 was -1.5 (1.1) % for semaglutide 1.0 mg, -1.7 (1.2) % for semaglutide 2.4 mg and -0.3 (1.3) % for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -1.23 (-1.42 to -1.05) %, p <0.0001; semaglutide 1 mg – placebo, -1.08 (-1.28 to -0.89) %, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -0.15 (-0.34 to -0.04) %, p = 0.1218.
- The mean (SD) change in SBP from baseline to Week 68 was -3 (15) mmHg for semaglutide 1.0 mg, -4 (14) mmHg for semaglutide 2.4 mg and 0 (15) mmHg for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -3.43 (-5.57 to -1.30) mmHg,

p = 0.0016; and semaglutide 2.4 mg – semaglutide 1.0 mg, -1.04 (-3.33 to 1.24) mmHg, p = 0.3713.

- The mean (SD) change in SF-36 physical functioning score from baseline to Week 68 was 2.1 (6.89) for semaglutide 1.0 mg, 2.8 (7.7) for semaglutide 2.4 mg and 0.8 (7.0) for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, 1.52 (0.44 to 2.61), p = 0.0061; and semaglutide 2.4 mg – semaglutide 1.0 mg, 0.12 (-0.95 to 1.20), p = 0.8235.
- The mean (SD) change in IWQOL-Lite-CT Physical Function from baseline to Week 68 was 8.5 (18.8) for semaglutide 1.0 mg, 11.4 (20.8) for semaglutide 2.4 mg and 4.9 (20.4) for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, 4.83 (1.79 to 7.86), p = 0.0018; and semaglutide 2.4 mg – semaglutide 1.0 mg, 1.41 (-1.50 to 4.32), p = 0.3423.

Supportive secondary efficacy outcome measures:

- The mean (SD) change in body weight (kg) from baseline to Week 68 was -7.1 (6.7) kg for semaglutide 1.0 mg, -9.9 (8.5) kg for semaglutide 2.4 mg and -3.4 (6.2) kg for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -7.48 (-8.51 to -6.45) kg, p <0.0001: and semaglutide 2.4 mg – semaglutide 1.0 mg, -3.13 (-4.16 to -2.10) kg, p <0.0001.
- The number (%) achieving weight loss ≥20% at Week 68 was 18 (5.1%) in the semaglutide 1 mg group, 50 (14.2%) in the semaglutide 2.4 mg and four (1.2%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 6.84 (2.86 to 16.33), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 2.83 (1.64 to 4.90), p = 0.0002.
- The mean (SD) change in BMI from baseline to Week 68 was -2.6 (2.4) kg/m^2 for semaglutide 1.0 mg, -3.6 (3.1) kg/m^2 for semaglutide 2.4 mg and -1.2 (2.1) kg/m^2 for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -2.26 (-2.63 to -1.88) kg/m^2, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -0.97 (-1.33 to -0.61) kg/m^2, p <0.0001. The change in BMI was greater for the semaglutide 2.4 mg group compared to the semaglutide 1 mg group, and BMI decreased to Week 52 and then appeared to stabilise (Figure 7.2.2.4).
- The number (%) achieving HbA_{1c} ≤6.5% at Week 68 was 221 (63.1%) in the semaglutide 1 mg group, 252 (72.0%) in the semaglutide 2.4 mg and 48 (14.2%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 10.91 (7.51 to 15.85), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 1.39 (1.03 to 1.88), p = 0.0336.
- The number (%) achieving HbA_{1c} <7.0% at Week 68 was 266 (76.0%) in the semaglutide 1 mg group, 288 (82.3%) in the semaglutide 2.4 mg and 87 (25.8%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 9.77 (6.85 to 13.93), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 1.40 (1.01 to 1.96), p = 0.0466.
- The number (%) achieving weight loss >10% and HbA_{1c} <7.0% at Week 68 was 105 (27.9%) in the semaglutide 1 mg group, 170 (44.6%) in the semaglutide 2.4 mg and 25 (6.7%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 8.53 (5.42 to 13.45), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 2.08 (1.54 to 2.81), p <0.0001.
- The number (%) achieving weight loss >15% and HbA_{1c} <7.0% at Week 68 was 49 (13.0%) in the semaglutide 1 mg group, 98 (25.7%) in the semaglutide 2.4 mg and 11 (2.9%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 8.01 (4.19 to 15.28), p <0.0001; and for semaglutide 2.4 mg/semaglutide 1 mg, 2.30 (1.57 to 3.35), p <0.0001.
- The mean (SD) change in FPG from baseline to Week 68 was -2.0 (2.5) mmol/L for semaglutide 1.0 mg, -2.1 (2.5) mmol/L for semaglutide 2.4 mg and -0.1 (2.9) mmol/L for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -2.03 (-2.40 to -1.67) mmol/L, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -0.32 (-0.69 to 0.05) mmol/L, p = 0.0893.
- There was no significant difference between the treatment groups in the ratio of fasting insulin at Week 68 to baseline: geometric mean (CV) 0.94 (58.6) for semaglutide 1 mg, 0.89 (65.3) for semaglutide 2.4 mg and 0.93 (53.1) for placebo.

- There was no significant difference in DBP. The mean (SD) change in DBP from baseline to Week 68 was -1 (9) mmHg for semaglutide 1.0 mg, -2 (9) mmHg for semaglutide 2.4 mg and -1 (9) mmHg for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -0.67 (-1.95 to -0.61) mmHg, p = 0.3070; and semaglutide 2.4 mg – semaglutide 1.0 mg, -0.91 (-2.20 to 0.38) mmHg, p = 0.1659.
- VLDL cholesterol, free fatty acids and triglycerides decreased in the semaglutide 2.4 mg group relative to placebo (Figure 7.2.2.5).
- The geometric mean (CV) ratio of Week 68 to baseline for hsCRP, on treatment, was 0.57 (114.4) for semaglutide 1.0 mg, 0.47 (124.4) for semaglutide 2.4 mg and 0.83 (87.9) for placebo; estimated treatment ratio (95% CI), semaglutide 2.4 mg / placebo, 0.61 (0.54 to 0.70), p <0.0001; and semaglutide 2.4 mg / semaglutide 1.0 mg, 0.88 (0.77 to 1.01) mmHg, p = 0.0621.
- The geometric mean (CV) ration of Week 68 to baseline for PAI-I activity, on treatment, was 1.20 (74.2) for semaglutide 1.0 mg, 1.04 (80.5) for semaglutide 2.4 mg and 1.41 (67.3) for placebo; estimated treatment ratio (95% CI), semaglutide 2.4 mg / placebo, 0.76 (0.71 to 0.82), p <0.0001; and semaglutide 2.4 mg / semaglutide 1.0 mg, 0.87 (0.81 to 0.93), p <0.0001.
- The number (%) achieving at least a 4.3-point increase from baseline in SF-36 Physical Functioning score at Week 68 was 88 (23.8%) in the semaglutide 1 mg group, 111 (29.5%) in the semaglutide 2.4 mg and 68 (18.6%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 1.72 (1.16 to 2.55), p = 0.0071; and for semaglutide 2.4 mg/semaglutide 1 mg, 1.09 (0.75 to 1.58), p = 0.6517.
- There were significant improvements in the Semaglutide 2.4 mg group relative to placebo for the physical functioning and general health components of the SF-36 (Figure 7.2.2.6).
- The number (%) achieving at least a 20-point increase from baseline in IWQOL-Lite-CT Physical Function at Week 68 was 107 (29.0%) in the semaglutide 1 mg group, 131 (34.8%) in the semaglutide 2.4 mg and 83 (22.7%) in the placebo: OR (95% CI), semaglutide 2.4 mg/placebo, 1.73 (1.20 to 2.49), p = 0.0030; and for semaglutide 2.4 mg/semaglutide 1 mg, 1.12 (0.80 to 1.56), p = 0.5231.
- Semaglutide 2.4 mg was superior to placebo for all the components of the IWQOL-Lite-CT but there were no significant differences in comparison with semaglutide 1 mg (Figure 7.2.2.7).
- Six-minute walking test improved from baseline for all the treatment groups, with the greatest improvement in the semaglutide 2.4 mg group: mean (SD) change from baseline 8.6 (114.0) m for semaglutide 1 mg, 92.7 (574.6) m for semaglutide 2.4 mg and 19.4 (112.6) m for placebo.
- Albuminuria and fatty liver index improved in the semaglutide 2.4 mg group relative to placebo. Hypothesis tests were not reported for these endpoints.

Exploratory secondary efficacy outcome measures:

- There was no significant difference between the study groups in time to discontinuation of trial product
- There was a relative increase in OAD in the placebo group relative to the semaglutide groups (Figure 7.2.2.8).
- There were no clear differences between the groups in change in hypertensive medication (Figure 7.2.2.9).
- There were no significant differences between the treatment groups in lipid-lowering medication (Figure 7.2.2.10)
- There were improvements in WPAI-SHP in all the treatment groups during the study, but the greatest improvement was in the semaglutide 2.4 mg group. There were no significant differences reported between the treatment groups.

7.2.2.14. Evaluator commentary

The design and conduct of Study NN9536-4374 was appropriate. The patient population was representative of the target population, who also have T2DM, in Australia, and the results are therefore generalisable.

The titration and dosing regimens were the same as those proposed for marketing in Australia. However, the formulations (specifically concentrations) used in titration were different to those proposed for marketing in Australia.

The background treatments were the same as those in the proposed indication: diet and exercise.

Bias was controlled through randomisation and blinding, except there was lack of blinding between the 1.0 mg / placebo groups and the 2.4 mg / placebo groups. However, the outcome measures were objective and the primary comparison was between semaglutide 2.4 mg and placebo.

Multiplicity was addressed. The statistical analysis was appropriate. The outcome measures were appropriate and measured different aspects of treatment effect.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period compared with both placebo and semaglutide 1.0 mg groups. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure in both semaglutide groups. There were improvements in glycaemic control in both semaglutide groups, with no significant differences between the dose levels. There were significant improvements in quality of life and physical functioning, that were greater in the semaglutide 2.4 mg group compared with both semaglutide 1.0 mg and placebo.

In patients with T2DM the decrease in body weight was not as great as in Study NN9536-4373, where T2DM was excluded. However, there was still significant benefit in this patient group.

7.2.3. Study NN9536-4375

7.2.3.1. Study design, objectives, locations and dates

Study NN9536-4375 was a randomised, placebo controlled, double blind, two-arm, parallel group study in patients with obesity or overweight with comorbidities. Treatment duration was 68 weeks, and there was a 7-week follow-up period. The primary objective of the study was to compare the effect of semaglutide 2.4 mg once weekly versus placebo as an adjunct to intensive behavioural therapy (IBT) in patients with overweight or obesity, on body weight. The study was conducted at 41 sites in the US from August 2018 to April 2020.

7.2.3.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females, aged ≥18 years
- BMI ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease
- History of at least one self-reported unsuccessful dietary effort to lose body weight

The exclusion criteria included:

- HbA_{1c} ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening
- History of type 1 or type 2 diabetes mellitus
- 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
- Treatment with any medication for the indication of obesity within the past 90 days before screening

- Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) lap banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening
- Uncontrolled thyroid disease, defined as TSH >6.0 mIU/L or <0.4 mIU/L
- History of major depressive disorder within 2 years before screening
- Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
- A Patient Health Questionnaire-9 (PHQ-9) score of ≥15
- A lifetime history of a suicidal attempt
- Suicidal behaviour within 30 days before screening
- Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening
- History of major depressive disorder within 2 years before screening
- Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)
- A Patient Health Questionnaire-9 (PHQ-9) score of ≥15 at screening
- Presence of acute pancreatitis within the past 180 days prior to the day of screening
- History or presence of chronic pancreatitis
- Calcitonin ≥100 ng/L
- Personal or first-degree relative(s) history of MEN-2 or MTC
- End stage renal disease defined as estimated Glomerular Filtration Rate (eGFR) value of <15 mL/min/1.73 m^2 as defined by KDIGO 2012
- History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ were allowed
- Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to screening
- Subject presently classified as being in NYHA Class IV

7.2.3.3. Study treatments

The study treatments were:

1. Semaglutide: initiated at 0.25 mg and increased every 4 weeks in the steps 0.5, 1.0, 1.7 and 2.4 mg/week. The maintenance dose of 2.4 mg/week was reached after 16 weeks. If 2.4 mg/week was not tolerated, then the dose could be reduced to 1.7 mg/week.
2. Placebo

The treatments were administered with a 3 mL PDS290 pre-filled pen-injector.

All patients received an intensive IBT program. Each IBT session covered a specific topic, for example, advice on diet or physical activity as well as lifestyle modification (e.g., challenging negative thoughts, obtaining social support). Patients received weekly intensive behavioural support by a dietician or a similarly qualified healthcare professional and discussed progress, reviewed food diary/app and addressed any compliance or other issues and prepared for transition to the next phase with structured diet. Most of the topics were accompanied by a homework assignment from the subject hand-outs to be completed before next visit according to the visit schedule. Behavioural support gradually decreased from weekly to biweekly and finally monthly sessions.

After randomisation the dietary intervention started. The first 8 weeks consisted of a 1000-1200 kcal/day low-calorie diet (LCD), at the discretion of the investigator, provided as meal replacements (e.g. liquid shakes and solid bars) and portion controlled meals.

Physical activity was initiated from randomization and prescribed with a target of 100 minutes physical activity per week. Patients should be physically active in bouts of >10 minutes in

duration with moderate intensity (such as brisk walking), and the physical activity should be spread equally across 4-5 days each week. Physical activity should progress gradually by 25 minutes every 4 weeks and up to 200 minutes/week, consistent with targets required for maintenance of lost weight.

After 8 weeks on LCD, subjects should gradually be transferred to a less strict hypo-caloric diet comprised of conventional foods. From Week 8 to 'end of treatment' daily caloric target was calculated based on body weight at randomisation (Visit 2) according to below algorithm:

- Patients weighing less than 200 lbs were prescribed a diet of 1200 kcal/day
- Patients weighing between 200 lbs and 300 lbs were prescribed a diet calculated as: Daily calorie target (kcal) = body weight (1b) x 6 (kcal/lb
- Patients weighing more than 300 lbs were prescribed 1800 kcal/day

This caloric target should be kept for the remainder of the trial. If a patient achieved a BMI ≤22.5 kg/m^2, the recommended energy intake should be re-calculated with no caloric deficit for the remainder of the trial.

Patients received and used an activity tracker and were instructed to record their food intake in order to assist their lifestyle intervention. The activity tracker, food diary/app and content of the patient hand out from IBT guide was used for counselling purposes by the dietician or a similarly qualified healthcare professional at all visits.

7.2.3.4. Efficacy variables and outcomes

The primary efficacy outcome measures were:

- Change from baseline at week 0 to week 68 in body weight (%)
- Patients who after 68 weeks achieve body weight reduction ≥5% from baseline (week 0)

The confirmatory secondary efficacy outcome measures were:

- Patients who after 68 weeks achieve body weight reduction ≥10% from baseline
- Patients who after 68 weeks achieve body weight reduction ≥15% from baseline
- Change from baseline at week 0 to week 68 in SBP (mmHg)
- Change from baseline at week 0 to week 68 in physical functioning score (SF-36)
- Change from baseline at week 0 to week 68 in waist circumference (cm)

The supportive secondary efficacy outcome measures were:

- Patients who after 68 weeks achieve body weight reduction ≥20% from baseline (week 0)
- Change from baseline at week 0 to week 8 in body weight (%)
- Change from baseline at week 0 to week 68 in BMI (kg/m^2)
- Change from baseline at week 0 to week 68 in DBP (mmHg)
- Change from baseline at week 0 to week 68 in lipids: total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids, triglycerides
- Change from baseline at week 0 to week 68 in CRP
- Change from baseline at week 0 to week 68 in PAI-1 activity
- Change from baseline at week 0 to week 68 in SF-36
- Responders for SF-36 physical functioning score
- Glucose metabolism: HbA1c, FPG and fasting serum insulin

The exploratory endpoints were:

- Glycaemic status: normo-glycaemia, pre-diabetes, T2DM
- Use of medication for hypertension and dyslipidaemia
- Work productivity: WPAI-SHP and WRSSM
- Treatment discontinuation and time to treatment discontinuation

The safety outcome measures were: AEs, vital signs, clinical laboratory tests including amylase, lipase and calcitonin.

The schedule of study procedures is summarised in Table 7.2.3.1.

7.2.3.5. Randomisation and blinding methods

Patients were allocated to treatment in a 2:1 ratio, semaglutide: placebo using IWRS. The study treatments were identical in appearance and presentation.

7.2.3.6. Analysis populations

The FAS included all randomised patients and was analysed as ITT.

The SAS included all randomised patients exposed to at least one dose of randomised treatment and was analysed "as treated".

7.2.3.7. Sample size

The sample size was based on tests of superiority for all of the primary efficacy and confirmatory secondary outcome measures. The assumptions are summarised in Table 7.2.3.2.

7.2.3.8. Statistical methods

For continuous outcome measures, hypothesis tests were performed using ANCOVA models with stratification groups and baseline measures as covariates. Dichotomous variables were analysed using logistic regression models with stratification groups and baseline measures as covariates.

Imputation was performed by RD-MI. The imputation was tested using sensitivity analyses.

Multiplicity was addressed using a hierarchical approach to hypothesis testing.

7.2.3.9. Participant flow

There were 742 patients screened and 611 were randomised: 407 to semaglutide 2.4 mg and 204 to placebo (Table 7.2.3.3). All randomised patients were exposed to study treatment and were included in the FAS and SAS. There were 339 (83.3%) patients in the semaglutide group and 166 (81.4%) in the placebo who completed treatment. There were 376 (92.4%) patients in the semaglutide group and 191 (93.6%) in the placebo who completed the study. There were 26 (6.4%) patients in the semaglutide group and six (2.9%) in the placebo who discontinued treatment because of AE.

7.2.3.10. Major protocol violations/deviations

There were no major protocol deviations that were considered to impact on the interpretation of the study results. The study was disrupted by the COVID-19 pandemic: 137 patients had their follow-up visits converted to phone visits and two patients had missing Week 68 assessments.

7.2.3.11. Baseline data

There were 495 (81.0%) females and 116 (19.0%) males (Table 7.2.3.4). There were 465 (76.1%) White patients and 116 (19.0%) Black or African American. The age range was 18 to 75 years (Table 7.2.3.5). The weight range was 66.9 to 216.8 kg. The BMI range was 27.0 to 69.0 kg/m^2. The treatment groups were balance by baseline demographic and clinical characteristics. The comorbidities were: dyslipidaemia (34.7% patients), hypertension: (34.7%), obstructive sleep apnoea (12.6%), knee osteoarthritis (17.5%), coronary artery disease (1.6%), elevated HbA_{1c} :(25.4%), and polycystic ovarian syndrome (5.5% of the female patients). Concomitant medications were: agents acting on the renin-angiotensin system (21.1% patients), beta blocking agents (8.3%), calcium channel blockers (8.5%), diuretics (14.2%), lipid modifying agents (18.7%), antithrombotic agents (10.3%), anti-inflammatory and antirheumatic products (28.2%), analgesics (17.7%), psycholeptics (13.6%), and psychoanaleptics (20.9%).

7.2.3.12. Results for the primary efficacy outcome

Semaglutide was superior to placebo for both primary efficacy outcome measures (Table 7.2.3.6). The mean (SD) change in body weight from baseline to Week 68 was -16.5 (10.1) % for semaglutide and -5.8 (7.7) % for placebo; treatment difference (95% CI), semaglutide – placebo, -10.27 (-11.97 to -8.57) %, p <0.0001. Weight loss occurred through to Week 56, and then appeared to stabilise (Figure 7.2.3.1).

s47 [redacted]

The sensitivity analyses, using alternative methods of imputation, confirmed the primary statistical analysis.

7.2.3.13. Results for other efficacy outcomes

Confirmatory secondary efficacy outcome measures:

- There was a higher proportion of patients in the semaglutide group achieving body weight loss ≥10% at Week 68: s47 [redacted] patients in the semaglutide group and s47 [redacted] in the placebo; OR (95% CI), semaglutide / placebo, s47 [redacted] p <0.0001.
- There was a higher proportion of patients in the semaglutide group achieving body weight loss ≥15% at Week 68: s47 [redacted] patients in the semaglutide group and s47 [redacted] in the placebo; OR (95% CI), semaglutide / placebo, s47 [redacted] p <0.0001.
- The mean (SD) change waist circumference from baseline to Week 68 was s47 [redacted] cm for semaglutide and s47 [redacted] cm for placebo; treatment difference (95% CI), semaglutide – placebo, s47 [redacted] cm, p <0.0001. Waist circumference decreased through to Week 52, and then appeared to stabilise (s47 [redacted]
- SBP decreased to a greater extent in the semaglutide group compared to placebo: the mean (SD) change from baseline to Week 68 was s47 [redacted] mmHg in the semaglutide group and s47 [redacted] mmHg in the placebo; treatment difference (95% CI) s47 [redacted], p = 0.0014.
- There was no significant difference between the treatment groups in SF-36 Physical Functioning. The observed mean (SD) change in SF-36 Physical Functioning from baseline to Week 68 was s47 [redacted] for semaglutide and s47 [redacted] for placebo: treatment difference (95% CI), semaglutide – placebo, s47 [redacted] p = 0.1249.

Supportive secondary efficacy outcome measures:

s47 [redacted]

s47

Exploratory endpoints:

s47

7.2.3.14. Evaluator commentary

The design and conduct of Study NN9536-4373 was appropriate. The patient population was representative of the target population in Australia, and the results are therefore generalisable.

The titration and dosing regimens were the same as those proposed for marketing in Australia. However, the formulations (specifically concentrations) used in titration were different to those proposed for marketing in Australia.

The background treatments included those in the proposed indication: diet and exercise. However, an additional background treatment was IBT. The IBT program used in the trial was properly termed intensive.

Bias was controlled through randomisation and blinding. Multiplicity was addressed. The statistical analysis was appropriate. The outcome measures were appropriate and measured different aspects of treatment effect.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period in patients who were also having IBT. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. There were improvements in glycaemic control.

However, there were improvements in quality of life and physical functioning in both treatment groups, with no significant differences between the treatment groups. Hence, there was no increase in well-being with semaglutide in patients who were undergoing IBT.

7.2.4. Study NN9536-4376

7.2.4.1. Study design, objectives, locations and dates

Study NN9536-4376 was a randomised, double-blind, two-arm, placebo-controlled efficacy and safety study. Treatment duration was 68 weeks: 20-week dose-titration and 48 weeks maintenance. The primary objective of the study was to compare the effect of semaglutide 2.4 mg once-weekly versus semaglutide placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity who have reached target dose of semaglutide during the run-in period, on body weight. The study was conducted in ten countries: Denmark (2 sites), Israel (6), Netherlands (3), Portugal (6), South Africa (6), Spain (7), Sweden (4), Switzerland (6), Ukraine (5) and the US (28). The study was conducted from June 2018 to March 2020.

7.2.4.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were near-identical to those for Study NN9536-4373 (Section 7.2.1.2)

7.2.4.3. Study treatments

The study treatments and background treatments were the same as for Study NN9536-4373 (Section 7.2.1.3).

7.2.4.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the change from randomisation at Week 20 to Week 68 in body weight (%).

The confirmatory secondary efficacy outcome measures were:

- Change from randomisation at Week 20 to Week 68 in waist circumference
- Change from randomisation at Week 20 to week 68 in SBP (mmHg)
- Change from randomisation at Week 20 to week 68 in physical functioning score (SF-36)

The supportive secondary efficacy outcome measures were:

- Change from randomisation at Week 20 to week 68 in BMI (kg/m^2)
- Change from randomisation at Week 20 to week 68 in DBP (mmHg)
- Change from randomisation at Week 20 to week 68 in lipids: total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids, triglycerides
- Change from randomisation at Week 20 to week 68 in SF-36
- Responders for SF-36 physical functioning score
- Glucose metabolism (change from randomisation at Week 20 to Week 68): HbA1c, FPG and fasting serum insulin
- Change from baseline at Week 0 to week 68 in body weight (%)
- Patients who after 68 weeks achieve body weight reduction <0% from baseline (week 0)
- Patients who after 68 weeks achieve body weight reduction ≥5% from baseline (week 0)
- Patients who after 68 weeks achieve body weight reduction ≥10% from baseline (week 0)
- Patients who after 68 weeks achieve body weight reduction ≥15% from baseline (week 0)
- Patients who after 68 weeks achieve body weight reduction ≥20% from baseline (week 0)

The exploratory endpoints were:

- Glycaemic status (change from Week 20 to Week 68): normo-glycaemia, pre-diabetes, T2DM
- Change from Week 20 to Week 68 in use of medication for hypertension and dyslipidaemia
- Change from Week 20 to Week 68 in work productivity: SPS-6, total score
- Change from Week 20 to Week 68 in WRSSM
- Treatment discontinuation and time to treatment discontinuation

The safety outcome measures were (from Week 20 to Week 75): AEs, vital signs, clinical laboratory tests including amylase, lipase and calcitonin.

The schedule of study procedures is summarised in Table 7.2.4.1.

7.2.4.5. Randomisation and blinding methods

Patients were randomised at Week 20 to either semaglutide 2.4 mg or placebo in a 2:1 ratio, semaglutide : placebo, using IWRS. The study treatments were identical in appearance and packaging.

7.2.4.6. Analysis populations

The FAS included all randomised patients according to the ITT principle.

The SAS included all randomised patients exposed to at least one dose of randomised treatment, and patients were analysed according to treatment received.

7.2.4.7. Sample size

The sample size was determined for the primary and confirmatory secondary endpoints using the assumptions in Table 7.2.4.2.

7.2.4.8. Statistical methods

Continuous outcome variables were tested using ANCOVA models with baseline measures as a covariate. Missing observations were imputed by RD-MI. Sensitivity analyses were performed using alternative imputation approaches.

Binary endpoints were tested using logistic regression models with baseline observations as a covariate.

Multiplicity was addressed by a hierarchical hypothesis testing procedure.

7.2.4.9. Participant flow

There were 1051 patients screened, and 902 entered the 20-week run-in phase. These patients were all included in the SAS. There were 803 patients randomised to treatment: 535 to semaglutide 2.4 mg and 268 to placebo (Table 7.2.4.3). There were 504 (94.2%) patients in the semaglutide group and 237 (88.4%) in the placebo who completed treatment. There were 31 (5.8%) patients in the semaglutide group and 31 (11.6%) in the placebo who permanently discontinued treatment. There were 13 (2.4%) patients in the semaglutide group and six (2.2%) in the placebo who permanently discontinued treatment because of AE.

7.2.4.10. Major protocol violations/deviations

Due to the COVID-19 pandemic, 12 patients had their follow-up visits changed to phone visits. No patients were excluded from the FAS due to protocol violations.

7.2.4.11. Baseline data

There were 634 (79.0%) females and 169 (21.0%) males (Table 7.2.4.4). There were 672 (83.7%) White patients, 104 (13.0%) Black or African American and 19 (2.4%) Asian. The age range was 18 to 78 years, the BMI range was 22.4 to 72.6 kg/m^2, and the weight range was 51.9 to 200.1 kg (Table 7.2.4.5). The treatment groups were similar in baseline demographic and physical characteristics. In the randomised group, the comorbidities were: dyslipidaemia in 35.9% patients, hypertension in 37.1%, obstructive sleep apnoea in 11.7%, knee osteoarthritis in 12.3%, coronary artery disease in 0.9%, impaired glucose tolerance in 5.2%, impaired fasting glucose in 7.6%, and polycystic ovarian syndrome in 3.9% of the female patients. Concomitant medication was: agents acting on the renin-angiotensin system (20.6% patients), beta blocking agents (8.1%), calcium channel blockers (6.8%), diuretics (14.2%), lipid modifying agents (15.4%), antithrombotic agents (8.5%), anti-inflammatory and antirheumatic products (19.3%),

analgesics (13.3%), psycholeptics (5.7%) and psychoanaleptics (11.6%). One patient initiated concomitant anti-obesity mediation during the randomisation period.

7.2.4.12. Results for the primary efficacy outcome

Semaglutide was superior to placebo for the primary efficacy outcome measure (Table 7.2.4.6). s47 [redacted]; treatment difference (95% CI), semaglutide – placebo, -14.75 (-16.00 to -13.50) %, p <0.0001. s47 [redacted]

7.2.4.13. Results for other efficacy outcomes

The confirmatory secondary efficacy outcome measures were:

- The change from randomisation at Week 20 to Week 68 in waist circumference was -6.9 (7.5) cm for semaglutide and 3.2 (7.0) cm for placebo; treatment difference (95% CI), semaglutide – placebo, -9.70 (-10.83 to -8.58) cm, p <0.0001.
- The observed change from randomisation at Week 20 to Week 68 in SBP was 0 (14) mmHg for semaglutide and 5 (13) mmHg for placebo; estimated treatment difference (95% CI), semaglutide – placebo, -3.92 (-5.82 to -2.03) mmHg, p <0.0001.
- The observed change from randomisation at Week 20 to Week 68 in physical functioning score (SF-36) was 1.0 (3.8) for semaglutide and -1.2 (4.5) for placebo; estimated treatment difference (95% CI), semaglutide – placebo, 2.45 (1.59 to 3.32), p <0.0001.

The supportive secondary efficacy outcome measures were:

- The observed change from randomisation at Week 20 to week 68 in BMI was -2.7 (2.7) kg/m^2 for semaglutide and 2.0 (2.4) kg/m^2 for placebo; treatment difference (95% CI), semaglutide – placebo, -4.74 (-5.16 to -4.32) kg/m^2, p <0.0001.
- The observed change from randomisation at Week 20 to Week 68 in DBP was 0 (9) mmHg for semaglutide and 1 (9) mmHg for placebo; estimated treatment difference (95% CI), semaglutide – placebo, -0.55 (-2.01 to -0.92) mmHg, p = 0.4646.
- There were significant decreases in total cholesterol, LDL cholesterol, VLDL cholesterol or triglycerides in the semaglutide group relative to placebo (Figure 7.2.4.2). However, there were no significant differences in HDL cholesterol or free fatty acids.
- There was statistically significant improvement in all the components of the SF-36, except for bodily pain, from randomisation to Week 68 (Figure 7.2.4.3).
- The number (%) patients who were responders for SF-36 physical functioning score (at least a 4.3-point increase from baseline) at Week 68 was 58 (11.3%) in the semaglutide group and 11 (4.7%) in the placebo: OR (95% CI), semaglutide / placebo, 2.72 (1.18 to 6.29), p = 0.0190.
- The mean (SD) change in HbA_{1c} from randomisation (Week 20) to Week 68 was -1.9 (9.8) mmol/mol for semaglutide and 1.2 (2.7) mmol/mol for placebo; treatment difference (95% CI), semaglutide – placebo, -2.62 (-3.13 to -2.12) %, p <0.0001.
- The mean (SD) change in FPG from randomisation (Week 20) to Week 68 was -0.1 (0.5) mmol/L for semaglutide and 0.4 (0.6) mmol/L for placebo; treatment difference (95% CI), semaglutide – placebo, -0.42 (-0.53 to -0.30) mmol/L, p <0.0001.
- The geometric mean ratio (CV), Week 68 / Week 20, for fasting serum insulin 0.81 (60.9) for semaglutide and 1.03 (64.6) for placebo; treatment ratio (95% CI), semaglutide / placebo, 0.82 (0.73 to 0.92), p = 0.0005.
- The mean (SD) change in body weight % from Week 0 to Week 68 was -17.7 (9.8) % for semaglutide and -5.4 (7.3) % for placebo; treatment difference (95% CI), semaglutide – placebo, -12.36 (-13.71 to -11.02) %, p <0.0001.

- The estimated mean change in body weight in kg from Week 20 to Week 68 was -7.12 kg for semaglutide and 6.06 kg for placebo; treatment difference (95% CI), semaglutide – placebo, -13.17 (-14.34 to -12.01) kg, p <0.0001.
- The number (%) patients who after 68 weeks achieve body weight reduction <0% from baseline (week 20) was 79 (15.2%) in the semaglutide group and 206 (82.4%) in the placebo; OR (95% CI), semaglutide / placebo, 0.04 (0.03 to 0.06), p <0.0001.
- The number (%) of patients who after 68 weeks achieved body weight reduction <0% from Week 0 was 22 (4.2%) in the semaglutide group and 51 (20.4%) in the placebo; OR (95% CI), semaglutide / placebo, 0.18 (0.11 to 0.30), p <0.0001.
- The number (%) of patients who after 68 weeks achieved body weight reduction ≥5% from Week 0 was 461 (88.7%) in the semaglutide group and 119 (47.6%) in the placebo; OR (95% CI), semaglutide / placebo, 8.52 (5.93 to 12.24), p <0.0001.
- The number (%) of patients who after 68 weeks achieved body weight reduction ≥10% from Week 0 was 411 (79.0%) in the semaglutide group and 51 (20.4%) in the placebo; OR (95% CI), semaglutide / placebo, 14.99 (10.30 to 21.80), p <0.0001.
- The number (%) of patients who after 68 weeks achieved body weight reduction ≥15% from Week 0 was 331 (63.7%) in the semaglutide group and 23 (9.2%) in the placebo; OR (95% CI), semaglutide / placebo, 19.07 (11.91 to 30.53), p <0.0001.
- The number (%) of patients who after 68 weeks achieved body weight reduction ≥20% from Week 0 was 206 (39.6%) in the semaglutide group and 12 (4.8%) in the placebo: OR (95% CI), semaglutide / placebo, 14.29 (7.77 to 26.28), p <0.0001.

The exploratory endpoints were:

- A higher proportion of patients in the placebo group shifted into the pre-diabetes category compared to the semaglutide group (Figure 7.2.4.4)
- There were no apparent changes from Week 20 to Week 68 in work productivity (SPS-6, total score) in either treatment group.
- The mean (SD) change from Week 20 to Week 68 in WRSSM was -0.1 (0.5) in the semaglutide group and 0.2 (0.6) in the placebo.
- Time to product discontinuation was shorter for placebo than semaglutide (Figure 7.2.4.5)
- There was lesser use of antihypertensive medication in the semaglutide group compared to placebo (Figure 7.2.4.6). There was no apparent difference in lipid-lowering medication usage between the two treatment groups.

7.2.4.14. Evaluator commentary

The design and conduct of Study NN9536-4373 was appropriate. The patient population was representative of the target population in Australia, and the results are therefore generalisable.

The titration and dosing regimens were the same as those proposed for marketing in Australia. However, the formulations (specifically concentrations) used in titration were different to those proposed for marketing in Australia.

The background treatments were the same as those in the proposed indication: diet and exercise.

Bias was controlled through randomisation and blinding. Multiplicity was addressed. The statistical analysis was appropriate. The outcome measures were appropriate and measured different aspects of treatment effect.

Semaglutide at a dose of 2.4 mg weekly resulted in a sustained and clinically significant loss of weight over a one-year period. This was matched by clinically significant decreases in waist circumference and BMI. There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. There were improvements in glycaemic control. There were significant improvements in quality of life and physical functioning.

There were significant improvements in the semaglutide group both for the randomisation phase, and the treatment period. However, the placebo group had loss of benefit following the titration phase. The initial gains in this group were lost over the remainder of the study. This indicates that the benefits that occur during treatment may be lost after treatment is ceased. Semaglutide is likely to be a long-term treatment for obesity.

7.3. Other efficacy studies

NA.

7.4. Analyses performed across trials: pooled and meta analyses

s47 [redacted]

In the two studies (Study NN9536-4373 [STEP 1] and Study NN9536-4374[STEP 2]) that used IQWOL-Lite-CT as an endpoint there was benefit for semaglutide across all the domains (Figure 7.4.2).

7.5. Evaluator's conclusions on clinical efficacy

The design and conduct of the Phase IIIa studies was appropriate and complied with the Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (EMA/CHMP/311805/2014) 23 June 2016. The primary outcome measure was weight loss, and this was analysed both as % body weight and by mass (kg). The studies were placebo controlled. The predictive value of short-term versus long-term treatment can be determined from the data. Waist circumference and BMI were used as secondary endpoints. DEXA was used to validate that the weight loss was due to loss of adipose and not due to loss of other body constituents. Cardiovascular risk and co-morbidities were also measured as outcomes. A relevant proportion of the study population had coexisting cardiovascular and other co-morbidities.

The patient populations were representative of the target population in Australia, and the results are therefore generalisable to Australia.

The titration and dosing regimens were the same as those proposed for marketing in Australia. However, the formulations (specifically concentrations) used in titration were different to those proposed for marketing in Australia. The Sponsor has demonstrated dose proportionality for semaglutide in other formulations, and this would be expected to also apply to the formulations intended for marketing in Australia.

The background treatments were the same as those in the proposed indication: diet and exercise. The background treatments were applied consistently and were clearly defined in the study protocols.

Bias was controlled through randomisation and blinding. Multiplicity was addressed. The statistical analysis was appropriate. The outcome measures were appropriate and measured different aspects of treatment effect.

The Phase IIIa studies demonstrated a statistically and clinically significant weight loss with semaglutide 2.4 mg weekly dosing. The magnitude of the weight loss was:

- Study NN9536-4373: The mean (SD) change in body weight (%) from baseline to Week 68 was -15.1 (10.1) % for semaglutide and -2.8 (6.5) % for placebo; treatment difference (95% CI), semaglutide – placebo, -12.44 (-13.37 to -11.51) %, p <0.0001.
- s47 : In patients with T2DM, the mean (SD) change in body weight (%) from baseline to Week 68 was -7.2 (6.6) % for semaglutide 1.0 mg, -9.9 (8.0) % for semaglutide 2.4 mg and -3.3 (5.5) % for placebo; estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -6.21 (-7.28 to -5.15) %, p <0.0001; and semaglutide 2.4 mg – semaglutide 1.0 mg, -2.65 (-3.66 to -1.64) %, p <0.0001.
- s47 With background treatment with IBT, the mean (SD) change in body weight from baseline to Week 68 was -16.5 (10.1) % for semaglutide and -5.8 (7.7) % for placebo; treatment difference (95% CI), semaglutide – placebo, -10.27 (-11.97 to -8.57) %, p <0.0001.
- s47 The mean (SD) change in body weight from Week 20 to Week 68 was -8.8 (7.8) % for semaglutide and 6.1 (7.7) % for placebo; treatment difference (95% CI), semaglutide – placebo, -14.75 (-16.00 to -13.50) %, p <0.0001.

The treatment effect was well in excess of a clinically significant 5% weight loss. The effect size was consistent across the four studies. The effect persisted in a patient group undergoing IBT.

The decrease in body weight was matched by decreases in waist circumference and in BMI.

There were improvements in cardiovascular endpoints: lipid profile, surrogate markers (hsCRP and PAI-I) and in blood pressure. The improvements in plasma lipids were primarily in total cholesterol, LDL-cholesterol and VLDL-cholesterol, with lesser effect on HDL-cholesterol. These improvements are associated with a lessening of cardiovascular risk.

Other clinical benefits were:

- There were improvements in glycaemic control. This was matched by a decrease in patients with pre-diabetes in the semaglutide 2.4 mg group.
- There were significant improvements in quality of life and physical functioning.
- In Study NN9536-4373 there were improvements in fatty liver index.

The remaining clinical issues that have not been addressed by the data are:

- Persistence of treatment effect beyond one year of treatment. The data indicate that treatment with semaglutide is likely to be required long-term. There was a return to baseline in the placebo group in Study NN9536-4376. This means the treatment effect does not persist after the treatment is ceased. Hence, it would be important to demonstrate that treatment effect continues with ongoing treatment beyond one year.
- Potential for rebound in weight once treatment is stopped. While the results of Study NN9536-4376 suggest this is unlikely, a rebound in weight might occur over the long term in patients who cease semaglutide treatment.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome in the dossier.

8.1.2. Pivotal and/or main efficacy studies

There were four Phase IIIa therapeutic confirmatory trials (referred to as the STEP trials) included in the dossier:

- Study NN9536-4373 (STEP 1) (Section 7.2.1)
- Study NN9536-4374 (STEP 2) (Section 7.2.2)
- Study NN9536-4375 (STEP 3) (Section 7.2.3)
- Study NN9536-4376 (STEP 4) (Section 7.2.4)

The safety outcome measures in these studies were: AEs, vital signs, clinical laboratory tests including amylase, lipase and calcitonin. Neuropsychiatric safety was also monitored through use of questionnaires: PHQ-9 and C-SSRS.

8.1.3. Other studies

8.1.3.1. Other efficacy studies

There was one Phase II dose-finding trial: Study NN9536-4153 (Section 6.2)

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

There were three clinical pharmacology trials (of which two are bioequivalence trials): Study NN9536-4590 (Section 19.1.1.1), Study NN9535-4588 (Section 19.1.1.2) and Study NN9536-4455 (Section 19.1.2.1).

8.1.3.3. Studies evaluable for safety only

There were no studies evaluable for safety only included in the dossier.

8.2. Studies that assessed safety as the sole primary outcome

NA.

8.3. Patient exposure

Total exposure to semaglutide in Phase III clinical trials is 14,520 patients in 21 trials (Table 8.3.1). There were 9.925 patients exposed for ≥12 months and 1,266 for ≥24 months. There were 7,432 males and 6,721 females. There were 3,408 patients aged 65 to 74 years, 680 aged 75 to 84 years and 23 aged ≥85 years. There were 9,649 White patients, 3,130 Asian and 934 Black/African American.

In completed Phase III trials for weight management, 402 patients have been exposed to semaglutide 1.0 mg and 3,018 to 2.4 mg. Exposure to semaglutide 1.0 mg was 361 patients for 12 months and semaglutide 2.4 mg was 2.389 patients for 12 months. There were 930 males and 2,123 females. There were 311 patients aged 65 to 74 years, 27 aged 75 to 84 years and one aged ≥85 years. There were 2,234 White patients, 410 Asian and 283 Black/African American.

The Summary of Clinical Safety reports that 3052 patients were exposed to semaglutide during the randomised periods of four Phase IIIa trials; and that in the semaglutide 2.4 mg group there were 2650 patients exposed for 3309 patient-years.

Phase I studies:

- In Study NN9536-4590 (Section 19.1.1.1) there were 68 participants exposed to subcutaneous weekly doses up to 2.4 mg for 21 weeks: 34 to Formulation D and 34 to Formulation B.
- In Study NN9535-4588 (Section 19.1.1.2) there were s47 participants exposed to weekly doses of subcutaneous semaglutide, from 2.5 mg up to 1 mg, for 7 weeks s47 xposed to Formulation D and s47 to Formulation B.
- In Study NN9536-4455 (Section 19.1.2.1) there were s47 participants exposed to weekly semaglutide, doses up to 2.4 mg, and s47 to placebo for up to 20 weeks.

Phase II study:

- In Study NN9536-4153 (Section 6.2) there were 103 patients exposed to semaglutide 0.05 mg/day, 102 to semaglutide 0.1 mg/day, 103 to 0.2 mg/day, 103 to 0.3 mg/day, 102 to 0.4 mg/day, 102 to semaglutide 0.3 mg/day fast titration, 103 to semaglutide 0.4 mg/day fast titration, 103 to liraglutide 3.0 mg/day and 136 to placebo. Treatment duration was up to 52 weeks.

Phase III studies:

- In Study NN9536-4373 (Section 7.2.1) there were 1306 patients exposed to semaglutide 2.4 mg and 655 to placebo for up to 68 weeks. There were 1706.1 patient-years exposure to semaglutide.
- In Study NN9536-4374 (Section 7.2.2) there were 402 patients exposed to semaglutide 1 mg, 403 to semaglutide 2.4 mg and 402 to placebo for up to 68 weeks. There were 533 patient-years exposure to semaglutide 2.4 mg.
- In Study NN9536-4375 (Section 7.2.3) there were 407 patients exposed to semaglutide 2.4 mg weekly, and 204 to placebo, for up to 68 weeks. The total exposure to semaglutide was 526.1 patient-years.
- In Study NN9536-4376 (Section 7.2.4) there were 534 patients in the semaglutide group, who were exposed to 68 weeks of semaglutide, with 52 weeks of 2.4 mg weekly; and there were 268 in the placebo, who were exposed to the run-in (titration) phase of semaglutide for 20 weeks.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

In the Summary of Safety concerns, adverse events presented early in treatment (Figure 8.4.1.1.1). There were increased rates of gastrointestinal disorders and neurological disorders with semaglutide in comparison with placebo (Figure 8.4.1.1.2). The gastrointestinal adverse events that occurred more frequently with semaglutide compared to placebo were: nausea, diarrhoea, vomiting, constipation, abdominal pain, decreased appetite, dyspepsia, eructation and abdominal distension (Figure 8.4.1.1.3). The neurological disorders that occurred more commonly with semaglutide were headache, fatigue and dizziness. Other AEs that were reported more frequently with semaglutide were alopecia (3.3% patients compared to 1.4% with placebo) and migraine (2.1% patients compared to 1.3% with placebo).

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA,

8.4.1.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were 9558 TEAEs in 1171 (89.7%) patients in the semaglutide group and 3302 in 566 (86.4%) in the placebo. Gastrointestinal disorders were the most frequently reported AEs in the semaglutide group: 4309 events in 969 (74.2%) patients in the semaglutide group and 739 in 314 (47.9%) in the placebo. Nausea, diarrhoea, vomiting, and constipation were the most frequent TEAEs in the semaglutide group, and occurred at a greater frequency than in the placebo (Figure 8.4.1.3.1). GI adverse events were reported more frequently in the first 3 months of the study.

In Study NN9536-4374 (Section 7.2.2) there were 1952 TEAEs in 336 (83.6%) patients in the semaglutide 1 mg group, 2313 in 354 (87.8%) in the semaglutide 2.4 mg and 1450 in 315 (78.4%) in the placebo. There were 724 gastrointestinal TEAEs in 231 (57.5%) patients in the semaglutide 1 mg group, 924 in 256 (63.5%) in the semaglutide 2.4 mg and 262 in 138 (34.4%) in the placebo. The most frequently reported TEAEs were nausea, vomiting and diarrhoea, which were more frequent in the semaglutide groups (Figure 8.4.1.3.2).

In Study NN9536-4375 (Section 7.2.3) there were 4035 TEAEs reported in 390 (95.8%) patients in the semaglutide group and 1325 in 196 (96.1%) in the placebo. Gastrointestinal TEAEs were more frequent in the semaglutide group: 1760 reported in 337 (82.8%) patients in the semaglutide group and 333 in 129 (63.2%) in the placebo. Nausea, constipation, diarrhoea and vomiting were more frequently reported in the semaglutide group (Figure 8.4.1.3.3).

In Study NN9536-4376 (Section 7.2.4) there were 1885 TEAEs in 434 (81.3%) patients in the semaglutide group and 779 in 201 (75.0%) in the placebo group. There were 607 gastrointestinal TEAEs in 224 (41.9%) patients in the semaglutide group and 124 in 70 (26.1%) in the placebo group. Diarrhoea, nausea, vomiting and constipation were reported more frequently in the semaglutide group (Figure 8.4.1.3.4).

8.4.1.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there were 539 TEAEs in 93 (90.3%) patients in the semaglutide 0.05 mg/day group, 729 in 94 (92.2%) in the semaglutide 0.1 mg/day, 732 in 96 (93.2%) in the 0.2 mg/day, 582 in 93 (90.3%) in the 0.3 mg/day, 766 in 98 (96.1%) in the 0.4 mg/day, 721 in 98 (96.1%) in the semaglutide 0.3 mg/day fast titration, 672 in 96 (93.2%) in the semaglutide 0.4 mg/day fast titration, 606 in 88 (85.4%) in the liraglutide 3.0 mg/day and 639 in 107 (78.7%) in the placebo. The rate of AEs was dose related, and the rate was greater in the first three months of treatment (Figure 8.4.1.4.1). There was a dose-related increase in nausea, diarrhoea and constipation in the active treatment groups (Figure 8.4.1.4.2). Gastrointestinal adverse events occurred more frequently early in treatment (Figure 8.4.1.4.3).

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) there were 135 TEAEs in 28 (82.4%) participants with Formulation D and 146 in 31 (91.2%) with Formulation B (Table 8.4.1.4.1). The most frequently reported TEAEs were gastrointestinal: nausea, dyspepsia, diarrhoea, abdominal distension and vomiting. The most commonly reported non-GI TEAE was headache. Early satiety and decreased appetite were reported as common AEs, but these are the intended treatment effects.

In Study NN9535-4588 (Section 19.1.1.2) there were 143 TEAEs reported in 32 (91.4%) participants in the Formulation D group and 94 in 30 (90.9%) in the Formulation B (Table 8.4.1.4.2). Overall, the most frequently reported TEAEs were decreased appetite in 36 (52.9%) participants, headache in 29 (42.6%), nausea in 17 (25.0%), vomiting in 12 (17.6%) diarrhoea in 11 (16.2%) and dyspepsia in 10 (14.7%).

In Study NN9536-4455 (Section 19.1.2.1) there were 271 TEAEs reported in 29 (80.6%) participants in the semaglutide group and 180 in 33 (91.7%) in the placebo. The most frequently reported TEAEs in the semaglutide group were nausea in 17 (47.2%) participants, diarrhoea in 16 (44.4%), headache in 11 (30.6%), vomiting in eight (22.2%), nasopharyngitis in eight (22.2%) and abdominal pain in seven (19.4%) (Table 19.4.1.4.3).

Studies evaluable for safety only

NA.

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

NA.

8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.2.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were 2148 probable treatment related TEAEs in 571 (43.7%) patients in the semaglutide group and 330 in 147 (22.4%) in the placebo. Gastrointestinal AEs, headache, fatigue and dizziness were more frequent in the semaglutide group (Table 8.4.2.3.1). Injection site AEs were reported in 65 (5.0%) patients in the semaglutide group and 44 (6.7%) in the placebo.

In Study NN9536-4374 (Section 7.2.2) there were 751 possible or probable treatment related TEAEs in 222 (55.2%) patients in the semaglutide 1 mg group, 990 in 257 (63.8%) in the semaglutide 2.4 mg and 270 in 129 (32.1%) in the placebo. Nausea related to treatment was reported in 128 (31.8%) patients in the semaglutide 1 mg group, 134 (33.3%) in the semaglutide 2.4 mg and 27 (6.7%) in the placebo. Vomiting related to treatment was reported in 49 (12.2%) patients in the semaglutide 1 mg group, 77 (19.1%) in the semaglutide 2.4 mg and six (1.5%) in the placebo. Diarrhoea related to treatment was reported in 72 (17.9%) patients in the semaglutide 1 mg group, 68 (16.9%) in the semaglutide 2.4 mg and 31 (7.7%) in the placebo. Injection site adverse reactions were reported in six (1.5%) patients in the semaglutide 1 mg group, 12 (3.0%) in the semaglutide 2.4 mg and ten (2.5%) in the placebo.

In Study NN9536-4375 (Section 7.2.3) there were 1956 possible or probable treatment-related TEAEs reported in 320 (78.6%) patients in the semaglutide group and 323 in 114 (55.9%) in the placebo. Nausea related to treatment was reported in 226 (55.5%) patients in the semaglutide group and 41 (20.1%) in the placebo. Diarrhoea related to treatment was reported in 128 (31.4%) patients in the semaglutide group and 36 (17.6%) in the placebo. Constipation related to treatment was reported in 126 (31.0%) patients in the semaglutide group and 38 (18.6%) in the placebo. Vomiting related to treatment was reported in 98 (24.1%) patients in the semaglutide group and 14 (6.9%) in the placebo. Injection site AEs were reported in 22 (5.4%) patients in the semaglutide group and 12 (5.9%) in the placebo.

In Study NN9536-4376 (Section 7.2.4) there were 672 possible or probable treatment related TEAEs in 241 (45.0%) patients in the semaglutide group and 133 in 69 (25.7%) in the placebo group. The excess in the semaglutide group was due to a higher frequency of gastrointestinal events related to treatment: nausea in 68 (12.7%) in the semaglutide group and 7 (2.6%) in the placebo; diarrhoea in 57 (10.7%) in the semaglutide group and 13 (4.9%) in the placebo; constipation in 48 (9.0%) in the semaglutide group and 9 (3.4%) in the placebo; and vomiting in 47 (8.8%) in the semaglutide group and 8 (3.0%) in the placebo. During the randomisation phase, injection site AEs were reported in 14 (2.6%) in the semaglutide group and six (2.2%) in the placebo.

8.4.2.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there were 48 probable treatment related TEAEs in 35 (34.0%) patients in the semaglutide 0.05 mg/day group, 114 in 48 (47.1%) in the semaglutide 0.1 mg/day, 83 in 44 (42.7%) in the 0.2 mg/day, 108 in 45 (43.7%) in the 0.3 mg/day, 123 in 51 (50.0%) in the 0.4 mg/day, 206 in 60 (58.8%) in the semaglutide 0.3 mg/day fast titration, 147 in 43 (41.7%) in the semaglutide 0.4 mg/day fast titration, 128 in 53 (51.5%) in the liraglutide 3.0 mg/day and 46 in 32 (23.5%) in the placebo. Treatment related AEs appear to be dose-related, but not greatly increased by fast titration. There were similar frequencies of injection site AEs in each of the treatment groups.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) there were 80 probable treatment related TEAEs in 23 (67.6%) participants with Formulation D and 81 in 25 (73.5%) with Formulation B. There was one injection site reaction in the Formulation D group.

In Study NN9535-4588 (Section 19.1.1.2) there were 73 probable treatment related TEAEs reported in 29 (82.9%) participants in the Formulation D group and 50 in 23 (69.7%) in the Formulation B. These were predominantly gastrointestinal AEs. Injection site reactions were reported in three (8.6%) participants in the Formulation D group and none in the Formulation B.

In Study NN9536-4455 (Section 19.1.2.1) there were 37 probable treatment related TEAEs reported in 14 (38.9%) participants in the semaglutide group and eight in four (11.1%) in the placebo.

Studies evaluable for safety only

NA.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

In the Summary of Clinical Safety there were eight deaths reported. There were three deaths at the semaglutide 2.4 mg dose level (classified as cardiovascular deaths). In one of these cases semaglutide had been discontinued 113 days prior to death. There was one death at the semaglutide 1.0 mg dose level (undetermined cause of death). There was one death in the 0.4 mg fast escalation group in Study NN9536-4153 (malignancy). There were three deaths under placebo treatment, all due to malignancy.

In the Phase IIIa pool, 341 SAEs were reported in 246 (9.3%) patients with semaglutide and 132 in 100 (6.4%) with placebo. The rate of SAEs was 10.5 /100 person-year with semaglutide and 6.8 /100 person-year with placebo. Hepatobiliary SAEs were reported at a rate of 1.2 100/person-year with semaglutide and 0.2 /100 person-year with placebo (Table 8.4.3.1.1). Gastrointestinal SAEs were reported at a rate of 1.1 /100 person-year with semaglutide and 0.6 /100 person-year with placebo

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.3.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there was one (0.1%) death in the semaglutide group (sudden cardiac death) and one (0.2%) in the placebo (brain tumour). There were 164 SAEs in 128 (9.8%) patients in the semaglutide group and 53 in 42 (6.4%) in the placebo. Gastrointestinal SAEs were reported in 18 (1.4%) patients in the semaglutide group and none in the placebo (Table 8.4.3.3.1). Hepatobiliary SAEs were reported in 17 (1.3%) patients in the semaglutide group and one (0.2%) in the placebo.

In Study NN9536-4374 (Section 7.2.2) there was one (0.2%) death in the semaglutide 1 mg group (cardiorespiratory arrest), one (0.2%) in the semaglutide 2.4 mg (myocardial infarction) and one (0.2%) in the placebo (metastatic hepatocellular carcinoma/ pulmonary embolism/ respiratory failure). There were 53 SAEs in 31 (7.7%) patients in the semaglutide 1 mg group, 71 in 40 (9.9%) in the semaglutide 2.4 mg and 53 in 37 (9.2%) in the placebo. Nervous system and gastrointestinal SAEs were more frequent in the semaglutide 2.4 mg group (Table 8.4.3.3.2).

In Study NN9536-4375 (Section 7.2.3) there were no deaths reported. There were 55 SAEs reported in 37 (9.1%) patients in the semaglutide group and seven in six (2.9%) in the placebo (Table 8.4.3.3.3). Hepatobiliary SAEs were reported in ten (2.5%) patients in the semaglutide group, and none in the placebo. There was cholelithiasis in seven (1.7%) patients in the semaglutide group.

In Study NN9536-4376 (Section 7.2.4) there was one (0.2%) death in the semaglutide group (undetermined cause) and one (0.4%) in the placebo (metastatic lung cancer/pericardial effusion). There were 52 SAEs in 42 (7.9%) patients in the semaglutide group and 24 in 15 (5.6%) in the placebo group (Table 8.4.3.3.4). There were higher rates of neoplastic SAEs in the

semaglutide group: eight (1.5%) patients in the semaglutide group and one (0.4%) in the placebo. Hepatobiliary SAEs were reported in six (1.1%) patients in the semaglutide group and two (0.7%) in the placebo.

8.4.3.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there was one fatality in the semaglutide 0.4 mg/day fast titration group (ovarian cancer metastatic and pneumonia). There were 17 SAEs in 13 (12.6%) patients in the semaglutide 0.05 mg/day group, nine in eight (7.8%) in the semaglutide 0.1 mg/day, seven in five (4.9%) in the 0.2 mg/day, eight in six (5.8%) in the 0.3 mg/day, 22 in 13 (12.7%) in the 0.4 mg/day, 11 in six (5.9%) in the semaglutide 0.3 mg/day fast titration, nine in seven (6.8%) in the semaglutide 0.4 mg/day fast titration, five in four (3.9%) in the liraglutide 3.0 mg/day and 16 in 11 (8.1%) in the placebo. Three (2.9%) patients had cholelithiasis in the semaglutide 0.3 mg/day fast titration group.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) there were no deaths. There was one SAE in one (2.9%) participant in the Formulation D group (supraventricular tachycardia).

In Study NN9535-4588 (Section 19.1.1.2) there were no deaths or SAEs.

In Study NN9536-4455 (Section 19.1.2.1) there were no deaths. There was one SAE reported in one (2.8%) participant in the semaglutide group (road traffic accident) and one in one (2.8%) in the placebo (colonic abscess).

Studies evaluable for safety only

NA.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

The Summary of Clinical Safety indicated an excess of patients discontinuing due to AEs in the semaglutide treatment groups compared to placebo. In the Phase IIIa pool there were 149 (5.7%) patients in the semaglutide group and 47 (3.0%) in the placebo discontinuing because of AEs. This was primarily due to gastrointestinal disorders: nausea, vomiting, diarrhoea, upper abdominal pain and constipation (Table 8.4.4.1.1).

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.4.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) AE leading to treatment discontinuation was reported in 92 (7.0%) patients in the semaglutide group and 20 (3.1%) in the placebo. The difference between the groups was due to more GI adverse events leading to discontinuation in the semaglutide group (Table 8.4.4.3.1).

In Study NN9536-4374 (Section 7.2.2) AE leading to permanent treatment discontinuation was reported in 20 (5.0%) patients in the semaglutide 1 mg group, 25 (6.2%) in the semaglutide 2.4 mg and 14 (3.5%) in the placebo. The difference between the groups was due to GI adverse events leading to discontinuation, with higher frequency in the semaglutide 2.4 mg group (Table 8.4.4.3.2).

In Study NN9536-4375 (Section 7.2.3) permanent treatment discontinuation due to AE was reported in 24 (5.9%) patients in the semaglutide group and six (2.9%) in the placebo. Gastrointestinal AEs lead to permanent treatment discontinuation in 14 (3.4%) patients in the semaglutide group and none in the placebo (Table 8.4.4.3.3).

In Study NN9536-4376 (Section 7.2.4), during the randomisation period, permanent treatment discontinuation due to AE was reported for eight (1.5%) patients in the semaglutide group and seven (2.6%) in the placebo group (Table 8.4.4.3.4). Four (1.5%) patients in the placebo group discontinued due to cholelithiasis.

8.4.4.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) discontinuation due to TEAEs was reported for seven (6.8%) patients in the semaglutide 0.05 mg/day group, eight (7.8%) in the semaglutide 0.1 mg/day, five (4.9%) in the 0.2 mg/day, four (3.9%) in the 0.3 mg/day, 15 (14.7%) in the 0.4 mg/day, 17 (16.7%) in the semaglutide 0.3 mg/day fast titration, eight (7.8%) in the semaglutide 0.4 mg/day fast titration, nine (8.7%) in the liraglutide 3.0 mg/day and four (2.9%) in the placebo. The majority of adverse events leading to discontinuation were gastrointestinal (nausea, diarrhoea and constipation) and the frequency was greatest in the semaglutide 0.4 mg/day arm (Figure 8.4.4.4.1).

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) there were no withdrawals due to AE, and one dose interruption due to AE in the Formulation B group.135 TEAEs in 28 (82.4%) participants with Formulation D and 146 in 31 (91.2%) with Formulation B.

In Study NN9535-4588 (Section 19.1.1.2) there no withdrawals related to AE.

In Study NN9536-4455 (Section 19.1.2.1) there was one AE leading to discontinuation in one (2.8%) participant in the placebo (colonic abscess).

Studies evaluable for safety only

NA.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

8.5.1.1. Integrated safety analyses

NA.

8.5.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.1.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were 31 (2.4%) patients with hepatic AEs in the semaglutide and 20 (3.1%) in the placebo. One (<0.1%) patient in the semaglutide group and three (0.5%) in the placebo had elevated ALT. One (<0.1%) patient in the semaglutide group and four (0.6%) in the placebo had elevated ALT. No patients met the criteria for Hy's law during the study.

In Study NN9536-4374 (Section 7.2.2) hepatobiliary disorders were reported in three (0.7%) patients in the semaglutide 1 mg group, one (0.2%) in the semaglutide 2.4 mg and three (0.7%) in the placebo. Elevated ALT was reported for one (0.2%) patient in the semaglutide 1 mg group and four (1.0%) in the placebo. Elevated AST was reported in one (0.2%) patient in the semaglutide 1 mg group and two (0.5%) in the placebo.

In Study NN9536-4375 (Section 7.2.3) hepatobiliary disorders were reported in 20 (4.9%) patients in the semaglutide group and three (1.5%) in the placebo. ALT was increased in one (0.2%) patient in the semaglutide group and one (0.5%) in the placebo. AST was increased in

three (0.7%) patients in the semaglutide group and none in the placebo. Three (0.7%) patients in the semaglutide group and three (1.5%) in the placebo were reported with hepatic steatosis.

s47 [redacted] Elevated ALT was reported for one (0.2%) patient in the semaglutide group and none in the placebo. Elevated AST was reported in one (0.2%) patient in the semaglutide group and none in the placebo.

8.5.1.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) no patients met the biochemical criteria for Hy's law (defined as elevated ALT or AST activity levels >3xUNR in combination with total bilirubin levels >2xUNR without elevated ALP)

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) and Study NN9536-4455 (Section 19.1.2.1) there were no clinically relevant abnormalities in hepatic function.

In Study NN9535-4588 (Section 19.1.1.2) one participant in the Formulation D group had elevated ALT and AST.

Studies evaluable for safety only

NA.

8.5.2. Renal function and renal toxicity

8.5.2.1. Integrated safety analyses

NA.

8.5.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.2.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were three (0.2%) patients with acute renal failure AEs in the semaglutide and two (0.3%) in the placebo.

In Study NN9536-4374 (Section 7.2.2) acute renal failure adverse events were reported in two (0.5%) patients in the semaglutide 1 mg group, four (1.0%) in the semaglutide 2.4 mg and two (0.5%) in the placebo. At Week 68, microalbuminuria was present in 42 (12.3%) in the semaglutide group, 20 (11.6%) in the semaglutide 2.4 mg and 73 (21.8%) in the placebo.

In Study NN9536-4375 (Section 7.2.3) there were no reports of acute renal failure.

In Study NN9536-4376 (Section 7.2.4) one patient had acute renal injury during the run-in period and one patient in each treatment group had acute renal failure during the randomisation period.

8.5.2.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there was one report of acute kidney injury in the semaglutide 0.4 mg/day group and one of acute kidney injury in the semaglutide 0.3 mg/day group.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1), Study NN9535-4588 (Section 19.1.1.2) and Study NN9536-4455 (Section 19.1.2.1) there were no clinically relevant abnormalities in renal function.

Studies evaluable for safety only

NA.

8.5.3. Other clinical chemistry

8.5.3.1. Integrated safety analyses

NA.

8.5.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.3.3. Pivotal and/or main efficacy studies

In Study NN9536-4374 (Section 7.2.2), Study NN9536-4375 (Section 7.2.3) and Study NN9536-4376 (Section 7.2.4) mean calcitonin concentrations were stable during the study.

8.5.3.4. Other studies

Other efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were no significant changes in mean calcitonin concentrations in either treatment group.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) there were no clinically relevant abnormalities in clinical chemistry.

In Study NN9535-4588 (Section 19.1.1.2) one participant in the Formulation D group had elevated CK.

Study NN9536-4455 (Section 19.1.2.1) in the semaglutide 2.4 mg group there was an increase in mean lipase from 20.8 U/L at screening to 39.0 U/L at Week 20.

Studies evaluable for safety only

NA.

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

NA.

8.5.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.4.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were no significant abnormalities in haematology in the semaglutide group and one patient with thrombocytopenia in the placebo.

In Study NN9536-4374 (Section 7.2.2) and Study NN9536-4375 (Section 7.2.3) there were no significant abnormalities in haematology.

Study NN9536-4376 (Section 7.2.4) thrombocytopenia was reported in three (0.6%) patients in the semaglutide group and one (0.4%) in the placebo. Leukopenia was reported in one (0.2%) patient in the semaglutide group. Pancytopenia was reported in one (0.2%) patient in the semaglutide group.

8.5.4.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there were no clinically significant abnormalities in haematology parameters.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) and Study NN9536-4455 (Section 19.1.2.1) there were no clinically relevant abnormalities in haematology.

Studies evaluable for safety only

8.5.5. Other laboratory tests

NA.

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

NA.

8.5.6.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.6.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) cardiovascular AEs were reported in 107 (8.2%) patients in the semaglutide group and 75 (11.5%) in the placebo. Eight patients in the semaglutide group and five in the placebo had worsening of ECGs during the study.

In Study NN9536-4374 (Section 7.2.2) cardiovascular adverse events were reported in 35 (8.7%) patients in the semaglutide 1 mg group, 50 (12.4%) in the semaglutide 2.4 mg and 39 (9.7%) in the placebo. There were no significant differences between the treatment groups in ECG shifts during the study.

In Study NN9536-4375 (Section 7.2.3) cardiovascular adverse events were reported in 40 (9.8%) patients in the semaglutide group and 22 (10.8%) in the placebo. There were no significant differences between the groups in shifts in ECGs.

In Study NN9536-4376 (Section 7.2.4) cardiovascular AEs were reported in 26 (4.9%) patients in the semaglutide group and 30 (11.2%) in the placebo group.

8.5.6.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) one patient in the semaglutide 0.2 mg/day group developed sinus bradycardia and first-degree atrioventricular block.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) one participant in the Formulation D group developed supraventricular tachycardia. There were no other clinically significant abnormalities in ECGs.

In Study NN9535-4588 (Section 19.1.1.2) there were no clinically significant abnormalities in ECGs.

Studies evaluable for safety only

NA.

8.5.7. Vital signs and clinical examination findings

8.5.7.1. Integrated safety analyses

NA.

8.5.7.2. Pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.7.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) mean pulse rate increased by 3 bpm relative to placebo.

In Study NN9536-4374 (Section 7.2.2) mean pulse rate increased by 2 bpm in the semaglutide groups and remained stable in the placebo.

In Study NN9536-4375 (Section 7.2.3) mean pulse rate increased by 3 bpm in the semaglutide group and 2 bpm in the placebo.

In Study NN9536-4376 (Section 7.2.4) mean pulse rate increased in both treatment groups during the run-in phase by 5 bpm, and then remained stable in the semaglutide group, but decreased to Week 0 rates in the placebo. During the randomisation period, one patient in the semaglutide group had an ECG shift to Long QT syndrome.

8.5.7.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) mean pulse rate increased by approximately 4 bpm in the active treatment groups.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) there was a mean increase in pulse rate of 7.4 bpm with Formulation D and 2.6 bpm with Formulation B.

In Study NN9535-4588 (Section 19.1.1.2) was a mean decrease in body weight over the 7 weeks of the study of 3.3 kg with Formulation D and 3.5 kg with Formulation B.

Study NN9536-4455 (Section 19.1.2.1) in the semaglutide 2.4 mg group there was an increase in mean pulse rate of 5 bpm from screening to Week 20.

Studies evaluable for safety only

NA.

8.5.8. Immunogenicity and immunological events

8.5.8.1. Integrated safety analyses

The dossier included an integrated summary of immunogenicity. Immunogenicity was assessed in s47 [redacted], Study NN9536-4590, Study NN9535-4588, Study NN9536-4373 and Study NN9536-4374. Immunogenicity was not assessed in Study NN9536-4375 and Study NN9536-4376. In the five studies where immunogenicity was assessed, there were 22796 samples from 2563 patients treated with semaglutide tested for antibodies.

In the Phase III studies (Study NN9536-4373 and Study NN9536-4374) there were 50 (2.9%) patients with treatment induced anti-semaglutide antibodies, none were neutralising and 28 (1.6%) had antibodies that cross-reacted with GLP-1. Anti-semaglutide antibodies did not appear to alter the PK of semaglutide. There was no significant difference in efficacy in the patients with antibodies compared to those without (Table 8.5.8.1.1). No patients in the Phase I or Phase II studies developed anti-semaglutide antibodies.

8.5.8.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.8.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were 96 (7.4%) patients with allergic reactions adverse events in the semaglutide group and 54 (8.2%) in the placebo. In the semaglutide group, there were 16 (1.6%) patients positive for anti-semaglutide antibodies at Week 68, and 10 with antibodies cross-reacting with GLP-1, but none of the patients had neutralising antibodies.

In Study NN9536-4374 (Section 7.2.2) allergic reaction adverse events were reported in 11 (5.5%) patients in the semaglutide 1 mg group, 26 (6.5%) in the semaglutide 2.4 mg and 18 (4.5%) in the placebo. Anti-semaglutide antibodies were not detected at baseline, but during the study there were four (1.0%) patients in the semaglutide 1 mg group and 12 (3.0%) in the semaglutide 2.4 mg with anti-semaglutide antibodies. In four (1.0%) patients in the semaglutide 1 mg group and seven (1.7%) in the semaglutide 2.4 mg the anti-semaglutide antibodies cross-reacted with endogenous GLP-1, but none were neutralising.

In Study NN9536-4375 (Section 7.2.3) allergic reaction AEs were reported in 35 (8.6%) patients in the semaglutide group and 19 (9.3%) in the placebo.

In Study NN9536-4376 (Section 7.2.4) allergic reaction AEs were reported in 26 (4.9%) in the semaglutide group and 11 (4.1%) in the placebo.

8.5.8.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) none of the participants developed antibodies to semaglutide. One participant in the semaglutide 0.4 mg/day arm had an anaphylactic reaction but this did not recur with subsequent dosing.

Studies with evaluable safety data: dose finding and pharmacology

In StudyNN9536-4590 (Section 19.1.1.1) no participant developed antibodies to semaglutide.

In Study NN9535-4588 (Section 19.1.1.2) one hypersensitivity reaction was reported in the Formulation D group (generalised pruritus).

Studies evaluable for safety only

NA.

8.5.9. Serious skin reactions

Serious skin reactions were not identified as a safety concern in the safety data.

8.5.10. Neoplasia

8.5.10.1. Integrated safety analyses

NA.

8.5.10.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.10.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) 93 (7.1%) patients in the semaglutide group and 49 (7.5%) in the placebo had malignancy events reported during the study.

In Study NN9536-4374 (Section 7.2.2) neoplasms were reported in 29 (7.2%) patients in the semaglutide 1 mg group, 21 (5.2%) in the semaglutide 2.4 mg and 28 (7.0%) in the placebo. No events of pancreatic or medullary thyroid carcinoma were reported.

In Study NN9536-4375 (Section 7.2.3) neoplastic AEs were reported in 43 (10.6%) patients in the semaglutide group and 15 (7.4%) in the placebo. There were three (0.7%) patients in the semaglutide group and one (0.5%) in the placebo reported with malignant neoplasm AEs.

In Study NN9536-4376 (Section 7.2.4) neoplastic AEs were reported in 30 (5.6%) patients in the semaglutide group and 16 (6.0%) in the placebo group. Malignant neoplasms were reported in six (1.1%) patients in the semaglutide group and one (0.4%) in the placebo (Table 8.5.10.3.1).

8.5.10.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) neoplasia was reported in three patients with semaglutide 0.05 mg/day, one with semaglutide 0.1 mg/day, three with semaglutide 0.2 mg/day, four with semaglutide 0.4 mg/day, three with liraglutide 3.0 mg/day, one with semaglutide 0.4 mg/day fast titration and four in the placebo group.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.11. Pancreatitis

8.5.11.1. Integrated safety analyses

NA.

8.5.11.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.11.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) acute pancreatitis was reported in three (0.2%) patients in the semaglutide group and none in the placebo. Gallbladder-related disorders were reported in 34 (2.6%) patients in the semaglutide group and eight (1.2%) in the placebo. In the semaglutide group mean lipase concentrations increased by 41% during the study and amylase concentrations by 14%.

In Study NN9536-4374 (Section 7.2.2) EAC confirmed pancreatitis was reported for one patient in the semaglutide 2.4 mg group and one in the placebo. Mean lipase and amylase concentrations increased in both semaglutide treatment groups. Mean lipase increased by 31% in the semaglutide 1 mg group and 41% in the semaglutide 2.4 mg group. Mean amylase increased by 19% in the semaglutide 1 mg group and 24% in the semaglutide 2.4 mg group.

In Study NN9536-4375 (Section 7.2.3) there were no reports of acute pancreatitis. Mean lipase concentrations increased by 31% in the semaglutide group and were stable in the placebo. Mean amylase concentrations increased by 12% in the semaglutide group and were stable in the placebo.

In Study NN9536-4376 (Section 7.2.4) there was one report of acute pancreatitis in the run-in period, and no further reports during the randomisation period. In the semaglutide group, mean lipase and amylase concentrations increased during the run-in period (lipase by 44% and amylase by 6%) and remained stable during the randomisation period. In the placebo group, mean lipase and amylase concentrations increased during the run-in period, and then decreased to approximately the same concentrations as Week 0.

8.5.11.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there were four reports of pancreatitis: one in the 0.05 mg/day group, two in the 0.3 mg/day fast titration group and one in the placebo. All of these reports had concurrent reports of cholelithiasis. Mean serum lipase and amylase concentrations increased with all the active treatments.

Studies with evaluable safety data: dose finding and pharmacology

NA

Studies evaluable for safety only

NA.

8.5.12. Hypoglycaemia

8.5.12.1. Integrated safety analyses

NA.

8.5.12.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.12.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were 0.9 hypoglycaemic events/100 patient-years in the semaglutide and 0.8 hypoglycaemic events/100 patient-years in the placebo.

In Study NN9536-4374 (Section 7.2.2) severe or blood glucose confirmed hypoglycaemic episodes were reported in 22 (5.5%) patients in the semaglutide 1 mg group, 23 (5.7%) in the semaglutide 2.4 mg and 12 (3.0%) in the placebo.

In Study NN9536-4375 (Section 7.2.3) there were two non-serious AEs of hypoglycaemia in the semaglutide group.

Study NN9536-4376 (Section 7.2.4) there were three AEs of hypoglycaemia in each treatment group during the randomisation period.

8.5.12.4. Other studies

Other efficacy studies

In Study NN9536-4153 (Section 6.2) there were no reports of severe hypoglycaemia.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.13. Mental Health

8.5.13.1. Integrated safety analyses

NA.

8.5.13.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.13.3. Pivotal and/or main efficacy studies

In Study NN9536-4373 (Section 7.2.1) there were 124 (9.5%) patients with psychiatric AEs in the semaglutide group and 83 (12.7%) in the placebo. Mental health scores (PHQ-9 and C-SSRS) did not deteriorate in the semaglutide group during the study.

In Study NN9536-4374 (Section 7.2.2) post-baseline on the C-SSRS, two (0.5%) patients in the semaglutide 1 mg group, two (0.5%) in the semaglutide 2.4 mg and one (0.3%) in the placebo had suicidal ideation. No patients had suicidal behaviour. There were no apparent differences in suicidality assessed by the PHQ-9.

In Study NN9536-4375 (Section 7.2.3) mental health AEs were reported in 60 (14.7%) patients in the semaglutide group and 24 (11.8%) in the placebo. There were no significant differences between the groups in PHQ-9 or C-SSRS. No patients in the semaglutide group had suicidal ideation or suicidal behaviour.

In Study NN9536-4376 (Section 7.2.4), during the randomisation phase, mental health AEs were reported in 46 (8.6%) in the semaglutide group and 35 (13.1%) in the placebo. PHQ-9 scores were higher in the placebo group than the semaglutide group during the randomisation phase. On the C-SSRS, during the randomisation phase, one (0.2%) patient in the semaglutide group and three (1.1%) in the placebo had suicidal ideation, and one patient in the placebo group had suicidal behaviour.

8.5.13.4. Other studies

Other efficacy studies

NA.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.14. Other safety parameters

8.5.14.1. Integrated safety analyses

NA.

8.5.14.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.14.3. Pivotal and/or main efficacy studies

In Study NN9536-4374 (Section 7.2.2) diabetic retinopathy was reported in 25 (6.2%) patients in the semaglutide 1 mg group, 28 (6.9%) in the semaglutide 2.4 mg and 17 (4.2%) in the placebo.

8.5.14.4. Other studies

Other efficacy studies

NA.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.6. Other safety issues

8.6.1. Safety in special populations

NA.

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

NA.

8.7. Post marketing experience

8.7.1. Post-marketing data

No post-marketing data were included in the dossier.

8.7.2. Risk Management Plan

s47 [redacted]

The RMP identifies the following safety concerns:

Important identified risks:

- Diabetic retinopathy complications

Important potential risks:

- Pancreatic cancer
- Medullary thyroid cancer
- Neoplasms (malignant and non-malignant)

Missing information:

- Pregnancy and lactation
- Patients with severe hepatic impairment

The RMP does not identify off-label use or misuse as important potential risks. The Sponsor states in the RMP: "Currently, no potential for misuse has been identified." However, this does not acknowledge the potential for off-label use in children and the potential for misuse in patients with eating disorders and in athletes. In some sports athletes can be expected to lose weight in order to comply with weight categories (e.g. boxing, horse racing). Prescribing of semaglutide to people with eating disorders or athletes is unlikely, but diversion to these groups is plausible.

The Sponsor intends to perform routine pharmacovigilance activities in Australia and no additional pharmacovigilance activities specific to Australia are planned.

Other than the warnings and precautions in the Product Information, no additional risk management activities are planned. The Sponsor proposes no Australian-specific evaluation of the effectiveness of risk minimisation measures.

The RMP acknowledges that: "The clinical development programmes are unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure."

8.8. Evaluator's overall conclusions on clinical safety

Semaglutide in the proposed usage has a favourable safety profile.

There were increased rates of gastrointestinal disorders and neurological disorders with semaglutide in comparison with placebo (Figure 8.4.1.1.2). The gastrointestinal adverse events that occurred more frequently with semaglutide compared to placebo were: nausea, diarrhoea, vomiting, constipation, abdominal pain, decreased appetite, dyspepsia, eructation and abdominal distension (Figure 8.4.1.1.3). The neurological disorders that occurred more commonly with semaglutide were headache, fatigue and dizziness. Other AEs that were reported more frequently with semaglutide were alopecia (3.3% patients compared to 1.4% with placebo) and migraine (2.1% patients compared to 1.3% with placebo). In Study NN9536-4153 (Section 6.2), the Phase II dose-finding study, gastrointestinal adverse effects (vomiting, diarrhoea and constipation) were dose-related.

Injection site reactions occurred at a similar frequency with semaglutide 2.4 mg in comparison with placebo.

Overall, there were few deaths reported and the rate of death was not increased in the semaglutide 2.4 mg group relative to placebo. There were three deaths at the semaglutide 2.4 mg dose level (classified as cardiovascular deaths). In one of these cases semaglutide had been discontinued 113 days prior to death. There was one death at the semaglutide 1.0 mg dose level (undetermined cause of death). There was one death in the 0.4 mg fast escalation group in Study NN9536-4153 (malignancy). There were three deaths under placebo treatment, all due to malignancy.

The rate of SAEs was increased relative to placebo. SAEs were reported in 246 (9.3%) patients with semaglutide and 132 in 100 (6.4%) with placebo. The rate of SAEs was 10.5 /100 person-year with semaglutide and 6.8 /100 person-year with placebo. Hepatobiliary SAEs were reported at a rate of 1.2 /100 person-year with semaglutide and 0.2 /100 person-year with placebo (Table 8.4.3.1.1). Gastrointestinal SAEs were reported at a rate of 1.1 /100 person-year with semaglutide and 0.6 /100 person-year with placebo.

There was an excess of patients discontinuing due to AEs in the semaglutide treatment groups compared to placebo. In the Phase IIIa pool there were 149 (5.7%) patients in the semaglutide group and 47 (3.0%) in the placebo discontinuing because of AEs. This was primarily due to gastrointestinal disorders: nausea, vomiting, diarrhoea, upper abdominal pain and constipation (Table 8.4.4.1.1).

Hepatobiliary disorders were more frequent with semaglutide 2.4 mg, but elevation of transaminases was not more frequent, and no patients fulfilled the criteria of Hy's law.

The rate of renal dysfunction was not increased with semaglutide 2.4 mg. Plasma calcitonin concentrations were not increased by semaglutide 2.4 mg. Haematology AEs occurred at similar rates to placebo.

Cardiovascular AEs were less frequent with semaglutide than placebo. This supports the improvement in surrogate measures of cardiovascular risk in the pivotal studies. In the pivotal studies, mean pulse rate increased by 2 to 5 bpm, but there was a significant decrease in SBP relative to placebo in the semaglutide groups.

In the clinical studies semaglutide 2.4 mg had low immunogenicity. In the two Phase III studies that tested for anti-semaglutide antibodies, there were 50 (2.9%) patients with treatment induced anti-semaglutide antibodies, none were neutralising and 28 (1.6%) had antibodies that cross-reacted with GLP-1. The rate of allergic AEs was similar to the placebo group.

The rates of neoplasia were similar for semaglutide 2.4 mg and placebo.

There were few reports of pancreatitis, but more in the semaglutide treated groups than in the placebo: in the pivotal studies there were four in the semaglutide groups and one in the placebo.

Hypoglycaemia was infrequent and was not identified as a safety concern in this population.

Mental health scores and suicidality did not differ significantly between semaglutide 2.4 mg and placebo.

Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
The Phase IIIa studies demonstrated a statistically and clinically significant weight loss with semaglutide 2.4 mg weekly dosing. The magnitude of the weight loss was: • Study NN9536-4373: treatment difference (95% CI), semaglutide – placebo, -12.44 (-13.37 to -11.51) %, p <0.0001. • Study NN9536-4374: estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -6.21 (-7.28 to -5.15) %, p <0.0001. • Study NN9536-4375: treatment difference (95% CI), semaglutide – placebo, -10.27 (-11.97 to -8.57) %, p <0.0001. • Study NN9536-4376: treatment difference (95% CI), semaglutide – placebo, -14.75 (-16.00 to -13.50) %, p <0.0001. The treatment effect was well in excess of a clinically significant 5% weight loss. The effect size was consistent across the four studies. The effect persisted in a patient group undergoing IBT and in patients with T2DM. The decrease in body weight was matched by decreases in waist circumference and in BMI. There were improvements in markers of cardiovascular risk. There were improvements in glycaemic control. There were significant improvements in quality of life and physical functioning.	The data indicate that semaglutide is likely to be used for long-term management of weight in this patient group. Hence, it would be desirable to demonstrate ongoing efficacy beyond a one-year treatment period.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
There were increased rates of gastrointestinal disorders and neurological disorders with semaglutide in comparison with placebo. These events were predominantly non-serious and were of limited duration and without long-term sequelae. The gastrointestinal adverse events that occurred more frequently with semaglutide compared to placebo were: nausea, diarrhoea, vomiting, constipation, abdominal pain, decreased appetite, dyspepsia, eructation and abdominal distension. The neurological disorders that occurred more commonly with semaglutide were headache, fatigue and dizziness. In the pivotal studies the rate of SAEs was 10.5 /100 person-year with semaglutide and 6.8 /100 person-year with placebo. Hepatobiliary SAEs were reported at a rate of 1.2 /100 person-year with semaglutide and 0.2 /100 person-year with placebo. Gastrointestinal SAEs were reported at a rate of 1.1 /100 person-year with semaglutide and 0.6 /100 person-year with placebo. Discontinuation due to AE occurred at a higher rate in the semaglutide groups compared to placebo. In the Phase IIIa pool there were 149 (5.7%) patients in the semaglutide group and 47 (3.0%) in the placebo discontinuing because of AEs. This was primarily due to gastrointestinal disorders: nausea, vomiting, diarrhoea, upper abdominal pain and constipation Cardiovascular AEs were less frequent with semaglutide than placebo.	Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data.

9.3. First round assessment of benefit-risk balance

The benefit risk profile for TRADENAME (semaglutide) for the proposed indication is favourable.

10. First round recommendation regarding authorisation

The Clinical Evaluator has no object to the approval of TRADENAME (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle, for the proposed indication of:

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

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

The Clinical Evaluator recommends that stopping criteria be developed for TRADENAME (semaglutide) to define the level of BMI at which treatment should be halted.

11. First round comments on product documentation

11.1. First round comments on draft PI (clinical aspects)

The dosing and method of administration are supported by the clinical data.

The special warnings and precautions for use section is supported by the clinical data.

The interactions section is supported by the clinical data. The Forrest plot is effective in communicating the extent of interactions.

Sections 4.6 and 4.7 are supported by the clinical data.

The section on adverse effects is supported by the data and Table 2 effectively communicates the risk of AEs compared to placebo.

The section on pharmacodynamics is supported by the clinical data.

The section on clinical trials is supported by the clinical data. The claims with regard to reduction of cardiovascular risk are stated to have been demonstrated with the 1.0 mg dose level and are supported by Study NN9535-3744 (SUSTAIN 6). Figure 8 demonstrates the benefit for each category of MACE.

The section on pharmacokinetics is supported by the clinical data.

11.2. First round comments on draft CMI (clinical aspects)

The CMI is appropriate and is supported by the dossier. The titration regiment may appear complex to some patients and the Sponsor might consider developing a resource to help patients through the titration phase, and its dose increments.

11.3. First round comments on draft RMP (Summary of Safety Concerns)

The waivers for Paediatric Investigation Plan in the EU and Pediatric Assessment in the USA may relate to the initial application for treatment of T2DM and may not relate to the current proposed indication of weight control. Obesity is recognised as a clinical condition in children that requires treatment. Hence, in the opinion of the Clinical Evaluator, efficacy and safety in the paediatric population is Missing Information.

Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse, and diversion, in other groups (such as people with eating disorders, athletes and actors) has not been addressed in the data. In the opinion of the Clinical Evaluator this is an Important Potential Risk.

12. Clinical questions

12.1. Clinical questions

12.1.1. Pharmacokinetics

s47 [redacted]

12.1.2. Pharmacodynamics

The Clinical Evaluator has no questions relating to pharmacodynamics.

12.1.3. Efficacy

The waivers for Paediatric Investigation Plan in the EU and Pediatric Assessment in the USA may relate to the initial application for treatment of T2DM and may not relate to the current proposed indication of weight control. Does the Sponsor intend to perform clinical trials in the paediatric and adolescent populations?

The data indicate that treatment with semaglutide is likely to be required long-term. There was a return to baseline in the placebo group in Study NN9536-4376. This means the treatment effect does not persist after the treatment is ceased. Hence, it would be important to demonstrate that treatment effect continues with ongoing treatment beyond one year. Has the Sponsor demonstrated persistence of treatment effect beyond one year of treatment?

There is potential for rebound in weight once treatment is stopped. While the results of Study NN9536-4376 suggest this is unlikely, a rebound in weight might occur over the long term in patients who cease semaglutide treatment. Has the Sponsor investigated the potential for rebound weight gain following cessation of treatment?

12.1.4. Safety

Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data. Does the Sponsor intend to monitor misuse and diversion in other patient populations?

12.1.5. PI and CMI

Has the sponsor developed stopping criteria for TRADENAME (semaglutide) to define the level of BMI at which treatment should be halted?

12.2. Additional expert input

The Clinical Evaluator does not have any recommendation for additional expert input.

13. First round evaluation errata

13.1. Minor editorial changes

There are no minor editorial changes.

13.2. Minor errors of fact

No minor errors of fact have been identified.

13.3. Significant errors of fact

No significant errors of fact have been identified.

14. Second round evaluation

The Sponsor has decided on the tradename WEGOVY®.

The Sponsor has provided the following responses to the clinical questions:

1.1 Pharmacokinetics

1.1.1 Question 1 (formulations)

Can the Sponsor please confirm that the formulation used in the Phase 3a trials is identical to those intended for marketing in Australia.

1.1.1.1 Sponsor's Response to Question 1

The formulation used in the phase 3a trials and the intended to-be-marketed formulation are presented in Summary 2.7.1, Section 1.2, seq 0000 and 3.2.P.2.2 Drug Product document, seq 0000. The formulations are not identical. Bioequivalence assessments between the to-be-marketed and phase 3a drug products are presented in Summary 2.7.1, Section 3, seq 0000.

The composition of semaglutide drug products used in the phase 3a trials (administered with the PDS290 pen-injector) and the intended to-be-marketed formulation (administered in the single-dose pen-injector) is shown in Table 1-1. Compared to semaglutide for use in the PDS290 pen-injector, the semaglutide formulation for use in the single-dose pen-injector does not contain phenol (preservative) as it is intended for single use. Furthermore, the isotonic agent is changed from propylene glycol to sodium chloride. All other ingredients are the same.

Table 1-1 Composition of semaglutide drug products

PDS290 pen-injector Phase 3a **Name of ingredient** **Drug substance**	**Single-dose pen-injector** *To-be-marketed* **Name of ingredient** **Drug substance**	**Function**	**Pharmacopoeia**
Semaglutide	Semaglutide	Active pharmaceutical ingredient	Novo Nordisk A/S
Other ingredients	**Other ingredients**		
Disodium hydrogen phosphate, dihydrate	Disodium hydrogen phosphate, dihydrate	Buffering agent	USP/Ph. Eur
Propylene glycol	Sodium chloride	Isotonic agent	USP/JP/Ph. Eur
Phenol	-	Preservative	USP/JP/Ph. Eur
Hydrochloric acid	Hydrochloric acid	pH adjustment	USP/JP/Ph. Eur
Sodium hydroxide	Sodium hydroxide	pH adjustment	USP/JP/Ph. Eur
Water for injection	Water for injection	Solvent	USP/JP/Ph. Eur

Abbreviations: JP: the Japanese Pharmacopoeia; Ph. Eu: European Pharmacopoeia; USP: United States Pharmacopoeia.

In the phase 3a clinical trials, drug product concentrations used in the semaglutide 2.4 mg treatment groups were mainly 1.0 mg/mL and 3.0 mg/mL semaglutide. Different volumes were injected by the PDS290 pen-injector in order to deliver the escalation doses (0.25 mg, 0.5 mg, 1 mg, 1.7 mg) and the maintenance dose (2.4 mg) tested in the phase 3a clinical trial programme (Table 1-2).

The single-dose pen-injector for semaglutide is a single-use device with an integrated prefilled syringe. The single-dose pen-injector will be available in five variants: one for each of the five doses of semaglutide (0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg). The dose volume will be 0.5 mL for the three lower doses of 0.25 mg, 0.5 mg and 1 mg, and 0.75 mL for the two higher doses of 1.7 mg and 2.4 mg. Thus, to support the five variants, the semaglutide drug product has been formulated in five concentrations: 0.5 mg/mL, 1.0 mg/mL, 2.0 mg/mL, 2.27 mg/mL and 3.2 mg/mL (Table 1-2).

For further information on the drug products and the single-dose pen-injector, please refer to 3.2.P.2.2 Drug Product document and Summary 3.2.P.7, Device description, seq 0000, respectively.

Table 1-2 Key features of semaglutide drug products used in phase 3a and semaglutide drug products *to-be-marketed*

Formulation	**Semaglutide** Phase 3a					**Semaglutide** *To-be-marketed*				
Delivery device	PDS290 pen-injector for semaglutide					Single-dose pen-injector for semaglutide				
Type of dose	Escalation				Mainte-nance	Escalation				Mainte-nance
Doses	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg
Injection volume	0.25 mL	0.5 mL	0.34 mL	0.57 mL	0.80 mL	0.5 mL	0.5 mL	0.5 mL	0.75 mL	0.75 mL
Semaglutide concentration	**1.0 mg/mL**		**3.0 mg/mL**			**0.5 mg/mL**	**1.0 mg/mL**	**2.0 mg/mL**	**2.27 mg/mL**	**3.2 mg/mL**

Cross-reference: Summary 2.7.1, Table 1-1, seq 0000

Clinical Evaluator's comments: The Sponsor's response is satisfactory. The primary differences between the clinical trial formulations and the to-be-marketed formulations are:

- Composition: the to-be-marketed formulations do not contain phenol or propylene glycol
- Concentration: the titration formulations and the maintenance dose formulations used in the clinical trials are different concentrations to the to-be-marketed formulations.

In the opinion of the Clinical Evaluator there may be some benefit in not having phenol or propylene glycol in the to-be-marketed formulations, and this may be why the Sponsor has replaced them. There is unlikely to be any effect on efficacy, especially as bioequivalence has been demonstrated for the maintenance formulations.

In the opinion of the Clinical Evaluator, the different concentrations in the titration formulations are unlikely to have any effect on efficacy, because efficacy is primarily from the maintenance formulations, which have been demonstrated to be bioequivalent.

1.2 Efficacy

1.2.1 Question 1 (paediatric trials)

The waivers for Paediatric Investigation Plan in the EU and Pediatric Assessment in the USA may relate to the initial application for treatment of T2DM and may not relate to the current proposed indication of weight control. Does the Sponsor intend to perform clinical trials in the paediatric and adolescent populations?

1.2.1.1 Sponsor's Response to Question 1

In the initial application, reference was erroneously made to the paediatric plans for semaglutide for treatment of T2DM instead of weight management.

For weight management in the adolescent and paediatric populations, two clinical trials are planned:

A trial in adolescents (12 to <18 years) with overweight or obesity (NN9536-4451, STEP TEENS) is currently ongoing. This is a 68-week double-blind, randomised, parallel group, placebo-controlled, multi-national clinical trial comparing semaglutide s.c. 2.4 mg once weekly with placebo, as adjunct to a reduced-calorie diet and increased physical activity, in pubertal adolescents, ages 12 to <18 years, with obesity or overweight with ≥1 weight-related comorbidity. The trial is planned to end (last patient last visit) in Q1 2022.

Furthermore, a trial in children and adolescents (6 to <18 years of age) will be conducted (first patient first visit planned for Q3 2023) (NN9536-4512, STEP YOUNG). This is an interventional 104-week double-blind, randomised, parallel group, placebo-controlled, multi-national clinical study. The study primarily compares the safety and efficacy of once-weekly semaglutide s.c. treatment with placebo, as an adjunct to a reduced-calorie diet and increased physical activity, in children (ages 6 to <12 years) with obesity. Additionally, the study compares the long-term (2 years) safety and tolerability of semaglutide s.c. treatment with placebo in children (ages 6 to <12 years) with obesity, and adolescents (ages 12 to <18 years) with obesity, or overweight with ≥1 weight-related comorbidity.

Clinical Evaluator's comments: The Sponsor's response is satisfactory. The proposed clinical trials are consistent with obesity also being a clinical issue in children and adolescents.

1.2.2 Question 2 (long-term efficacy)

The data indicate that treatment with semaglutide is likely to be required long-term. There was a return to baseline in the placebo group in Study NN9536-4376. This means the treatment effect does not persist after the treatment is ceased. Hence, it would be important to demonstrate that treatment effect continues with ongoing treatment beyond one year. Has the Sponsor demonstrated persistence of treatment effect beyond one year of treatment?

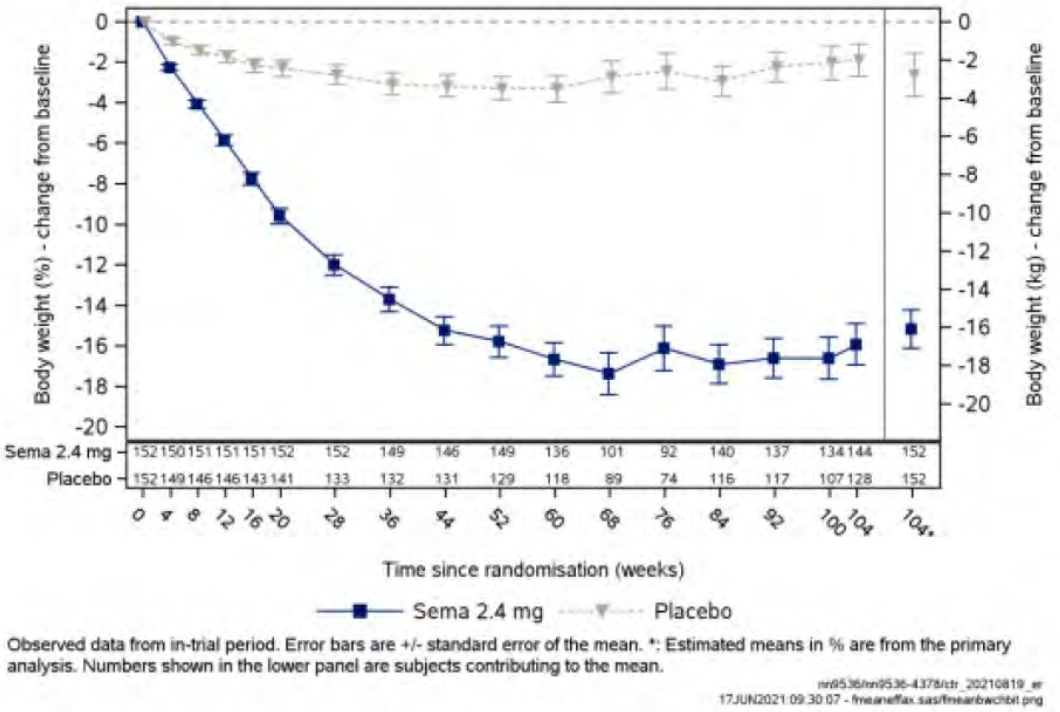
1.2.2.1 Response to Question 2

Novo Nordisk acknowledges the consideration that treatment effect of semaglutide 2.4 mg does not persist after ceased treatment, and that data indicate that Wegovy® is likely to be required longterm.

As part of the STEP program, Novo Nordisk has carried out a phase 3b trial (NN9536-4378, STEP 5, publicly available in 2022) aiming to examine the long-term effect of semaglutide 2.4 mg treatment. STEP 5 is a trial similar to STEP 1 with respect to inclusion and exclusion criteria, study design and primary endpoint investigated. However, STEP 5 has a treatment duration of 104 weeks (as compared to 68 weeks in STEP 1). In STEP 5, mean body weight decreased from baseline to week 68 with semaglutide 2.4 mg, based on observed data from the in-trial period (Figure 1-1), which is similar to what was seen in STEP 1 (Trial 4373 [M 5.3.5.1], Figure 11-1, seq 0000). From week 68 to week 104, a plateau in mean body weight was reached in the semaglutide 2.4 mg treatment group, showing that the weight loss obtained after approximately one year of semaglutide 2.4 mg treatment, persisted up until end of treatment of semaglutide 2.4 mg (week 104) (Figure 1-1).

In conclusion, the STEP 5 trial demonstrates persistence of semaglutide 2.4 mg treatment effect beyond one year of treatment.

Figure 1-1 Body weight change (%) from baseline by week – in-trial – STEP 5



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 subjects contributing to the mean.

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Clinical Evaluator's comments: The Sponsor's response is satisfactory. The persistence of effect for up to 2 years of treatment is reassuring. However, it could be anticipated that treatment will be required for a prolonged period, much in excess of 2 years. Hence, in the Clinical Evaluator's opinion, ongoing studies of the long term efficacy and safety of WEGOVY® are desirable.

1.2.3 Question 3 (rebound effect)

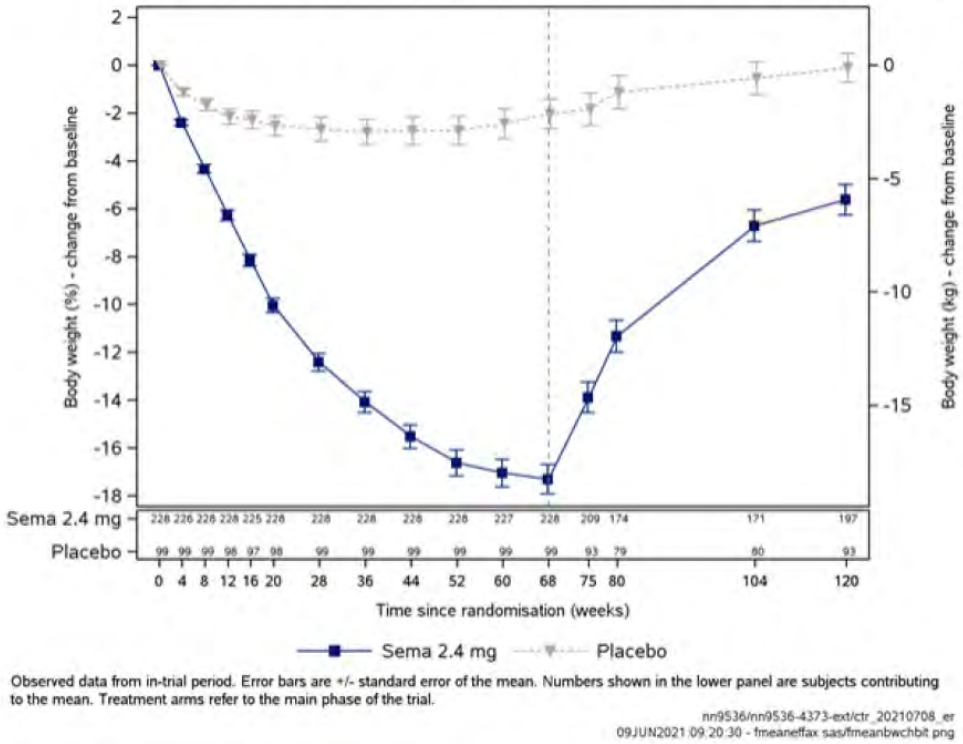
There is potential for rebound in weight once treatment is stopped. While the results of Study NN9536-4376 suggest this is unlikely, a rebound in weight might occur over the long term in patients who cease semaglutide treatment. Has the Sponsor investigated the potential for rebound weight gain following cessation of treatment?

1.2.3.1 Response to Question 3

The effect on body weight after treatment cessation with semaglutide 2.4 mg was investigated in the STEP 1 extension trial (publicly available in 2022). This trial explored the change in body weight from week 68 to week 120 (off-intervention period with no structured lifestyle intervention) in a subset of subjects from STEP 1 after having completed treatment on the target dose of semaglutide 2.4 mg or placebo for 68 weeks (for an overview of the entire trial, refer to Trial 4373 [M 5.3.5.1] Figure 9-1, seq 0000).

In the in-trial period, mean body weight decreased from baseline to week 68 with semaglutide 2.4 mg. With placebo, mean body weight decreased less and a plateau was reached after approximately 20 weeks of treatment (Figure 1-2). In the off-intervention period from week 68 to week 120, mean body weight increased in both groups. However, at week 120, the semaglutide 2.4 mg group retained a clinically relevant weight loss from baseline of 5.6% compared to 0.1% for the placebo group.

Figure 1-2 Body weight change (%, kg) from baseline by week – in-trial – STEP 1 extension



Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

nn9536/nn9536-4373-ext/ctr_20210708_er
09JUN2021 09:20:30 - fmeaneffax sas/fmeanbwchbit png

Clinical Evaluator's comments: The Sponsor's response is satisfactory. The trajectory of weight gain in the WEGOVY® group after treatment cessation indicates a return towards baseline, but not rebound (i.e. weight gain in excess of baseline weight).

1.3 Safety

1.3.1 Question 1 (misuse)

Misuse of semaglutide was addressed in the clinical studies, but only in the group of patients included in the indication. The potential for misuse in other patient groups, such as eating disorders and athletes, has not been addressed in the data. Does the Sponsor intend to monitor misuse and diversion in other patient populations?

1.3.1.1 Response to Question 1

Wegovy® will be a prescription only medicine, limiting the risk of use outside intended (BMI ≥30 kg/m² or a BMI ≥27 kg/m² in the presence of at least one weight-related comorbidity). Patients, including athletes and patients with eating disorders, will only be eligible to be prescribed Wegovy® if they meet these criteria.

Novo Nordisk will be undertaking post-marketing surveillance for misuse of Wegovy® as part of the routine pharmacovigilance activities. The following searches will be encompassed: abuse/misuse (NNMQ), medication error (SMQ) and off-label use (NNMQ). Potential cases of misuse identified from these searches, will be reported in our regular PSURs. If any issues are identified, they will be addressed accordingly.

Clinical Evaluator's comments: The Sponsor's response is satisfactory. The Sponsor intends to monitor this issue through routine pharmacovigilance activities. However, illicit diversion of WEGOVY® may be difficult to detect because those affected may have an interest in concealing their use and any adverse effects. Hence, in the opinion of the Clinical Evaluator some communication with the health professions will be required in order to alert them to the potential for diversion.

1.4 PI and CMI

1.4.1 Question 1 (stopping rule)

Has the sponsor developed stopping criteria for TRADENAME (semaglutide) to define the level of BMI at which treatment should be halted?

1.4.1.1 Response to Question 1

As explained below, Novo Nordisk does not believe that a stopping criterion for treatment with Wegovy® based on BMI obtained will benefit the patients.

Overweight/obesity is a chronic disease, and as demonstrated from the weight regains in both the placebo group in STEP 4 (Trial 4376 [M 5.3.5.1], Figure 11-1, seq 0000) and the semaglutide 2.4 mg group in the STEP 1 extension, patients on average will start to gain weight when treatment with semaglutide 2.4 mg is stopped; see further details on body weight data from the STEP 1 extension in the response to question 3 on rebound effects (Section 1.2.3.1). On the other hand, if treatment with semaglutide 2.4 mg is continued, patients on average are expected to maintain their weight loss. In the 2-year trial STEP 5, the average weight loss in the semaglutide 2.4 mg group reached a plateau around week 68 and persisted until end of treatment at week 104; see further details on body weight data from STEP 5 in the response to question 2 on long-term efficacy (Section 1.2.2.1).

Thus, patients who reach a certain BMI are expected to benefit from continued treatment with Wegovy®, as it increases the likelihood that they will be able to maintain their weight loss. The decision to stop or continue treatment with Wegovy® after a certain BMI has been reached should be based on the prescriber's assessment of the individual patient's needs. Factors like the patient's weight history (including dietary intake and physical activity habits), comorbidities, and any other possibilities for supporting the patient in maintaining a weight loss, need to be taken into account.

Clinical Evaluator's comments: The Sponsor's response is satisfactory. However, in the opinion of the Clinical Evaluator, there may be some patients with sufficient weight loss that ceasing treatment might be considered. It would be useful for these patients to have some guidance as to when the benefit-risk assessment for WEGOVY® supports stopping treatment.

15. Second round benefit-risk assessment

15.1. Second round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
The Phase IIIa studies demonstrated a statistically and clinically significant weight loss with semaglutide 2.4 mg weekly dosing. The magnitude of the weight loss was: • Study NN9536-4373: treatment difference (95% CI), semaglutide – placebo, -12.44 (-13.37 to -11.51) %, p <0.0001. • Study NN9536-4374: estimated treatment difference (95% CI), semaglutide 2.4 mg – placebo, -6.21 (-7.28 to -5.15) %, p <0.0001.	The data indicate that semaglutide is likely to be used for long-term management of weight in this patient group. Although the Sponsor has provided evidence that efficacy is maintained for up to 2 years, it would be desirable to demonstrate ongoing efficacy for a prolonged treatment period.

Indication	
Benefits	**Strengths and Uncertainties**
• Study NN9536-4375: treatment difference (95% CI), semaglutide – placebo, -10.27 (-11.97 to -8.57) %, p <0.0001. • Study NN9536-4376: treatment difference (95% CI), semaglutide – placebo, -14.75 (-16.00 to -13.50) %, p <0.0001. The treatment effect was well in excess of a clinically significant 5% weight loss. The effect size was consistent across the four studies. The effect persisted in a patient group undergoing IBT and in patients with T2DM. The decrease in body weight was matched by decreases in waist circumference and in BMI. There were improvements in markers of cardiovascular risk. There were improvements in glycaemic control. There were significant improvements in quality of life and physical functioning.	

15.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of WEGOVY® in the proposed usage are unchanged from those identified in Section 9.2.

15.3. Second round assessment of benefit-risk balance

The benefit risk profile for WEGOVY® (semaglutide) for the proposed indication is favourable.

16. Second round recommendation regarding authorisation

The Clinical Evaluator has no object to the approval of TRADENAME (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, single use prefilled pen with pre-assembled needle, for the proposed indication of:

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

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

17. Second round comments on product documentation

17.1. Second round comments on draft PI (clinical aspects)

The Sponsor provided new clinical information after the first round but did not change any clinical aspects of the draft PI. After consideration of the new clinical information, the PI comments made in Section 11.1 are unchanged.

17.2. Second round comments on draft CMI (clinical aspects)

The Sponsor provided new clinical information after the first round but did not change any clinical aspects of the draft CMI. After consideration of the new clinical information, the PI comments made in Section 11.2 are unchanged.

17.3. Second round comments on draft RMP (Summary of Safety Concerns)

The Sponsor provided new clinical information after the first round but did not change the Summary of Safety Concerns in the draft RMP. After consideration of the new clinical information, the comments on the Summary of Safety Concerns made in Section 11.3 are unchanged.

18. References

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Look AR, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 2010;170(17):1566–75.

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Data presented in the dossier:

- Clinical pharmacology trials (of which two are bioequivalence trials)
  - Study NN9536-4590 (Section 19.1.1.1)
  - Study NN9535-4588 (Section 19.1.1.2)
  - Study NN9536-4455 (Section 19.1.2.1)
- Phase II dose-finding trial
  - Study NN9536-4153 (Section 6.2)
- PKPD modelling reports:
  - Modelling of data from Study NN9536-4153 (Section 19.1.3.1).
  - Modelling of data from Study NN9536-4373 and Study NN9536-4374 (Section19.1.3.2)
- Phase IIIa therapeutic confirmatory trials (referred to as the STEP trials)
  - Study NN9536-4373 (STEP 1) (Section 7.2.1)
  - Study NN9536-4374 (STEP 2) (Section 7.2.2)
  - Study NN9536-4375 (STEP 3) (Section 7.2.3)
  - Study NN9536-4376 (STEP 4) (Section 7.2.4)
- Analyses of data from more than one study:
  - Integrated Summary of Immunogenicity
  - Integrated Summary of Patient Reported Outcomes

Studies of the injector device:

- DV3396-s47 [redacted]

Studies that have previously been submitted to the TGA for evaluation:

- s47 [redacted]
- Study NN9535-4010 (Section 19.1.1.4)
- Study NN9535-3687 (Section 19.1.1.5)
- s47 [redacted]
- Study NN9535-3789 (Section 19.1.1.7)
- Study NN9535-3633 (Section 19.1.1.8)
- s47 [redacted]
- Study NN9535-3616 (Section 19.1.1.10)

- Study NN9535-3651 (Section 19.1.1.11)
- Study NN9535-3819 (Section 19.1.1.12)
- Study NN9535-3817 (Section 19.1.1.13)
- Study NN9535-3818 (Section 19.1.1.14)
- s47
- s47
- s47
- s47
- s47

19. Supporting information, tables and figures

19.1. Clinical pharmacology study synopses

19.1.1. Synopses of pharmacokinetic studies

19.1.1.1. Study NN9536-4590

Study NN9536-4590 was a bioequivalence study comparing the semaglutide Formulation D with the DV3396 pen-injector with Formulation B with the PDS290 pen-injector. The study was open-label, randomised, parallel group, two-arm, multiple dose bioequivalence study. The study was conducted at a single centre in Germany from December 2019 to September 2020. The study included males and females aged 18 to 65 years, with BMI ≥27.0 and ≤34.9 kg/m^2, and body weight ≥70.0 and ≤130.0 kg. The study treatments were:

Test product:

- Semaglutide D, 0.5 mg/mL; 0.25 mg, Batch Number JX51022
- Semaglutide D, 1.0 mg/mL; 0.5 mg, Batch Number JX51021
- Semaglutide D, 2.0 mg/mL; 1.0 mg, Batch Number JX51031
- Semaglutide D, 2.27 mg/mL; 1.7 mg, Batch Number JX51033
- Semaglutide D, 3.2 mg/mL; 2.4 mg, Batch Number JX51032

Reference product:

- Semaglutide B, 1.0 mg/mL; 0.25 mg, 0.5 mg, Batch Number JP51852
- Semaglutide B, 3.0 mg/mL; 1.0 mg, 1.7 mg, 2.4 mg, Batch Number JP51975

Participants were randomised to test or reference, and received 21 once-weekly doses administered by pen-injector. The dose commenced at 0.25 mg and was escalated every 4 weeks to 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg (maintenance dose). Injections were to be administered subcutaneously into flat skin in the anterior region of the abdomen at any time of day, irrespective for meals, once weekly on the same day of the week.

Blood sampling was performed on the last dose days for the 1 mg and 2.4 mg doses, pre-dose and at Hours 3, 6, 12, 18, 24, 30, 36,42, 48, 54, 60, 72, 84, 120 and 168 post-dose. Semaglutide was measured in plasma using a LC-MS/MS assay.

There were 68 participants randomised to treatment (34 in each study group), all of whom received at least one dose of study treatment. There were 31 (91.2%) participants in the Test (Formulation D) group and 30 (88.2%) in the Reference (Formulation B) who completed treatment. No participants withdrew because of an adverse event.

There were 48 (75.0%) males, 16 (25.0%) females and all the participants were White. The age range was 18 to 65 years. The BMI range was 26.8 to 35.4 kg/m^2.

There were four important protocol deviations, none of which were considered to have had an impact on the analysis of the results.

The two formulations were bioequivalent at the 2.4 mg dose level for AUC but not for C_{max} (Table 19.1.1.1.1). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}168h}$ was 1.0539 (1.0003 to 1.1104). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.1556 (1.0800 to 1.2365). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.1.1).

The two formulations were bioequivalent at the 1 mg dose level for AUC and C_{max} (Table 19.1.1.1.2). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}168h}$ was 1.0357 (0.9860 to 1.0879). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.1014 (1.0202 to 1.1891). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.1.2).

CL, t½, Tmax and Vss were similar for both formulations at the 2.4 mg dose level (Table 19.1.1.1.3). For Formulation D, geometric mean (CV%) CL/F was 0.040 (22.6) L/h, t½ was 155 (9.8) h, and Vss/F was 9.8 (23.4) L. Median (range) Tmax was 24 (3 to 48) h. At the 1 mg dose level, for Formulation D, geometric mean (CV%) CL/F was 0.042 (20.7) L/h and median (range) Tmax was 18 (6 to 42) h. There was dose proportionality between the 1 mg and 2.4 mg dose levels: ratio (95% CI), 2.4 mg/ 1 mg, 2.57 (2.49 to 2.65) for AUC and 2.57 (2.42 to 2.73) for C_{max}.

Change in body weight from baseline was similar for the two formulations (Figure 19.1.1.1.3). The mean (SE) weight loss over the duration of the study was 9.3 (0.8) % for Formulation D and 9.0 (0.8) % for Formulation B.

19.1.1.2. Study NN9535-4588

Study NN9535-4588 was conducted to demonstrate bioequivalence between the semaglutide Formulation D for the DV3396 Pen-Injector and the Formulation B for the PDS290 semaglutide Pen-Injector. The study was open-label, randomised, parallel group, and multiple dose. The study was conducted at a single site in Germany from November 2019 to May 2020. The study included generally healthy males and females aged 18 to 65 years, with BMI ≥25.0 and ≤34.9 kg/m^2, and body weight ≥65.0 and ≤130.0 kg. The study treatments were:

1. Test: Semaglutide Formulation D, using the DV3396 pen-injector
   - 0.5 mg/mL, 0.25 mg single dose
   - 1.0 mg/mL, 0.5 mg single dose
   - 2.0 mg/mL, 1 mg single dose
2. Reference: Semaglutide Formulation B, using the PDS290 pen-injector
   - Doses of 0.25 mg, 0.5 mg and 1 mg

The treatments were administered weekly. Treatment duration was for 7 weeks: four weeks of 0.25 mg, two weeks of 0.5 mg and one of 1 mg. Treatments were administered by trained staff, subcutaneously into flat skin in the anterior region of the abdomen.

Blood was collected pre-dose and 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, 120, 144, and 168 hours post-dose with the fourth dose of 0.25 mg and the 1 mg dose.

The two formulations were bioequivalent at the 1 mg dose level for AUC but not for C_{max} (Table 19.1.1.2.1). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}840h}$ was 1.10 (1.04 to 1.17). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.27 (1.20 to 1.34). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.2.1).

The two formulations were bioequivalent at the 0.25 mg dose level for AUC and C_{max} (Table 19.1.1.2.2). The ratio (90% CI) Formulation D/formulation B for $AUC_{0\text{-}168h}$ was 1.08 (1.03 to 1.13). The ratio (90% CI) Formulation D/formulation B for C_{max} was 1.10 (1.05 to 1.15). The Formulation D resulted in slightly higher exposure (Figure 19.1.1.2.2).

The t½ of semaglutide was similar for the two formulations: mean (SD) 148 (13.82) h for formulation D and 151 (15.58) h for Formulation B (Table 19.1.1.2.3). Tmax was earlier for Formulation D: mean (SD) 21.3 (14.90) h for formulation D and 64.5 (16.84) h for Formulation B.

Studies Previously submitted in previous applications for semaglutide:

19.1.1.3. Study NN9535-3679

Study NN9535-3679 was a randomised, single centre, double-blind, incomplete block trial to test for equivalence between single, subcutaneous injections of semaglutide at concentrations of 1.0 mg/mL, 3.0 mg/mL and 10.0 mg/mL. The single doses were of 0.8 mg semaglutide. Equivalence between semaglutide 1 mg/mL, 3 mg/mL and 10 mg/mL was demonstrated for the primary

endpoint $AUC_{0-\infty}$. Equivalence was demonstrated for C_{max} between semaglutide 1 mg/mL and 3 mg/mL and between 3 mg/mL and 10 mg/mL, but not between semaglutide 1 mg/mL and 10 mg/mL.

19.1.1.4. Study NN9535-4010

Study NN9535-4010 was a randomised, single centre, double-blind, two-period, crossover trial investigating bioequivalence between subcutaneous injections of semaglutide produced by two different manufacturing processes: synthetic semaglutide (1.34 mg/mL) and recombinant semaglutide (1.34 mg/mL); single s.c. dose of 0.5 mg semaglutide. Bioequivalence was demonstrated between synthetic semaglutide and recombinant semaglutide.

19.1.1.5. Study NN9535-3687

Study NN9535-3687 was a randomised, single centre, two period, incomplete crossover trial investigating the pharmacokinetics of subcutaneous injections of semaglutide and the absolute bioavailability of semaglutide at concentrations of 1.0 mg/mL, 3.0 mg/mL and 10.0 mg/mL; at a single s.c. dose of 0.5 mg semaglutide, and a single i.v. dose of 0.25 mg semaglutide. Equivalence was demonstrated for semaglutide total exposure for the pairwise comparison between the three strengths of s.c. semaglutide when given in equimolar doses; 1 vs. 3 mg/mL, 1 vs. 10 mg/mL and 3 vs. 10 mg/mL strengths. C_{max} increased with increasing strengths and only the comparison between 1 vs. 3 mg/mL fulfilled the equivalence criterion. The geometric mean of terminal t½ of s.c. semaglutide (range 143−152 hours) and i.v. semaglutide was comparable (137 hours). The absolute bioavailability of s.c. semaglutide was 89%.

19.1.1.6. Study NN9535-1820

Study NN9535-1820 was a randomised, double-blind, placebo-controlled, dose escalation trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics. The semaglutide dose levels were: 0.625, 1.25, 2.5, 5, 10, 20, 40 and 80 µg/kg; administered as single s.c. doses. Semaglutide was acceptable at maximum tolerated dose of 15 μ g/kg body weight. No serious adverse events were reported. Dose proportionality was demonstrated in the dose range 10, 15 and 20 µg/kg.

19.1.1.7. Study NN9535-3789

Study NN9535-3789 (Section 19.1.1.7) was an open-label, single centre trial investigating absorption, metabolism and excretion of semaglutide 0.5 mg, as a single s.c. dose. The total recovery (measured as the total excretion) of [3H]-semaglutide related material was 75.1% of the administered dose: 53.0% in urine, 18.6% in faeces and 3.2% in expired air. In plasma, semaglutide was the primary component circulating at all timepoints. Six metabolites were detected in plasma, each accounting for 0.4−7.7% of the semaglutide-related material based on AUC. Semaglutide was extensively metabolised prior to elimination. In urine, 22 components were detected, and one component was considered likely to be semaglutide (3.1% of dose). In faeces, 7 minor metabolites were detected. [3H]-semaglutide related material was primarily distributed in the plasma compartment.

19.1.1.8. Study NN9535-3633

Study NN9535-3633 (Section 19.1.1.8) was a randomised, double blind, placebo-controlled, parallel-group, multiple doses, dose escalation trial to assess the safety, tolerability and pharmacokinetics profiles of semaglutide 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (0.4 mg once-weekly in the first week, then 0.8 mg once-weekly for the remainder of the trial) and 1.2 mg (0.4 mg once-weekly in the first week, 0.8 mg once-weekly in the second week, then 1.2 mg once-weekly for the remainder of the trial), as multiple s.c. doses. The study found no differences in pharmacokinetic properties between Caucasian and Japanese subjects.

19.1.1.9. Study NN9535-3634

Study NN9535-3634 (Section 19.1.1.9) was a single-centre, parallel-group, randomised, double-blind, multiple-dose trial to assess the safety and tolerability of semaglutide 1.34 mg/mL; 0.5 and 1.0 mg, multiple s.c. doses. The exposure and maximum concentration of semaglutide at steady state was comparable between Japanese and Caucasian subjects, with an expected dose-dependent increase. A dose-dependent weight loss was shown for semaglutide at steady state for both Japanese and Caucasian subjects

19.1.1.10. Study NN9535-3616

Study NN9535-3616 (Section 19.1.1.10) was an open-label trial investigating the pharmacokinetics and tolerability of semaglutide 0.5 mg and 10 µg/kg, as single s.c. doses in subjects with renal failure. The 'no-effect' criterion was met for all renal impairment groups, except for the severe renal impairment group, as compared to the group with normal renal function. The $AUC_{0-\infty}$ for the group with severe renal impairment was approximately 22% higher than for the group with normal renal function. There was no clinically relevant relationship was found between creatinine clearance (CLCR) and either exposure ($AUC_{0-\infty}$) or maximum concentration (C_{max}). Based on these results, a dose adjustment of semaglutide may not be warranted in subjects with renal impairment.

19.1.1.11. Study NN9535-3651

Study NN9535-3651 (Section 19.1.1.11) was a multicentre, open-label, parallel-group trial investigating the pharmacokinetics, safety and tolerability of semaglutide 1.34 mg/mL; 0.5 mg, as single s.c. doses, in subjects with hepatic impairment. Exposure of semaglutide was not affected by hepatic impairment. Pharmacokinetic properties for the hepatically impaired subjects were similar to those of the subjects with normal hepatic function. Fraction unbound assessed with *in vitro* assay was less than 0.5% for all subjects

19.1.1.12. Study NN9535-3819

Study NN9535-3819 was an open-label, one-sequence, cross-over, single centre trial investigating the influence of semaglutide on an oral contraceptive combination drug. Semaglutide 1.0 mg was administered as multiple s.c. doses; and ethinylestradiol (EE) 0.03 mg and levonorgestrel (LN) 0.15 mg combination, was also administered as multiple oral doses. Bioequivalence was demonstrated for the primary endpoint AUCτ for EE but not for LN. The estimated ratios and the corresponding CIs were:

- EE: Semaglutide steady state versus semaglutide free period: 1.11 (90% CI [1.06; 1.15])
- LN: Semaglutide steady state versus semaglutide free period: 1.20 (90% CI [1.15; 1.26])

AUCτ for both components of OC, EE and LN was slightly increased during semaglutide treatment. For C_{max}, the estimated ratios and the corresponding CIs were:

- EE: Semaglutide steady state versus semaglutide free period: 1.04; 90% CI [0.98; 1.10])
- LN: Semaglutide steady state versus semaglutide free period: 1.05 (90% CI: [0.99; 1.12])

There were no apparent differences in any of the other oral contraceptive PK parameters between the two treatment periods.

19.1.1.13. Study NN9535-3817

Study NN9535-3817 was an open-label, one-sequence cross over, single centre trial investigating the influence of semaglutide on pharmacokinetics and pharmacodynamics of warfarin and pharmacokinetics of metformin. Semaglutide 1.34 mg/mL was administered as 1.0 mg, multiple s.c. doses; warfarin 5 mg tablets as a single dose 25 mg oral dose; and metformin 500 mg twice daily as multiple oral doses. There was no significant effect on metformin PK at steady state when co-administered with semaglutide 1.0 mg at steady state. The estimated ratios (semaglutide steady state period/semaglutide free period) and the corresponding CIs were:

- AUCτ treatment ratio: 1.03 [0.96; 1.11]90% CI
- C_{max} treatment ratio: 0.90 [0.83; 0.98]90% CI

There was no effect on warfarin PK for semaglutide 1.0 mg at steady state. The estimated ratios (semaglutide steady state period/semaglutide free period) and the corresponding CIs were:

- $AUC_{0-168hours,S\text{-}war}$ treatment ratio: 1.05 [0.99; 1.11]90% CI
- $C_{max,S\text{-}war}$ treatment ratio: 0.91 [0.85; 0.98]90% CI
- $AUC_{0-168hours,R\text{-}war}$ treatment ratio: 1.04 [0.98; 1.10]90% CI
- $C_{max,R\text{-}war}$ treatment ratio: 0.93 [0.87; 1.00]90% CI

For INR, the estimated ratio (semaglutide steady state period/semaglutide free period) and the corresponding CI was:

- $iAUC_{0-168hours}$ response ratio: 1.05 [0.87; 1:28]90% CI

19.1.1.14. Study NN9535-3818

Study NN9535-3818 (Section 19.1.1.14) was an open-label, one-sequence, crossover, single centre trial investigating the influence of semaglutide on the pharmacokinetics of single doses of atorvastatin and digoxin. Semaglutide 1.34 mg/mL was administered as 1.0 mg, multiple s.c. doses; atorvastatin 40 mg as a single oral dose; and digoxin 0.25 mg tablets; as a 0.5 mg single oral dose. Atorvastatin exposure was not significantly changed when co-administered with semaglutide 1.0 mg at steady state. The estimated ratio (atorvastatin co-administered with semaglutide vs. atorvastatin alone) and the corresponding CI was: AUC treatment ratio: 1.02 [0.93 ; 1.12]90%CI. However, C_{max} was lower by 38% when co-administered with semaglutide: estimated ratio (atorvastatin co-administered with semaglutide vs. atorvastatin alone) and the corresponding CI was 0.62 [0.47 ; 0.82]90%CI.

Semaglutide did not have a significant effect on digoxin exposure: estimated ratio (digoxin co-administered with semaglutide 1.0 mg at steady state vs. digoxin alone) and the corresponding CI for AUC was: 1.02 [0.97 ; 1.08]90%CI; and for C_{max} was 0.93 [0.84 ; 1.03]90%CI.

For semaglutide exposure did not appear to affected by co-administration with atorvastatin or digoxin: area under the curve (geometric mean) was 7020 nmol*h/L, and the maximum concentration (geometric mean) was 48.6 nmol/L.

19.1.2. Synopses of pharmacodynamics studies

19.1.2.1. Study NN9536-4455

Study NN9536-4455 was a study of the effect of semaglutide 2.4 mg once weekly on gastric emptying in participants with obesity. The study was randomised, double-blind, parallel group, and placebo controlled. The study was conducted at a single site in Germany from February 2019 to November 2019. The study included males and females, aged ≥18 and ≤65 years, with BMI ≥30.0 and ≤45.0 kg/m^2. The study treatment was:

1. Semaglutide: commencing at 0.25 mg weekly with dose escalation every fourth week through 0.5 mg, 1.0 mg and 1.7 mg up to 2.4 mg weekly.
2. Placebo

Treatments were administered subcutaneously in the thigh, abdomen or upper arm, and at any time of the day irrespective of meals.

Paracetamol 1500 mg, single dose, was used as the marker for gastric emptying. On Day 1 and at Week 20, paracetamol was administered along with a standard breakfast. Blood samples were collected prior to doing and for 5 hours subsequently. Weight and height were measured, and the Control of Eating Questionnaire (COEQ). The safety outcome measures were AEs, ECGs, vital signs and physical examination.

There were 125 subjects screened, 72 randomised and exposed to study treatment and 70 completed. One participant in the placebo group withdrew due to AE. There were 44 (61.1%) males, 28 (38.9%) females and 71 (98.6%) participants were White. The age range was 24 to 63 years and the BMI range was 29.6 to 42.7 kg/m^2.

There was no significant effect of semaglutide, at doses of 2.4 mg subcutaneously, on gastric emptying (Figure 19.1.2.1.1). There was no effect on exposure to paracetamol: ratio (95% CI) semaglutide/placebo 1.08 (1.02 to 1.14) for paracetamol $AUC_{0\text{-}5h}$, and 0.94 (0.82 to 1.07) for C_{max}. There was no delay in absorption: mean T_{max} for semaglutide was 0.45 h and for placebo was 0.44 h, ratio (95% CI), semaglutide/placebo, 1.02 (0.88 to 1.19).

Energy intake at the end of study *ad libitum* lunch was lower in the semaglutide group: treatment difference (95% CI), semaglutide – placebo, -940 (-1364 to -516) p <0.0001.

There were no significant differences between semaglutide and placebo in hunger or satiety ratings, but there was a decrease in hunger and increase in satiety in both groups from baseline to end of study (Figure 19.1.2.1.2). The COEQ demonstrated improvement in food cravings in the semaglutide group (Figure 19.1.2.1.3). There was a mean decrease in body weight of 9.9% (10.4 kg) in the semaglutide group and 0.4% (0.4 kg) in the placebo.

19.1.2.2. Study NN9535-3652

Study NN9535-3652 (Section 19.1.2.2) was a randomised, double-blind, three-arm parallel, placebo-controlled trial; with a nested cross-over design for positive control with moxifloxacin, to evaluate the effect of semaglutide on cardiac repolarisation. Semaglutide 1.34 mg/mL was administered as multiple 1.5 mg s.c. doses; and moxifloxacin 400 mg as a single oral dose. Semaglutide did not result in an unacceptable prolongation in cardiac repolarisation compared to placebo

19.1.2.3. Study NN9535-3685

Study NN9535-3685 was a single-centre, randomised, double-blind, placebo-controlled, two-period, crossover trial to investigate the effect of semaglutide on energy intake, appetite sensations, postprandial glucose and triglyceride metabolism, and gastric emptying. Semaglutide 1.34 mg/mL was administered as multiple 1.0 mg s.c. doses. *Ad libitum* energy intake was lower for subjects when treated with semaglutide compared with placebo. Fasting and postprandial appetite sensations were lower for subjects when treated with semaglutide compared with placebo. Postprandial increments of the composite endpoint, overall appetite score, was however not significantly different between treatments. Control of eating and food cravings was overall improved for subjects when treated with semaglutide compared with placebo. Relative preference for fat food items was lower and relative preference for sweet food items was higher for subjects when treated with semaglutide compared with placebo. Overall gastric emptying was comparable between semaglutide and placebo. A delay during the first hour after meal intake was however observed for subjects when treated with semaglutide compared with placebo. Fasting, as well as postprandial, glucose and lipid metabolism were improved for subjects when treated with semaglutide compared with placebo.

19.1.2.4. Study NN9535-3635

Study NN9535-3635 (Section 19.1.2.4) was a single-centre, randomised, double-blind, placebo-controlled, multiple-dose, parallel-group trial to investigate the effects of semaglutide on β-cell function. Semaglutide 1.34 mg/mL was administered as multiple 1.0 mg s.c. doses. Insulin secretion in both the first and the second insulin secretion phase was increased in subjects with T2DM treated with semaglutide as compared to placebo as measured by the IVGTT. Semaglutide increased the maximal insulin secretory capacity as compared to placebo as measured by the arginine stimulation test. Semaglutide reduced postprandial glucose and glucagon, and increased C-peptide as compared to placebo in the 24-hour profiles. β-cell responsiveness was increased

after treatment with semaglutide compared to placebo, and at end-of-treatment it closely resembled that of healthy subjects as measured by the graded glucose infusion test.

19.1.2.5. Study NN9535-3635

Study NN9535-3635 (Section 19.1.2.5) was a single-centre, randomised, double-blind, cross-over trial investigating the effect of semaglutide on hypoglycaemia counter-regulation compared to placebo. Semaglutide 1.34 mg/mL was administered as multiple 1.0 mg s.c. doses. During hypoglycaemia, treatment with semaglutide did not compromise the increase in glucagon level; trended to attenuate the increase in adrenaline, noradrenaline and cortisol levels, but did not change the increase in growth hormone level; did not compromise the plasma glucose dependent decrease in C-peptide level; resulted in a similar AUC_{GIR}, indicating an overall comparable counter-regulation; lowered the overall hypoglycaemic symptoms score and hypoglycaemic awareness and resulted in a similar decrease in cognitive function. Treatment with semaglutide did not affect the ability to recover from hypoglycaemia compared with placebo treatment.

19.1.3. Synopses of population pharmacokinetics analyses

19.1.3.1. Modelling Report for Data from Study NN9536-4153

Modelling of data from Study NN9536-4153 (Section 6.2) was performed. There were 5853 plasma concentration observations from 718 participants. The data were successfully described by a one-compartment model with first order absorption and elimination. The covariate analysis indicated body weight was the most important covariate influencing exposure (Figure 19.1.3.1.1). The concentration response relationship was described by the model (Figure 19.1.3.1.2). An E_{max} relationship was described for the proportion of patients achieving a 5% weight loss (Figure 19.1.3.1.3). The proportion of patients discontinuing due to AEs increased with exposure to semaglutide (Figure 19.1.3.1.4).

19.1.3.2. Modelling Report for Data from Study NN9536-4373 and Study NN9536-4374

Modelling of data from Study NN9536-4373 (Section 7.2.1) and Study NN9536-4374 (Section 7.2.2) was performed. There were 11827 semaglutide plasma concentration observations form 2077 participants. For a typical participant, CL/F was estimated as 0.0475 L/h and V/F as 12.4 L. Dose proportionality was demonstrated in the dose range 0.25 to 2.4 mg (Figure 19.1.3.2.1). Interindividual variability in CL/F in the final model was 18.7 CV%. Body weight had a significant effect on exposure (Figure 19.1.3.2.2). The presence of antibodies did not affect the PK of semaglutide. The exposure-response relationship for this concentration range appeared to be linear (Figure 19.1.3.2.3). However, the responder analysis indicated an E_{max} relationship (Figure 19.1.3.2.4). The proportion of patients reporting GI AEs also demonstrated an E_{max} relationship (Figure 19.1.2.3.5). The report concluded that the benefit of a larger weight loss with 2.4 mg compared to 1.0 mg semaglutide was associated with only marginally increased risk in terms of GI adverse events.

19.2. Other supporting tables and figures

Table 2.2.1 Summary of effects of weight management interventions (from Table 6.4, Management of overweight and obesity in adults, adolescents and children in Australia. NHMRC 2013

Intervention	Summary of effect
Lifestyle change (see Tables C5–C9; Appendix C)	Least effective (>10% weight loss in few studies; weight loss not likely to be maintained in most participants) Dietary change—3–5 kg at 12 months; 0 kg at 5 years Dietary change and exercise—5–10 kg at 12 months; 0–3 kg at 5 years Exercise—0 kg at 12 months; 0–5 kg at 5 years Lifestyle change and psychological intervention—3–4 kg at 5 years
Combined lifestyle change and pharmacotherapy (see Tables C10 and C11)	Moderately effective (>10% weight loss across some but not all studies; weight loss maintained >5 years in some but not all participants) Medication (e.g. orlistat) and dietary change—6–10 kg at 12 months; 2–3 kg at 5 years
Bariatric surgery with maintained lifestyle changes (see Tables C18–C20)	Most effective (consistently >10% weight loss across studies; weight loss likely to be maintained >5 years) Laparoscopic adjustable gastric banding—20% at 12 months; 12% at 10 years Vertical banded gastroplasty—20% at 12 months; 15% at 10 years Roux-en-Y gastric bypass—33% at 12 months; 30% at 10 years

Table 6.2.1 Subject disposition - summary - all subjects (copied from Table 10-1, Study NN9536-4135)

	Sema 0.05 mg N (%)	Sema 0.1 mg N (%)	Sema 0.2 mg N (%)	Sema 0.3 mg N (%)	Sema 0.4 mg N (%)	Sema 0.3 mg F N (%)	Sema 0.4 mg F N (%)	Lira 3.0 mg N (%)	Placebo pool N (%)	Total N (%)
Screened										1111
Randomised	103 (100)	102 (100)	103 (100)	103 (100)	102 (100)	102 (100)	103 (100)	103 (100)	136 (100)	957 (100)
Exposed	103 (100)	102 (100)	103 (100)	103 (100)	102 (100)	102 (100)	103 (100)	103 (100)	136 (100)	957 (100)
On-treatment at week 52[a]	77 (74.8)	88 (86.3)	87 (84.5)	88 (85.4)	82 (80.4)	75 (73.5)	91 (88.3)	86 (83.5)	103 (75.7)	777 (81.2)
Discontinued trial product:	26 (25.2)	14 (13.7)	16 (15.5)	15 (14.6)	20 (19.6)	27 (26.5)	12 (11.7)	17 (16.5)	33 (24.3)	180 (18.8)
Adverse event	7 (6.8)	8 (7.8)	5 (4.9)	4 (3.9)	15 (14.7)	17 (16.7)	8 (7.8)	9 (8.7)	4 (2.9)	77 (8.0)
Protocol violation	6 (5.8)	1 (1.0)	2 (1.9)	3 (2.9)	1 (1.0)	1 (1.0)	1 (1.0)	3 (2.9)	4 (2.9)	22 (2.3)
Pregnancy	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Other	13 (12.6)	5 (4.9)	8 (7.8)	8 (7.8)	4 (3.9)	9 (8.8)	3 (2.9)	5 (4.9)	25 (18.4)	80 (8.4)
Retrieved at visit 22x[b]	15 (14.6)	7 (6.9)	7 (6.8)	8 (7.8)	18 (17.6)	21 (20.6)	9 (8.7)	10 (9.7)	20 (14.7)	115 (12.0)
Withdrawn from trial:	11 (10.7)	7 (6.9)	9 (8.7)	7 (6.8)	2 (2.0)	6 (5.9)	3 (2.9)	7 (6.8)	13 (9.6)	65 (6.8)
Withdrawal by subject	5 (4.9)	4 (3.9)	6 (5.8)	4 (3.9)	1 (1.0)	1 (1.0)	0 (0)	1 (1.0)	7 (5.1)	29 (3.0)
Lost to follow-up	5 (4.9)	3 (2.9)	2 (1.9)	3 (2.9)	1 (1.0)	5 (4.9)	2 (1.9)	6 (5.8)	6 (4.4)	33 (3.4)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	1 (0.1)
Other	1 (1.0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.2)
Full analysis set	103 (100)	102 (100)	103 (100)	103 (100)	102 (100)	102 (100)	103 (100)	103 (100)	136 (100)	957 (100)
Safety analysis set	103 (100)	102 (100)	103 (100)	103 (100)	102 (100)	102 (100)	103 (100)	103 (100)	136 (100)	957 (100)

Abbreviations: F = fast dose escalation; Lira = liraglutide; N = number of subjects; Sema = semaglutide.

[a]'On-treatment at week 52' completed week 52 visit without discontinuation of trial product. [b]'Retrieved at visit 22x' completed week 52 visit after discontinuation of trial product.

Table 7.2.1.1 Flowchart (copied from protocol for Study NN9536-7373)

	Screening	Randomisation	Dose escalation period								Maintenance period													End of treatment	End of trial
Visit (V), Phone (P)	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																									
Informed consent and Demography[a] (Appendix 3)	X																								
Childbearing potential[b] (Appendix 5)	X																								
Inclusion criteria (6.1)	X	X																							
Exclusion criteria (6.2)	X	X																							
Randomisation criteria and randomisation (6.3)		X																							
Medical history/Concomitant illness (9.4)	X																								
Weight History (9)		X																							
History of Gallbladder Disease (9.4)	X																								
History of Breast Neoplasm[b] (9.4)	X																								
History of Colon Neoplasm (9.4)	X																								
History of Skin Cancer (9.4)	X																								
History of Psychiatric Disorder (9.4)	X																								
Visit (V), Phone (P)	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Tobacco Use[c] (6.4.1)	X																								
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Trial Product Compliance (7.1, 7.6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluation of lipid-lowering treatment (9)													X											X	
Evaluation of antihypertensive treatment (9)													X											X	
Evaluation of glycaemic status (9)		X											X											X	
Evaluation of diet and physical activity (9)				X		X		X		X		X		X		X		X		X		X		X	
EFFICACY																									
Body measurements (9.1.1)																									
Height	X																								
Body Weight	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X
Waist Circumference	X	X		X		X		X		X		X		X		X		X		X		X		X	
HbA1c (Appendix 2)	X	X										X								X				X	
Fasting plasma glucose (Appendix 2)		X										X								X				X	
Fasting serum insulin (Appendix 2)		X																						X	

Table 7.2.1.1 (cont)

	Screening	Randomisation	Dose escalation period								Maintenance period													End of treatment	End of trial
Visit (V), Phone (P)	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Lipids (Appendix 2)		X										X												X	
Biomarkers (9.8, Appendix 2)		X										X												X	
Vital Signs (9.4.3)																									
Systolic blood Pressure	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Diastolic Blood Pressure	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Clinical Outcome Assessments (9.1.2)																									
Short Form-36 (SF-36)		X				X				X		X				X				X				X	
Impact of weight on quality of life – Lite Clinical Trials version (IWQoL-Lite for CT)		X				X				X		X				X				X				X	
Patient Global Impression of Status (PGI-S)		X				X				X		X				X				X				X	
Patient Global Impression of Change (PGI-C)		X				X				X		X				X				X				X	
Stanford Presenteeism Scale-6 (SPS-6)		X										X												X	
International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF)[b]		X																						X	
DEXA scan[d] (9)	X[e]																							X	
SAFETY																									
Physical examination (9.4.2)	X																							X	
Pregnancy test (9.4.5, Appendix 5)	X	X		X		X		X		X		X		X		X		X		X		X		X	X
ECG (9.4.4)		X										X												X	
Adverse event (9.2, Appendix 4)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaint (9.2.9, Appendix 4)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[b] (9.4)																								X	X
Colon neoplasms follow-up (9.4)																								X	X
Haematology (Appendix 2)	X											X								X				X	
Biochemistry (Appendix 2)	X											X								X				X	
Anti-Semaglutide Antibody (9.4.6)		X	X	X		X		X						X						X				X	X
Vital Signs (9.4.3)																									
Pulse	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Clinical Outcome Assessments (9.4.1)																									
Patient Health Questionnaire–9 (PHQ-9) (9.4.1)	X	X						X				X				X				X				X	
Columbia-Suicide Severity Rating Scale (C-SSRS) (9.4.1)	X	X						X				X				X				X				X	

Table 7.2.1.1 (cont)

	Screening	Randomisation	Dose escalation period								Maintenance period													End of treatment	End of trial
Visit (V), Phone (P)	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
OTHER ASSESSMENTS																									
Semaglutide plasma concentration (9.5)			X	X		X		X						X						X				X	X
Biosamples for future analysis[f] (Appendix 7)		X																						X	
TRIAL MATERIAL																									
First date on trial product			X																						
IWRS session	X	X				X				X		X		X		X		X		X		X		X	
Administration of trial product (7.1, 7.5)																									
Dispensing visit		X				X				X		X		X		X		X		X		X			
Drug accountability		X				X				X		X		X		X		X		X		X		X	
REMINDERS																									
Criteria for discontinuation (8.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Barriers and motivation interview (9)	X																								
Diet and physical activity counselling (7.1.2)		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Training in trial product, pen-handling (7.1.1)		X	X	X		X		X		X		X		X		X		X		X		X			
Hand out direction for use (7.1.1)		X																							
Visit (V), Phone (P)	V1	V2	V3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Hand out dose reminder card (7.1)		X		X		X		X		X															
Hand out and instruct in food diary (9)	X																								
Hand out and instruct in PK dairy (9)		X	X	X		X						X						X				X			
Collect, review and transcribe diaries		X	X	X		X		X		X		X		X		X		X		X		X		X	
Hand out ID card	X																								
Attend visit fasting (6.4.1)		X										X								X				X	X[g]

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] For all female subjects.

[c] Smoking is defined as smoking at least one cigarette or equivalent daily.

[d] DEXA scan is performed in a sub-population.

[e] DEXA scan should be performed in fasting state prior to randomisation (after informed consent is obtained).

[f] Only for subjects where the separate informed consent for future research has been signed.

[g] Fasting at V25 is defined as at least 2 hours without food and drink intake except water before attending the visit.

Table 7.2.1.2 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 1950 randomised subjects (copied from Table 10-2, protocol for Study NN9536-4373)

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight change #	14 (±10)	3 (±10)	12.5 (±11)	9.5%-points	> 99	> 99
2	5% responders	82%	42%	76%	1.8	> 99	> 99
3	10% responders	66%	24%	60%	2.5	> 99	> 99
4	15% responders	46%	12%	41%	3.4	> 99	> 99
5	WC change (cm) #	11 (±10)	4 (±10)	10 (±10)	6 cm	> 99	> 99
6	sBP change (mmHg) #	6.2 (±13)	1.5 (±13)	5.5 (±13)	4 mmHg	> 99	> 99
7	SF-36 PF score change	6 (±10)	2 (±10)	5.4 (±11)	3.4 score-points	> 99	> 99
8	IWQoL-Lite PFD score change	*To be confirmed. Is currently being validated in trials N9536-4153 and NN9924-4233*					

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; # shown as a positive number

Table 7.2.1.3 Subject disposition - all subjects (copied from Table 10-1, Study NN9536-4373)

	Sema 2.4 mg N	(%)	Placebo N	(%)	Total N	(%)
Screened					2303	
Screening failures					305	
Withdrawn before randomisation					37	
Randomised	1306	(100)	655	(100)	1961	(100)
Randomised in violation of incl., excl. and/or randomisation criteria	17	(1.3)	9	(1.4)	26	(1.3)
Exposed	1306	(100)	655	(100)	1961	(100)
Analysis sets						
Full analysis set	1306	(100)	655	(100)	1961	(100)
Safety analysis set	1306	(100)	655	(100)	1961	(100)
Treatment completion						
On-treatment at week 68 (treatment completers)	1083	(82.9)	508	(77.6)	1591	(81.1)
After at least one temporary interruption	119	(9.1)	58	(8.9)	177	(9.0)
Attended end-of-treatment visit without permanent discontinuation of trial product	1080	(82.7)	506	(77.3)	1586	(80.9)
Trial product permanently discontinued	223	(17.1)	147	(22.4)	370	(18.9)
Primary reason for permanent discontinuation of trial product						
Adverse event	91	(7.0)	21	(3.2)	112	(5.7)
Protocol violation	3	(0.2)	5	(0.8)	8	(0.4)
Randomised in violation of incl., excl. and/or randomisation criteria	2	(0.2)	2	(0.3)	4	(0.2)
Intention of becoming pregnant	0		1	(0.2)	1	(<0.1)
Other	1	(<0.1)	2	(0.3)	3	(0.2)
Pregnancy	7	(0.5)	3	(0.5)	10	(0.5)
Lack of efficacy	1	(<0.1)	16	(2.4)	17	(0.9)
At the discretion of the investigator	4	(0.3)	1	(0.2)	5	(0.3)
Safety concern as judged by the investigator	15	(1.1)	0		15	(0.8)
Withdrawal of consent	9	(0.7)	10	(1.5)	19	(1.0)
Lost to follow-up	26	(2.0)	25	(3.8)	51	(2.6)
Other	67	(5.1)	66	(10.1)	133	(6.8)
Attended end-of-treatment visit after permanent discontinuation of trial product	161	(12.3)	95	(14.5)	256	(13.1)
Trial completion						
Attended end-of-trial visit (trial completers)	1240	(94.9)	609	(93.0)	1849	(94.3)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	1072	(82.1)	506	(77.3)	1578	(80.5)
Withdrawn from trial	66	(5.1)	46	(7.0)	112	(5.7)
Primary reason for trial withdrawal						
Withdrawal by subject	26	(2.0)	17	(2.6)	43	(2.2)
Lost to follow-up	39	(3.0)	28	(4.3)	67	(3.4)
Death	1	(<0.1)	1	(0.2)	2	(0.1)
Withdrawn from trial before week 68	43	(3.3)	35	(5.3)	78	(4.0)
Withdrawn from trial without prior permanent discontinuation of trial product	3	(0.2)	4	(0.6)	7	(0.4)

N: Number of subjects, %: Percentages are based on randomised subjects.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).
Only reasons for permanent discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.

Table 7.2.1.4 Demographics and baseline characteristics - categorical variables (copied from Table 10-2, Study NN9536-4373)

	Sema 2.4 mg N	(%)	Placebo N	(%)	Total N	(%)
Number of subjects	1306		655		1961	
Age (years)						
N	1306	(100)	655	(100)	1961	(100)
18-<65	1198	(91.7)	607	(92.7)	1805	(92.0)
65-<75	99	(7.6)	46	(7.0)	145	(7.4)
75-<85	8	(0.6)	2	(0.3)	10	(0.5)
>=85	1	(<0.1)	0		1	(<0.1)
Sex						
N	1306	(100)	655	(100)	1961	(100)
Female	955	(73.1)	498	(76.0)	1453	(74.1)
Male	351	(26.9)	157	(24.0)	508	(25.9)
Country of residence						
N	1306	(100)	655	(100)	1961	(100)
Argentina	39	(3.0)	26	(4.0)	65	(3.3)
Belgium	39	(3.0)	21	(3.2)	60	(3.1)
Bulgaria	32	(2.5)	13	(2.0)	45	(2.3)
Canada	39	(3.0)	24	(3.7)	63	(3.2)
Germany	70	(5.4)	30	(4.6)	100	(5.1)
Denmark	34	(2.6)	16	(2.4)	50	(2.5)
Finland	38	(2.9)	22	(3.4)	60	(3.1)
France	38	(2.9)	17	(2.6)	55	(2.8)
United Kingdom	135	(10.3)	83	(12.7)	218	(11.1)
India	82	(6.3)	35	(5.3)	117	(6.0)
Japan	67	(5.1)	33	(5.0)	100	(5.1)
Mexico	47	(3.6)	23	(3.5)	70	(3.6)
Poland	42	(3.2)	18	(2.7)	60	(3.1)
Russian Federation	73	(5.6)	27	(4.1)	100	(5.1)
Taiwan	26	(2.0)	9	(1.4)	35	(1.8)
United States	505	(38.7)	258	(39.4)	763	(38.9)
Ethnic origin						
N	1306	(100)	655	(100)	1961	(100)
Not Hispanic or Latino	1118	(85.6)	551	(84.1)	1669	(85.1)
Hispanic or Latino	150	(11.5)	86	(13.1)	236	(12.0)
Not Applicable	38	(2.9)	17	(2.6)	55	(2.8)
Unknown	0		1	(0.2)	1	(<0.1)
Race						
N	1306	(100)	655	(100)	1961	(100)
White	973	(74.5)	499	(76.2)	1472	(75.1)
Asian	181	(13.9)	80	(12.2)	261	(13.3)
Black or African American	72	(5.5)	39	(6.0)	111	(5.7)
Not Applicable	38	(2.9)	17	(2.6)	55	(2.8)
Other	25	(1.9)	8	(1.2)	33	(1.7)
American Indian or Alaska Native	17	(1.3)	10	(1.5)	27	(1.4)
Native Hawaiian or Other Pacific Islander	0		2	(0.3)	2	(0.1)
BMI (kg/m^2)						
N	1306	(100)	655	(100)	1961	(100)
<30	81	(6.2)	36	(5.5)	117	(6.0)
30-<35	436	(33.4)	207	(31.6)	643	(32.8)
35-<40	406	(31.1)	208	(31.8)	614	(31.3)
>=40	383	(29.3)	204	(31.1)	587	(29.9)

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index. Ethnic origin and race are recorded as 'Not Applicable' for France.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.2.1.5 Demographics and baseline characteristics - continuous variables (copied from Table 10-3, Study NN9536-4373)

	Sema 2.4 mg	Placebo	Total
Number of subjects	1306	655	1961
Age (years)			
N	1306	655	1961
Mean (SD)	46 (13)	47 (12)	46 (13)
Median	46	48	46
P5 ; P95	25 ; 68	26 ; 66	25 ; 67
Min ; Max	18 ; 86	18 ; 82	18 ; 86
Body weight (kg)			
N	1306	655	1961
Mean (SD)	105.4 (22.1)	105.2 (21.5)	105.3 (21.9)
Median	102.1	101.3	101.8
P5 ; P95	76.1 ; 144.3	78.1 ; 143.2	76.6 ; 144.2
Min; Max	61.8 ; 245.6	66.3 ; 211.0	61.8 ; 245.6
BMI (kg/m^2)			
N	1306	655	1961
Mean (SD)	37.8 (6.7)	38.0 (6.5)	37.9 (6.7)
Median	36.7	36.5	36.7
P5 ; P95	29.7 ; 51.0	29.8 ; 50.6	29.7 ; 50.8
Min; Max	26.5 ; 83.0	27.5 ; 67.0	26.5 ; 83.0
Waist circumference (cm)			
N	1306	655	1961
Mean (SD)	114.6 (14.8)	114.8 (14.4)	114.7 (14.6)
Median	113.0	113.2	113.0
P5 ; P95	93.5 ; 140.0	94.0 ; 139.5	94.0 ; 139.7
Min; Max	85.0 ; 180.0	83.8 ; 182.9	83.8 ; 182.9
HbA1c (%)			
N	1306	655	1961
Mean (SD)	5.7 (0.3)	5.7 (0.3)	5.7 (0.3)
Median	5.7	5.7	5.7
P5 ; P95	5.2 ; 6.2	5.2 ; 6.3	5.2 ; 6.2
Min; Max	4.1 ; 6.6	4.6 ; 6.6	4.1 ; 6.6
Fasting plasma glucose (mmol/L)			
N	1291	649	1940
Mean (SD)	5.3 (0.6)	5.3 (0.6)	5.3 (0.6)
Median	5.2	5.2	5.2
P5 ; P95	4.5 ; 6.3	4.5 ; 6.3	4.5 ; 6.3
Min ; Max	3.8 ; 9.2	3.7 ; 8.4	3.7 ; 9.2
Fasting plasma glucose (mg/dL)			
N	1291	649	1940
Mean (SD)	95.4 (10.7)	94.7 (10.5)	95.2 (10.6)
Median	94.4	93.7	94.2
P5 ; P95	80.2 ; 114.2	80.5 ; 112.8	80.4 ; 113.5
Min ; Max	68.1 ; 166.0	66.5 ; 150.5	66.5 ; 166.0

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, HbA1c: Haemoglobin A1c.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.2.1.6 Primary and confirmatory secondary endpoints - primary statistical analyses - treatment policy estimand (copied from Table 11-1, Study NN9536-4373)

Endpoint	Est. 95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoints					
Body weight (%) change from baseline to week 68					
Sema 2.4 mg - Placebo	-12.44 [-13.37; -11.51]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=5% at week 68					
Sema 2.4 mg / Placebo	11.22 [8.88; 14.19]	<.0001	0.05	Superiority	Confirmed
Other confirmatory endpoints					
Odds of achieving baseline body weight loss >=10% at week 68					
Sema 2.4 mg / Placebo	14.68 [11.08; 19.44]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=15% at week 68					
Sema 2.4 mg / Placebo	19.26 [12.89; 28.76]	<.0001	0.05	Superiority	Confirmed
Waist circumference (cm) change from baseline to week 68					
Sema 2.4 mg - Placebo	-9.42 [-10.30; -8.53]	<.0001	0.05	Superiority	Confirmed
Systolic blood pressure (mmHg) change from baseline to week 68					
Sema 2.4 mg - Placebo	-5.10 [-6.34; -3.87]	<.0001	0.05	Superiority	Confirmed
SF-36 Physical Functioning score change from baseline to week 68					
Sema 2.4 mg - Placebo	1.80 [1.18; 2.42]	<.0001	0.05	Superiority	Confirmed
IWQOL-Lite-CT Physical Function score change from baseline to week 68					
Sema 2.4 mg - Placebo	9.43 [7.50; 11.35]	<.0001	0.05	Superiority	Confirmed

Est.: Estimate, alpha: Local significance level, CI: Confidence interval, p-value: Unadjusted two-sided p-value for test of no difference.

Table 7.2.1.7 Body composition (DEXA) at week -1 and 68 - observed in-trial data - DEXA sub-population (copied from Table 11-3, Study NN9536-4373)

	Sema 2.4 mg	Placebo	Total
Number of subjects	95	45	140
Total fat mass (kg) - Mean (SD)			
Week -1	42.1 (10.1)	43.3 (9.2)	42.5 (9.8)
Week 68	32.5 (10.4)	42.4 (10.5)	
Change from baseline at week 68	-9.3 (8.5)	-1.5 (5.1)	
Total fat mass (%) - Mean (SD)			
Week -1	43.4 (7.5)	44.6 (8.1)	43.8 (7.7)
Week 68	39.4 (7.9)	44.2 (7.7)	
Change from baseline at week 68	-3.9 (5.4)	-0.3 (2.8)	
Lean body mass (kg) - Mean (SD)			
Week -1	52.4 (11.6)	51.5 (10.8)	52.1 (11.3)
Week 68	46.7 (10.2)	50.5 (9.4)	
Change from baseline at week 68	-5.8 (4.6)	-1.8 (2.5)	
Lean body mass (%) - Mean (SD)			
Week -1	53.9 (7.4)	52.7 (7.7)	53.5 (7.5)
Week 68	57.4 (7.6)	53.0 (7.4)	
Change from baseline at week 68	3.4 (5.1)	0.2 (2.7)	
Visceral fat mass (kg) - Mean (SD)			
Week -1	1.3 (0.6)	1.5 (0.7)	1.3 (0.6)
Week 68	0.9 (0.5)	1.4 (0.6)	
Change from baseline at week 68	-0.4 (0.3)	-0.1 (0.3)	
Visceral fat mass (%) - Mean (SD)			
Week -1	33.8 (9.9)	36.3 (12.3)	34.6 (10.7)
Week 68	31.6 (9.3)	35.6 (11.4)	
Change from baseline at week 68	-2.2 (4.4)	-0.1 (4.5)	

N: Number of subjects with an observation at the visit, SD: Standard deviation, DEXA: Dual energy x-ray absorpmetry.
Observed data from in-trial period including on-treatment data for end of treatment visit (week 68).

Table 7.2.2.1 Study flowchart (copied from: 2 Flowchart, Protocol for Study NN9536-4374)

	Screening	Randomisation	Dose escalation period							Maintenance period												End of treatment	End of trial
Visit (V), Phone (P)	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																									
Informed consent and Demography[a] (Appendix 3)	X																								
Childbearing potential[b] (Appendix 5)	X																								
Inclusion criteria (6.1)	X	X																							
Exclusion criteria (6.2)	X	X																							
Randomisation criteria and randomisation (6.3)		X																							
Medical history/Concomitant illness (9.4)	X																								
Weight History (9)		X																							
Diabetes history and complications	X																								
History of Gallbladder Disease 9.4	X																								
History of Breast Neoplasm[b] 9.4	X																								
History of Colon Neoplasm 9.4	X																								
History of Skin Cancer 9.4	X																								
History of Psychiatric disorder 9.4	X																								
Tobacco use[c]	X																								
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Trial product compliance (7.1, 7.6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluation of lipid-lowering treatment (9)													X											X	
Evaluation of antihypertensive treatment (9)													X											X	
Evaluation of Oral Anti Diabetes Medication (9)													X											X	
EFFICACY																									
Body measurements (9.1.1)																									
Height	X																								
Body Weight	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Waist Circumference	X	X		X		X		X		X		X		X		X		X		X		X		X	
HbA1c	X	X				X						X		X				X		X				X	
Fasting plasma glucose (Appendix 2)		X				X						X								X				X	
Fasting serum insulin		X				X						X								X				X	
Self-measured fasting plasma glucose (9.1.3)				X				X		X				X		X		X				X		X	
Lipids (Appendix 2)		X										X												X	
Biomarkers (9.8, Appendix 2)		X										X												X	
Vital Signs (6.4.2, 9.4.3)	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Systolic Blood Pressure	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Diastolic Blood Pressure	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Clinical Outcome Assessments (9.1.2)																									
Impact of weight on quality of Life-lite (IWQoL-Lite)		X				X				X		X				X				X				X	
Patient Global Impression of Status (PGI-S)		X				X				X		X				X				X				X	
Patient Global Impression of Change (PGI-C)		X				X				X		X				X				X				X	
Work Productivity activity impairment (WPAI-I- SHP)		X										X												X	
Short Form-36 (SF-36)		X				X				X		X				X				X				X	
Six-minute walk test (6 MWT)		X														X								X	
SAFETY																									
Physical examination (9.4.2)	X																							X	
Eye examination (9.4.5)	X																			X				X	
Urinalysis (9.4.6, Appendix 2)		X										X												X	
Pregnancy test (9.4.6, Appendix 5)	X	X		X		X		X		X		X		X		X		X		X		X		X	X
ECG (9.4.4)		X										X												X	
Adverse event (9.2, Appendix 4)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaint (9.2.9, Appendix 6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[b] 9.4																								X	X

Table 7.2.2.1 (cont)

	Scree-ning	Rando-misation	Dose escalation period								Maintenance period												End of treat-ment	End of trial
Visit (V), Phone (P)	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Colon neoplasms follow-up 9.4																								X	X
Haematology (Appendix 2)	X											X								X				X	
Biochemistry (Appendix 2)	X											X								X				X	
Vital Signs (6.4.2, 9.4.3)																									
Pulse	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Clinical Outcome Assessments (9.4.1)																									
Patient Health Questionnaire – 9 (PHQ-9)	X	X						X				X				X				X				X	
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X						X				X				X				X				X	
Anti-Semaglutide Antibody (9.4.7)		X		X		X		X						X						X				X	X
OTHER ASSESSMENTS																									
Semaglutide plasma concentration (9.5)				X		X		X						X						X				X	X
Biosamples for future analysis[d] (Appendix 7)		X																						X	
TRIAL MATERIAL																									
First date on trial product			X																						
IWRS session	X	X				X				X		X		X		X		X		X		X		X	
Administration of trial product (7.1, 7.5)		X				X				X		X		X		X		X		X		X		X	
Dispensing visit		X				X				X		X		X		X		X		X		X			
Drug accountability		X				X				X		X		X		X		X		X		X		X	
REMINDERS																									
Criteria for discontinuation (8.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Barriers and motivation interview (9)	X																								
Diet and physical activity counselling (7.1.2)		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Training in trial product, pen-handling (7.1.1)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hand out directions for use (7.1.1)		X																							
Hand out dose reminder card (7.1)		X		X		X		X		X															
Hand out and instruct in food diary (9)	X																								
Hand out and instruct in diabetes diary (9.1.3)		X		X		X		X		X		X		X		X		X		X		X		X	
Hand out and instruct in PK diary (9)		X		X		X						X						X				X			
Hand out ID card	X																								
Hand out and instruct in BG-meter (7.1)		X																							
Attend visit fasting (6.4.1)		X				X						X								X				X	X[e]

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] For all female subjects

[c] Smoking is defined as smoking at least one cigarette or equivalent daily

[d] Only for subjects where the separate informed consent for future research has been signed

[e] Fasting at V25 is defined as at least 2 hours without food and drink intake except water before attending the visit

Table 7.2.2.2 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number 1200 randomised subjects (400 in each arm) (copied from Table 10-2, Study NN9536-4374)

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo I/II				
1	% weight change #	11.6 (±10)	1.7 (±10)	10.2 (±11)	8.5%-points	> 99	> 99
2	5% responders	75%	37%	69%	1.8	> 99	> 99
3	10% responders	56%	20%	51%	2.6	> 99	> 99
4	15% responders	37%	9%	33%	3.7	> 99	> 99
5	WC change (cm) #	9.1 (±10)	2.8 (±10)	8.2 (±11)	5.4 cm	> 99	> 99
6	% weight change #, *	11.6 (±10)	8.1 (±10)	10.2 vs 7.2 (±11)	3.0%-points	97	97
7	HbA1c (%) change #	1.4 (±1.0)	0.5 (±1.0)	1.3 (±1.5)	0.8%-points	> 99	96
8	sBP change (mmHg) #	5.1 (±13)	0.4 (±13)	4.4 (±14)	4 mmHg	98	94
9	SF-36 PF score change	6 (±10)	2 (±10)	5.4 (±11)	3.4 score-points	> 99	94
10	IWQoL-Lite PFD score change	*To be confirmed. Is currently being validated in trial NN9536-4153 and NN9924-4233*					

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; # shown as a positive number; * semaglutide 2.4 mg vs semaglutide 1.0 mg

Table 7.2.2.3 Subject disposition (copied from Table 10-1, Study NN9536-4373)

	Sema 1.0 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Screened				1595
Screening failures				361
Withdrawn before randomisation				24
Randomised	403 (100)	404 (100)	403 (100)	1210 (100)
Randomised in violation of incl., excl. and/or randomisation criteria	21 (5.2)	11 (2.7)	17 (4.2)	49 (4.0)
Exposed	402 (99.8)	403 (99.8)	402 (99.8)	1207 (99.8)
Analysis sets				
Full analysis set	403 (100)	404 (100)	403 (100)	1210 (100)
Safety analysis set	402 (99.8)	403 (99.8)	402 (99.8)	1207 (99.8)
Treatment completion				
On-treatment at week 68 (treatment completers)	354 (87.8)	357 (88.4)	347 (86.1)	1058 (87.4)
After at least one temporary interruption	27 (6.7)	34 (8.4)	28 (6.9)	89 (7.4)
Attended end-of-treatment visit without permanent discontinuation of trial product	354 (87.8)	357 (88.4)	347 (86.1)	1058 (87.4)
Trial product permanently discontinued	49 (12.2)	47 (11.6)	56 (13.9)	152 (12.6)
Primary reason for permanent discontinuation of trial product				
Adverse event	19 (4.7)	26 (6.4)	13 (3.2)	58 (4.8)
Protocol violation	5 (1.2)	1 (0.2)	7 (1.7)	13 (1.1)
Randomised in violation of incl., excl. and/or randomisation criteria	5 (1.2)	1 (0.2)	5 (1.2)	11 (0.9)
Other	0	0	2 (0.5)	2 (0.2)
At the discretion of the investigator	2 (0.5)	0	1 (0.2)	3 (0.2)
Safety concern as judged by the investigator	1 (0.2)	1 (0.2)	0	2 (0.2)
Withdrawal of consent	5 (1.2)	2 (0.5)	7 (1.7)	14 (1.2)
Lost to follow-up	2 (0.5)	5 (1.2)	3 (0.7)	10 (0.8)
Other	15 (3.7)	12 (3.0)	25 (6.2)	52 (4.3)
Attended end-of-treatment visit after permanent discontinuation of trial product	37 (9.2)	37 (9.2)	42 (10.4)	116 (9.6)
Trial completion				
Attended end-of-trial visit (trial completers)	390 (96.8)	391 (96.8)	383 (95.0)	1164 (96.2)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	354 (87.8)	356 (88.1)	344 (85.4)	1054 (87.1)
Withdrawn from trial	13 (3.2)	13 (3.2)	20 (5.0)	46 (3.8)
Primary reason for trial withdrawal				
Withdrawal by subject	10 (2.5)	5 (1.2)	12 (3.0)	27 (2.2)
Lost to follow-up	2 (0.5)	7 (1.7)	7 (1.7)	16 (1.3)
Death	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Withdrawn from trial before week 68	12 (3.0)	11 (2.7)	15 (3.7)	38 (3.1)
Withdrawn from trial without prior permanent discontinuation of trial product	2 (0.5)	0	0	2 (0.2)

Table 7.2.2.4 Baseline characteristics and demographics - categorical variables (copied from Table 10-2, Study NN9536-4374)

	Sema 1.0 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	403	404	403	1210
Age (years)				
N	403 (100)	404 (100)	403 (100)	1210 (100)
18-<65	320 (79.4)	316 (78.2)	317 (78.7)	953 (78.8)
65-<75	78 (19.4)	78 (19.3)	78 (19.4)	234 (19.3)
75-<85	5 (1.2)	10 (2.5)	8 (2.0)	23 (1.9)
>=85	0	0	0	0
Sex				
N	403 (100)	404 (100)	403 (100)	1210 (100)
Female	203 (50.4)	223 (55.2)	190 (47.1)	616 (50.9)
Male	200 (49.6)	181 (44.8)	213 (52.9)	594 (49.1)
Country of residence				
N	403 (100)	404 (100)	403 (100)	1210 (100)
United Arab Emirates	12 (3.0)	13 (3.2)	13 (3.2)	38 (3.1)
Argentina	28 (6.9)	17 (4.2)	17 (4.2)	62 (5.1)
Canada	24 (6.0)	18 (4.5)	13 (3.2)	55 (4.5)
Germany	20 (5.0)	31 (7.7)	19 (4.7)	70 (5.8)
Spain	21 (5.2)	15 (3.7)	20 (5.0)	56 (4.6)
United Kingdom	28 (6.9)	28 (6.9)	30 (7.4)	86 (7.1)
Greece	15 (3.7)	11 (2.7)	21 (5.2)	47 (3.9)
India	45 (11.2)	66 (16.3)	53 (13.2)	164 (13.6)
Japan	36 (8.9)	42 (10.4)	47 (11.7)	125 (10.3)
Russian Federation	37 (9.2)	23 (5.7)	36 (8.9)	96 (7.9)
United States	117 (29.0)	128 (31.7)	116 (28.8)	361 (29.8)
South Africa	20 (5.0)	12 (3.0)	18 (4.5)	50 (4.1)
Ethnic origin				
N	403 (100)	404 (100)	403 (100)	1210 (100)
Not Hispanic or Latino	344 (85.4)	357 (88.4)	354 (87.8)	1055 (87.2)
Hispanic or Latino	59 (14.6)	47 (11.6)	49 (12.2)	155 (12.8)
Not Applicable	0	0	0	0
Race				
N	403 (100)	404 (100)	403 (100)	1210 (100)
White	272 (67.5)	237 (58.7)	242 (60.0)	751 (62.1)
Asian	97 (24.1)	112 (27.7)	108 (26.8)	317 (26.2)
Black or African American	28 (6.9)	35 (8.7)	37 (9.2)	100 (8.3)
Other	6 (1.5)	16 (4.0)	13 (3.2)	35 (2.9)
American Indian or Alaska Native	0	4 (1.0)	2 (0.5)	6 (0.5)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.2)	1 (<0.1)
Not Applicable	0	0	0	0
BMI (kg/m^2)				
N	403 (100)	404 (100)	403 (100)	1210 (100)
<30	66 (16.4)	68 (16.8)	77 (19.1)	211 (17.4)
30-<35	163 (40.4)	140 (34.7)	135 (33.5)	438 (36.2)
35-<40	100 (24.8)	103 (25.5)	97 (24.1)	300 (24.8)
>=40	74 (18.4)	93 (23.0)	94 (23.3)	261 (21.6)
Smoking habits				
N	403 (100)	404 (100)	403 (100)	1210 (100)
Never smoked	219 (54.3)	247 (61.1)	222 (55.1)	688 (56.9)
Previous smoker	117 (29.0)	108 (26.7)	119 (29.5)	344 (28.4)
Current smoker	67 (16.6)	49 (12.1)	62 (15.4)	178 (14.7)
Renal function, eGFR (mL/min/1.73 m^2)				
N	403 (100)	404 (100)	403 (100)	1210 (100)
Normal (>=90)	265 (65.8)	271 (67.1)	259 (64.3)	795 (65.7)
Mild RI (60-<90)	121 (30.0)	114 (28.2)	120 (29.8)	355 (29.3)
Moderate RI (30-<60)	17 (4.2)	18 (4.5)	24 (6.0)	59 (4.9)
Severe RI (15-<30)	0	1 (0.2)	0	1 (<0.1)
End-stage renal disease (<15)	0	0	0	0

Table 7.2.2.4 (cont)

	Sema 1.0 mg N	(%)	Sema 2.4 mg N	(%)	Placebo N	(%)	Total N	(%)
DRUGS USED IN DIABETES, A10	387	(96.0)	387	(95.8)	382	(94.8)	1156	(95.5)
BIGUANIDES	372	(92.3)	364	(90.1)	355	(88.1)	1091	(90.2)
SULFONYLUREAS	99	(24.6)	108	(26.7)	97	(24.1)	304	(25.1)
SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	90	(22.3)	95	(23.5)	99	(24.6)	284	(23.5)
THIAZOLIDINEDIONES	16	(4.0)	19	(4.7)	19	(4.7)	54	(4.5)
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	7	(1.7)	8	(2.0)	8	(2.0)	23	(1.9)
DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	2	(0.5)	0		1	(0.2)	3	(0.2)
ALPHA GLUCOSIDASE INHIBITORS	1	(0.2)	1	(0.2)	0		2	(0.2)
GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES	1	(0.2)	0		0		1	(<0.1)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	0		0		1	(0.2)	1	(<0.1)
OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	0		1	(0.2)	0		1	(<0.1)

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, RI: Renal impairment, HbA1c: Haemoglobin A1c, SGLT2i: Sodium-glucose co-transporter 2 inhibitors, SU: Sulphonylurea, OAD: Oral antidiabetic drug.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.
eGFR calculated based on creatinine value using the CKD-EPI equation.

Table 7.2.2.5 Baseline characteristics and demographics - continuous variables (copied from Table 10-3, Study NN9536-4374)

	Sema 1.0 mg	Sema 2.4 mg	Placebo	Total
Number of subjects	403	404	403	1210
Age (years)				
N	403	404	403	1210
Mean (SD)	56 (10)	55 (11)	55 (11)	55 (11)
Median	56	56	56	56
P5 ; P95	38 ; 71	37 ; 72	37 ; 72	37 ; 71
Min ; Max	20 ; 81	19 ; 84	20 ; 82	19 ; 84
Body weight (kg)				
N	403	404	403	1210
Mean (SD)	99.0 (21.1)	99.9 (22.5)	100.5 (20.9)	99.8 (21.5)
Median	96.1	97.5	98.3	97.1
P5 ; P95	69.6 ; 136.8	69.9 ; 141.6	72.0 ; 139.1	70.9 ; 139.4
Min ; Max	59.2 ; 184.8	54.4 ; 199.2	62.4 ; 184.6	54.4 ; 199.2
BMI (kg/m^2)				
N	403	404	403	1210
Mean (SD)	35.3 (5.9)	35.9 (6.4)	35.9 (6.5)	35.7 (6.3)
Median	33.8	34.6	34.6	34.3
P5 ; P95	27.9 ; 46.3	28.0 ; 47.8	27.8 ; 48.2	27.9 ; 47.7
Min ; Max	26.9 ; 58.4	27.0 ; 66.2	26.5 ; 65.4	26.5 ; 66.2
eGFR (mL/min/1.73m^2)				
N	403	404	403	1210
Geometric mean (CV)	93.43 (21.43)	94.25 (22.10)	92.32 (23.47)	93.33 (22.35)
Median	97.42	98.23	97.20	97.64
P5 ; P95	61.76 ; 119.80	61.82 ; 123.30	57.04 ; 122.05	60.95 ; 121.31
Min ; Max	39.24 ; 163.11	29.27 ; 146.94	35.91 ; 144.38	29.27 ; 163.11
Diabetes duration (years)				
N	403	404	402	1209
Mean (SD)	7.7 (5.9)	8.2 (6.2)	8.2 (6.2)	8.0 (6.1)
Median	6.5	6.8	6.8	6.7
P5 ; P95	0.9 ; 19.4	0.8 ; 19.7	1.0 ; 20.5	0.9 ; 19.7
Min ; Max	0.5 ; 34.7	0.5 ; 37.7	0.6 ; 29.9	0.5 ; 37.7
Waist circumference (cm)				
N	403	404	403	1210
Mean (SD)	113.9 (14.0)	114.5 (14.3)	115.5 (13.9)	114.6 (14.1)
Median	111.9	112.0	113.5	112.0
P5 ; P95	95.0 ; 138.0	94.0 ; 140.0	96.0 ; 140.3	95.0 ; 140.0
Min ; Max	85.0 ; 162.0	84.0 ; 172.7	80.0 ; 174.0	80.0 ; 174.0
HbA1c (%)				
N	403	404	403	1210
Mean (SD)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Median	8.0	8.0	8.0	8.0
P5 ; P95	7.0 ; 9.5	7.1 ; 9.6	7.1 ; 9.6	7.0 ; 9.6
Min ; Max	5.8 ; 10.2	6.7 ; 10.6	5.7 ; 10.3	5.7 ; 10.6
HbA1c (mmol/mol)				
N	403	404	403	1210
Mean (SD)	65.4 (8.5)	65.3 (8.7)	65.3 (9.0)	65.3 (8.7)
Median	63.9	63.9	63.9	63.9
P5 ; P95	53.0 ; 80.3	54.1 ; 81.4	54.1 ; 81.4	53.0 ; 81.4
Min ; Max	39.9 ; 88.0	49.7 ; 92.4	38.8 ; 89.1	38.8 ; 92.4
Fasting plasma glucose (mg/dL)				
N	395	396	400	1191
Mean (SD)	155.7 (41.5)	152.7 (40.9)	157.9 (42.1)	155.4 (41.5)
Median	149.2	146.3	151.8	148.3
P5 ; P95	100.2 ; 228.3	97.1 ; 229.4	102.3 ; 241.9	99.3 ; 234.6
Min ; Max	70.5 ; 369.0	72.4 ; 329.2	55.3 ; 352.3	55.3 ; 369.0

Table 7.2.2.5 (cont)

	Sema 1.0 mg	Sema 2.4 mg	Placebo	Total
Fasting plasma glucose (mmol/L)				
N	395	396	400	1191
Mean (SD)	8.6 (2.3)	8.5 (2.3)	8.8 (2.3)	8.6 (2.3)
Median	8.3	8.1	8.4	8.2
P5 ; P95	5.6 ; 12.7	5.4 ; 12.7	5.7 ; 13.4	5.5 ; 13.0
Min ; Max	3.9 ; 20.5	4.0 ; 18.3	3.1 ; 19.6	3.1 ; 20.5

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, CV: Coefficient of variation, HbA1c: Haemoglobin A1c.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.
eGFR calculated based on creatinine value using the CKD-EPI equation.

Table 7.2.2.6 Primary and confirmatory secondary analyses (test hierarchy) - treatment policy estimand (copied from Table 11-1, Study NN9536-4374)

Endpoint	Est. 95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoints					
Body weight (%) change from baseline to week 68					
Sema 2.4 mg - Placebo	-6.21 [-7.28; -5.15]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=5% at week 68					
Sema 2.4 mg / Placebo	4.88 [3.58; 6.64]	<.0001	0.05	Superiority	Confirmed
Other confirmatory endpoints					
Odds of achieving baseline body weight loss >=10% at week 68					
Sema 2.4 mg / Placebo	7.41 [4.89; 11.24]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=15% at week 68					
Sema 2.4 mg / Placebo	7.65 [4.11; 14.22]	<.0001	0.05	Superiority	Confirmed
Waist circumference (cm) change from baseline to week 68					
Sema 2.4 mg - Placebo	-4.88 [-5.97; -3.79]	<.0001	0.05	Superiority	Confirmed
Body weight (%) change from baseline to week 68					
Sema 2.4 mg - Sema 1.0 mg	-2.65 [-3.66; -1.64]	<.0001	0.05	Superiority	Confirmed
HbA1c (%) change from baseline to week 68					
Sema 2.4 mg - Placebo	-1.23 [-1.42; -1.05]	<.0001	0.05	Superiority	Confirmed
HbA1c (mmol/mol) change from baseline to week 68					
Sema 2.4 mg - Placebo	-13.48 [-15.53; -11.43]	<.0001	0.05	Superiority	Confirmed
Systolic blood pressure (mmHg) change from baseline to week 68					
Sema 2.4 mg - Placebo	-3.43 [-5.57; -1.30]	0.0016	0.05	Superiority	Confirmed
SF-36 Physical Functioning score change from baseline to week 68					
Sema 2.4 mg - Placebo	1.52 [0.44; 2.61]	0.0061	0.05	Superiority	Confirmed
IWQOL-Lite-CT Physical Function score change from baseline to week 68					
Sema 2.4 mg - Placebo	4.83 [1.79; 7.86]	0.0018	0.05	Superiority	Confirmed

Est.: Estimate, alpha: Local significance level, CI: Confidence interval, p-value: Unadjusted two-sided p-value for test of no difference. HbA1c: Haemoglobin A1c.

Table 7.2.3.1 Flowchart (from: 2 Flowchart, Protocol for Study NN9536-4373)

	Screening	Randomisation	Dose escalation period														Maintenance period													End of treatment	End of trial
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Timing of Visit (Weeks)	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																																
Informed consent and Demography[a] (Appendix 3)	X																															
Childbearing potential[b] (Appendix 5)	X																															
Inclusion criteria (6.1)	X	X																														
Exclusion criteria (6.2)	X	X																														
Randomisation criteria and randomisation (6.3)		X																														
Medical history/Concomitant illness (9.4)	X																															
Weight History (9)		X																														
History of Gallbladder Disease	X																															
History of Breast Neoplasm[b]	X																															
History of Colon Neoplasm	X																															
History of Skin Cancer (9.4)	X																															
History of Psychiatric disorder	X																															
Tobacco use[c]	X																															
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Trial product compliance (7.1, 7.6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluation of lipid-lowering treatment (9)																				X											X	
Evaluation of antihypertensive treatment (9)																				X											X	
Evaluation of glycaemia status		X																		X											X	
EFFICACY																																
Body measurements (9.1.1)																																
Height	X																															
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference	X	X				X				X				X		X		X			X		X		X		X			X	X	
HbA1c (Appendix 2)	X	X																X									X				X	
Fasting plasma glucose (Appendix 2)		X																X									X				X	
Fasting serum insulin (Appendix 2)		X																													X	
Lipids (Appendix 2		X																X													X	
Biomarkers (9.8)		X																X													X	
Vital Signs (9.4.3)																																
Systolic Blood Pressure	X	X				X				X				X		X		X			X		X		X		X			X	X	X
Diastolic Blood Pressure	X	X				X				X				X		X		X			X		X		X		X			X	X	X
Clinical Outcome Assessments (9.1.2)																																
Short Form- 36 (SF-36)		X								X						X		X					X				X			X		
Weight related signs and symptom measure (WRSSM)		X								X						X		X					X				X			X		
Patient Global Impression of Severity (PGI-S)		X								X						X		X					X				X			X		
Patient Global Impression of Change (PGI-C)		X								X						X		X					X				X			X		
Work productivity activity impairment (WPAI-I- SHP)		X																X													X	
SAFETY																																
Physical examination (9.4.2)	X																														X	
Pregnancy test (9.4.5, Appendix 5)	X	X				X				X				X		X		X			X		X		X		X			X	X	X
ECG (9.4.4)		X																X													X	
Adverse event (9.2, Appendix 4)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaint (9.2.9)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[b]																															X	X

Table 7.2.3.1 (cont)

	Screening	Randomisation	Dose escalation period														Maintenance period														End of treatment	End of trial
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Timing of Visit (Weeks)	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Colon neoplasms follow-up																															X	X
Haematology (Appendix 2)	X																	X									X				X	
Biochemistry (Appendix 2)	X																	X									X				X	
Vital signs (9.4.3)																																
Pulse	X	X				X				X				X		X		X			X		X		X		X		X		X	X
Clinical Outcome Assessments (9.4.1)																																
Patient Health Questionnaire –9 (PHQ-9)	X	X												X				X					X				X				X	
Columbia Suicidality Sev. Rating Scale (C-SSRS)	X	X												X				X					X				X				X	
TRIAL MATERIAL																																
First date on trial product			X																													
IWRS session	X	X								X						X		X			X		X		X		X		X		X	
Administration of trial product (7.1, 7.5)																																
Dispensing visit		X								X						X		X			X		X		X		X		X			
Drug accountability		X								X						X		X			X		X		X		X		X		X	
REMINDERS																																
Criteria for discontinuation (8.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Barriers and motivation interview (9)	X																															
Diet and physical activity counselling (7.1.2)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense activity tracker (7.1.2)		X																														
Hand out directions for use (7.1.1)		X																														
Hand out dose reminder card (7.1.1)		X				X				X				X		X																
Training in trial product, pen-handling (7.1.1)		X		X		X				X				X		X		X			X		X		X		X		X			
Hand out and instruct in food diary (9)	X																															
Hand out ID card	X																															
Attend visit fasting (6.4.1)		X																X								X				X	

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation).

[b] For all female subjects.

[c] Smoking is defined as smoking at least one cigarette or equivalent daily

Table 7.2.3.2 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number 600 randomised subjects (copied from Table 10-2, Study NN9536-4375)

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight loss #	17 (10)	7 (10)	15.6 (11)	8.6 %-points	> 99	> 99
2	5% responders	88%	58%	85%	1.5	> 99	> 99
3	10% responders	76%	38%	71%	1.9	> 99	> 99
4	15% responders	58%	21%	53%	2.5	> 99	> 99
5	WC change (cm) #	17 (11)	8 (11)	15.7 (12)	7.7 cm	> 99	> 99
6	sBP change (mmHg) #	9.1 (13)	4.5 (13)	8.5 (14)	4 mmHg	91	91
7	SF-36 PF score change	6 (±10)	2 (±10)	5.4 (±11)	3.4 score-points	95	86
8	WRSSM total score change	*To be confirmed. Is currently being validated in trials N8022-4272 and -4274.*					

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; WRSSM = Weight Related Sign and Symptom Measure; # shown as a positive number

Table 7.2.3.3 Subject disposition - all subjects (copied from Table 10-1, Study NN9536-4375)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Screened			742
Screening failures			129
Withdrawn before randomisation			2
Randomised	407 (100)	204 (100)	611 (100)
Randomised in violation of incl., excl. and/or randomisation criteria	0	1 (0.5)	1 (0.2)
Exposed	407 (100)	204 (100)	611 (100)
Analysis sets			
Full analysis set	407 (100)	204 (100)	611 (100)
Safety analysis set	407 (100)	204 (100)	611 (100)
Treatment completion			
On-treatment at week 68 (treatment completers)	339 (83.3)	166 (81.4)	505 (82.7)
After at least one temporary interruption	46 (11.3)	23 (11.3)	69 (11.3)
Attended end-of-treatment visit without permanent discontinuation of trial product	338 (83.0)	166 (81.4)	504 (82.5)
Trial product permanently discontinued	68 (16.7)	38 (18.6)	106 (17.3)
Primary reason for permanent discontinuation of trial product			
Adverse event	26 (6.4)	6 (2.9)	32 (5.2)
Protocol violation	0	1 (0.5)	1 (0.2)
Other	0	1 (0.5)	1 (0.2)
Pregnancy	1 (0.2)	2 (1.0)	3 (0.5)
Lack of efficacy	0	1 (0.5)	1 (0.2)
At the discretion of the investigator	1 (0.2)	0	1 (0.2)
Safety concern as judged by the investigator	1 (0.2)	2 (1.0)	3 (0.5)
Withdrawal of consent	4 (1.0)	3 (1.5)	7 (1.1)
Lost to follow-up	18 (4.4)	7 (3.4)	25 (4.1)
Other	17 (4.2)	16 (7.8)	33 (5.4)
Attended end-of-treatment visit after permanent discontinuation of trial product	36 (8.8)	24 (11.8)	60 (9.8)
Trial completion			
Attended end-of-trial visit (trial completers)	376 (92.4)	191 (93.6)	567 (92.8)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	335 (82.3)	165 (80.9)	500 (81.8)
Withdrawn from trial	31 (7.6)	13 (6.4)	44 (7.2)
Primary reason for trial withdrawal			
Withdrawal by subject	7 (1.7)	3 (1.5)	10 (1.6)
Lost to follow-up	24 (5.9)	10 (4.9)	34 (5.6)
Withdrawn from trial before week 68	26 (6.4)	10 (4.9)	36 (5.9)
Withdrawn from trial without prior permanent discontinuation of trial product	14 (3.4)	5 (2.5)	19 (3.1)

N: Number of subjects, %: Percentages are based on randomised subjects.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).
Only reasons for permanent discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.

Table 7.2.3.4 Demographics and baseline characteristics - categorical variables (copied from Table 10-2, Study NN9536-4375)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	407	204	611
Age (years)			
N	407 (100)	204 (100)	611 (100)
18-<65	379 (93.1)	186 (91.2)	565 (92.5)
65-<75	27 (6.6)	16 (7.8)	43 (7.0)
75-<85	1 (0.2)	2 (1.0)	3 (0.5)
>=85	0	0	0
Sex			
N	407 (100)	204 (100)	611 (100)
Female	315 (77.4)	180 (88.2)	495 (81.0)
Male	92 (22.6)	24 (11.8)	116 (19.0)
Country of residence			
N	407 (100)	204 (100)	611 (100)
United States	407 (100)	204 (100)	611 (100)
Ethnic origin			
N	407 (100)	204 (100)	611 (100)
Not Hispanic or Latino	332 (81.6)	158 (77.5)	490 (80.2)
Hispanic or Latino	75 (18.4)	46 (22.5)	121 (19.8)
Not Applicable	0	0	0
Race			
N	407 (100)	204 (100)	611 (100)
White	307 (75.4)	158 (77.5)	465 (76.1)
Black or African American	80 (19.7)	36 (17.6)	116 (19.0)
Other	11 (2.7)	4 (2.0)	15 (2.5)
Asian	5 (1.2)	6 (2.9)	11 (1.8)
Native Hawaiian or Other Pacific Islander	3 (0.7)	0	3 (0.5)
American Indian or Alaska Native	1 (0.2)	0	1 (0.2)
Not Applicable	0	0	0
BMI (kg/m^2)			
N	407 (100)	204 (100)	611 (100)
<30	23 (5.7)	15 (7.4)	38 (6.2)
30-<35	126 (31.0)	58 (28.4)	184 (30.1)
35-<40	136 (33.4)	76 (37.3)	212 (34.7)
>=40	122 (30.0)	55 (27.0)	177 (29.0)
Smoking habits			
N	407 (100)	204 (100)	611 (100)
Never smoked	298 (73.2)	144 (70.6)	442 (72.3)
Previous smoker	88 (21.6)	47 (23.0)	135 (22.1)
Current smoker	21 (5.2)	13 (6.4)	34 (5.6)

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.2.3.5 Demographics and baseline characteristics - continuous variables (copied from Table 10-3, Study NN9536-4375)

	Sema 2.4 mg	Placebo	Total
Number of subjects	407	204	611
Age (years)			
N	407	204	611
Mean (SD)	46 (13)	46 (13)	46 (13)
Median	46	46	46
P5 ; P95	25 ; 66	27 ; 67	26 ; 67
Min ; Max	18 ; 75	19 ; 75	18 ; 75
Body weight (kg)			
N	407	204	611
Mean (SD)	106.9 (22.8)	103.7 (22.9)	105.8 (22.9)
Median	102.6	99.0	101.0
P5 ; P95	77.4 ; 151.5	77.2 ; 154.6	77.2 ; 152.5
Min ; Max	68.6 ; 216.8	66.9 ; 182.7	66.9 ; 216.8
BMI (kg/m^2)			
N	407	204	611
Mean (SD)	38.1 (6.7)	37.8 (6.9)	38.0 (6.7)
Median	36.7	36.4	36.7
P5 ; P95	29.8 ; 50.1	29.2 ; 52.1	29.7 ; 50.4
Min ; Max	27.1 ; 65.7	27.0 ; 69.0	27.0 ; 69.0
Waist circumference (cm)			
N	407	204	611
Mean (SD)	113.6 (15.1)	111.8 (16.2)	113.0 (15.5)
Median	111.0	109.9	110.5
P5 ; P95	92.7 ; 141.0	89.4 ; 140.1	91.3 ; 141.0
Min ; Max	84.0 ; 164.0	77.7 ; 175.0	77.7 ; 175.0
HbA1c (%)			
N	407	204	611
Mean (SD)	5.7 (0.3)	5.8 (0.3)	5.7 (0.3)
Median	5.7	5.8	5.7
P5 ; P95	5.2 ; 6.3	5.2 ; 6.3	5.2 ; 6.3
Min ; Max	4.8 ; 7.0	4.6 ; 6.5	4.6 ; 7.0
Fasting plasma glucose (mg/dL)			
N	397	200	597
Mean (SD)	93.9 (9.4)	94.0 (9.8)	94.0 (9.6)
Median	93.3	93.3	93.3
P5 ; P95	80.2 ; 110.6	80.5 ; 112.9	80.2 ; 111.0
Min ; Max	60.4 ; 141.5	71.5 ; 122.5	60.4 ; 141.5
Fasting plasma glucose (mmol/L)			
N	397	200	597
Mean (SD)	5.2 (0.5)	5.2 (0.5)	5.2 (0.5)
Median	5.2	5.2	5.2
P5 ; P95	4.5 ; 6.1	4.5 ; 6.3	4.5 ; 6.2
Min ; Max	3.4 ; 7.9	4.0 ; 6.8	3.4 ; 7.9

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, HbA1c: Haemoglobin A1c.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.2.3.6 Confirmatory statistical analyses addressing the treatment policy estimand - in trial - RD-MI (copied from Table 11-1, Study NN9536-4375)

Endpoint	ETD / odds ratio	[95% CI]	Conclusion	Refer to Section
PRIMARY				
Change in body weight (%) from baseline to week 68, semaglutide 2.4 mg – placebo	-10.27%	[-11.97; -8.57]	Superiority confirmed with 2-sided p-value <0.0001	11.3.2.1
Subjects achieving ≥5% reduction in body weight from baseline to week 68, semaglutide 2.4 mg / placebo	6.11	[4.04; 9.26]	Superiority confirmed with 2-sided p-value <0.0001	11.3.3.1
CONFIRMATORY SECONDARY				
Subjects achieving ≥10% reduction in body weight from baseline to week 68, semaglutide 2.4 mg / placebo	7.36	[4.93; 10.99]	Superiority confirmed with 2-sided p-value <0.0001	11.4.1
Subjects achieving ≥15% reduction in body weight from baseline to week 68, semaglutide 2.4 mg / placebo	7.87	[4.90; 12.63]	Superiority confirmed with 2-sided p-value <0.0001	11.4.1
Change from baseline to week 68 in waist circumference, semaglutide 2.4 mg – placebo	-8.34 cm	[-10.08; -6.59]	Superiority confirmed with 2-sided p-value <0.0001	11.4.2
Change from baseline to week 68 in SBP, semaglutide 2.4 mg – placebo	-3.94 mmHg	[-6.36; -1.52]	Superiority confirmed with 2-sided p-value 0.0014	11.5.1.1
Change from baseline to week 68 in SF-36 physical functioning score, semaglutide 2.4 mg – placebo	0.84	[-0.23; 1.92]	Superiority not confirmed with 2-sided p-value 0.1249	11.6.1.1

Abbreviations: CI: confidence interval; ETD: estimated treatment difference; RD-MI: retrieved dropout; SBP: systolic blood pressure; SF-36: short form 36

Table 7.2.4.1 Flowchart (copied from 2, Study NN9536-4376 Protocol)

	Screening	Run-in										Rando-misation	Maintenance period											End of treatment	End of trial
Visit(V), Phone (P)	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																									
Informed consent and Demography[a] (Appendix 3)	X																								
Childbearing potential[b] (Appendix 5)	X																								
Inclusion criteria (6.1)	X	X																							
Exclusion criteria (6.2)	X	X																							
Run-in criteria (6.3.1)		X																							
Randomisation criteria and randomisation[c] (6.3.2)												X													
Medical history/Concomitant illness (9.4)	X																								
Weight History (9)		X																							
History of Gallbladder Disease (9.4)	X																								
History of Breast Neoplasm[b] (9.4)	X																								
History of Colon Neoplasm (9.4)	X																								
History of Skin Cancer (9.4)	X																								
History of Psychiatric Disorder (9.4)	X																								
Tobacco Use[d]	X																								
Concomitant medication (7.7)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Trial product compliance (7.1, 7.6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluation of lipid-lowering treatment (9)													X											X	
Evaluation of antihypertensive treatment (9)													X											X	
Evaluation of glycaemic status (9)		X											X											X	
EFFICACY																									
Body measurements (9.1.1)																									
Height	X																								
Body Weight	X	X		X		X		X		X		X	X	X		X		X		X		X		X	X
Waist Circumference	X	X		X		X		X		X		X	X	X		X		X		X		X		X	
HbA1c	X	X										X								X				X	
Fasting plasma glucose		X										X								X				X	
Fasting serum insulin		X										X												X	
Lipids (Appendix 2)		X										X												X	
Vital Signs (6.4.2, 9.4.3)																									
Systolic Blood Pressure	X	X		X		X		X		X		X	X	X		X		X		X		X		X	X
Diastolic Blood Pressure	X	X		X		X		X		X		X	X	X		X		X		X		X		X	X
Clinical Outcome Assessments (9.1.2)																									
Short Form-36 (SF-36)		X				X				X		X				X				X				X	
Weight Related Sign and Symptom Measure (WRSSM)		X				X				X		X				X				X				X	
Patient Global Impression of Severity (PGI-S)		X				X				X		X				X				X				X	

Table 7.2.4.1 (cont)

	Screening	Run-in										Rando-misation	Maintenance period											End of treatment	End of trial
Visit(V), Phone (P)	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	V25
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7 to 0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0 to +5
Patient Global Impression of Change (PGI-C)		X				X				X		X				X				X				X	
Stanford Presenteeism Scale (SPS-6)		X										X												X	
SAFETY																									
Physical examination (9.4.2)	X											X												X	
Pregnancy test (9.4.5, Appendix 5)	X	X		X		X		X		X		X	X	X		X		X		X		X		X	X
ECG (9.4.4)		X										X												X	
Adverse event (9.2, Appendix 4)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaint (9.2.9, Appendix 6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[b] (9.4)																								X	X
Colon neoplasms follow-up (9.4)																								X	X
Haematology (Appendix 2)	X											X								X				X	
Biochemistry (Appendix 2)	X											X								X				X	
Vital Signs (6.4.2, 9.4.3)																									
Pulse	X	X		X		X		X		X		X	X	X		X		X		X		X		X	X
Clinical Outcome Assessments (9.4.1)																									
Patient Health Questionnaire – 9 (PHQ-9)	X	X						X				X				X				X				X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X						X				X				X				X				X	
TRIAL MATERIAL																									
First date on trial product			X																						
IWRS session	X	X				X				X		X		X		X		X		X		X		X	
Administration of trial product (7.1, 7.5)																									
Dispensing visit		X				X				X		X		X		X		X		X		X			
Drug accountability		X				X				X		X		X		X		X		X		X		X	
REMINDERS																									
Criteria for discontinuation (8.1)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Barriers and motivation interview (9)	X																								
Diet and physical activity counselling (7.1.2)		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Training in trial product, pen-handling (7.1.1)		X		X		X		X		X		X		X		X		X		X		X			
Hand out direction for use (7.1.1)		X																							
Hand out dose reminder card (7.1)		X		X		X		X		X															
Hand out and instruct in food diary (9)	X																								
Hand out ID card	X																								
Attend visit fasting (6.4.1)		X										X								X				X	

[a] Demography consists of date of birth, sex, ethnicity, and race (according to local regulation)
[b] For all female subjects
[c] If subjects not fulfil randomisation criteria see Section 6.3.2
[d] Smoking is defined as smoking at least one cigarette or equivalent daily

Table 7.2.4.2 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 750 randomised subjects (from Table 2-2, Statistical Analysis Plan, Study NN9536-4376)

Order	Endpoint	Assumed mean (±SD) for completers		Expected mean (±SD)	Expected difference	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo	Semaglutide 2.4 mg			
1	% weight change	-4 (±10)	+5 (±10)	-3.7 (±11)	8.7 %-points	> 99	> 99
2	WC change (cm)	-3 (±10)	+3 (±10)	-2.8 (±11)	5.8 cm	> 99	> 99
3	sBP change (mmHg)	-3.1 (±13)	+1 (±13)	-3 (±14)	4 mmHg	95	95
4	SF-36 PF score change	+6 (±10)	+2 (±10)	+5.9 (±11)	3.9 score-points	> 99	95

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning
All tests in the hierarchy are based on the primary estimand

Table 7.2.4.3 Subject disposition – randomised period – all subjects (copied from Table 10-2, Study NN9536-4376)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Randomised	535 (100)	268 (100)	803 (100)
Randomised in violation of incl., excl., run-in and/ or randomisation criteria	4 (0.7)	4 (1.5)	8 (1.0)
Analysis sets			
Full analysis set	535 (100)	268 (100)	803 (100)
Safety analysis set (only randomised)	535 (100)	268 (100)	803 (100)
Exposed after randomisation	534 (99.8)	268 (100)	802 (99.9)
Treatment completion after randomisation			
On-treatment at week 68 (treatment completers)	504 (94.2)	237 (88.4)	741 (92.3)
After at least one temporary interruption	31 (5.8)	15 (5.6)	46 (5.7)
Attended end-of-treatment visit without permanent discontinuation of trial product	504 (94.2)	237 (88.4)	741 (92.3)
Trial product permanently discontinued	31 (5.8)	31 (11.6)	62 (7.7)
Primary reason for permanent discontinuation of trial product			
Adverse event	13 (2.4)	6 (2.2)	19 (2.4)
Protocol violation	1 (0.2)	0	1 (0.1)
Intention of becoming pregnant	1 (0.2)	0	1 (0.1)
Pregnancy	2 (0.4)	0	2 (0.2)
Withdrawal of consent	1 (0.2)	1 (0.4)	2 (0.2)
Lost to follow-up	2 (0.4)	1 (0.4)	3 (0.4)
Other	12 (2.2)	23 (8.6)	35 (4.4)
Attended end-of-treatment visit after permanent discontinuation of trial product	23 (4.3)	20 (7.5)	43 (5.4)
Trial completion after randomisation			
Attended end-of-trial visit (trial completers)	527 (98.5)	260 (97.0)	787 (98.0)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	503 (94.0)	237 (88.4)	740 (92.2)
Withdrawn from trial	8 (1.5)	8 (3.0)	16 (2.0)
Primary reason for trial withdrawal			
Withdrawal by subject	2 (0.4)	4 (1.5)	6 (0.7)
Lost to follow-up	5 (0.9)	3 (1.1)	8 (1.0)
Death	1 (0.2)	1 (0.4)	2 (0.2)
Withdrawn from trial before week 68	7 (1.3)	8 (3.0)	15 (1.9)
Withdrawn from trial without prior permanent discontinuation of trial product	1 (0.2)	1 (0.4)	2 (0.2)

N: Number of subjects, %: Percentages are based on either subjects included in run-in or randomised subjects.
Run-in period starts with week 0 visit.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at randomisation (week 20) / end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before the end of the treatment period (week 68). Reasons for permanent discontinuation of trial product or trial withdrawal which were not fulfilled by any subjects are not shown.

Table 7.2.4.4 Characteristics and demographics at week 20 (randomisation) – categorical variables – FAS (copied from Table 10-3, Study NN9536-4376)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	535	268	803
Age (years)			
N	535 (100)	268 (100)	803 (100)
18-<65	503 (94.0)	252 (94.0)	755 (94.0)
65-<75	29 (5.4)	15 (5.6)	44 (5.5)
75-<85	3 (0.6)	1 (0.4)	4 (0.5)
>=85	0	0	0
Sex			
N	535 (100)	268 (100)	803 (100)
Female	429 (80.2)	205 (76.5)	634 (79.0)
Male	106 (19.8)	63 (23.5)	169 (21.0)
Country of residence			
N	535 (100)	268 (100)	803 (100)
Switzerland	42 (7.9)	25 (9.3)	67 (8.3)
Denmark	39 (7.3)	15 (5.6)	54 (6.7)
Spain	49 (9.2)	19 (7.1)	68 (8.5)
Israel	31 (5.8)	24 (9.0)	55 (6.8)
Netherlands	28 (5.2)	14 (5.2)	42 (5.2)
Portugal	20 (3.7)	14 (5.2)	34 (4.2)
Sweden	30 (5.6)	14 (5.2)	44 (5.5)
Ukraine	43 (8.0)	19 (7.1)	62 (7.7)
United States	208 (38.9)	104 (38.8)	312 (38.9)
South Africa	45 (8.4)	20 (7.5)	65 (8.1)
Ethnic origin			
N	535 (100)	268 (100)	803 (100)
Not Hispanic or Latino	493 (92.1)	247 (92.2)	740 (92.2)
Hispanic or Latino	42 (7.9)	21 (7.8)	63 (7.8)
Not Applicable	0	0	0
Race			
N	535 (100)	268 (100)	803 (100)
White	446 (83.4)	226 (84.3)	672 (83.7)
Black or African American	69 (12.9)	35 (13.1)	104 (13.0)
Asian	15 (2.8)	4 (1.5)	19 (2.4)
Other	5 (0.9)	3 (1.1)	8 (1.0)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not Applicable	0	0	0
BMI (kg/m^2)			
N	535 (100)	268 (100)	803 (100)
<25	7 (1.3)	9 (3.4)	16 (2.0)
25-<30	153 (28.6)	69 (25.7)	222 (27.6)
30-<35	166 (31.0)	97 (36.2)	263 (32.8)
35-<40	116 (21.7)	52 (19.4)	168 (20.9)
>=40	93 (17.4)	41 (15.3)	134 (16.7)
Smoking habits			
N	535 (100)	268 (100)	803 (100)
Never smoked	351 (65.6)	174 (64.9)	525 (65.4)
Previous smoker	143 (26.7)	62 (23.1)	205 (25.5)
Current smoker	41 (7.7)	32 (11.9)	73 (9.1)

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index.
Baseline: Randomisation (week 20). The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.2.4.6 Confirmatory statistical analyses addressing the primary estimand (treatment policy) – in trial – RD-MI (copied from Table 11-1, Study NN9536-4376)

Endpoint	ETD	[95% CI]	Conclusion	Refer to Section
PRIMARY				
Change in body weight (%) from baseline (week 20) to week 68, semaglutide 2.4 mg – placebo	-14.75%	[-16.00; -13.50]	Superiority confirmed with 2-sided p-value <0.0001	11.3.2
CONFIRMATORY SECONDARY				
Change from baseline (week 20) to week 68 in waist circumference (cm), semaglutide 2.4 mg – placebo	-9.74 cm	[-10.94; -8.54]	Superiority confirmed with 2-sided p-value <0.0001	11.3.3.1
Change from baseline (week 20) to week 68 in systolic blood pressure, semaglutide 2.4 mg – placebo	-3.92 mmHg	[-5.82; -2.03]	Superiority confirmed with 2-sided p-value <0.0001	11.4.1.1
Change from baseline (week 20) to week 68 in SF-36 v2.0 acute physical functioning score, semaglutide 2.4 mg – placebo	2.46	[1.59; 3.32]	Superiority confirmed with 2-sided p-value <0.0001	11.5.1.1

FAS: full analysis set; ETD: estimated treatment difference; RD-MI: retrieved dropout, multiple imputation; CI: confidence interval

Table 7.2.4.5 Characteristics and demographics at week 20 (randomisation) – continuous variables – FAS (copied from Table 10-4, Study NN9536-4376)

	Sema 2.4 mg	Placebo	Total
Number of subjects	535	268	803
Age (years)			
N	535	268	803
Mean (SD)	47 (12)	46 (12)	46 (12)
Median	46	46	46
P5 ; P95	26 ; 66	26 ; 65	26 ; 65
Min ; Max	18 ; 77	20 ; 78	18 ; 78
Height (m)			
N	535	268	803
Mean (SD)	1.67 (0.09)	1.67 (0.09)	1.67 (0.09)
Median	1.66	1.65	1.66
P5 ; P95	1.54 ; 1.85	1.55 ; 1.83	1.54 ; 1.85
Min ; Max	1.43 ; 1.97	1.43 ; 1.90	1.43 ; 1.97
Body weight (kg)			
N	535	268	803
Mean (SD)	96.5 (22.5)	95.4 (22.7)	96.1 (22.6)
Median	92.7	91.0	92.0
P5 ; P95	69.1 ; 143.3	66.8 ; 134.6	68.2 ; 137.2
Min ; Max	57.6 ; 200.1	51.9 ; 193.7	51.9 ; 200.1
BMI (kg/m^2)			
N	535	268	803
Mean (SD)	34.5 (6.9)	34.1 (7.1)	34.4 (7.0)
Median	33.2	32.4	32.8
P5 ; P95	26.4 ; 48.5	25.4 ; 49.4	26.2 ; 48.5
Min ; Max	22.4 ; 72.6	22.7 ; 67.4	22.4 ; 72.6
Waist circumference (cm)			
N	535	268	803
Mean (SD)	105.5 (15.9)	104.7 (16.9)	105.3 (16.2)
Median	103.0	103.1	103.0
P5 ; P95	83.8 ; 137.2	81.0 ; 136.0	82.5 ; 136.5
Min ; Max	73.0 ; 171.0	71.1 ; 181.0	71.1 ; 181.0
HbA1c (%)			
N	535	268	803
Mean (SD)	5.4 (0.3)	5.4 (0.3)	5.4 (0.3)
Median	5.4	5.4	5.4
P5 ; P95	4.9 ; 5.8	4.9 ; 5.8	4.9 ; 5.8
Min ; Max	4.5 ; 6.2	4.5 ; 6.1	4.5 ; 6.2
Fasting plasma glucose (mmol/L)			
N	535	268	803
Mean (SD)	4.9 (0.4)	4.8 (0.4)	4.9 (0.4)
Median	4.9	4.8	4.9
P5 ; P95	4.2 ; 5.6	4.2 ; 5.5	4.2 ; 5.5
Min ; Max	3.0 ; 6.6	3.7 ; 7.3	3.0 ; 7.3
Fasting plasma glucose (mg/dL)			
N	535	268	803
Mean (SD)	87.9 (7.7)	86.9 (7.6)	87.6 (7.7)
Median	87.8	86.7	87.4
P5 ; P95	76.2 ; 100.4	74.8 ; 98.7	75.9 ; 99.3
Min ; Max	54.1 ; 119.3	66.3 ; 130.8	54.1 ; 130.8

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, HbA1c: Haemoglobin A1c.
Baseline: Randomisation (week 20). The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 8.3.1 Overview of clinical trials included in the RMP (copied from Table 2-6, Risk Management Plan).

SUSTAIN (semaglutide s.c. for T2D)		PIONEER (oral semaglutide for T2D)		STEP (semaglutide s.c. 2.4 mg for WM)	
Trial name	**Trial ID**	**Trial name**	**Trial ID**	**Trial name**	**Trial ID**
SUSTAIN 1	NN9535-3623	PIONEER 1	NN9924-4233	STEP 1	NN9536-4373
SUSTAIN 2	NN9535-3626	PIONEER 2	NN9924-4223	STEP 2	NN9536-4374
SUSTAIN 3	NN9535-3624	PIONEER 3	NN9924-4222	STEP 3	NN9536-4375
SUSTAIN 4	NN9535-3625	PIONEER 4	NN9924-4224	STEP 4	NN9536-4376
SUSTAIN 5	NN9535-3627	PIONEER 5	NN9924-4234	–	–
SUSTAIN 6 (CVOT)	NN9535-3744	PIONEER 6 (CVOT)	NN9924-4221	–	–
SUSTAIN 7	NN9535-4216	PIONEER 7	NN9924-4257	–	–
SUSTAIN JP	NN9535-4091	PIONEER 8	NN9924-4280	–	–
SUSTAIN JP	NN9535-4092	–	–	–	–

Abbreviations: CVOT = cardiovascular outcomes trial; RMP = risk management plan; s.c. = subcutaneous(-ly); T2D = type 2 diabetes mellitus; WM = weight management.

Table 8.4.1.4.1 Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set (copied from Table 14.3.1.2, Study NN9536-4590)

	Semaglutide D, DV3396 N (%)	E	Semaglutide B, PDS290 N (%)	E	Total N (%)	E
Number of subjects	34		34		68	
Events	28 (82.4)	135	31 (91.2)	146	59 (86.8)	281
Gastrointestinal disorders	22 (64.7)	59	24 (70.6)	60	46 (67.6)	119
Nausea	8 (23.5)	10	11 (32.4)	13	19 (27.9)	23
Dyspepsia	8 (23.5)	10	8 (23.5)	8	16 (23.5)	18
Diarrhoea	7 (20.6)	12	6 (17.6)	8	13 (19.1)	20
Abdominal distension	7 (20.6)	7	5 (14.7)	6	12 (17.6)	13
Vomiting	3 (8.8)	3	5 (14.7)	6	8 (11.8)	9
Abdominal pain upper	2 (5.9)	2	5 (14.7)	5	7 (10.3)	7
Eructation	3 (8.8)	3	4 (11.8)	4	7 (10.3)	7
Abdominal pain	4 (11.8)	4	2 (5.9)	2	6 (8.8)	6
Constipation	3 (8.8)	3	2 (5.9)	2	5 (7.4)	5
Dry mouth	3 (8.8)	3	1 (2.9)	1	4 (5.9)	4
Flatulence	2 (5.9)	2	1 (2.9)	1	3 (4.4)	3
Infrequent bowel movements	0		2 (5.9)	2	2 (2.9)	2
Abdominal discomfort	0		1 (2.9)	1	1 (1.5)	1
Faeces hard	0		1 (2.9)	1	1 (1.5)	1
Nervous system disorders	10 (29.4)	22	17 (50.0)	27	27 (39.7)	49
Headache	9 (26.5)	19	13 (38.2)	18	22 (32.4)	37
Dizziness	1 (2.9)	1	4 (11.8)	4	5 (7.4)	5
Taste disorder	1 (2.9)	1	2 (5.9)	2	3 (4.4)	3
Sciatica	0		2 (5.9)	2	2 (2.9)	2
Dizziness postural	1 (2.9)	1	0		1 (1.5)	1
Lumbosacral radiculopathy	0		1 (2.9)	1	1 (1.5)	1
General disorders and administration site conditions	12 (35.3)	17	15 (44.1)	21	27 (39.7)	38
Early satiety	5 (14.7)	5	9 (26.5)	9	14 (20.6)	14
Asthenia	2 (5.9)	3	4 (11.8)	4	6 (8.8)	7
Catheter site haematoma	2 (5.9)	2	0		2 (2.9)	2
Fatigue	1 (2.9)	1	1 (2.9)	1	2 (2.9)	2
Hunger	1 (2.9)	1	1 (2.9)	1	2 (2.9)	2
Catheter site irritation	1 (2.9)	1	0		1 (1.5)	1
Catheter site phlebitis	0		1 (2.9)	1	1 (1.5)	1
Discomfort	0		1 (2.9)	1	1 (1.5)	1
General physical health deterioration	1 (2.9)	1	0		1 (1.5)	1
Infusion site thrombosis	0		1 (2.9)	1	1 (1.5)	1
Injection site pain	1 (2.9)	1	0		1 (1.5)	1
Injection site pruritus	1 (2.9)	1	0		1 (1.5)	1
Pyrexia	0		1 (2.9)	1	1 (1.5)	1
Thirst	0		1 (2.9)	1	1 (1.5)	1
Thirst decreased	1 (2.9)	1	0		1 (1.5)	1
Vessel puncture site reaction	0		1 (2.9)	1	1 (1.5)	1
Metabolism and nutrition disorders	10 (29.4)	11	14 (41.2)	15	24 (35.3)	26
Decreased appetite	10 (29.4)	11	12 (35.3)	12	22 (32.4)	23
Food aversion	0		1 (2.9)	1	1 (1.5)	1
Food craving	0		1 (2.9)	1	1 (1.5)	1
Increased appetite	0		1 (2.9)	1	1 (1.5)	1
Infections and infestations	7 (20.6)	8	8 (23.5)	9	15 (22.1)	17
Nasopharyngitis	2 (5.9)	2	3 (8.8)	3	5 (7.4)	5
Influenza	1 (2.9)	1	2 (5.9)	2	3 (4.4)	3
Gastroenteritis	0		2 (5.9)	3	2 (2.9)	3
Conjunctivitis	1 (2.9)	1	0		1 (1.5)	1
Ear infection	1 (2.9)	1	0		1 (1.5)	1

N: Number of subjects, %: Percentage of subjects, E: Number of events

Table 8.4.1.4.1 (cont)

	Semaglutide D, DV3396 N (%)	E	Semaglutide B, PDS290 N (%)	E	Total N (%)	E
Gastrointestinal infection	1 (2.9)	1	0		1 (1.5)	1
Genital herpes	1 (2.9)	1	0		1 (1.5)	1
Rhinitis	0		1 (2.9)	1	1 (1.5)	1
Vulvovaginal mycotic infection	1 (2.9)	1	0		1 (1.5)	1
Musculoskeletal and connective tissue disorders	3 (8.8)	3	4 (11.8)	4	7 (10.3)	7
Arthralgia	2 (5.9)	2	1 (2.9)	1	3 (4.4)	3
Musculoskeletal discomfort	0		1 (2.9)	1	1 (1.5)	1
Myalgia	0		1 (2.9)	1	1 (1.5)	1
Pain in jaw	1 (2.9)	1	0		1 (1.5)	1
Torticollis	0		1 (2.9)	1	1 (1.5)	1
Injury, poisoning and procedural complications	3 (8.8)	3	2 (5.9)	2	5 (7.4)	5
Contusion	1 (2.9)	1	0		1 (1.5)	1
Incorrect dose administered	0		1 (2.9)	1	1 (1.5)	1
Joint injury	1 (2.9)	1	0		1 (1.5)	1
Limb injury	0		1 (2.9)	1	1 (1.5)	1
Muscle rupture	1 (2.9)	1	0		1 (1.5)	1
Immune system disorders	2 (5.9)	3	1 (2.9)	1	3 (4.4)	4
Seasonal allergy	2 (5.9)	3	1 (2.9)	1	3 (4.4)	4
Respiratory, thoracic and mediastinal disorders	2 (5.9)	2	1 (2.9)	1	3 (4.4)	3
Oropharyngeal pain	1 (2.9)	1	1 (2.9)	1	2 (2.9)	2
Hiccups	1 (2.9)	1	0		1 (1.5)	1
Skin and subcutaneous tissue disorders	1 (2.9)	1	1 (2.9)	2	2 (2.9)	3
Cold sweat	0		1 (2.9)	2	1 (1.5)	2
Skin disorder	1 (2.9)	1	0		1 (1.5)	1
Cardiac disorders	2 (5.9)	2	0		2 (2.9)	2
Arrhythmia supraventricular	1 (2.9)	1	0		1 (1.5)	1
Palpitations	1 (2.9)	1	0		1 (1.5)	1
Renal and urinary disorders	1 (2.9)	1	1 (2.9)	1	2 (2.9)	2
Polyuria	1 (2.9)	1	1 (2.9)	1	2 (2.9)	2
Congenital, familial and genetic disorders	1 (2.9)	1	0		1 (1.5)	1
Muscular dystrophy	1 (2.9)	1	0		1 (1.5)	1
Eye disorders	0		1 (2.9)	1	1 (1.5)	1
Uveitis	0		1 (2.9)	1	1 (1.5)	1
Psychiatric disorders	0		1 (2.9)	1	1 (1.5)	1
Insomnia	0		1 (2.9)	1	1 (1.5)	1
Reproductive system and breast disorders	0		1 (2.9)	1	1 (1.5)	1
Oligomenorrhoea	0		1 (2.9)	1	1 (1.5)	1
Surgical and medical procedures	1 (2.9)	1	0		1 (1.5)	1
Dental care	1 (2.9)	1	0		1 (1.5)	1
Vascular disorders	1 (2.9)	1	0		1 (1.5)	1
Hypertension	1 (2.9)	1	0		1 (1.5)	1

N: Number of subjects, %: Percentage of subjects, E: Number of events

Table 8.4.1.4.2 Adverse events by system organ class and preferred term - treatment-emergent - summary - safety analysis set (copied from Table 12-2, Study NN9535-4588)

	SEMAGLUTIDE D, DV3396			SEMAGLUTIDE B, PDS290			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of subjects	35			33			68		
Events	32	(91.4)	143	30	(90.9)	94	62	(91.2)	237
Gastrointestinal disorders	25	(71.4)	59	19	(57.6)	38	44	(64.7)	97
Nausea	9	(25.7)	11	8	(24.2)	13	17	(25.0)	24
Vomiting	8	(22.9)	9	4	(12.1)	7	12	(17.6)	16
Diarrhoea	7	(20.0)	9	4	(12.1)	5	11	(16.2)	14
Dyspepsia	6	(17.1)	7	4	(12.1)	4	10	(14.7)	11
Gastrooesophageal reflux disease	5	(14.3)	7	1	(3.0)	1	6	(8.8)	8
Constipation	3	(8.6)	3	3	(9.1)	4	6	(8.8)	7
Abdominal pain upper	2	(5.7)	3	2	(6.1)	2	4	(5.9)	5
Abdominal pain	3	(8.6)	4	0	(0.0)	0	3	(4.4)	4
Abdominal distension	2	(5.7)	2	1	(3.0)	1	3	(4.4)	3
Eructation	3	(8.6)	3	0	(0.0)	0	3	(4.4)	3
Faeces hard	0	(0.0)	0	1	(3.0)	1	1	(1.5)	1
Flatulence	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Nervous system disorders	17	(48.6)	29	13	(39.4)	16	30	(44.1)	45
Headache	17	(48.6)	26	12	(36.4)	15	29	(42.6)	41
Sciatica	1	(2.9)	2	0	(0.0)	0	1	(1.5)	2
Dizziness	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Orthostatic intolerance	0	(0.0)	0	1	(3.0)	1	1	(1.5)	1
Metabolism and nutrition disorders	18	(51.4)	19	18	(54.5)	18	36	(52.9)	37
Decreased appetite	18	(51.4)	19	18	(54.5)	18	36	(52.9)	37
Infections and infestations	8	(22.9)	11	6	(18.2)	7	14	(20.6)	18
Nasopharyngitis	8	(22.9)	10	5	(15.2)	5	13	(19.1)	15
Catheter site infection	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Conjunctivitis	0	(0.0)	0	1	(3.0)	1	1	(1.5)	1
Gastroenteritis	0	(0.0)	0	1	(3.0)	1	1	(1.5)	1
General disorders and administration site conditions	8	(22.9)	11	5	(15.2)	6	13	(19.1)	17
Fatigue	3	(8.6)	3	3	(9.1)	3	6	(8.8)	6
Catheter site related reaction	2	(5.7)	2	1	(3.0)	2	3	(4.4)	4
Injection site reaction	3	(8.6)	3	0	(0.0)	0	3	(4.4)	3
Early satiety	1	(2.9)	1	1	(3.0)	1	2	(2.9)	2
Catheter site pain	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Influenza like illness	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Musculoskeletal and connective tissue disorders	5	(14.3)	6	4	(12.1)	4	9	(13.2)	10
Back pain	4	(11.4)	4	2	(6.1)	2	6	(8.8)	6
Cervical spinal stenosis	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Musculoskeletal chest pain	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Myalgia	0	(0.0)	0	1	(3.0)	1	1	(1.5)	1
Tendon pain	0	(0.0)	0	1	(3.0)	1	1	(1.5)	1
Investigations	2	(5.7)	3	1	(3.0)	1	3	(4.4)	4
Blood creatine phosphokinase increased	1	(2.9)	1	1	(3.0)	1	2	(2.9)	2
C-reactive protein increased	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Transaminases increased	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Respiratory, thoracic and mediastinal disorders	2	(5.7)	2	2	(6.1)	2	4	(5.9)	4
Oropharyngeal pain	0	(0.0)	0	2	(6.1)	2	2	(2.9)	2
Cough	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1
Epistaxis	1	(2.9)	1	0	(0.0)	0	1	(1.5)	1

N: Number of subjects, %: Percentage of subjects, E: Number of events

Table 8.4.1.4.2 (cont)

	SEMAGLUTIDE D, DV3396		SEMAGLUTIDE B, PDS290		Total	
	N (%)	E	N (%)	E	N (%)	E
Skin and subcutaneous tissue disorders	1 (2.9)	2	0 (0.0)	0	1 (1.5)	2
Erythema	1 (2.9)	1	0 (0.0)	0	1 (1.5)	1
Pruritus	1 (2.9)	1	0 (0.0)	0	1 (1.5)	1
Ear and labyrinth disorders	0 (0.0)	0	1 (3.0)	1	1 (1.5)	1
Ear pain	0 (0.0)	0	1 (3.0)	1	1 (1.5)	1
Injury, poisoning and procedural complications	0 (0.0)	0	1 (3.0)	1	1 (1.5)	1
Ligament rupture	0 (0.0)	0	1 (3.0)	1	1 (1.5)	1
Reproductive system and breast disorders	1 (2.9)	1	0 (0.0)	0	1 (1.5)	1
Metrorrhagia	1 (2.9)	1	0 (0.0)	0	1 (1.5)	1

N: Number of subjects, %: Percentage of subjects, E: Number of events

Table 8.4.1.4.3 Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set (copied from Table 14.3.1.2, Study NN9536-4455)

	Sema 2.4 mg N	(%)	E	Placebo N	(%)	E	Total N	(%)	E
Number of subjects	36			36			72		
Events	29	(80.6)	271	33	(91.7)	180	62	(86.1)	451
Gastrointestinal disorders	25	(69.4)	151	14	(38.9)	50	39	(54.2)	201
Nausea	17	(47.2)	37	6	(16.7)	14	23	(31.9)	51
Diarrhoea	16	(44.4)	41	4	(11.1)	23	20	(27.8)	64
Vomiting	8	(22.2)	16	1	(2.8)	1	9	(12.5)	17
Abdominal pain	7	(19.4)	18	1	(2.8)	1	8	(11.1)	19
Eructation	5	(13.9)	11	3	(8.3)	3	8	(11.1)	14
Dyspepsia	5	(13.9)	13	0			5	(6.9)	13
Abdominal distension	3	(8.3)	3	2	(5.6)	2	5	(6.9)	5
Faeces hard	3	(8.3)	4	0			3	(4.2)	4
Abdominal pain upper	1	(2.8)	1	1	(2.8)	1	2	(2.8)	2
Frequent bowel movements	0			2	(5.6)	2	2	(2.8)	2
Dry mouth	0			1	(2.8)	2	1	(1.4)	2
Retching	1	(2.8)	2	0			1	(1.4)	2
Abdominal discomfort	1	(2.8)	1	0			1	(1.4)	1
Constipation	1	(2.8)	1	0			1	(1.4)	1
Faeces discoloured	0			1	(2.8)	1	1	(1.4)	1
Flatulence	1	(2.8)	1	0			1	(1.4)	1
Gastrointestinal sounds abnormal	1	(2.8)	1	0			1	(1.4)	1
Infrequent bowel movements	1	(2.8)	1	0			1	(1.4)	1
Nervous system disorders	15	(41.7)	41	16	(44.4)	54	31	(43.1)	95
Headache	11	(30.6)	32	11	(30.6)	35	22	(30.6)	67
Dizziness	1	(2.8)	1	5	(13.9)	14	6	(8.3)	15
Paraesthesia	3	(8.3)	3	0			3	(4.2)	3
Hypoaesthesia	1	(2.8)	1	1	(2.8)	1	2	(2.8)	2
Hypogeusia	0			1	(2.8)	2	1	(1.4)	2
Migraine	1	(2.8)	2	0			1	(1.4)	2
Disturbance in attention	0			1	(2.8)	1	1	(1.4)	1
Dysgeusia	0			1	(2.8)	1	1	(1.4)	1
Peroneal nerve palsy	1	(2.8)	1	0			1	(1.4)	1
Somnolence	1	(2.8)	1	0			1	(1.4)	1
Metabolism and nutrition disorders	20	(55.6)	22	10	(27.8)	13	30	(41.7)	35
Decreased appetite	20	(55.6)	22	10	(27.8)	13	30	(41.7)	35
Infections and infestations	9	(25.0)	14	10	(27.8)	13	19	(26.4)	27
Nasopharyngitis	8	(22.2)	11	8	(22.2)	9	16	(22.2)	20
Colonic abscess	0			1	(2.8)	1	1	(1.4)	1
Cystitis	1	(2.8)	1	0			1	(1.4)	1
Gingivitis	0			1	(2.8)	1	1	(1.4)	1
Otitis media acute	0			1	(2.8)	1	1	(1.4)	1
Pyelonephritis	0			1	(2.8)	1	1	(1.4)	1
Rhinitis	1	(2.8)	1	0			1	(1.4)	1
Sinusitis	1	(2.8)	1	0			1	(1.4)	1
Musculoskeletal and connective tissue disorders	6	(16.7)	9	11	(30.6)	12	17	(23.6)	21
Back pain	1	(2.8)	1	4	(11.1)	4	5	(6.9)	5
Pain in extremity	2	(5.6)	2	2	(5.6)	2	4	(5.6)	4
Arthralgia	0			2	(5.6)	2	2	(2.8)	2
Muscle spasms	1	(2.8)	1	1	(2.8)	1	2	(2.8)	2
Musculoskeletal pain	2	(5.6)	2	0			2	(2.8)	2
Myalgia	1	(2.8)	1	1	(2.8)	1	2	(2.8)	2
Limb discomfort	1	(2.8)	1	0			1	(1.4)	1

N: Number of subjects, %: Percentage of subjects, E: Number of events

Table 8.4.2.3.1 Adverse events possibly or probably related to trial product by system organ class and preferred term - selected SOCs and PTs - on-treatment (copied from Table 12-3, Study NN9536-4373)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1306				655			
Patient years of exposure (PYE)	1706.1				829.6			
Events	926	(70.9)	4848	284.2	295	(45.0)	885	106.7
Gastrointestinal disorders	872	(66.8)	3690	216.3	233	(35.6)	543	65.5
Nausea	550	(42.1)	1017	59.6	100	(15.3)	126	15.2
Diarrhoea	359	(27.5)	659	38.6	82	(12.5)	112	13.5
Vomiting	283	(21.7)	560	32.8	33	(5.0)	41	4.9
Constipation	259	(19.8)	333	19.5	49	(7.5)	58	7.0
Dyspepsia	123	(9.4)	164	9.6	18	(2.7)	24	2.9
Eructation	108	(8.3)	134	7.9	3	(0.5)	3	0.4
Abdominal pain	105	(8.0)	140	8.2	21	(3.2)	22	2.7
Abdominal pain upper	103	(7.9)	147	8.6	25	(3.8)	27	3.3
Abdominal distension	86	(6.6)	123	7.2	27	(4.1)	37	4.5
Gastrooesophageal reflux disease	65	(5.0)	73	4.3	16	(2.4)	17	2.0
Flatulence	58	(4.4)	76	4.5	20	(3.1)	21	2.5
Abdominal discomfort	47	(3.6)	64	3.8	8	(1.2)	8	1.0
Gastritis	36	(2.8)	52	3.0	3	(0.5)	3	0.4
Hyperchlorhydria	18	(1.4)	35	2.1	3	(0.5)	5	0.6
Nervous system disorders	174	(13.3)	323	18.9	42	(6.4)	71	8.6
Headache	86	(6.6)	185	10.8	27	(4.1)	32	3.9
Dizziness	53	(4.1)	68	4.0	10	(1.5)	19	2.3
General disorders and administration site cond.	162	(12.4)	252	14.8	60	(9.2)	104	12.5
Fatigue	56	(4.3)	64	3.8	13	(2.0)	14	1.7
Asthenia	29	(2.2)	41	2.4	3	(0.5)	4	0.5
Early satiety	26	(2.0)	26	1.5	2	(0.3)	2	0.2
Metabolism and nutrition disorders	145	(11.1)	177	10.4	30	(4.6)	36	4.3
Decreased appetite	120	(9.2)	134	7.9	21	(3.2)	25	3.0
Skin and subcutaneous tissue disorders	62	(4.7)	77	4.5	16	(2.4)	19	2.3
Alopecia	27	(2.1)	28	1.6	3	(0.5)	3	0.4
Hepatobiliary disorders	18	(1.4)	22	1.3	4	(0.6)	4	0.5
Cholelithiasis	8	(0.6)	9	0.5	1	(0.2)	1	0.1

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, cond.: condition. PYE: The duration of the on-treatment period in years. Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Relationship to trial product is based on assessment by investigator. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event. MedDRA version 22.1

Table 8.4.3.1.1 SAEs (PTs ≥ 0.2% of subjects) by SOC and PT – on-treatment – phase 3a pool (copied from Table 2-7, Summary of Clinical Safety)

System organ class Preferred term	Sema 2.4 mg N (Adj.%)	E	Adj.R	Placebo N (Adj.%)	E	Adj.R
Number of subjects	2650			1529		
Patient years of exposure (PYE)	3309.5			1885.4		
Events	246 (9.3)	341	10.5	100 (6.4)	132	6.8
Infections and infestations	50 (1.9)	56	1.7	23 (1.5)	30	1.5
Gastroenteritis	10 (0.4)	10	0.3	1 (<0.1)	1	<0.1
Appendicitis	10 (0.4)	11	0.3	3 (0.2)	3	0.2
Pneumonia	2 (<0.1)	2	<0.1	4 (0.2)	4	0.2
Hepatobiliary disorders	35 (1.3)	43	1.2	4 (0.3)	4	0.2
Cholelithiasis	25 (0.9)	25	0.7	3 (0.2)	3	0.2
Cholecystitis	7 (0.2)	7	0.2	0		
Cholecystitis acute	6 (0.2)	6	0.2	1 (<0.1)	1	<0.1
Gastrointestinal disorders	27 (1.1)	37	1.1	9 (0.6)	10	0.6
Vomiting	7 (0.3)	7	0.2	0		
Abdominal pain	5 (0.2)	5	0.1	1 (<0.1)	1	<0.1
Musculoskeletal and connective tissue disorders	19 (0.7)	22	0.6	7 (0.5)	8	0.4
Osteoarthritis	7 (0.3)	8	0.2	2 (0.1)	2	0.1
Cardiac disorders	15 (0.6)	19	0.6	16 (1.0)	16	0.8
Atrial fibrillation	5 (0.2)	7	0.2	5 (0.3)	5	0.3
Acute myocardial infarction	3 (0.1)	3	<0.1	3 (0.2)	3	0.2
Respiratory, thoracic and mediastinal disorders	7 (0.3)	8	0.3	6 (0.4)	7	0.4
Asthma	1 (<0.1)	1	<0.1	3 (0.2)	3	0.2
Ear and labyrinth disorders	6 (0.2)	6	0.2	0		
Vertigo	5 (0.2)	5	0.1	0		

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 patient-years of exposure, Adj.: Adjusted. Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials. Adverse events with onset prior to randomisation are not included. Sorted in descending order by system organ class and preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event. PTs occurring in ≥0.2% of subjects in any treatment group is presented, note the SOCs include total numbers within the SOCs, i.e. total: N, adj %, E and adj R. The % and R are adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials. Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days. MedDRA version 22.1

Table 8.4.3.3.1 Serious adverse events by system organ class - on-treatment (copied from Table 12-5, Study NN9536-4373)

System organ class	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1306				655			
Patient years of exposure (PYE)	1706.1				829.6			
Events	128	(9.8)	164	9.6	42	(6.4)	53	6.4
Infections and infestations	27	(2.1)	27	1.6	10	(1.5)	12	1.4
Gastrointestinal disorders	18	(1.4)	25	1.5	0			
Hepatobiliary disorders	17	(1.3)	21	1.2	1	(0.2)	1	0.1
Musculoskeletal and connective tissue disorders	11	(0.8)	11	0.6	5	(0.8)	6	0.7
Neoplasms benign, malignant and unspecified#	9	(0.7)	9	0.5	3	(0.5)	3	0.4
Injury, poisoning and procedural complications	8	(0.6)	13	0.8	3	(0.5)	3	0.4
Nervous system disorders	8	(0.6)	8	0.5	3	(0.5)	4	0.5
Cardiac disorders	7	(0.5)	10	0.6	7	(1.1)	7	0.8
General disorders and administration site cond.	5	(0.4)	5	0.3	0			
Ear and labyrinth disorders	4	(0.3)	4	0.2	0			
Respiratory, thoracic and mediastinal disorders	4	(0.3)	4	0.2	5	(0.8)	6	0.7
Blood and lymphatic system disorders	3	(0.2)	3	0.2	0			
Eye disorders	3	(0.2)	4	0.2	0			
Pregnancy, puerperium and perinatal conditions	3	(0.2)	3	0.2	0			
Psychiatric disorders	3	(0.2)	3	0.2	1	(0.2)	1	0.1
Reproductive system and breast disorders	3	(0.2)	3	0.2	1	(0.2)	1	0.1
Skin and subcutaneous tissue disorders	3	(0.2)	3	0.2	0			
Surgical and medical procedures	3	(0.2)	3	0.2	5	(0.8)	5	0.6
Metabolism and nutrition disorders	2	(0.2)	2	0.1	0			
Renal and urinary disorders	2	(0.2)	2	0.1	0			
Investigations	1	(<0.1)	1	0.1	1	(0.2)	1	0.1
Immune system disorders	0				1	(0.2)	1	0.1
Vascular disorders	0				2	(0.3)	2	0.2

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years, cond.: Condition, #: incl cysts and polyps. Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event. MedDRA version 22.1

Table 8.4.3.3.2 Serious adverse events by system organ class - on-treatment (copied from Table 12-4, Study NN9536-4374)

System organ class	Sema 1.0 mg N	(%)	E	R	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	402				403				402			
Patient years of exposure (PYE)	529.8				533.0				528.3			
Events	31	(7.7)	53	10.0	40	(9.9)	71	13.3	37	(9.2)	53	10.0
Infections and infestations	9	(2.2)	11	2.1	9	(2.2)	11	2.1	9	(2.2)	14	2.6
Nervous system disorders	2	(0.5)	2	0.4	7	(1.7)	9	1.7	3	(0.7)	3	0.6
Cardiac disorders	7	(1.7)	9	1.7	6	(1.5)	7	1.3	6	(1.5)	6	1.1
Gastrointestinal disorders	3	(0.7)	7	1.3	6	(1.5)	7	1.3	3	(0.7)	3	0.6
Injury, poisoning and procedural complications	3	(0.7)	3	0.6	4	(1.0)	12	2.3	4	(1.0)	4	0.8
Metabolism and nutrition disorders	5	(1.2)	6	1.1	4	(1.0)	4	0.8	4	(1.0)	4	0.8
Renal and urinary disorders	2	(0.5)	2	0.4	3	(0.7)	5	0.9	3	(0.7)	3	0.6
Vascular disorders	1	(0.2)	1	0.2	3	(0.7)	3	0.6	1	(0.2)	1	0.2
Hepatobiliary disorders	1	(0.2)	1	0.2	2	(0.5)	3	0.6	1	(0.2)	1	0.2
Musculoskeletal and connective tissue disorders	2	(0.5)	2	0.4	2	(0.5)	2	0.4	2	(0.5)	2	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	(1.5)	6	1.1	2	(0.5)	2	0.4	5	(1.2)	6	1.1
Respiratory, thoracic and mediastinal disorders	1	(0.2)	1	0.2	2	(0.5)	3	0.6	1	(0.2)	1	0.2
Eye disorders	0				1	(0.2)	1	0.2	1	(0.2)	1	0.2
Reproductive system and breast disorders	0				1	(0.2)	1	0.2	0			
Surgical and medical procedures	1	(0.2)	1	0.2	1	(0.2)	1	0.2	2	(0.5)	2	0.4
General disorders and administration site conditions	0				0				1	(0.2)	1	0.2
Immune system disorders	1	(0.2)	1	0.2	0				0			
Pregnancy, puerperium and perinatal conditions	0				0				1	(0.2)	1	0.2

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event. MedDRA version 22.1

Table 8.4.3.3.3 Serious adverse events by system organ class (>1% in any treatment group) and preferred term - summary - on-treatment (copied from Table 12-4, Study NN9536-4375)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	407				204			
Patient years of exposure (PYE)	526.1				261.4			
Events	37	(9.1)	55	10.5	6	(2.9)	7	2.7
Hepatobiliary disorders	10	(2.5)	13	2.5	0			
Cholelithiasis	7	(1.7)	7	1.3	0			
Cholecystitis acute	3	(0.7)	3	0.6	0			
Cholecystitis	2	(0.5)	2	0.4	0			
Biliary dyskinesia	1	(0.2)	1	0.2	0			
Infections and infestations	8	(2.0)	12	2.3	0			
Appendicitis	3	(0.7)	4	0.8	0			
Abdominal abscess	1	(0.2)	1	0.2	0			
Cellulitis	1	(0.2)	1	0.2	0			
Gastroenteritis viral	1	(0.2)	1	0.2	0			
Large intestine infection	1	(0.2)	1	0.2	0			
Pelvic inflammatory disease	1	(0.2)	1	0.2	0			
Pneumonia	1	(0.2)	1	0.2	0			
Sepsis	1	(0.2)	1	0.2	0			
Urinary tract infection	1	(0.2)	1	0.2	0			
Musculoskeletal and connective tissue disorders	5	(1.2)	8	1.5	0			
Osteoarthritis	3	(0.7)	4	0.8	0			
Cervical spinal stenosis	2	(0.5)	2	0.4	0			
Back pain	1	(0.2)	1	0.2	0			
Intervertebral disc protrusion	1	(0.2)	1	0.2	0			

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Table 8.4.3.3.4 Serious adverse events by system organ class and preferred term - summary - in-trial - randomised period - safety analysis set (copied from 14.3.1.20, Study NN9536-4376)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	535				268			
Patient years of observation (PYO)	565.4				280.7			
Events	42	(7.9)	52	9.2	15	(5.6)	24	8.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	(1.5)	8	1.4	1	(0.4)	3	1.1
Endometrial adenocarcinoma	1	(0.2)	1	0.2	0			
Haemangioma	1	(0.2)	1	0.2	0			
Intraductal proliferative breast lesion	1	(0.2)	1	0.2	0			
Invasive breast carcinoma	1	(0.2)	1	0.2	0			
Invasive ductal breast carcinoma	1	(0.2)	1	0.2	0			
Malignant melanoma	1	(0.2)	1	0.2	0			
Marginal zone lymphoma	1	(0.2)	1	0.2	0			
Uterine leiomyoma	1	(0.2)	1	0.2	0			
Lung cancer metastatic	0				1	(0.4)	1	0.4
Metastases to central nervous system	0				1	(0.4)	1	0.4
Pericardial effusion malignant	0				1	(0.4)	1	0.4
Hepatobiliary disorders	6	(1.1)	6	1.1	2	(0.7)	2	0.7
Cholelithiasis	5	(0.9)	5	0.9	2	(0.7)	2	0.7
Cholecystitis	1	(0.2)	1	0.2	0			
Infections and infestations	6	(1.1)	6	1.1	4	(1.5)	4	1.4
Gastroenteritis	2	(0.4)	2	0.4	0			
Appendicitis	1	(0.2)	1	0.2	1	(0.4)	1	0.4
Diverticulitis	1	(0.2)	1	0.2	0			
Pertussis	1	(0.2)	1	0.2	0			
Pyelonephritis acute	1	(0.2)	1	0.2	0			
Induced abortion infection	0				1	(0.4)	1	0.4
Tooth abscess	0				1	(0.4)	1	0.4
Urinary tract infection	0				1	(0.4)	1	0.4
Injury, poisoning and procedural complications	5	(0.9)	5	0.9	3	(1.1)	3	1.1
Fall	1	(0.2)	1	0.2	0			
Incisional hernia	1	(0.2)	1	0.2	0			
Meniscus injury	1	(0.2)	1	0.2	1	(0.4)	1	0.4
Post lumbar puncture syndrome	1	(0.2)	1	0.2	0			
Spinal compression fracture	1	(0.2)	1	0.2	0			
Ankle fracture	0				1	(0.4)	1	0.4
Road traffic accident	0				1	(0.4)	1	0.4
Nervous system disorders	5	(0.9)	7	1.2	2	(0.7)	3	1.1
Migraine	2	(0.4)	2	0.4	0			
Hemiparesis	1	(0.2)	1	0.2	0			
Paraesthesia	1	(0.2)	2	0.4	0			
Quadriplegia	1	(0.2)	1	0.2	0			
Transient global amnesia	1	(0.2)	1	0.2	0			
Brain oedema	0				1	(0.4)	1	0.4
Carotid sinus syndrome	0				1	(0.4)	1	0.4
Intracranial haematoma	0				1	(0.4)	1	0.4
Cardiac disorders	2	(0.4)	2	0.4	3	(1.1)	3	1.1
Atrial fibrillation	1	(0.2)	1	0.2	2	(0.7)	2	0.7
Supraventricular tachycardia	1	(0.2)	1	0.2	0			

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYO: The duration of the in-trial period in years.
Only AEs with onset in the randomised period included. Only randomised subjects in the safety analysis set contribute. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Table 8.4.3.3.4 (cont)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Acute myocardial infarction	0				1	(0.4)	1	0.4
General disorders and administration site conditions	2	(0.4)	2	0.4	1	(0.4)	1	0.4
Death	1	(0.2)	1	0.2	0			
Non-cardiac chest pain	1	(0.2)	1	0.2	0			
Gait disturbance	0				1	(0.4)	1	0.4
Renal and urinary disorders	2	(0.4)	2	0.4	0			
Nephrolithiasis	1	(0.2)	1	0.2	0			
Ureterolithiasis	1	(0.2)	1	0.2	0			
Surgical and medical procedures	2	(0.4)	2	0.4	0			
Abortion induced	1	(0.2)	1	0.2	0			
Orthognathic surgery	1	(0.2)	1	0.2	0			
Vascular disorders	2	(0.4)	2	0.4	0			
Hypertension	1	(0.2)	1	0.2	0			
Hypotension	1	(0.2)	1	0.2	0			
Blood and lymphatic system disorders	1	(0.2)	1	0.2	0			
Pancytopenia	1	(0.2)	1	0.2	0			
Ear and labyrinth disorders	1	(0.2)	1	0.2	0			
Vertigo	1	(0.2)	1	0.2	0			
Endocrine disorders	1	(0.2)	1	0.2	0			
Hypothyroidism	1	(0.2)	1	0.2	0			
Gastrointestinal disorders	1	(0.2)	3	0.5	4	(1.5)	4	1.4
Abdominal pain	1	(0.2)	1	0.2	1	(0.4)	1	0.4
Nausea	1	(0.2)	1	0.2	0			
Vomiting	1	(0.2)	1	0.2	0			
Constipation	0				1	(0.4)	1	0.4
Diverticular perforation	0				1	(0.4)	1	0.4
Intestinal obstruction	0				1	(0.4)	1	0.4
Metabolism and nutrition disorders	1	(0.2)	1	0.2	0			
Type 2 diabetes mellitus	1	(0.2)	1	0.2	0			
Musculoskeletal and connective tissue disorders	1	(0.2)	1	0.2	0			
Intervertebral disc protrusion	1	(0.2)	1	0.2	0			
Pregnancy, puerperium and perinatal conditions	1	(0.2)	1	0.2	0			
Morning sickness	1	(0.2)	1	0.2	0			
Product issues	1	(0.2)	1	0.2	0			
Lead dislodgement	1	(0.2)	1	0.2	0			
Reproductive system and breast disorders	0				1	(0.4)	1	0.4
Menorrhagia	0				1	(0.4)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYO: The duration of the in-trial period in years.
Only AEs with onset in the randomised period included. Only randomised subjects in the safety analysis set contribute. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Table 8.4.4.1.1 AEs (PTs ≥ 0.2% of subjects) leading to permanent treatment discontinuation by SOC and PT – on-treatment – phase 3a pool (copied from Table 2-9, Summary of Clinical Safety)

System organ class Preferred term	Sema 2.4 mg N	(Adj.%)	E	Adj.R	Placebo N	(Adj.%)	E	Adj.R
Number of subjects	2650				1529			
Patient years of exposure (PYE)	3309.5				1885.4			
Events	149	(5.7)	200	5.9	47	(3.0)	57	3.0
Gastrointestinal disorders	92	(3.5)	124	3.7	13	(0.8)	16	0.9
Nausea	38	(1.5)	38	1.1	3	(0.2)	3	0.2
Vomiting	26	(1.0)	26	0.8	0			
Diarrhoea	16	(0.6)	16	0.5	3	(0.2)	3	0.2
Abdominal pain upper	7	(0.3)	7	0.2	1	(<0.1)	1	<0.1
Constipation	6	(0.2)	6	0.2	0			
Hepatobiliary disorders	4	(0.1)	4	0.1	5	(0.3)	5	0.3
Cholelithiasis	2	(<0.1)	2	<0.1	4	(0.3)	4	0.3

Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials. Adverse events with onset prior to randomisation are not included. Sorted in descending order by system organ class and preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event. PTs occurring in ≥0.2% of subjects is presented, note the SOCs include total numbers within the SOCs, i.e. total: N, adj %, E and adj R. The % and R are adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials. Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days. MedDRA version 22.1
N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 patient-years of exposure, Adj.: Adjusted

Table 8.4.4.3.1 Adverse events leading to permanent trial product discontinuation by system organ class - on-treatment (copied from Table 12-8, Study NN9536-4373)

System organ class	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1306				655			
Patient years of exposure (PYE)	1706.1				829.6			
Events	92	(7.0)	123	7.2	20	(3.1)	23	2.8
Gastrointestinal disorders	59	(4.5)	78	4.6	5	(0.8)	5	0.6
Psychiatric disorders	7	(0.5)	7	0.4	3	(0.5)	4	0.5
Skin and subcutaneous tissue disorders	5	(0.4)	5	0.3	2	(0.3)	2	0.2
Infections and infestations	4	(0.3)	4	0.2	1	(0.2)	1	0.1
Nervous system disorders	4	(0.3)	4	0.2	1	(0.2)	1	0.1
General disorders and administration site cond.	3	(0.2)	3	0.2	0			
Metabolism and nutrition disorders	3	(0.2)	3	0.2	0			
Eye disorders	2	(0.2)	2	0.1	1	(0.2)	1	0.1
Hepatobiliary disorders	2	(0.2)	2	0.1	1	(0.2)	1	0.1
Injury, poisoning and procedural complications	2	(0.2)	4	0.2	2	(0.3)	2	0.2
Investigations	2	(0.2)	2	0.1	0			
Musculoskeletal and connective tissue disorders	2	(0.2)	3	0.2	0			
Neoplasms benign, malignant and unspecified	2	(0.2)	2	0.1	2	(0.3)	2	0.2
Ear and labyrinth disorders	1	(<0.1)	1	0.1	0			
Renal and urinary disorders	1	(<0.1)	1	0.1	0			
Surgical and medical procedures	1	(<0.1)	1	0.1	1	(0.2)	1	0.1
Vascular disorders	1	(<0.1)	1	0.1	0			
Blood and lymphatic system disorders	0				1	(0.2)	1	0.1
Cardiac disorders	0				1	(0.2)	1	0.1
Respiratory, thoracic and mediastinal disorders	0				1	(0.2)	1	0.1

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, cond.: Condition, #: incl cysts and polyps. PYE: The duration of the on-treatment period in years. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event. MedDRA version 22.1

Table 8.4.4.3.2 Adverse events leading to permanent trial product discontinuation by system organ class - on-treatment (copied from Table 12-7, Study NN9536-4374)

System organ class	Sema 1.0 mg				Sema 2.4 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	402				403				402			
PYE	529.8				533.0				528.3			
Events	20	(5.0)	23	4.3	25	(6.2)	34	6.4	14	(3.5)	18	3.4
GI disorders	14	(3.5)	16	3.0	17	(4.2)	24	4.5	4	(1.0)	6	1.1
Nervous system dis	0				2	(0.5)	2	0.4	2	(0.5)	2	0.4
Eye disorders	1	(0.2)	1	0.2	1	(0.2)	1	0.2	0			
General dis & adm site	1	(0.2)	1	0.2	1	(0.2)	1	0.2	1	(0.2)	1	0.2
Injury, pois and proc	0				1	(0.2)	1	0.2	1	(0.2)	1	0.2
Musc & connect tis dis	0				1	(0.2)	1	0.2	0			
Neoplasms	1	(0.2)	1	0.2	1	(0.2)	1	0.2	3	(0.7)	3	0.6
Resp, thoracic, med dis	0				1	(0.2)	1	0.2	0			
Skin, s.c. tissue dis	0				1	(0.2)	1	0.2	2	(0.5)	2	0.4
Hepatobiliary disorders	1	(0.2)	1	0.2	0				0			
Inf, infestations	0				0				1	(0.2)	1	0.2
Met and nutr disorders	1	(0.2)	1	0.2	0				1	(0.2)	1	0.2
Psych disorders	1	(0.2)	1	0.2	0				1	(0.2)	1	0.2

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified
PYE: The duration of the on-treatment period in years, GI: gastrointestinal, dis: disorders, adm: administration, pois: poisoning, proc: procedural, musc: musculoskeletal, connect: connective, tis: tissue, resp: respiratory, med: medical, s.c.: subcutaneous, inf: infections, met: metabolic, nutr: nutrition, psych: psychiatric. Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event. MedDRA version 22.1

Table 8.4.4.3.3 Adverse events leading to permanent trial product discontinuation by system organ class and preferred term - summary - on-treatment - safety analysis set (copied from 14.3.1.22, Study NN9536-4375)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	407				204			
Patient years of exposure (PYE)	526.1				261.4			
Events	24	(5.9)	34	6.5	6	(2.9)	6	2.3
Gastrointestinal disorders	14	(3.4)	20	3.8	0			
Nausea	7	(1.7)	7	1.3	0			
Vomiting	6	(1.5)	6	1.1	0			
Constipation	2	(0.5)	2	0.4	0			
Diarrhoea	2	(0.5)	2	0.4	0			
Eructation	1	(0.2)	1	0.2	0			
Flatulence	1	(0.2)	1	0.2	0			
Retching	1	(0.2)	1	0.2	0			
Psychiatric disorders	3	(0.7)	3	0.6	1	(0.5)	1	0.4
Anxiety	3	(0.7)	3	0.6	1	(0.5)	1	0.4
Hepatobiliary disorders	2	(0.5)	2	0.4	0			
Biliary colic	1	(0.2)	1	0.2	0			
Biliary dyskinesia	1	(0.2)	1	0.2	0			
Nervous system disorders	2	(0.5)	2	0.4	0			
Headache	1	(0.2)	1	0.2	0			
Migraine	1	(0.2)	1	0.2	0			
Skin and subcutaneous tissue disorders	2	(0.5)	2	0.4	2	(1.0)	2	0.8
Alopecia	1	(0.2)	1	0.2	1	(0.5)	1	0.4
Skin burning sensation	1	(0.2)	1	0.2	0			
Rash pruritic	0				1	(0.5)	1	0.4
Injury, poisoning and procedural complications	1	(0.2)	1	0.2	0			
Concussion	1	(0.2)	1	0.2	0			
Investigations	1	(0.2)	3	0.6	0			
Amylase increased	1	(0.2)	1	0.2	0			
Blood creatine phosphokinase increased	1	(0.2)	1	0.2	0			
Lipase increased	1	(0.2)	1	0.2	0			
Metabolism and nutrition disorders	1	(0.2)	1	0.2	0			
Decreased appetite	1	(0.2)	1	0.2	0			
General disorders and administration site conditions	0				1	(0.5)	1	0.4
Injection site haematoma	0				1	(0.5)	1	0.4
Infections and infestations	0				1	(0.5)	1	0.4
Diverticulitis	0				1	(0.5)	1	0.4
Musculoskeletal and connective tissue disorders	0				1	(0.5)	1	0.4
Flank pain	0				1	(0.5)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified
PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Table 8.4.4.3.4 Adverse events leading to permanent trial product discontinuation by system organ class and preferred term - summary - on-treatment - randomised period (copied from Table 12-6, Study NN9536-4376)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	535				268			
Patient years of exposure (PYE)	544.3				266.1			
Events	8	(1.5)	9	1.7	7	(2.6)	10	3.8
Gastrointestinal disorders	2	(0.4)	2	0.4	4	(1.5)	5	1.9
Diarrhoea	1	(0.2)	1	0.2	1	(0.4)	1	0.4
Haemorrhoids	1	(0.2)	1	0.2	0			
Abdominal pain	0				2	(0.7)	2	0.8
Intestinal obstruction	0				1	(0.4)	1	0.4
Nausea	0				1	(0.4)	1	0.4
Blood and lymphatic system disorders	1	(0.2)	1	0.2	0			
Pancytopenia	1	(0.2)	1	0.2	0			
General disorders and administration site conditions	1	(0.2)	1	0.2	0			
Adverse drug reaction	1	(0.2)	1	0.2	0			
Investigations	1	(0.2)	1	0.2	0			
Laboratory test abnormal	1	(0.2)	1	0.2	0			
Metabolism and nutrition disorders	1	(0.2)	1	0.2	0			
Abnormal loss of weight	1	(0.2)	1	0.2	0			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.2)	1	0.2	0			
Invasive breast carcinoma	1	(0.2)	1	0.2	0			
Pregnancy, puerperium and perinatal conditions	1	(0.2)	1	0.2	0			
Morning sickness	1	(0.2)	1	0.2	0			
Renal and urinary disorders	1	(0.2)	1	0.2	0			
Nephrolithiasis	1	(0.2)	1	0.2	0			
Hepatobiliary disorders	0				4	(1.5)	4	1.5
Cholelithiasis	0				4	(1.5)	4	1.5
Psychiatric disorders	0				1	(0.4)	1	0.4
Depression	0				1	(0.4)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Only AEs with onset in the randomised period included. Only randomised subjects in the safety analysis set contribute. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Table 8.5.8.1.1 Body weight (%) change from baseline by occurrence of anti-semaglutide antibodies – on-treatment – STEP 1 and STEP 2 (copied from Table 4-4, Integrated Summary of Immunogenicity)

	STEP 1 WM		STEP 2 WM in T2D	
	Subjects with antibodies	Subjects without antibodies	Subjects with antibodies	Subjects without antibodies
Number of subjects	39	1267	12	391
Body weight (%)				
Change from baseline at week 68 visit				
N	34	1025	11	340
Mean (SD)	-14.9 (8.7)	-16.9 (9.4)	-9.0 (4.3)	-10.8 (7.9)
Median	-14.4	-16.1	-9.9	-10.0
P5 ; P95	-29.7 ; -1.6	-33.9 ; -2.6	-15.0 ; -1.2	-24.9 ; 0.9
Min; Max	-34.2 ; 3.8	-44.9 ; 8.5	-15.0 ; -1.2	-36.6 ; 8.2

STEP 1 and STEP 2 data from subjects randomised to Sema 2.4 mg.
Subjects are categorised with/without antibodies if they have ever/never tested positive for anti-semaglutide antibodies during the trial.
WM: Weight management, T2D: Type 2 diabetes, N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile.

Table 8.5.10.3.1 Malignant neoplasms AEs by SOC and PT – pre-defined MedDRA search – summary – in-trial – randomised period (copied from Table 12-18, Study NN9536-4376)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	535				268			
Patient years of observation (PYO)	565.4				280.7			
Events	6	(1.1)	6	1.1	1	(0.4)	2	0.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	(1.1)	6	1.1	1	(0.4)	2	0.7
Endometrial adenocarcinoma	1	(0.2)	1	0.2	0			
Intraductal proliferative breast lesion	1	(0.2)	1	0.2	0			
Invasive breast carcinoma	1	(0.2)	1	0.2	0			
Invasive ductal breast carcinoma	1	(0.2)	1	0.2	0			
Malignant melanoma	1	(0.2)	1	0.2	0			
Marginal zone lymphoma	1	(0.2)	1	0.2	0			
Lung cancer metastatic	0				1	(0.4)	1	0.4
Metastases to central nervous system	0				1	(0.4)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYO: The duration of the in-trial period in years.
Only AEs with onset in the randomised period included. Only randomised subjects in the safety analysis set contribute. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Table 19.1.1.1.1 Pharmacokinetic endpoints of semaglutide 2.4 mg at steady state – statistical analysis – bioequivalence – full analysis set (copied from Table 11-1, Study NN9536-4590)

	FAS	N	Estimate	95% CI	90% CI
AUC, 0-168h (nmol*h/L)					
Mean					
Semaglutide D, DV3396	33	29	14572	[13937 ; 15236]	
Semaglutide B, PDS290	31	30	13827	[13234 ; 14446]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.0539		[1.0003 ; 1.1104]
Cmax (nmol/L)					
Mean					
Semaglutide D, DV3396	33	29	118	[112 ; 125]	
Semaglutide B, PDS290	31	30	102	[96.8 ; 108]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.1556		[1.0800 ; 1.2365]

FAS: Number of subjects in full analysis set
N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is logarithmically transformed and analysed using an ANCOVA model with treatment and stratification as factors and logarithm of body weight as covariate. Subject 101005 was excluded form this analysis due to trial product spillage during injection at V15. Subject 101024 was excluded from this analysis due to insufficient data to derive endpoints at 2.4 mg dose. Subjects 101027, 101028 and 101056 did not take all of the last 3 planned 2.4 mg doses, and thus were excluded from this analysis, as per protocol.

Figure 19.1.1.1.2 Pharmacokinetic endpoints of semaglutide 1.0 mg at steady state – statistical analysis – bioequivalence – full analysis set (copied from Table 11-2, Study NN9536-4590)

	FAS	N	Estimate	95% CI	90% CI
AUC, 0-168h (nmol*h/L)					
Mean					
Semaglutide D, DV3396	33	33	5729	[5500 ; 5968]	
Semaglutide B, PDS290	31	31	5532	[5303 ; 5770]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.0357		[0.9860 ; 1.0879]
Cmax (nmol/L)					
Mean					
Semaglutide D, DV3396	33	33	46.3	[43.4 ; 49.3]	
Semaglutide B, PDS290	31	31	42.0	[39.3 ; 44.9]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.1014		[1.0202 ; 1.1891]

FAS: Number of subjects in full analysis set
N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is logarithmically transformed and analysed using an ANCOVA model with treatment and stratification as factors and logarithm of body weight as covariate

Table 19.1.1.1.3 Supportive pharmacokinetic endpoints of semaglutide 2.4 mg at steady state – descriptive statistics – full analysis set (copied from Table 11-3, Study NN9536-4590)

	Semaglutide D, DV3396	Semaglutide B, PDS290
Number of subjects*	31	30
tmax (h)		
N	29	30
Median (min; max)	24 (3;48)	24 (6;81)
t half (h)		
N	29	30
Geometric mean (CV)	155 (9.8)	151 (7.3)
CL/F (L/h)		
N	29	30
Geometric mean (CV)	0.040 (22.6)	0.043 (17.6)
Vss/F sema (L)		
N	29	30
Geometric mean (CV)	9.8 (23.4)	11.0 (20.6)

*) Number of subjects in full analysis set who received all of the last 3 doses of 2.4 mg
N: Number of subjects with available data, CV: Coefficient of variation in %

Table 19.1.1.2.1 Pharmacokinetic endpoints of semaglutide after 1 mg dose of semaglutide s.c. - statistical analysis - full analysis set (copied from Table 11-1, Study NN9535-4588)

	Number of subjects in FAS	N	Estimate	90% CI	95% CI
AUC semaglutide, 0-840h [1mg] (nmol*h/L)					
Mean					
SEMAGLUTIDE D, DV3396	34	34	9214		[8769.94 ; 9679.73]
SEMAGLUTIDE B, PDS290	32	32	8374		[7958.51 ; 8810.99]
Treatment ratio					
SEMAGLUTIDE D, DV3396 / SEMAGLUTIDE B, PDS290			1.10	[1.04 ; 1.17]	
Cmax, Semaglutide [1mg] (nmol/L)					
Mean					
SEMAGLUTIDE D, DV3396	34	34	36.3		[34.70 ; 38.03]
SEMAGLUTIDE B, PDS290	32	32	28.7		[27.34 ; 30.05]
Treatment ratio					
SEMAGLUTIDE D, DV3396 / SEMAGLUTIDE B, PDS290			1.27	[1.20 ; 1.34]	

FAS: Full analysis set, N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is log-transformed and analysed using a Gaussian linear normal model with treatment as a fixed factor and the logarithm of the baseline body weight as covariate.

Table 19.1.1.2.2 Pharmacokinetic endpoints of semaglutide after 0.25 mg doses of semaglutide s.c. - statistical analysis - full analysis set (copied from Table 11-2, Study NN9535-4588)

	Number of subjects in FAS	N	Estimate	90% CI	95% CI
AUC semaglutide, 0-168h [0.25mg] (nmol*h/L)					
Mean					
SEMAGLUTIDE D, DV3396	34	33	1463		[1408.26 ; 1519.75]
SEMAGLUTIDE B, PDS290	32	32	1360		[1308.33 ; 1413.59]
Treatment ratio					
SEMAGLUTIDE D, DV3396 / SEMAGLUTIDE B, PDS290			1.08	[1.03 ; 1.13]	
Cmax, Semaglutide [0.25mg] (nmol/L)					
Mean					
SEMAGLUTIDE D, DV3396	34	33	10.6		[10.16 ; 11.03]
SEMAGLUTIDE B, PDS290	32	32	9.6		[9.24 ; 10.04]
Treatment ratio					
SEMAGLUTIDE D, DV3396 / SEMAGLUTIDE B, PDS290			1.10	[1.05 ; 1.15]	

FAS: Full analysis set, N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is log-transformed and analysed using a Gaussian linear normal model with treatment as a fixed factor and the logarithm of the baseline body weight as covariate.
Subject 102107(Semaglutide D, DV3396) has been excluded for 0.25 mg analysis due to COVID-19

Table 19.1.1.2.3 Pharmacokinetic endpoints - descriptive statistics - full analysis set (copied from 14.2.1, Study NN9535-4588)

	SEMAGLUTIDE D, DV3396	SEMAGLUTIDE B, PDS290
Number of subjects	34	32
AUC semaglutide, 0-840h [1mg] (nmol*h/L)		
N	34	32
Mean (SD)	9432 (1458.63)	8446 (1741.74)
Geometric mean (CV)	9321 (15.91)	8272 (21.09)
Median	9533	8204
Min ; Max	6531 ; 13644	5581 ; 11940
Cmax, Semaglutide [1mg] (nmol/L)		
N	34	32
Mean (SD)	37.1 (5.28)	28.9 (5.90)
Geometric mean (CV)	36.8 (14.86)	28.3 (20.85)
Median	37.5	28.4
Min ; Max	27.1 ; 47.9	19.9 ; 39.9
t half, Semaglutide [1mg] (h)		
N	34	32
Mean (SD)	148 (13.82)	151 (15.58)
Geometric mean (CV)	148 (9.32)	150 (10.56)
Harmonic mean	147	149
Median	147	153
Min ; Max	120 ; 178	117 ; 177
tmax, Semaglutide [1mg] (h)		
N	34	32
Mean (SD)	21.3 (14.90)	64.5 (16.84)
Geometric mean (CV)	18.1 (59.30)	62.1 (29.90)
Median	15.0	71.6
Min ; Max	6.0 ; 83.2	30.0 ; 96.0
AUC Semaglutide, 0-INF [1mg] (nmol*h/L)		
N	34	32
Mean (SD)	9647 (1536.55)	8662 (1814.66)
Geometric mean (CV)	9527 (16.33)	8477 (21.47)
Median	9692	8460
Min ; Max	6615 ; 14199	5624 ; 12328
AUC semaglutide, 0-168h [0.25mg] (nmol*h/L)		
N	33	32
Mean (SD)	1494 (176.72)	1363 (262.04)
Geometric mean (CV)	1484 (12.21)	1340 (18.64)
Median	1523	1333
Min ; Max	1100 ; 1853	993 ; 2059
Cmax, Semaglutide [0.25mg] (nmol/L)		
N	33	32
Mean (SD)	10.8 (1.47)	9.7 (1.89)
Geometric mean (CV)	10.7 (14.13)	9.5 (19.23)
Median	10.8	9.5
Min ; Max	7.4 ; 13.8	6.9 ; 14.1
tmax, Semaglutide [0.25mg] (h)		
N	33	32
Mean (SD)	41.6 (21.86)	48.2 (23.83)
Geometric mean (CV)	35.4 (69.59)	40.4 (77.36)
Median	36.0	48.0
Min ; Max	6.0 ; 83.1	6.0 ; 98.4

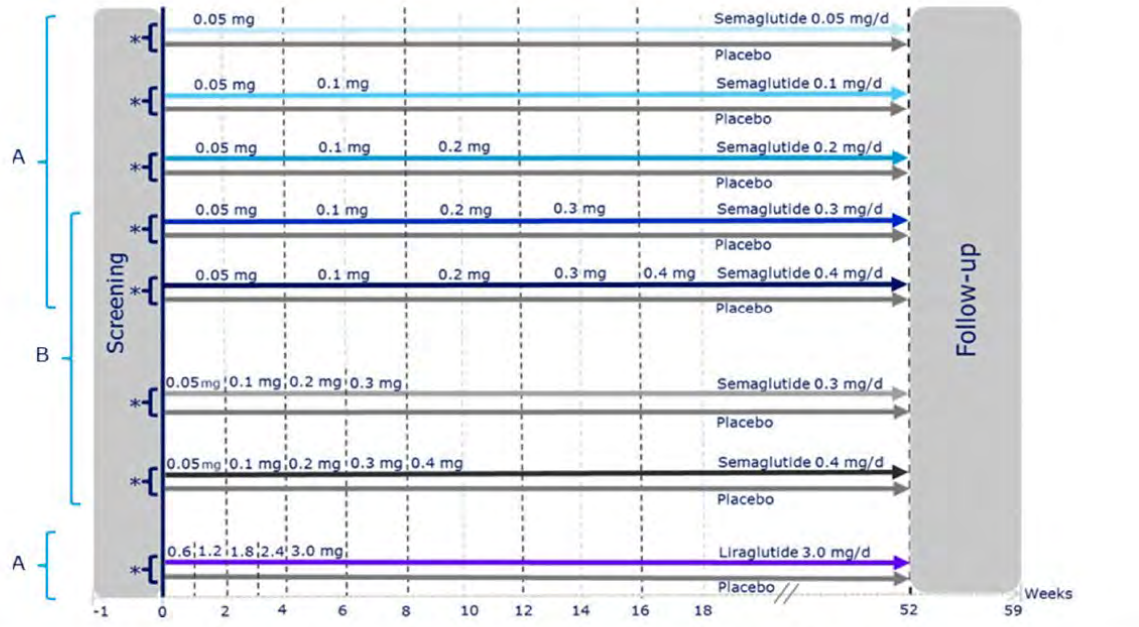
N: Number of subjects with available data, SD: Standard deviation, CV: Coefficient of variation in %
Subject 102107(Semaglutide D, DV3396) has been excluded from 0.25 mg analysis due to COVID-19
Subject 102079 had a pre treatment concentration of 4.41 nmol/L.

Table 19.1.2.1.1 Gastric emptying – week 20 – statistical analysis (copied from Table 11-1, Study NN9536-4455)

	FAS	N	Estimate	95% CI	p-value
Primary endpoint					
AUC paracetamol, 0-5h (ug*h/mL)					
Mean					
Sema 2.4 mg	36	35	47.1	[45.3 ; 48.9]	
Placebo	36	35	43.5	[41.9 ; 45.2]	
Treatment ratio					
Sema 2.4 mg / Placebo			1.08	[1.02 ; 1.14]	0.0054
Secondary endpoints					
AUC paracetamol, 0-1h (ug*h/mL)					
Mean					
Sema 2.4 mg	36	35	12.8	[11.7 ; 13.9]	
Placebo	36	35	12.9	[11.8 ; 14.1]	
Treatment ratio					
Sema 2.4 mg / Placebo			0.99	[0.87 ; 1.12]	0.8474
Cmax paracetamol, 0-5h (ug/mL)					
Mean					
Sema 2.4 mg	36	35	18.2	[16.6 ; 20.0]	
Placebo	36	35	19.4	[17.7 ; 21.3]	
Treatment ratio					
Sema 2.4 mg / Placebo			0.94	[0.82 ; 1.07]	0.3299
tmax paracetamol, 0-5h (h)					
Mean					
Sema 2.4 mg	36	35	0.45	[0.40 ; 0.50]	
Placebo	36	35	0.44	[0.39 ; 0.49]	
Treatment ratio					
Sema 2.4 mg / Placebo			1.02	[0.88 ; 1.19]	0.7540

FAS: Number of subjects in full analysis set
N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is log transformed and analysed using an ANCOVA with log transformed baseline value of the respective endpoint as covariate and treatment as factor.

Figure 6.2.1 Dosing regimens and escalation (copied from Synopsis, Study NN9536-4153)



*Each active treatment arm was blinded towards placebo with matching injection volumes, but not towards the other treatment arms. A. The dose-finding part of the trial (part A). B. The dose escalation part of the trial (part B).

Figure 6.2.2 Change in body weight (%) from baseline at week 52 - randomised active arms and placebo pool - observed data on-treatment - cumulative distribution plot - full analysis set (copied from Figure 11‑1, Study NN9536-4153)

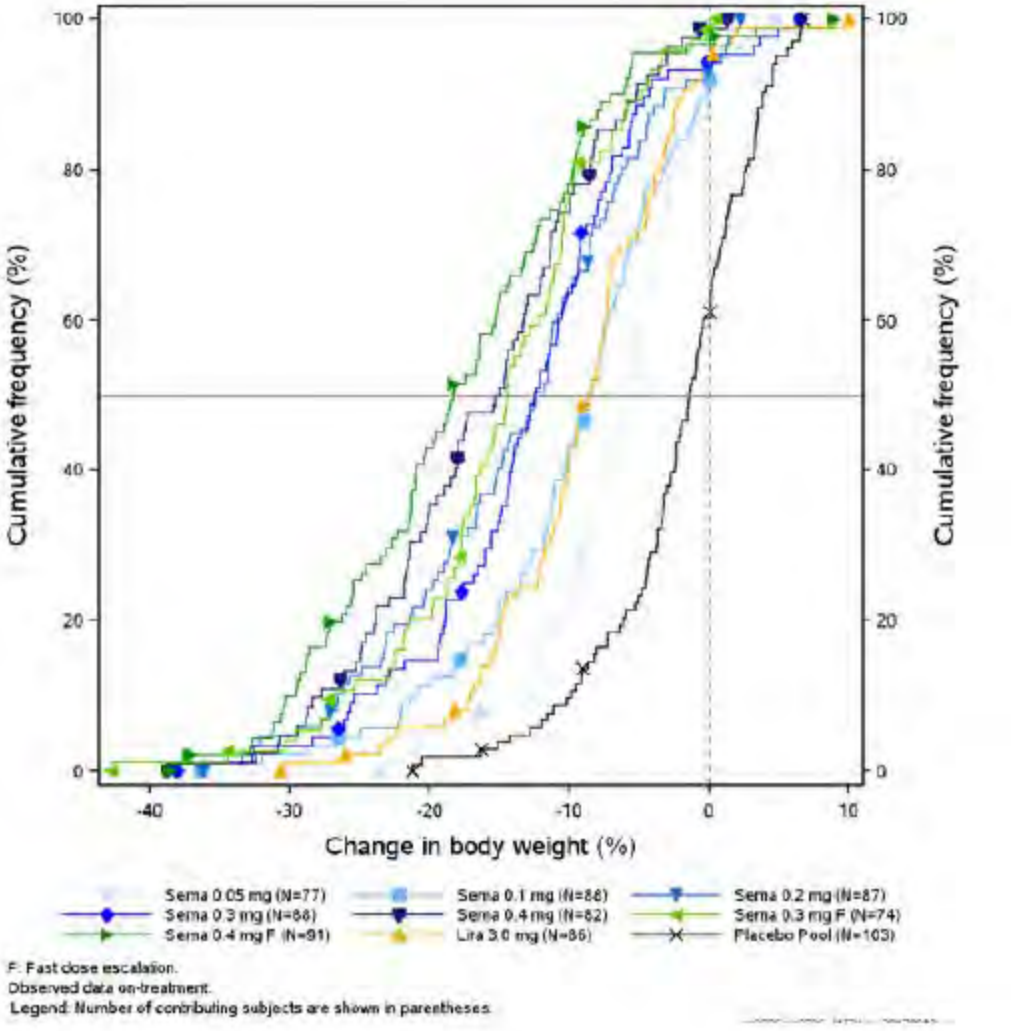
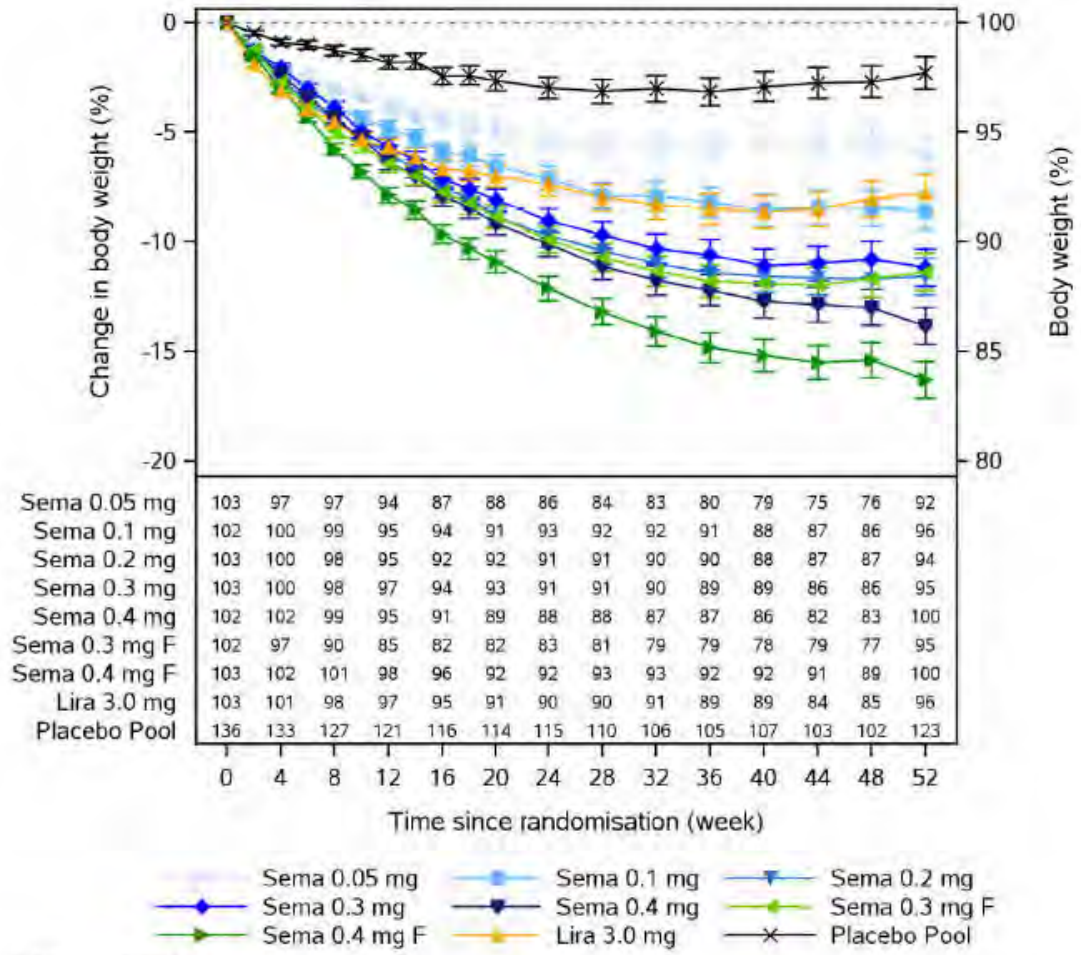
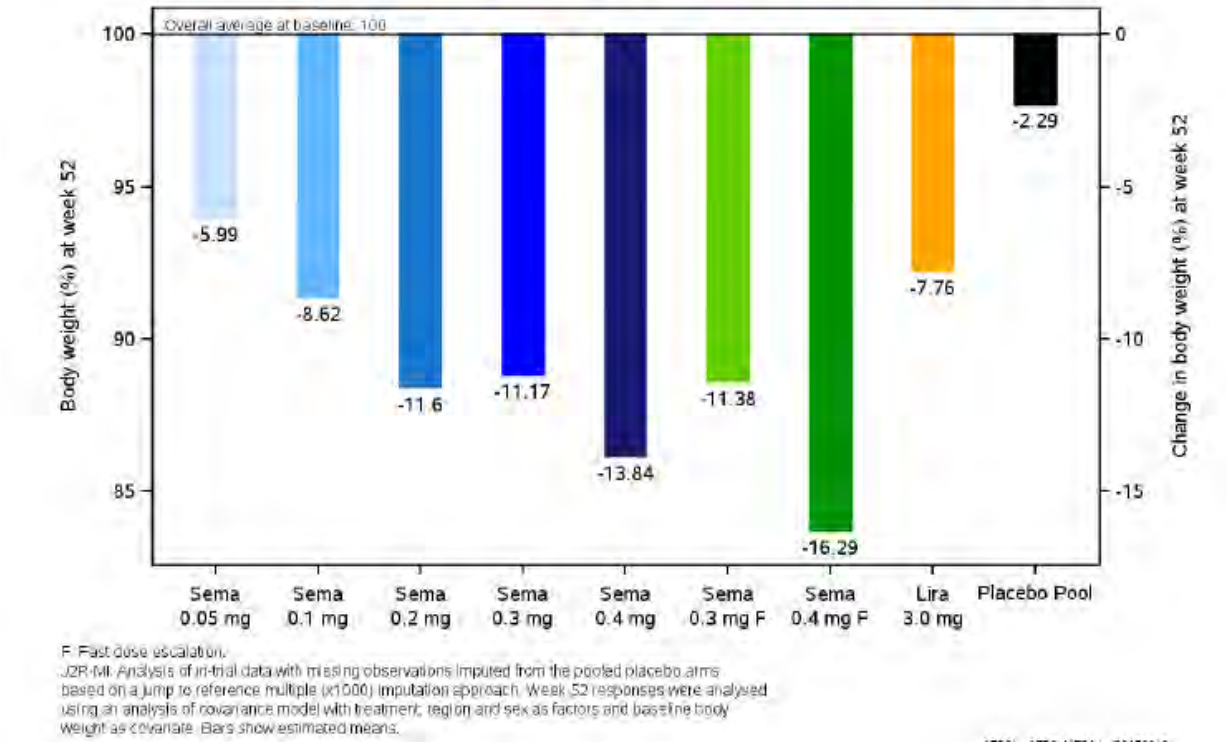


Figure 6.2.3 Change in body weight (%) from baseline by treatment week – randomized active arms and placebo pool - ANCOVA - J2R-MI - mean plot - full analysis set (copied from Figure 11‑2, Study NN9536-4153)



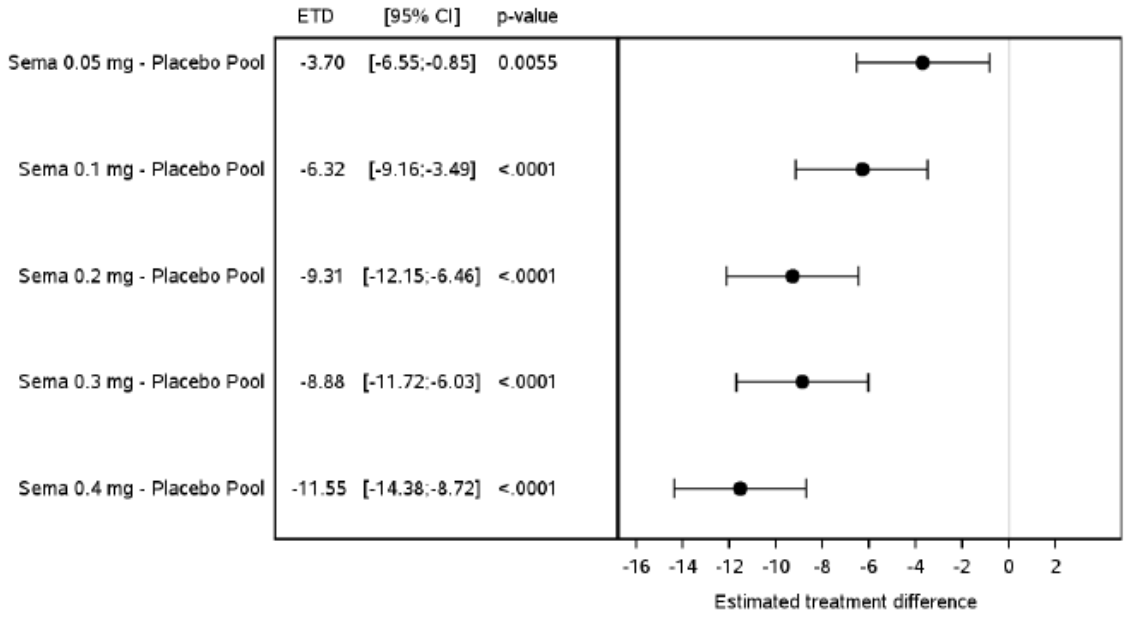
F: Fast dose escalation.
J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 missing observations were additionally multiply (x1000) imputed from retrieved subjects of the same randomised treatment arm. Responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Means show estimated means and error bars show standard errors.
Bottom panel: Number of contributing subjects by treatment arm

Figure 6.2.4 Change in body weight (%) from baseline at week 52 - randomised active arms and placebo pool - ANCOVA - J2R-MI - bar plot - full analysis set (copied from Figure 11‑3, Study NN9536-4153)



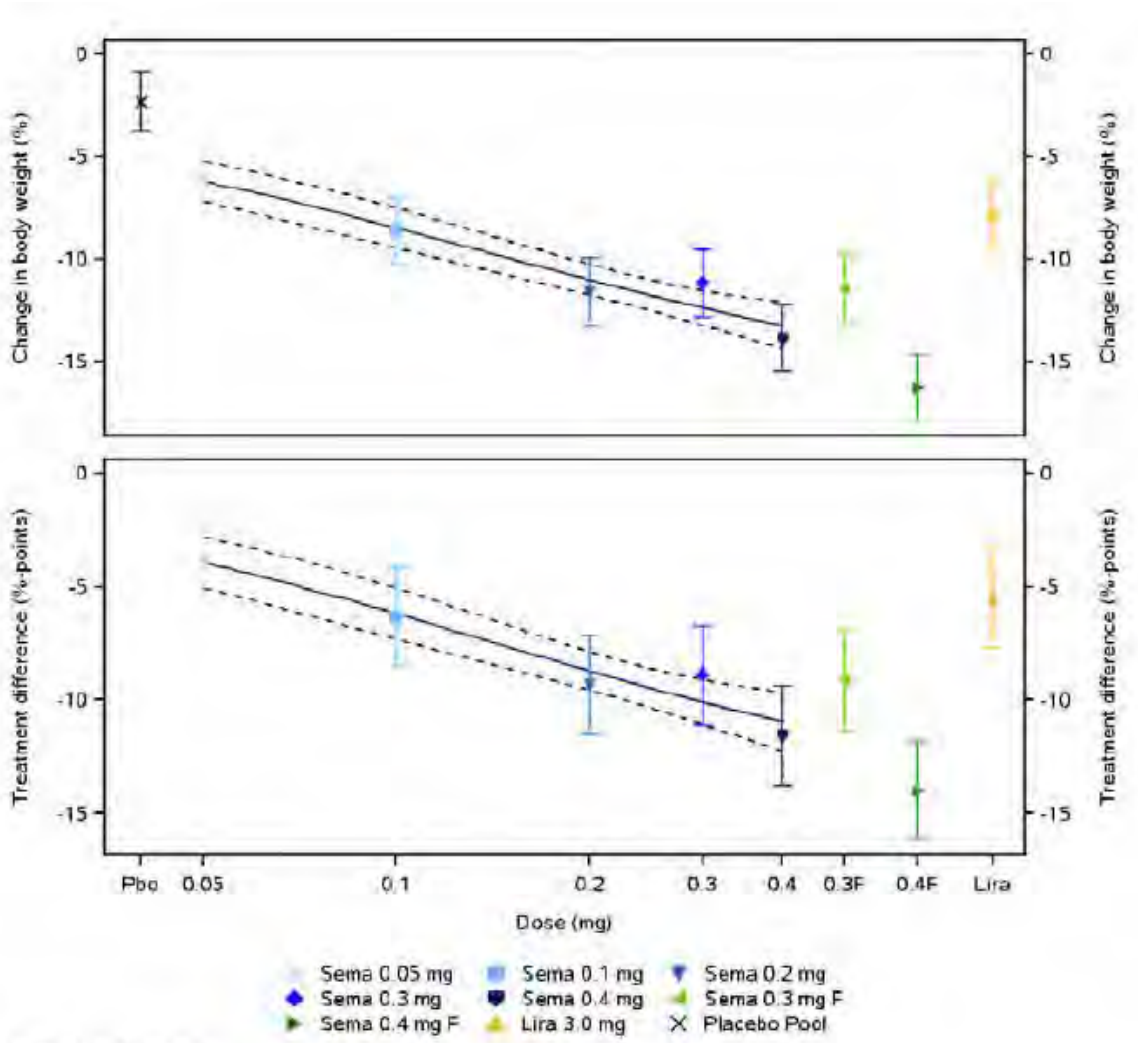
F: Fast dose escalation.
J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Bars show estimated means.

Figure 6.2.5 Change in body weight (%) from baseline at week 52 - confirmatory primary statistical analysis (part A) - ANCOVA - J2R-MI - forest plot - full analysis set (copied from Figure 11‑4, Study NN9536-4153)



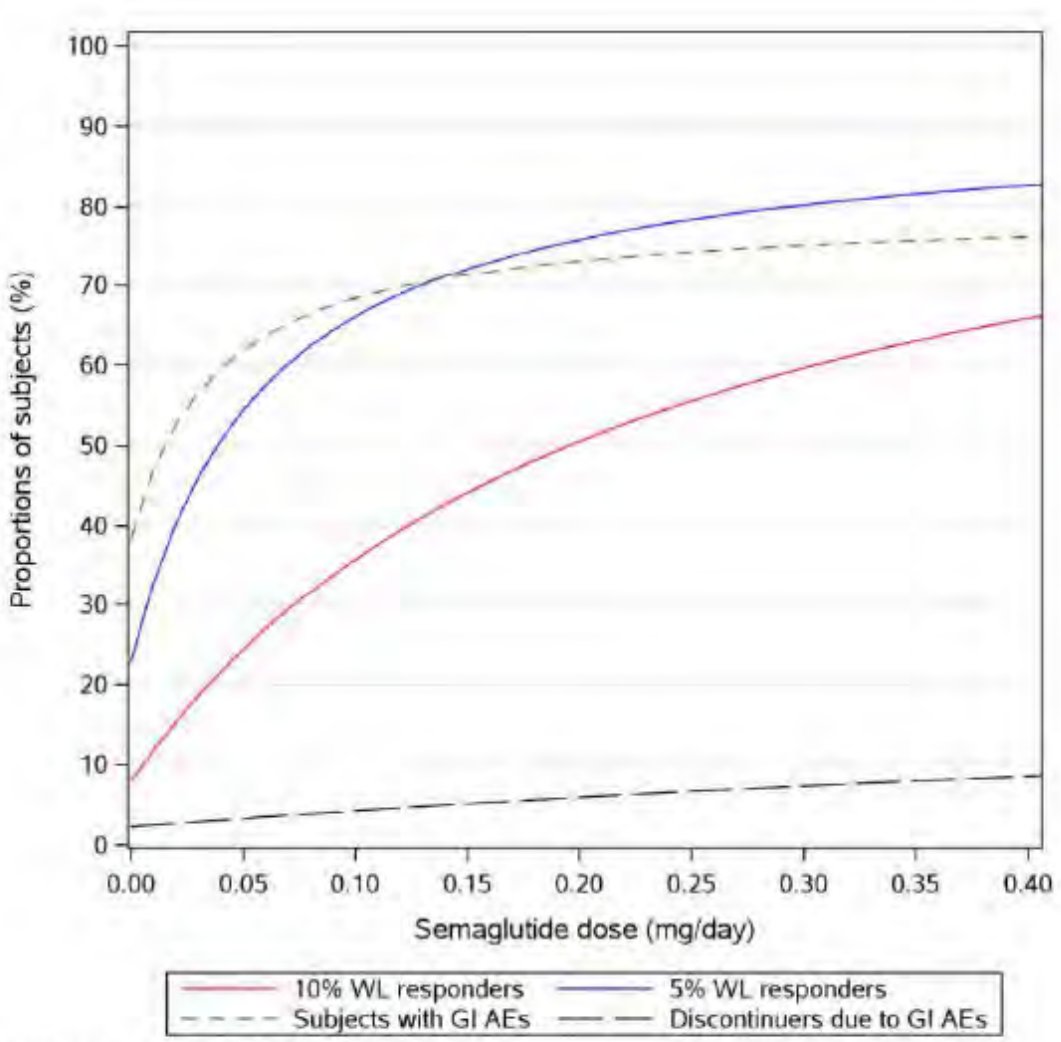
ETD: Estimated treatment difference, CI: Confidence interval. J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1 000) imputation approach. Week 52 responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Dunnett<s method was used to adjust for multiple comparisons.

Figure 6.2.6 Change in body weight (%) from baseline at week 52 - randomised active arms and placebo pool - ANCOVA - J2R-MI - Emax dose-response plot - full analysis set (copied from Figure 11‑7, Study NN9536-4153)



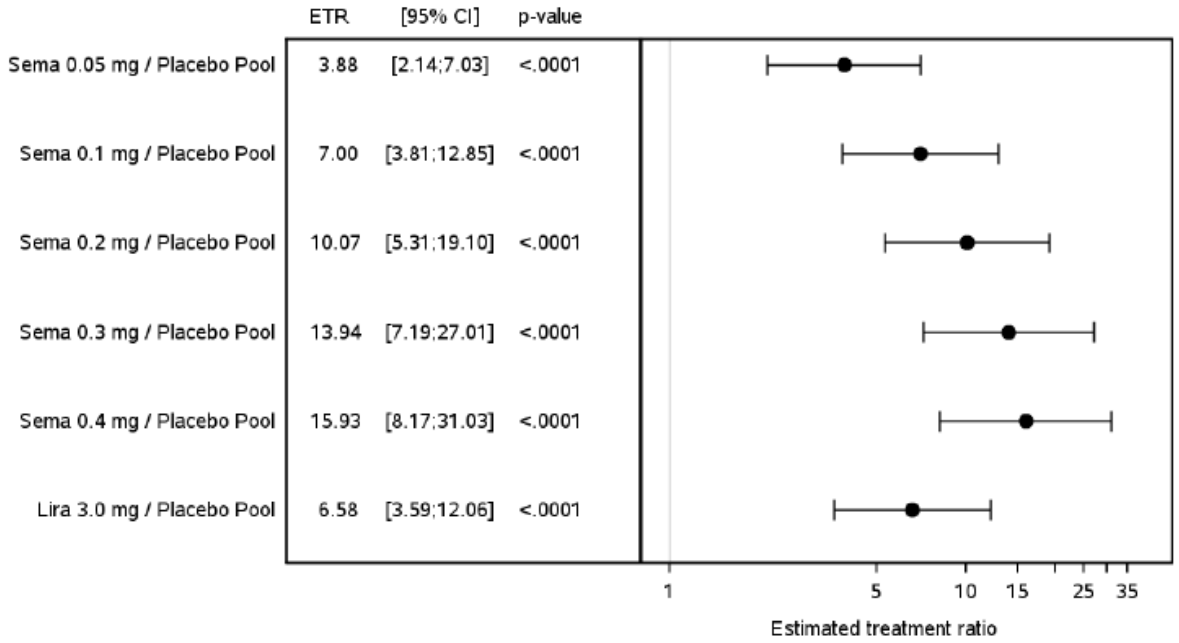
F: Fast dose escalation
J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Upper panel: Means show pooled estimated means and error bars show pooled standard errors. Lower panel: Means show placebo pool adjusted estimated means and error bars show 95% confidence intervals.

Figure 6.2.7 Proportions of subjects with at least 5 and 10% baseline body weight loss and gastrointestinal adverse events at week 52 by dose (copied from Figure 11‑8, Study NN9536-4153)



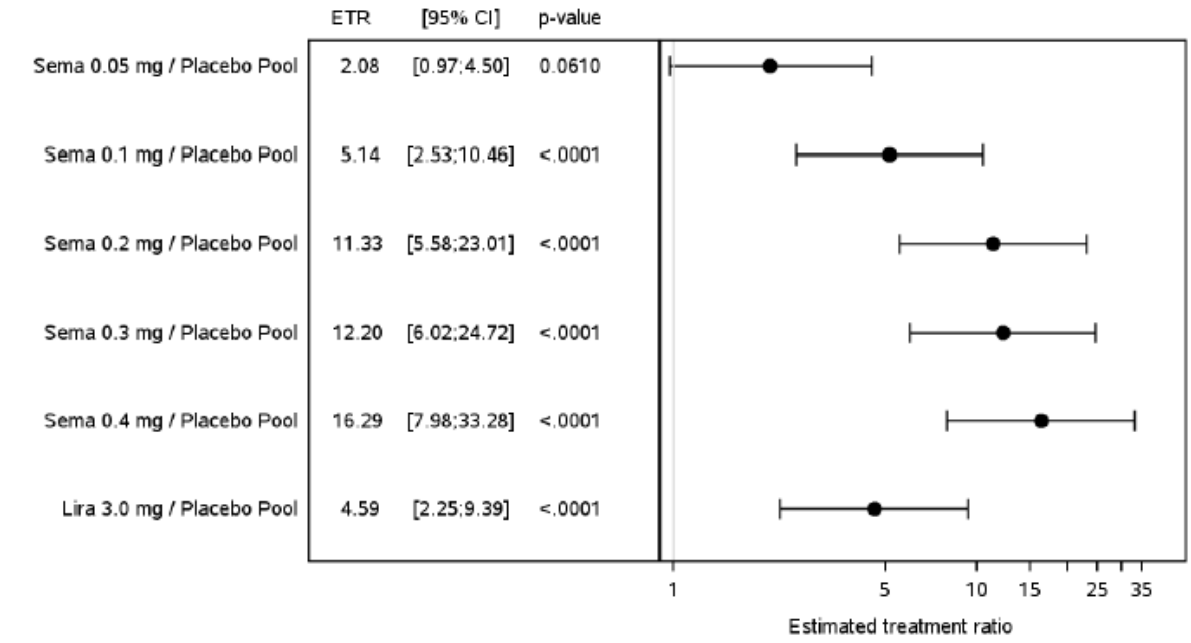
WL: weight loss, GI: gastrointestinal.
The dose-response is estimated via an Emax model of the frequencies of gastrointestional adverse events, or 5% and 10% weight loss responders estimated from a jump to reference multiple imputation approach.

Figure 6.2.8 Subjects with at least 5% baseline body weight loss at week 52 – statistical analysis (part A, comparisons with placebo pool) - logistic regression - J2R-MI - forest plot - full analysis set (copied from Figure 11‑10, Study NN9536-4153)



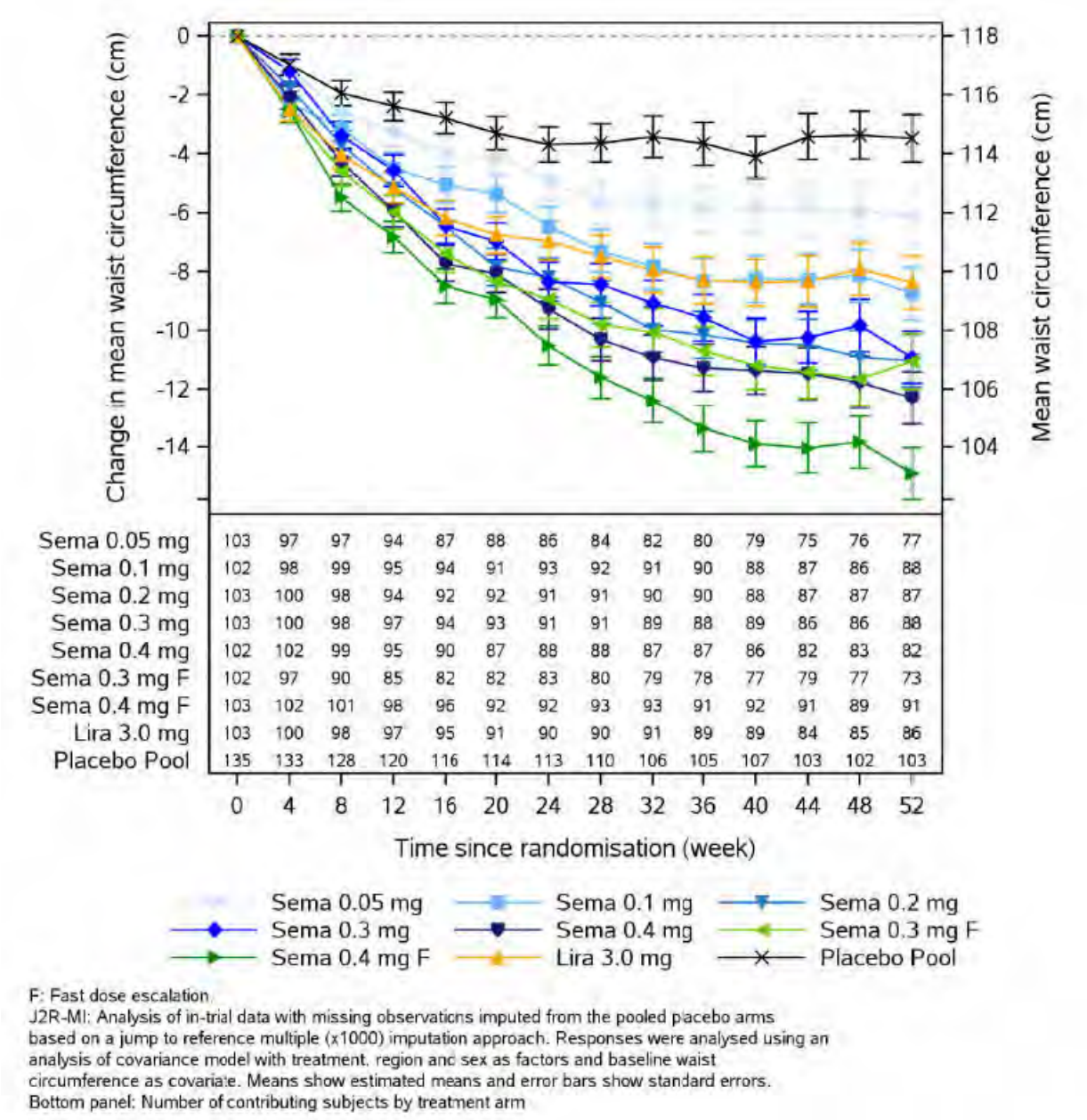
ETR: Estimated treatment odds ratio, CI: Confidence interval. J2R-MI: Analysis of observed in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using a binary logistic regression model with treatment, region and sex as factors and baseline body weight as covariate. Treatment comparisons are not adjusted for multiple testing.

Figure 6.2.9 Subjects with at least 10% baseline body weight loss at week 52 – statistical analysis (part A, comparisons with placebo pool) - logistic regression - J2R-MI - forest plot - full analysis set (copied from Figure 11‑13, Study NN9536-4153)



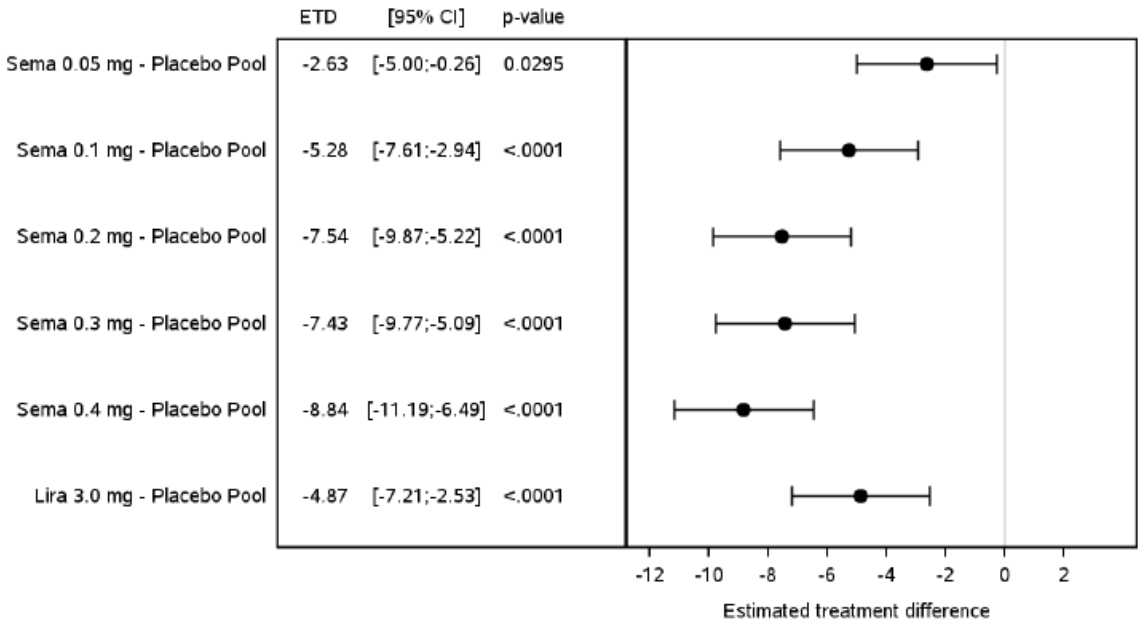
ETR: Estimated treatment odds ratio, CI: Confidence interval. J2R-MI: Analysis of observed in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using a binary logistic regression model with treatment, region and sex as factors and baseline body weight as covariate. Treatment comparisons are not adjusted for multiple testing.

Figure 6.2.10 Change in waist circumference (cm) from baseline by treatment week - randomised active arms and placebo pool - ANCOVA - J2R-MI - mean plot - full analysis set (copied from Figure 11‑17, Study NN9536-4153)



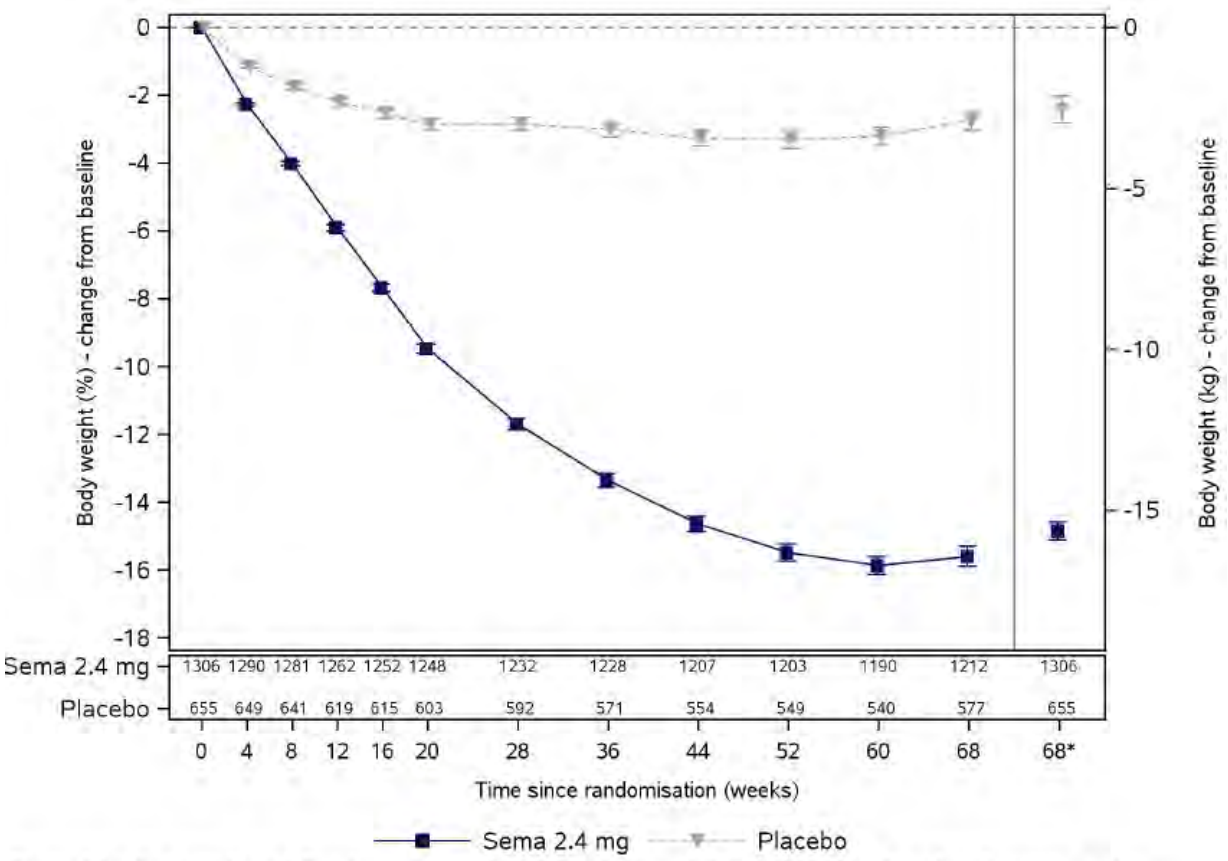
F: Fast dose escalation
J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline waist circumference as covariate. Means show estimated means and error bars show standard errors.
Bottom panel: Number of contributing subjects by treatment arm

Figure 6.2.11 Change in waist circumference (cm) from baseline at week 52 – statistical analysis (part A, comparisons with placebo pool) - ANCOVA - J2R-MI – forest plot - full analysis set (copied from Figure 11‑19, Study NN9536-4153)



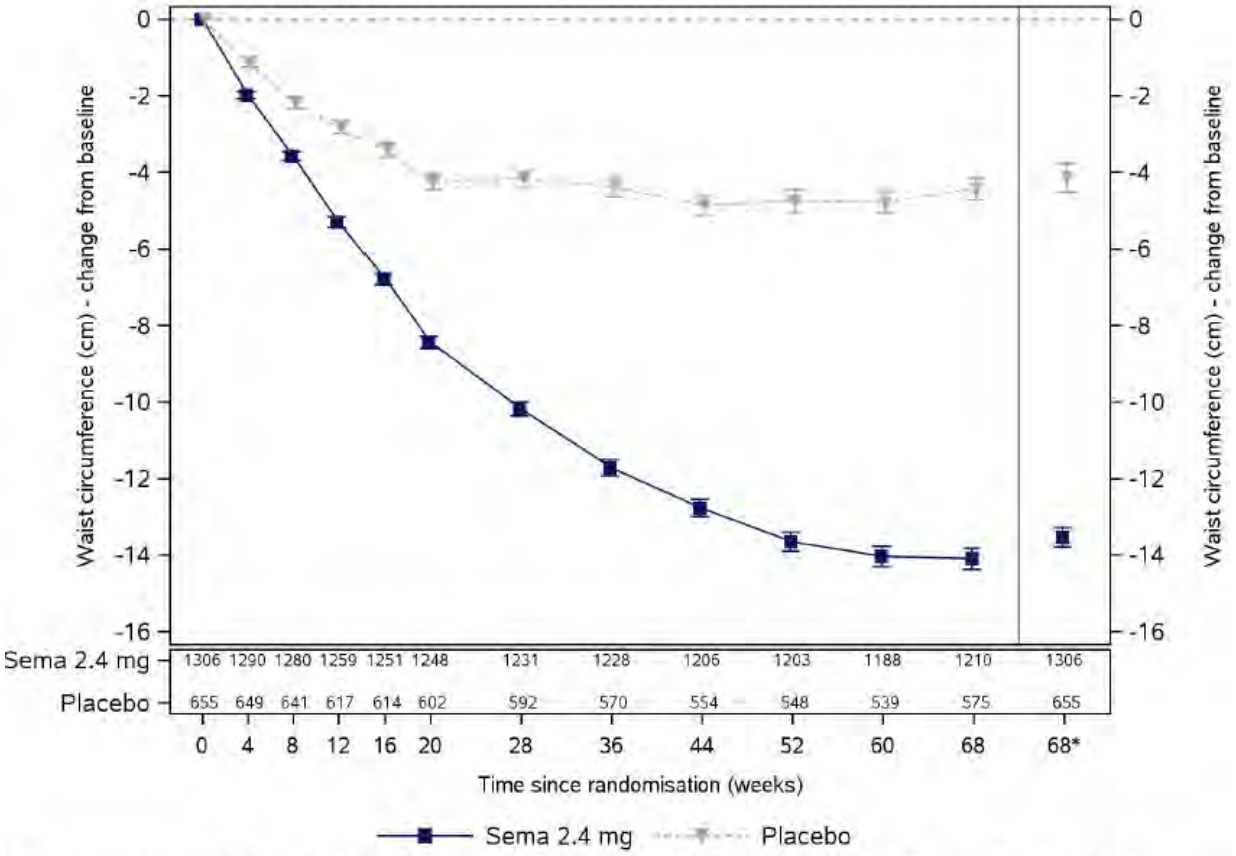
ETD: Estimated treatment difference, CI: Confidence interval. J2R-MI: Analysis of observed in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline waist circumference as covariate. Treatment comparisons are not adjusted for multiple testing.

Figure 7.2.1.1 Body weight change from baseline (%) by week - mean plot - treatment policy estimand (copied from Figure 11-1, Study NN9536-4373)



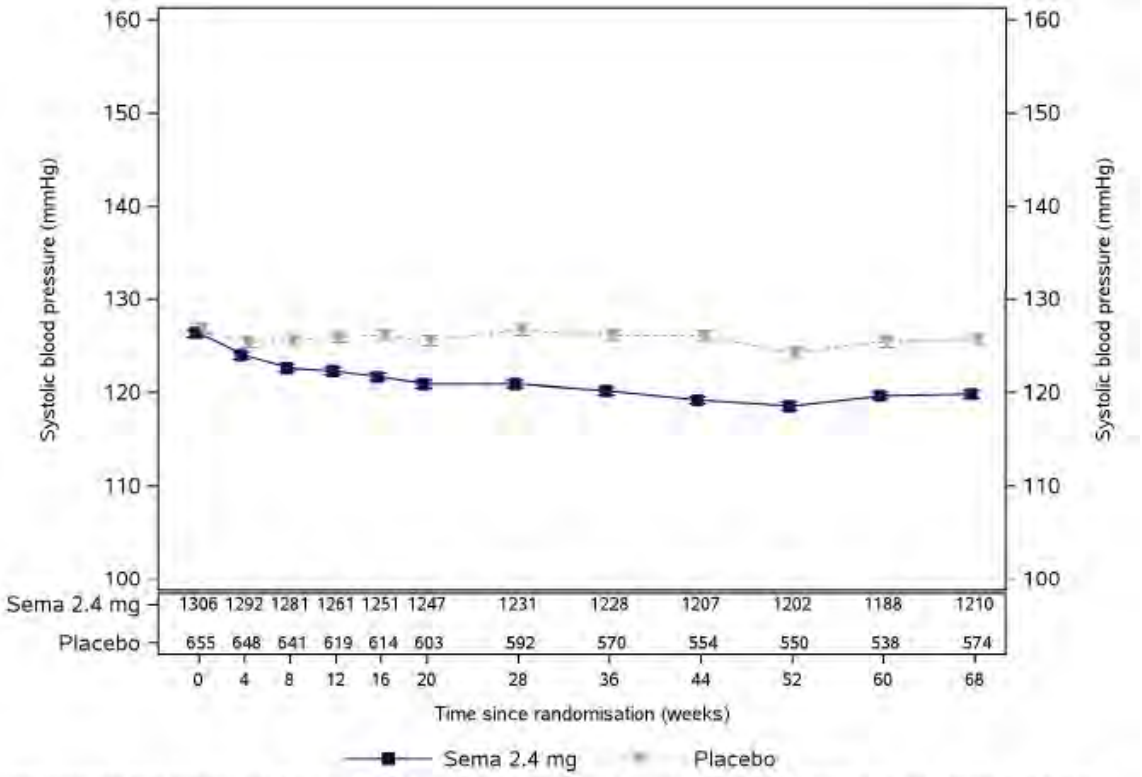
Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.2 Waist circumference change from baseline by week - mean plot - treatment policy estimand - full analysis set (copied from Figure 14.2.53, Study NN9536-4373)



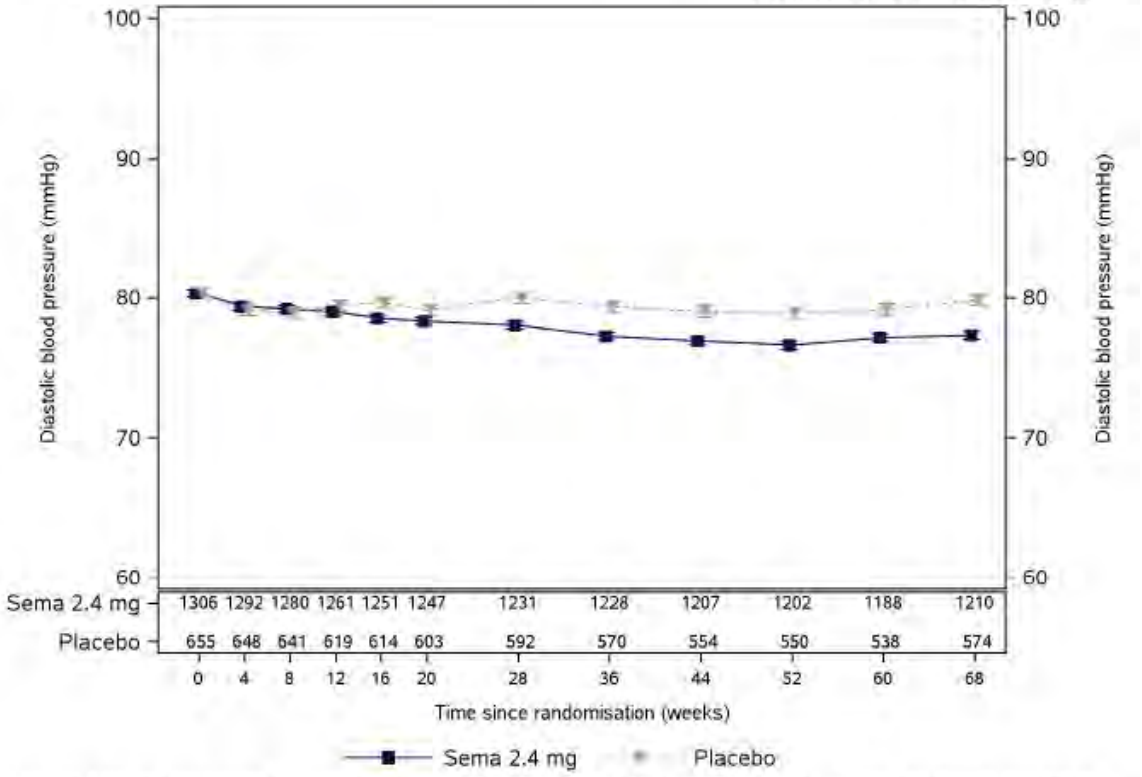
Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the confirmatory secondary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.3 Systolic and diastolic blood pressure by week − mean plot - observed in-trial data (copied from Figure 11-16, Study NN9536-4373)



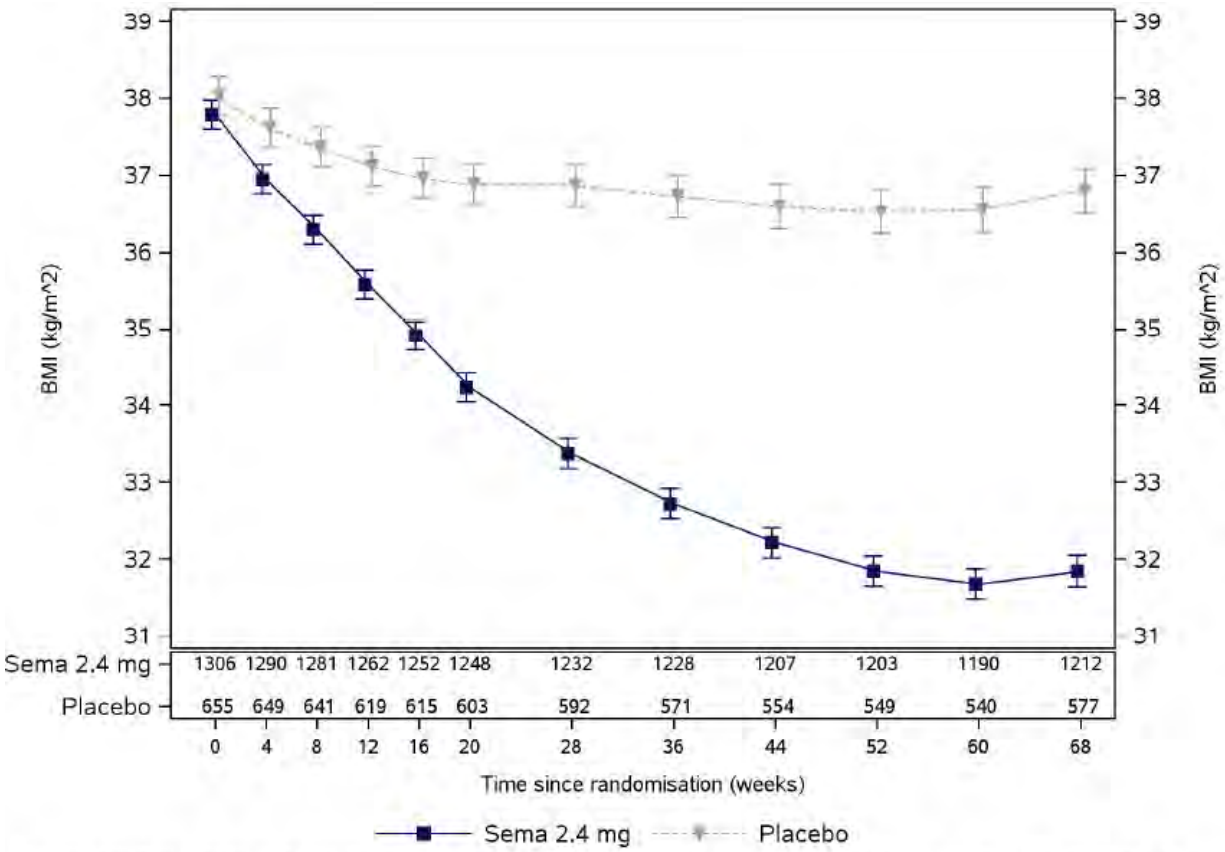
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

nn9536/nn9536-4373/ctr_20200811_er
07AUG2020:15:57:32 - fmeaneff.sas/fmeansbpit.png



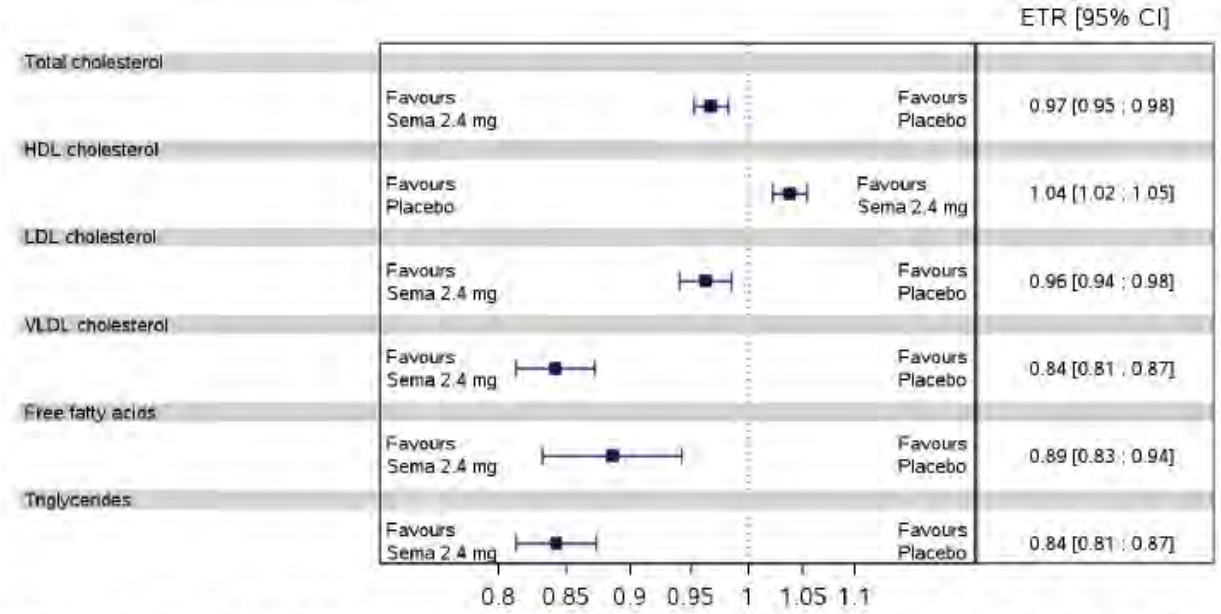
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.4 Body mass index by week - mean plot - observed in-trial data (copied from Figure 11-12, Study NN9536-4373)



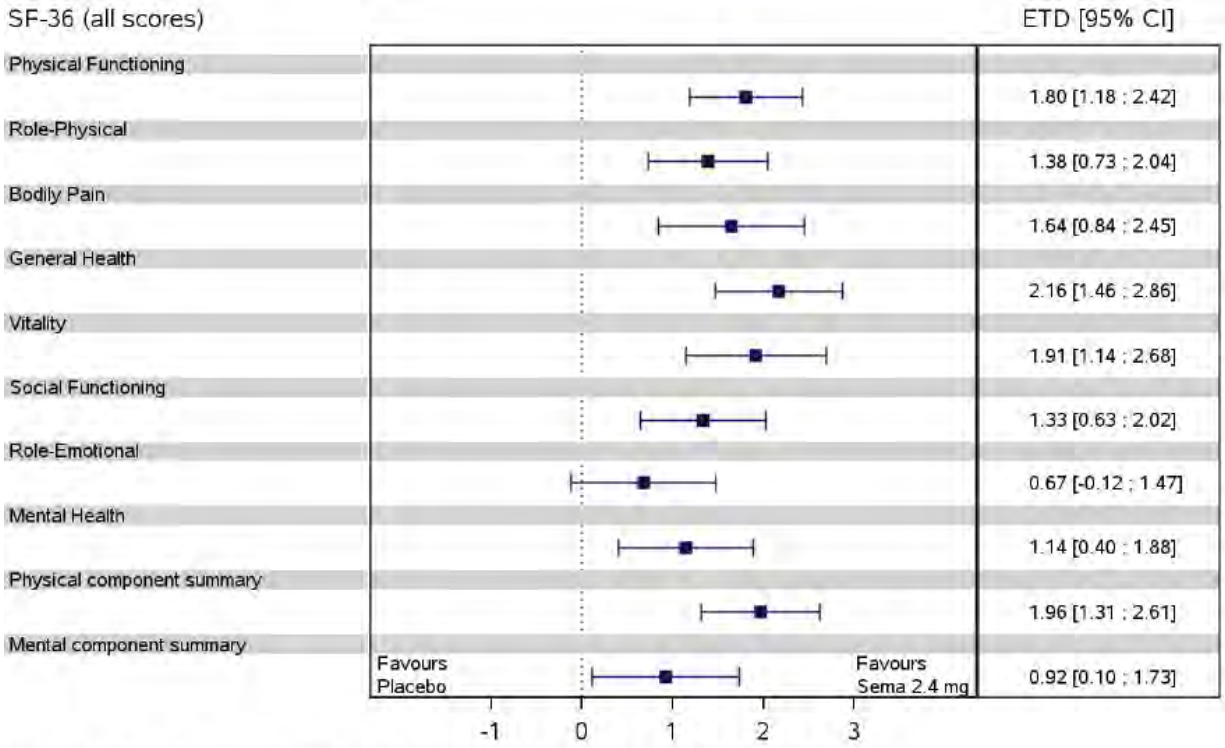
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.5 Lipids ratio to baseline at week 68 - forest plot - treatment policy estimand - full analysis set (copied from 14.2.97, Study NN9536-4373)



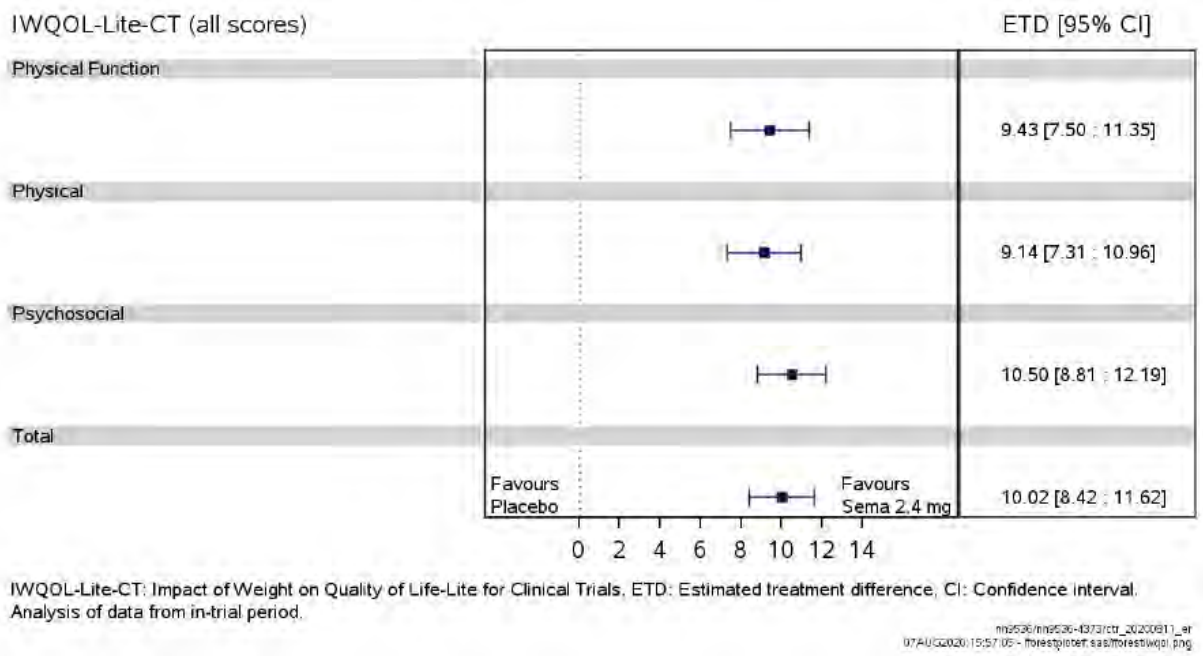
ETR: Estimated treatment ratio, CI: Confidence interval, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Figure 7.2.1.6 SF-36 (all individual health domain scores) change from baseline to week 68 - forest plot – treatment policy estimand (copied from Figure 11-26, Study NN9536-4373)



SF-36: Short Form 36 v2.0 acute, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

Figure 7.2.1.7 IWQOL-Lite-CT (all scores) change from baseline to week 68 - forest plot - treatment policy estimand (copied from Figure 11-31, Study NN9536-4373)



IWQOL-Lite-CT: Impact of Weight on Quality of Life-Lite for Clinical Trials. ETD: Estimated treatment difference. CI: Confidence interval. Analysis of data from in-trial period.

Figure 7.2.1.8 Fatty liver index score - shift plot - in-trial (copied from Figure 11-14, Study NN9536-4373)

Figure 7.2.1.9 Lipid-lowering medication during trial - in trial data (copied from Figure 11-20, Study NN9536-4373)

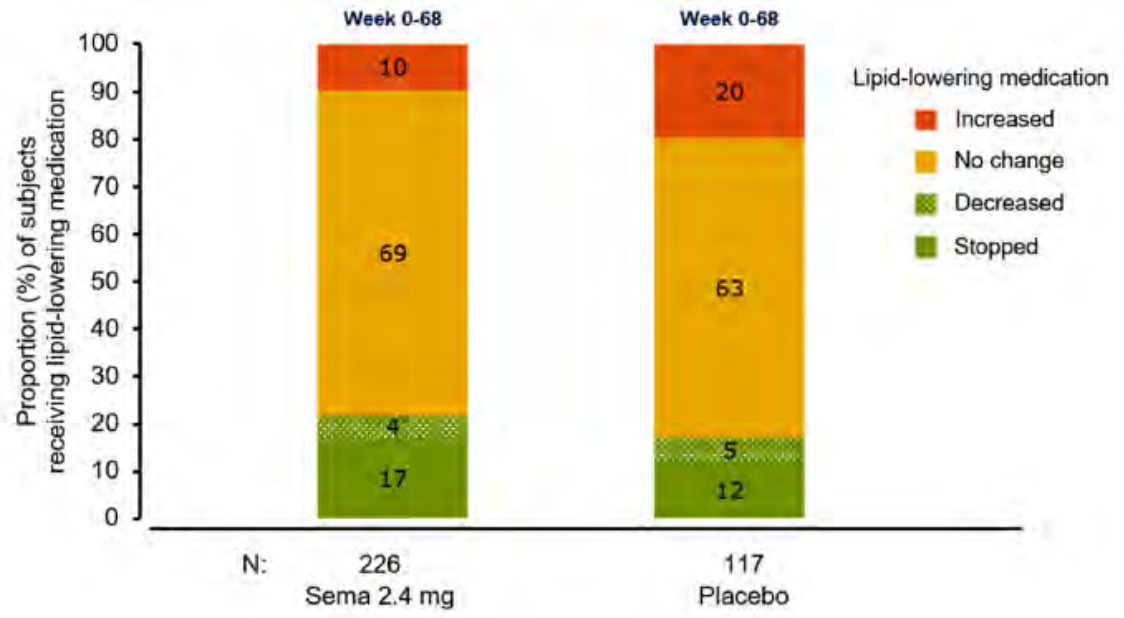
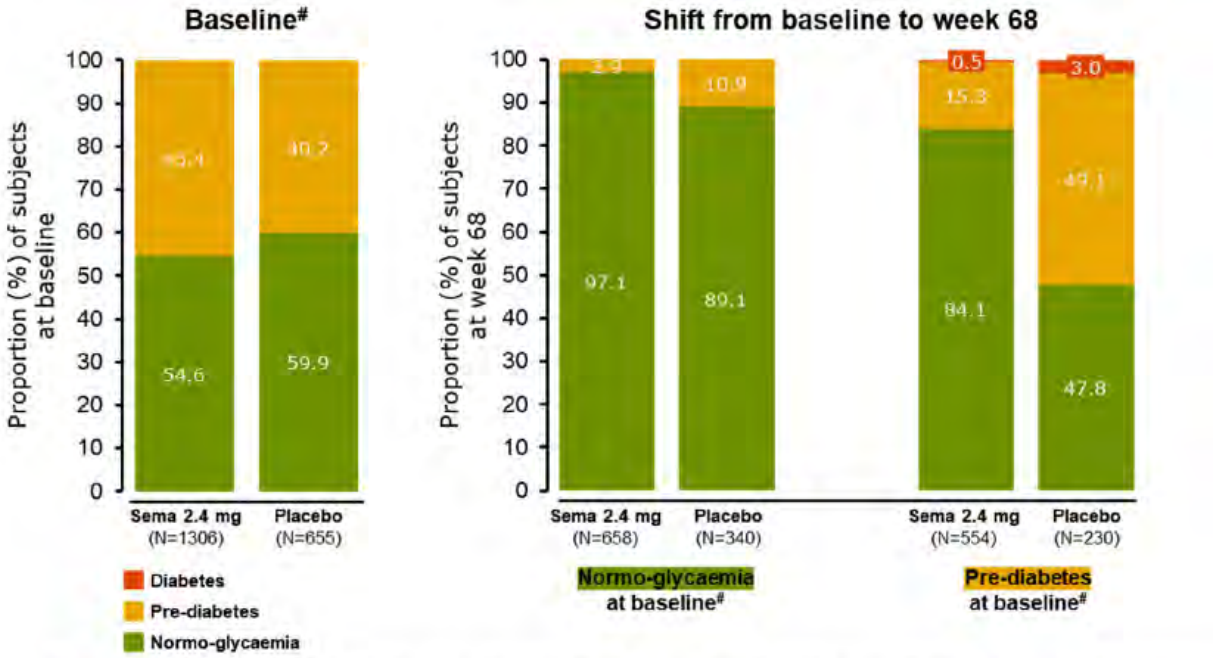
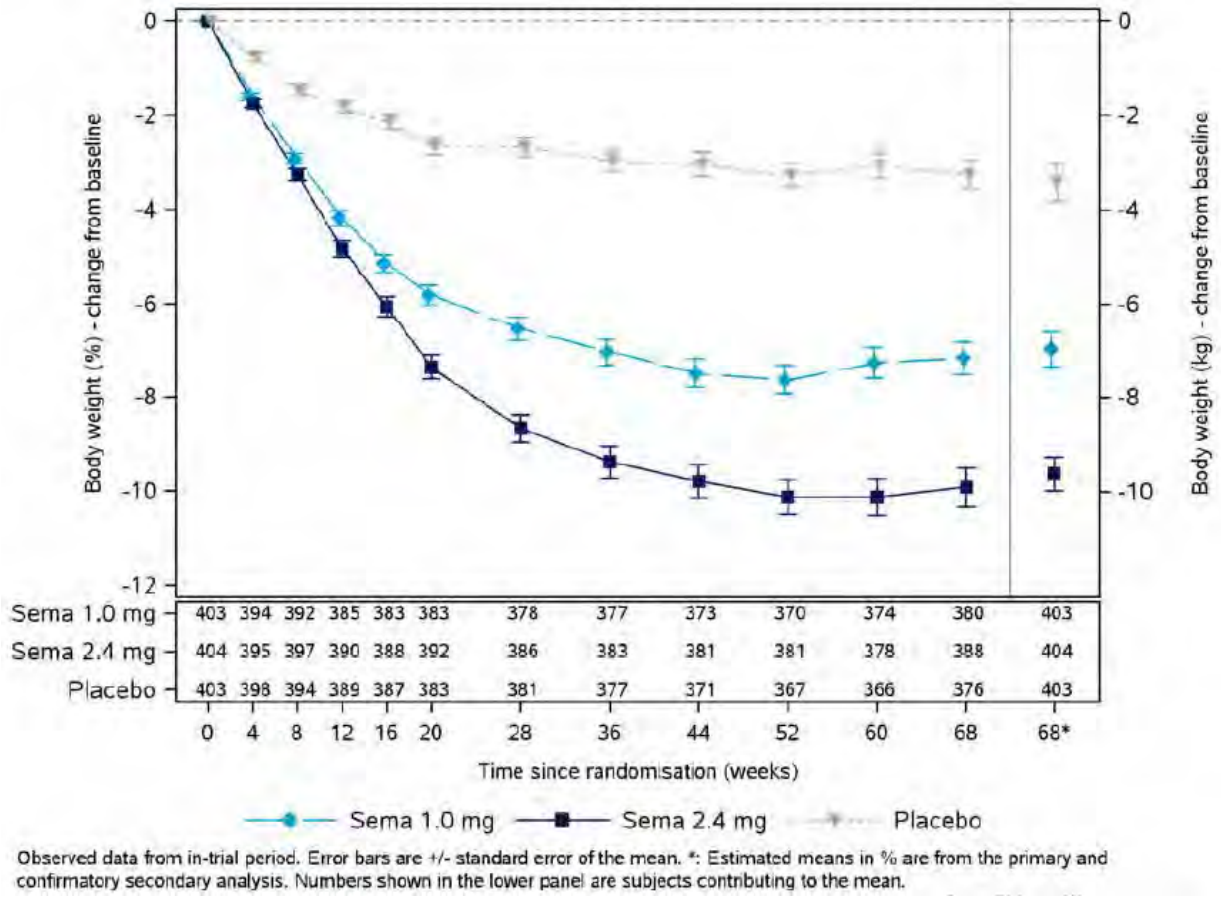


Figure 7.2.1.10 Glycaemic category - shift from baseline to week 68 - observed in-trial data (copied from Figure 11-32, Study NN9536-4373)



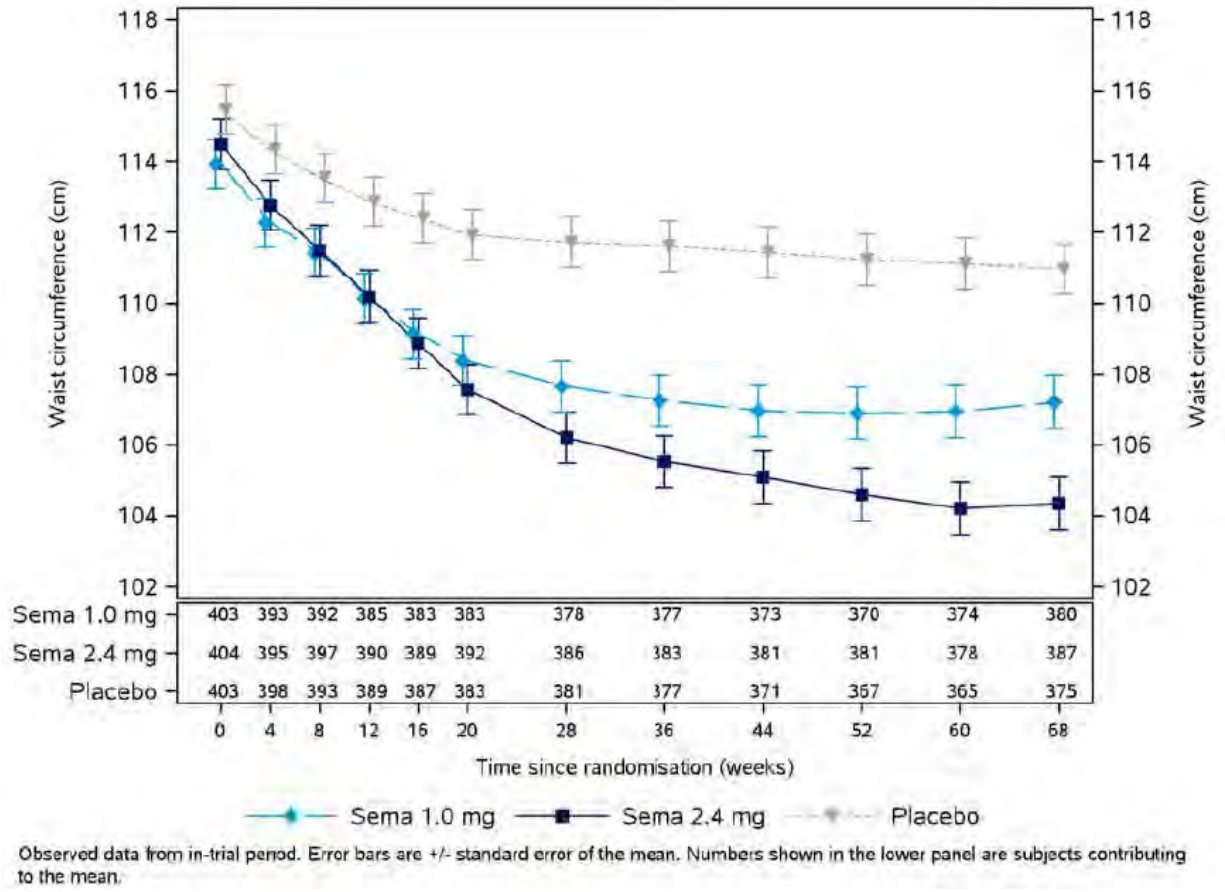
#Glycaemic category evaluated at baseline by the investigator based on available relevant information

Figure 7.2.2.1 Body weight change from baseline by week - mean plot - treatment policy estimand – full analysis set (copied from Figure 14.2.8, Study NN9536-4374)



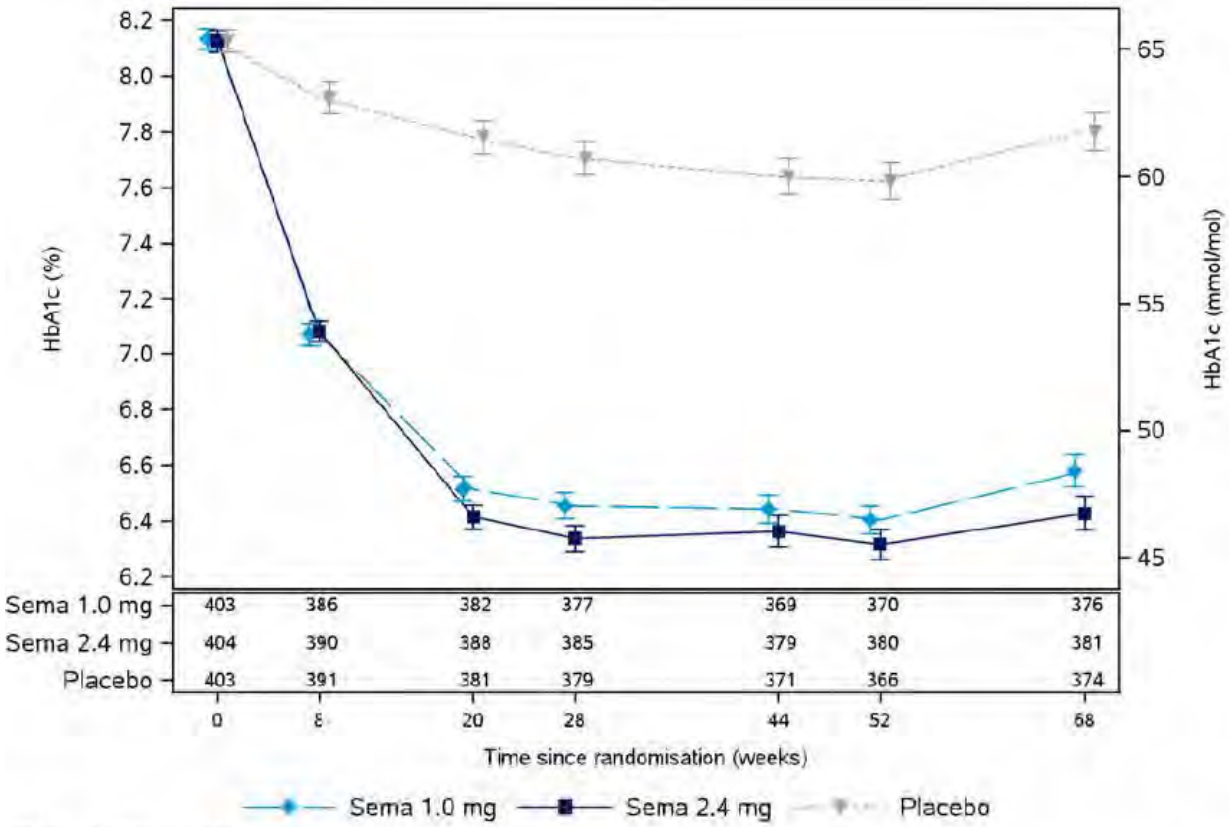
Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary and confirmatory secondary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.2.2 Waist circumference (cm) - by week - mean plot - observed in-trial data (copied from Figure 11-10, Study NN9536-4374)



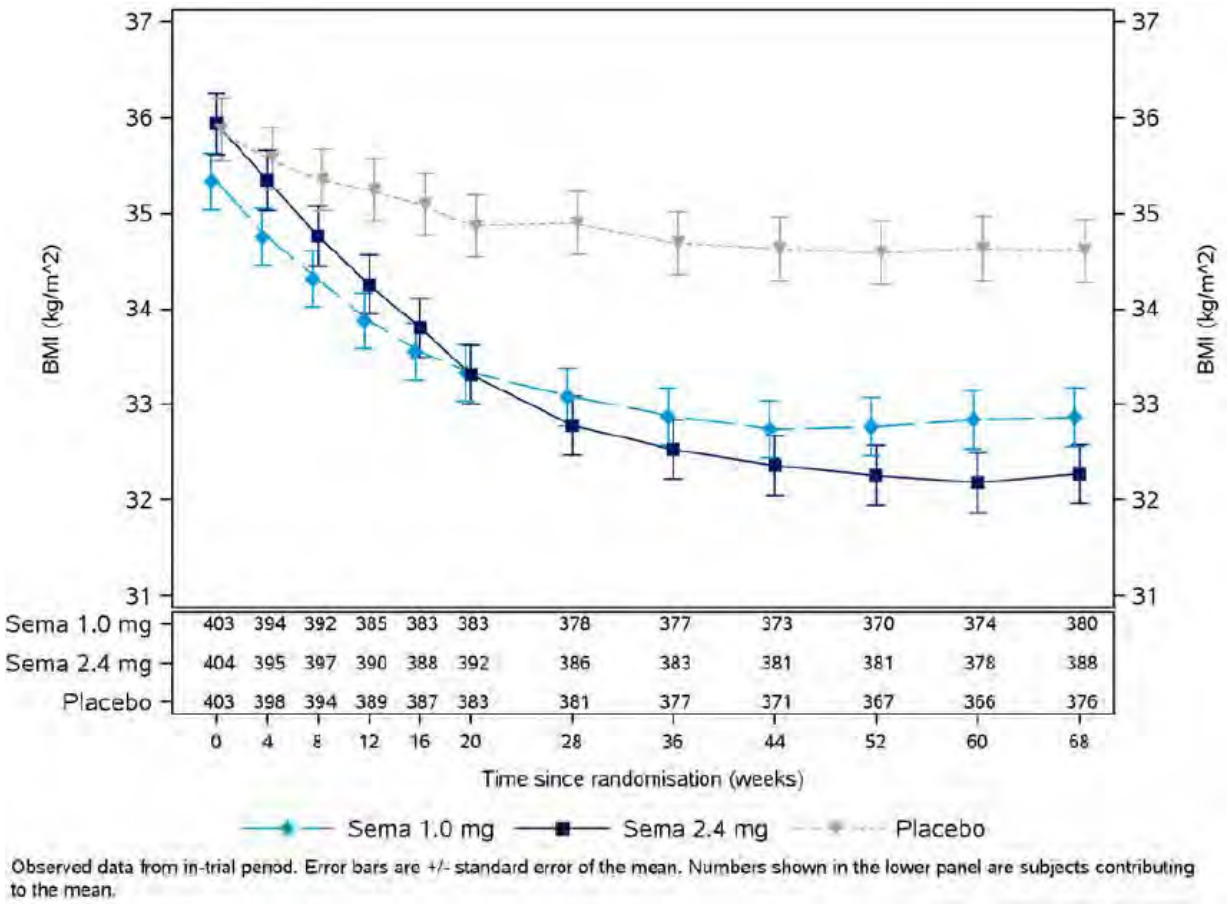
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.2.3 HbA1c by week - mean plot – observed in-trial data (copied from Figure 11-13, Study NN9536-4374)



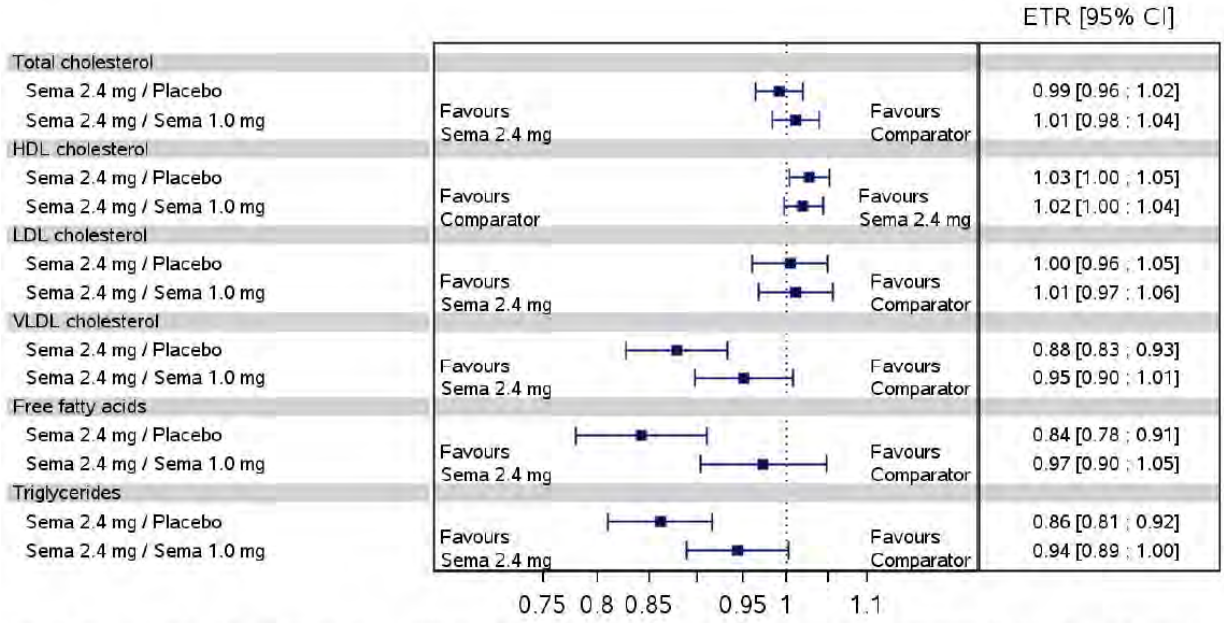
HbA1c: Haemoglobin A1c.
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.2.4 Body mass index by week - mean plot – observed in-trial data (copied from Figure 11-12, Study NN9536-4374)



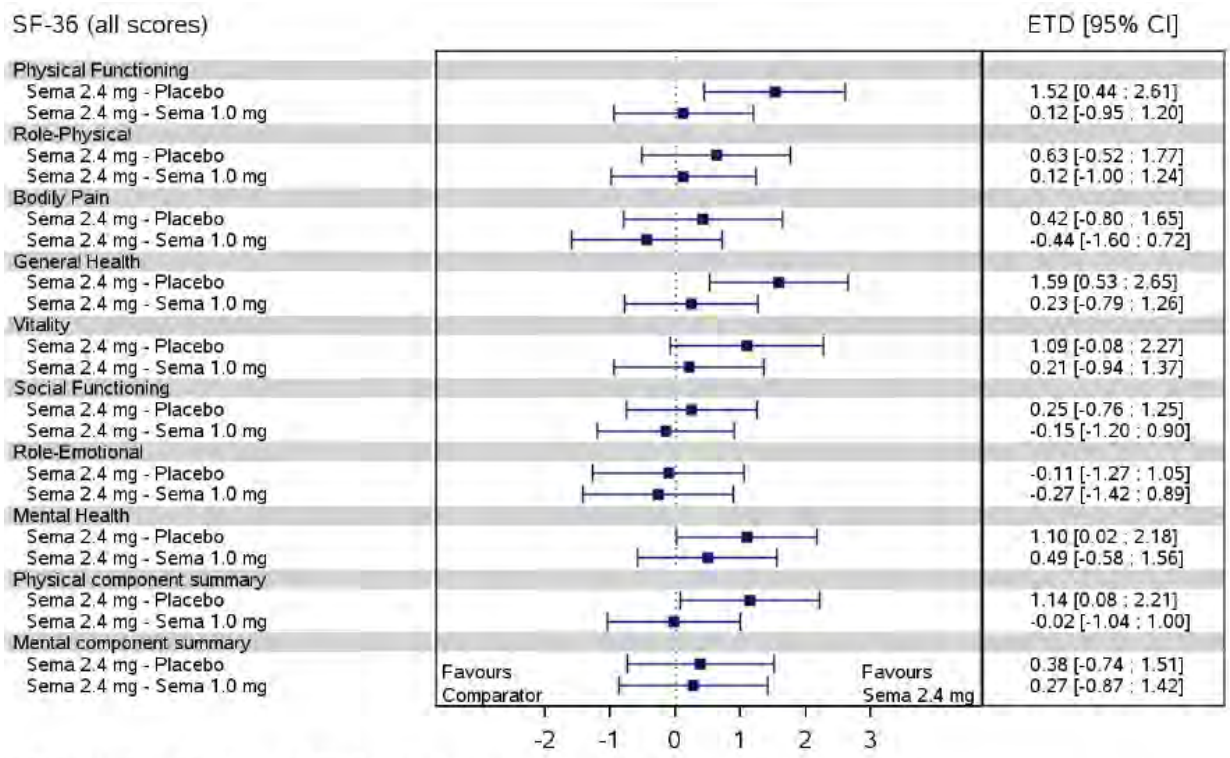
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.2.5 Lipids ratio to baseline at week 68 – forest plot – treatment policy estimand (copied from Figure 11-24, Study NN9536-4373)



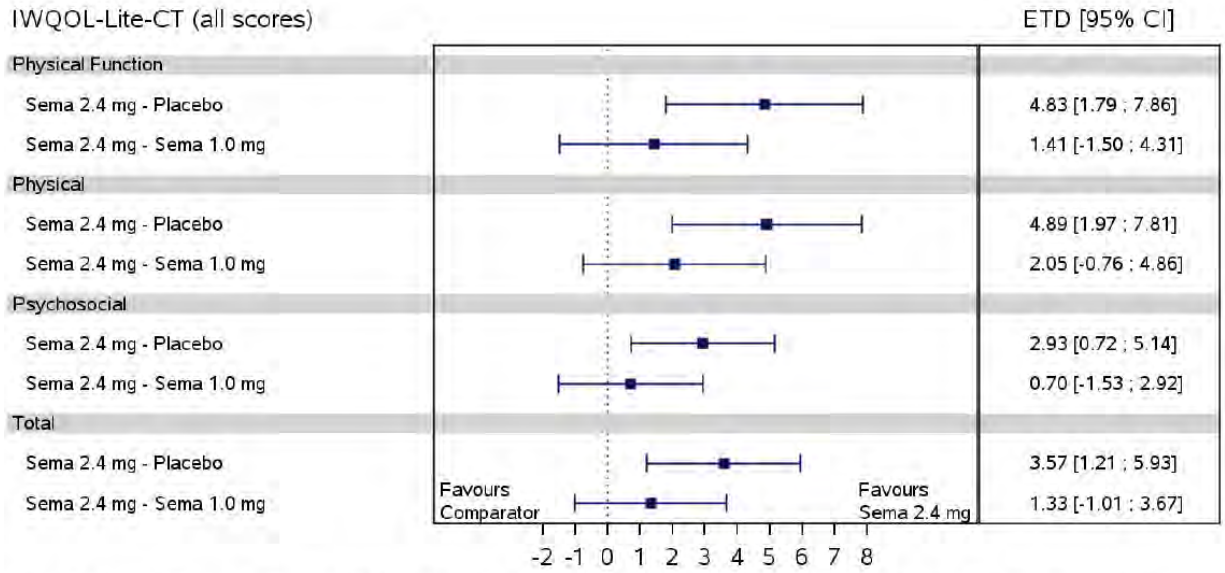
ETR: Estimated treatment ratio, CI: Confidence interval, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Figure 7.2.2.6 SF-36 (all scores) change from baseline to week 68 – forest plot – treatment policy estimand (copied from Figure 11-31, Study NN9536-4374)



SF-36: Short Form 36 v2 0 acute, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

Figure 7.2.2.7 IWQOL-Lite-CT (all scores) change from baseline to week 68 - forest plot - treatment policy estimand (copied from Figure 11-36, Study NN9536-4374)



IWQOL-Lite-CT: Impact of Weight on Quality of Life-Lite for Clinical Trials, ETD: Estimated treatment difference, CI: Confidence interval. Analysis of data from in-trial period.

Figure 7.2.2.8 OAD medication – observed in-trial data (copied from Figure 11-19, Study NN9536-4374)

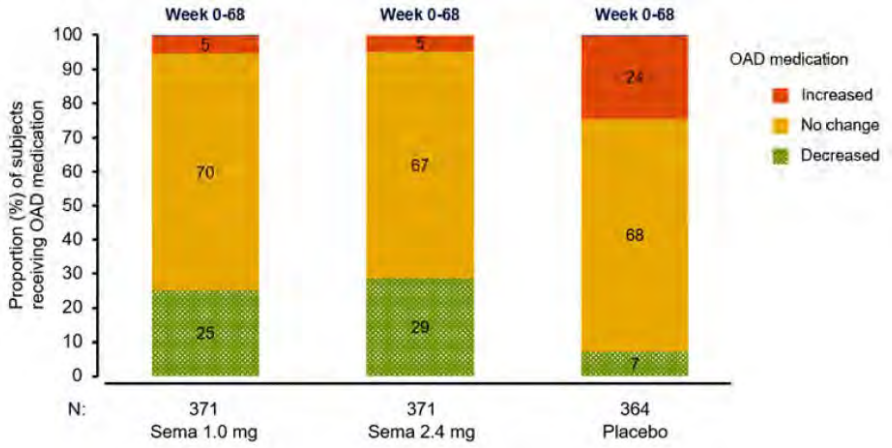


Figure 7.2.2.9 Antihypertensive medication - observed in-trial data (copied from Figure 11-23, Study NN9536-4374)

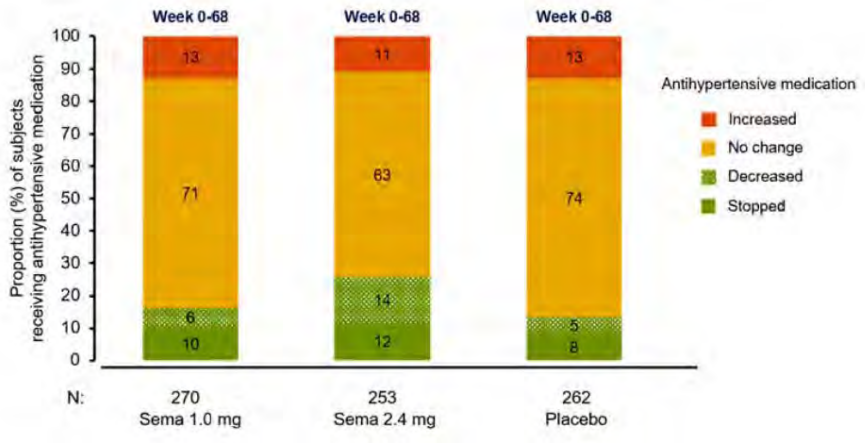


Figure 7.2.2.10 Lipid-lowering medication - observed in trial data (copied from Figure 11-25, Study NN9536-4374)

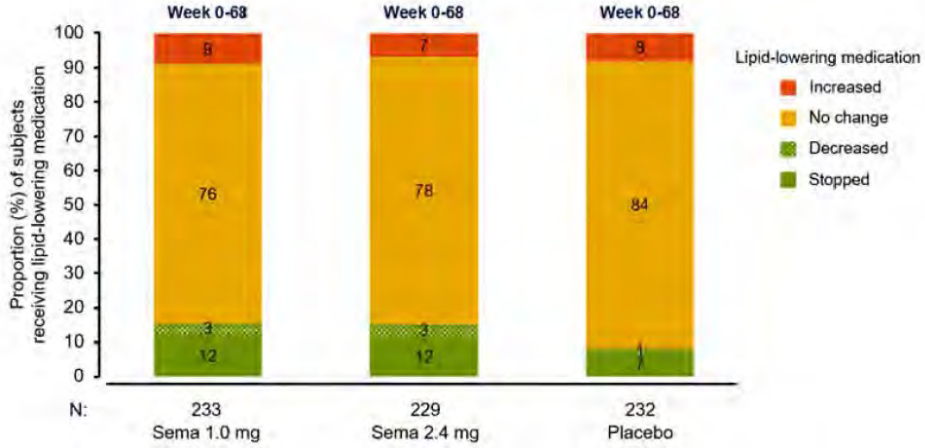


Figure 7.2.3.1 Body weight change from baseline (%) by week - mean plot - treatment policy estimand (copied from Figure 11-1, Study NN9536-4375)

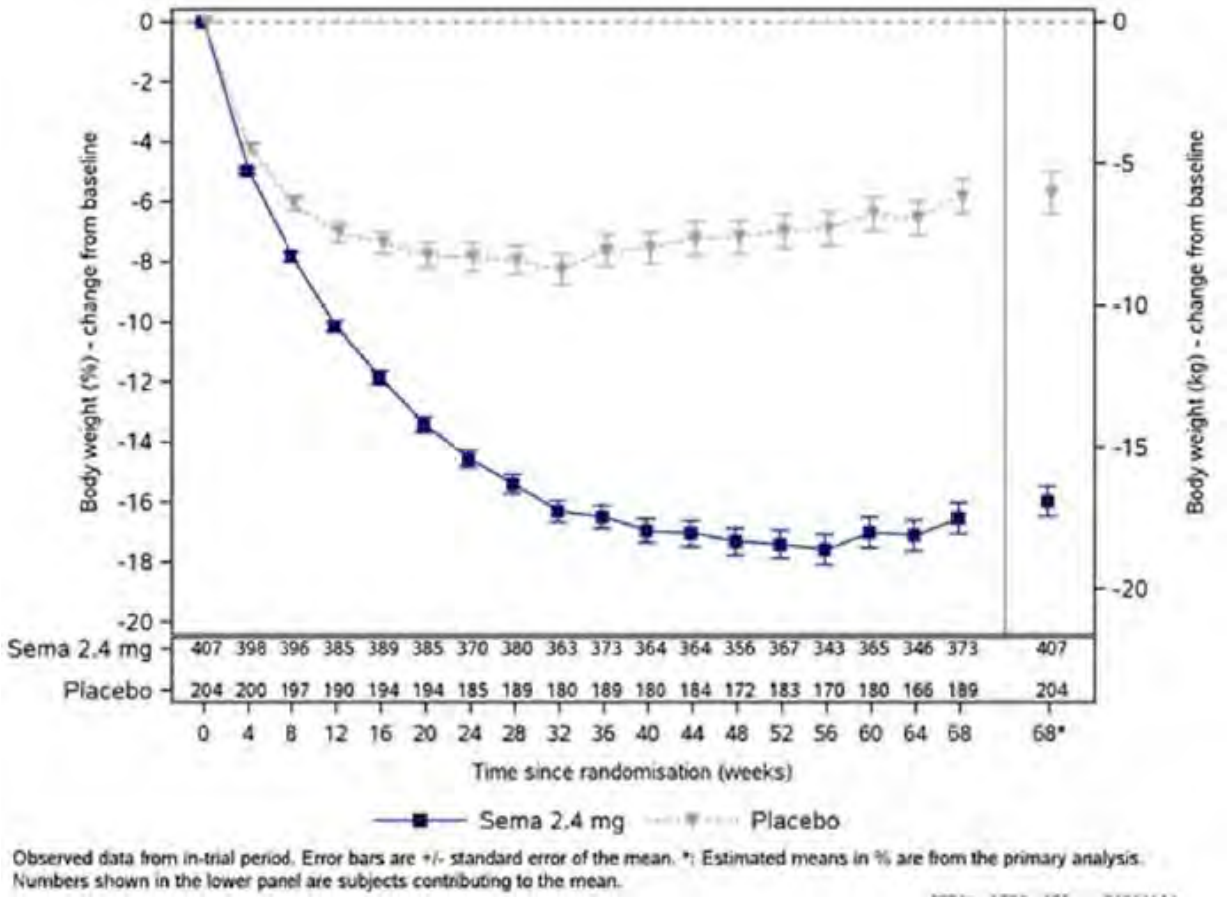
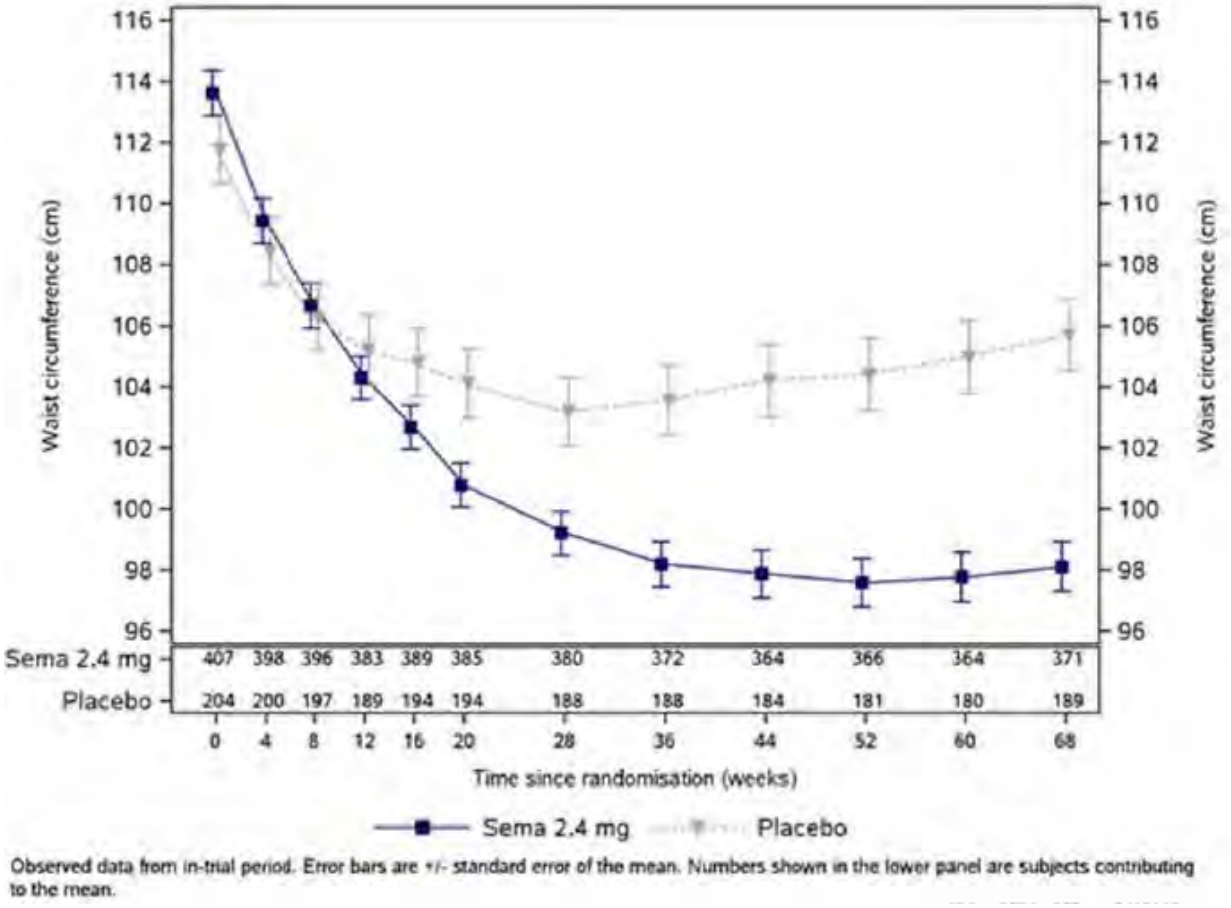
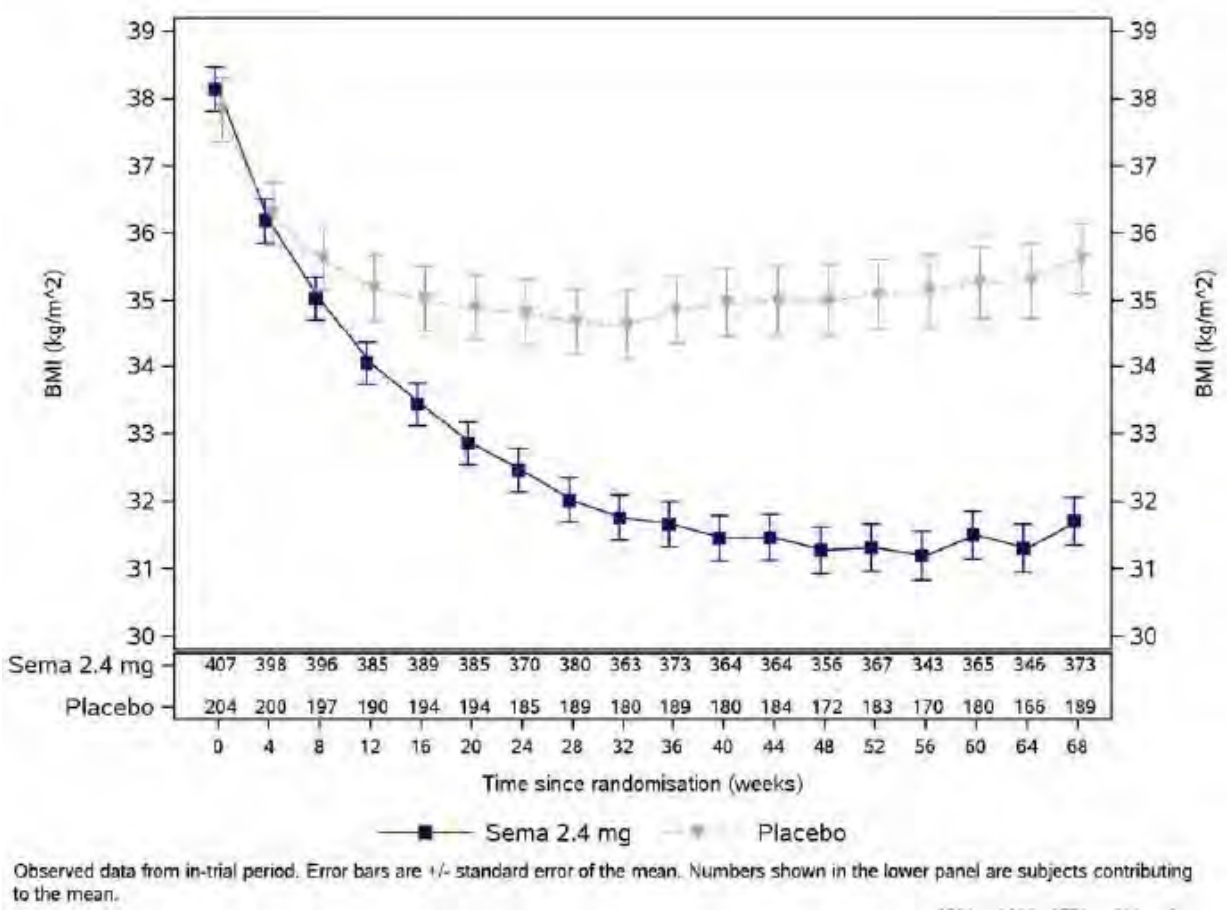


Figure 7.2.3.2 Waist circumference by week - mean plot - in-trial (copied from Figure 11-10, Study NN9536-4375)



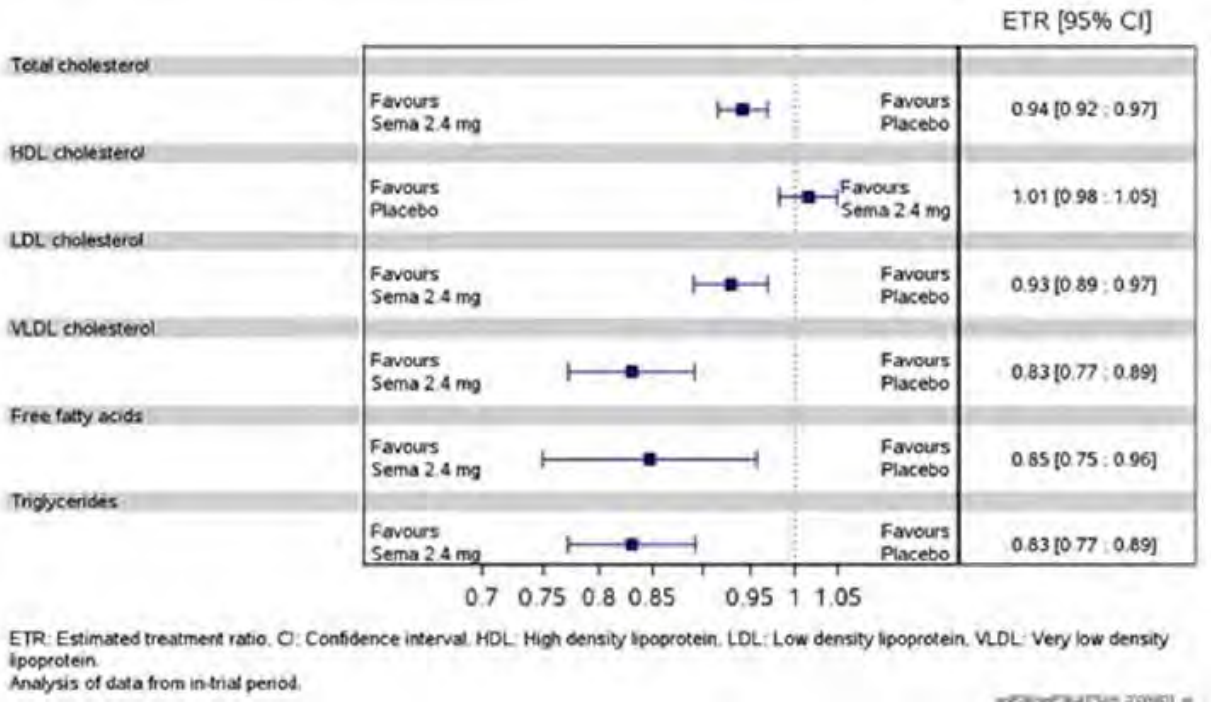
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.3.3 BMI by week - mean plot - in-trial - full analysis set (copied from 14.2.47, Study NN9536-4375)



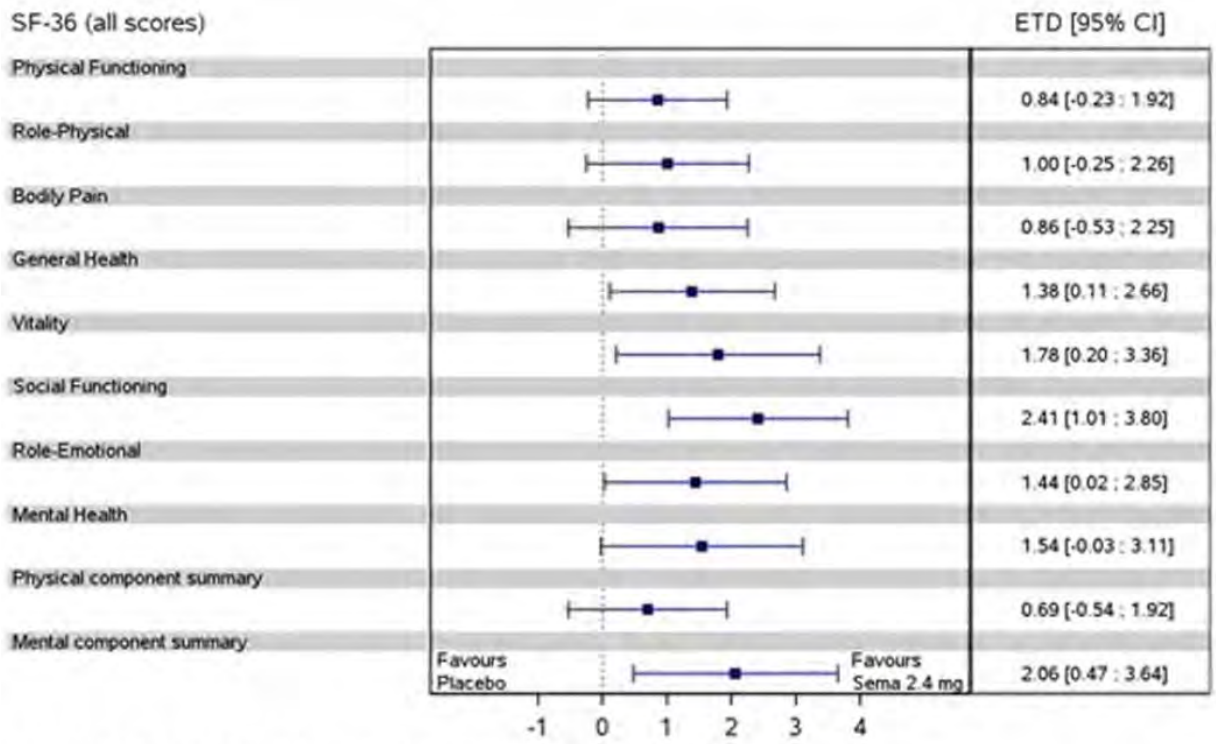
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.3.4 Lipids ratio to baseline at week 68 - forest plot - treatment policy estimand (copied from Figure 11-17, Study NN9536-4375)



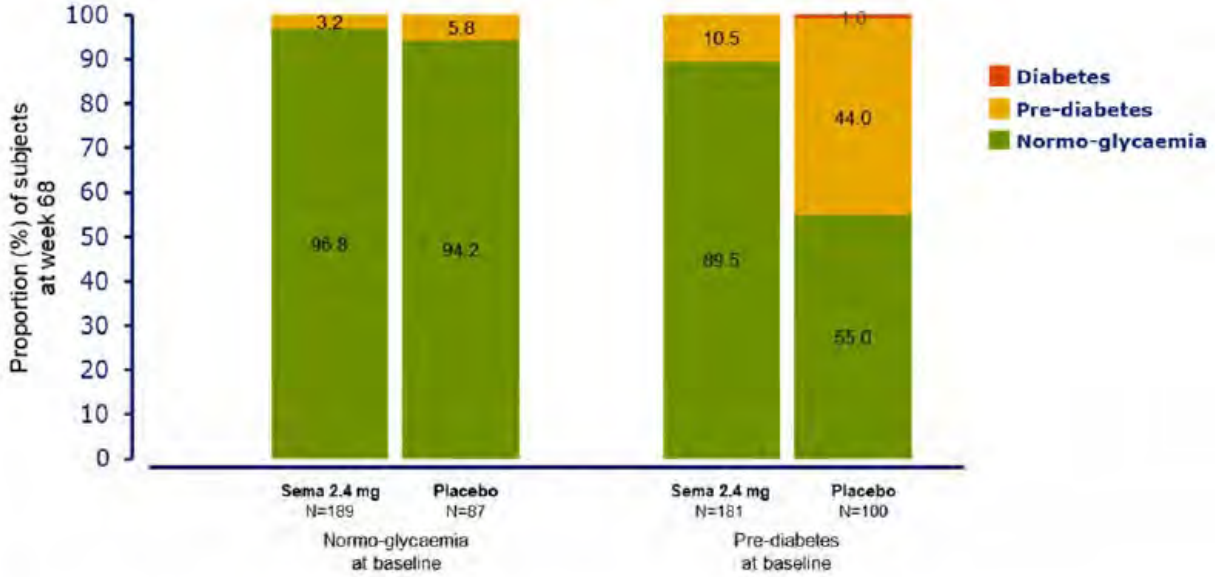
ETR: Estimated treatment ratio. CI: Confidence interval. HDL: High density lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Figure 7.2.3.5 SF-36 (all scores) change from baseline to week 68 - forest plot - treatment policy estimand (copied from Figure 11-22, Study NN9536-4375)



SF-36: Short Form 36 v2.0 acute, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

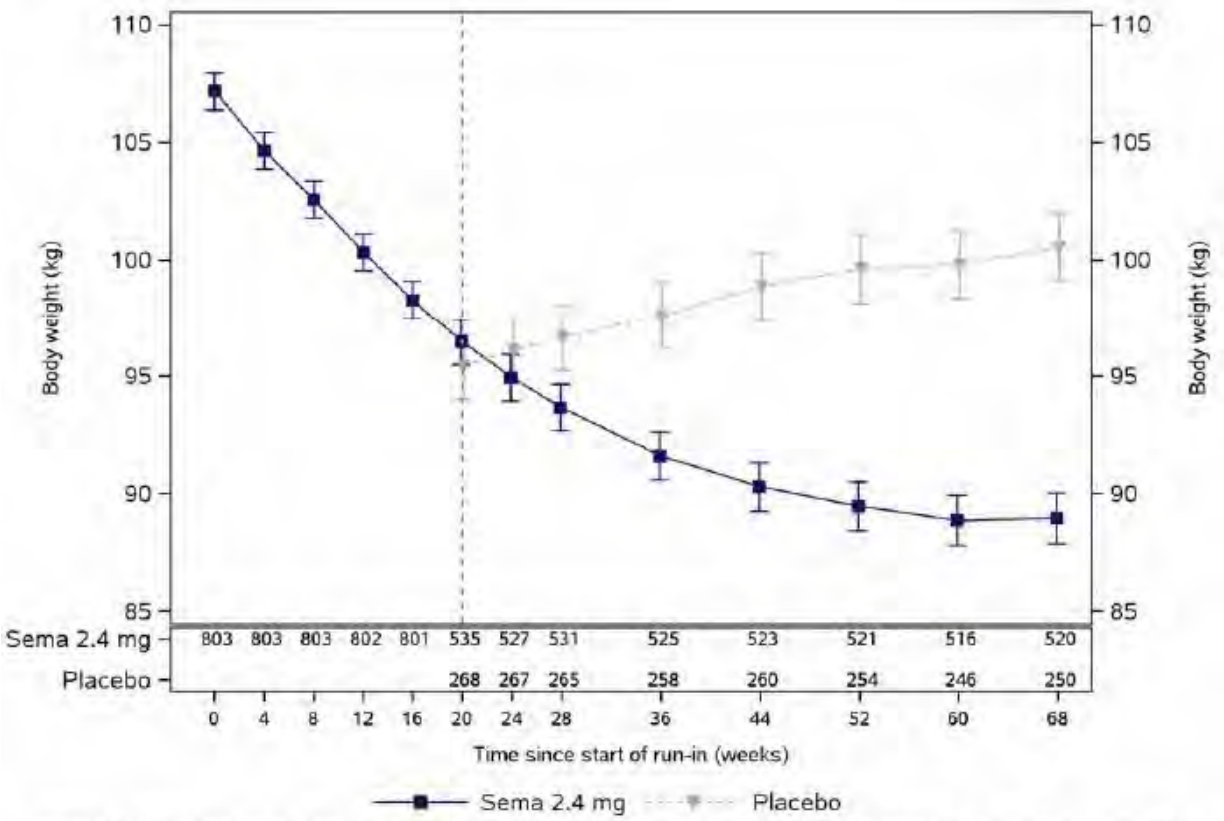
Figure 7.2.3.6 Glycaemic category - shift from baseline to week 68 - in-trial (copied from Figure 11-23, Study NN9536-4375)



Abbreviations: N: Number of subjects; sema: semaglutide

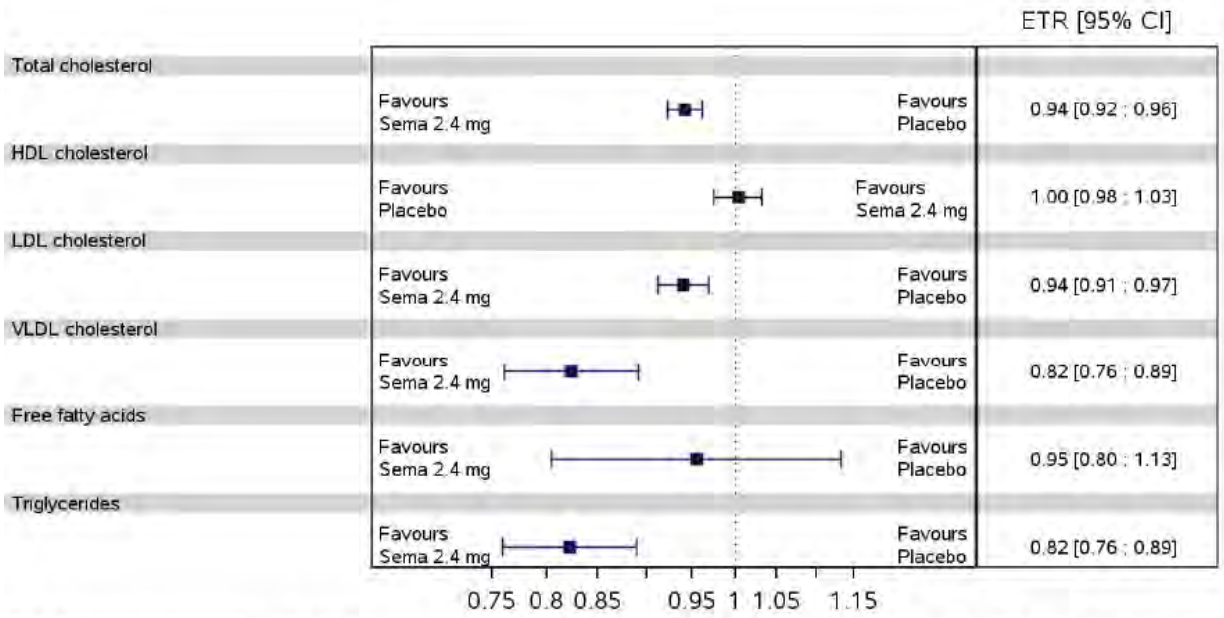
Notes: Proportions (%) are based on subjects with an observation at the visit. Observed data from the in-trial period.

Figure 7.2.4.1 Body weight (kg) by week - mean plot - in-trial - full analysis set (copied from 14.2.3, Study NN9536-4376)



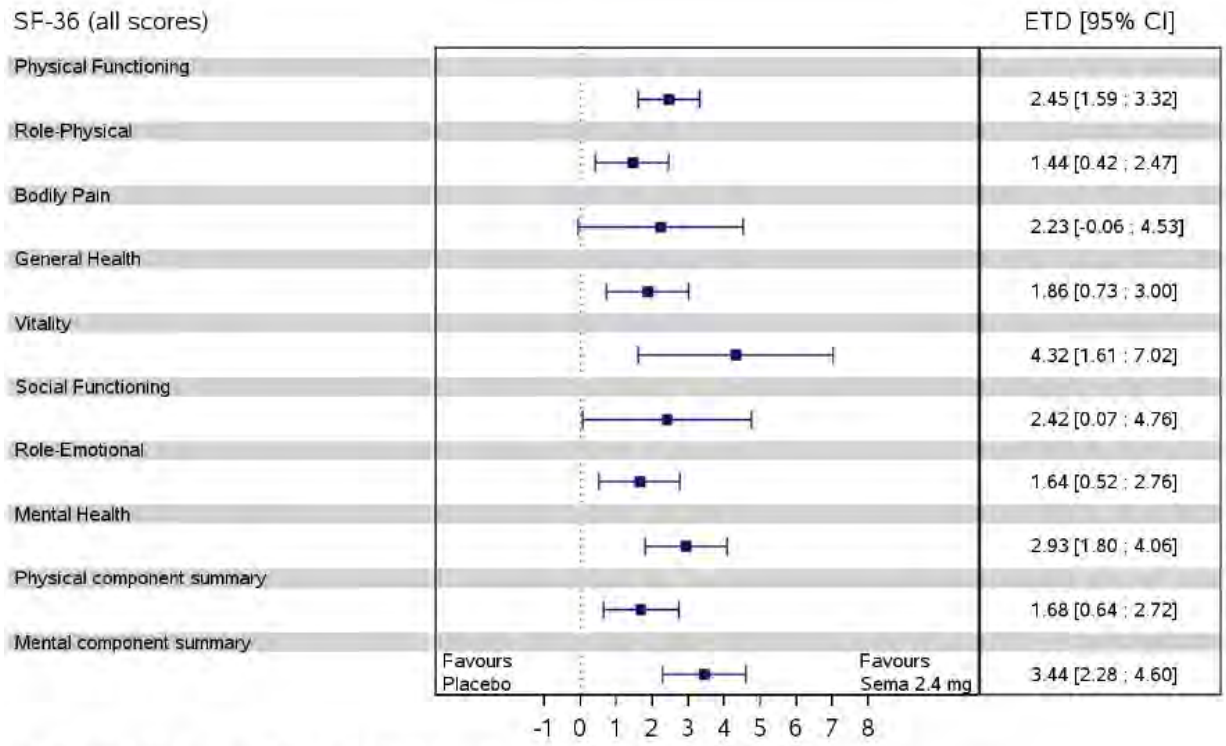
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. The full analysis set includes all randomised subjects.

Figure 7.2.4.2 Lipids ratio to baseline (week 20) at week 68 - forest plot - treatment policy estimand (copied from Figure 11-12, Study NN9536-4376)



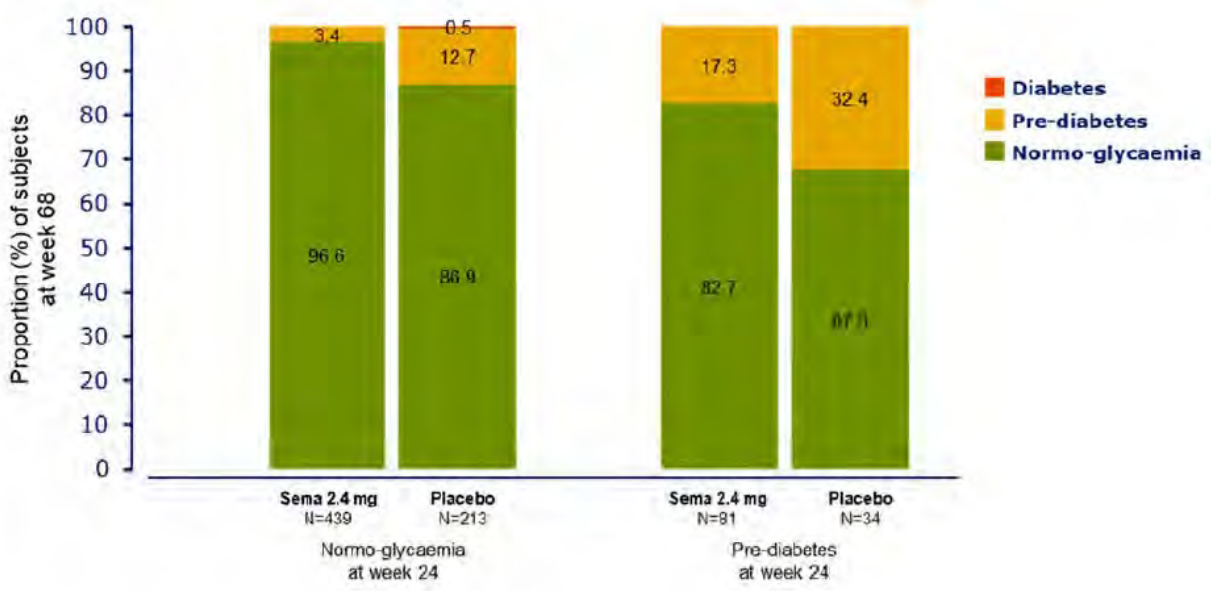
ETR: Estimated treatment ratio. CI: Confidence interval. HDL: High density lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein.
Analysis of data from in-trial period. Randomised period starts with week 20 visit. Baseline: Randomisation (week 20).

Figure 7.2.4.3 SF-36 (all scores) change from baseline (week 20) to week 68 - forest plot - treatment policy estimand (copied from Figure 11-15, Study NN9536-4376)



SF-36: Short Form 36 v2.0 acute. ETD: Estimated treatment difference. CI: Confidence interval.
Analysis of data from in-trial period. Randomised period starts with week 20 visit. Baseline: Randomisation (week 20).
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

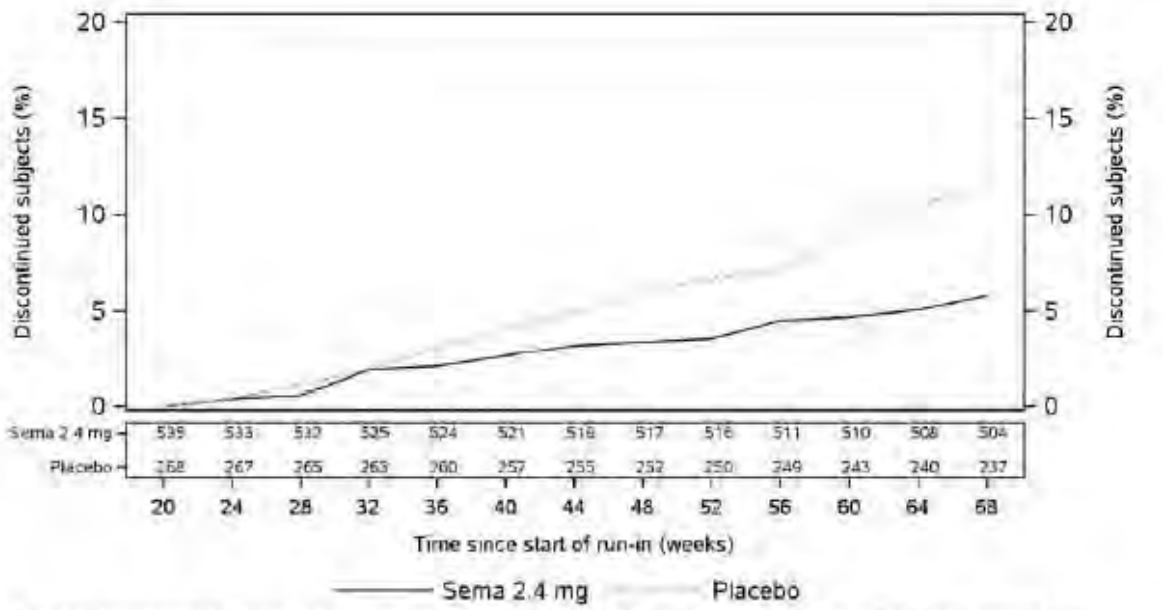
Figure 7.2.4.4 Glycaemic category by weeks - shift from week 24 to week 68 - in-trial (copied from Figure 11-16, Study NN9536-4376)



N: number of subjects; sema: semaglutide

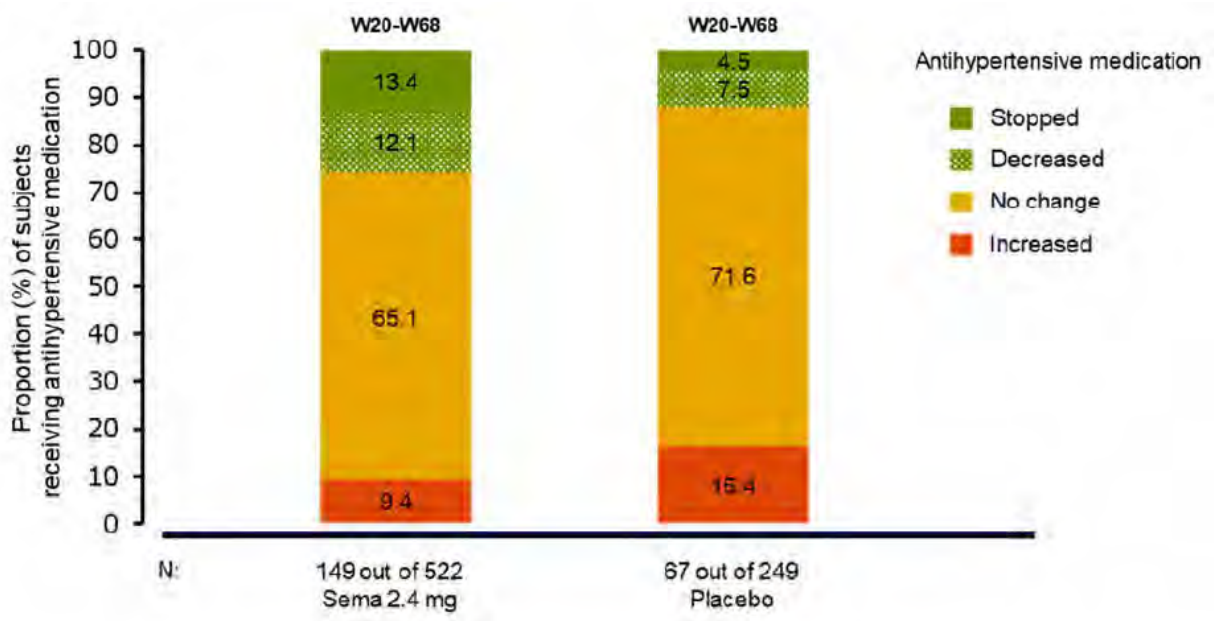
Proportions (%) are based on subjects with an observation at the visit. Observed data from the in-trial period.

Figure 7.2.4.5 Time to permanent discontinuation of trial product (weeks) – plot – randomized period (copied from Figure 10-1, Study NN9536-4376)



Time from randomisation (week 20) to permanent discontinuation of trial product. Numbers shown in the lower panel are subjects who have not discontinued trial product permanently. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuations occurring after week 68 are not shown.

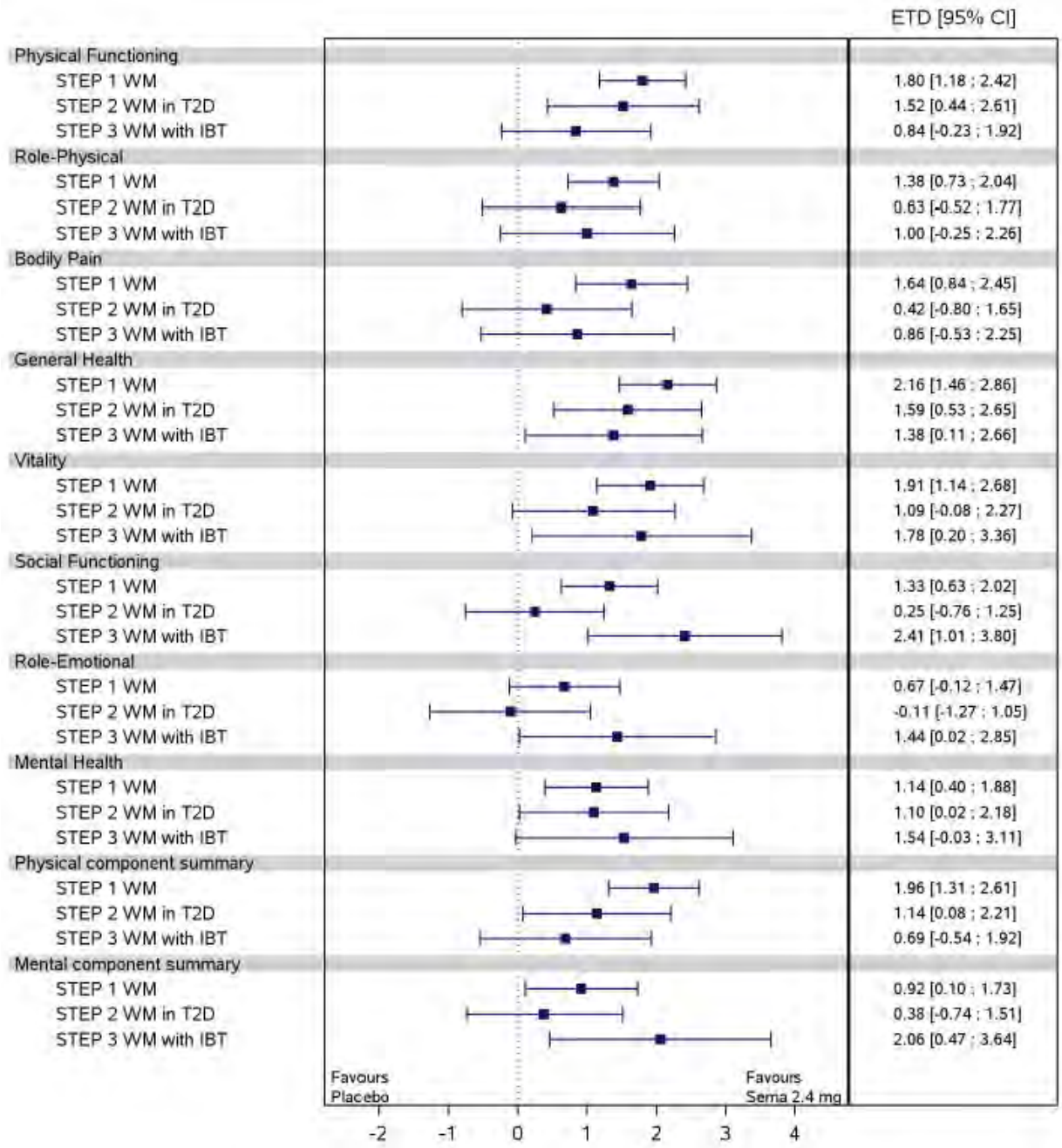
Figure 7.2.4.6 Antihypertensive medication during trial – in-trial (copied from Figure 11-11, Study NN9536-4376)



N: Number of subjects receiving antihypertensive medication between baseline (week 20) and week 68 out of the total treatment group; sema: semaglutide

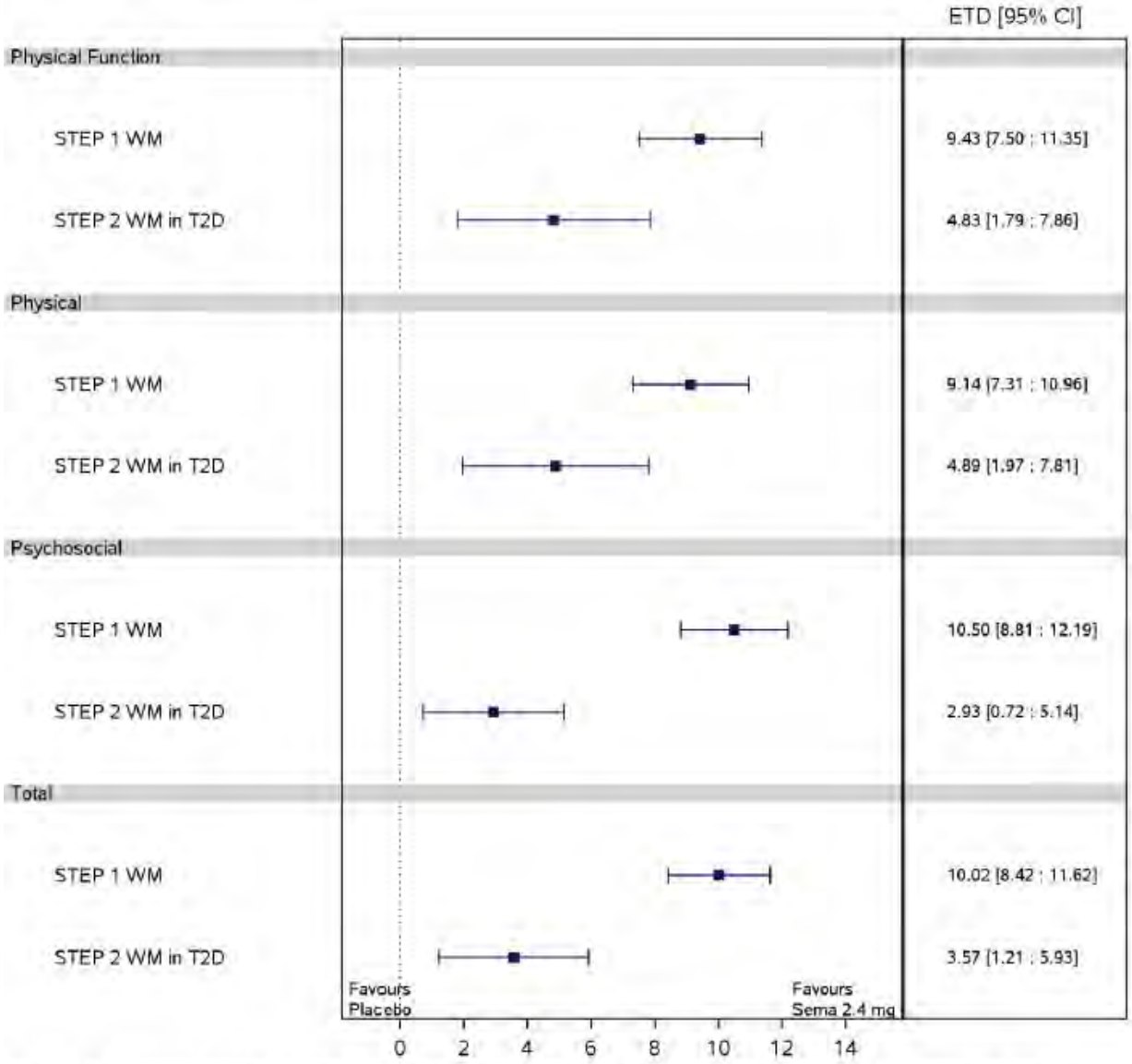
%: Percentages are based on subjects with an observation at the visit. Observed data from the in-trial period.

Figure 7.4.1 SF-36 endpoints change from baseline to week 68 - forest plot - treatment policy estimand - STEP 1, 2 and 3 (copied from Figure 2-9, PRO Report)



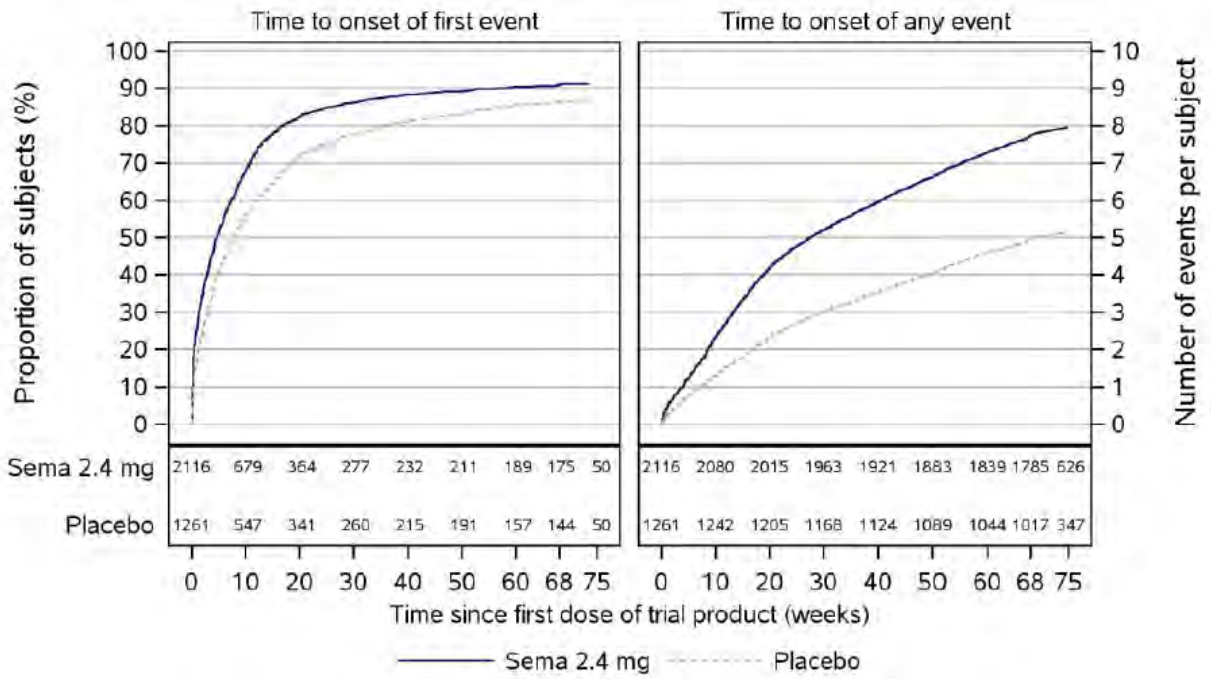
SF-36: Short Form 36 v2.0 acute, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

Figure 7.4.2 IWQOL-Lite-CT endpoints change from baseline to week 68 - forest plot - treatment policy estimand - STEP 1 and 2 (copied from Figure 2-10, PRO Report)



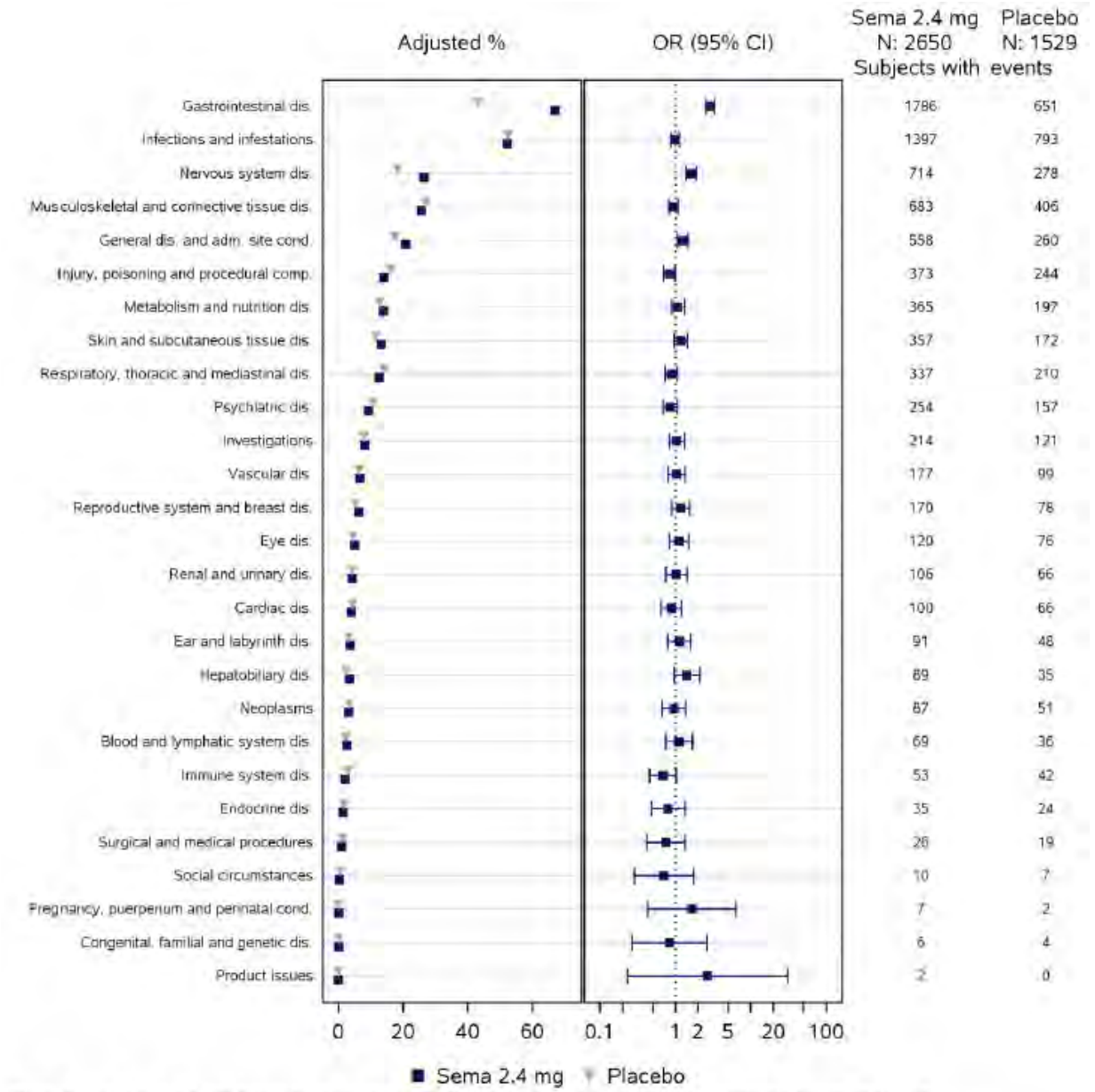
IWQOL-Lite-CT: Impact of Weight on Quality of Life-Lite for Clinical Trials, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

Figure 8.4.1.1.1 AEs – plot over time – on-treatment – phase 3a dose escalation group (copied from Figure 2-5, Summary of Clinical Safety)



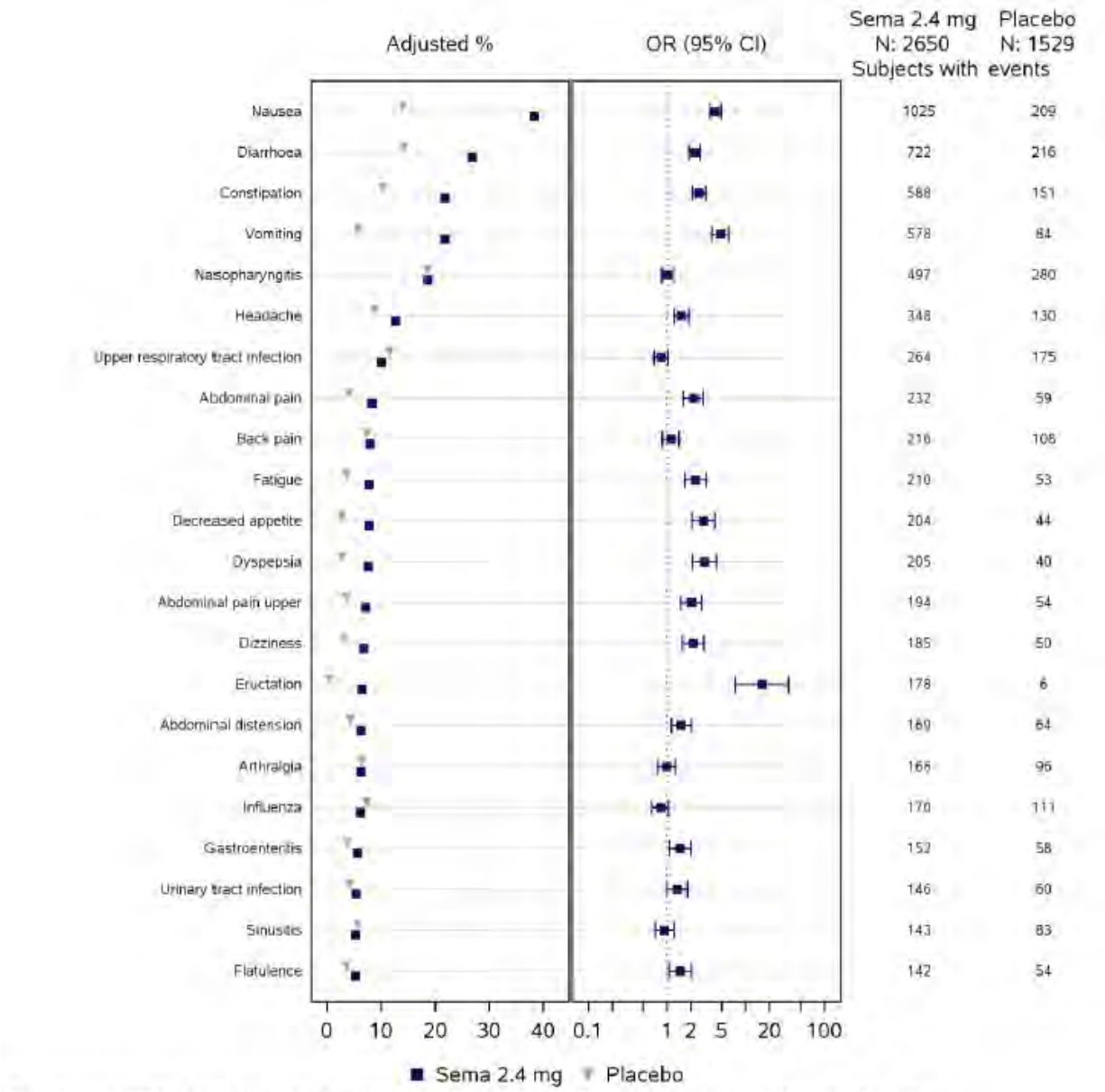
Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Numbers shown in the lower panel are subjects at risk.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

Figure 8.4.1.1.2 AEs – statistical analysis by SOC – forest plot – on-treatment – phase 3a pool (copied from Figure 2-6, Summary of Clinical Safety)



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
Sorted in descending order by system organ class based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
%: Percentage of subjects experiencing at least one event, OR: Odds ratio, CI: Confidence interval, N: Number of subjects, dis.: disorders, cond.: conditions, adm.: administration, comp.: complications. Neoplasms include benign, malignant and unspecified (incl cysts and polyps)
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 trial as factors.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

Table 8.4.1.1.3 AEs – statistical analysis by PT – most frequent (≥ 5%) – forest plot – on-treatment – phase 3a pool (copied from Figure 2-7, Summary of Clinical Safety)



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms.
Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
%: Percentage of subjects experiencing at least one event. OR: Odds ratio. CI: Confidence interval. N: Number of subjects
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 trial as factors.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

Figure 8.4.1.3.1 Adverse events by preferred term - most frequent (>=5%) - on-treatment (copied from Figure 12-3, Study NN9536-4373)

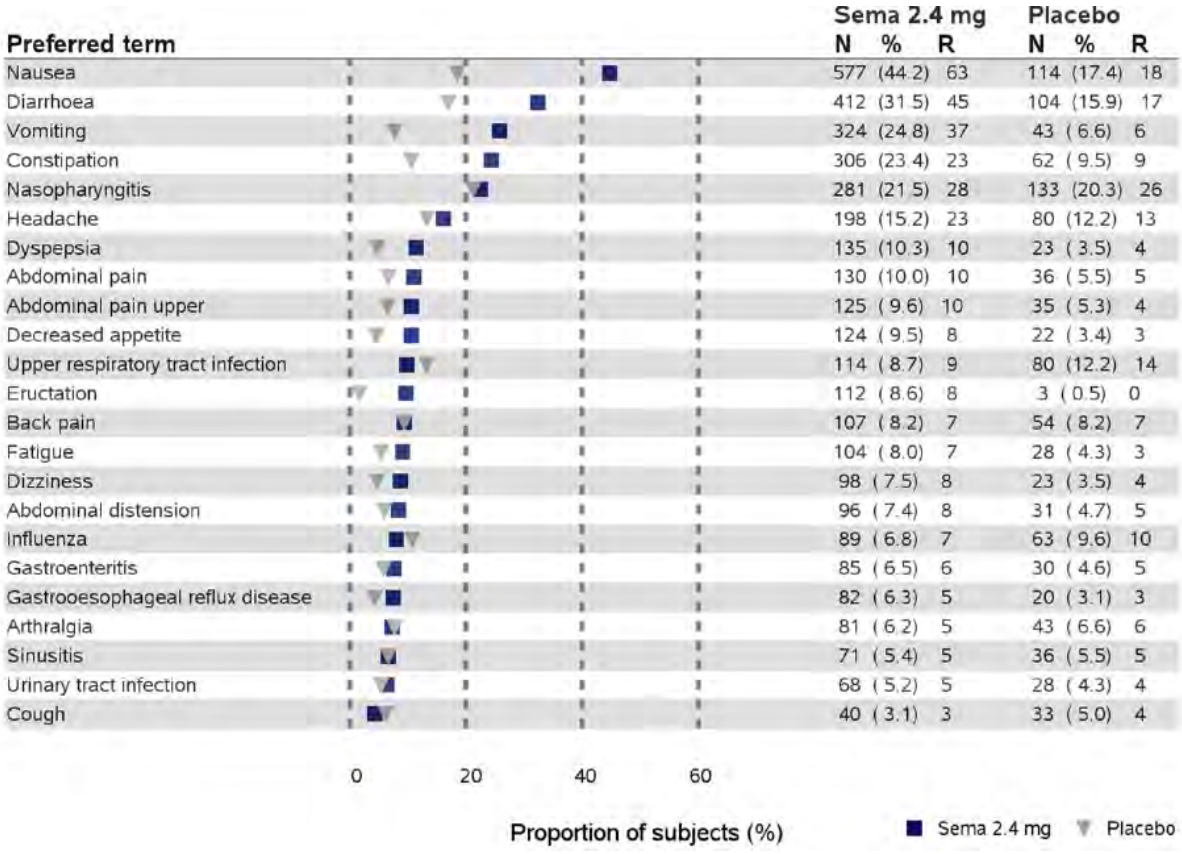
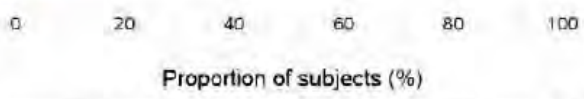


Figure 8.4.1.3.2 Adverse events by preferred term - most frequent (≥ 5%) - on-treatment (copied from Figure 12-3, Study NN9536-4374)

Preferred term	Sema 1.0 mg N	%	R	Sema 2.4 mg N	%	R	Placebo N	%	R
Nausea	129	(32.1)	37	136	(33.7)	47	37	(9.2)	9
Vomiting	54	(13.4)	18	88	(21.8)	35	11	(2.7)	2
Diarrhoea	89	(22.1)	30	86	(21.3)	26	48	(11.9)	12
Constipation	51	(12.7)	13	70	(17.4)	15	22	(5.5)	5
Nasopharyngitis	47	(11.7)	13	68	(16.9)	22	59	(14.7)	17
Upper respiratory tract infection	37	(9.2)	10	42	(10.4)	9	38	(9.5)	9
Decreased appetite	29	(7.2)	6	38	(9.4)	8	15	(3.7)	3
Headache	33	(8.2)	9	31	(7.7)	8	20	(5.0)	5
Fatigue	19	(4.7)	5	28	(6.9)	5	4	(1.0)	1
Back pain	28	(7.0)	6	27	(6.7)	6	14	(3.5)	3
Dyspepsia	27	(6.7)	5	25	(6.2)	6	5	(1.2)	1
Abdominal distension	9	(2.2)	2	24	(6.0)	6	11	(2.7)	2
Arthralgia	24	(6.0)	5	23	(5.7)	5	20	(5.0)	4
Flatulence	21	(5.2)	5	16	(4.0)	4	7	(1.7)	2
Gastroenteritis	24	(6.0)	5	14	(3.5)	3	13	(3.2)	3



N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, R: Event rate per 100 years, NEC: Not elsewhere classified.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days.
Adverse events with preferred terms reported for at least 5% of subjects in any arm. Sorted in descending order by preferred term based on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 22.1

Figure 8.4.1.3.3 Adverse events by preferred term - most frequent (>=5%) - on-treatment (copied from Figure 12-3, Study NN9536-4375)

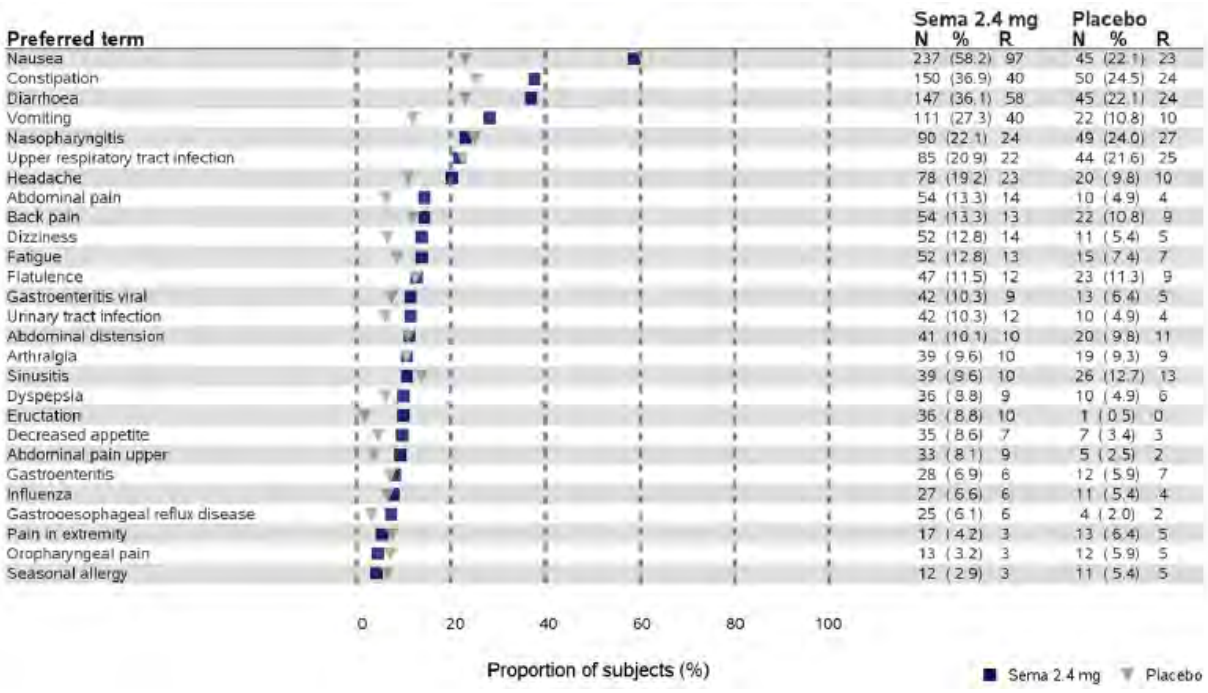
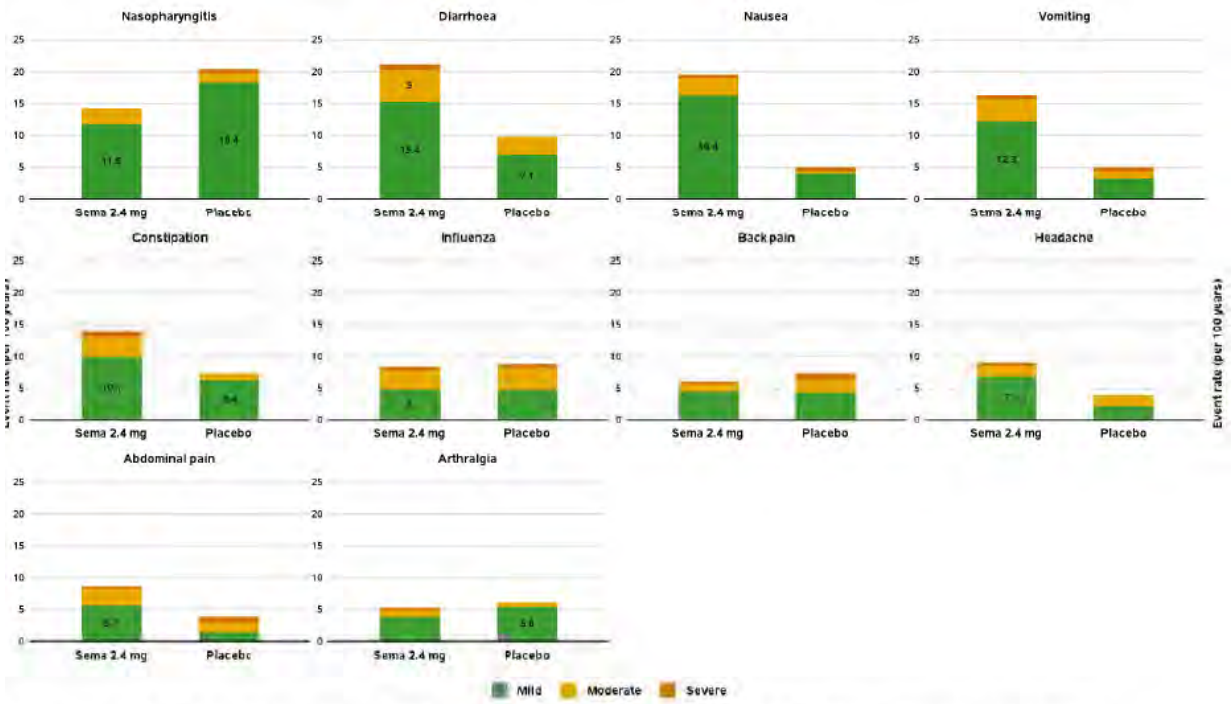
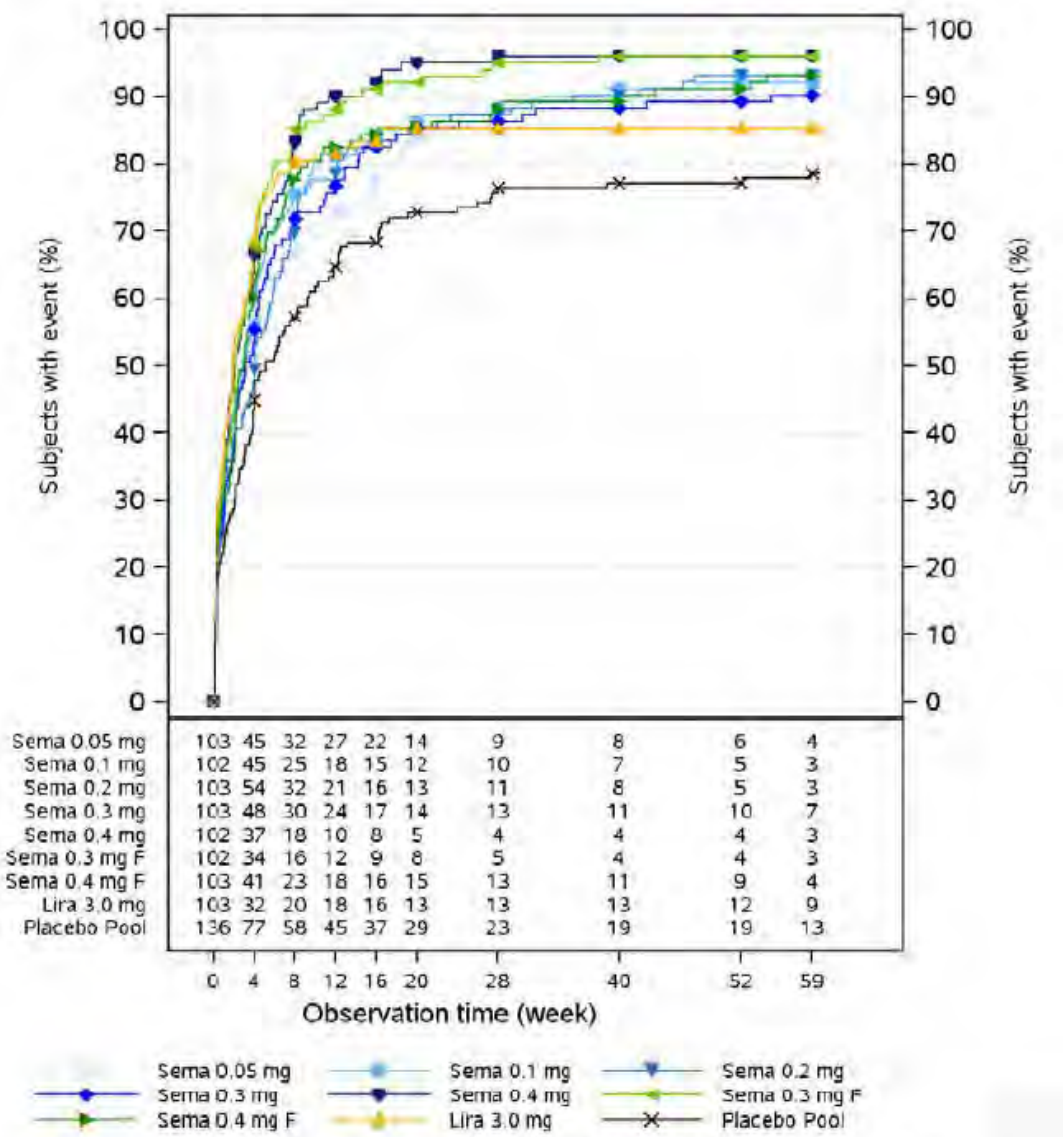


Figure 8.4.1.3.4 Adverse events by preferred term and severity - most frequent (>=5%) - bar plot - on-treatment - randomised period (copied from Figure 12-3, Study NN9536-4376)



Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Only AEs with onset in the randomised period included. Event rate per 100 years based on patient years of exposure. Adverse events with preferred terms reported for at least 5% of subjects in any arm. Event rates <5.0 are shown in bar plots but numbers are not displayed. Only randomised subjects in the safety analysis set contribute.
MedDRA version 22.1

Figure 8.4.1.4.1 Adverse events - proportion of subjects with first event over time - randomized active arms and placebo pool - plot - on-treatment - safety analysis set (copied from Figure 12-1, Study NN9536-4153)



On-treatment. Adverse events with onset date from first trial product administration to last trial product administration with a 7 weeks ascertainment window.
Bottom panels. At risk tables

Figure 8.4.1.4.2 Adverse events by preferred term - most frequent (≥5%) - summary plot - on treatment - safety analysis set (copied from Figure 12-3, Study NN9536-4153)

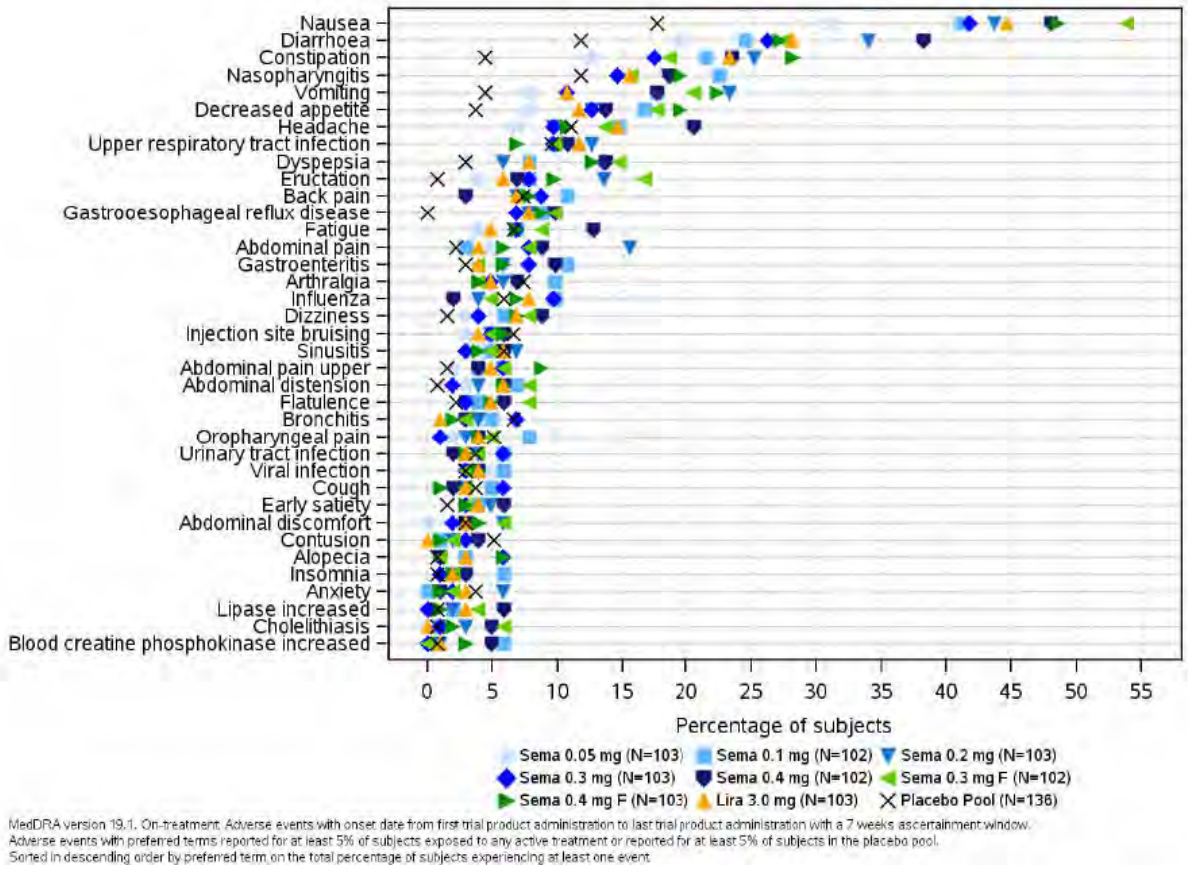
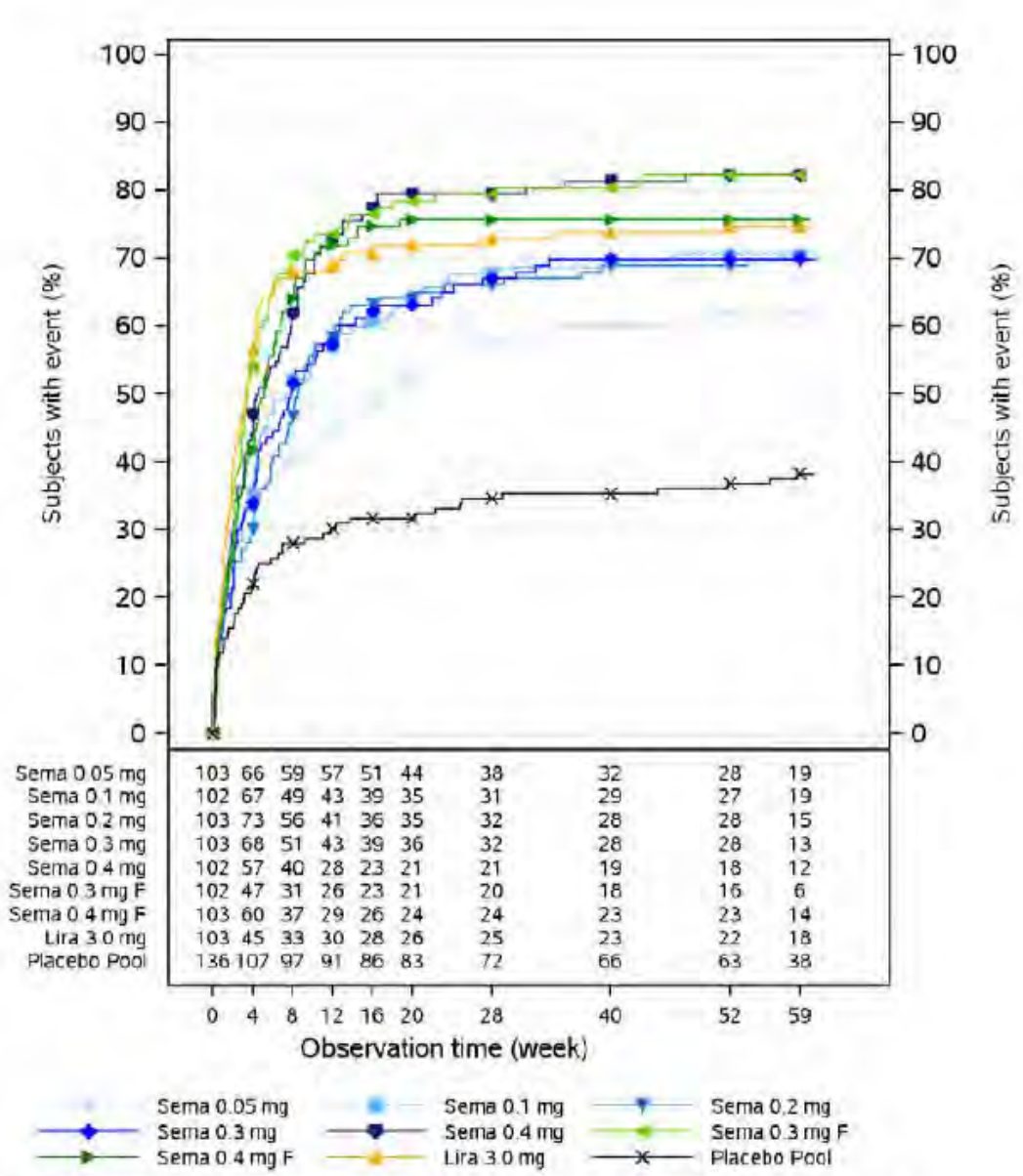


Figure 8.4.1.4.3 Gastrointestinal adverse events - pre-defined MedDRA search - proportion of subjects with first event over time - randomised active arms and placebo pool - plot - on-treatment - safety analysis set (copied from Figure 12-7, Study NN9536-4153)



On-treatment: Adverse events with onset date from first trial product administration to last trial product administration with a 7 weeks ascertainment window.
Bottom panels: At risk tables

Figure 8.4.4.4.1 Adverse events leading to premature discontinuation by preferred term - randomised active arms and placebo pool - summary plot - on-treatment - safety analysis set (copied from Figure 12‑5, Study NN9536-4153)

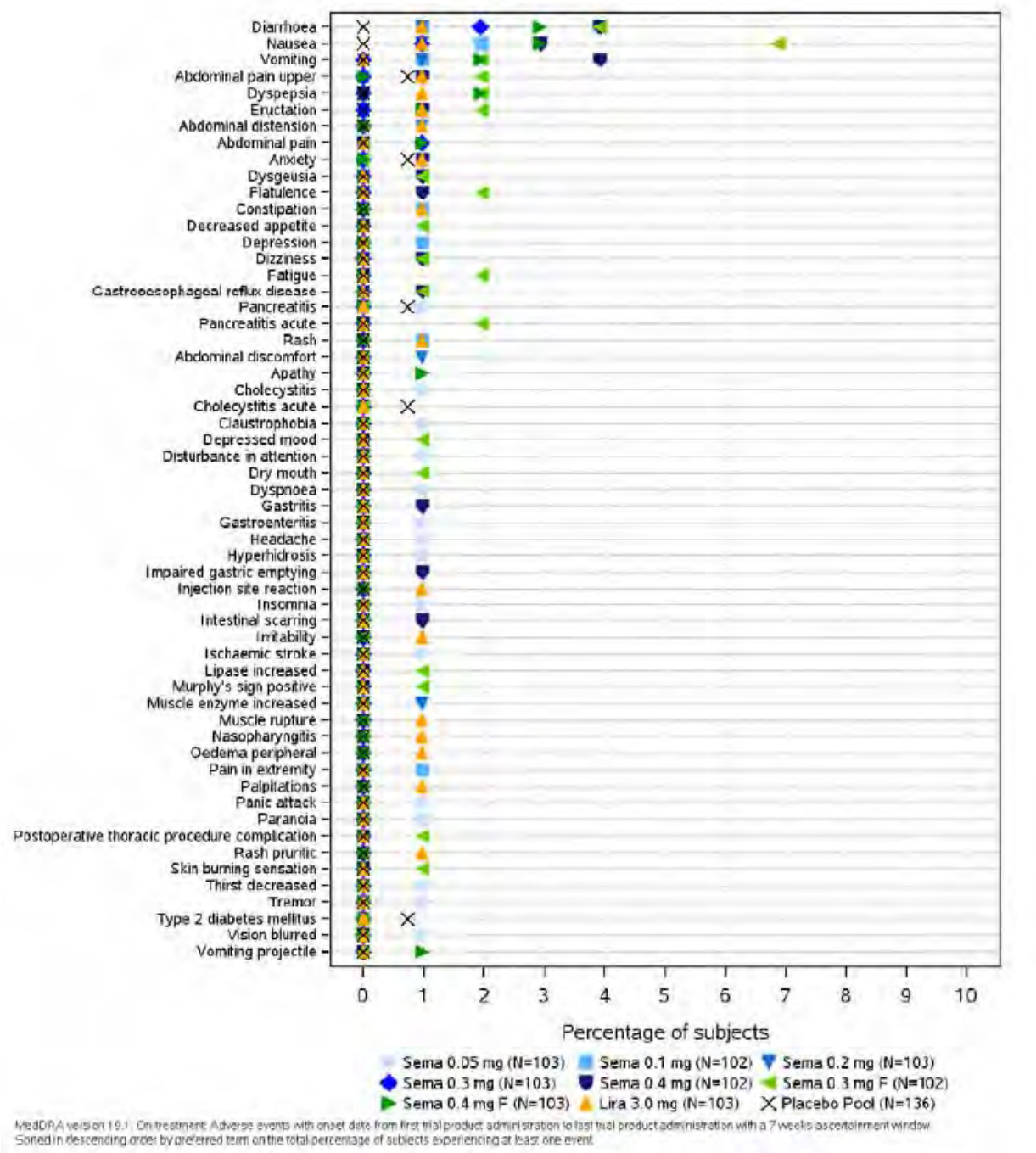
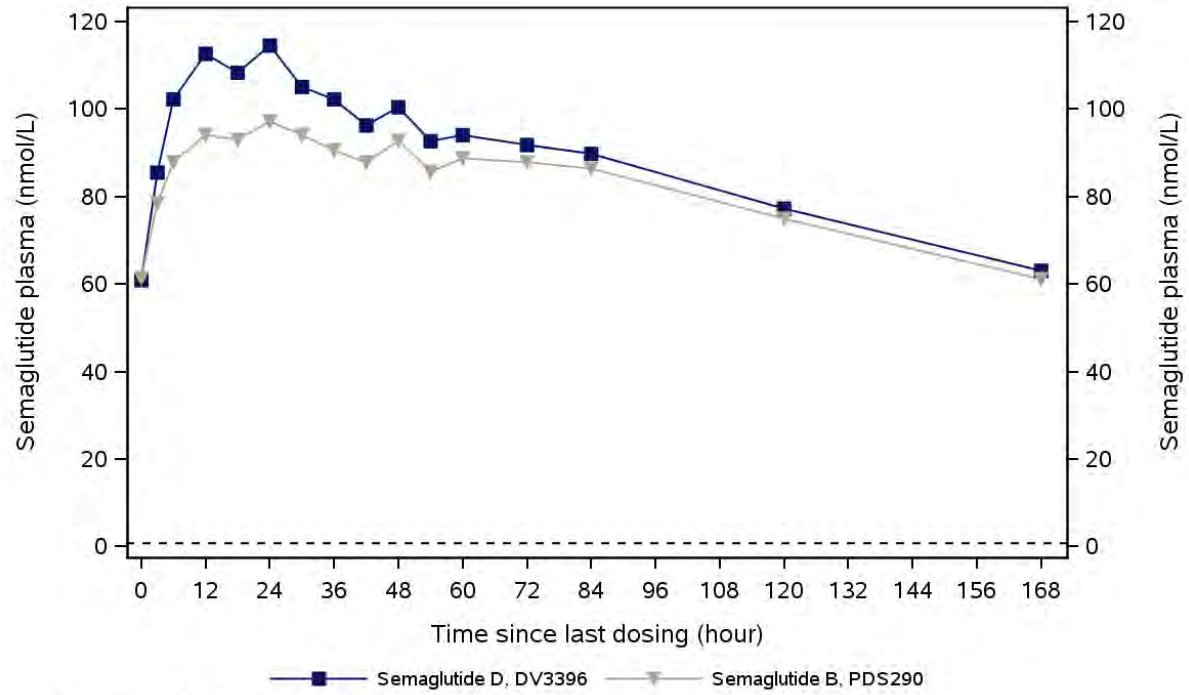
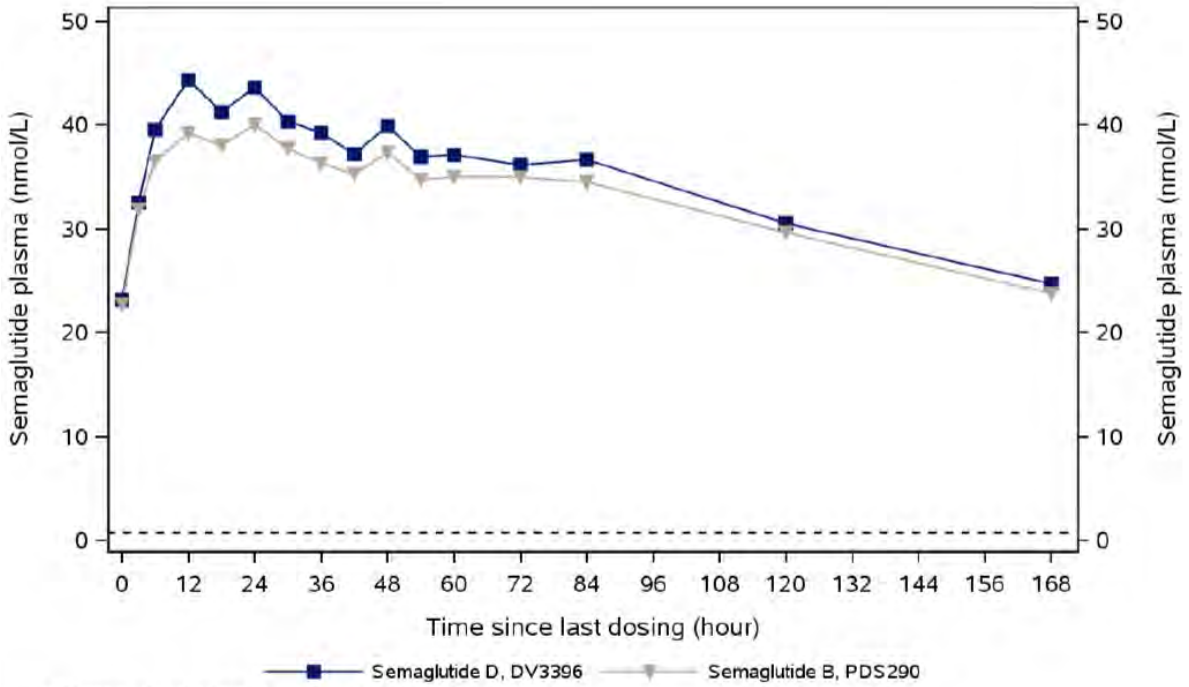


Figure 19.1.1.1.1 Semaglutide 2.4 mg dosing interval profiles at steady state – geometric mean plot – full analysis set (copied from Figure 11-1, Study NN9536-4590)



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

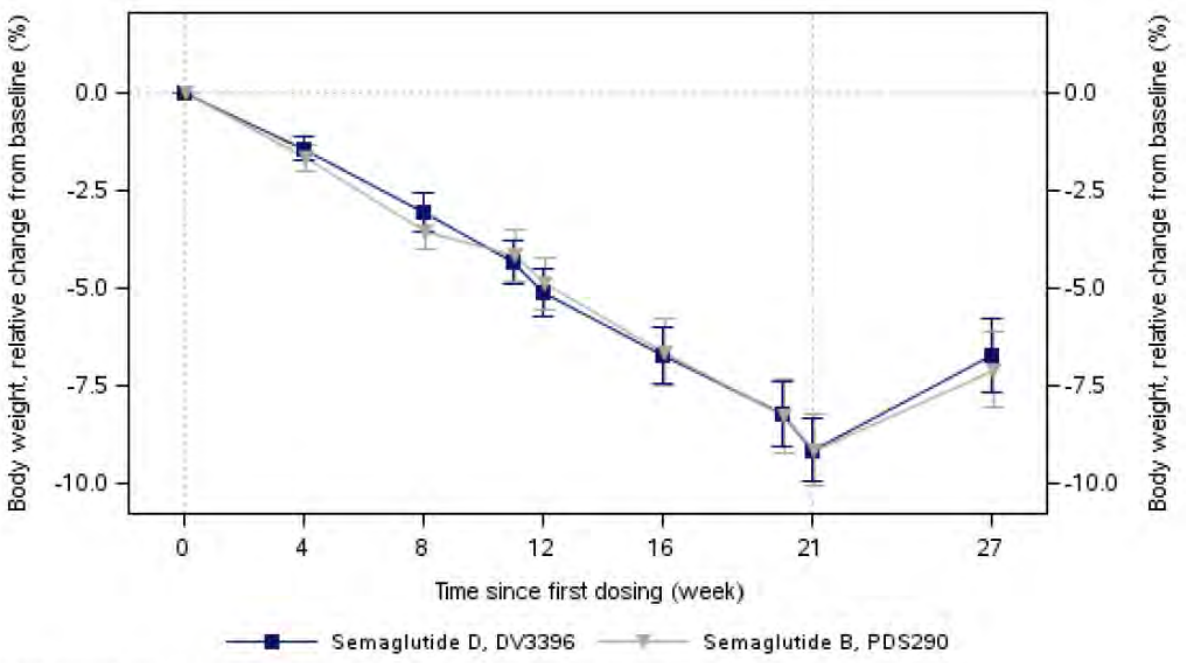
Figure 19.1.1.1.2 Semaglutide 1.0 mg dosing interval profiles at steady state – geometric mean plot – full analysis set (copied from Study NN9536-4590)



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

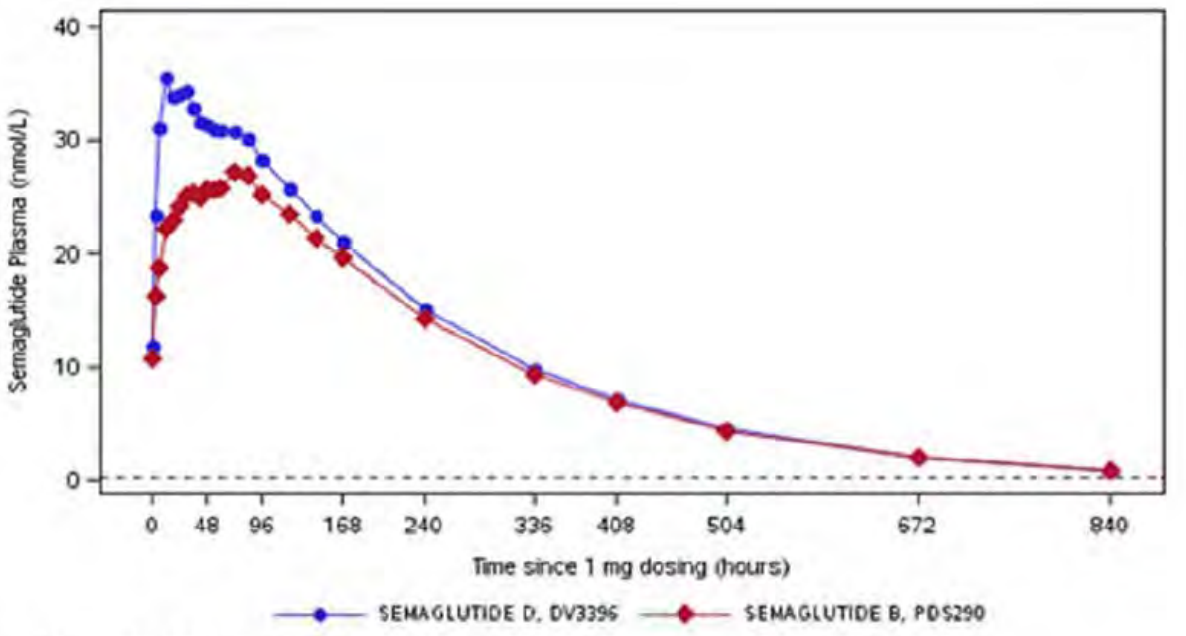
Figure 19.1.1.1.3 Change in body weight (%) from baseline – mean plot – full analysis set (copied from Figure 11-3, StudyNN9536-4590)

Cross-



Vertical reference lines represent first and last dosing of semaglutide.
Error bar is +/- standard error of mean.

Figure 19.1.1.2.1 Semaglutide profiles after 1 mg dose of semaglutide s.c.– geometric mean plot - full analysis set (copied from Figure 11-1, Study NN9535-4588)



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

Figure 19.1.1.2.2 Semaglutide profiles after 0.25 mg dose of semaglutide s.c. at steady state – geometric mean plot - full analysis set (copied from Figure 11-2, Study NN9535-4588)

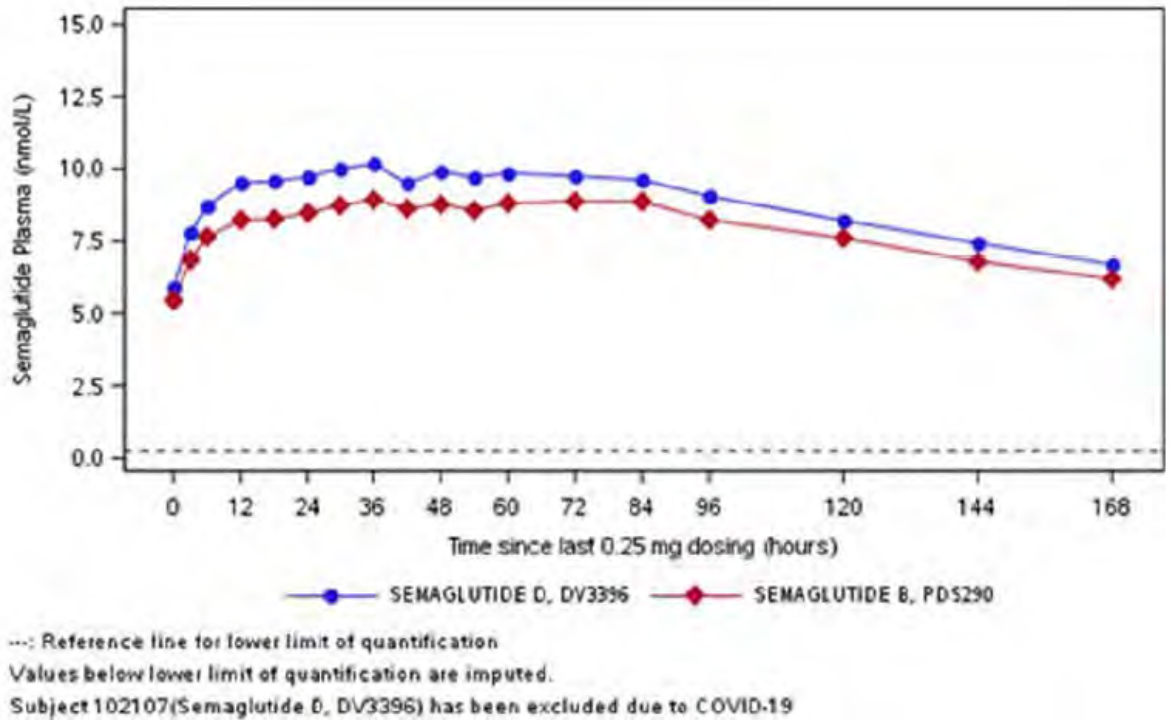


Figure 19.1.2.1.1 Gastric emptying – paracetamol concentration profile (copied from Figure 11-1, Study NN9536-4455)

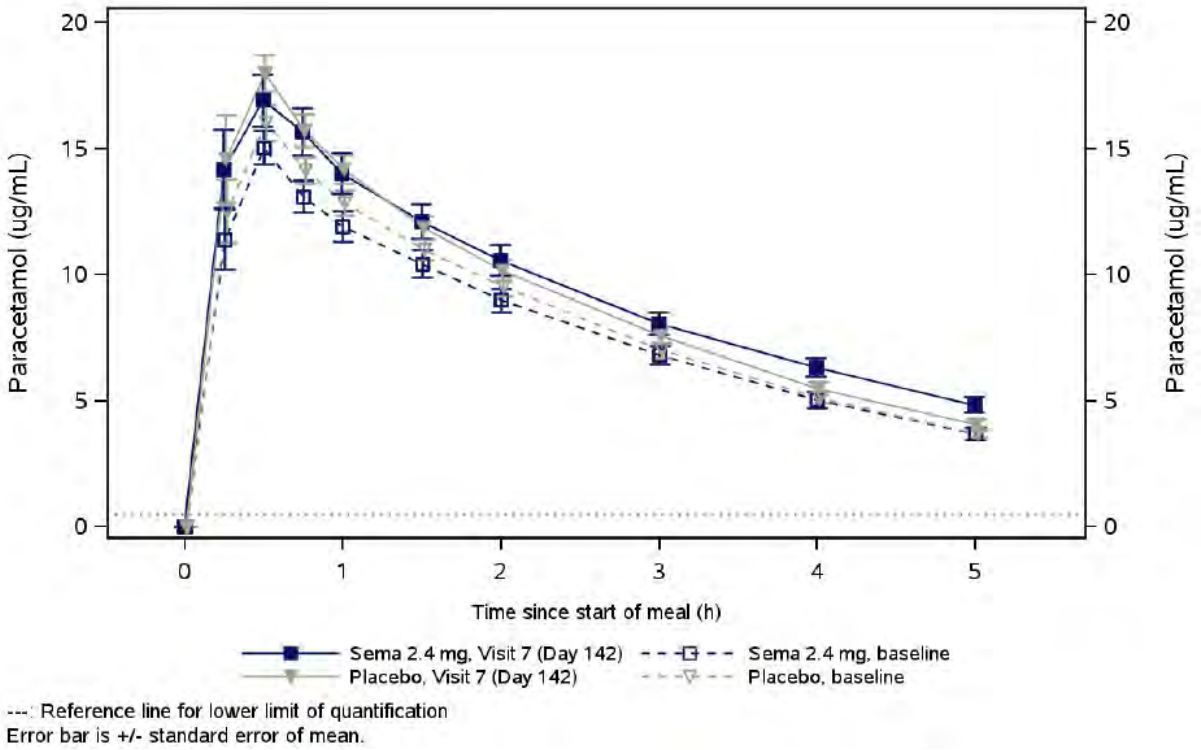
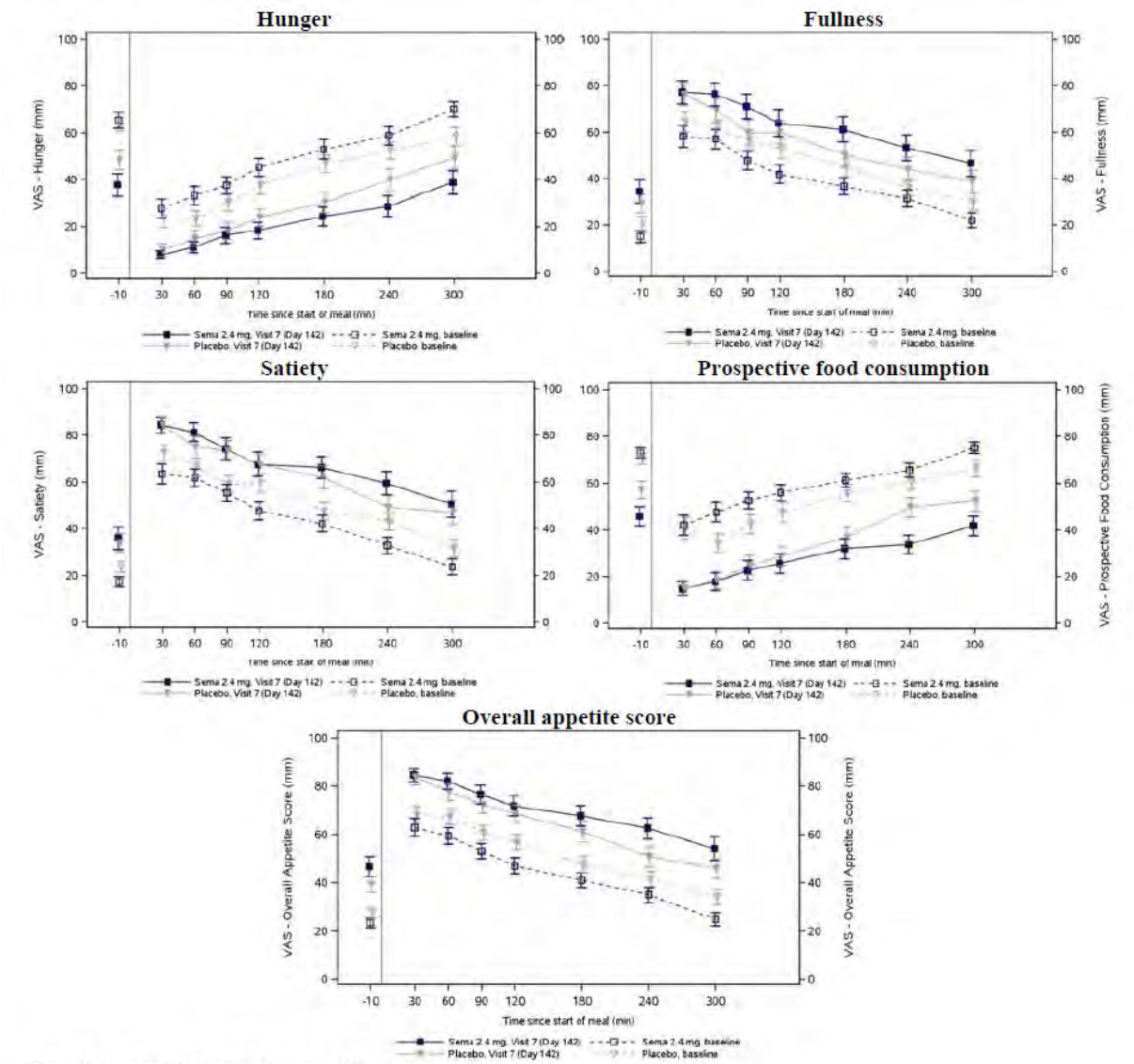
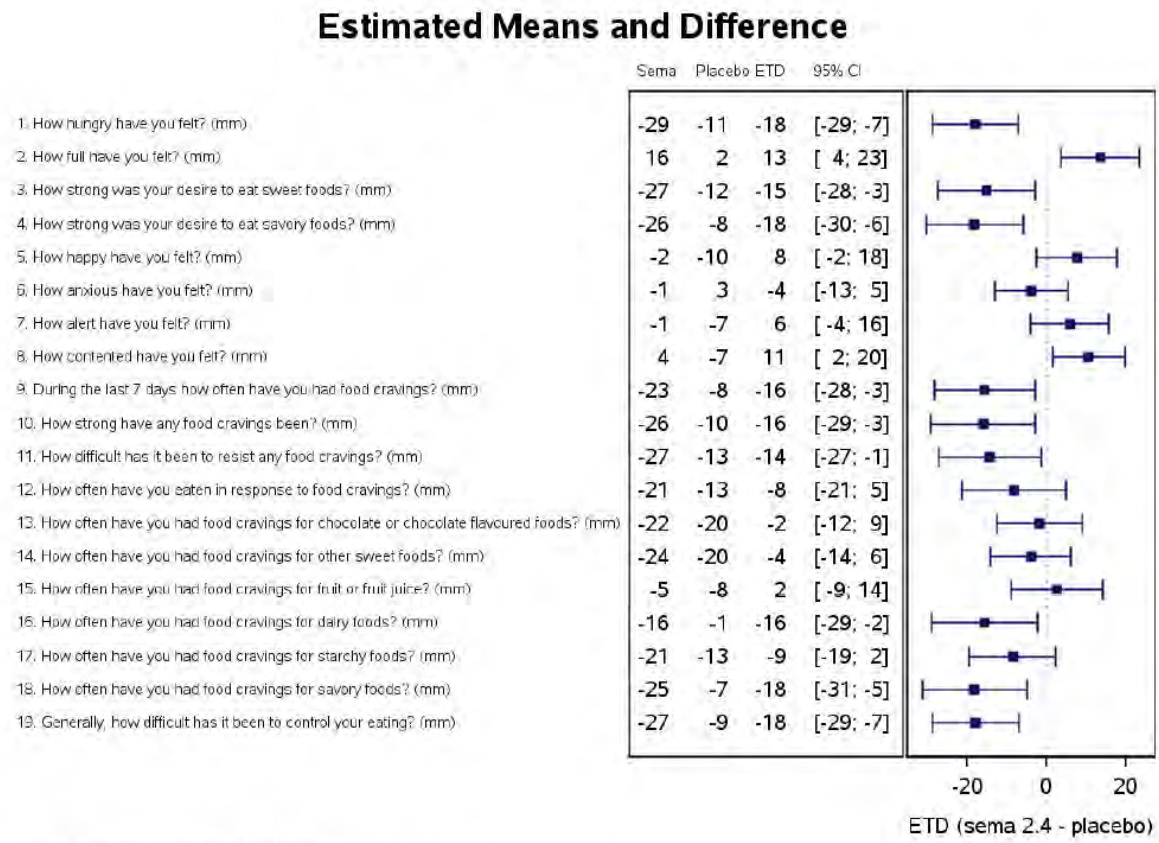


Figure 19.1.2.1.2 Hunger, fullness, satiety, prospective food consumption and OAS – VAS (copied from Figure 11-2, Study NN9536-4455)



Error bars are +/- standard error of the mean
Vertical reference lines indicate start of the breakfast.
Hunger: 0 mm = not hungry at all. 100 mm = I have never been more hungry
Fullness: 0 mm = not at all full. 100 mm = totally full
Satiety: 0 mm = I am completely empty. 100 mm = I cannot eat another bite
Prospective food consumption: 0 mm = Nothing at all. 100 mm = a lot
Overall appetite score = (satiety + fullness + [100 - hunger] + [100 - prospective food consumption])/4

Figure 19.1.2.1.3 Control of Eating Questionnaire (COEQ) at week 20 (copied from Figure 11-6, Study 9536-4455)



ETD: Estimated treatment difference
1: 0 mm = not at all hungry, 100 mm = Extremely hungry
2: 0 mm = Not at all full, 100 mm = Extremely full
3, 4, 10 : 0 mm = Not at all Strong, 100 mm = Extremely strong
5: 0 mm = Not at all happy, 100 mm = Extremely happy
6: 0 mm = Not at all anxious, 100 mm = Extremely anxious
7: 0 mm = Not at all alert, 100 mm = Extremely alert
8: 0 mm = Not at all contented, 100 mm = Extremely contented
9: 0 mm = Not at all, 100 mm = Very often
11, 19: 0 mm = Not at all difficult, 100 mm = Extremely difficult
12: 0 mm = Not at all, 100 mm = after every one
13, 14, 15, 16, 17, 18 : 0 mm = Not at all, 100 mm = Extremely often

Figure 19.1.3.1.1 Forest plot of covariate analysis for semaglutide exposure expressed as steady-state dose-normalised average semaglutide concentrations relative to a reference subject (copied from Figure 4, Modelling Study 2)

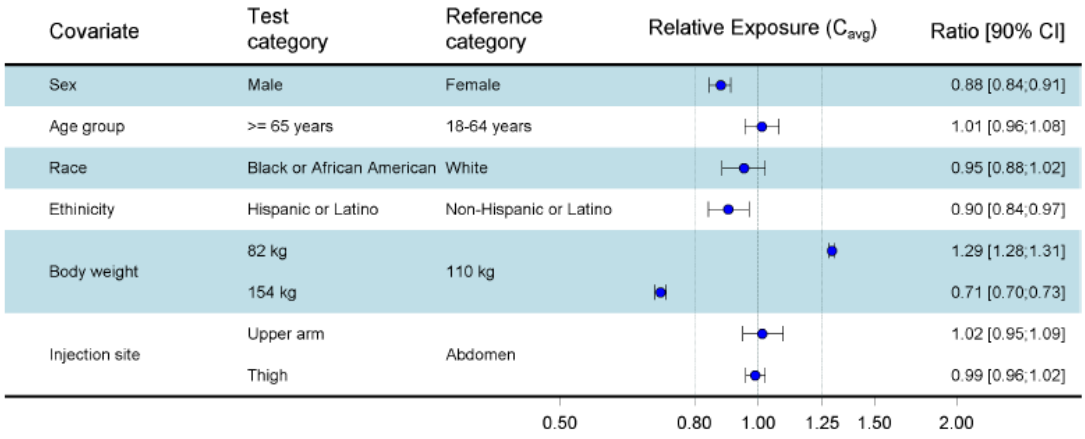
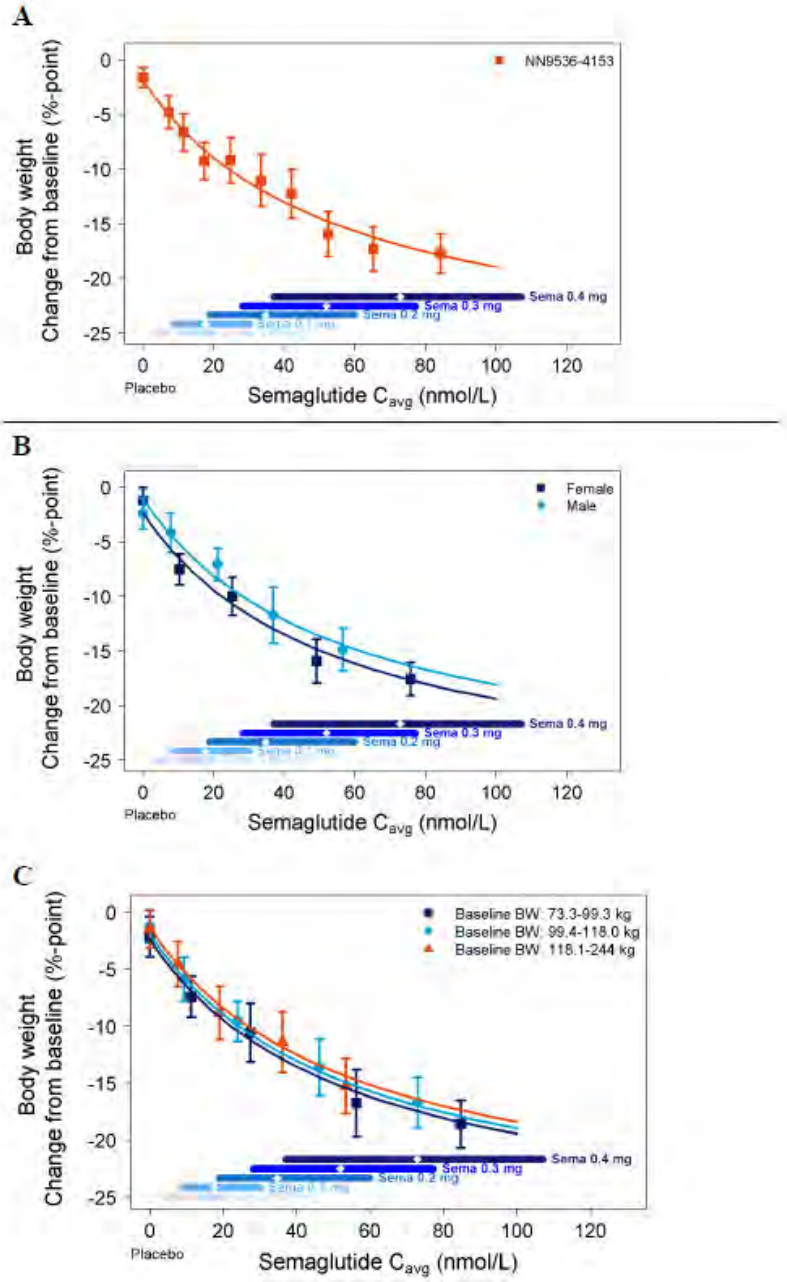
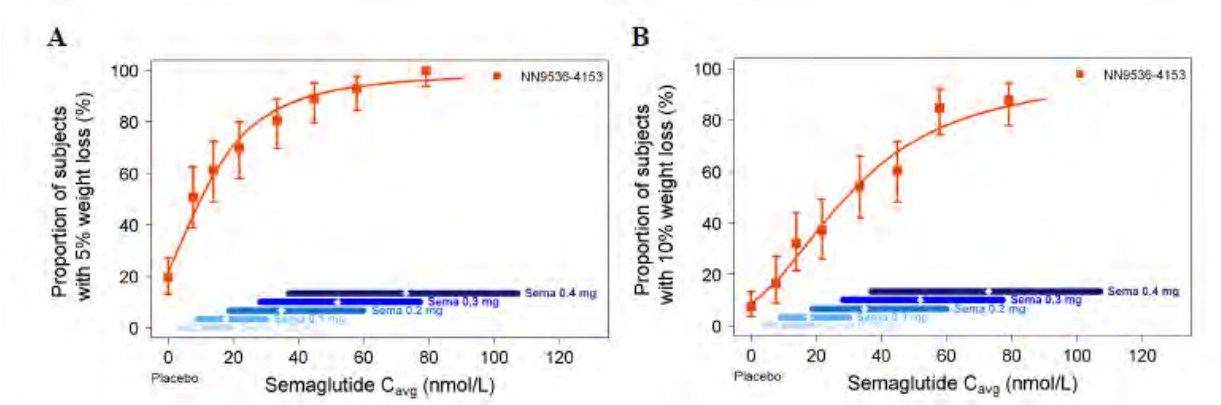


Figure 19.1.3.1.2 Body weight change from baseline versus exposure of semaglutide for all subjects (A) and shown by sex (B) and body weight quantile (C) (copied from Figure 7, Modelling Report 2)



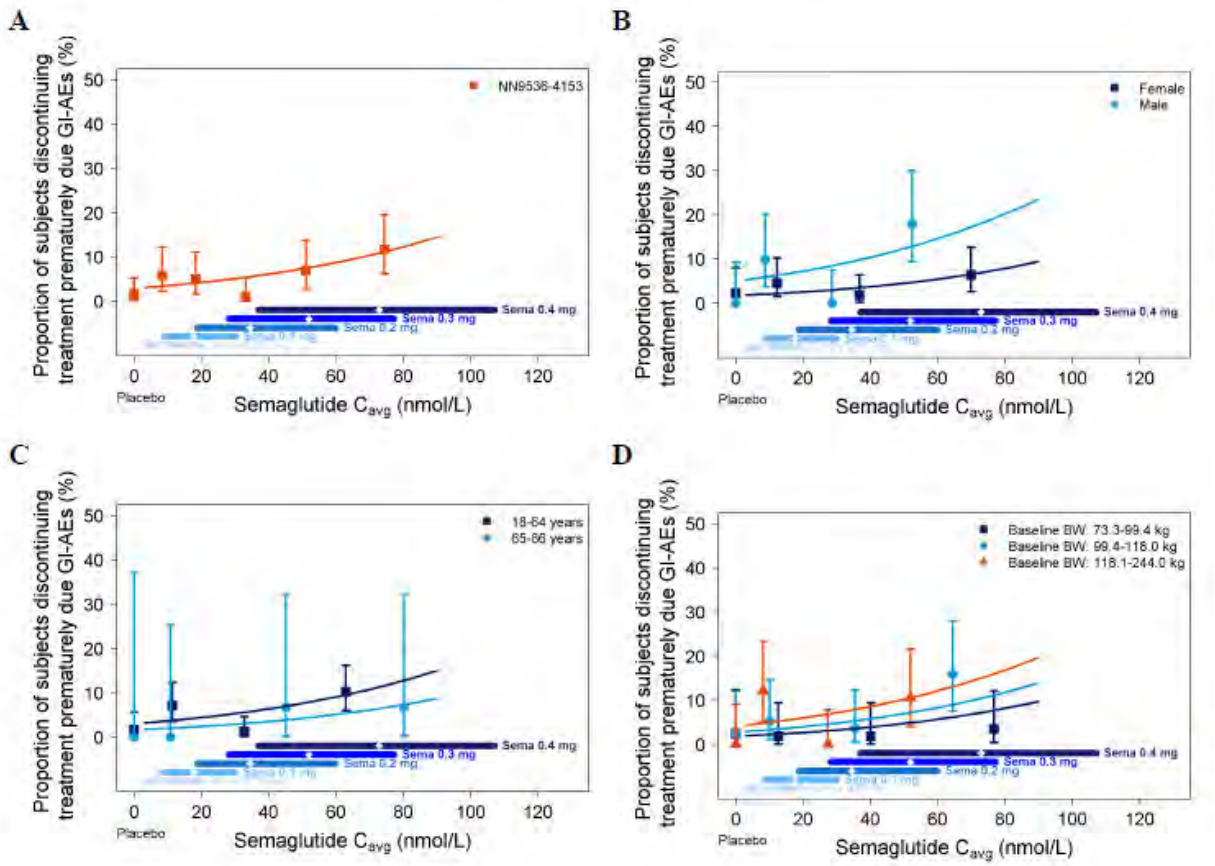
Data are mean body weight changes with 95% CI obtained after 52 weeks versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-derived exposure-response relations. Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges. Data from trial 4153 excluding treatment with fast dose escalation.

Figure 19.1.3.1.3 Proportions of subjects reaching at least 5 % (A) and 10% (B) weight loss versus semaglutide exposure (copied from Figure 8, Modelling Report 2)



Data are mean proportions with 95%CI versus exposure expressed as quantiles of model-derived C_{avg} values plus placebo (at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-based estimates for each trial population. The horizontal lines with diamonds along the abscissa represent medians and 95% exposure ranges for each dose level. Data from trial 4153 excluding treatment with fast dose escalation.

Figure 19.1.3.1.4 Proportion of subjects discontinuing treatment due to GIAEs versus exposure for all subjects (A), by sex (B) by age group (C) and by BW quantile (D) (copied from Figure 9, Modelling Report 2)



Data are mean response values with 95% CI versus exposure expressed as quantiles of C_{avg} (plus placebo at 0 nmol/L). Lines through data represent covariate-adjusted model-derived estimates for each group of subjects. Horizontal lines with diamonds along the x-axes represent median and 95% CI exposure ranges for each dose level. Data from trial 4153 excluding treatment with fast dose escalation.

Figure 19.1.3.2.1 Dose proportionality plots for semaglutide exposure in subjects STEP 1 (A) and STEP 2 (B) (copied from Figure 5-3, Modelling report 3)

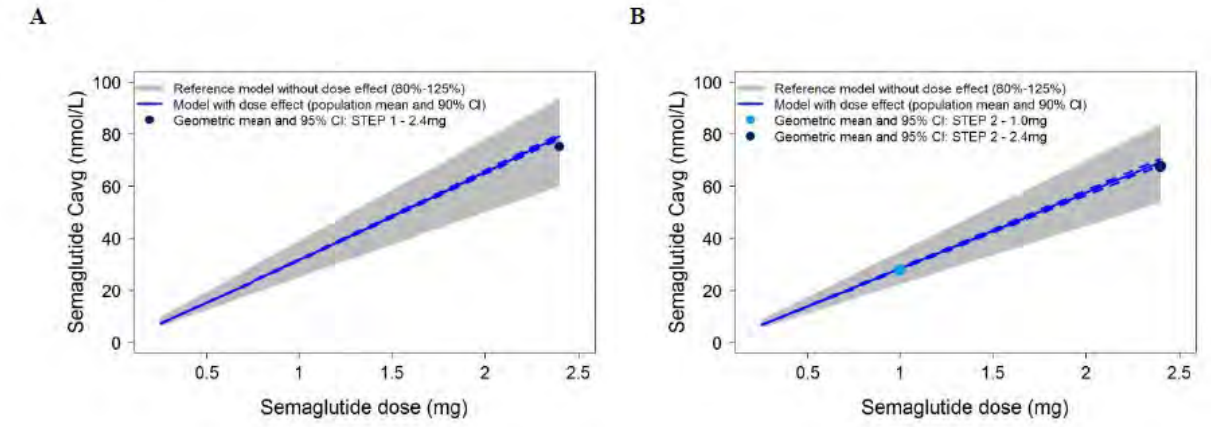
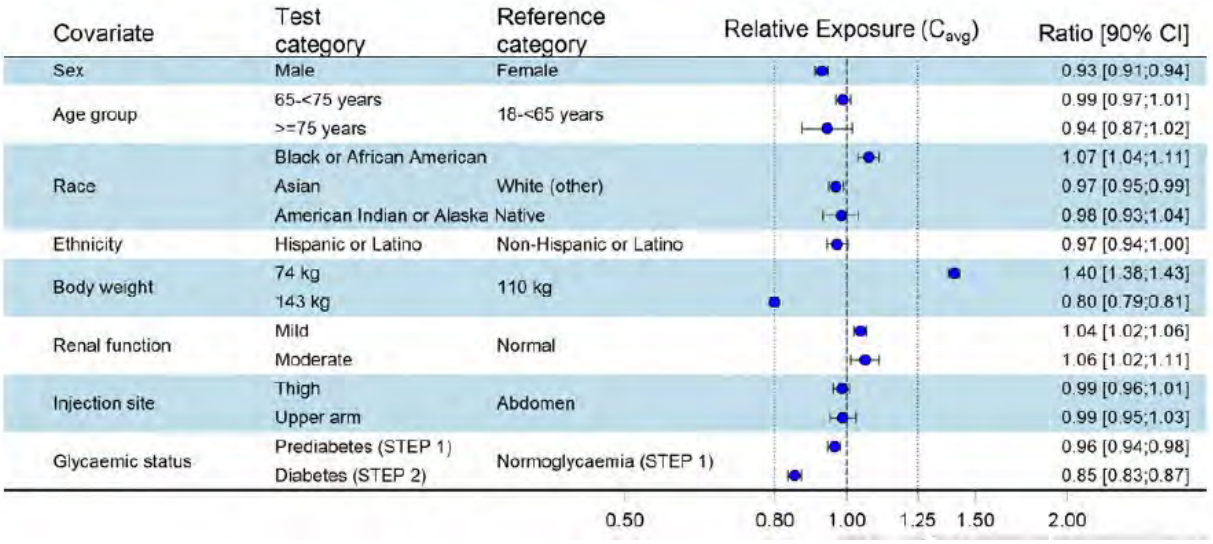
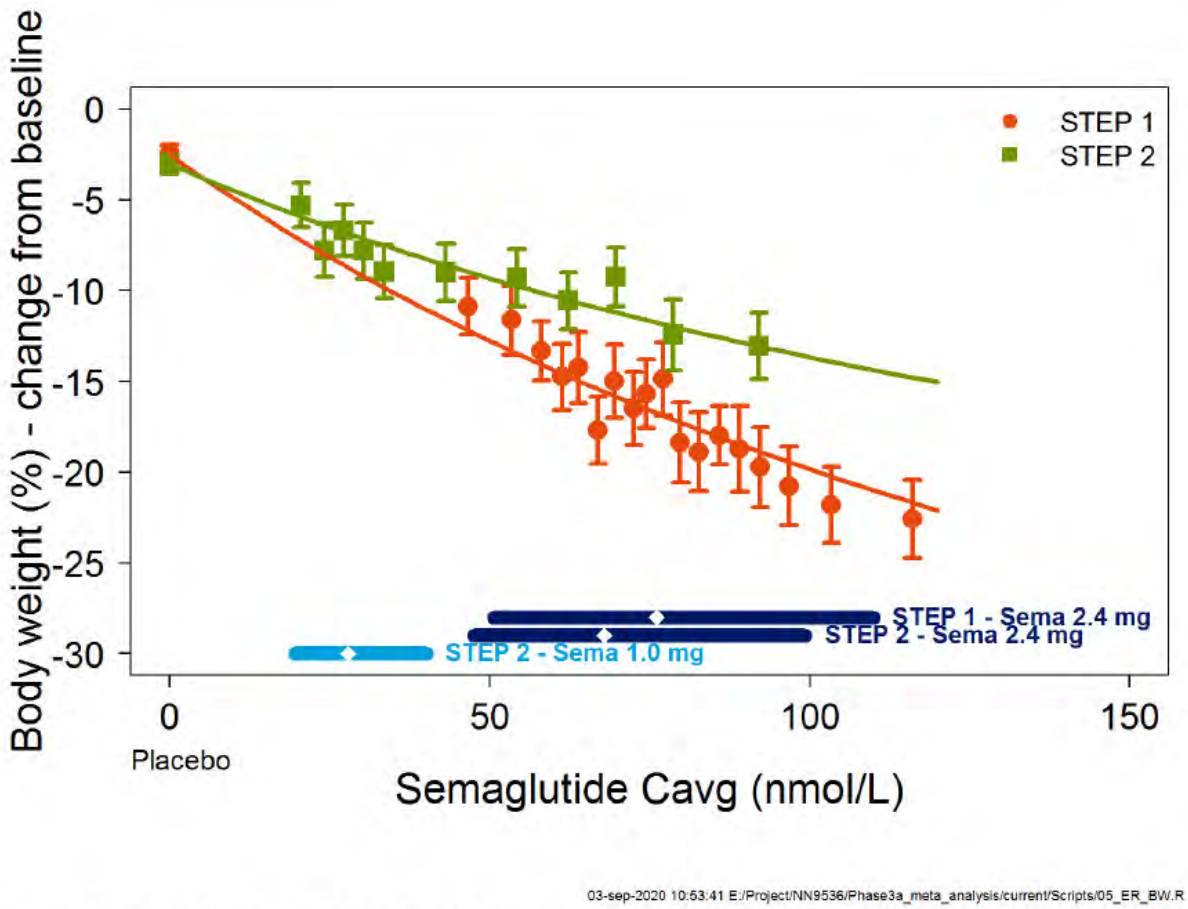


Figure 19.1.3.2.2 Forest plot of covariate effects for semaglutide exposure (copied from Figure 5-4, Modelling Report 3)



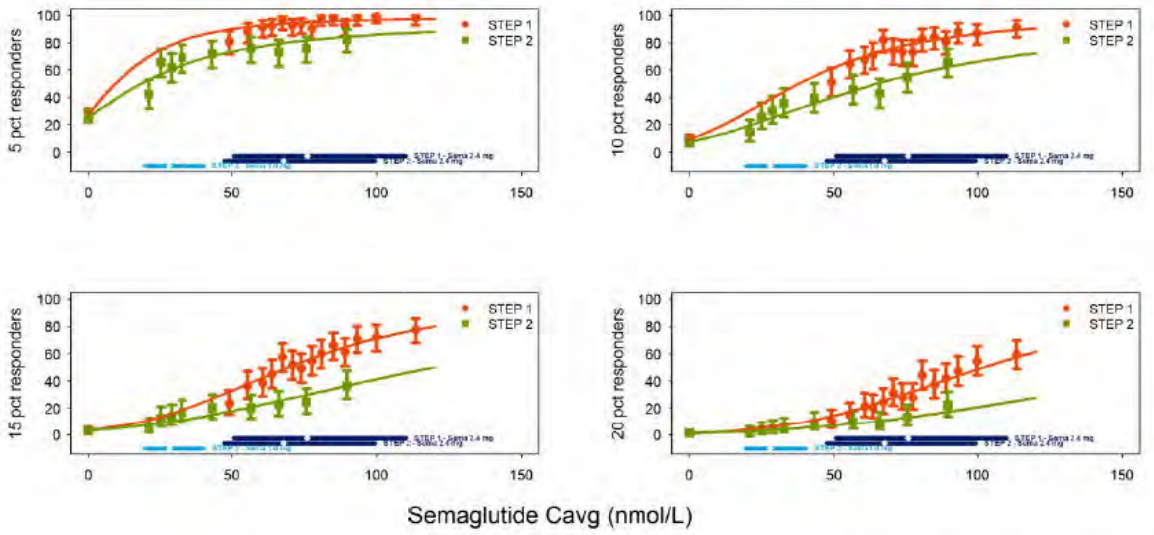
Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino, normoglycaemic (STEP 1) white female aged 18-<65 years, with a body weight of 110 kg and normal renal function, who injected in the abdomen). The forest plot and the column to the right show means and 90% CI for the relative exposures. Body weight test categories (74 and 143 kg) represent the 5% and 95% percentiles, respectively in the data set. There were 1 subject with severe renal impairment included in the moderate group. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80;1.25).

Figure 19.1.3.2.3 Body weight % change from baseline for subjects versus semaglutide exposure by trial (copied from Figure 5-9, Modelling Report 3)



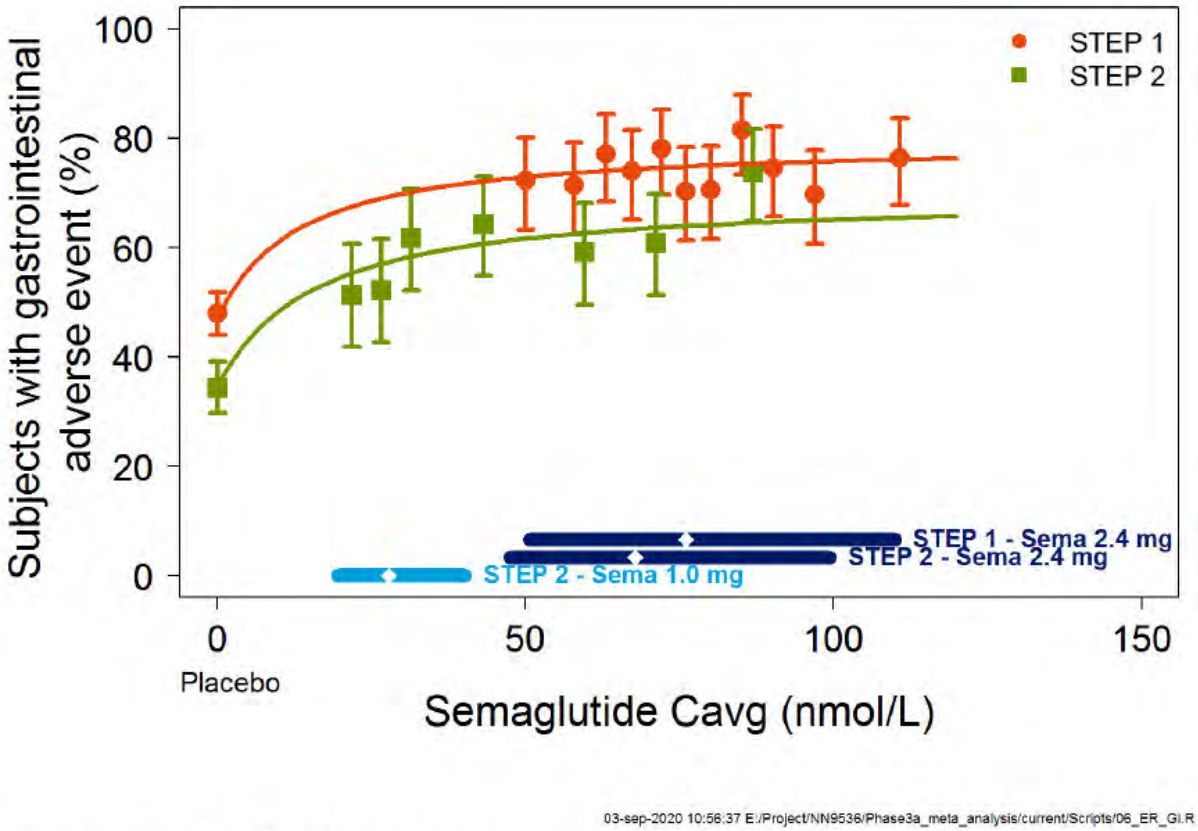
Data points with error bars are mean body weight changes with 95% CI obtained after 68 weeks of treatment versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nmol/L). Lines through data are covariate-adjusted model-derived exposure-response relations. Horizontal lines with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

Figure 19.1.3.2.4 Proportions of subjects reaching at least 5%, 10%, 15% and 20% weight loss versus semaglutide exposure (copied from Figure 5-15, Modelling Report 3)



Data are proportions with 95% CI versus exposure expressed as quantiles of model-derived C_{avg} values plus placebo (at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-derived estimates for each trial population. Horizontal lines with diamonds represent the median and 90% exposure range. Missing data at week 68 were predicted using a mixed model for repeated measures, using treatment as factor and baseline BW as covariate all nested within visit. Data from trials STEP 1 and STEP 2.

Figure 19.1.2.3.5 Proportion of subjects reporting GI adverse events of any kind and severity for all subjects (copied from Figure 5-17, Modelling report 3)



Data are proportions with 95% CI versus exposure expressed as quantiles of model-derived C_{avg} values plus placebo (at C_{avg} of 0 nmol/L). Horizontal lines with diamonds represent the median and 90% exposure range. The lines through data represent covariate-adjusted model-derived estimates for each trial population, using the on-treatment safety analysis set. Data from trials STEP 1 and STEP 2.

20. Attachment: additional evaluation material

NA.

21. Information about the evaluator

Appendix: study summary and commentary

NA.

Therapeutic Goods Administration

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https://www.tga.gov.au

Document 4

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: Semaglutide

Product name: WEGOVY

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Submission number: PM-2022-04980-1-5

eSubmission number: e005802

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
Ab	Antibody
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification
ATTD	Advanced Technologies & Treatments for Diabetes
AUC	Area under the curve
BG	Blood glucose
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
BSV	Between subject variability
BW	Body weight
C_{avg}	Average concentration over dosing interval
CDC	Centres for Disease Control and Prevention
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CLAE	Clinical laboratory adverse event
CL/F	Clearance / absorbed fraction
COA	Clinical outcome assessment
CoEQ	Control of eating questionnaire

Abbreviation	Meaning
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
C-SSRS	Columbia Suicidality Severity Rating Scale
CTZ1	Type 1 c-telopeptide
CV	Coefficient of variation
CWRES	Conditional weighted residual
DBP	Diastolic blood pressure
DHEAS	Dehydroepiandrosterone sulfate
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4 (inhibitors)
DRE	Disease related event
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ETD	Estimated treatment difference
ETR	Estimated treatment ratio
EU	European Union
F	Bioavailability
FAS	Full analysis set
FDA	US Food and Drug Administration
FPFV	First patient first visit
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GCP	Good clinical practice

Abbreviation	Meaning
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP-1 RA	Glucagon-like-peptide-1 receptor antagonist
HbA_{1c}	Glycated haemoglobin
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HLGT	High-level group term, MedDRA classification
HOMA-B	Homeostatic model assessment of beta cell function
HOMA-IR	Homeostatic model assessment of insulin resistance
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IIV	Inter-individual variability
INR	International normalised ratio
ISPAD	International Society for Pediatric and Adolescent Diabetes
IU	International units
IWQOL	Impact of Weight on Quality of Life questionnaire
IWRS	Interactive web response system
J2R-MI	Jump to reference – multiple imputation
k_a	Absorption rate constant
KDIGO	Kidney Disease: Improving Global Outcomes
LAM	Lactation amenorrhoea method
LAO	Last available observation
LC-MS/MS	Liquid chromatography with tandem mass spectroscopy
LDL	Low-density lipoprotein

Abbreviation	Meaning
LH	Luteinising hormone
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
LR	Logistic regression
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	Multiple endocrine neoplasia type 2
MMRM	Mixed model for repeated measures
MTC	Medullary thyroid carcinoma
MTD	Maximum tolerated dose
NA	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NONMEM	Nonlinear mixed effects modelling software
NTX1	Type 1 collagen n-telopeptide
NYHA	New York Heart Association
OFV	Objective function value
P1NP	Procollagen 1 n-terminal propeptide
PD	Pharmacodynamic
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
popPK	Population pharmacokinetic
PT	Preferred term, MedDRA classification
PYE	Patient years of exposure

Abbreviation	Meaning
PYO	Patient years of observation
QRS	Ventricular depolarisation period on ECG output
QT(L)	Ventricular depolarisation and repolarisation period on ECG output (length)
RD-MI	Multiple imputation using retrieved subjects
RSE	Residual standard error
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SBP	Systolic blood pressure
s.c.	Sub-cutaneous
SD	Standard deviation
SDS	Standard deviation score
SMPG	Self-measured plasma glucose
SOC	System organ class, MedDRA classification
STEP	Semaglutide Treatment Effect in People with obesity
SUSAR	Suspected unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
T4	Thyroxine
TEAE	Treatment emergent adverse event
TFL	Tables, figures and listings
TP-MI	Tipping point multiple imputation
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
V	Volume of distribution

Abbreviation	Meaning
VLDL	Very low-density lipoprotein
WHO	World Health Organisation

1. Submission details

1.1. Identifying information

Submission number	PM-2022-04980-1-5
eSubmission number	e005802
eSubmission sequences covered in this report	0006, 0007 and 0008
Sponsor	Novo Nordisk Pharmaceuticals Pty Ltd
Trade name	WEGOVY
Active substance	Semaglutide

1.2. Submission type

This is a Category 1, Type C (extension of indications) application relating to WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection. The application is to extend the weight loss indication to include adolescents from 12 years of age and above.

1.3. Drug class and therapeutic indication

Semaglutide is a glucagon-like peptide-1 analogue (GLP-1 RA) with a high degree of homology to human GLP-1. Semaglutide is a potent and selective agonist on the GLP-1 receptor (GLP-1R), displaying the known pharmacological effects of the GLP-1 RA class, i.e. lowering of blood glucose and reduction of body weight. Both native GLP-1 and GLP-1 RAs reduce body weight by lowering energy intake via inducing feelings of satiety and fullness, and lowering feelings of hunger.

Semaglutide has a 94% homology to human GLP-1. Compared to native GLP-1, the semaglutide molecule has the following structural modifications in order to obtain a longer half-life:

- Substituting the alanine in position 8 of the peptide backbone to 2-aminoisobutyric acid to increase stability against the DPP-4 enzyme
- Substituting the lysine in position 34 to arginine to prevent acylation in this position
- Addition of a hydrophilic spacer between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached
- Addition of a C18 fatty di-acid with a terminal acidic group

The spacer and the fatty acid both contribute to increased albumin binding which slows the degradation of semaglutide in plasma and decreases the renal clearance, which combined with the increased stability against the DPP-4 enzyme, prolong the half-life of semaglutide to approximately 1 week, thus enabling once weekly s.c. administration.

Semaglutide is produced in *Saccharomyces cerevisiae* by recombinant DNA technology followed by protein purification.

The currently approved indication is:

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

- *≥30 kg/m² (obesity), or*
- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).*

The proposed new indication is:

Adults

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

- *≥30 kg/m² (obesity), or*
- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).*

Adolescents

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- *obesity* or*
- *overweight* and at least one weight-related comorbidity*

**Obesity (BMI ≥ 95th percentile) and overweight (BMI ≥ 85th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Figure 1).*

1.4. Dosage forms and strengths

The following dosage forms and strengths are currently approved:

- ARTG 356270, WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), solution for injection, pre-filled pen with pre-assembled needle.
- ARTG 356285, WEGOVY (semaglutide) 0.5 mg (1.0 mg/mL), solution for injection, pre-filled pen with pre-assembled needle.
- ARTG 356286, WEGOVY (semaglutide) 1.0 mg (2.0 mg/mL), solution for injection, pre-filled pen with pre-assembled needle.

- ARTG 356287, WEGOVY (semaglutide) 1.7 mg (2.27 mg/mL), solution for injection, pre-filled pen with pre-assembled needle.
- ARTG 356288, WEGOVY (semaglutide) 2.4 mg (3.2 mg/mL), solution for injection, pre-filled pen with pre-assembled needle.

No new dosage forms or strengths are proposed.

1.5. Dosage and administration

The proposed dosing and administration for the proposed extension to the indication is:

Children and adolescents

Safety and efficacy of Wegovy in children below 12 years have not been studied.

For adolescents ages 12 years and above, the same dose escalation schedule as for adults should be applied (see Table 1). The dose should be increased until 2.4 mg (maintenance dose) or maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended.

Table 1: Dose escalation schedule

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

1.6. Proposed changes to the product documentation

The Sponsor has included dosing, efficacy, pharmacokinetics and adverse event data relating to the adolescent population.

In addition to the proposed extension of indication the Sponsor proposes to include information from the following Phase 3a trials in the PI:

- STEP 5: sustained weight reduction at 2 years of treatment: extensive information has been included in the PI
- STEP 4: refers to previously submitted data. The information on body weight after cessation after 20 weeks of treatment is provided to indicate the paucity of the available data s47 [redacted]
- STEP 1ext: effects of treatment discontinuation after 68 weeks treatment
- STEP 8: efficacy in comparison with liraglutide: extensive information about this trial has been included

The proposed changes to the CMI relate only to the new indication including adolescents and are restricted to information about the indication, dosage and age groups included in the product approval.

2. Background

2.1. Information on the condition being treated

Adult population:

Obesity is a common condition with high associated morbidity and mortality.

Body mass Index (BMI) is used as a measure of being overweight and obese. The definitions for obesity and overweight used by the Australian Institute of Health and Welfare (AIHW) are:

- A BMI of 25.0 to 29.9 kg/m^2 is classified as overweight but not obese
- A BMI of ≥30.0 kg/m^2 is classified as obese.
- A BMI of >35.0 kg/m^2 is classified as severely obese.

These definitions of obesity and overweight align with the World Health Organisation definitions.

BMI is a composite measure of weight and height:

$$BMI = \frac{body\ weight\ (kg)}{(height\ [cm])^2}$$

Hence, this measure is not a direct measure of adiposity, but is a surrogate measure. Hence, these definitions may not apply to a highly muscled individual or to children and adolescents. Interpretation of BMI may vary between ethnic groups. Waist circumference in adults may be a better measure of adiposity and a better measure of obesity-related morbidity.

The AIHW (AIHW 2021) reports that in 2017–18, an estimated 2 in 3 (67%) Australians aged 18 and over were overweight or obese, 36% were overweight but not obese, and 31% were obese. This equates to approximately 12.5 million adults in Australia. The prevalence of overweight and obesity was higher in males (75% compared to 60% in females) and also the prevalence of obesity was higher in males (33% compared to 30% in females). Obesity is more prevalent in older age groups: 16% of adults aged 18–24 compared with 41% of adults aged 65 to 74 years.

Obesity is associated with increased prevalence of cardiovascular disease, hypertension, type 2 diabetes mellitus (T2DM) and metabolic syndrome, non-alcoholic fatty liver disease, cholelithiasis, cancer, sleep apnoea, osteoarthritis and reduced psychosocial function (Bray 2004). Overall, obesity is associated with increased mortality, increased morbidity and decreased quality of life.

It has been estimated that in 2015 high BMI accounted for 4.0 million deaths globally, representing 7.1% of deaths from any cause, and 120 million disability-adjusted life-years, representing 4.9% of disability adjusted life-years (Afshin 2017). More than two thirds of deaths related to high BMI were due to cardiovascular disease.

Adolescent population:

Measuring obesity in the paediatric and adolescent population differs from the adult in that normal body proportions change with development. Hence, particularly in younger children, the normal ranges of BMI are different in paediatric populations compared to adults. It may be more appropriate in the paediatric population to refer to age appropriate Z-scores (number of SDs from the mean, also referred to by the sponsor as Standard Deviation Score [SDS]) which indicate the degree of variation from the average. A higher Z-score represents a greater BMI in relation to the age group. Centile charts for BMI for boys and girls are presented as Figure 2.1.1 and Figure 2.1.2. Similar charts including Z score ranges are presented as Figure 2.1.3 and Figure 2.1.4. Response to treatment would therefore be best expressed as a decrease in the Z-score.

The AIHW has prepared a report on the prevalence of obesity and overweight in children and adolescents in Australia (AIHW 2020). When interpreting this report, it is important to recognise that the age bands used differ from those used in medicines regulation. In particular, the age band used for adolescents is 15 to <20 years, and not 12 to <18 years. The key findings of the report are:

- One quarter (25%) of Australian children and adolescents aged 2 to 17 were overweight or obese in 2017 to 2018, and 8.2% were obese.
- The obesity rate in the lowest socioeconomic areas (11%) was more than twice as high as the rate in the highest areas (4.4%).
- The proportion of Aboriginal and Torres Strait Islander children and adolescents aged 2 to 17 who were overweight or obese increased from 31% in 2012 to 2013 to 38% in 2018 to 2019. The biggest increase was for those aged 5 to 9 years (from 27% to 36%).
- The prevalence of overweight and obesity, and obesity alone, increased for 5 to 17 year old Australians between 1995 and 2007 to 2008, but has been relatively stable since.
- When measuring the same children every 2 years in the Longitudinal Study of Australian Children, overweight and obesity generally increased with age. Over 4 in 10 were overweight or obese at least once but only a small proportion of children were overweight or obese every time they were measured.
- Adolescents and young people aged 15 to 24 years in 2017 to 2018 were more likely to be overweight or obese compared with people at the same age 10 and 22 years earlier.

The consequences of obesity in adolescents and children are abnormal serum lipids, hypertension, non-alcoholic fatty liver disease, polycystic ovarian syndrome, obstructive sleep apnoea, insulin resistance and type 2 diabetes, gastrointestinal, musculoskeletal and orthopaedic complications, asthma, gallstones, and heartburn (Kelsey 2014, CDC 2023). These consequences translate to both short- and long-term poorer health outcomes.

Hence, obesity in adolescents is common, has a high disease burden and disproportionately affects disadvantaged sections of the Australian community.

2.2. Current treatment options

Currently there are limited treatment options for adolescents with obesity or who are overweight. The NHMRC guideline (2013) recommends weight maintenance rather than weight loss in most children and many adolescents, with the anticipation that with linear growth weight maintenance will result in improvement in BMI and waist circumference measurements. However, particularly in adolescents, weight maintenance may be insufficient to result in significant benefit.

In adults, a 5% decrease in body weight, in patients with obesity, is associated with significant improvements in cardiovascular risk factors, such as hypertension and lipid profile (Look 2010). Hence, this has become the target for measuring treatment effectiveness, and treatments should achieve at least a 5% sustained reduction in body weight. However, in children the effectiveness of an intervention should take into account linear growth, therefore changes in indexes, such as BMI or waist circumference, may be better measures of efficacy.

The following treatment options are available for adolescents who are overweight or obese:

Lifestyle modification: diet and exercise with or without psychological support. In adolescents these interventions may be family interventions in preference to individual.

Pharmacological treatments approved for adults:

- Orlistat: a selective inhibitor of pancreatic lipase, resulting in decreased absorption of fat. Orlistat is a Schedule 3 drug in Australia and is available over the counter. However, the Product Information for Xenical (orlistat) contains the warning: “The safety and efficacy of XENICAL in children have not been established.”
- Liraglutide: a GLP-1 agonist, is approved in Australia for the indication:

  SAXENDA (liraglutide) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of

- *≥30 kg/m² (obese) or*
- *≥27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.*

Treatment with SAXENDA should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

However, the Product Information for SAXENDA (liraglutide) states: "The safety and efficacy of SAXENDA in children and adolescents below 18 years of age have not been established [see section 5.1 Pharmacodynamic Properties]. No data are available. SAXENDA is not indicated for use in paediatric patients."

- Phentermine: sympathomimetic agent with anorectic actions. Phentermine is approved for adolescents aged over 12 years, but has cardiovascular and CNS adverse effects that may discourage use in the adolescent age group.
- Naltrexone/bupropion is approved for the following indication in Australia:

  CONTRAVE is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of

  - *≥ 30 kg/m² (obese), or*
  - *≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of one or more weight-related comorbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)*

  Treatment with CONTRAVE should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS).

Pharmacological treatments not approved in Australia:

- Phentermine/topiramate: is approved in the US for weight control. Topiramate is associated with weight loss due to an unknown mechanism (approved in the US).
- Lorcaserin: an appetite suppressant through activation of hypothalamic 5-HT^{2C} receptors (approved in the US)

Pharmacological treatments in development:

Products in development include GLP-1 agonists (such as semaglutide), dual GLP-1/GIP receptor antagonists and GLP-1/GIP/glucagon triple agonists (Williams 2020). SGLT-2 inhibitors are also under development as potential weight control agents. Amylin mimetics, leptin analogues and ghrelin vaccines and antagonists, neuropeptide Y inhibitors and melanocortin-4 receptor antagonists are potential therapeutic agents for this indication (Williams 2020).

Bariatric surgery:

Bariatric surgery is available for adolescents and is usually reserved for patients with severe obesity: a BMI ≥40 kg/m² or >35 kg/m² with obesity-related co-morbidity (Williams 2020, NHMRC 2013). Surgical interventions include devices (e.g., intragastric balloon, endoscopic sleeve gastroplasty, vagal nerve blockade, hydrogels) and surgery [e.g., laparoscopic adjustable gastric banding (LAGB), roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD-DS)]. These surgical interventions have considerable peri-operative and post-operative morbidity.

2.3. Clinical rationale

The Sponsor has not stated a clear rationale in the Clinical Overview or the Clinical Summary.

However, in the above Section 2.1 obesity and overweight in adolescents are found to be common, have a high disease burden and disproportionately affect disadvantaged sections of the Australian community. Section 2.2 demonstrates that currently there are limited therapeutic options for the adolescent age group compared with the adult age group. Together, this presents a strong case for developing further therapeutic options for the adolescent age group.

2.4. Formulation

2.4.1. Formulation development

No new formulations are proposed.

2.4.2. Excipients

No changes to the composition of the currently approved formulation are proposed.

2.5. Regulatory history

2.5.1. Australian regulatory history

WEGOVY (semaglutide) was approved in Australia for the adult population on 1st September 2022.

Semaglutide 1.34 mg/mL is currently also approved with the trade name Ozempic® s47 s47 for use in type 2 diabetes mellitus (T2DM). The current application does not propose any changes to the Ozempic indications, dosage information or other registered details.

2.5.2. Orphan drug designation

Orphan drug designation does not apply to the present application.

2.5.3. Related submissions

There are no related submissions.

2.5.4. Overseas regulatory history

The Sponsor has submitted similar applications in the US on 29th June 2022 and in the EU on 30th August 2022. The applications have not been refused market approval or withdrawn.

Similar applications have not been submitted in Canada, New Zealand, Singapore or Switzerland.

2.6. Guidance

The following regulatory guidance applies to the present application:

- Guideline on Clinical Evaluation of Medicinal Products Used in Weight Management (EMA/CHMP/311805/2014) 23 June 2016
- Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control (CPMP/EWP/281/96 Rev. 1) Addendum on Weight Control in Children
- Reflection Paper on Investigation of Pharmacokinetics and Pharmacodynamics in the Obese Population - draft (EMA/CHMP/535116/2016) 25 January 2018
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses. (CHMP/EWP/185990/06) 21 June 2007.

2.7. Evaluator's commentary on the background information

The present application is for an extension of indications to include the adolescent age-group, from 12 to <18 years. The background information indicates an unmet need for effective treatments for patients with obesity, or overweight with comorbidity, in this age group.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier contained data from one population pharmacokinetic study (NN9536-4451 Modelling Report) and four Phase III studies:

- Study NN9536-4451 (STEP TEENS): weight management in adolescents with overweight or obesity
- Study NN9536-4378 (STEP 5): extended treatment
- Study NN9536-4376 (STEP 8): comparison with liraglutide
- Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide

3.2. Paediatric data

Data are presented in the dossier for the 12 to 17 years age group.

There is an agreed Paediatric Investigation Plan in Europe. As part of this plan there is a waiver for the paediatric population from birth to less than 10 years; for solution for injection, subcutaneous use; on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

In the US there is a similar partial waiver from conducting pediatric studies in the following age group: pediatric population less than 10 years of age.

3.3. Good clinical practice

The studies submitted in the dossier are stated to have been conducted according to GCP and appear to have been conducted according to GCP.

3.4. Evaluator's commentary on the clinical dossier

The dossier is submitted in support of the proposed extension to the indication, but also contains extensive data in support of the proposed changes to the product information. The dossier was easy to navigate and the studies were reported in standard format. The links within the dossier and the studies operated effectively, and the reports were clearly written.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The dossier contained PK data from one population pharmacokinetic study (NN9536-4451 Modelling Report) to support the proposed dosing for semaglutide in adolescents (aged 12 to <18 years).

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

Semaglutide is a human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in a Saccharomyces cerevisiae strain followed by purification.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

There were no new data relating to absorption.

4.2.2.2. Bioavailability

There were no new data relating to bioavailability.

4.2.2.3. Distribution

There were no new data relating to distribution.

4.2.2.4. Metabolism

There were no new data relating to metabolism.

4.2.2.5. Excretion

There were no new data relating to excretion.

4.2.2.6. Intra and inter individual variability of pharmacokinetics

NA.

4.2.3. Pharmacokinetics in the target population

See Section 4.2.5.1.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

NA.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

NA.

4.2.4.3. Pharmacokinetics according to age

See Section 4.2.5.1.

s47 [redacted]

4.2.4.5. Pharmacokinetics in other special population / with other population characteristic

NA.

4.2.5. Population pharmacokinetics

4.2.5.1. Study NN9536-4451 Modelling Report

The Study NN9536-4451 Modelling Report (Section 19.1.3.1) conducted a population PK analysis of plasma concentration and covariate data from STEP TEEN (Section 7.2.1) and STEP1 (a Phase IIIa study conducted in adults). In the analysis, the only clinically significant covariate for exposure was body weight, with decreased semaglutide exposure with increasing body weight (Figure 19.1.3.1.5). From the model, in the adolescent population geometric mean

(CV%) C_{avg} was 74 nmol/L (26%), $AUC_{0\text{-}168h}$ was 12366 nmol•h/L (26%) and CL/F was 0.047 L/h (26%) (Table 19.1.3.1.5).

Using the model, CL/F and C_{avg} were simulated for a semaglutide 2.4 mg dose, for a population with body weight from 47.2 to 114.1 kg, representing a population with overweight or obesity aged 6 to <18 years (Figure 19.1.3.1.6). The starting dose of 0.25 mg in the paediatric population did not result in greater exposure than the 0.5 mg dose in the adult population (Figure 19.1.3.1.7). The Sponsor concluded with the flexibility of dose escalation, that the adult dosing regimen would be appropriate for the STEP Young trial population of ages 6 to <12 years.

4.2.6. Pharmacokinetic interactions

NA.

4.2.7. Clinical implications of *in vitro* findings

NA.

4.3. Evaluator's overall conclusions on pharmacokinetics

The population PK study indicated that the only significant covariate effect on semaglutide exposure was body weight. The modelling study demonstrates increased exposure to semaglutide in subjects with lower body weight. Given a median weight of 100 kg, the increase in exposure for a subject of 76 kg was approximately 25% and the decrease in exposure in a subject of 47 kg was approximately 25% (Figure 19.1.3.1.5). In the opinion of the Clinical Evaluator, this range of variation is unlikely to be clinically important. Hence, the PK data support the proposed dosing regimen for the 12 to <18 years population.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

The dossier contained PD data from the population pharmacokinetic study (NN9536-4451 Modelling Report) to support the proposed dosing for semaglutide in adolescents (aged 12 to <18 years).

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Semaglutide acts as a GLP-1 receptor agonist (GLP-1 RA) that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

In the Study NN9536-4451 Modelling Report (Section 19.1.3.1) there was a linear relationship between exposure and decrease in BMI with decreasing BMI with increasing exposure (Figure 19.1.3.1.8). There was poor precision for the estimate of baseline BMI effect, but the remaining parameters were estimated with adequate precision (Table 19.1.3.1.7).

5.2.2.2. Secondary pharmacodynamic effects

In the Study NN9536-4451 Modelling Report (Section 19.1.3.1) there was no strong relationship between exposure and nausea and the parameters in the model were estimated with poor

precision (Figure 19.1.3.1.9 and Table 19.1.3.1.8). There was no strong relationship between exposure and vomiting and the parameters in the model were estimated with poor precision (Figure 19.1.3.1.10 and Table 19.1.3.1.9).

5.2.3. Time course of pharmacodynamic effects

NA.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

As per Section 5.2.2.1.

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

NA.

5.2.6. Pharmacodynamic interactions

NA.

5.3. Evaluator's overall conclusions on pharmacodynamics

Increasing exposure was associated with greater relative decreases in BMI. However, this could be biased because the lower weight individuals, with greater exposure, would still have been growing, and therefore had an advantage in weight change relative to height (i.e. BMI). This relationship between exposure and BMI decrease was more pronounced in the adolescent group.

There was no clear relationship between either nausea or vomiting and exposure in these analyses. There was poor precision of the estimates in the linear models and the plots of exposure vs % subjects effected did not have a slope significantly different to 0.

The model developed in the population pharmacokinetic study (NN9536-4451 Modelling Report) was used to explore dosing in the 6 to ≤12 year age group. The model confirmed the dosing regimen used in Study NN9536-4451 (STEP TEENS) but did not explore alternative dosing regimens in the 12 to ≤18 years age group.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The population pharmacokinetic study (NN9536-4451 Modelling Report) analysed the PK and PD data from Study NN9536-4451 (STEP TEENS) in comparison with an adult population from Study NN9536-4373 (STEP 1). The model developed in the study was used to explore dosing in the 6 to ≤12 year age group. The model also confirmed the dosing regimen used in Study NN9536-4451 (STEP TEENS) but did not explore alternative dosing regimens in the 12 to ≤18 years age group.

6.2. Phase II dose finding studies

NA.

6.3. Phase III pivotal studies investigating more than one dose regimen

Study NN9536-4451 (STEP TEENS) used a single dosing regimen.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

Study NN9536-4451 (STEP TEENS) used the same dosing regimen as that used in the pivotal studies performed in adults. The NN9536-4451 Modelling Report was a confirmatory study that did not explore alternative dosing regimens in the 12 to ≤18 years age group. However, the NN9536-4451 Modelling Report confirmed that the dosing regimen used in Study NN9536-4451 (STEP TEENS) was suitable for that population.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

There was one pivotal efficacy study submitted to support the extension of indications to include weight management in adolescents with overweight or obesity: Study NN9536-4451 (STEP TEENS).

There were three other efficacy studies submitted to support changes to the Product Information:

- Study NN9536-4378 (STEP 5): extended treatment
- Study NN9536-4376 (STEP 8): comparison with liraglutide
- Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide

7.2. Pivotal or main efficacy studies (Efficacy in Adolescents)

7.2.1. Study NN9536-4451 (STEP TEENS)

7.2.1.1. Study design, objectives, locations and dates

Study NN9536-4451 (STEP TEENS) was a Phase IIIa, randomised, parallel group, placebo-controlled study of the effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity. The study duration was 68 weeks. The study was conducted from October 2019 to March 2022. The study was conducted at 37 sites in eight countries: Austria (3 sites), Belgium (4), Croatia (3), Ireland (1), Mexico (1), Russia (7), Great Britain (6) and the US (12).

7.2.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, aged 12 to <18 years
- BMI ≥95th percentile, or ≥85th percentile (on gender and age-specific CDC growth charts) with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or type 2 diabetes
- History of at least one self-reported unsuccessful dietary effort to lose weight
- For subjects with T2DM, HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening; and: subject treated with either diet and exercise alone or stable treatment for at least 90 days prior to screening with metformin

The exclusion criteria included:

- Prepubertal subjects (Tanner stage 1)
- History of type 1 diabetes (T1DM)
- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records

- Subjects with secondary causes of obesity (i.e., hypothalamic, monogenic or endocrine causes)
- For subjects with T2DM, uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination
- Treatment with any medication for the indication of obesity within the past 90 days before screening
- Previous surgical treatment for obesity (excluding liposuction if performed >1 year before screening)
- Uncontrolled thyroid disease at screening, in the opinion of the investigator
- History of major depressive disorder within 2 years before screening
- Diagnosis of other severe psychiatric disorders (e.g., schizophrenia, bipolar disorder)
- A Patient Health Questionnaire-9 (PHQ-9) score of ≥15 at screening
- A lifetime history of suicidal attempt
- Suicidal behaviour within 30 days before screening
- Suicidal ideation corresponding to type 4 or 5 based on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening
- Subjects with confirmed diagnosis of bulimia nervosa disorder
- History or presence of pancreatitis (acute or chronic)
- Calcitonin ≥50 ng/L
- Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 (MEN-2) or medullary thyroid carcinoma (MTC)
- History of type 1 diabetes
- Impaired renal function defined as serum-creatinine >upper normal range (UNR) for age in children unless renal function is proven normal by further assessments at the discretion of the investigator
- History of malignant neoplasms within the past 5 years prior to the day of screening
- Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator
- Known history of heart disease (including history of clinically significant arrhythmias or conduction delays on ECG) within 180 days before screening, new clinically significant arrhythmias or conduction delays on ECG identified at screening
- Treatment with glucose-lowering agent(s) within 90 days before screening (except for metformin)
- Treatment with a GLP-1 receptor agonist within 180 days before screening

7.2.1.3. Study treatments

The study treatments were:

1. Semaglutide: initially 0.25 mg once weekly and then followed a fixed-dose escalation regimen, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week).
2. Placebo

The treatments were administered by s.c. injection once weekly, in the thigh, abdomen or upper arm at any time of day irrespective of meals. The device used for injections was a 3 mL PDS290 pre-filled pen-injector. If a subject did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose level, if the subject would otherwise discontinue trial product completely and if it was considered safe to continue on trial product.

7.2.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the % change in body mass index (BMI) from baseline (week 0) to week 68. The confirmatory secondary efficacy outcome measure was the

proportion of subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68. Supportive secondary efficacy outcome measures were:

- Change in body weight (kg)
- Change in body weight (%)
- Proportion of subjects achieving ≥10% reduction of body weight
- Proportion of subjects achieving ≥15% reduction of body weight
- Proportion of subjects achieving ≥20% reduction of body weight
- BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov)
- Improvement in weight category
- BMI (standard deviation score)
- BMI (kg/m^2)
- Waist circumference (cm)
- Proportion of subjects achieving ≥5% reduction of BMI

Exploratory efficacy endpoints were:

- Change in BMI from baseline (week 0) to week 52 (%)
- Change in BMI from baseline (week 0) to week 75 (%)

Supportive secondary efficacy endpoints to explore effects on cardiovascular risk factors and glucose metabolism were:

- Change in systolic blood pressure
- Change in diastolic blood pressure
- HbA1c
- Fasting plasma glucose
- Fasting insulin
- Serum lipids:
  - Total cholesterol
  - High-density lipoprotein (HDL) cholesterol
  - Low-density lipoprotein (LDL) cholesterol
  - Very low-density lipoprotein (VLDL) cholesterol
  - Triglycerides
- Alanine aminotransferase

Exploratory secondary efficacy endpoints to explore effects on glucose metabolism were:

- Homeostasis model assessment (HOMA-B and HOMA-IR)

The safety outcome measures were AEs, pulse rate, amylase, lipase, and calcitonin. Additional safety outcome measures were:

- Occurrence of anti-semaglutide antibodies
- Bone age assessment, x-ray
- ECG
- Laboratory parameters
- Pubertal status (Tanner staging) (stage 2-5 where 5 is full sexual maturity)
- Height standard deviation score
- Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS)
- Patient-Reported Health Questionnaire 9 (PHQ-9)

The safety endpoints in patients with diabetes were:

- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes
- Number of treatment-emergent hypoglycaemic episodes

- Ophthalmological evaluation

The patient reported outcomes were:

- Impact of Weight on Quality of Life Kids (IWQOL-Kids)
  - physical comfort domain score
  - body esteem domain score
  - social life domain score
  - family-relations score
  - total score

The schedule of study procedures is summarised in Table 7.2.1.1.

7.2.1.5. Randomisation and blinding methods

Subjects were randomised to semaglutide: placebo in a 2:1 ratio using an Interactive Web Response System (IWRS). Randomisation was stratified by gender and Tanner stage (2 to 3 versus 4 to 5). Subjects and investigators were blinded to treatment allocation, but the Sponsors Global Safety Department was not blinded for assessment of suspected unexpected serious adverse reactions (SUSARs).

7.2.1.6. Analysis populations

The full analysis set (FAS) included all randomised subjects according to the intention-to-treat principle. The subjects in the FAS contributed to evaluation "as randomised".

The safety analysis set (SAS) included all randomised subjects exposed to at least one dose of randomised treatment. The subjects in the SAS contributed to evaluation "as treated".

7.2.1.7. Sample size

The sample size calculation was performed using a t-test that assumed equal variances. The calculation was for a test of superiority, a randomisation for semaglutide: placebo of 2:1, a discontinuation rate of 35%, retrieval rate for discontinued subjects (using imputation) of >50%, and an expected treatment difference of 5.5%. This determined a sample size of 192, with 128 in the semaglutide arm and 64 in the placebo arm. The trial was designed with an effective power of 90% and 72% to detect differences on the primary endpoint and confirmatory secondary endpoint, respectively, with an α of 0.05.

7.2.1.8. Statistical methods

For the primary endpoint, % change in BMI, a linear regression (ANCOVA) on randomised treatment, using the stratification groups (gender and Tanner stage group) and the interaction between gender and Tanner stage as factors, and baseline BMI (kg/m^2) as a covariate. Secondary binary endpoints were tested using logistic regression.

Missing data were imputed using multiple imputation using retrieved subjects.

The report discusses that the secondary analyses were adjusted for multiplicity but it is not clear how this was performed.

7.2.1.9. Participant flow

There were 229 subjects screened and 201 were randomised to treatment: 134 to semaglutide and 67 to placebo (Table 7.2.1.2). All randomised subjects were included in the efficacy analysis. There were 133 (99.3%) subjects in the semaglutide group and 67 (100%) in the placebo who were exposed to treatment. All exposed subjects were included in the safety analysis.

There were 120 (89.6%) subjects in the semaglutide group and 60 (89.6%) in the placebo who completed treatment. The most frequent reason for discontinuing treatment was AE: six (4.5%) subjects in the semaglutide group and four (6.0%) in the placebo. There were 132 (98.5%)

subjects in the semaglutide group and 64 (95.5%) in the placebo who attended the end-of-trial visit (i.e. completed the study).

7.2.1.10. Major protocol violations/deviations

There were no protocol deviations that were considered to have a significant impact on the accuracy and reliability of the study data. As a result of COVID there were 139 visits that were converted to phone visit and 58 visits that were out of window. There were no cases of unintentional unblinding. There were 15 cases of intentional unblinding during the assessment of SUSAR.

7.2.1.11. Baseline data

There were 125 (62.2%) females and 76 (37.8%) males (Table 7.2.1.3). There were 159 (79.1%) White subjects and 16 (8.0%) Black or African American. The treatment groups were similar in weight and pubertal staging. The age range was 12 to 18 years (Table 7.2.1.4). The BMI range was 26.6 to 60.0 kg/m^2 and the BMI SDS score ranged from 2.0 to 6.6. The treatment groups were similar in anthropomorphic measures. There were 25 (18.7%) subjects in the semaglutide group and eight (11.9%) in the placebo with pre-existing hepatic disorders (predominantly hepatic steatosis). The incidence of comorbidity was dyslipidaemia 18.4%; hypertension 13.4%, T2DM 4.0%; and obstructive sleep apnoea 1.5%. There were 29 (21.6%) subjects in the semaglutide group and 13 (19.4%) in the placebo treated with biguanides at baseline. There were eight (6.0%) subjects in the semaglutide group and four (6.0%) in the placebo treated with thyroid hormones at baseline.

7.2.1.12. Results for the primary efficacy outcome

The primary and confirmatory efficacy analyses demonstrated superiority for semaglutide.

The mean (SD) % change in BMI from baseline to Week 68 was -16.2 (12.9) % in the semaglutide group and -0.1 (8.6) % in the placebo, difference (95% CI) -16.75 (-20.27 to -13.23) % P <0.0001. The rate of weight loss was greatest in the first 44 weeks of treatment (Figure 7.2.1.1).

The proportion of subjects in the semaglutide group with body weight loss ≥5% at week 68 was 72.5% and in the placebo group was 17.7%, OR (95% CI) 14.02 (6.34 to 31.02), p <0.001 (Figure 7.2.1.2).

7.2.1.13. Results for other efficacy outcomes

Supportive secondary efficacy outcome measures were:

- There was a significant decrease in body weight in the semaglutide group relative to placebo at Week 68; treatment difference (95% CI) semaglutide – placebo: -17.73 (-21.76 to -13.70) kg.
- There was a significant decrease in % in body weight in the semaglutide group relative to placebo; treatment difference (95% CI) semaglutide – placebo: -17.42 (21.08 to 13.75) (%) (Figure 7.2.1.3).
- The proportion of subjects in the semaglutide group with body weight loss ≥10% at week 68 was 61.8% and in the placebo group was 8.1%, OR (95% CI) 23.04 (8.34 to 63.67), p <0.001 (Figure 7.2.1.2).
- The proportion of subjects in the semaglutide group with body weight loss ≥15% at week 68 was 53.4% and in the placebo group was 4.8%, OR (95% CI) 25.78 (7.55 to 88.01), p <0.001 (Figure 7.2.1.2).
- The proportion of subjects in the semaglutide group with body weight loss ≥20% at week 68 was 37.4% and in the placebo group was 3.2%, OR (95% CI) 19.99 (4.63 to 86.30), p <0.001 (Figure 7.2.1.2).
- **The estimated mean change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) from baseline to Week 68 was -24.58 %-points**

with semaglutide and -4.18 %-points with placebo; estimated mean treatment difference (95% CI) -20.40 (-25.01 to -15.79) %-points.

- Improvement in weight category was recorded for 71.8% subjects in the semaglutide group compared with 21.0% in the placebo
- **The mean change in BMI standard deviation score was -1.22 in the semaglutide group and -0.05 in the placebo: estimated mean treatment difference (95% CI) -1.17 (-1.41 to -0.93) p <0.0001** (Table 7.2.1.5 and Figure 7.2.1.4).
- The estimated mean change in BMI from baseline to Week 68 was -5.85 kg/m^2 in the semaglutide group and 0.11 kg/m^2 in the placebo: estimated treatment difference (95% CI) -5.96 (-7.29 to -4.62) kg/m^2.
- **The mean change in waist circumference from baseline to Week 68 was -12.69 cm in the semaglutide group and -0.55 cm in the placebo; estimated on-trial mean treatment difference (95% CI) -12.14 (-15.59 to -8.69) cm, p <0.0001.**
- The proportion of subjects achieving ≥5% reduction of BMI was 77.1% in the semaglutide group and 19.7% in the placebo; OR (95% CI), semaglutide/placebo, 13.76 (6.31 to 30.02).

Exploratory efficacy endpoints were:

- The change in BMI from baseline (week 0) to week 52 was -16.01 % in the semaglutide group and -0.40 % in the placebo; estimated treatment difference (95% CI) -15.61 (-18.74 to -12.48) %, p <0.0001
- The change in BMI from baseline (week 0) to week 75 was -13.20 % in the semaglutide group and -1.24 % in the placebo; estimated treatment difference (95% CI) -14.43 (-17.82 to -11.05) %, p <0.0001

The results of the supportive secondary efficacy endpoints to explore effects on cardiovascular risk factors and glucose metabolism were:

- At Week 68 there was no significant difference in mean SBP between the semaglutide group and placebo (Figure 7.2.1.5)
- At Week 68 there was no significant difference in mean DBP between the semaglutide group and placebo (Figure 7.2.1.6)
- There were significant improvements in total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides with semaglutide relative to placebo (Figure 7.2.1.7)
- For subjects without T2DM there was a significant decrease in HbA1c with semaglutide relative to placebo: estimated treatment difference (95% CI) -0.22 (-0.29 to -0.14) %-point.
- For subjects without T2DM there was a significant decrease in fasting plasma glucose with semaglutide relative to placebo: estimated treatment difference (95% CI) -0.17 (-0.31 to -0.03) mmol/L
- At Week 68, geometric mean (CV%) fasting insulin was 97.4 pmol/L (70.1%) in the semaglutide group and 125.4 pmol/L (59.9%) in the placebo.
- Mean ALT levels decreased in the semaglutide group relative to placebo: mean estimated treatment ratio 0.86 (0.75 to 0.99).
- There was no significant difference between the groups in HOMA-B.
- At Week 68, geometric mean (CV%) HOMA-IR was 3.00 (78.3%) in the semaglutide group and 4.00 (68.3%) in the placebo.
- For Impact of Weight on Quality of Life Kids (IWQOL-Kids) there were significant improvements in total score and physical function score with semaglutide (Figure 7.2.1.8).

7.2.1.14. Evaluator commentary

The design and conduct of Study NN9536-4451 were appropriate for the objectives of the study and conformed with regulatory guidance.

The results indicate a weight loss in the adolescent group that is comparable to that in the adult age group. This supports extending the indications to include the adolescent age group (12 to ≤18 years). The mean difference (95% CI) compared to placebo in BMI was -16.75 (-20.27 to -13.23) % p <0.0001. This demonstrates a clinically significant treatment effect. The proportion of subjects in the semaglutide group with body weight loss ≥5% at week 68 was 72.5% and in the placebo group was 17.7%, OR (95% CI) 14.02 (6.34 to 31.02), p <0.001. These results established comparability with the treatment effect in the adult population.

However, as discussed in Section 2.1, efficacy outcome measures also need to account for the growth and development that occur in a longitudinal study of one year duration in the adolescent population. The efficacy measures that did this were:

- The estimated mean change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) from baseline to Week 68 was -24.58 %-points with semaglutide and -4.18 %-points with placebo; estimated mean treatment difference (95% CI) -20.40 (-25.01 to -15.79) %-points.
- The mean change in BMI standard deviation score was -1.22 in the semaglutide group and -0.05 in the placebo: estimated mean treatment difference (95% CI) -1.17 (-1.41 to -0.93) p <0.0001 (Table 7.2.1.5 and Figure 7.2.1.4).
- The mean change in waist circumference from baseline to Week 68 was -12.69 cm in the semaglutide group and -0.55 cm in the placebo; estimated on-trial mean treatment difference (95% CI) -12.14 (-15.59 to -8.69) cm, p <0.0001.

Hence, after accounting for growth and development, there is a clinically and statistically significant improvement in measures of obesity and overweight in the adolescent population with semaglutide treatment.

In addition, there were improvements in serum lipids (a cardiovascular risk factor) and in glycaemic indices (HbA1c in subjects with T2DM, and FPG in subjects without T2DM.

7.3. Other efficacy studies (submitted in support of changes to the PI)

7.3.1. Study NN9536-4378 (STEP 5): extended treatment

Study NN9536-4378 was a randomised, double-blind, placebo-controlled, two-armed, parallel group, clinical trial comparing semaglutide 2.4 mg once weekly with semaglutide placebo in subjects with overweight or obesity. The objective of the study was to examine the efficacy and safety of semaglutide 2.4 mg over a 2-year period. The study was conducted at 41 sites in five countries: Canada (9 sites), Hungary (6), Italy (5), Spain (6) and the US (15). The study was conducted from October 2018 to March 2021.

The study included males and females, aged ≥18 years, with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease; and a history of at least one self-reported unsuccessful dietary effort to lose body weight. The study excluded subjects with HbA_{1c} ≥48 mmol/mol (6.5%); or a self-reported change in body weight >5 kg (11 lbs) within 90 days before screening.

The study treatments were:

1. Semaglutide 2.4 mg weekly
2. Placebo

Semaglutide was administered using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL (depending on dose level). Dose escalation was to take place during the first 16 weeks after randomisation with dose increase every 4 weeks (from 0.25 mg/week to doses of 0.5, 1.0, 1.7 and 2.4 mg/week). If a subject could not

tolerate the recommended dose of semaglutide 2.4 mg, the subject could stay at a lower dose level.

The primary efficacy outcome measures were:

- Change from baseline (week 0) to week 104 in body weight (%)
- Proportion of subjects with body weight reduction ≥5% from baseline at 104 weeks

The secondary efficacy outcome measures were:

- Proportion of subjects who at Week 104 achieved body weight reduction from baseline ≥10%, ≥15% and ≥ 20%
- Change from baseline to Week 104 in: waist circumference (cm), body weight (kg) and BMI (kg/m^2)
- Cardiovascular endpoints: Change from baseline to Week 104 in: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), serum lipids and CRP
- Glucose metabolism endpoints: Change from baseline to Week 104 in HbA1c, FPG and fasting serum insulin

One-year endpoints were:

- Change from baseline to Week 52 in body weight, BMI and waist circumference
- Proportion of subjects who after 52 weeks achieved body weight reduction ≥5%, ≥10%, ≥15% and ≥20%

The safety outcome measures were: AEs, vital signs, amylase, lipase and calcitonin.

The Full Analysis Set (FAS) included all randomised subjects and the Safety Analysis Set (SAS) included all randomised subjects exposed to at least one dose of randomised treatment. Continuous outcome measures were tested using ANOVA models and dichotomous outcome measures were tested using logistic regression models. Hypothesis testing was hierarchical, using a decision criteria of $p < 0.05$. The sample size estimation was based on a power of 43% for the first six endpoints, and was for 150 subjects in each group.

There were 347 subjects screened, and 304 were randomised to treatment: 152 to semaglutide and 152 to placebo (Table 7.3.1.1). All were included in both the FAS and SAS. There were 148 (97.4%) subjects in the semaglutide group and 134 (88.2%) in the placebo who completed the trial. There were 132 (86.8%) subjects in the semaglutide group and 111 (73.0%) in the placebo who completed treatment.

There were 236 (77.6%) females, 68 (22.4%) males and the age range was 21 to 78 years (Table 7.3.1.2). The range for BMI was 27.6 to 82.7 kg/m^2. The range for waist circumference was 83.0 to 193.4 cm. The treatment groups were similar in demographic and baseline characteristics.

Note: When discussing the results the Clinical Evaluator has provided the observed results for the effect sizes of each individual treatment, and the estimand results from the ANOVA and logistic regression models for the treatment differences. This is because the observed results allow presentation of SD and individual interpretation.

Semaglutide was superior to placebo for both primary endpoints. The mean (SD) -change in body weight from baseline to Week 104 was -17.3 (11.9) % in the semaglutide group and -2.0 (8.6%) in the placebo: treatment difference (95% CI) -12.55 (-15.33 to -9.77) %, $p < 0.0001$. There was weight loss to Week 68 of treatment, after which the weight loss was maintained to Week 104 (Figure 7.3.1.1). The proportion of subjects with body weight reduction ≥5% from baseline at 104 weeks was 77.1% in the semaglutide group and 34.4% in the placebo: OR (95% CI) 4.99 (2.95 to 8.42) $p < 0.0001$.

For the secondary efficacy endpoints:

- The proportion of subjects with body weight reduction ≥10% from baseline at 104 weeks was 61.8% in the semaglutide group and 13.3% in the placebo: OR (95% CI) 7.23 (3.95 to 13.23) p <0.0001.
- The proportion of subjects with body weight reduction ≥15% from baseline at 104 weeks was 52.1% in the semaglutide group and 7.0% in the placebo: OR (95% CI) 9.40 (4.41 to 20.04) p <0.0001.
- The proportion of subjects with body weight reduction ≥20% from baseline at 104 weeks was 36.1% in the semaglutide group and 2.3% in the placebo: OR (95% CI) 12.84 (3.94 to 41.88) p <0.0001.
- The mean (SD) change from baseline to Week 104 in waist circumference was -16.4 (12.2) cm in the semaglutide group and -4.4 (9.2) cm in the placebo: treatment difference (95% CI), semaglutide – placebo, -9.17 (-12.17 to -6.17) cm, p <0.0001. There was a decrease in mean waist circumference in the semaglutide group to Week 60, and after that the improvement was maintained to Week 104 (Figure 7.3.1.2).
- The mean (SD) change from baseline to Week 104 in body weight was -18.3 (13.7) kg in the semaglutide group and -2.2 (9.5) kg in the placebo: treatment difference (95% CI) -12.91 (-16.05 to -9.77) kg, p <0.0001. The decrease in weight was to Week 68, after which time weight stabilised to Week 104 (Figure 7.3.1.3).
- The mean (SD) change from baseline to Week 104 in BMI was -6.8 (5.2) kg/m^2 in the semaglutide group and -0.8 (3.4) kg/m^2 in the placebo: treatment difference, semaglutide – placebo, -4.30 (-5.73 to -2.87), p <0.0001. The decrease in BMI was to Week 68, after which time BMI stabilised to Week 104 (Figure 7.3.1.4).
- There was a decrease in SBP and DBP in the semaglutide group from baseline to Week 20, which was then maintained throughout the treatment period (Figure 7.3.1.5). The proportion of subjects who had a decrease or stopped taking antihypertensive medication was higher with semaglutide 2.4 mg (32%) compared to placebo (16%) and a lower proportion of subjects had an increase with semaglutide 2.4 mg (6%) compared to placebo (23%).
- There was a decrease in total cholesterol, VLDL cholesterol and triglycerides in the semaglutide group relative to the placebo from baseline to Week 104 (Figure 7.3.1.6).
- For CRP, the estimated ratio to baseline at Week 104 was 0.43 for semaglutide, and 0.92 for placebo: estimated treatment ratio (95% CI) 0.47 (0.37 to 0.60).
- HBA_{1c} decreased in the semaglutide group relative to placebo: for the treatment policy estimand, the estimated mean change in HbA1c from baseline to Week 104 was −0.43%-points with semaglutide and −0.10 %-points with placebo: ETD (95% CI) −0.33 (−0.41 to −0.25) %-points.
- FPG decreased in the semaglutide group relative to placebo: for the treatment policy estimand, the estimated mean change in FPG from baseline to Week 104 was −0.42 for semaglutide and 0.09 mmol/L for placebo; ETD (95% CI) −0.51 (−0.66 to −0.36) mmol/L.
- Fasting serum insulin decreased in the semaglutide group relative to placebo: estimated mean ratio to baseline at Week 104 was 0.67 for semaglutide and 0.93 for placebo: treatment ratio (95% CI) 0.73 (0.61 to 0.87).
- Of the subjects who had pre-diabetes at baseline, 80% treated with semaglutide switched to being normo-glycaemic by Week 104 and 20% remained having pre-diabetes. None of the subjects treated with semaglutide switched to having diabetes. For subjects treated with placebo, a lower proportion of subjects switched from having pre-diabetes to being normo-glycaemic (37%), while higher proportions of subjects remained having pre-diabetes (59%) and 4% switched to having diabetes. The Control of Eating Questionnaire indicated better control for semaglutide compared to placebo (Figure 7.3.1.7).

7.3.2. Study NN9536-4376 (STEP 8): comparison with liraglutide

Study NN9536-4376 was a randomised, open-label, pairwise placebo-controlled, efficacy and safety study comparing semaglutide with liraglutide. The objective of the study was to compare

the efficacy and safety of semaglutide with liraglutide. The study was conducted over a 68 week period. The study was conducted at 19 sites in the US from 11th September 2019 to 11th May 2021.

The inclusion criteria included:

- Male or female, age ≥18 years at the time of signing informed consent.
- Body mass index (BMI) ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.
- History of at least one self-reported unsuccessful dietary effort to lose body weight.

The exclusion criteria included:

- HbA_{1c} ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening.
- History of Type 1 or Type 2 diabetes mellitus.
- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.

The study treatments were:

1. Semaglutide: dose escalation of semaglutide was to take place during the first 16 weeks after randomisation with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), aiming at reaching the maintenance dose of 2.4 mg once weekly after 16 weeks. If a subject did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose of 1.7 mg semaglutide once weekly.
2. Placebo for semaglutide.
3. Liraglutide: Dose escalation of liraglutide was to take place during the first 4 weeks after randomisation with dose increases every week (to doses of 1.2, 1.8, 2.4 and 3.0 mg), aiming at reaching the maintenance dose of 3.0 mg once daily after 4 weeks.
4. Placebo for liraglutide.

Semaglutide was administered using a PDS290 pre-filled pen-injector up to Week 44, then subsequently a DV3396 single-dose pen-injector. Liraglutide was administered using aPDS290 pre-filled pen-injector.

The primary efficacy outcome measures were:

- Change from baseline (week 0) to Week 68 in body weight (%)

The secondary efficacy outcome measures were:

- Proportion of subjects who at Week 68 achieved body weight reduction from baseline ≥10%, ≥15% and ≥ 20%
- Change from baseline to Week 68 in: waist circumference (cm) and body weight (kg)
- Cardiovascular endpoints: Change from baseline to Week 68 in: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), serum lipids and hsCRP
- Glucose metabolism endpoints: Change from baseline to Week 68 in HbA1c, FPG, fasting serum insulin, and glycaemic category.

The exploratory endpoint was:

- Proportion of subjects with body weight reduction ≥5% from baseline at 68 weeks

The safety outcome measures were AEs and vital signs.

The Full Analysis Set (FAS) included all randomised subjects (analyses as randomised) and the Safety Analysis Set (SAS) included all randomised subjects exposed to at least one dose of randomised treatment (analysed as treated).

The sample size calculation was based on a test of superiority between semaglutide and liraglutide, and also their respective placebos, based on the first four efficacy endpoints. The estimation calculated a power of 92% with 126 in each active group and 42 in each placebo group. Randomisation was in the ratio 3:1:3:1 for semaglutide: placebo: liraglutide: placebo.

There were 387 subjects screened and 338 were randomised, all of whom were treated: 126 in the semaglutide group, 127 in the liraglutide and 85 in the placebo (Table 7.3.2.1). There were 109 (86.5%) in the semaglutide group, 92 (72.4%) in the liraglutide and 70 (82.4%) in the placebo who completed treatment.

There were 265 (78.4%) females and 73 (21.6%) males (Table 7.3.2.2). The age range was 18 to 79 years, and the BMI range was 26.5 to 81.0 kg/m^2 (Table 7.3.2.3). The treatment groups were similar in demographic and baseline variables.

Note: When discussing the results the Clinical Evaluator has provided the observed results for the effect sizes of each individual treatment, and the estimand results from the ANOVA and logistic regression models for the treatment differences. This is because the observed results allow presentation of SD and individual interpretation.

Semaglutide was superior to liraglutide for the primary and confirmatory secondary efficacy outcome measures. The mean (SD) change in body weight % at Week 68 was -16.4 (10.5) % for semaglutide, -6.4 (7.7) % for liraglutide and -1.6 (8.6) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -9.38 (-11.97 to -6.80) %, p <0.0001 (Table 7.3.2.4).

For the secondary efficacy outcome measures:

- The % subjects with change in body weight ≥10% at Week 68 was 70.9% for semaglutide, 25.6% for liraglutide and 15.4% for placebo: OR (95% CI), semaglutide / liraglutide, 6.28 (3.53 to 11.18) %, p <0.0001
- The % subjects with change in body weight ≥15% at Week 68 was 55.6% for semaglutide, 12.0% for liraglutide and 6.4% for placebo: OR (95% CI), semaglutide / liraglutide, 7.90 (4.06 to 15.38) %, p <0.0001
- The % subjects with change in body weight ≥20% at Week 68 was 38.5% for semaglutide, 6.0% for liraglutide and 2.6% for placebo: OR (95% CI), semaglutide / liraglutide, 8.19 (3.51 to 19.13) %, p <0.0001
- The mean (SD) change in body weight (kg) at Week 68 was -15.8 (10.2) kg for semaglutide, -6.8 (9.5) kg for liraglutide and -1.4 (9.6) kg for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -8.49 (-11.24 to -5.74) kg, p <0.0001; semaglutide – placebo, estimand (95% CI) -13.79 (-16.83 to -10.74) kg, p <0.0001; and liraglutide – placebo, estimand (95% CI) -5.30 (-8.30 to -2.29) kg, p = 0.0006
- The mean (SD) change in waist circumference (cm) at Week 68 was -13.6 (10.0) cm for semaglutide, -6.8 (8.4) cm for liraglutide and -2.0 (7.2) kg for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -6.61 (-9.06 to -4.16) cm, p <0.0001
- SBP decreased to a similar extent in the semaglutide and liraglutide groups relative to placebo (Figure 7.3.2.1)
- For the majority of the treatment period there was no significant difference in DBP between the study groups (Figure 7.3.2.2)
- Between baseline and week 68, the proportion of subjects who had a decrease or stopped taking antihypertensive medication was higher with semaglutide 2.4 mg (29.2%) compared to liraglutide 3.0 mg (16.3%) and pooled placebo (9.7%) and a lower proportion of subjects had an increase in antihypertensive medication with semaglutide 2.4 mg (20.8%) compared to liraglutide 3.0 mg (23.3%) and pooled placebo (22.6%)
- The semaglutide group had a decrease in total serum cholesterol, VLDL cholesterol and triglycerides relative to liraglutide (Figure 7.3.2.3).

- The ratio of hsCRP at Week 68 to baseline was 0.5 for semaglutide, 0.8 for liraglutide and 0.8 for placebo; estimated treatment ratio (95% CI) semaglutide / liraglutide, 0.6 (0.5 to 0.8).
- The mean (SD) change in HbA_{1c} at Week 68 was -0.3 (0.2) % for semaglutide, -0.1 (0.2) % for liraglutide and 0.1 (0.2) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -0.16 (-0.22 to -0.09) cm, p <0.0001
- The mean (SD) change in FPG at Week 68 was -0.5 (0.5) mmol/L for semaglutide, -0.3 (0.6) mmol/L for liraglutide and 0.1 (0.6) mmol/L for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -0.22 (-0.40 to -0.04) mmol/L, p = 0.0174
- The geometric mean ratio (CV%) for fasting serum insulin at Week 68 / baseline was 0.73 (57.3) semaglutide, 0.85 (47.5) for liraglutide and 0.98 (56.8): treatment ratio (95% CI), semaglutide / liraglutide 0.85 (0.73 to 1.00) p = 0.0540
- Of subjects who were normoglycaemic at baseline, the proportion who shifted to pre-diabetes at Week 68 was 2.8% for semaglutide, 12.2% for liraglutide and 27.7% for placebo. Of subjects who were pre-diabetic at baseline, the proportion who shifted to normoglycaemic at Week 68 was 89.5% for semaglutide, 64.9% for liraglutide and 13.3% for placebo.
- The % subjects with change in body weight ≥5% at Week 68 was 87.2% for semaglutide, 58.1% for liraglutide and 129.5% for placebo (hypothesis not tested as was exploratory endpoint)

7.3.3. Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide

Study NN9536-4373 (STEP 1) was randomised, double-blind, two-armed, parallel group, placebo-controlled study of the effect on body weight of semaglutide as an adjunct to reduced-calorie diet and increased physical activity. The results of the 68-week main phase have previously been submitted and the results of the 52-week off-treatment extension phase were included in the present submission. The extension study was conducted at 37 sites in five countries: Canada (6), Germany (13), Japan (3), United Kingdom (10) and US (5). The trial was commenced in June 2018 and the extension phase was completed in March 2021.

The trial included Males and females, aged ≥18 years; with BMI ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease; and a history of at least one self-reported unsuccessful dietary effort to lose body weight.

There was no intervention treatment for the extension phase.

There were 333 patients included in the extension study, 232 from the semaglutide group and 101 from the placebo. There were 216 (93.1%) subjects in the semaglutide group and 96 (95.0%) in the placebo who completed the extension phase. There were 228 (98.3%) subjects in the semaglutide group and 99 (98.0%) in the placebo who were included in the extension analysis set. There were 219 (67.0%) females and 108 (33.0%) males and the age range was 18 to 83 years.

In the semaglutide group there was weight loss through to Week 68 when on treatment with semaglutide, but when treatment was ceased weight was regained through to Week 120 (Figure 7.3.3.1). At Week 68, in the semaglutide group the mean (SD) body weight was 87.5 (21.4) kg and at Week 120 it was 99.0 (22.5) kg; mean (SD) increase 12.0 (8.4) kg. This was a mean (SD) increase of 14.8 (10.7) % in the semaglutide group. At Week 68, in the placebo group the mean (SD) body weight was 103.2 (25.6) kg and at Week 120 it was 105.5 (26.2) kg; mean (SD) increase 2.0 (4.8) kg. This was a mean (SD) increase of 2.1 (4.9) % in the placebo group.

In the semaglutide group there was decrease in BMI through to Week 68 when on treatment with semaglutide, but when treatment was ceased BMI increased through to Week 120, but with some preservation of treatment effect over the year without treatment (Figure 7.3.3.2). At Week 68, in the semaglutide group the mean (SD) BMI was 31.2 (7.2) kg/m^2 and at Week 120 it

was 35.0 (7.1) kg/m^2; mean (SD) increase 4.3 (2.9) kg/m^2. At Week 68, in the placebo group the mean (SD) BMI was 36.9 (8.0) kg/m^2 and at Week 120 it was 37.6 (8.2) kg/m^2; mean (SD) increase 0.7 (1.7) kg/m^2.

In the semaglutide group there was an increase in HbA_{1c} after treatment was ceased, predominantly in the first 12 weeks, and by one year off treatment was not significantly different to the placebo group (Figure 7.3.3.3). At Week 68, in the semaglutide group the mean (SD) HbA_{1c} was 33.6 (3.1) mmol/mol and at Week 120 it was 37.5 (3.8) mmol/mol; mean (SD) increase 3.9 (2.9) mmol/mol. At Week 68, in the placebo group the mean (SD) HbA_{1c} was 37.1 (4.2) mmol/mol and at Week 120 it was 38.4 (5.6) mmol/mol; mean (SD) increase 1.4 (2.9) mmol/mol.

The benefits in decreased blood pressure with semaglutide treatment were lost within 12 weeks of ceasing treatment (Figure 7.3.3.4).

Total cholesterol and LDL cholesterol were decreased during semaglutide treatment, and returned to the same concentrations as placebo within 12 weeks of ceasing treatment. However, HDL cholesterol increased with semaglutide treatment, and remained elevated after treatment was ceased (Figure 7.3.3.5). Higher concentrations of HDL cholesterol are associated with decreased cardiovascular risk.

CRP concentrations decreased with semaglutide treatment, and increased following ceasing treatment, but were still less than those of the placebo group after one year off treatment (Figure 7.3.3.6).

7.3.4. Evaluator commentary: other efficacy studies

In Study NN9536-4378 (STEP 5) for a two year treatment duration, there was weight loss for the first year, and preservation of weight loss for the second year, with weekly semaglutide 2.4 mg. The treatment difference (95% CI), semaglutide – placebo, in % body weight was -12.55 (-15.33 to -9.77) %, p <0.0001 (i.e. treatment effect size). There was weight loss to Week 68 of treatment, after which the weight loss was maintained to Week 104 (Figure 7.3.1.1). The improvements in cardiovascular risk factors and glycaemic indices were also preserved during the second year of treatment.

Study NN9536-4376 reported superiority for semaglutide in comparison with liraglutide. The mean (SD) change in body weight % at Week 68 was -16.4 (10.5) % for semaglutide, -6.4 (7.7) % for liraglutide and -1.6 (8.6) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -9.38 (-11.97 to -6.80) %, p <0.0001. The dosing regimen for both treatments was the same as recommended in their respective Product Information. In the SAXENDA product information, in the SCALE Obesity and Pre-diabetes studies the weight loss with liraglutide over a 56 week treatment period, relative to placebo, was -5.4 (-5.8 to 5.0) %. Mean baseline weight was 106.3 kg for the SCALE Obesity and Pre-diabetes studies and 104.5 kg for Study NN9536-4376. This is a similar effect size, in a similar population, for liraglutide to Study 9536-4376, which was -4.48 (-7.25 to -1.71) % p = 0.0015 (from 14.2.9, Study NN9536-4376 study report). The effect size for semaglutide was also consistent with previous studies. Hence, the superiority of semaglutide to liraglutide demonstrated in Study NN9536-4376 is consistent with other available data.

Study NN9536-4373 (STEP 1) demonstrated that the weight loss following one year of semaglutide treatment is not preserved when the treatment is ceased. There was some preservation of weight loss after one year off treatment, but this was despite a clinically significant increase in weight in the semaglutide group after cessation of treatment. There was also loss of the benefits of glycaemic control and blood pressure. However, the semaglutide group retained the benefits of an increase in HDL cholesterol and a decrease in CRP. In conclusion, the results of the study demonstrate that continuing treatment with semaglutide is necessary to preserve weight loss, and the improvements in glycaemic control and cardiovascular risk.

7.4. Analyses performed across trials: pooled and meta analyses

NA.

7.5. Evaluator's conclusions on clinical efficacy

The four Phase III studies presented in the dossier were designed and conducted in accordance with regulatory guidance and were appropriate for the objectives of the studies.

Efficacy in the adolescent population (age range 12 to ≤18 years)

Study NN9536-4451 demonstrated a weight loss in the adolescent group that is comparable to that in the adult age group. This supports extending the indications to include the adolescent age group (12 to ≤18 years). The mean difference (95% CI) compared to placebo in BMI was -16.75 (-20.27 to -13.23) % p <0.0001. This demonstrates a clinically significant treatment effect. The proportion of subjects in the semaglutide group with body weight loss ≥5% at week 68 was 72.5% and in the placebo group was 17.7%, OR (95% CI) 14.02 (6.34 to 31.02), p <0.001. These results established comparability with the treatment effect in the adult population.

In addition, efficacy was demonstrated using outcome measures that accounted for the growth and development that occur in a longitudinal study of one year duration in the adolescent population. These were:

- The estimated mean change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) from baseline to Week 68 was -24.58 %-points with semaglutide and -4.18 %-points with placebo; estimated mean treatment difference (95% CI) -20.40 (-25.01 to -15.79) %-points.
- The mean change in BMI standard deviation score was -1.22 in the semaglutide group and -0.05 in the placebo: estimated mean treatment difference (95% CI) -1.17 (-1.41 to -0.93) p <0.0001 (Table 7.2.1.5 and Figure 7.2.1.4).
- The mean change in waist circumference from baseline to Week 68 was -12.69 cm in the semaglutide group and -0.55 cm in the placebo; estimated on-trial mean treatment difference (95% CI) -12.14 (-15.59 to -8.69) cm, p <0.0001.

Hence, after accounting for growth and development, there is a clinically and statistically significant improvement in measures of obesity and overweight in the adolescent population with semaglutide treatment. In addition, there were improvements in serum lipids (a cardiovascular risk factor) and in glycaemic indices (HbA_{1c} in subjects with T2DM, and FPG in subjects without T2DM).

Extended treatment (treatment over a 2 year period)

Study NN9536-4378 (STEP 5), with a two year treatment duration, demonstrated weight loss for the first year, and preservation of weight loss for the second year, with weekly semaglutide 2.4 mg. The treatment difference (95% CI), semaglutide – placebo, in % body weight was -12.55 (-15.33 to -9.77) %, p <0.0001 (i.e. treatment effect size). There was weight loss to Week 68 of treatment, after which the weight loss was maintained to Week 104 (Figure 7.3.1.1). The improvements in cardiovascular risk factors and glycaemic indices were also preserved during the second year of treatment.

Comparison with liraglutide

Study NN9536-4376 demonstrated superiority for semaglutide in comparison with liraglutide. The mean (SD) change in body weight % at Week 68 was -16.4 (10.5) % for semaglutide, -6.4 (7.7) % for liraglutide and -1.6 (8.6) % for placebo: treatment difference, semaglutide – liraglutide, estimand (95% CI) -9.38 (-11.97 to -6.80) %, p <0.0001. The dosing regimen for both treatments was the same as recommended in their respective Product Information. In the

SAXENDA product information, in the SCALE Obesity and Pre-diabetes studies the weight loss with liraglutide over a 56 week treatment period, relative to placebo, was -5.4 (-5.8 to 5.0) %. Mean baseline weight was 106.3 kg for the SCALE Obesity and Pre-diabetes studies and 104.5 kg for Study NN9536-4376. This is a similar effect size, in a similar population, for liraglutide to Study 9536-4376, which was -4.48 (-7.25 to -1.71) p = 0.0015 (from 14.2.9, Study NN9536-4376 study report). The effect size for semaglutide was also consistent with previous studies. Hence, the superiority of semaglutide to liraglutide demonstrated in Study NN9536-4376 is consistent with other available data.

Effect of ceasing semaglutide after one year

Study NN9536-4373 (STEP 1) demonstrated that the weight loss following one year of semaglutide treatment is not preserved when the treatment is ceased. There was some preservation of weight loss after one year off treatment, but this was despite a clinically significant increase in weight in the semaglutide group after cessation of treatment. There was also loss of the benefits of glycaemic control and blood pressure. However, the semaglutide group retained the benefits of an increase in HDL cholesterol and a decrease in CRP. In conclusion, the results of the study demonstrate that continuing treatment with semaglutide is necessary to preserve weight loss, and the improvements in glycaemic control and cardiovascular risk.

Knowledge gaps

The Sponsor has demonstrated that continued treatment for a second year with semaglutide is required to preserve the weight loss that was achieved during the first year of treatment, and the following questions arise:

- How long is it necessary to continue treatment with semaglutide. Is this a lifelong treatment?
- Do additional treatments result in additional weight loss?
- Does treatment with semaglutide result in decreased long-term morbidity?

These questions are particularly relevant to the adolescent population because of their greater life expectancy.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.1.2. Pivotal and/or main efficacy studies

In the pivotal study (Study NN9536-4451) the safety outcome measures were AEs, pulse rate, amylase, lipase, and calcitonin. Additional safety outcome measures were:

- Occurrence of anti-semaglutide antibodies
- Bone age assessment, x-ray
- ECG
- Laboratory parameters
- Pubertal status (Tanner staging) (stage 2-5 where 5 is full sexual maturity)
- Height standard deviation score
- Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS)
- Patient-Reported Health Questionnaire 9 (PHQ-9)

The safety endpoints in patients with diabetes were:

- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes
- Number of treatment-emergent hypoglycaemic episodes
- Ophthalmological evaluation

8.1.3. Other studies

8.1.3.1. Other efficacy studies

In Study NN9536-4376 and Study NN9536-4378 the safety outcome measures were AEs, vital signs, clinical laboratory tests (including lipase, amylase and calcitonin) and ECGs.

In Study NN9536-4373 Extension AEs were not systematically collected. There were no reports of deaths, SAEs or withdrawals due to AE. Clinical laboratory tests were not performed routinely. Vital signs were recorded as part of the efficacy assessment.

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

NA.

8.1.3.3. Studies evaluable for safety only

NA.

8.2. Studies that assessed safety as the sole primary outcome

NA.

8.3. Patient exposure

In Study NN9536-4451 there were 133 adolescents exposed to semaglutide and 67 to placebo. Overall exposure to semaglutide was 181.8 patient-years.

In Study NN9536-4378 there were 152 subjects exposed to semaglutide for a total of 301.7 patient years and 152 exposed to placebo for a total of 267.9 patient years.

In Study NN9536-4376 there were 126 subjects exposed to semaglutide group, 127 to liraglutide and 85 to placebo for up to 68 weeks.

In Study NN9536-4373 Extension subjects were followed up for one year after ceasing the study treatments. There were 333 patients included in the extension study, 232 from the semaglutide group and 101 from the placebo.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

NA.

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.1.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were 812 TEAEs reported in 106 (79.7%) subjects in the semaglutide group and 333 in 56 (83.6%) in the placebo. Gastrointestinal disorders were the most frequently reported group of disorders and were more frequent in the semaglutide group:

82 (61.7%) subjects compared with 28 (41.8%) in the placebo (Figure 8.4.1.3.1). There was a higher incidence of nausea with semaglutide (56 [42.1%] subjects compared with 12 [17.9%] in the placebo) and vomiting (48 [36.1%] subjects compared with seven [10.4%] in the placebo) (Figure 8.4.1.3.2). The prevalence of gastrointestinal adverse events in the semaglutide group was constant over the period of treatment (Figure 8.4.1.3.3).

8.4.1.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were 1606 adverse events reported in 146 (96.1%) patients in the semaglutide group and 1004 in 136 (89.5%) in the placebo. The most frequently reported TEAEs, which were also more frequent in the semaglutide group, were nausea, diarrhoea, constipation and vomiting (Figure 8.4.1.4.1). Most TEAEs were reported in the first 20 weeks of treatment. There were 696 gastrointestinal AEs reported in 125 (82.2%) subjects in the semaglutide group and 252 in 82 (53.9%) in the placebo. There were four (2.6%) subjects with hepatobiliary disorders in the semaglutide group and two (1.3%) in the placebo.

In Study NN9536-4376 there were 904 TEAEs reported in 120 (95.2%) subjects in the semaglutide group, 823 in 122 (96.1%) in the liraglutide and 522 in 81 (95.3%) in the placebo. Gastrointestinal AEs were more frequent with semaglutide and liraglutide than placebo, particularly nausea, with no clear differences between semaglutide and liraglutide (Figure 8.4.1.4.2).

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

NA.

8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.2.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were 396 possible or probable treatment related TEAEs reported in 77 (57.9%) subjects in the semaglutide group and 98 in 26 (38.8%) in the placebo. There was a higher incidence of nausea attributed to treatment with semaglutide (52 [39.1%] subjects compared with 12 [17.9%] in the placebo), vomiting (40 [30.1%] subjects compared with four [6.0%] in the placebo), abdominal pain (17 [12.8%] subjects compared with two [3.0%] in the placebo) and headache (13 [9.8%] subjects compared with two [3.0%] in the placebo). Injection site AEs were recorded for four (3.0%) subjects in the semaglutide group and three (4.5%) in the placebo.

8.4.2.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were 734 adverse events possibly or probably related to study drug reported in 123 (80.9%) patients in the semaglutide group and 267 in 77 (50.7%) in the placebo. There were 600 gastrointestinal adverse events possibly or probably related to study drug reported in 119 (78.3%) patients in the semaglutide group and 191 in 62 (40.8%) in the placebo. There were 17 administration site AEs reported in 10 (6.6%) subjects in the semaglutide group and 18 in 15 (9.9%) in the placebo.

In Study NN9536-4376 there were 483 AEs possibly or probably related to study treatment reported in 107 (84.9%) subjects in the semaglutide group, 350 in 106 (83.5%) in the liraglutide and 141 in 49 (57.6%) in the placebo. Gastrointestinal AEs attributed to study treatment were more frequent with semaglutide and liraglutide than placebo, to a similar extent for both active treatments (Table 8.4.2.4.1). There were no injection site AEs in the semaglutide group, 16 in 14 (11.0%) subjects in the liraglutide and seven in five (5.9%) in the placebo.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

NA.

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.3.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were no deaths. There were 17 SAEs reported in 15 (11.3%) subjects in the semaglutide group and seven in six (9.0%) in the placebo. There were four (3.0%) subjects with hepatobiliary disorders and two (1.5%) with appendicitis in the semaglutide group and none with either of these conditions in the placebo (Table 8.4.3.3.1). There were six SUSARs in the semaglutide group and two in the placebo. These were predominantly gastrointestinal (Table 8.4.3.3.2).

8.4.3.4. Other studies

Other efficacy studies

In Study NN9536-4378 there was one death in the semaglutide group (acute myocardial infarction). There were 18 SAEs reported in 12 (7.9%) patients in the semaglutide group and 20 in 18 (11.8%) in the placebo. There was no apparent pattern to the SAEs (Table 8.4.3.4.1). There five unblinded SUSARs: three in the semaglutide group (gastroesophageal reflux, cholecystitis, abdominal adhesions), and two in the placebo (gastritis, tension headache).

In Study NN9536-4376 there were no deaths. There were 14 SAEs reported in 10 (7.9%) subjects in the semaglutide group, 18 in 14 (11.0%) in the liraglutide and nine in six (7.1%) in the placebo. There was no apparent pattern to the SAEs (Table 8.4.3.4.2).

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

NA.

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.4.4.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were six (4.5%) subjects with AEs leading to permanent discontinuation of treatment in the semaglutide group (abdominal discomfort, gastritis, vomiting, malaise, decreased appetite, rash) and three (4.5%) in the placebo (nausea, injection site pruritus, mental disorder). There were 14 (10.5%) subjects with AEs leading to temporary interruption of trial product the semaglutide group and five (7.5%) in the placebo. These were predominantly gastrointestinal disorders (Table 8.4.4.3.1). There were 16 (12.0%) subjects with AEs leading to dose reduction of trial product in the semaglutide group and one (1.5%) in the placebo. These were gastrointestinal disorders in 13 (9.8%) of the semaglutide subjects (Table 8.4.4.3.2).

8.4.4.4. Other studies

Other efficacy studies

In Study NN9536-4378 TEAEs leading to permanent discontinuation of study drug were reported in nine (5.9%) patients in the semaglutide group and seven (4.6%) in the placebo. There were more gastrointestinal AEs leading to discontinuation in the semaglutide group: six (3.9%) subjects compared to one (0.7%) in the placebo. TEAEs leading to temporary discontinuation of study drug were reported in 22 (14.5%) patients in the semaglutide group and 13 (8.6%) in the placebo. TEAEs leading to dose reduction of study drug were reported in 17 (11.2%) patients in the semaglutide group and one (0.7%) in the placebo. The TEAEs leading to dose reduction in the semaglutide group were predominantly gastrointestinal.

In Study NN9536-4376 there were four AEs leading to permanent discontinuation reported in four (3.2%) subjects in the semaglutide group, 21 in 16 (12.6%) in the liraglutide and three in three (3.5%) in the placebo. The excess in the liraglutide group was due to gastrointestinal disorders. There were 25 AEs leading to temporary discontinuation reported in 10 (7.9) subjects in the semaglutide group, 29 in 16 (12.6%) in the liraglutide and 15 in six (7.1%) in the placebo. There were 16 AEs leading to dose reduction of trial product reported in 10 (7.9) subjects in the semaglutide group, seven in five (3.9%) in the liraglutide and none in the placebo.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

8.5.1.1. Integrated safety analyses

NA.

8.5.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.1.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 the incidence of hepatic AEs was higher in the semaglutide group: 13 events in 10 (7.5%) subjects, compared with one in one (1.5%) in the placebo (Table 8.5.1.3.1). There were three (2.3%) subjects with increased ALT in the semaglutide group.

8.5.1.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were three (2.0%) subjects with hepatic AEs in the semaglutide group and three (2.0%) in the placebo. Two subjects in each group had elevated ALT.

In Study NN9536-4376 there was one (0.8%) subject in the semaglutide group with elevated ALT.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.2. Renal function and renal toxicity

8.5.2.1. Integrated safety analyses

NA.

8.5.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.2.3. Pivotal and/or main efficacy studies

NA.

8.5.2.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were no events of acute renal failure.

In Study NN9536-4376 there was one subject in the semaglutide group and one in the placebo with acute kidney injury.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.3. Other clinical chemistry

8.5.3.1. Integrated safety analyses

NA.

8.5.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.3.3. Pivotal and/or main efficacy studies

In Study NN95364451 there was one subject in each treatment group with elevated lipase, and one subject in the placebo group with elevated calcitonin.

8.5.3.4. Other studies

Other efficacy studies

In Study NN95364378 there were no treatment emergent cases of pancreatitis. Mean amylase and lipase concentrations increased in the semaglutide group but not to abnormal levels (Figure 8.5.3.4.1 and Figure 8.5.3.4.2). There were no elevations of amylase or lipase >3xULN.

There was no increase in mean calcitonin concentrations. There were no calcitonin concentrations >100 ng/L during the on-treatment period.

In Study NN9536-4376 there was one subject with acute pancreatitis in the liraglutide group and none in the semaglutide or placebo groups. At Week 68, there were eight (7.7%) subjects in the semaglutide group, seven (7.9%) in the liraglutide and one (1.5%) in the placebo with elevated serum lipase. At Week 68, there were three (2.9%) subjects in the semaglutide group, four (4.5%) in the liraglutide and one (1.5%) in the placebo with elevated serum amylase.

At Week 68, there were seven (6.7%) subjects in the semaglutide group, one (1.1%) in the liraglutide and two (3.0%) in the placebo with elevated calcitonin. There were no cases of medullary thyroid carcinoma (MTC).

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

NA.

8.5.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.4.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were no clinically significant abnormalities in haematology parameters.

8.5.4.4. Other studies

Other efficacy studies

In Study NN9536-4378 and Study NN9536-4376 there were no significant differences between the treatment group in mean haematology parameters.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.5. Other laboratory tests

8.5.5.1. Integrated safety analyses

NA.

8.5.5.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.5.3. Pivotal and/or main efficacy studies

NA.

8.5.5.4. Other studies

Other efficacy studies

NA.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

NA.

8.5.6.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.6.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were 13 cardiovascular AEs in 10 (7.5%) subjects in the semaglutide group and seven in seven (10.4%) in the placebo. There were no clinically significant abnormalities in ECGs.

8.5.6.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were fewer cardiovascular AEs in the semaglutide group (19 events in 17 [11.2%] subjects) than in the placebo group (41 events in 30 [19.7%) subjects). There were three subjects in the semaglutide group and two in the placebo with post-baseline clinically significant ECG abnormalities (Table 8.5.6.4.1).

In Study NN9536-4376, cardiovascular AEs were reported in 16 (12.7%) subjects in the semaglutide group, 18 (14.2%) in the liraglutide and nine (10.6%) in the placebo. There were no clinically significant changes in ECG findings.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.7. Vital signs and clinical examination findings

8.5.7.1. Integrated safety analyses

NA.

8.5.7.2. Pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.7.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 mean pulse rate was similar for the two treatment groups. There were no significant differences in vital signs or physical examination findings between the treatment groups.

8.5.7.4. Other studies

Other efficacy studies

In Study NN9536-4378 there was an increase in pulse rate in the semaglutide group relative to placebo: estimated EOT treatment difference (95% CI) 4.14 (2.05 to 6.24) bpm. There was a decrease in SBP and DBP in the semaglutide group from baseline to Week 20, which was then maintained throughout the treatment period (Figure 7.3.1.5).

In Study NN9536-4376 an increase in pulse rate was recorded on-treatment for both the semaglutide and liraglutide treatment groups (Figure 8.5.7.4.1). SBP decreased to a similar extent in the semaglutide and liraglutide groups relative to placebo (Figure 7.3.2.1). For the majority of the treatment period there was no significant difference in DBP between the study groups (Figure 7.3.2.2)

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.8. Immunogenicity and immunological events

8.5.8.1. Integrated safety analyses

NA.

8.5.8.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.8.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were 14 allergic AEs in 12 (9.0%) subjects in the semaglutide group and four in four (6.0%) in the placebo. In the semaglutide group these were predominantly dermatological (Table 8.5.8.3.1). One subject in the semaglutide group was positive for anti-semaglutide antibodies at Week 68, but negative at Week 75.

8.5.8.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were 36 allergic reaction AEs in 23 (15.1%) subjects in the semaglutide group and nine in eight (5.3%) in the placebo. The excess in reactions in the semaglutide group was due to more dermatological reactions, including urticaria and contact dermatitis (Table 8.5.8.4.1).

In Study NN9536-4376 there were 13 allergic reactions in nine (7.1%) subjects in the semaglutide group, 12 in 11 (8.7%) in the liraglutide and 13 in 10 (11.8%) in the placebo. The majority of these events were dermatological (Table 8.5.8.4.2).

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.9. Serious skin reactions

8.5.9.1. Integrated safety analyses

NA.

8.5.9.2. Pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.9.3. Pivotal and/or main efficacy studies

NA.

8.5.9.4. Other studies

Other efficacy studies

NA.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.10. Malignant neoplasms

8.5.10.1. Integrated safety analyses

NA.

8.5.10.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.10.3. Pivotal and/or main efficacy studies

NA.

8.5.10.4. Other studies

Other efficacy studies

In Study NN9536-4378 there were 24 reports of neoplastic events in 19 (12.5%) subjects in the semaglutide group and 23 in 19 (12.5%) in the placebo. There were two reports of malignant neoplastic events in two (1.3%) subjects in the semaglutide group and four in four (2.6%) in the placebo.

In Study NN9536-4376, there were 16 reports of neoplastic events in 13 (10.3%) subjects in the semaglutide group, 24 in 17 (13.4%) in the liraglutide and 16 in 12 (14.1%) in the placebo. There were three malignant neoplasms reported in the semaglutide group, three in the liraglutide and one in the placebo. There were no clinically significant changes in ECG findings.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.11. Mental Health

8.5.11.1. Integrated safety analyses

NA.

8.5.11.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.11.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there were no significant differences between the treatment groups in PHQ-9. By end of treatment there were no subjects in the semaglutide group with suicidal ideation and/or behaviour (on the C-SSRS questionnaire) and three (4.8%) in the placebo.

8.5.11.4. Other studies

Other efficacy studies

In Study NN9536-4378 psychiatric disorders were reported in 26 (17.1%) subjects in the semaglutide group and 25 (16.4%) in the placebo. There were no significant differences between the treatment groups in PHQ-9 or C-SSRS.

In Study NN9536-4376 psychiatric AEs were reported in seven (5.6%) subjects in the semaglutide group, 19 (15.0%) in the liraglutide and nine (10.6%) in the placebo. There were no significant differences between the treatment groups in PHQ-9 or C-SSRS.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.5.12. Growth

8.5.12.1. Integrated safety analyses

NA.

8.5.12.2. Main/pivotal studies that assessed safety as the sole primary outcome

NA.

8.5.12.3. Pivotal and/or main efficacy studies

In Study NN9536-4451 there was no significant difference between the treatment groups in growth parameters (Table 8.5.12.3.1). The mean (SD) change from baseline in height was 1.3 (2.1) cm for semaglutide and 2.1 (2.6) cm for placebo. The mean (SD) change from baseline in height SDS was -0.076 (0.252) for semaglutide and -0.048 (0.249) for placebo. The mean (SD) change from baseline in bone age was 1.3 (0.8) years for semaglutide and 1.5 (0.9) years for placebo. There were no significant differences between the treatment groups in bone metabolism biomarkers. There were no significant differences between the treatment groups in the shifts in pubertal status from baseline to Week 68 (Figure 8.5.12.3.1). There were no clinically significant differences between the treatment groups in the serum concentrations of TSH, FT_4, dehydroepiandrosterone sulfate, estradiol, FSH, IGF-1, LH, or prolactin.

8.5.12.4. Other studies

Other efficacy studies

NA.

Studies with evaluable safety data: dose finding and pharmacology

NA.

Studies evaluable for safety only

NA.

8.6. Other safety issues

8.6.1. Safety in special populations

In Study NN9536-4451 there was one subject who became pregnant during treatment with semaglutide. Exposure to semaglutide was for the first 2 months of pregnancy. There was a spontaneous vaginal delivery at term of a live female infant, birth weight 2820 g (10th centile for birth weight). The child was normal on examination with no congenital malformations.

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

NA.

8.7. Post marketing experience

NA.

8.8. Evaluator's overall conclusions on clinical safety

The profile of adverse effects in the adolescent population is similar to the adult population. There were more adverse effects with semaglutide than with placebo, primarily due to an increase in gastrointestinal AEs. However, although a large proportion of the semaglutide treated patients experienced gastrointestinal AEs there were relatively few SAEs. There were double the number of SAEs in the semaglutide group compared with placebo, also due to an excess of gastrointestinal SAEs. There were few discontinuations due to AEs. There were dose reductions in 12% of adolescent subjects, primary related to GI disturbance. Hence, the majority of gastrointestinal AEs were tolerable, with or without dose reduction.

Semaglutide did not interfere with growth, development or puberty in the adolescent population. There were no malignancies reported in the adolescent population. There was one subject treated with semaglutide with elevated lipase, and no reports of pancreatitis. There were no subjects in the semaglutide group with elevated calcitonin.

With extended treatment, over a two year period, most TEAEs were reported in the first 20 weeks of treatment. These were predominantly gastrointestinal in the semaglutide treatment group and did not increase over time. The rate of SAEs in the semaglutide population was similar to that in the placebo. There was one death in the semaglutide group that was not attributed to study treatment. Over a two-year period the incidence of neoplasia in the semaglutide group was that same as the placebo group. The incidence of cardiovascular AEs was approximately half that of the placebo group.

The profile of adverse effects was similar for semaglutide and liraglutide. Both treatments had increased incidences of gastrointestinal AEs compared to placebo. There were more AEs leading to discontinuation in the liraglutide group, and more leading to dose reductions in the semaglutide. Hence, semaglutide may have better tolerability than liraglutide.

With discontinuation of semaglutide, there was weight gain and other losses of treatment effect. However, there were no reports of AEs related to withdrawal and no rebound effects.

In conclusion, the data presented in the dossier confirm the known adverse event profile of semaglutide and no new safety concerns were identified.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
With semaglutide, weight loss in the adolescent group is comparable to that in the adult age group. The mean difference (95% CI) compared to placebo in BMI was -16.75 (-20.27 to -13.23) % p <0.0001. Efficacy was demonstrated using outcome measures that accounted for the growth and development that occur in a longitudinal study of one year duration in the adolescent population. The mean change in BMI standard deviation score was -1.22 in the semaglutide group and -0.05 in the placebo: estimated mean treatment difference (95% CI) -1.17 (-1.41 to -0.93) p <0.0001. With a two year treatment duration, there was clinically significant weight loss for the first year, and preservation of weight loss for the second year. Over two years of treatment the treatment difference (95% CI), semaglutide – placebo, in % body weight was -12.55 (-15.33 to -9.77) %, p <0.0001 (i.e. treatment effect size). The improvements in cardiovascular risk factors and glycaemic indices were also preserved during the second year of treatment. There is superiority for semaglutide in comparison with liraglutide: treatment difference for change in body weight % at Week 68, semaglutide – liraglutide, estimand (95% CI) -9.38 (-11.97 to -6.80) %, p <0.0001. The weight loss following one year of semaglutide treatment is not preserved when the treatment is ceased, necessitating long-term treatment in order to preserve weight loss.	As the efficacy data indicate long-term treatment with semaglutide is required to preserve weight loss, the following knowledge gaps arise: • How long is it necessary to continue treatment with semaglutide. Is this a lifelong treatment? • Do additional treatments result in additional weight loss? • Does treatment with semaglutide result in decreased long-term morbidity? These questions are particularly relevant to the adolescent population because of their greater life expectancy.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
The profile of adverse effects in the adolescent population is similar to the adult population. There were more adverse effects with semaglutide than with placebo, but the majority of gastrointestinal AEs were tolerable, with or without dose reduction. Semaglutide did not interfere with growth, development or puberty in the adolescent population. With extended treatment, over a two year period, most TEAEs were reported in the first 20 weeks of treatment. These were predominantly gastrointestinal in the semaglutide treatment group and did not increase over time. Over a two-year period the incidence of neoplasia in the semaglutide group was that same as the placebo group. The incidence of cardiovascular AEs was approximately half that of the placebo group. The profile of adverse effects was similar for semaglutide and liraglutide. With discontinuation of semaglutide, there was weight gain and other losses of treatment effect, but there were no reports of AEs related to withdrawal and no rebound effects.	Semaglutide is likely to be used for prolonged periods, due to the loss of effect when treatment is ceased. Hence, there is still uncertainty about the safety of semaglutide with prolonged treatment (e.g. 5 to 10 years).

9.3. First round assessment of benefit-risk balance

Semaglutide has a favourable benefit-risk balance in the 12 to ≤18 years age group. The effects on weight are similar to the adult population as is the adverse events profile. There were no adverse effects on growth, development and puberty in the adolescent population.

10. First round recommendation regarding authorisation

The Clinical Evaluator has no objection to the approval of the Category 1, Type C (extension of indications) application relating to WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, for the indication of:

Adults

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

- *≥30 kg/m² (obesity), or*
- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties - Clinical trials).*

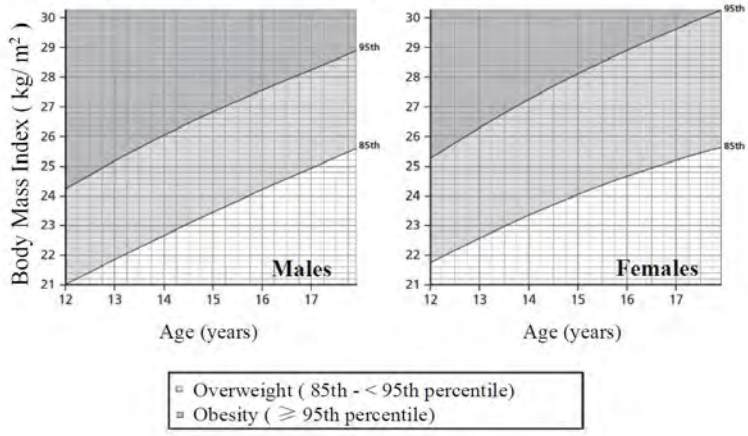
Adolescents

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- *obesity* or*
- *overweight* and at least one weight-related comorbidity*

**Obesity (BMI ≥95th percentile) and overweight (BMI ≥85th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Figure 1).*

Figure 1 BMI cut-off points for obesity (≥95th percentile) and overweight (≥85th percentile)



11. First round comments on product documentation

11.1. First round comments on draft PI (clinical aspects)

The proposed new dosing for adolescents is consistent with the inclusion criteria and dosing regimen used in Study NN9536-4451 and confirmed in Study NN9536-4451 Modelling Report. The proposed dosing escalation schedule is also consistent with these study reports.

The additions in Section 4.8 are consistent with the data presented in the dossier, which indicate a similar adverse event profile in the adolescent population to that in the adult population.

The comments in Section 5.1 with regard to the Control of Eating Questionnaire (CoEQ) are supported by the results of Study NN9536-4378 (Figure 7.3.1.7).

The discussion of the results from Study NN9536-4373 (STEP 1) Extension state that "However, for patients that had been treated with semaglutide for the main trial period the weight remained 5.6% below baseline compared to 0.1% for the placebo group5." This understates the results of the extension where the benefit at 68 weeks decreased to less than one third by Week 120. This would better inform patients and prescribers if the PI stated that when treatment was ceased weight was regained through to Week 120 and there was a mean (SD) increase of 14.8 (10.7) % in the semaglutide group. This should be illustrated with the inclusion of Figure 7.3.3.1.

Table 8, the table of results from Study NN95364378 (STEP 5), appears to be using the estimands for the outcome measures, from the ANCOVA models, rather than the observed changes. However, this does not increase the treatment effect sizes and the Clinical Evaluator does not object.

Table 9, the table of results from Study NN9536-4376 (STEP 8) appears to be using the estimands for the outcome measures, from the ANCOVA and logistic regression models, rather than the observed changes. However, this does not increase the treatment effect sizes for semaglutide and the Clinical Evaluator does not object.

Table 11, the table of results from Study NN9536-5551 (STEP TEENS) is in general agreement with the results from the study. Effect sizes are not overstated in the table. Table 13, and the related text, are in agreement with the study results.

In Section 5.2, the amended text on pharmacokinetics in paediatrics is in agreement with Study NN9536-4451 Modelling Report.

11.2. First round comments on draft CMI (clinical aspects)

The proposed changes to the CMI relate only to the proposed extension of the indication to the adolescent population. The changes relate to the dosing and the indication only. The Clinical Evaluator has no objection to these changes.

11.3. First round comments on draft RMP (Summary of Safety Concerns)

In the Australian Specific Annex of the RMP the summary of safety concerns has been updated to align with the European RMP.

Important Identified Risks have been changed from:

- Diabetic retinopathy complications

to:

- Diabetic retinopathy complications (only for patients with type 2 diabetes)

Important Potential Risks have been changed from:

- Neoplasms (malignant and non-malignant)
- Pancreatic cancer
- Medullary thyroid cancer
- Pregnancy and lactation

To:

- Pancreatic cancer
- Medullary thyroid cancer

Missing Information has been changed from:

- Patients with severe hepatic impairment

to:

- Pregnancy and lactation
- Patients with severe hepatic impairment

In the opinion of the Clinical Evaluator, neoplasia may have a long lead time before becoming clinically apparent. Hence, although there are no indications from the data presented in the dossier that neoplasia is a risk with semaglutide, the duration studied (i.e. 2 years) may be insufficient to detect such a risk, especially in the paediatric and adolescent populations. Hence, removal of neoplasia from Important Potential Risks may be premature.

12. Clinical questions

12.1. Clinical questions

Can the Sponsor please provide an update on the similar applications in the US and EU?

How do the dossiers submitted in the US and EU differ to the dossier submitted in Australia?

12.1.1. Pharmacokinetics

The Clinical Evaluator has no questions relating to pharmacokinetics.

12.1.2. Pharmacodynamics

The Clinical Evaluator has no questions relating to pharmacodynamics.

12.1.3. Efficacy

The Sponsor has demonstrated that continued treatment for a year with semaglutide is required to preserve the weight loss that was achieved during the first year of treatment, and the following questions arise:

- How long is it necessary to continue treatment with semaglutide. Is this a lifelong treatment?
- Do additional treatments result in additional weight loss?
- Does treatment with semaglutide result in decreased long-term morbidity?

These questions are particularly relevant to the adolescent population because of their greater life expectancy.

12.1.4. Safety

Semaglutide is likely to be used for prolonged periods, due to the loss of effect when treatment is ceased. Hence, there is still uncertainty about the safety of semaglutide with prolonged treatment (e.g. 5 to 10 years). Does the Sponsor have any data relating to safety during prolonged treatment (e.g. 5 to 10 years)?

12.1.5. PI and CMI

The Clinical Evaluator has no questions relating to either the PI or CMI.

12.2. Additional expert input

The Clinical Evaluator has no recommendation for additional expert input.

13. First round evaluation errata

13.1. Minor editorial changes

There are no minor editorial changes to the Round 1 Clinical Evaluation Report.

13.2. Minor errors of fact

The Sponsor has identified the following minor error of fact in the Round 1 Clinical Evaluation Report:

Page 20, Section 4.2.5.1 Study NN9536-4451 Modelling Report

Paragraph 1, sentence 1 states:

The Study NN9536-4451 Modelling Report (Section 19.1.3.1) conducted a population PK analysis of plasma concentration and covariate data from STEP TEEN (Section 7.2.1) and STEP1 (a Phase II study conducted in adults).

The sponsor notes that STEP1 is a Phase IIIa study therefor this sentence should read as follows:

The Study NN9536-4451 Modelling Report (Section 19.1.3.1) conducted a population PK analysis of plasma concentration and covariate data from STEP TEEN (Section 7.2.1) and STEP1 (a Phase ~~II~~ IIIa study conducted in adults).

Clinical Evaluator's comments: This error has been corrected in the report.

13.3. Significant errors of fact

No significant errors of fact were identified in the Round 1 Clinical Evaluation Report.

14. Second round evaluation

The Sponsor has provided the following responses to the Clinical Questions:

1.1.1 Question 1

Can the Sponsor please provide an update on the similar application in the US and EU?

Sponsor's response:

The adolescent indication application received market approval in EU 28 April 2023 and in US 23 December 2022.

s47 [redacted]

Clinical Evaluator's comments: The Sponsor's response is satisfactory. The Clinical Evaluator notes that the adolescent indication application has received market approval in the EU and in the US.

1.1.2 Question 2

How do the dossiers submitted in the US and EU differ to the dossier submitted in Australia?

Sponsor's response:

For the adolescent indication data, the same module 2 & 5 documents submitted in EU and US were submitted in Australia.

For the 2-year efficacy data, the same module 2 & 5 documents submitted in EU were submitted in Australia.

Clinical Evaluator's response: The Sponsor's response is satisfactory. The Sponsor has clarified the similarities between the dossiers.

1.2 Efficacy

1.2.1 Question 3

The Sponsor has demonstrated that continued treatment for a year with semaglutide is required to preserve the weight loss that was achieved during the first year of treatment, and the following questions arise:

- **How long is it necessary to continue treatment with semaglutide. Is this a lifelong treatment?**

- **Do additional treatments result in additional weight loss?**
- **Does treatment with semaglutide result in decreased long-term morbidity?**

These questions are particularly relevant to the adolescent population because of their greater life expectancy.

Sponsor's response:

1.2.1.1 Response to Question 3

How long is it necessary to continue treatment with semaglutide. Is this a lifelong treatment?

Wegovy® is indicated for the treatment of chronic weight management (including weight loss and weight maintenance) as an adjunct to a reduced-energy diet and increased physical activity.

Obesity has previously been characterised as a lifestyle-related issue that could be effectively addressed by dietary modifications and increased physical activity. However, a vast body of scientific evidence shows that, like other chronic diseases, obesity is a heterogeneous condition caused by complex interactions of a multitude of sociological, psychological and biological factors that promote excessive weight gain and ultimately impair health.[1]

Recognising the serious complications associated with obesity, a number of leading global institutions, such as the Obesity Society,[2, 3] the World Obesity Federation,[4] the American Medical Association,[5] the Canadian Medical Association,[6] WHO,[7] the American Association of Clinical Endocrinologists[8, 9] and the European Association for the Study of Obesity,[10] now classify obesity as a disease. Recently (March 2021), the European Commission has classified obesity as a chronic disease.[11] The Royal Australian College of General Practitioners (RACGP) recognises that obesity is one of the most important health issues in Australia, with the condition being linked directly and indirectly to many chronic conditions and also causes significant morbidity.[12]

Most importantly, once obesity is established, powerful neuro-hormonal factors effectively defend the body against weight loss, thereby often making obesity a life-long problem, where weight regain is the rule rather than the exception following weight loss attempts.[13]

The effect of discontinuing treatment for any chronic therapy will likely result in a return towards baseline of disease symptoms. Novo Nordisk acknowledges the consideration that the treatment effect of semaglutide 2.4 mg does not persist after ceased treatment, and that data indicate that Wegovy® is likely to be required long-term to maintain the weight loss.

Clinical Evaluator's comments: The Sponsor's response is satisfactory. However, in the opinion of the Clinical Evaluator, in recognition of the likely long-term, or even lifelong, treatment duration of semaglutide for obesity the Sponsor should conduct ongoing long-term studies of safety and efficacy, particularly in those patients commencing treatment in adolescence.

Sponsor's response:

Do additional treatments result in additional weight loss?

Although no data beyond 2 years are currently available, the results from 104 weeks of treatment with semaglutide 2.4 mg in the phase 3b trial (NN9536-4378; STEP 5) did not indicate any waning of the weight loss effect of semaglutide 2.4 mg over time. The STEP 5 trial demonstrated persistence of semaglutide 2.4 mg treatment effect beyond one year of treatment. At present there is no data to suggest that the effect of semaglutide 2.4 mg on weight loss will decrease beyond 2 years of treatment. Based on the sustained and clinically significant results over 2 years, the long-term data are therefore highly supportive of Wegovy® as long-term treatment for chronic weight management.

It is still to be investigated whether higher doses of semaglutide or adding other anti-obesity medications to semaglutide will result in additional weight loss. A higher dose of 7.2 mg semaglutide s.c. is currently being investigated in adult patients with obesity (NN9536-4999; STEP

UP) and in adult patients with obesity and T2D (NN9536-7545; STEP UP T2D). s47 [redacted] ***In addition, a fixed dose combination of semaglutide and cagrilintide (CagriSema) is currently being investigated in adult patients with obesity and T2D and in adult patients with obesity in the phase 3a development programme REDEFINE. The results from the phase 2 trial (NN9838-4862) in patients with obesity and T2D exploring CagriSema versus the mono components indicated that CagriSema reduced blood sugar more than semaglutide alone and the weight loss seen in the trial confirmed the substantial weight lowering potential of CagriSema.***

Clinical Evaluator's comments: The Sponsor's response is satisfactory. At the present time, the Sponsor does not have any additional data with regard to with regard to additional treatments resulting in additional weight loss. The Clinical Evaluator notes that the Sponsor is investigating this issue.

Sponsor's response:

Does treatment with semaglutide result in decreased long-term morbidity?

In the STEP development programme, treatment with semaglutide 2.4 mg of up to 2 years, was associated with persistent beneficial effect on cardiovascular risk factors including hsCRP, systolic blood pressure, lipids, body weight, and glucose metabolism. These results were supported by data from the SUSTAIN (semaglutide s.c. 0.5 mg and 1.0 mg once weekly) phase 3a programme for treatment of T2D. Similarly, in adolescents, treatment with semaglutide 2.4 mg was associated with beneficial effect on cardiovascular risk factors including hsCRP, systolic blood pressure, lipids, body weight, and glucose metabolism.

Furthermore, in the SUSTAIN T2D development programme, the CV safety of semaglutide s.c. 0.5 mg and 1.0 mg once-weekly was assessed in a pre-approval non-inferiority CVOT (NN9535-3744; SUSTAIN 6) in patients with T2D and high CV risk. The trial indicated a statistically significant 26% risk reduction (hazard ratio (HR): 0.74 [0.58; 0.95]95% CI) with semaglutide compared to placebo for the primary endpoint of time to first EAC-confirmed MACE, comprising CV death, non-fatal MI and non-fatal stroke.

Thus, semaglutide has unique therapeutic potential for weight management, including weight loss and weight maintenance, due to its combined effects not only on body weight but also on glucose metabolism and other weight-related comorbidities.

Although no data beyond 2 years are currently available for Wegovy®, the cardiovascular outcomes trial (CVOT), EX9536-4388, hereafter referred to as the SELECT trial is currently ongoing and expected supportive long-term efficacy and safety results will be available later in 2023. Approximately 300 subjects from Australia were included in SELECT.

The SELECT trial is a phase 3b CVOT that is designed to demonstrate superiority of semaglutide 2.4 mg once-weekly vs placebo, both added to standard of care in participants with established CV disease and overweight or obesity, but without diabetes, in reducing the risk of MACE (defined as CV death, non-fatal MI or non-fatal stroke). The primary endpoint is time from randomisation to first occurrence of a composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke. Supportive secondary endpoints included change in body weight (%), waist circumference (cm), blood pressure (mmHg), lipids (mg/dL), and hsCRP (mg/L) from randomisation to year 2/week 104.

In conclusion, available data indicate that semaglutide s.c. improves cardiovascular risk factors in patients, including adolescents, with obesity and/or T2D and reduces the risk of MACE in adult patients with T2D and high CV risk. Long-term results with semaglutide 2.4 mg from SELECT is expected to further inform on the potential for decreased long-term morbidity.

Clinical Evaluator's comments: The Sponsor's response is satisfactory. At the present time, the Sponsor does not have any additional data with regard to decreased long-term morbidity

beyond 2 years of treatment. However, the Clinical Evaluator notes that the Sponsor is investigating this issue with the SELECT study.

1.3 Safety

1.3.1 Question 4

Semaglutide is likely to be used for prolonged periods, due to the loss of effect when treatment is ceased. Hence, there is still uncertainty about the safety of semaglutide with prolonged treatment (e.g. 5 to 10 years). Does the Sponsor have any data relating to safety during prolonged treatment (e.g. 5 to 10 years)?

Sponsor's response:

No safety data has been collected for Wegovy® for prolonged treatment of 5 to 10 years.

Extending treatment with semaglutide 2.4 mg beyond one year as carried out in the 104-week STEP 5 trial did not change the overall safety conclusion compared to the 68-week phase 3a trials. There were no unexpected safety findings in the two-year trial and the overall safety and tolerability profile reflected that of the 68-week phase 3a trials and the GLP-1 RA class generally, with gastrointestinal events as the most common events. Based on these results, it is not expected that treatment beyond 2 years would cause any new safety issues compared to shorter-term treatment.

Wegovy® was first marketed in the US on 16 June 2021. Hence, post-marketing data beyond 2 years does not currently exist.

Semaglutide s.c. for T2D (marketed under the tradename Ozempic®) with a maintenance dose of 1.0 mg once-weekly have been marketed since 09 January 2018. s47 [redacted]

Clinical Evaluator's comments: The Sponsor's response is satisfactory. The Sponsor does have safety data for semaglutide at a lower dose for use beyond 2 years, but does not have data for treatment beyond 5 years. The Clinical Evaluator notes that the Sponsor will be performing routine pharmacovigilance according to the RMP.

In addition to the above responses, the Sponsor has included the following table in the revised Product Information document:

Table 1 BMI cut-off points for obesity (≥95th percentile) and overweight (≥85th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 85th Percentile		BMI (kg/m2) at 95th Percentile	
	Males	Females	Males	Females
12	s47	[redacted]	24.2	25.2
12.5			24.7	25.7
13			25.1	26.3
13.5			25.6	26.8
14			26.0	27.2
14.5			26.4	27.7
15			26.8	28.1
15.5			27.2	28.5
16			27.5	28.9
16.5			27.9	29.3
17			28.2	29.6
17.5			28.6	30.0

In the opinion of the Clinical Evaluator, the table provides additional useful information to prescribers and should be included in the PI.

15. Second round benefit-risk assessment

15.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of semaglutide in the proposed usage are unchanged from those identified in Section 9.1.

15.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of semaglutide in the proposed usage are unchanged from those identified in Section 9.2.

15.3. Second round assessment of benefit-risk balance

Semaglutide has a favourable benefit-risk balance in the 12 to ≤18 years age group. The effects on weight are similar to the adult population as is the adverse events profile. There were no adverse effects on growth, development and puberty in the adolescent population.

16. Second round recommendation regarding authorisation

The Clinical Evaluator has no objection to the approval of the Category 1, Type C (extension of indications) application relating to WEGOVY (semaglutide) 0.25 mg (0.5 mg/mL), 0.5 mg (1.0 mg/mL), 1.0 mg (2.0 mg/mL), 1.7 mg (2.27 mg/mL) and 2.4 mg (3.2 mg/mL), solution for injection, for the indication of:

Adults

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

- *≥30 kg/m² (obesity), or*
- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).*

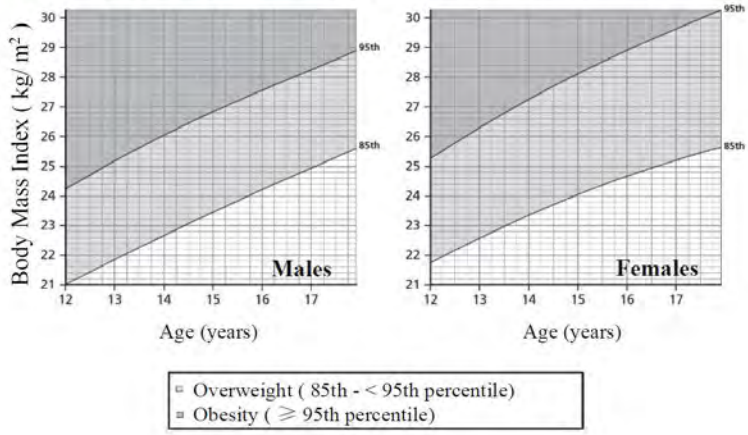
Adolescents

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- *obesity* or*
- *overweight* and at least one weight-related comorbidity*

**Obesity (BMI ≥95th percentile) and overweight (BMI ≥85th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Figure 1).*

Figure 1 BMI cut-off points for obesity (≥95th percentile) and overweight (≥85th percentile)



17. Second round comments on product documentation

17.1. Second round comments on draft PI (clinical aspects)

The Sponsor has made amendments to the PI. These are:

- The addition of a new Table 1 to provide BMI cutoff points for obesity by age category.
- The following alterations to Section 4.2:

> *Children and adolescents*
> Safety and efficacy of Wegovy in children ~~and adolescents~~ below ~~18~~ 12 years have not been studied.
>
> For adolescents ages 12 years and above, the same dose escalation schedule as for adults should be applied (see Table 2). The dose should be increased until 2.4 mg (maintenance dose) or maximum tolerated dose has been reached. Weekly doses higher than 2.4 mg are not recommended[2].

- The following alterations to Section 4.4:

> **Paediatric use**
> Safety and efficacy of Wegovy in children ~~and adolescents~~ below ~~18~~ 12 years have not been studied.

The Clinical Evaluator has no objection to these amendments.

17.2. Second round comments on draft CMI (clinical aspects)

The Sponsor has included “gliclazide or glimepiride” as examples of sulfonylureas in the CMI. The Clinical Evaluator has no objection to this amendment.

17.3. Second round comments on draft RMP (Summary of Safety Concerns)

The Sponsor has updated the ASA to add section 3.3 Summary table of additional pharmacovigilance activities, a table for ongoing and planned additional pharmacovigilance activities corresponding to the table EU-RMP.

The Clinical Evaluator has no objection to this amendment.

The comments on the Summary of Safety Concerns made in Section 11.3 are unchanged.

18. References

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Data presented in the dossier:

Population pharmacokinetic study:

- (NN9536-4451 Modelling Report)

Phase III studies:

- Study NN9536-4451 (STEP TEENS): weight management in adolescents with overweight or obesity
- Study NN9536-4378 (STEP 5): extended treatment
- Study NN9536-4376 (STEP 8): comparison with liraglutide
- Study NN9536-4373 (STEP 1) Extension: effect of ceasing semaglutide

19. Supporting information, tables and figures

19.1. Clinical pharmacology study synopses

19.1.1. Synopses of pharmacokinetic studies

NA.

19.1.2. Synopses of pharmacodynamics studies

NA.

19.1.3. Synopses of population pharmacokinetics analyses

19.1.3.1. NN9536-4451 Modelling Report: Population PK and Exposure-Response Analysis

Objectives:

The objective of the analysis was to support the dose selection in the target adolescent population (12 to <18 years), and in the STEP Young trial in children (6 to <12 years), specifically by addressing the following key questions:

PK-questions (based on across trial comparison):

- Are semaglutide exposure levels similar in adolescents (12 to <15 years and 15 to <18 years) and adult subjects?
- What are the expected semaglutide concentration levels in children from 6 to <12 years of age?

Exposure-response questions (based on across trial comparison):

- Does exposure-response analysis indicate improvement in BMI with increasing exposure in adolescents?
- And is the exposure-response relationship similar to adults?
- Does exposure-response analysis indicate increasing proportion of subjects reporting gastrointestinal adverse events with increasing exposure in adolescents?
- Is the exposure-response relationship similar to adults?

Data:

The data were provided by two studies:

- STEP1: a randomised, placebo controlled study of semaglutide 2.4 mg in overweight or obese adult subjects
- STEP TEENS (Study NN9536-4451, Section 7.2.1), a randomised placebo controlled study of semaglutide 2.4 mg in overweight or obese adolescents

There were 8395 concentration samples from 1419 subjects: 1295 adults and 124 adolescents. In the study population, there were 1440 subjects, with 1039 females and 401 males (Table 19.1.3.1.1). There were 47 subjects aged 12 to <15 years and 87 aged 15 to <18 years.

There were 375 (4.3%) observations excluded from eight subjects: 206 (2.3%) were <LLOQ, 168 (1.9%) had inadequate dosing history and one had a non-positive time.

The plasma samples were analysed using a liquid chromatography-mass spectrometry (LC/MS/MS) assay. The LLOQ was 0.729 nmol/L.

Methods:

R version 3.5.3 was used for data file processing, explorative data analysis and plotting. NONMEM (ICON Development Solutions, Ellicott City, MD, USA) ver. 7.3 and Perl-speaks-NONMEM ver. 4.6.0 were used for the population PK analysis.

The base model used a previously developed one-compartment model. The error model included between subject variability on CL/F and V/F. The residual variability was described by a dual proportional error model (with separate proportional error terms for each trial, STEP1 and STEP TEENS).

The covariates tested were sex, age group (12 to <15 years, 15 to <18 years and ≥65 years), race (Black or African American), Ethnicity (Hispanic or Latino), baseline body weight and glycaemic status.

Neither variability nor covariates were modelled for K_a due to the limited data that would describe absorption.

Missing on-treatment BMI and weight data were imputed using MMRM.

Model selection criteria included:

Diagnostic plots:

- Observed concentration vs individual predicted concentrations
- Observed concentrations vs population predicted concentrations
- CWRES vs time since first dose
- CWRES vs population predicted concentrations
- CWRES distribution vs standard normal distribution

Visual predictive checks were also used to evaluate the reduced and full models.

Sensitivity analyses were performed with datasets that included imputation of samples <LLOQ, imputing missing dosing data and excluding data records with CWRES >5 (potential outliers).

Semaglutide exposure for a population of children and adolescents aged from 6 to <18 years was simulated using the model developed in the study.

For the exposure response models, exposure parameters (C_{avg} and $AUC_{0\text{-}168h}$) were predicted from the popPK model. The exposure response models were linear regression models with % change in BMI and gastrointestinal AEs as the outcome variables, and as covariates: baseline BMI, sex, log-transformed C_{avg} by sex interaction and log-transformed C_{avg} by trial interaction.

The results of the sensitivity analysis did not diverge significantly from the primary analysis.

Results:

The parameter estimates for the base model had good precision for the estimates and acceptable shrinkage for the residual error terms, but shrinkage was high for the IIV on V/F (43.5%) (Table 19.1.3.1.2). The diagnostic plots showed a good fit for the model (Figure 19.1.3.1.1).

For the full model, precision of the estimates was acceptable, except for dose-effect on CL/F in STEP TEENs which had %RSE of 40.3% (Table 19.1.3.1.3). Shrinkage on V/F was still high at 45.1%. The diagnostic plots indicate some divergence from a normal distribution for the CWRES (Figure 19.1.3.1.2). This may indicate a problem with the error model.

For the reduced model there was excellent precision for the estimates, and shrinkage was acceptable except for V/F which remained high at 44.6% (Table 19.1.3.1.4). The diagnostic plots also indicate some divergence from a normal distribution for the CWRES (Figure 19.1.3.1.3). This may indicate a problem with the error model. There were some observations that appear to be outliers (CWRES >5) but these did not have an influence on the estimates in the sensitivity analysis. The VPCs for the final model are acceptable and indicate a good predictive ability for the model (Figure 19.1.3.1.4).

The only clinically significant covariate for exposure was body weight, with decreased exposure with increasing body weight (Figure 19.1.3.1.5).

From the model, in the adolescent population geometric mean (CV%) C_{avg} was 74 nmol/L (26%), $AUC_{0\text{-}168h}$ was 12366 nmol•h/L (26%) and CL/F was 0.047 L/h (26%) (Table 19.1.3.1.5).

Using the model, CL/F and C_{avg} were simulated for a semaglutide 2.4 mg dose, for a population with body weight from 47.2 to 114.1 kg, representing a population with overweight or obesity aged 6 to <18 years (Figure 19.1.3.1.6). The starting dose of 0.25 mg in the paediatric population did not result in greater exposure than the 0.5 mg dose in the adult population (Figure 19.1.3.1.7). The Sponsor concluded with the flexibility of dose escalation, that the adult dosing regimen would be appropriate for the STEP Young trial population of ages 6 to <12 years.

The exposure response analysis for effect on BMI included 201 subjects from STEP TEENS and 1961 subjects from STEP 1; and the analysis for safety included 200 subjects from STEP TEENS and 1961 subjects from STEP 1. The covariates are summarised in Table 19.1.3.1.6.

There was a linear relationship between exposure and decrease in BMI with decreasing BMI with increasing exposure (Figure 19.1.3.1.8). There was poor precision for the estimate of baseline BMI effect, but the remaining parameters were estimated with adequate precision (Table 19.1.3.1.7).

There was no strong relationship between exposure and nausea and the parameters in the model were estimated with poor precision (Figure 19.1.3.1.9 and Table 19.1.3.1.8).

There was no strong relationship between exposure and vomiting and the parameters in the model were estimated with poor precision (Figure 19.1.3.1.10 and Table 19.1.3.1.9).

Clinical Evaluator's Comments

The modelling study demonstrates increased exposure to semaglutide in subjects with lower body weight. Given a median weight of 100 kg, the increase in exposure for a subject of 76 kg was approximately 25% and the decrease in exposure in a subject of 147 kg was approximately 25% (Figure 19.1.3.1.5). In the opinion of the Clinical Evaluator, this range of variation is unlikely to be clinically important. There were no other significant covariate effects on exposure.

Increasing exposure was associated with greater decreases in BMI. However, this could be biased because the lower weight individuals, with greater exposure, would still have been growing, and therefore had an advantage in weight change relative to height (i.e. BMI). This relationship between exposure and BMI decrease was more pronounced in the adolescent group.

There was no clear relationship between nausea or vomiting and exposure in these analyses. There was poor precision of the estimates in the linear models and the plots of exposure vs % subjects effected did not have a slope significantly different to 0.

With regard to extrapolation of the results to the 6 to <12 years population, there are some limitations to the model. The shrinkage on V/F was high which means there may be some issues with the individual predicted values. This could bias the simulation of exposure in the 6

to <18 years age group. The exponent for body weight on CL/F was 0.885 and on V/F was 0.806. These differ from the usual allometric exponents of 0.75 on CL and 1.0 on V. This may also result in some bias when extrapolating the model to a younger age group. However, for the purpose of designing the dosing regimen for a study in the 6 to <12 years age group, the model is adequate for the purpose. The dosing regimen can be modified if indicated by the results of the proposed clinical study.

19.2. Other supporting tables and figures

Table 7.2.1.1 Flowchart (copied from Table 9-3, Study NN9536-4451)

	Screening	Run-in						Randomisation	Dose escalation								Maintenance													End of treatment	End of trial
Visit[a]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	P25	V26	P27	V28	P29	V30	V31
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7/0	±3	±7	±3	±7	±3	±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Attend visit fasting (Appendix 16.1.1 [Protocol Section 6.5.1])		X						X												X										X	X
Informed consent, Informed assent and Demography[b] (Appendix 16.1.1 [Protocol, Appendix 3])	X																														
Inclusion and exclusion criteria (Appendix 16.1.1 [Protocol, Sections 6.1 and 6.2])	X	X																													
Run-in criteria (Appendix 16.1.1 [Protocol, Section 6.3])			X	X	X	X	X																								
Randomisation criteria and randomisation (Appendix 16.1.1 [Protocol, Section 6.4])								X																							
Medical history/ Concomitant illness and Tobacco Use[c] (Appendix 16.1.1 [Protocol, Sections 6.5.2 and 9.4])	X																														
Concomitant medication (Appendix 16.1.1 [Protocol, Section 7.7])	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childbearing potential[d], Menstrual cycle[e] and Pregnancy test[f] (Appendix 16.1.1 [Protocol, Sections 9.2.6, 9.4.7, 9.10.2 and Appendix 5])	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pubertal Status (Appendix 16.1.1 [Protocol, Section 9.4.3])	X							X												X										X	
ECG (Appendix 16.1.1 [Protocol, Section 9.4.6])	X							X																						X	
Vital Signs (Appendix 16.1.1 [Protocol, Section 9.4.4])	X							X		X		X		X		X		X		X		X		X		X		X		X	X
Laboratory assessments (Appendix 16.1.1 [Protocol, Appendix 2])	X	X						X[g]				X[h]				X[h]				X[h]		X[h]				X[h]				X[h]	X
Biosamples for future analysis[i] (Appendix 16.1.1 [Protocol, Sections 9.7 and 9.9])								X																						X	

Table 7.2.1.1 (cont)

	Screening	Run-in						Randomisation	Dose escalation								Maintenance													End of treatment	End of trial
Visit[a]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	P13	V14	P15	V16	P17	V18	P19	V20	P21	V22	P23	V24	P25	V26	P27	V28	P29	V30	V31
Timing of Visit (Weeks)	-14	-12	-10	-8	-6	-4	-2	0	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56	60	64	68	75
Visit Window (Days)	-7/0	±3	±7	±3	±7	±3	±7	±0	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Clinical Outcome Assessments (Appendix 16.1.1 [Protocol, Sections 9.1.2 and 9.4.1])	X							X												X										X	
Physical examination (Appendix 16.1.1 [Protocol, Section 9.4.2])	X							X												X										X	
Height (Appendix 16.1.1 [Protocol, Section 9.1.1])	X							X						X						X				X		X				X	X
Body Weight (Appendix 16.1.1 [Protocol, Section 9.1.1])	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
Waist Circumference (Appendix 16.1.1 [Protocol, Section 9.1.1])	X							X												X										X	
Bone age measurement (x-ray) (Appendix 16.1.1 [Protocol, Section 9.4.5])								X																						X	
Evaluation of glycaemic status (Appendix 16.1.1 [Protocol, Section 9])								X												X										X	
Adverse event (Appendix 16.1.1 [Protocol, Section 9.2, Appendix 4 and Appendix 6])		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet and physical activity counselling[j] (Appendix 16.1.1 [Protocol, Sections 7.1.2 and 7.1.3])		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand out and instruct in Diary (Appendix 16.1.1 [Protocol, Section 9])	X[k]									X				X				X		X				X				X			
Collect, review and transcribe diary (Appendix 16.1.1 [Protocol, Sections 9.10])								X[k]				X				X				X		X				X				X	
Connect to IWRS (Appendix 16.1.1 [Protocol, Section 7.3])	X							X																						X	
Training in trial product, pen-handling (Appendix 16.1.1 [Protocol, Section 7.1.1])								X				X				X		X		X		X		X		X		X			
Drug handling (Appendix 16.1.1 [Protocol, Sections 7.1, 7.3 and 7.5])								X				X				X		X		X		X		X		X		X		X	
Trial product compliance (Appendix 16.1.1 [Protocol, Sections 7.1 and 7.6])									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 7.2.1.1 (cont)

a) Visits marked as phone visits could be replaced by site visits or video calls to ensure flexibility for the subjects
b) Demography consists of date of birth, sex, ethnicity, and race (according to local regulation)
c) Smoking is defined as smoking at least one daily cigarette or equivalent (e.g. cigar, hookah or e-cigarette)
d) Only for females
e) Only for females that have started their menstrual period (of childbearing potential)
f) Only for females that have started their menstrual period (of childbearing potential): Urine pregnancy test should also be performed at any time during the trial if pregnancy was suspected, if a menstrual period was missed, and/or according to local regulations/law. If a female became of childbearing potential (had first menstrual period) during the trial a urine pregnancy test was to be performed for that subject at the latest at the next site visit. For country specific requirements, see Appendix 16.1.1 (Protocol, Appendix 11).
g) Blood samples should be taken prior to product dosing
h) Due to PK sampling, subjects was to be instructed to withhold their trial product dose in the morning until blood sampling had been performed at the visit. This was not applicable for subjects that had discontinued trial product
i) Only for subjects where the separate informed consent for future research had been signed
j) The counselling could be done independent of the site visits within the visit window and flexibly as site visits or phone or video call
k) Only for females (for menstrual period record in run-in period)

Table 7.2.1.2 Subject disposition - summary - all subjects (copied from Table 10-1, Study NN9536-4451)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Screened			229
Screening failures			21
Withdrawn before randomisation*			7
Randomised	134 (100)	67 (100)	201 (100)
Randomised in violation of incl., excl. criteria	2 (1.5)	1 (1.5)	3 (1.5)
Exposed	133 (99.3)	67 (100)	200 (99.5)
Analysis sets			
Full analysis set	134 (100)	67 (100)	201 (100)
Safety analysis set	133 (99.3)	67 (100)	200 (99.5)
Treatment completion			
On-treatment at week 68 (treatment completers)	120 (89.6)	60 (89.6)	180 (89.6)
After at least one temporary interruption	11 (8.2)	4 (6.0)	15 (7.5)
Attended end-of-treatment visit without permanent discontinuation of trial product	120 (89.6)	59 (88.1)	179 (89.1)
Trial product permanently discontinued	14 (10.4)	7 (10.4)	21 (10.4)
Primary reason for permanent discontinuation of trial product			
Adverse event	6 (4.5)	4 (6.0)	10 (5.0)
Protocol violation	2 (1.5)	1 (1.5)	3 (1.5)
Randomised in violation of incl., excl. criteria	2 (1.5)	1 (1.5)	3 (1.5)
Intention of becoming pregnant	0	0	0
Simultaneous participation in another clinical trial	0	0	0
Other	0	0	0
Pregnancy	1 (0.7)	0	1 (0.5)
Lack of efficacy	0	0	0
At the discretion of the investigator	0	0	0
Safety concern as judged by the investigator	0	0	0
Withdrawal of consent	1 (0.7)	1 (1.5)	2 (1.0)
Lost to follow-up	0	0	0
Other	4 (3.0)	1 (1.5)	5 (2.5)
Attended end-of-treatment visit after permanent discontinuation of trial product	13 (9.7)	5 (7.5)	18 (9.0)
Trial completion			
Attended end-of-trial visit (trial completers)	132 (98.5)	64 (95.5)	196 (97.5)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	120 (89.6)	59 (88.1)	179 (89.1)
Withdrawn from trial	2 (1.5)	3 (4.5)	5 (2.5)
Primary reason for trial withdrawal			
Withdrawal by subject	1 (0.7)	2 (3.0)	3 (1.5)
Withdrawal by parent/guardian	0	1 (1.5)	1 (0.5)
Lost to follow-up	1 (0.7)	0	1 (0.5)
Death	0	0	0
Withdrawn from trial before week 68	2 (1.5)	2 (3.0)	4 (2.0)
Withdrawn from trial without prior permanent discontinuation of trial product	0	0	0

N: Number of subjects, %: Percentages are based on randomised subjects.
* Includes two subjects who were withdrawn before the run-in period started.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).
Only reasons for permanent discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.

Table 7.2.1.3 Demographics and baseline characteristics – categorial variables (copied from Table 10-2, Study NN9536-4451)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	134	67	201
Age (years)			
N	134 (100)	67 (100)	201 (100)
12-<15	47 (35.1)	25 (37.3)	72 (35.8)
15-<18	87 (64.9)	42 (62.7)	129 (64.2)
Sex			
N	134 (100)	67 (100)	201 (100)
Female	84 (62.7)	41 (61.2)	125 (62.2)
Male	50 (37.3)	26 (38.8)	76 (37.8)
Country			
N	134 (100)	67 (100)	201 (100)
Austria	4 (3.0)	7 (10.4)	11 (5.5)
Belgium	15 (11.2)	9 (13.4)	24 (11.9)
Croatia	12 (9.0)	4 (6.0)	16 (8.0)
Ireland	3 (2.2)	1 (1.5)	4 (2.0)
Mexico	13 (9.7)	5 (7.5)	18 (9.0)
Russian Federation	37 (27.6)	18 (26.9)	55 (27.4)
United Kingdom	15 (11.2)	7 (10.4)	22 (10.9)
United States	35 (26.1)	16 (23.9)	51 (25.4)
Ethnic origin			
N	134 (100)	67 (100)	201 (100)
Not Hispanic or Latino	120 (89.6)	59 (88.1)	179 (89.1)
Hispanic or Latino	14 (10.4)	8 (11.9)	22 (10.9)
Not Applicable	0	0	0
Race			
N	134 (100)	67 (100)	201 (100)
White	104 (77.6)	55 (82.1)	159 (79.1)
Other	14 (10.4)	6 (9.0)	20 (10.0)
Black or African American	11 (8.2)	5 (7.5)	16 (8.0)
Asian	3 (2.2)	1 (1.5)	4 (2.0)
American Indian or Alaska Native	2 (1.5)	0	2 (1.0)
Native Hawaiian or Other Pacific Islander	0	0	0
BMI (kg/m^2)			
N	134 (100)	67 (100)	201 (100)
<30	12 (9.0)	8 (11.9)	20 (10.0)
30-<35	45 (33.6)	26 (38.8)	71 (35.3)
35-<40	33 (24.6)	19 (28.4)	52 (25.9)
>=40	44 (32.8)	14 (20.9)	58 (28.9)
Smoking habits			
N	134 (100)	67 (100)	201 (100)
Never smoked	129 (96.3)	64 (95.5)	193 (96.0)
Previous smoker	2 (1.5)	1 (1.5)	3 (1.5)
Current smoker	3 (2.2)	2 (3.0)	5 (2.5)
Stratification on Tanner Stage and sex			
N	134 (100)	67 (100)	201 (100)
Female with Tanner Stage 2-3	4 (3.0)	1 (1.5)	5 (2.5)
Female with Tanner Stage 4-5	80 (59.7)	40 (59.7)	120 (59.7)
Male with Tanner Stage 2-3	10 (7.5)	7 (10.4)	17 (8.5)
Male with Tanner Stage 4-5	40 (29.9)	19 (28.4)	59 (29.4)

CDC: Centers for Disease Control and Prevention. N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index. Overall Tanner Stage for each subject is calculated as maximum Tanner Stage combining all the categorical questions per visit.
The last available and eligible observation at or prior to the randomisation visit was selected for summary except for age where date of informed consent was used. Weight categories according to CDC are based on BMI growth charts: Normal weight: BMI <85th percentile; Overweight: BMI >=85th - <95th percentile; Obesity class I: BMI >=95th - <120% of the 95th percentile; Obesity class II: BMI >=120% of the 95th percentile - <140% of the 95th percentile; Obesity class III: BMI >=140% of the 95th percentile.

Table 7.2.1.4 Demographics and baseline characteristics – continuous variables (copied from Table 10-3, Study NN9536-4451)

	Sema 2.4 mg	Placebo	Total
Number of subjects	134	67	201
Age (years)			
N	134	67	201
Mean (SD)	15.5 (1.5)	15.3 (1.6)	15.4 (1.6)
Median	15.8	15.4	15.7
P5 ; P95	13 ; 18	12 ; 18	13 ; 18
Min ; Max	12 ; 18	12 ; 18	12 ; 18
Height (m)			
N	134	67	201
Mean (SD)	170.1 (9.4)	168.8 (10.6)	169.7 (9.8)
Median	170.1	167.8	169.3
P5 ; P95	156.2 ; 186.3	152.9 ; 188.0	154.0 ; 187.9
Min ; Max	146.5 ; 193.0	146.6 ; 192.1	146.5 ; 193.0
Body weight (kg)			
N	134	67	201
Mean (SD)	109.9 (25.2)	102.6 (22.3)	107.5 (24.5)
Median	106.4	97.8	104.3
P5 ; P95	75.7 ; 156.8	73.5 ; 140.7	75.1 ; 151.8
Min ; Max	61.6 ; 211.9	61.0 ; 147.4	61.0 ; 211.9
BMI (kg/m^2)			
N	134	67	201
Mean (SD)	37.7 (6.7)	35.7 (5.4)	37.0 (6.4)
Median	36.7	34.9	36.2
P5 ; P95	28.7 ; 49.8	28.0 ; 45.7	28.5 ; 49.4
Min ; Max	26.8 ; 60.0	26.6 ; 49.9	26.6 ; 60.0
BMI CDC % of 95th percentile			
N	134	67	201
Mean (SD)	133.8 (22.7)	127.8 (17.6)	131.8 (21.2)
Median	130.0	125.1	128.0
P5 ; P95	104.4 ; 174.3	104.9 ; 162.8	104.9 ; 167.0
Min ; Max	99.5 ; 206.4	101.7 ; 166.2	99.5 ; 206.4
BMI SDS (score)			
N	134	67	201
Mean (SD)	3.39 (0.92)	3.15 (0.71)	3.31 (0.86)
Median	3.24	2.96	3.09
P5 ; P95	2.2 ; 5.1	2.3 ; 4.4	2.2 ; 4.9
Min ; Max	2.0 ; 6.6	2.1 ; 5.0	2.0 ; 6.6
Height SDS (score)			
N	134	67	201
Mean (SD)	0.74 (1.03)	0.61 (1.13)	0.70 (1.06)
Median	0.74	0.64	0.67
P5 ; P95	-1.0 ; 2.4	-1.3 ; 2.3	-1.2 ; 2.4
Min ; Max	-2.0 ; 3.5	-2.3 ; 3.3	-2.3 ; 3.5
Waist circumference (cm)			
N	134	67	201
Mean (SD)	111.9 (16.9)	107.3 (13.4)	110.4 (16.0)
Median	110.0	107.5	110.0
P5 ; P95	87.5 ; 141.0	87.0 ; 131.0	87.5 ; 138.5
Min ; Max	79.0 ; 163.0	84.5 ; 140.0	79.0 ; 163.0
HbA1c (%)			
N	134	67	201
Mean (SD)	5.5 (0.4)	5.5 (0.4)	5.5 (0.4)
Median	5.5	5.4	5.5
P5 ; P95	5.0 ; 6.0	4.9 ; 6.1	5.0 ; 6.0
Min ; Max	4.8 ; 9.0	4.8 ; 7.0	4.8 ; 9.0

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, SDS: Standard Deviation Score (reference WHO 2007), HbA1c: Haemoglobin A1c. BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) (%). CDC: Centers for Disease Control and Prevention.
The last available and eligible observation at or prior to the randomisation visit was selected for summary except for age where date of informed consent was used.

Table 7.2.1.5 BMI (standard deviation score) change from baseline to week 68 - statistical analysis - hypothetical estimand - full analysis set (copied from 14.2.76, Study NN9536-4451)

	FAS	N	Estimate	95% CI	p-value
BMI SDS (score)					
MMRM					
Mean at Visit 30 (week 68)					
Sema 2.4 mg	134	108	2.09		
Placebo	67	55	3.26		
Change from baseline to Visit 30 (week 68)					
Sema 2.4 mg	134	108	-1.22		
Placebo	67	55	-0.05		
Treatment difference					
Sema 2.4 mg - Placebo			-1.17	[-1.41; -0.93]	<0.0001

FAS: Full analysis set, N: Number of subjects with an observation at the visit, CI: Confidence interval, SDS: Standard Deviation Score (reference WHO 2007).
Analysis of data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. MMRM: All responses prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline body weight as covariate, all nested within visit.

Table 7.3.1.1 Subject disposition - summary - all subjects (copied from Table -2, Synopsis, Study NN9536-4378)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Screened			347
Screening failures			42
Withdrawn before randomisation			1
Randomised	152 (100)	152 (100)	304 (100)
Randomised in violation of incl., excl. and/or randomisation criteria	2 (1.3)	1 (0.7)	3 (1.0)
Exposed	152 (100)	152 (100)	304 (100)
Analysis sets			
Full analysis set	152 (100)	152 (100)	304 (100)
Safety analysis set	152 (100)	152 (100)	304 (100)
Treatment completion			
On-treatment at week 104 (treatment completers)	132 (86.8)	111 (73.0)	243 (79.9)
After at least one temporary interruption	19 (12.5)	10 (6.6)	29 (9.5)
Attended end-of-treatment visit without permanent discontinuation of trial product	132 (86.8)	111 (73.0)	243 (79.9)
Trial product permanently discontinued	20 (13.2)	41 (27.0)	61 (20.1)
Primary reason for permanent discontinuation of trial product			
Adverse event	10 (6.6)	7 (4.6)	17 (5.6)
Protocol violation	0	1 (0.7)	1 (0.3)
Simultaneous participation in another clinical trial	0	1 (0.7)	1 (0.3)
Pregnancy	1 (0.7)	0	1 (0.3)
Lack of efficacy	2 (1.3)	7 (4.6)	9 (3.0)
Safety concern as judged by the investigator	1 (0.7)	1 (0.7)	2 (0.7)
Withdrawal of consent	0	4 (2.6)	4 (1.3)
Lost to follow-up	3 (2.0)	12 (7.9)	15 (4.9)
Other	3 (2.0)	9 (5.9)	12 (3.9)
Attended end-of-treatment visit after permanent discontinuation of trial product	16 (10.5)	26 (17.1)	42 (13.8)
Trial completion			
Attended end-of-trial visit (trial completers)	148 (97.4)	134 (88.2)	282 (92.8)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	132 (86.8)	110 (72.4)	242 (79.6)
Withdrawn from trial	4 (2.6)	18 (11.8)	22 (7.2)
Primary reason for trial withdrawal			
Withdrawal by subject	0	4 (2.6)	4 (1.3)
Lost to follow-up	3 (2.0)	14 (9.2)	17 (5.6)
Death	1 (0.7)	0	1 (0.3)
Withdrawn from trial before week 104	4 (2.6)	16 (10.5)	20 (6.6)
Withdrawn from trial without prior permanent discontinuation of trial product	1 (0.7)	4 (2.6)	5 (1.6)

N: Number of subjects, %: Percentages are based on randomised subjects.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 104). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 104).
Only reasons for permanent discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.

Table 7.3.1.2 Demographics and baseline characteristics – summary (copied from Table -3, Synopsis, Study NN9536-4378)

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	152	152	304
Age (years)			
N	152 (100)	152 (100)	304 (100)
18-<65	140 (92.1)	145 (95.4)	285 (93.8)
65-<75	11 (7.2)	7 (4.6)	18 (5.9)
75-<85	1 (0.7)	0	1 (0.3)
>=85	0	0	0
Sex			
N	152 (100)	152 (100)	304 (100)
Female	123 (80.9)	113 (74.3)	236 (77.6)
Male	29 (19.1)	39 (25.7)	68 (22.4)
BMI (kg/m^2)			
N	152 (100)	152 (100)	304 (100)
<30	6 (3.9)	3 (2.0)	9 (3.0)
30-<35	47 (30.9)	58 (38.2)	105 (34.5)
35-<40	49 (32.2)	33 (21.7)	82 (27.0)
>=40	50 (32.9)	58 (38.2)	108 (35.5)
Body weight (kg)			
N	152	152	304
Mean (SD)	105.6 (20.8)	106.5 (23.1)	106.0 (22.0)
Median	100.8	102.8	102.1
P5 ; P95	78.4 ; 141.9	77.0 ; 143.8	78.4 ; 143.5
Min ; Max	68.3 ; 197.5	65.4 ; 251.4	65.4 ; 251.4
BMI (kg/m^2)			
N	152	152	304
Mean (SD)	38.6 (6.7)	38.5 (7.2)	38.5 (6.9)
Median	38.0	36.7	37.6
P5 ; P95	30.2 ; 50.5	30.5 ; 50.1	30.4 ; 50.3
Min ; Max	27.6 ; 63.5	27.7 ; 82.7	27.6 ; 82.7
Waist circumference (cm)			
N	152	152	304
Mean (SD)	115.8 (14.3)	115.7 (15.5)	115.7 (14.8)
Median	114.0	113.0	114.0
P5 ; P95	95.0 ; 142.0	95.1 ; 142.2	95.1 ; 142.0
Min ; Max	83.0 ; 166.0	88.0 ; 193.4	83.0 ; 193.4
HbA1c (%)			
N	152	152	304
Mean (SD)	5.7 (0.3)	5.7 (0.4)	5.7 (0.3)
Median	5.7	5.7	5.7
P5 ; P95	5.2 ; 6.3	5.2 ; 6.3	5.2 ; 6.3
Min ; Max	4.9 ; 6.5	4.8 ; 7.0	4.8 ; 7.0

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.3.1.3 Overview of primary endpoints and confirmatory secondary endpoints (test hierarchy) – primary analyses - treatment policy estimand (copied from Table 11-1, Study NN9536-4378)

Endpoint	Est.	95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoints						
Body weight (%) change from baseline to week 104						
Sema 2.4 mg - Placebo	-12.55	[-15.33; -9.77]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=5% at week 104						
Sema 2.4 mg / Placebo	4.99	[2.95; 8.42]	<.0001	0.05	Superiority	Confirmed
Other confirmatory endpoints						
Odds of achieving baseline body weight loss >=10% at week 104						
Sema 2.4 mg / Placebo	7.23	[3.95; 13.23]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=15% at week 104						
Sema 2.4 mg / Placebo	9.40	[4.41; 20.04]	<.0001	0.05	Superiority	Confirmed
Waist circumference (cm) change from baseline to week 104						
Sema 2.4 mg - Placebo	-9.17	[-12.17; -6.17]	<.0001	0.05	Superiority	Confirmed
Systolic blood pressure (mmHg) change from baseline to week 104						
Sema 2.4 mg - Placebo	-4.15	[-7.32; -0.98]	0.0102	0.05	Superiority	Confirmed

Est.: Estimate, alpha: Local significance level, CI: Confidence interval, p-value: Unadjusted two-sided p-value for test of no difference.

Table 7.3.2.1 Subject disposition – all subjects (copied from Table 10-1, Study NN9536-4376)

	Sema 2.4 mg N (%)	Lira 3.0 mg N (%)	Pooled Placebo N (%)	Total N (%)
Screened				387
Screening failures				47
Withdrawn before randomisation				2
Randomised	126 (100)	127 (100)	85 (100)	338 (100)
Exposed	126 (100)	127 (100)	85 (100)	338 (100)
Analysis sets				
Full analysis set	126 (100)	127 (100)	85 (100)	338 (100)
Safety analysis set	126 (100)	127 (100)	85 (100)	338 (100)
Treatment completion				
On-treatment at week 68 (treatment completers)	109 (86.5)	92 (72.4)	70 (82.4)	271 (80.2)
After at least one temporary interruption	12 (9.5)	2 (1.6)	3 (3.5)	17 (5.0)
Attended end-of-treatment visit without permanent discontinuation of trial product	109 (86.5)	92 (72.4)	70 (82.4)	271 (80.2)
Trial product permanently discontinued	17 (13.5)	35 (27.6)	15 (17.6)	67 (19.8)
Primary reason for permanent discontinuation of trial product				
Adverse event	3 (2.4)	15 (11.8)	3 (3.5)	21 (6.2)
Protocol violation	2 (1.6)	1 (0.8)	0	3 (0.9)
Simultaneous participation in another clinical trial	2 (1.6)	0	0	2 (0.6)
Other	0	1 (0.8)	0	1 (0.3)
Pregnancy	2 (1.6)	1 (0.8)	0	3 (0.9)
Lack of efficacy	0	0	2 (2.4)	2 (0.6)
Safety concern as judged by the investigator	0	1 (0.8)	0	1 (0.3)
Withdrawal of consent	1 (0.8)	3 (2.4)	1 (1.2)	5 (1.5)
Lost to follow-up	3 (2.4)	7 (5.5)	4 (4.7)	14 (4.1)
Other	6 (4.8)	7 (5.5)	5 (5.9)	18 (5.3)
Attended end-of-treatment visit after permanent discontinuation of trial product	9 (7.1)	25 (19.7)	10 (11.8)	44 (13.0)
Trial completion				
Attended end-of-trial visit (trial completers)	120 (95.2)	118 (92.9)	81 (95.3)	319 (94.4)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	108 (85.7)	92 (72.4)	70 (82.4)	270 (79.9)
Withdrawn from trial	6 (4.8)	9 (7.1)	4 (4.7)	19 (5.6)
Primary reason for trial withdrawal				
Withdrawal by subject	2 (1.6)	4 (3.1)	1 (1.2)	7 (2.1)
Lost to follow-up	4 (3.2)	5 (3.9)	3 (3.5)	12 (3.6)
Withdrawn from trial before week 68	4 (3.2)	6 (4.7)	2 (2.4)	12 (3.6)
Withdrawn from trial without prior permanent discontinuation of trial product	1 (0.8)	2 (1.6)	1 (1.2)	4 (1.2)

N: Number of subjects, %: Percentages are based on randomised subjects.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).
Only reasons for permanent discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.

Table 7.3.2.2 Demographics and baseline characteristics for categorical variables (copied from Table 10-2, Study NN9536-4376)

	Sema 2.4 mg N (%)	Lira 3.0 mg N (%)	Pooled Placebo N (%)	Total N (%)
Number of subjects	126	127	85	338
Age (years)				
N	126 (100)	127 (100)	85 (100)	338 (100)
18-<65	107 (84.9)	110 (86.6)	76 (89.4)	293 (86.7)
65-<75	17 (13.5)	15 (11.8)	9 (10.6)	41 (12.1)
75-<85	2 (1.6)	2 (1.6)	0	4 (1.2)
>=85	0	0	0	0
Sex				
N	126 (100)	127 (100)	85 (100)	338 (100)
Female	102 (81.0)	97 (76.4)	66 (77.6)	265 (78.4)
Male	24 (19.0)	30 (23.6)	19 (22.4)	73 (21.6)
Ethnic origin				
N	126 (100)	127 (100)	85 (100)	338 (100)
Not Hispanic or Latino	111 (88.1)	110 (86.6)	78 (91.8)	299 (88.5)
Hispanic or Latino	15 (11.9)	17 (13.4)	7 (8.2)	39 (11.5)
Race				
N	126 (100)	127 (100)	85 (100)	338 (100)
White	94 (74.6)	95 (74.8)	60 (70.6)	249 (73.7)
Black or African American	25 (19.8)	20 (15.7)	19 (22.4)	64 (18.9)
Asian	4 (3.2)	6 (4.7)	3 (3.5)	13 (3.8)
Other	2 (1.6)	3 (2.4)	2 (2.4)	7 (2.1)
Native Hawaiian or Other Pacific Islander	1 (0.8)	3 (2.4)	1 (1.2)	5 (1.5)
American Indian or Alaska Native	0	0	0	0
BMI (kg/m^2)				
N	126 (100)	127 (100)	85 (100)	338 (100)
<30	9 (7.1)	11 (8.7)	4 (4.7)	24 (7.1)
30-<35	51 (40.5)	42 (33.1)	20 (23.5)	113 (33.4)
35-<40	37 (29.4)	38 (29.9)	31 (36.5)	106 (31.4)
>=40	29 (23.0)	36 (28.3)	30 (35.3)	95 (28.1)
Smoking habits				
N	126 (100)	127 (100)	85 (100)	338 (100)
Never smoked	81 (64.3)	94 (74.0)	51 (60.0)	226 (66.9)
Previous smoker	36 (28.6)	23 (18.1)	31 (36.5)	90 (26.6)
Current smoker	9 (7.1)	10 (7.9)	3 (3.5)	22 (6.5)
Glycaemic status				
N	126 (100)	127 (100)	85 (100)	338 (100)
Normo-glycaemia	83 (65.9)	82 (64.6)	51 (60.0)	216 (63.9)
Pre-diabetes	43 (34.1)	45 (35.4)	34 (40.0)	122 (36.1)

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index. The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.3.2.3 Demographics and baseline characteristics for continuous variables (copied from Table 10-3, Study NN9536-4376)

	Sema 2.4 mg	Lira 3.0 mg	Pooled Placebo	Total
Number of subjects	126	127	85	338
Age (years)				
N	126	127	85	338
Mean (SD)	48 (14)	49 (13)	51 (12)	49 (13)
Median	49	49	52	49
P5 ; P95	25 ; 71	29 ; 70	29 ; 68	27 ; 71
Min ; Max	18 ; 78	19 ; 79	25 ; 74	18 ; 79
Height (m)				
N	126	127	85	338
Mean (SD)	1.66 (0.09)	1.67 (0.09)	1.67 (0.09)	1.67 (0.09)
Median	1.64	1.64	1.66	1.65
P5 ; P95	1.55 ; 1.84	1.54 ; 1.85	1.54 ; 1.83	1.54 ; 1.84
Min ; Max	1.50 ; 1.93	1.50 ; 1.92	1.45 ; 2.02	1.45 ; 2.02
Body weight (kg)				
N	126	127	85	338
Mean (SD)	102.5 (25.3)	103.7 (22.5)	108.8 (23.1)	104.5 (23.8)
Median	95.6	101.8	109.1	100.7
P5 ; P95	77.5 ; 145.5	74.5 ; 147.9	80.6 ; 145.4	76.6 ; 146.8
Min ; Max	67.5 ; 248.1	62.0 ; 204.2	64.1 ; 225.8	62.0 ; 248.1
BMI (kg/m^2)				
N	126	127	85	338
Mean (SD)	37.0 (7.4)	37.2 (6.4)	38.8 (6.5)	37.5 (6.8)
Median	35.2	35.9	37.9	36.3
P5 ; P95	29.8 ; 48.6	29.2 ; 48.8	30.0 ; 48.8	29.6 ; 48.8
Min ; Max	26.5 ; 81.0	27.6 ; 67.5	28.4 ; 68.4	26.5 ; 81.0
Waist circumference (cm)				
N	126	127	85	338
Mean (SD)	111.8 (16.3)	113.5 (15.0)	115.4 (15.1)	113.3 (15.5)
Median	110.0	113.5	115.0	112.0
P5 ; P95	92.7 ; 141.3	94.4 ; 141.0	93.0 ; 141.0	93.0 ; 141.3
Min ; Max	87.0 ; 211.4	81.3 ; 165.1	88.6 ; 176.2	81.3 ; 211.4
HbA1c (%)				
N	126	127	85	338
Mean (SD)	5.5 (0.3)	5.5 (0.3)	5.6 (0.4)	5.5 (0.3)
Median	5.5	5.5	5.6	5.5
P5 ; P95	4.9 ; 6.1	5.1 ; 6.1	5.1 ; 6.3	5.0 ; 6.1
Min ; Max	4.8 ; 6.4	4.6 ; 6.3	4.9 ; 6.7	4.6 ; 6.7
HbA1c (mmol/mol)				
N	126	127	85	338
Mean (SD)	36.9 (3.7)	36.9 (3.5)	37.7 (3.9)	37.1 (3.7)
Median	36.6	36.6	37.7	36.6
P5 ; P95	30.1 ; 43.2	32.2 ; 43.2	32.2 ; 45.4	31.2 ; 43.2
Min ; Max	29.0 ; 46.5	26.8 ; 45.4	30.1 ; 49.7	26.8 ; 49.7
Fasting plasma glucose (mg/dL)				
N	125	125	84	334
Mean (SD)	96.1 (10.2)	95.2 (8.5)	97.6 (12.2)	96.1 (10.2)
Median	94.1	94.2	95.6	94.4
P5 ; P95	84.7 ; 114.1	83.4 ; 110.1	81.5 ; 121.1	82.7 ; 115.7
Min ; Max	71.0 ; 136.8	73.3 ; 124.7	77.8 ; 131.0	71.0 ; 136.8
Fasting plasma glucose (mmol/L)				
N	125	125	84	334
Mean (SD)	5.3 (0.6)	5.3 (0.5)	5.4 (0.7)	5.3 (0.6)
Median	5.2	5.2	5.3	5.2
P5 ; P95	4.7 ; 6.3	4.6 ; 6.1	4.5 ; 6.7	4.6 ; 6.4
Min ; Max	3.9 ; 7.6	4.1 ; 6.9	4.3 ; 7.3	3.9 ; 7.6

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile, BMI: Body mass index, HbA1c: Haemoglobin A1c.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Table 7.3.2.4 Overview of primary endpoints and confirmatory secondary endpoints (test hierarchy) - primary analyses – treatment policy estimand (copied from Table 11-1, Study NN9536-4376)

Endpoint	Est. 95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoint					
Body weight (%) change from baseline to week 68					
Sema 2.4 mg - Lira 3.0 mg	-9.38 [-11.97; -6.80]	<.0001	0.05	Superiority	Confirmed
Other confirmatory endpoints					
Odds of achieving baseline body weight loss >=10% at week 68					
Sema 2.4 mg / Lira 3.0 mg	6.28 [3.53; 11.18]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=15% at week 68					
Sema 2.4 mg / Lira 3.0 mg	7.90 [4.06; 15.38]	<.0001	0.05	Superiority	Confirmed
Odds of achieving baseline body weight loss >=20% at week 68					
Sema 2.4 mg / Lira 3.0 mg	8.19 [3.51; 19.13]	<.0001	0.05	Superiority	Confirmed

Est.: Estimate, alpha: Local significance level, CI: Confidence interval, p-value: Unadjusted two-sided p-value for test of no difference.

Table 8.4.2.4.1 Adverse events possibly or probably related to trial product by SOC and PTs (>=2% in any treatment group) – on-treatment (copied from Table 12-2, Study NN9536-4376)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Lira 3.0 mg N	(%)	E	R	Pooled Placebo N	(%)	E	R
Number of subjects	126				127				85			
Patient years of exposure (PYE)	170.2				160.6				111.2			
Events	107	(84.9)	483	283.8	106	(83.5)	350	218.0	49	(57.6)	141	126.8
Gastrointestinal disorders	104	(82.5)	390	229.2	98	(77.2)	266	165.7	42	(49.4)	102	91.7
Nausea	76	(60.3)	124	72.9	72	(56.7)	98	61.0	18	(21.2)	22	19.8
Constipation	48	(38.1)	77	45.2	37	(29.1)	47	29.3	15	(17.6)	18	16.2
Diarrhoea	34	(27.0)	47	27.6	20	(15.7)	31	19.3	20	(23.5)	21	18.9
Vomiting	29	(23.0)	44	25.9	22	(17.3)	29	18.1	4	(4.7)	5	4.5
Eructation	16	(12.7)	19	11.2	5	(3.9)	5	3.1	2	(2.4)	2	1.8
Gastrooesophageal reflux disease	12	(9.5)	13	7.6	10	(7.9)	12	7.5	3	(3.5)	3	2.7
Dyspepsia	11	(8.7)	14	8.2	15	(11.8)	16	10.0	5	(5.9)	7	6.3
Flatulence	9	(7.1)	12	7.1	4	(3.1)	4	2.5	6	(7.1)	6	5.4
Abdominal distension	7	(5.6)	9	5.3	9	(7.1)	10	6.2	7	(8.2)	8	7.2
Abdominal pain	6	(4.8)	6	3.5	2	(1.6)	2	1.2	0			
Dry mouth	5	(4.0)	5	2.9	4	(3.1)	5	3.1	4	(4.7)	5	4.5
Abdominal pain lower	4	(3.2)	4	2.4	0				0			
Gastritis	4	(3.2)	4	2.4	3	(2.4)	3	1.9	1	(1.2)	1	0.9
Metabolism and nutrition disorders	17	(13.5)	17	10.0	17	(13.4)	20	12.5	3	(3.5)	3	2.7
Decreased appetite	15	(11.9)	15	8.8	16	(12.6)	18	11.2	3	(3.5)	3	2.7
General disorders and administration site conditions	16	(12.7)	16	9.4	23	(18.1)	29	18.1	7	(8.2)	9	8.1
Fatigue	8	(6.3)	8	4.7	8	(6.3)	9	5.6	1	(1.2)	1	0.9
Early satiety	5	(4.0)	5	2.9	4	(3.1)	4	2.5	1	(1.2)	1	0.9
Injection site bruising	0				1	(0.8)	1	0.6	2	(2.4)	2	1.8
Injection site erythema	0				3	(2.4)	3	1.9	0			
Injection site reaction	0				6	(4.7)	6	3.7	1	(1.2)	1	0.9
Nervous system disorders	16	(12.7)	37	21.7	12	(9.4)	13	8.1	5	(5.9)	8	7.2
Headache	13	(10.3)	32	18.8	7	(5.5)	8	5.0	4	(4.7)	6	5.4
Dizziness	2	(1.6)	3	1.8	4	(3.1)	4	2.5	2	(2.4)	2	1.8
Skin and subcutaneous tissue disorders	4	(3.2)	6	3.5	2	(1.6)	2	1.2	2	(2.4)	2	1.8
Alopecia	3	(2.4)	3	1.8	0				0			

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Relationship to trial product is based on assessment by investigator. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event. MedDRA version 23.1

Table 8.4.3.3.1 Serious adverse events by system organ class and preferred term - summary - in-trial – safety analysis set (copied from 14.3.1.18, Study NN9536-4451)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	133				67			
Patient years of observation (PYO)	192.0				94.0			
Events	15	(11.3)	17	8.9	6	(9.0)	7	7.4
Hepatobiliary disorders	4	(3.0)	5	2.6	0			
Cholelithiasis	3	(2.3)	3	1.6	0			
Cholecystitis acute	1	(0.8)	1	0.5	0			
Hepatic function abnormal	1	(0.8)	1	0.5	0			
Infections and infestations	4	(3.0)	4	2.1	0			
Appendicitis	2	(1.5)	2	1.0	0			
COVID-19	1	(0.8)	1	0.5	0			
COVID-19 pneumonia	1	(0.8)	1	0.5	0			
Gastrointestinal disorders	3	(2.3)	3	1.6	1	(1.5)	1	1.1
Abdominal pain	1	(0.8)	1	0.5	0			
Gastritis	1	(0.8)	1	0.5	0			
Vomiting	1	(0.8)	1	0.5	0			
Abdominal pain upper	0				1	(1.5)	1	1.1
Injury, poisoning and procedural complications	1	(0.8)	2	1.0	2	(3.0)	2	2.1
Post procedural constipation	1	(0.8)	1	0.5	0			
Urinary retention postoperative	1	(0.8)	1	0.5	0			
Clavicle fracture	0				1	(1.5)	1	1.1
Contusion	0				1	(1.5)	1	1.1
Investigations	1	(0.8)	1	0.5	1	(1.5)	1	1.1
Transaminases increased	1	(0.8)	1	0.5	1	(1.5)	1	1.1
Psychiatric disorders	1	(0.8)	1	0.5	0			
Depression	1	(0.8)	1	0.5	0			
Respiratory, thoracic and mediastinal disorders	1	(0.8)	1	0.5	0			
Sleep apnoea syndrome	1	(0.8)	1	0.5	0			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(1.5)	1	1.1
Ovarian germ cell teratoma benign	0				1	(1.5)	1	1.1
Nervous system disorders	0				2	(3.0)	2	2.1
Loss of consciousness	0				1	(1.5)	1	1.1
Tension headache	0				1	(1.5)	1	1.1

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYO: The duration of the in-trial period in years.
Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

Table 8.4.3.3.2 Reported SUSARs – in-trial (copied from Table 12-4, Study NN9536-4451)

Subject ID/Case no.	Preferred Term	Trial day of onset	Severity	Action	Outcome
Semaglutide					
201001/ 751531	Gastritis	Day 56	Severe	Permanent discontinuation	Recovered
403004/ 756395	Abdominal pain	Day 95	Moderate	Dose reduction	Recovered
501002/ 756774	Vomiting	Day 212	Moderate	Permanent discontinuation	Recovered
509001/ 763162	Cholecystitis acute	Day 241	Moderate	Temporary interruption	Recovered
404003/ 831536	Depression	Day 493	Severe	Not applicable	Not recovered
206002/ 853106	Hepatic function abnormal	Day 392	Severe	Temporary interruption	Recovered
Placebo					
301001/ 751060	Abdominal pain upper	Day 75	Moderate	Temporary interruption	Recovered
801008/ 880034	Transaminases increased	Day 472	Mild	Not applicable	Recovered

Table 8.4.3.4.1 Serious adverse events by system organ class and preferred term - summary - on-treatment - safety analysis set (copied from 14.3.1.14, Study NN9536-4378)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	152				152			
Patient years of exposure (PYE)	301.7				267.9			
Events	12	(7.9)	18	6.0	18	(11.8)	20	7.5
Infections and infestations	4	(2.6)	5	1.7	7	(4.6)	7	2.6
Appendicitis perforated	1	(0.7)	1	0.3	0			
COVID-19	1	(0.7)	1	0.3	2	(1.3)	2	0.7
Colonic abscess	1	(0.7)	1	0.3	0			
Diverticulitis	1	(0.7)	1	0.3	0			
Perineal abscess	1	(0.7)	1	0.3	0			
Anal abscess	0				1	(0.7)	1	0.4
Appendicitis	0				1	(0.7)	1	0.4
COVID-19 pneumonia	0				1	(0.7)	1	0.4
Herpes zoster	0				1	(0.7)	1	0.4
Pneumonia	0				1	(0.7)	1	0.4
Hepatobiliary disorders	3	(2.0)	4	1.3	0			
Cholelithiasis	2	(1.3)	2	0.7	0			
Cholecystitis	1	(0.7)	1	0.3	0			
Cholecystitis acute	1	(0.7)	1	0.3	0			
Gastrointestinal disorders	2	(1.3)	2	0.7	1	(0.7)	1	0.4
Abdominal adhesions	1	(0.7)	1	0.3	0			
Gastrooesophageal reflux disease	1	(0.7)	1	0.3	0			
Gastritis	0				1	(0.7)	1	0.4
Cardiac disorders	1	(0.7)	1	0.3	0			
Acute myocardial infarction	1	(0.7)	1	0.3	0			
Musculoskeletal and connective tissue disorders	1	(0.7)	1	0.3	2	(1.3)	2	0.7
Foot deformity	1	(0.7)	1	0.3	1	(0.7)	1	0.4
Rotator cuff syndrome	0				1	(0.7)	1	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.7)	1	0.3	4	(2.6)	4	1.5
Benign uterine neoplasm	1	(0.7)	1	0.3	0			
Invasive ductal breast carcinoma	0				2	(1.3)	2	0.7
Lung adenocarcinoma	0				1	(0.7)	1	0.4
Small cell lung cancer metastatic	0				1	(0.7)	1	0.4
Psychiatric disorders	1	(0.7)	1	0.3	0			
Panic disorder	1	(0.7)	1	0.3	0			
Renal and urinary disorders	1	(0.7)	1	0.3	0			
Nephrolithiasis	1	(0.7)	1	0.3	0			
Respiratory, thoracic and mediastinal disorders	1	(0.7)	1	0.3	0			
Pulmonary embolism	1	(0.7)	1	0.3	0			
Vascular disorders	1	(0.7)	1	0.3	0			
Deep vein thrombosis	1	(0.7)	1	0.3	0			
Congenital, familial and genetic disorders	0				1	(0.7)	1	0.4
Arnold-Chiari malformation	0				1	(0.7)	1	0.4
Injury, poisoning and procedural complications	0				2	(1.3)	2	0.7
Jaw fracture	0				1	(0.7)	1	0.4
Rib fracture	0				1	(0.7)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified
PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

Table 8.4.3.4.1 (cont)

Serious adverse events by system organ class and preferred term - summary - in-trial - safety analysis set

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Injury, poisoning and procedural complications	0				2	(1.3)	2	0.7
Jaw fracture	0				1	(0.7)	1	0.3
Rib fracture	0				1	(0.7)	1	0.3
Surgical and medical procedures	0				1	(0.7)	1	0.3
Thyroidectomy	0				1	(0.7)	1	0.3

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified
PYO: The duration of the in-trial period in years.
Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

Table 8.4.3.4.2 Serious AEs by SOC – on-treatment (copied from Table 12-3, Study NN9536-4376)

System organ class	Sema 2.4 mg N	(%)	E	R	Lira 3.0 mg N	(%)	E	R	Pooled Placebo N	(%)	E	R
Number of subjects	126				127				85			
Patient years of exposure (PYE)	170.2				160.6				111.2			
Events	10	(7.9)	14	8.2	14	(11.0)	18	11.2	6	(7.1)	9	8.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(2.4)	3	1.8	2	(1.6)	2	1.2	1	(1.2)	1	0.9
Cardiac disorders	1	(0.8)	1	0.6	0				1	(1.2)	4	3.6
General disorders and administration site conditions	1	(0.8)	1	0.6	0				1	(1.2)	1	0.9
Hepatobiliary disorders	1	(0.8)	1	0.6	2	(1.6)	2	1.2	1	(1.2)	1	0.9
Immune system disorders	1	(0.8)	1	0.6	0				0			
Infections and infestations	1	(0.8)	2	1.2	4	(3.1)	5	3.1	0			
Musculoskeletal and connective tissue disorders	1	(0.8)	1	0.6	2	(1.6)	2	1.2	0			
Renal and urinary disorders	1	(0.8)	1	0.6	0				0			
Reproductive system and breast disorders	1	(0.8)	1	0.6	0				0			
Respiratory, thoracic and mediastinal disorders	1	(0.8)	1	0.6	1	(0.8)	1	0.6	1	(1.2)	1	0.9
Vascular disorders	1	(0.8)	1	0.6	0				0			
Ear and labyrinth disorders	0				1	(0.8)	1	0.6	0			
Metabolism and nutrition disorders	0				1	(0.8)	1	0.6	0			
Nervous system disorders	0				1	(0.8)	1	0.6	1	(1.2)	1	0.9
Psychiatric disorders	0				1	(0.8)	1	0.6	0			
Surgical and medical procedures	0				2	(1.6)	2	1.2	0			

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

Table 8.4.4.3.1 Adverse events leading to temporary interruption of trial product by system organ class and preferred term - summary - on-treatment - safety analysis set (copied from 14.3.1.24, Study NN9536-4451)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	133				67			
Patient years of exposure (PYE)	181.8				90.4			
Events	14	(10.5)	31	17.1	5	(7.5)	7	7.7
Gastrointestinal disorders	7	(5.3)	19	10.5	3	(4.5)	5	5.5
Vomiting	6	(4.5)	7	3.9	1	(1.5)	1	1.1
Nausea	5	(3.8)	5	2.8	1	(1.5)	1	1.1
Abdominal pain	3	(2.3)	3	1.7	0			
Diarrhoea	3	(2.3)	3	1.7	0			
Gastrooesophageal reflux disease	1	(0.8)	1	0.6	0			
Abdominal distension	0				1	(1.5)	1	1.1
Abdominal pain upper	0				1	(1.5)	1	1.1
Constipation	0				1	(1.5)	1	1.1
Hepatobiliary disorders	4	(3.0)	5	2.8	0			
Cholelithiasis	3	(2.3)	3	1.7	0			
Cholecystitis acute	1	(0.8)	1	0.6	0			
Hepatic function abnormal	1	(0.8)	1	0.6	0			
Investigations	3	(2.3)	4	2.2	0			
Blood thyroid stimulating hormone decreased	1	(0.8)	1	0.6	0			
Thyroxine free increased	1	(0.8)	1	0.6	0			
Transaminases increased	1	(0.8)	1	0.6	0			
Weight decreased	1	(0.8)	1	0.6	0			
General disorders and administration site conditions	1	(0.8)	1	0.6	0			
Non-cardiac chest pain	1	(0.8)	1	0.6	0			
Nervous system disorders	1	(0.8)	1	0.6	1	(1.5)	1	1.1
Syncope	1	(0.8)	1	0.6	0			
Tension headache	0				1	(1.5)	1	1.1
Skin and subcutaneous tissue disorders	1	(0.8)	1	0.6	0			
Alopecia	1	(0.8)	1	0.6	0			
Surgical and medical procedures	0				1	(1.5)	1	1.1
Post coital contraception	0				1	(1.5)	1	1.1

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

Table 8.4.4.3.2 Adverse events leading to dose reduction of trial product by system organ class and preferred term - summary - on-treatment - safety analysis set (copied from 14.3.1.25, Study NN9536-4451)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	133				67			
Patient years of exposure (PYE)	181.8				90.4			
Events	16	(12.0)	42	23.1	1	(1.5)	4	4.4
Gastrointestinal disorders	13	(9.8)	29	16.0	1	(1.5)	4	4.4
Vomiting	8	(6.0)	9	5.0	1	(1.5)	2	2.2
Abdominal pain	5	(3.8)	6	3.3	0			
Diarrhoea	4	(3.0)	5	2.8	0			
Nausea	4	(3.0)	4	2.2	1	(1.5)	2	2.2
Abdominal discomfort	1	(0.8)	2	1.1	0			
Abdominal pain upper	1	(0.8)	1	0.6	0			
Chronic gastritis	1	(0.8)	1	0.6	0			
Constipation	1	(0.8)	1	0.6	0			
Nervous system disorders	4	(3.0)	5	2.8	0			
Dizziness	1	(0.8)	2	1.1	0			
Dizziness postural	1	(0.8)	1	0.6	0			
Headache	1	(0.8)	1	0.6	0			
Presyncope	1	(0.8)	1	0.6	0			
Metabolism and nutrition disorders	2	(1.5)	3	1.7	0			
Decreased appetite	2	(1.5)	2	1.1	0			
Abnormal loss of weight	1	(0.8)	1	0.6	0			
Ear and labyrinth disorders	1	(0.8)	3	1.7	0			
Vertigo	1	(0.8)	3	1.7	0			
Infections and infestations	1	(0.8)	1	0.6	0			
Helicobacter infection	1	(0.8)	1	0.6	0			
Vascular disorders	1	(0.8)	1	0.6	0			
Hypotension	1	(0.8)	1	0.6	0			

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

Table 8.4.4.4.1 Adverse events leading to permanent trial product discontinuation by system organ class and preferred term - summary - on-treatment (copied from Table 12-5, Study NN9536-4378)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	152				152			
Patient years of exposure (PYE)	301.7				267.9			
Events	9	(5.9)	12	4.0	7	(4.6)	8	3.0
Gastrointestinal disorders	6	(3.9)	7	2.3	1	(0.7)	1	0.4
Diarrhoea	2	(1.3)	2	0.7	1	(0.7)	1	0.4
Breath odour	1	(0.7)	1	0.3	0			
Flatulence	1	(0.7)	1	0.3	0			
Nausea	1	(0.7)	1	0.3	0			
Regurgitation	1	(0.7)	1	0.3	0			
Vomiting	1	(0.7)	1	0.3	0			
Nervous system disorders	1	(0.7)	1	0.3	1	(0.7)	1	0.4
Allodynia	1	(0.7)	1	0.3	0			
Dizziness	0				1	(0.7)	1	0.4
Psychiatric disorders	1	(0.7)	1	0.3	1	(0.7)	1	0.4
Libido decreased	1	(0.7)	1	0.3	0			
Anxiety	0				1	(0.7)	1	0.4
Reproductive system and breast disorders	1	(0.7)	1	0.3	0			
Erectile dysfunction	1	(0.7)	1	0.3	0			
Skin and subcutaneous tissue disorders	1	(0.7)	2	0.7	1	(0.7)	2	0.7
Alopecia	1	(0.7)	2	0.7	0			
Chronic spontaneous urticaria	0				1	(0.7)	2	0.7
Injury, poisoning and procedural complications	0				2	(1.3)	2	0.7
Jaw fracture	0				1	(0.7)	1	0.4
Medication error	0				1	(0.7)	1	0.4
Musculoskeletal and connective tissue disorders	0				1	(0.7)	1	0.4
Muscular weakness	0				1	(0.7)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified
PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

Table 8.5.1.3.1 Hepatic adverse events by system organ class and preferred term - pre-defined MedDRA search - summary - on-treatment - safety analysis set (copied from Table 12-11, Study NN9536-4451)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	133				67			
Patient years of exposure (PYE)	181.8				90.4			
Events	10	(7.5)	13	7.2	1	(1.5)	1	1.1
Investigations	7	(5.3)	9	5.0	1	(1.5)	1	1.1
Alanine aminotransferase increased	3	(2.3)	3	1.7	0			
Gamma-glutamyltransferase increased	2	(1.5)	2	1.1	0			
Hepatic enzyme increased	2	(1.5)	2	1.1	0			
Aspartate aminotransferase increased	1	(0.8)	1	0.6	0			
Transaminases increased	1	(0.8)	1	0.6	1	(1.5)	1	1.1
Hepatobiliary disorders	3	(2.3)	4	2.2	0			
Hepatic function abnormal	1	(0.8)	1	0.6	0			
Hepatic lesion	1	(0.8)	1	0.6	0			
Hepatic steatosis	1	(0.8)	1	0.6	0			
Non-alcoholic steatohepatitis	1	(0.8)	1	0.6	0			

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

Table 8.5.6.4.1 ECG - Subjects with abnormal clinically significant findings – summary – on treatment (copied from Table 12-13, Study NN9536-4378)

Subject ID/Age/ Sex/BMI	Preferred Term	Visit week of finding	Seriousness/ Severity	Relation/Action	Event outcome	Trial product
101005 64/F/34.6	First degree atrioventricular block	Week 0	Non-serious /Mild	NA/NA	Not recovered	semaglutide
104002 70/F/29.3	First degree atrioventicular block	Week 84	Non-Serious /Mild	Unlikely/Dose not changed	Recovered	semaglutide
253001 62/F/38.0	Arrhythmia, Ventricular premature complexes	Week 84	Non-Serious /Mild	Unlikely/Dose not changed	Recovered	semaglutide
312004 59/F/39.1	New left bundle branch block	Week 84	Non-Serious /Mild	Unlikely/Dose not changed	Not recovered	semaglutide
162002 46/M/48.9	Frequent trigeminal ventricular extrasystoles	Week 52	Non-Serious /Moderate	Unlikely/Dose not changed	Recovered	placebo
252001 64/M/52.0	New onset atrial fibrillation	Week 20	Non-Serious /Moderate	Unlikely/Dose not changed	Not recovered	placebo

Table 8.5.8.3.1 Allergic reactions adverse events by system organ class and preferred term - pre-defined MedDRA search - summary - on-treatment - safety analysis set (copied from Table 12-9, Study NN9536-4451)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	133				67			
Patient years of exposure (PYE)	181.8				90.4			
Events	12	(9.0)	14	7.7	4	(6.0)	4	4.4
Skin and subcutaneous tissue disorders	10	(7.5)	12	6.6	1	(1.5)	1	1.1
Rash	4	(3.0)	5	2.8	0			
Urticaria	4	(3.0)	4	2.2	0			
Dermatitis contact	1	(0.8)	1	0.6	0			
Eczema	1	(0.8)	1	0.6	0			
Toxic skin eruption	1	(0.8)	1	0.6	0			
Dermatitis acneiform	0				1	(1.5)	1	1.1
Eye disorders	1	(0.8)	1	0.6	1	(1.5)	1	1.1
Conjunctivitis allergic	1	(0.8)	1	0.6	1	(1.5)	1	1.1
Respiratory, thoracic and mediastinal disorders	1	(0.8)	1	0.6	0			
Rhinitis allergic	1	(0.8)	1	0.6	0			
Gastrointestinal disorders	0				1	(1.5)	1	1.1
Lip swelling	0				1	(1.5)	1	1.1
General disorders and administration site conditions	0				1	(1.5)	1	1.1
Injection site urticaria	0				1	(1.5)	1	1.1

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

Table 8.5.8.4.1 Allergic reactions adverse events by system organ class and preferred term - pre-defined MedDRA search - summary - on-treatment (copied from Table 12-24, Study NN9536-4378)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	152				152			
Patient years of exposure (PYE)	301.7				267.9			
Events	23	(15.1)	36	11.9	8	(5.3)	9	3.4
Skin and subcutaneous tissue disorders	18	(11.8)	26	8.6	4	(2.6)	4	1.5
Urticaria	6	(3.9)	8	2.7	1	(0.7)	1	0.4
Dermatitis contact	4	(2.6)	4	1.3	0			
Rash	4	(2.6)	6	2.0	1	(0.7)	1	0.4
Dermatitis	2	(1.3)	2	0.7	2	(1.3)	2	0.7
Eczema	2	(1.3)	2	0.7	0			
Rash pruritic	2	(1.3)	2	0.7	0			
Angioedema	1	(0.7)	1	0.3	0			
Rash vesicular	1	(0.7)	1	0.3	0			
Immune system disorders	5	(3.3)	7	2.3	1	(0.7)	1	0.4
Hypersensitivity	5	(3.3)	7	2.3	0			
Drug hypersensitivity	0				1	(0.7)	1	0.4
Respiratory, thoracic and mediastinal disorders	2	(1.3)	2	0.7	2	(1.3)	2	0.7
Rhinitis allergic	2	(1.3)	2	0.7	2	(1.3)	2	0.7
Eye disorders	1	(0.7)	1	0.3	0			
Conjunctivitis allergic	1	(0.7)	1	0.3	0			
Gastrointestinal disorders	0				1	(0.7)	1	0.4
Intestinal angioedema	0				1	(0.7)	1	0.4
General disorders and administration site conditions	0				1	(0.7)	1	0.4
Swelling face	0				1	(0.7)	1	0.4

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, NEC: Not elsewhere classified
PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

Table 8.5.8.4.2 Allergic reactions AEs by SOC and PT - pre-defined MedDRA search - summary - on-treatment (copied from Table 12-23, Study NN9536-4376)

System organ class Preferred term	Sema 2.4 mg N	(%)	E	R	Lira 3.0 mg N	(%)	E	R	Pooled Placebo N	(%)	E	R
Number of subjects	126				127				85			
Patient years of exposure (PYE)	170.2				160.6				111.2			
Events	9	(7.1)	13	7.6	11	(8.7)	12	7.5	10	(11.8)	13	11.7
Skin and subcutaneous tissue disorders	8	(6.3)	9	5.3	4	(3.1)	4	2.5	7	(8.2)	8	7.2
Rash	3	(2.4)	3	1.8	2	(1.6)	2	1.2	5	(5.9)	6	5.4
Urticaria	2	(1.6)	3	1.8	0				0			
Dermatitis	1	(0.8)	1	0.6	1	(0.8)	1	0.6	0			
Dermatitis atopic	1	(0.8)	1	0.6	0				0			
Rash erythematous	1	(0.8)	1	0.6	0				0			
Dermatitis contact	0				1	(0.8)	1	0.6	2	(2.4)	2	1.8
Immune system disorders	1	(0.8)	4	2.4	3	(2.4)	3	1.9	1	(1.2)	1	0.9
Anaphylactic reaction	1	(0.8)	1	0.6	0				0			
Hypersensitivity	1	(0.8)	3	1.8	1	(0.8)	1	0.6	0			
Drug hypersensitivity	0				2	(1.6)	2	1.2	1	(1.2)	1	0.9
Eye disorders	0				1	(0.8)	1	0.6	0			
Swelling of eyelid	0				1	(0.8)	1	0.6	0			
General disorders and administration site conditions	0				3	(2.4)	3	1.9	0			
Injection site rash	0				2	(1.6)	2	1.2	0			
Injection site urticaria	0				1	(0.8)	1	0.6	0			
Respiratory, thoracic and mediastinal disorders	0				1	(0.8)	1	0.6	3	(3.5)	4	3.6
Laryngeal oedema	0				0				1	(1.2)	1	0.9
Rhinitis allergic	0				1	(0.8)	1	0.6	2	(2.4)	3	2.7

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.MedDRA version 23.1

Table 8.5.12.3.1 Change from baseline, height, chronological age and bone age – in trial – full analysis set (copied from Table 12-23, Study NN9536-4451)

	Sema 2.4 mg				Placebo			
	Height (cm)	Height SDS	Chron. age(yrs)	Bone age(yrs)	Height (cm)	Height SDS	Chron. age(yrs)	Bone age(yrs)
Total Change from Baseline								
N	131	131	63	63	62	62	29	29
Mean	1.3	-0.076	1.3	1.3	2.1	-0.048	1.3	1.5
SD	2.1	0.252	0.0	0.8	2.6	0.249	0.0	0.9
Median	0.8	-0.046	1.3	1.5	1.0	-0.022	1.3	1.5
P5	-0.6	-0.544	1.3	0.0	-0.2	-0.529	1.3	0.0
P95	5.7	0.325	1.3	2.0	8.6	0.326	1.4	3.0
Min	-1.8	-1.168	1.2	0.0	-1.2	-0.713	1.3	0.0
Max	9.1	0.577	1.4	3.0	9.8	0.451	1.4	3.0

N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile
Observed data from in-trial period.

Table 19.1.3.1.1 Baseline characteristics of subjects for the population PK analysis (copied from Table 6-1, Study NN9536-4451 Modelling Report)

Category	Group	STEP 1	STEP TEENS	Total
All	N	1306	134	1440
Age (years)	12-<15	0	47	47
	15-<18	0	87	87
	18-<65	1198	0	1198
	>=65	108	0	108
Sex	Female	955	84	1039
	Male	351	50	401
Race[a]	White (other)	1234	123	1357
	Black or African American	72	11	83
Ethnicity[b]	Hispanic or Latino	150	14	164
	Not Hispanic or Latino	1156	120	1276
Glycaemic status[c]	Normoglycaemia	713	110	823
	Prediabetes	593	24	617
Body mass index groups	<30	81	12	93
	30-<35	436	45	481
	35-<40	406	33	439
	>=40	383	44	427
With PK data[d]	Subjects with PK	1295	124	1419
	Subjects without PK	11	10	21
Body weight (kg)	Mean (SD)	105.4 (22.1)	109.9 (25.2)	105.8 (22.4)
	Range	[61.8-245.6]	[61.6-211.9]	[61.6-245.6]
Body mass index (kg/m2)	Mean (SD)	37.8 (6.7)	37.7 (6.7)	37.8 (6.7)
	Range	[26.5-83]	[26.8-60]	[26.5-83]

a. Race categories: Other, not applicable, Native Hawaiian or Other Pacific Islander, Asian and American Indian or Alaska Native are pooled with white in the population PK analysis.

b. Ethnicity categories: Not applicable are pooled with Not Hispanic or Latino in the population PK analysis.

c. Glycaemic status: There were 5 subjects in STEP TEENS with diabetes (at screening) included in the prediabetes group.

d. Subjects without PK data in STEP TEENS: 6 of 10 subjects without PK data were from the same site and the missing PK data was caused by a sample collection error at the site. This was reported as protocol deviation.

Table 19.1.3.1.2 Parameter estimates for base PK model (copied from Table 9-4, Study NN9536-4451 Modelling Report)

Parameter	Labels	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
KA [1/h]	Absorption rate constant	0.0607	0.0449	0.0765	13.3	NA	NA
CL/F [L/h]	Apparent clearance	0.045	0.0442	0.0458	0.9	27.7	8.65
V/F [L]	Apparent volume of distribution	11.8	11.4	12.3	1.98	34.7	43.5
Prop. Error STEP 1 [%]	Proportional residual error STEP TEENS	26.6	NA	NA	NA	NA	8.78
Prop. Error STEP TEENS [%]	Proportional residual error STEP 1	31.2	NA	NA	NA	NA	9.61

Table 19.1.3.1.3 Parameter estimates for full PK model (copied from Table 9-5, Study NN9536-4451 Modelling Report)

Parameter	Labels	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
KA [1/h]	Absorption rate constant	0.0385	0.0266	0.0504	15.8	NA	NA
CL/F [L/h]	Apparent clearance	0.0416	0.0408	0.0424	1	18	16.1
V/F [L]	Apparent volume of distribution	10.5	9.9	11	2.73	37.1	45.1
CL.sex	Sex factor on CL/F	1.08	1.05	1.11	1.36	NA	NA
CL.age12	Age group factor on CL/F (12-<15 years)	1.12	1.06	1.19	2.92	NA	NA
CL.age15	Age group factor on CL/F (15-<18 years)	1.04	0.981	1.1	3.01	NA	NA
CL.age65	Age group factor on CL/F (>=65 years)	0.985	0.951	1.02	1.78	NA	NA
CL.black	Race factor on CL/F (Black or African American)	0.963	0.917	1.01	2.41	NA	NA
CL.hisp	Ethnicity factor on CL/F (Hispanic or Latino)	1.05	1	1.09	2.21	NA	NA
CL.BW	Baseline body weight exponent on CL/F	0.893	0.833	0.952	3.38	NA	NA
CL.predia	Glycaemic status factor on CL/F (Prediabetes)	1.04	1.02	1.06	1.14	NA	NA
V.BW	Baseline body weight exponent on V/F	0.808	0.644	0.973	10.4	NA	NA
CL.DSTEP1	Dose effect on CL/F (STEP 1)	-0.0441	-0.0535	-0.0347	10.8	NA	NA
CL.DSTEPTEENS	Dose effect on CL/F (STEP TEENS)	-0.0603	-0.108	-0.0127	40.3	NA	NA
Prop. Error STEP 1 [%]	Proportional residual error STEP 1	26.2	NA	NA	NA	NA	8.22
Prop. Error STEP TEENS [%]	Proportional residual error STEP TEENS	31.1	NA	NA	NA	NA	9.1

Table 19.1.3.1.4 Parameter estimates for final reduced PK model (copied from Table 9-6, Study NN9536-4451 Modelling Report)

Parameter	Labels	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
KA [1/h]	Absorption rate constant	0.0565	0.0425	0.0705	12.6	NA	NA
CL/F [L/h]	Apparent clearance	0.0415	0.0408	0.0422	0.87	17.9	16.3
V/F [L]	Apparent volume of distribution	11.3	10.8	11.7	1.86	35	44.6
CL.sex	Sex factor on CL/F	1.08	1.06	1.11	1.31	NA	NA
CL.hisp	Ethnicity factor on CL/F (Hispanic or Latino)	1.05	1.01	1.09	2.15	NA	NA
CL.BW	Baseline body weight exponent on CL/F	0.885	0.827	0.942	3.33	NA	NA
CL.predia	Glycaemic status factor on CL/F (Prediabetes)	1.03	1.01	1.06	1.1	NA	NA
V.BW	Baseline body weight exponent on V/F	0.806	0.644	0.968	10.3	NA	NA
Prop. Error STEP 1 [%]	Proportional residual error STEP 1	26.6	NA	NA	NA	NA	8.14
Prop. Error STEP TEENS [%]	Proportional residual error STEP TEENS	31.1	NA	NA	NA	NA	9

Table 19.1.3.1.5 Summary of model-derived PK endpoints1 for STEP TEENS (copied from Table 6-2, Study NN9536-4451 Modelling Report)

Parameters	FAS	N	Geometric Mean	Median	5th percentile	95th percentile	CV %	Min	Max
CAVG (nmol/L)	134	124	74	73	50	110	26	40	160
AUC 0-168h (nmol.h/L)	134	124	12366	12229	8383	18527	26	6648	26849
CL/F (L/h)	134	124	0.047	0.048	0.031	0.07	26	0.022	0.088

[1]Exposures (C_{avg} and $AUC_{0\text{-}168h}$) were obtained from the final population PK model with significant covariates included. FAS is the full analysis set and N is number of subjects contributing with PK data.

Table 19.1.3.1.6 Summary of baseline characteristics for the exposure response analysis (copied from Table 6-3, Study NN9536-4451 Modelling Report)

Category	Group	STEP 1 Placebo	STEP 1 Sema 2.4 mg	STEP TEENS Placebo	STEP TEENS Sema 2.4 mg	Total
All	N	655	1306	67	134	2162
Age (years)	12-<15	0	0	25	47	72
	15-<18	0	0	42	87	129
	18-<65	607	1198	0	0	1805
	>=65	48	108	0	0	156
Sex	Female	498	955	41	84	1578
	Male	157	351	26	50	584
Race[a]	White (other)	616	1234	62	123	2035
	Black or African American	39	72	5	11	127
Ethnicity[b]	Hispanic or Latino	86	150	8	14	258
	Not Hispanic or Latino	569	1156	59	120	1904
Glycaemic status[c]	Normoglycaemia	392	713	56	110	1271
	Prediabetes	263	593	11	24	891
Body mass index groups	<30	36	81	8	12	137
	30-<35	207	436	26	45	714
	35-<40	208	406	19	33	666
	>=40	204	383	14	44	645
With PK data	Subjects with PK	0	1295	0	124	1419
	Subjects without PK	655	11	67	10	743
Body weight (kg)	Mean (SD)	105.2 (21.5)	105.4 (22.1)	102.6 (22.3)	109.9 (25.2)	105.5 (22.1)
	Range	[66.3-211]	[61.8-245.6]	[61-147.4]	[61.6-211.9]	[61-245.6]
Body mass index (kg/m2)	Mean (SD)	38 (6.5)	37.8 (6.7)	35.7 (5.4)	37.7 (6.7)	37.8 (6.6)
	Range	[27.5-67]	[26.5-83]	[26.6-49.9]	[26.8-60]	[26.5-83]

a. Race categories: Other, not applicable, Native Hawaiian or Other Pacific Islander, Asian and American Indian or Alaska Native are pooled with white in the population PK analysis.

b. Ethnicity categories: Not applicable are pooled with Not Hispanic or Latino in the population PK analysis.

c. Glycaemic status: There were 8 subjects in STEP TEENS with diabetes (at screening) included in the prediabetes group.

Table 19.1.3.1.7 Parameter estimates for the exposure-response model of BMI % change from baseline (copied from Table 9-9, Study NN9536-4451 Modelling Report)

Label	Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE
Intercept	(Intercept)	79.733	50.551	108.916	18.7
Baseline BMI	bbmi	0.025	-0.064	0.115	180.2
Male	sexMale	-22.271	-41.070	-3.472	43.0
STEP 1	TRIALSTEP 1	-48.692	-75.723	-21.661	28.3
Slope	log(CAVG)	-23.073	-29.538	-16.609	14.3
Male:slope	sexMale:log(CAVG)	5.970	1.574	10.366	37.5
STEP1:slope	TRIALSTEP 1:log(CAVG)	11.685	5.426	17.945	27.3
Residual		8.670	NA	NA	NA

Table 19.1.3.1.8 Parameter estimates for the exposure-response model for nausea (copied from Table 9-10, Study NN9536-4451 Modelling Report)

Label	Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE
Intercept	(Intercept)	-0.064	-7.011	6.889	5514.7
Baseline BMI	bbmi	0.016	-0.005	0.037	65.7
Male	sexMale	-1.519	-6.131	3.062	154.1
STEP 1	TRIALSTEP 1	-2.796	-9.252	3.694	117.5
Slope	log(CAVG)	-0.142	-1.686	1.398	549.5
Male:slope	sexMale:log(CAVG)	0.190	-0.883	1.268	287.7
STEP1:slope	TRIALSTEP 1:log(CAVG)	0.644	-0.856	2.140	118.0

Estimated parameters are expressed on the underlying logit scale.

Table 19.1.3.1.9 Parameter estimates for the exposure-response model for vomiting (copied from Table 9-11, Study NN9536-4451 Modelling Report)

Label	Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE
Intercept	(Intercept)	-3.003	-10.322	4.281	123.4
Baseline BMI	bbmi	0.031	0.008	0.054	38.2
Male	sexMale	-4.101	-9.438	1.203	66.1
STEP 1	TRIALSTEP 1	0.280	-6.468	7.131	1233.5
Slope	log(CAVG)	0.344	-1.264	1.957	237.4
Male:slope	sexMale:log(CAVG)	0.826	-0.419	2.071	76.8
STEP1:slope	TRIALSTEP 1:log(CAVG)	-0.211	-1.791	1.351	377.7

Estimated parameters are expressed on the underlying logit scale.

Figure 2.1.1 CDC BMI centile chart for boys

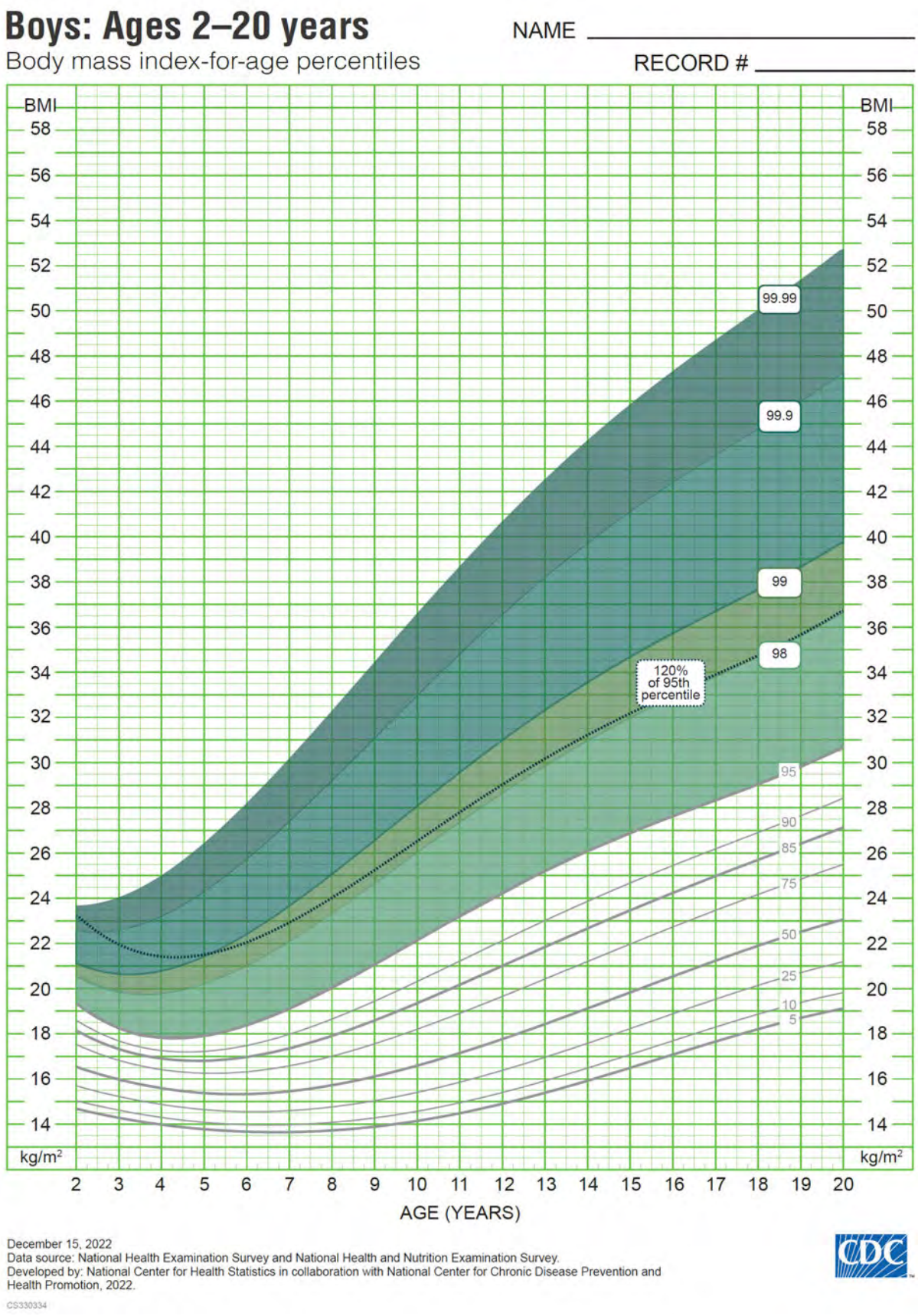


Figure 2.1.2 CDC BMI centile chart for girls

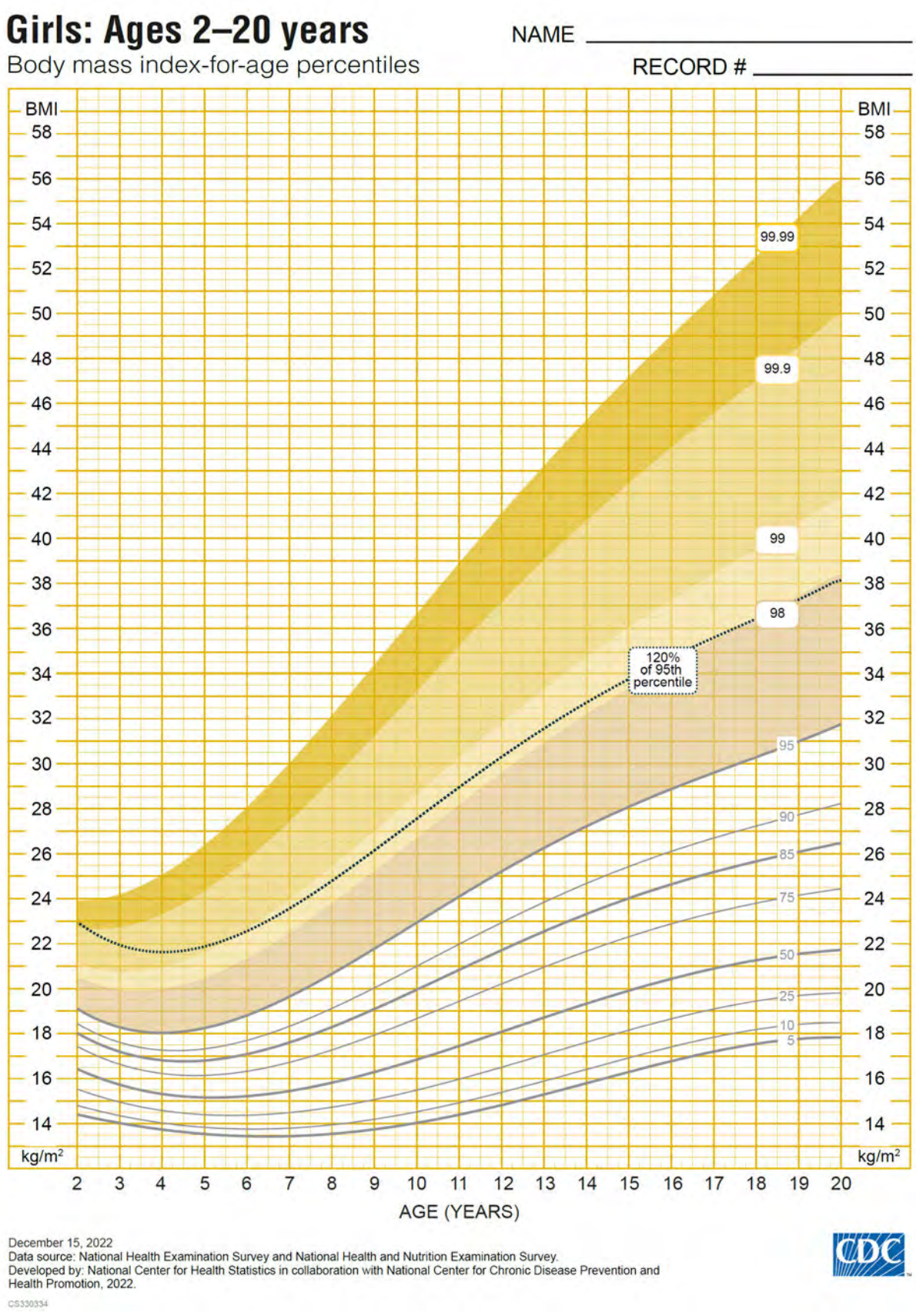


Figure 2.1.3 CDC BMI centile chart for boys with Z-score bands

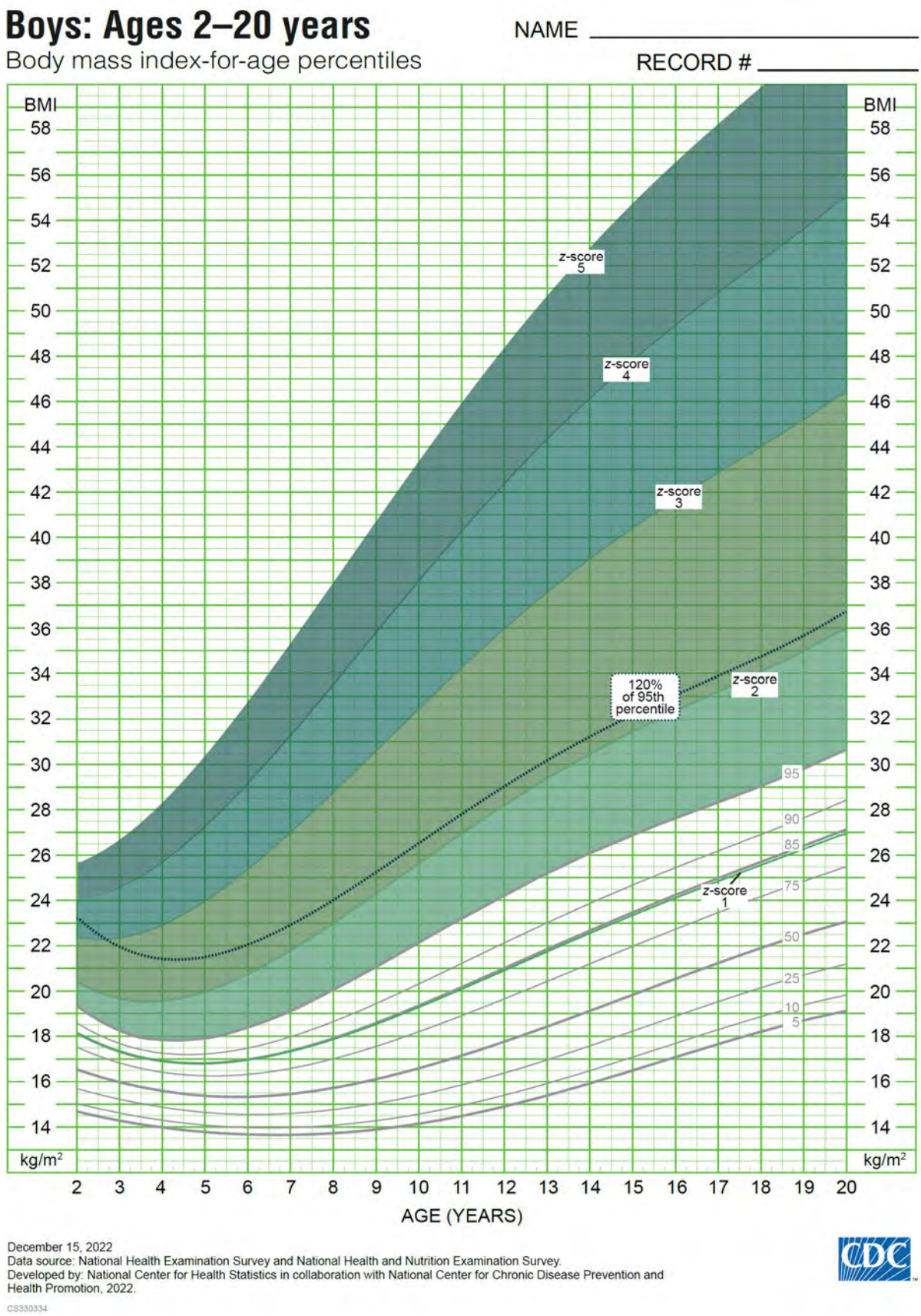


Figure 2.1.4 CDC BMI centile chart for girls with Z-score bands

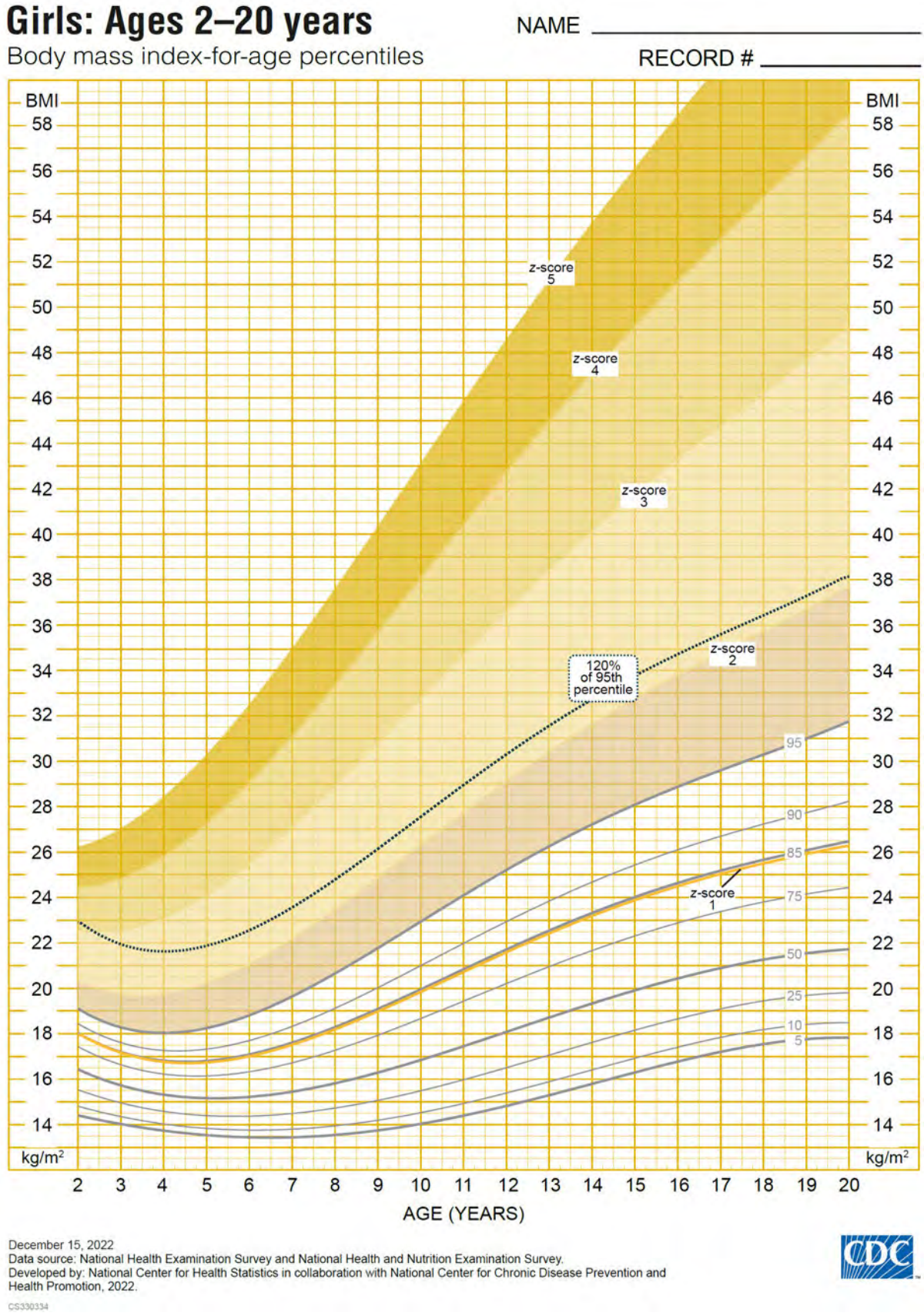
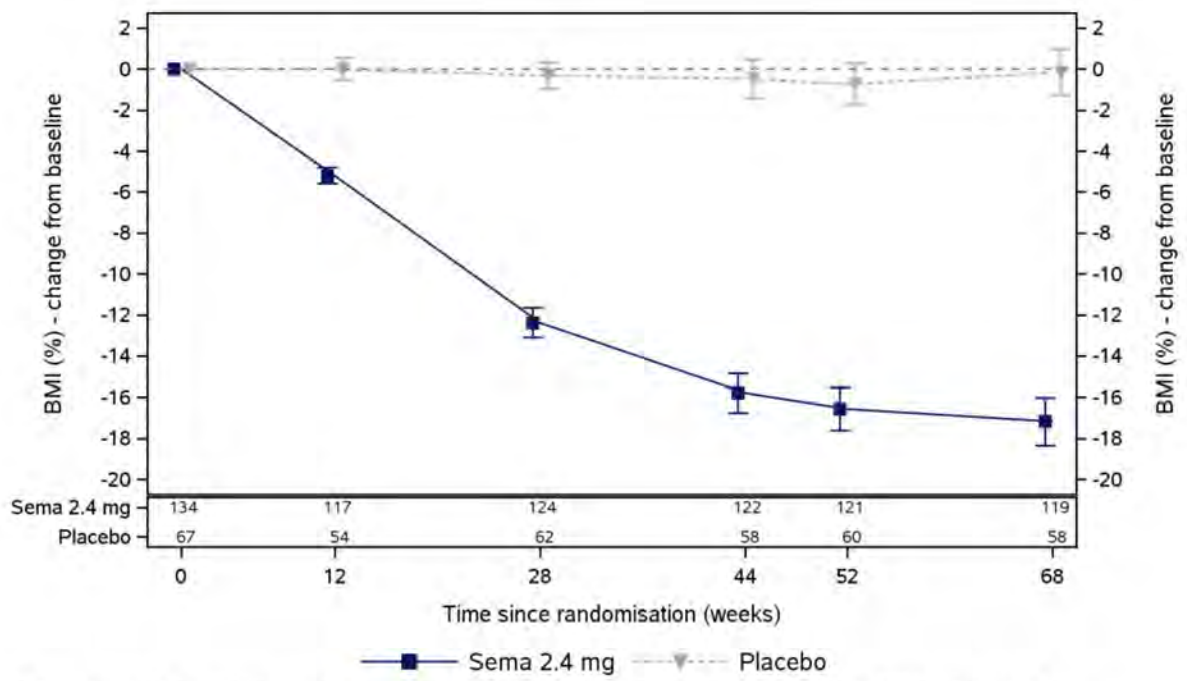
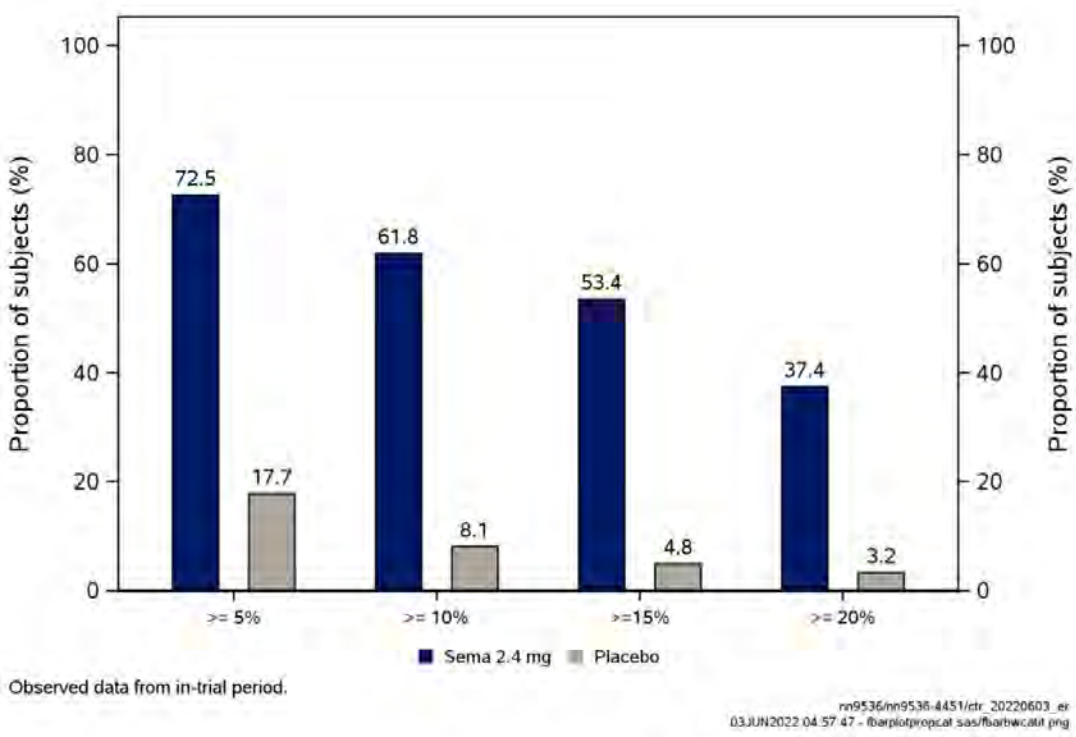


Figure 7.2.1.1 BMI (%) change from baseline by week - mean plot - on-treatment - full analysis set (copied from 14.2.18, Study NN9536-4451)



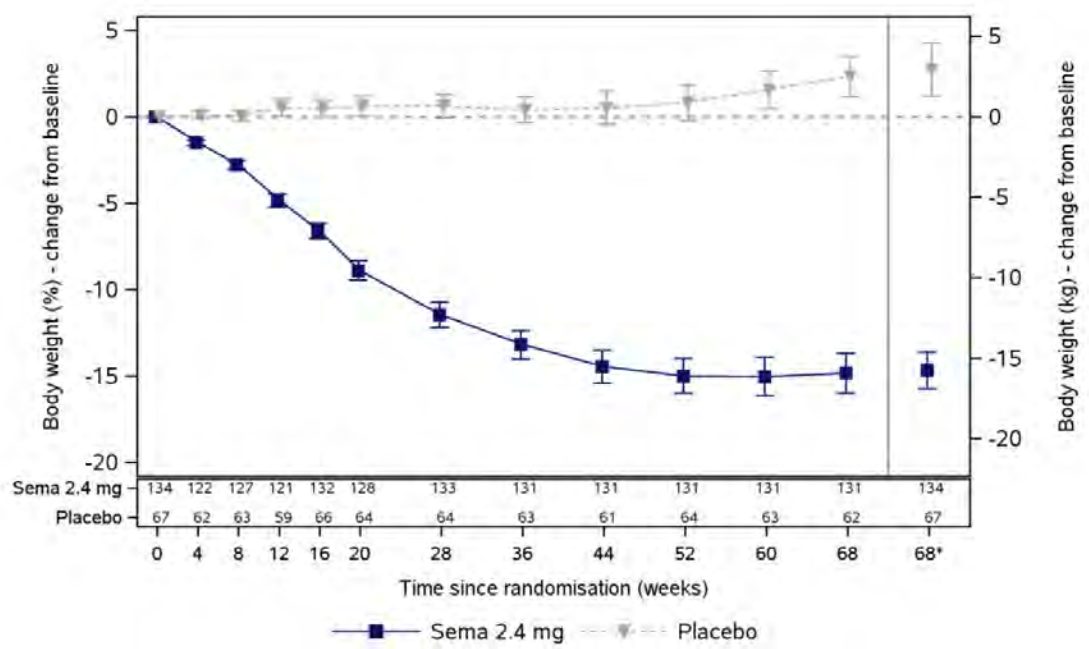
Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.2 Proportion of subjects achieving body weight loss response criteria since baseline at week 68 - bar plot - in-trial - full analysis set (copied from Figure 11-7, Study NN9536-4451)



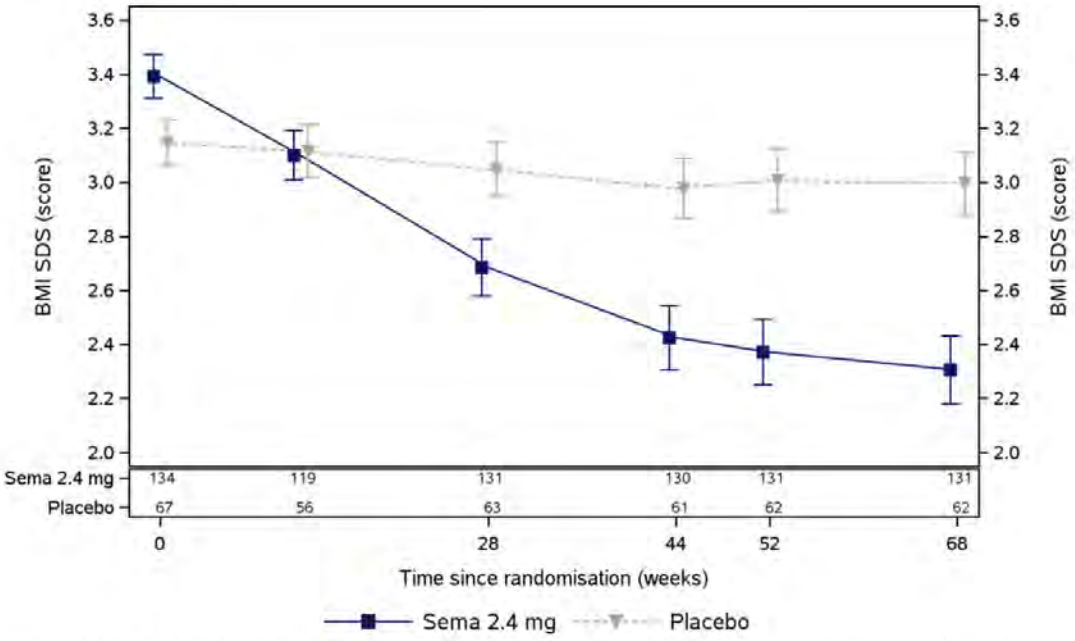
Observed data from in-trial period.

Figure 7.2.1.3 Body weight (kg, %) change from baseline by week - mean plot – treatment policy estimand - full analysis set (copied from Figure 11-9, Study NN9536-4451)



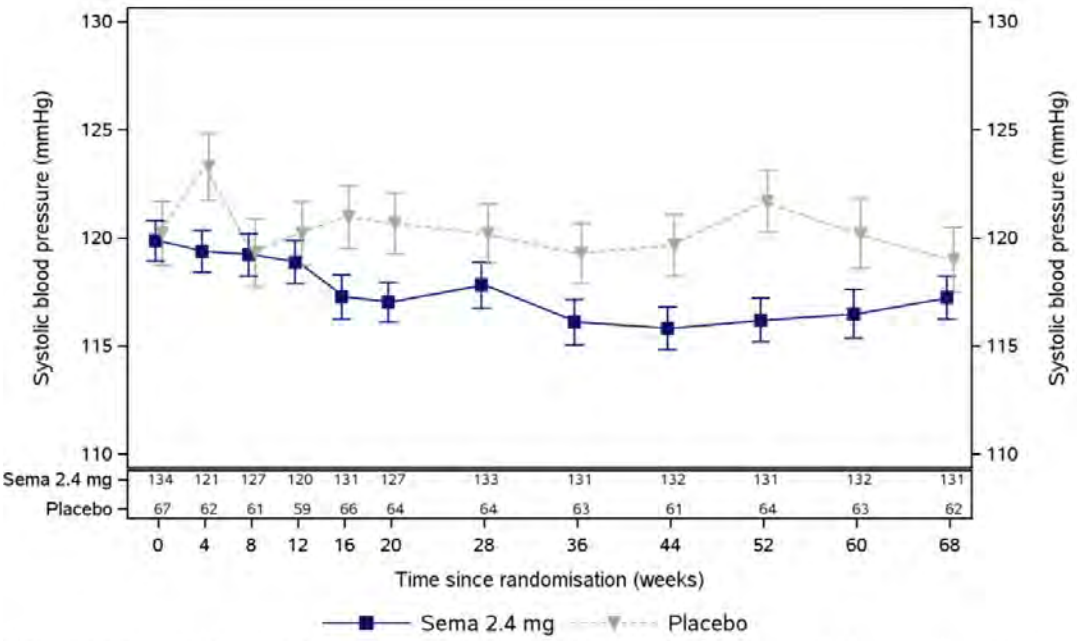
Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the supportive secondary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.4 BMI (standard deviation score) by week - mean plot - in-trial - full analysis set (copied from Figure 11-12, Study NN9536-4451)



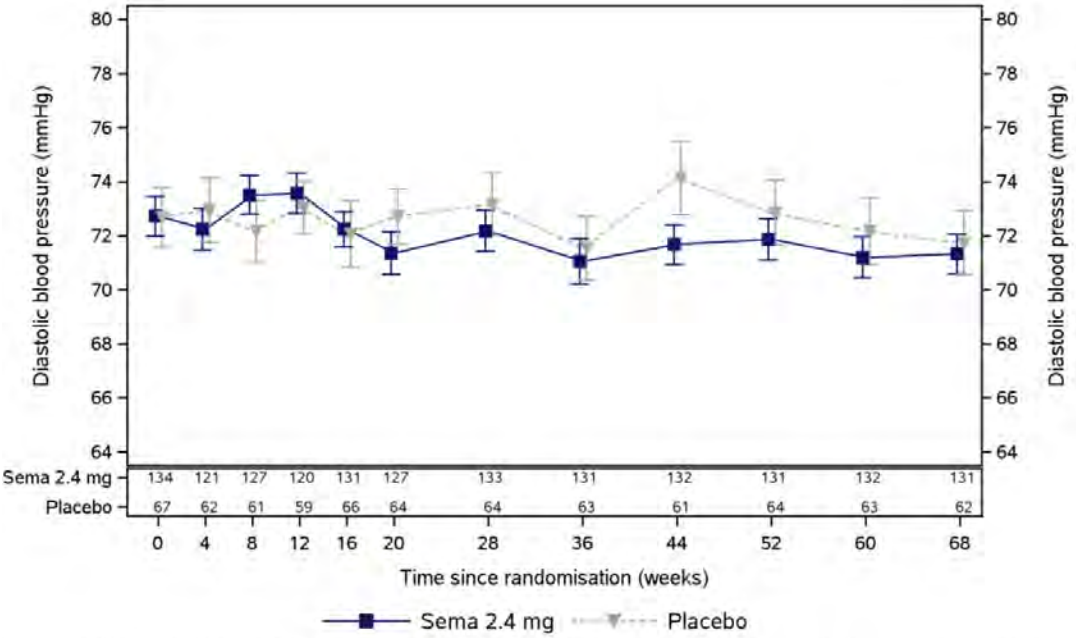
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. SDS: Standard Deviation Score (reference WHO 2007).

Figure 7.2.1.5 Systolic blood pressure by week - mean plot – in trial- full analysis set (copied from Figure 11-14, Study NN9536-4451)



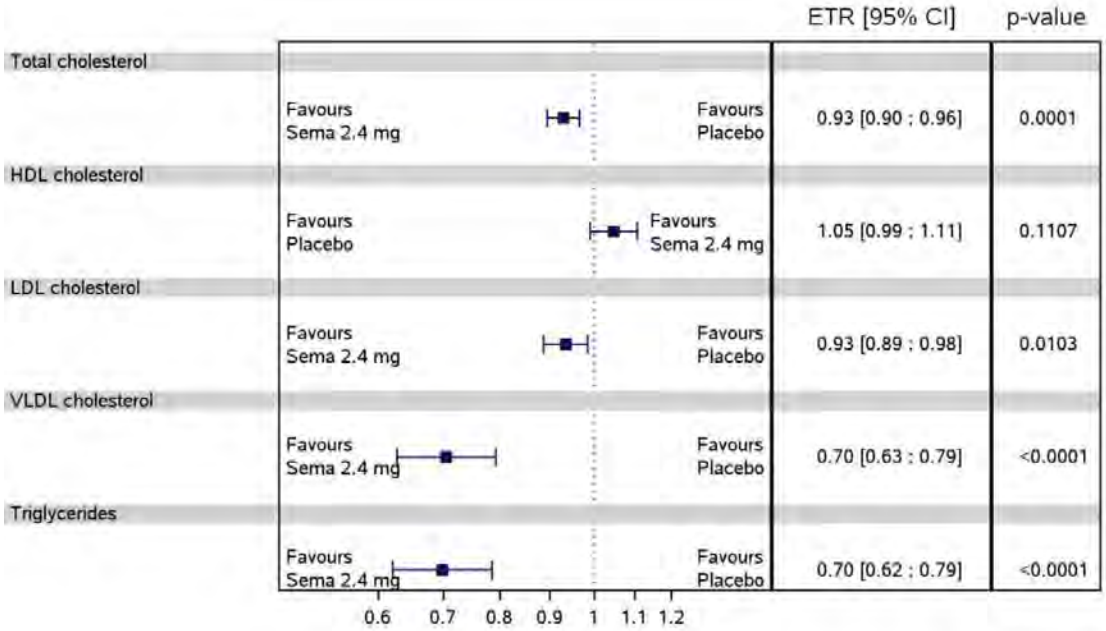
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.6 Diastolic blood pressure by week - mean plot – in trial - full analysis set (copied from Figure 11-15, Study NN9536-4451)



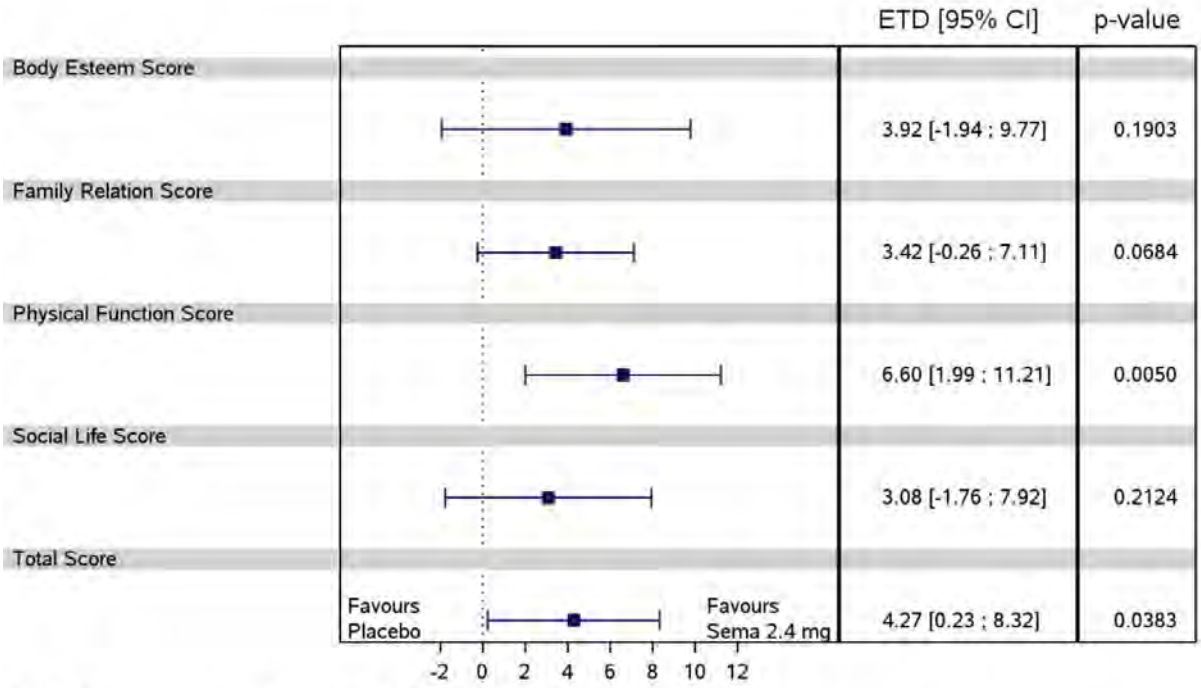
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.2.1.7 Lipids ratio to baseline at week 68 - forest plot - treatment policy estimand – full analysis set (copied from Figure 11-16, Study NN9536-4451)



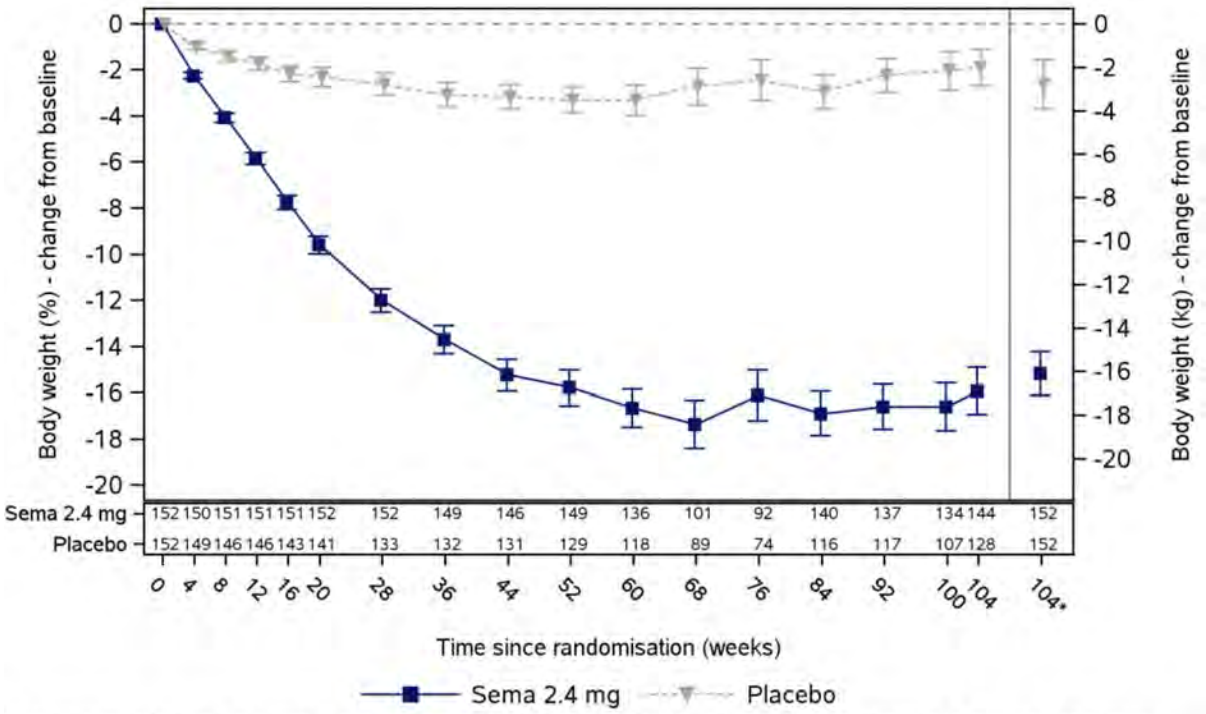
ETR: Estimated treatment ratio, CI: Confidence interval, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Figure 7.2.1.8 IWQoL-Kids change from baseline to week 68 - forest plot - treatment policy estimand - full analysis set (copied from Figure 11-20, Study NN9536-4451)



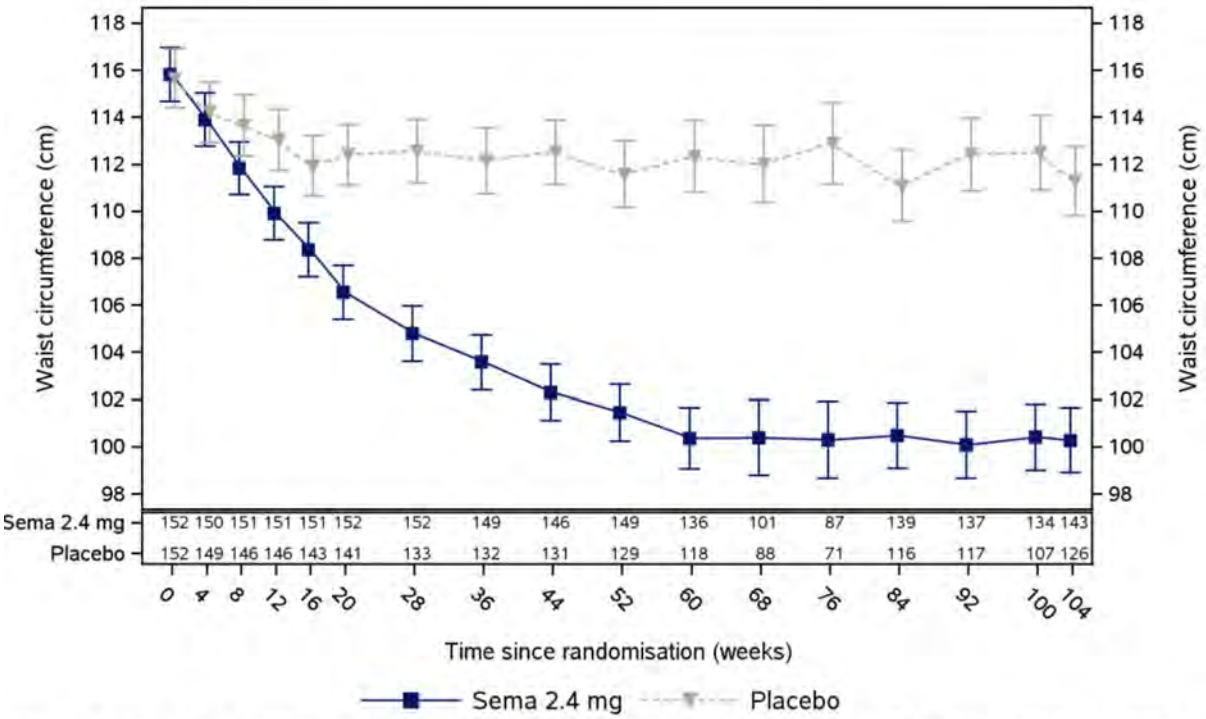
ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment differences and corresponding confidence intervals are from the exploratory analysis.

Figure 7.3.1.1 Body weight change from baseline by week - mean plot - treatment policy estimand (copied from Figure 11-1, Study NN9536-4378)



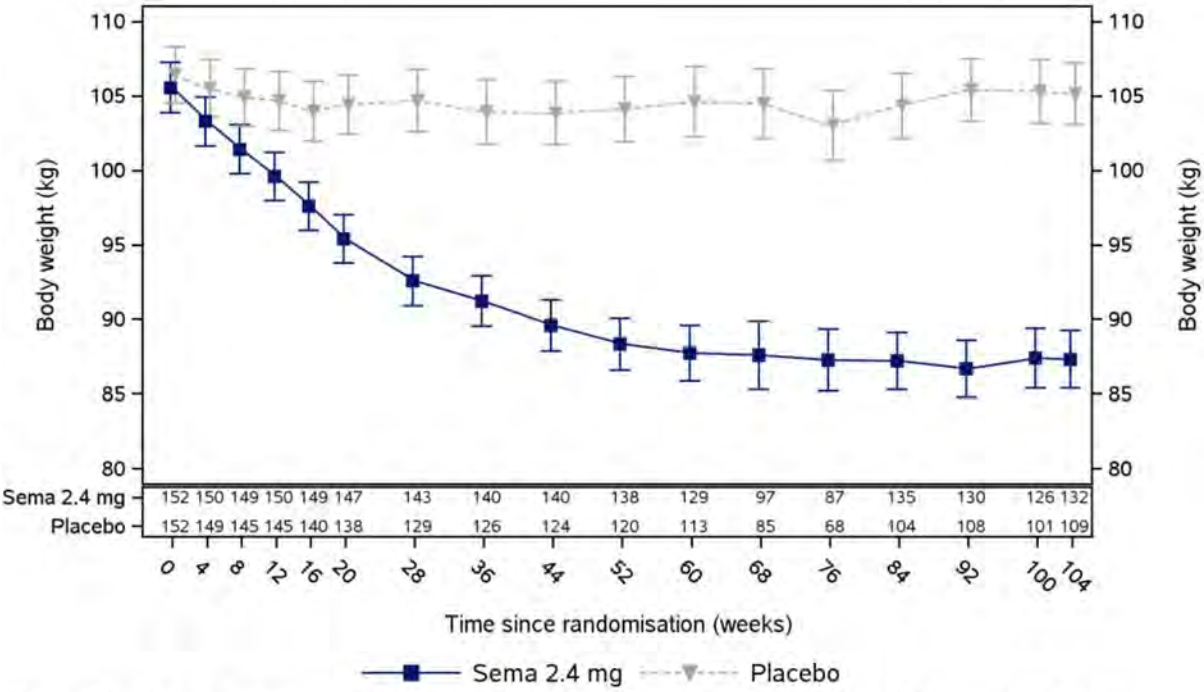
Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.3.1.2 Waist circumference by week - mean plot - in-trial - full analysis set (copied from 14.2.58, Study NN9536-4378)



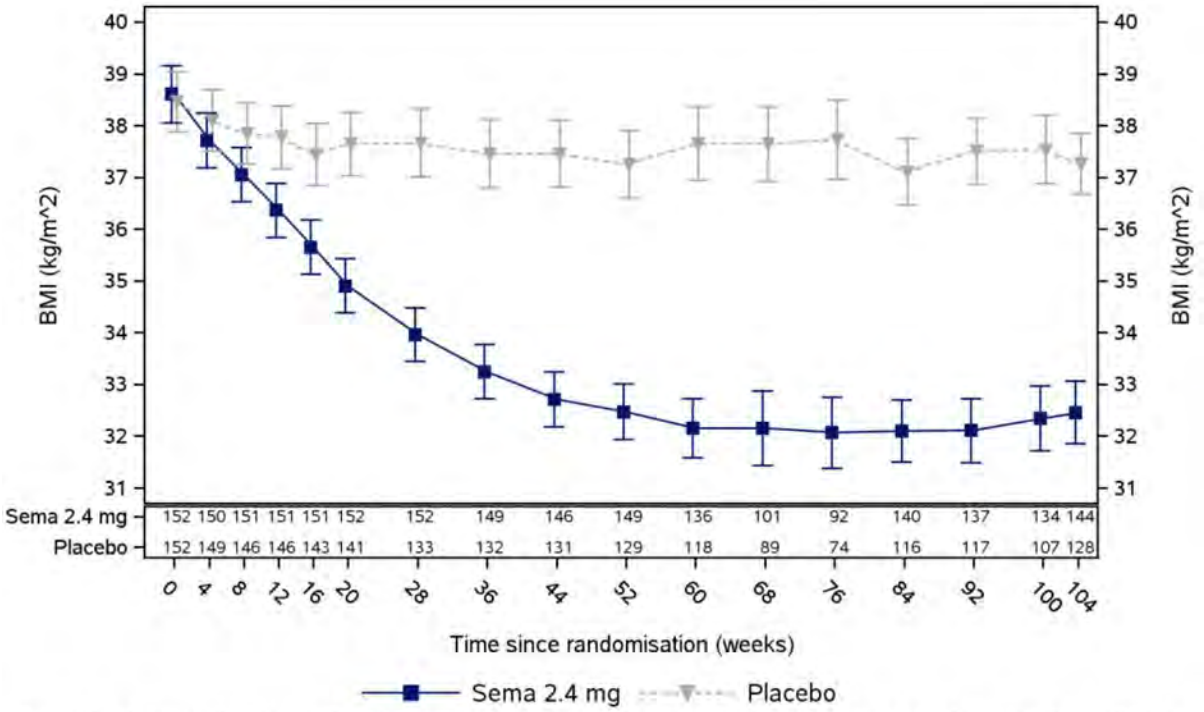
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.3.1.3 Body weight (kg) by week - mean plot - on-treatment - full analysis set (copied from 14.2.18, Study NN9536-4378)



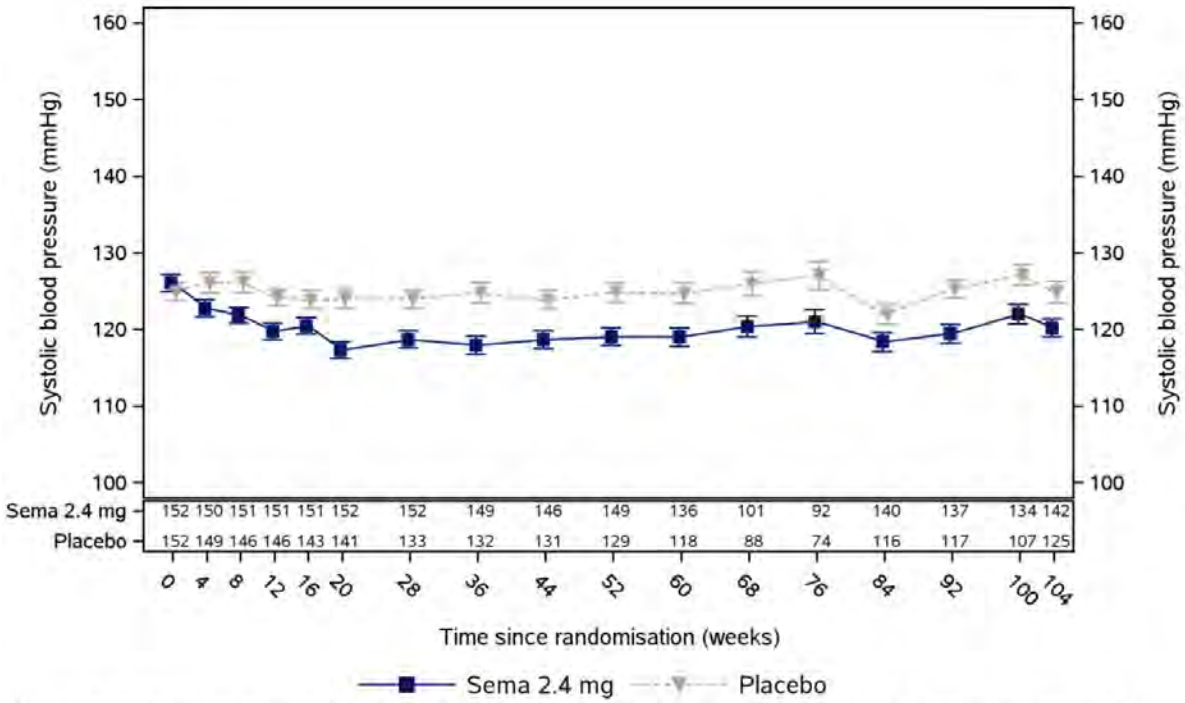
Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.3.1.4 BMI by week - mean plot - in-trial - full analysis set (copied from 14.2.52, Study NN9536-4378)



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

Figure 7.3.1.5 Systolic and diastolic blood pressure by week – mean plot – observed in-trial data (copied from Figure 11-13, Study NN9536-4378)



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

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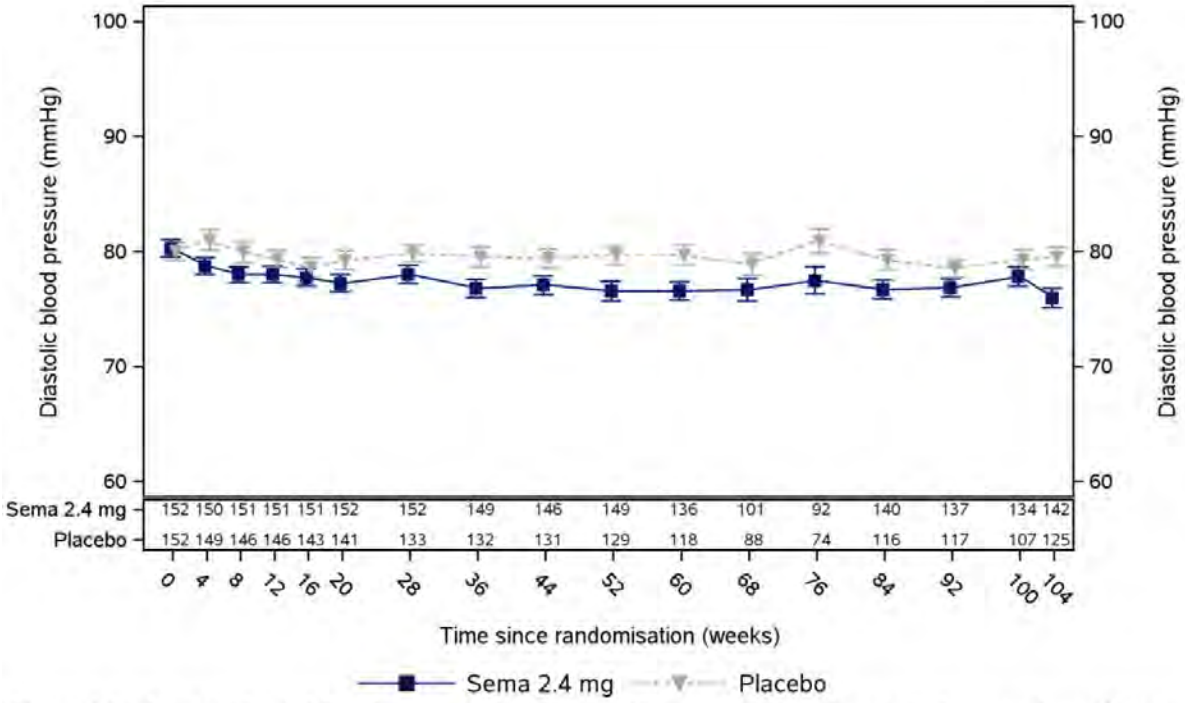
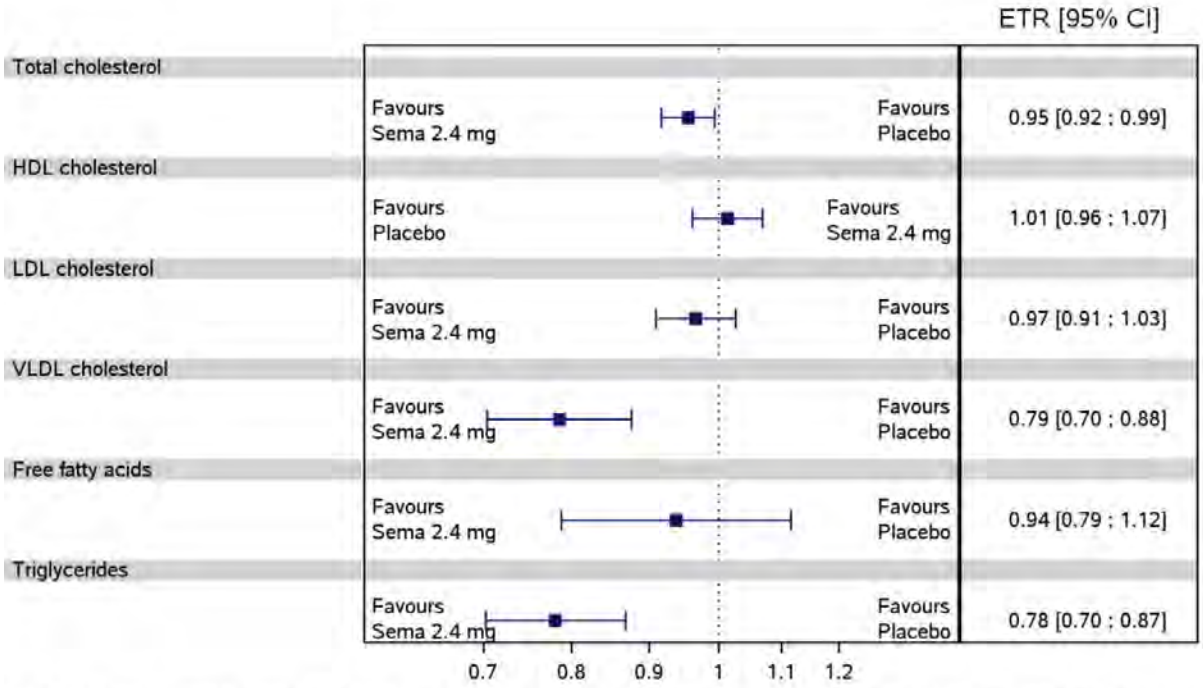
17JUN2021 09:30:00 - fmeaneff.sas/fmeansbpit.png



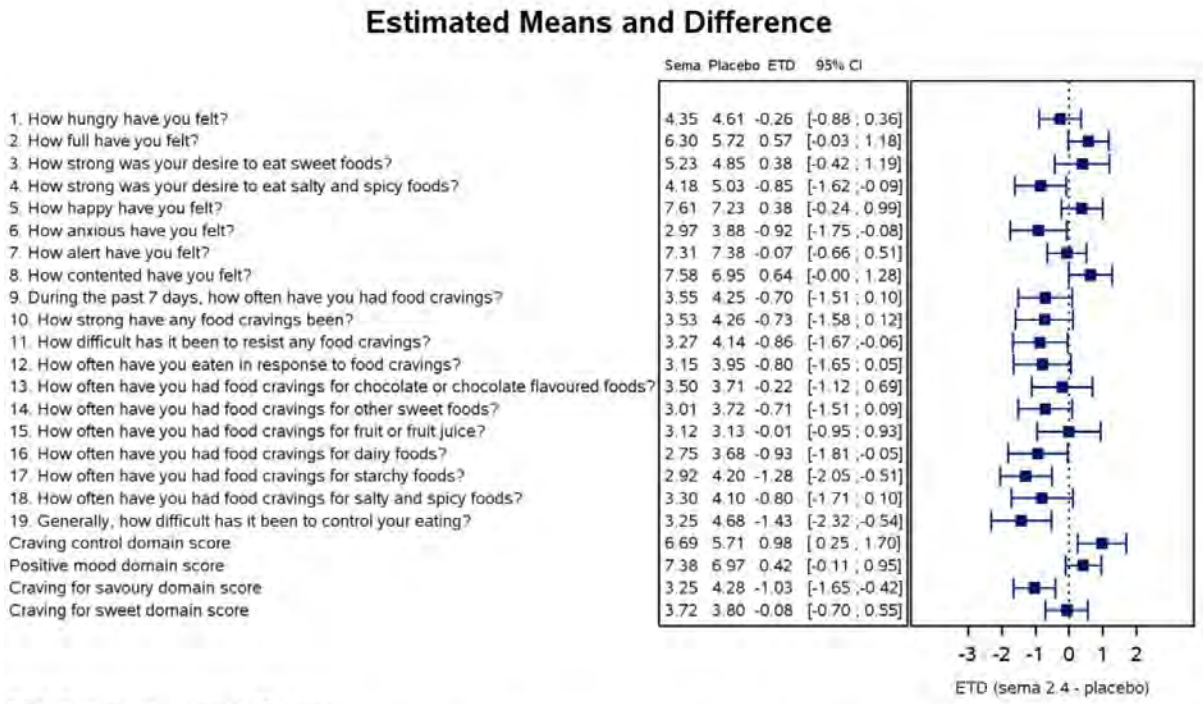
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.3.1.6 Lipids ratio to baseline at week 104 - forest plot - treatment policy estimand (copied from Figure 11-16, Study NN9536-4378)



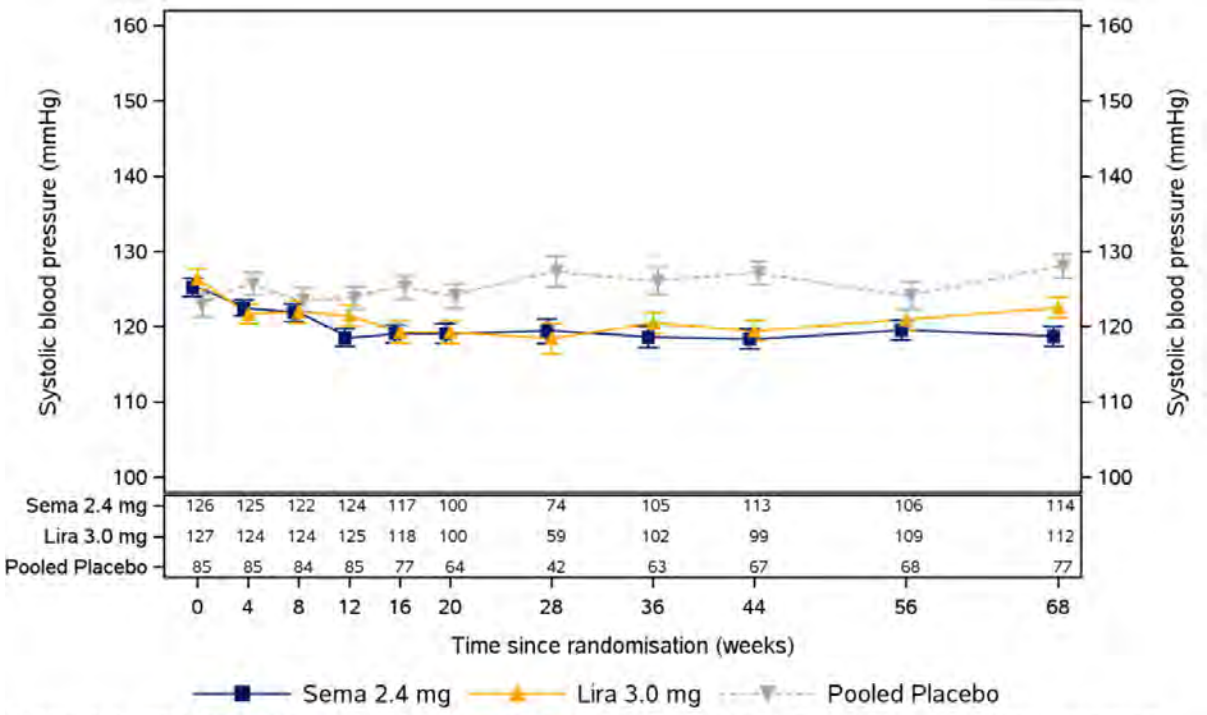
ETR: Estimated treatment ratio, CI: Confidence interval, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Figure 7.3.1.7 Control of Eating Questionnaire (CoEQ) domain score at week 104 - forest plot - treatment policy estimand (copied from Figure 11-20, Study NN9536-4378)



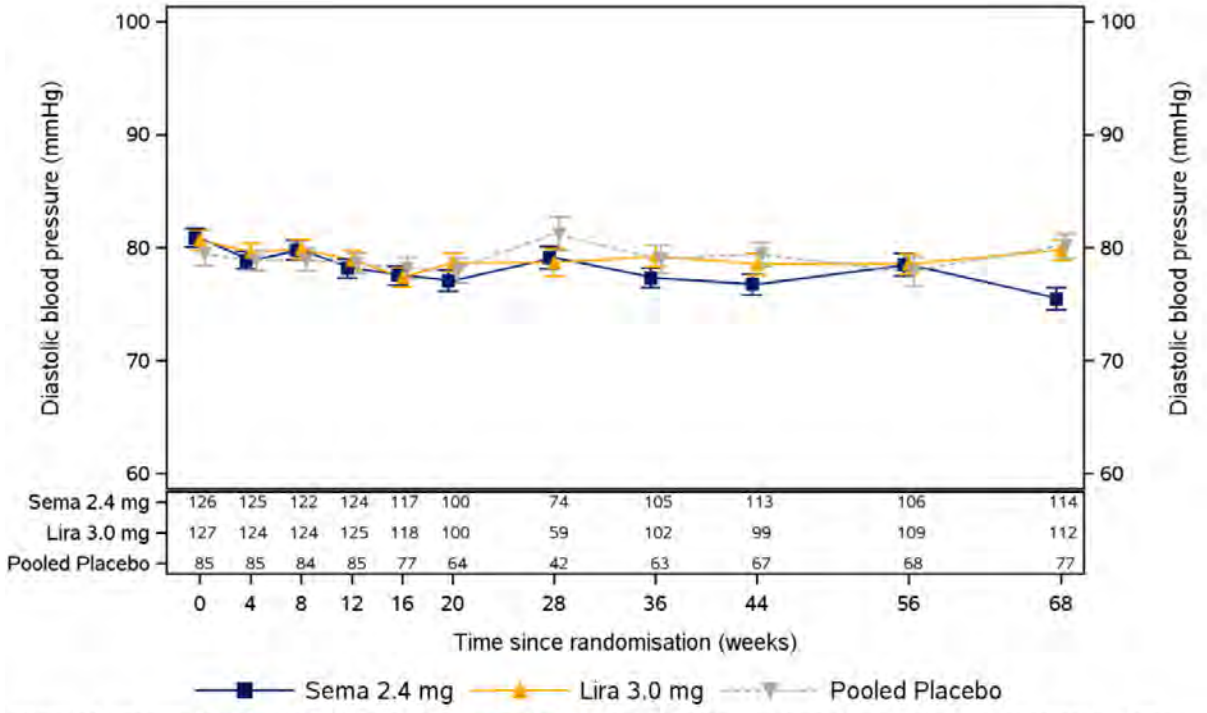
ETD: Estimated treatment difference
Item scores represent subject experience from 0 (not at all) to 10 (extremely) over the last 7 days.
The CoEQ is only applicable for US and Canada.

Figure 7.3.2.1 Systolic blood pressure by week – mean plot – observed in trial data (copied from Figure 11-9, Study NN9536-4376)



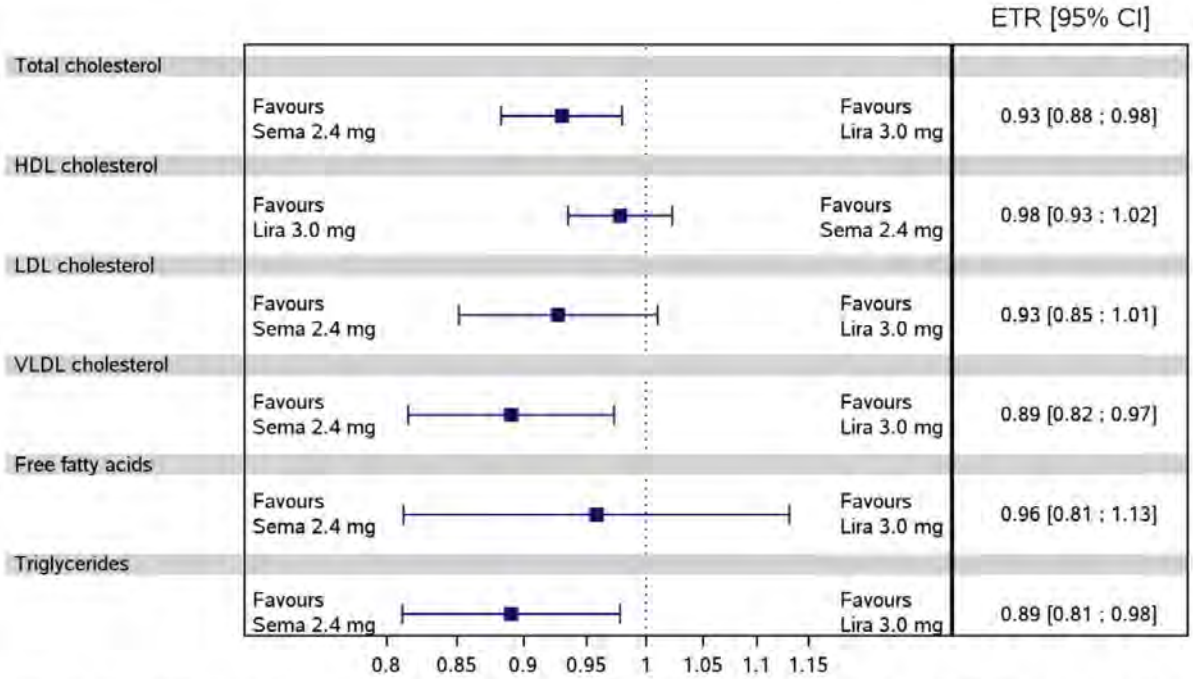
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.3.2.2 Diastolic blood pressure by week – mean plot – observed in trial data (copied from Figure 11-11, Study NN9536-4376)



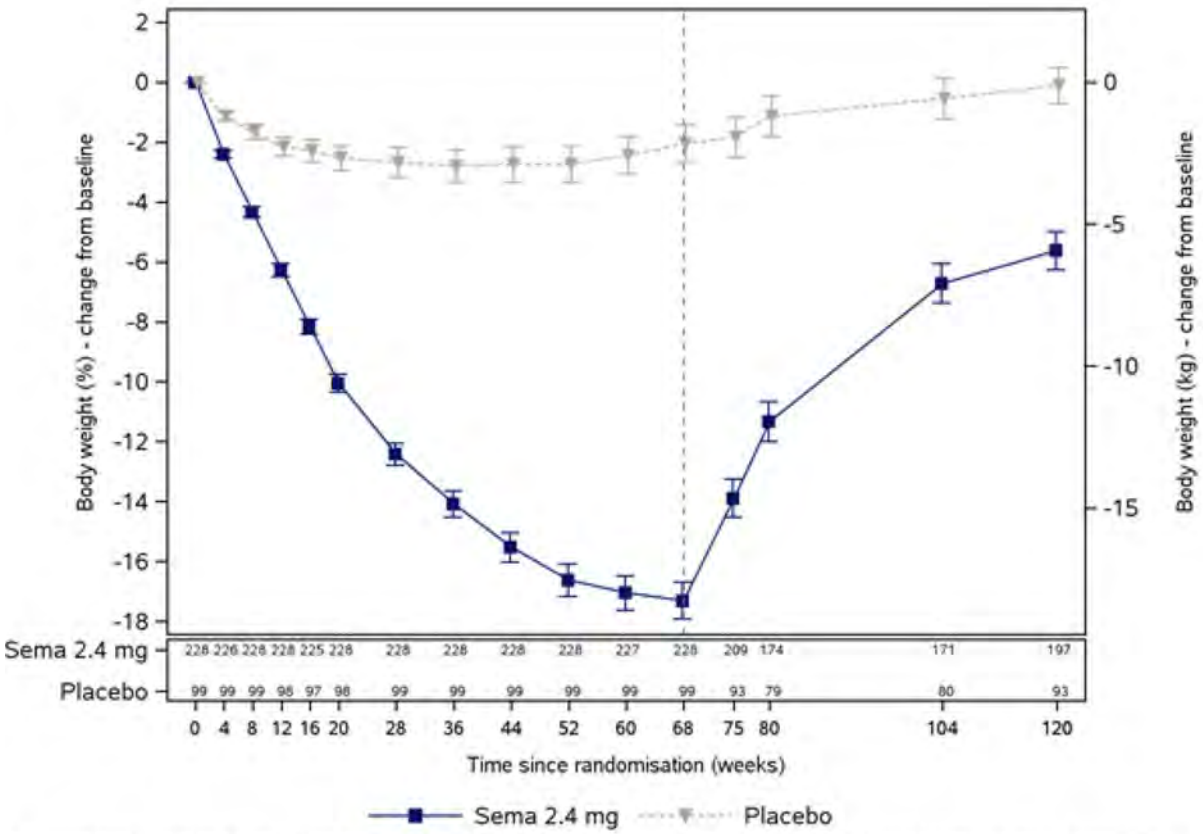
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 7.3.2.3 Lipids ratio to baseline at week 68 – forest plot – treatment policy estimand (copied from Figure 11-13, Study NN9536-4376)



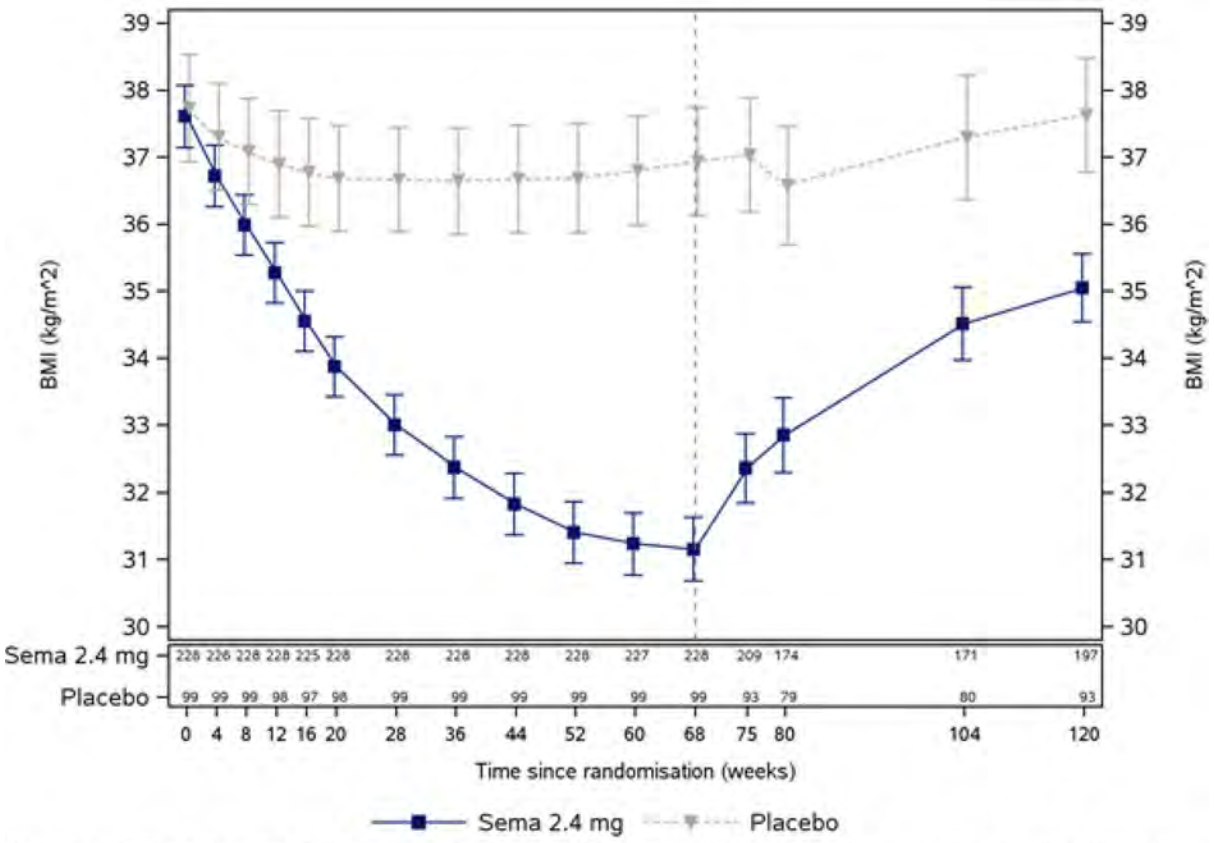
ETR: Estimated treatment ratio, CI: Confidence interval, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Analysis of data from in-trial period.

Figure 7.3.3.1 Body weight change (%, kg) from baseline by week- mean plot – in-trial – extension analysis set (copied from Figure 11-1, Study NN9536-4373 Extension)



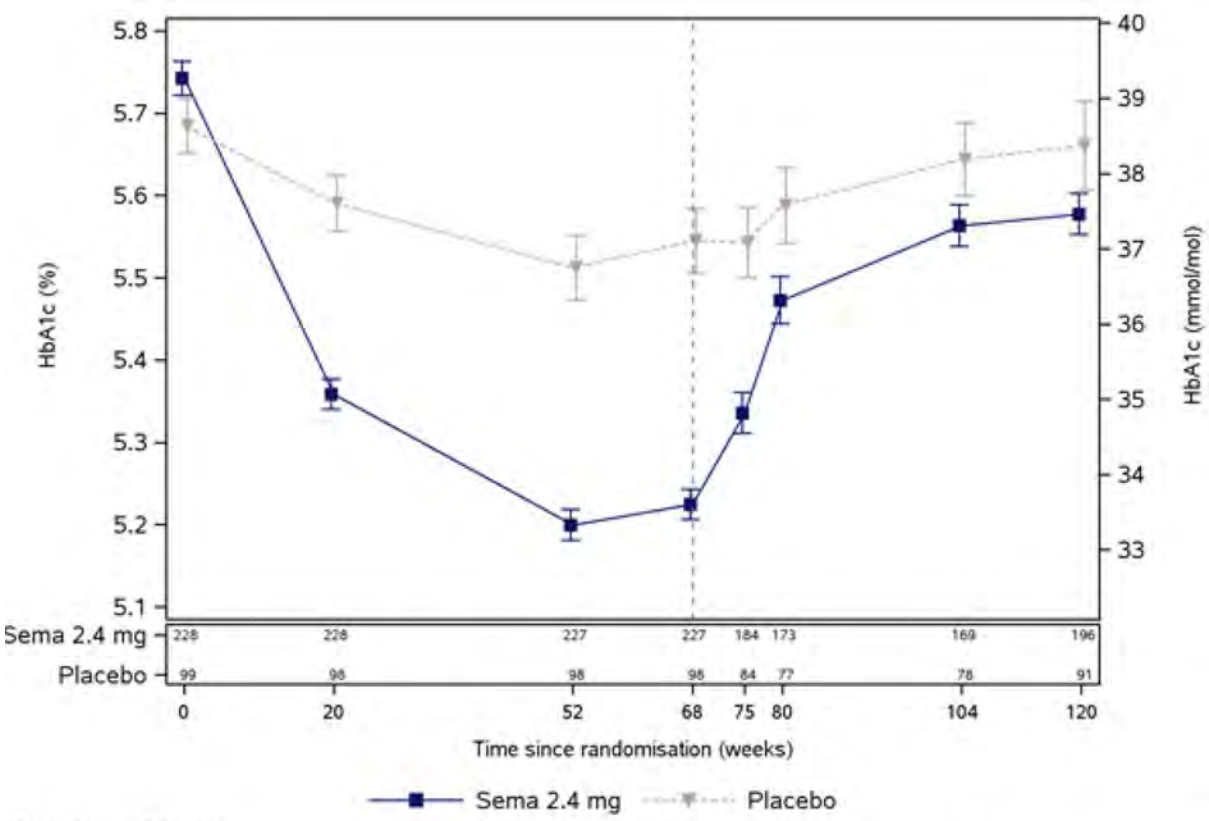
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

Figure 7.3.3.2 BMI from baseline to week 120 by week - mean plot - in-trial - extension analysis set (copied from Figure 11-4, Study NN9536-4373 Extension)



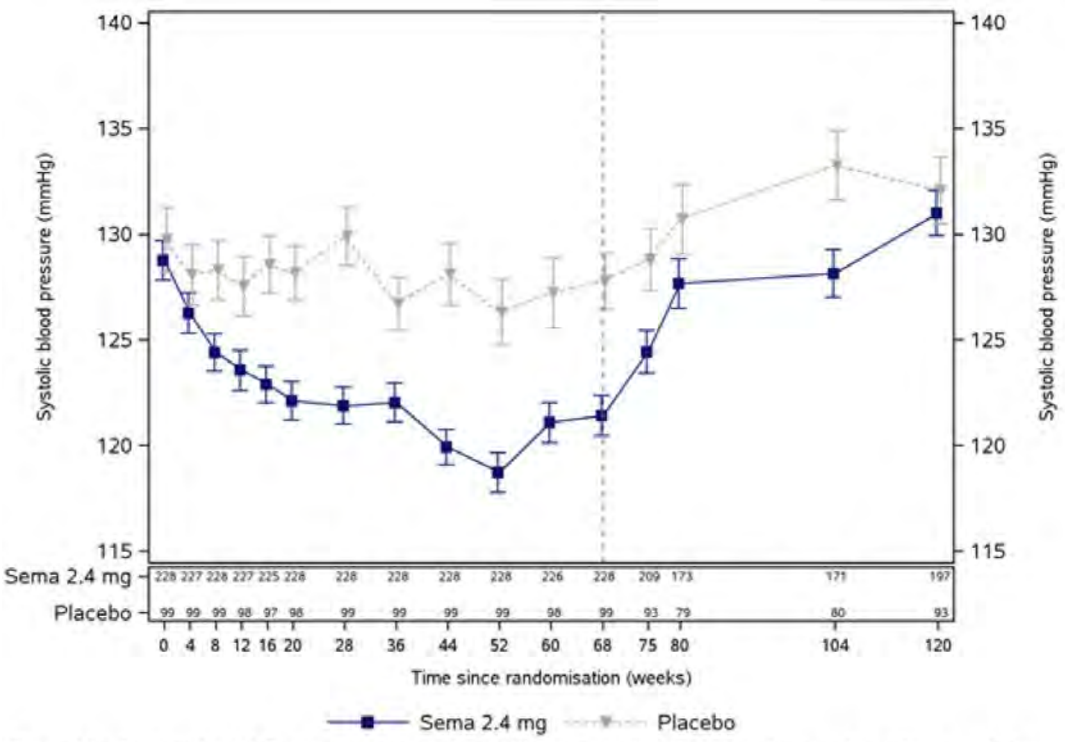
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

Figure 7.3.3.3 HbA1c from baseline to week 120 by week - mean plot - in-trial – extension analysis set (copied from Figure 11-5, Study NN9536-4373 Extension)



HbA1c: Haemoglobin A1c.
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

Figure 7.3.3.4 Blood pressure from baseline to week 120 by week - mean plot - in-trial - extension analysis set (copied from Figure 11-6, Study NN9536-4373 Extension)



Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

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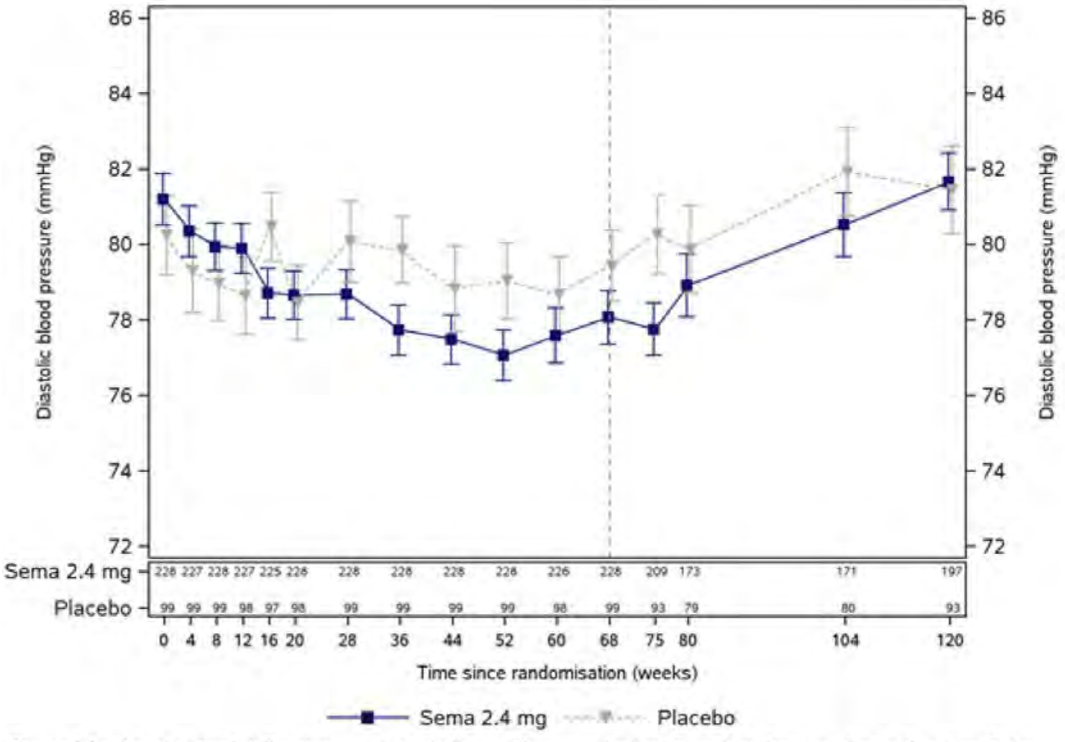
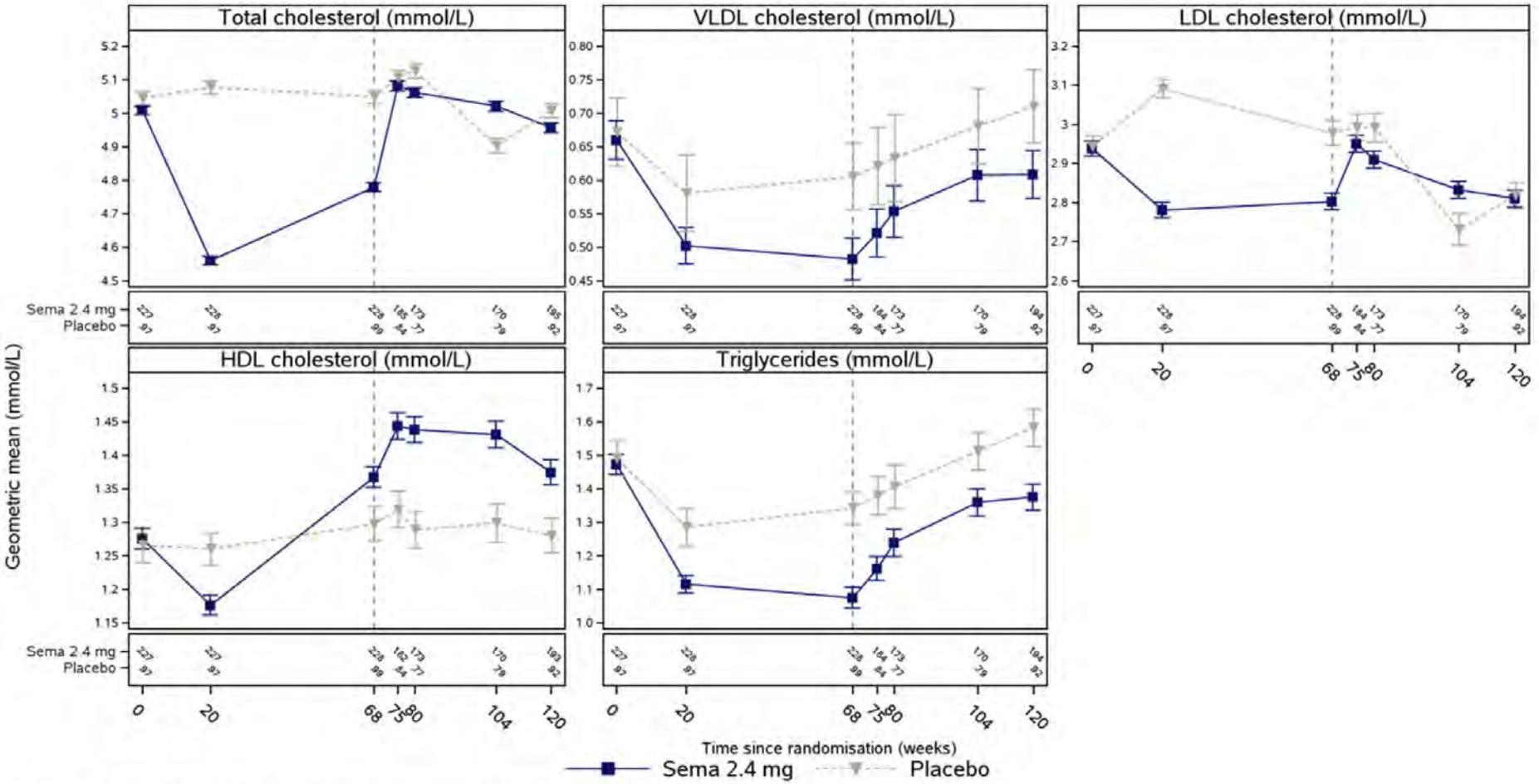
09JUN2021 09:20:09 - fmeaneff.sas/fmearisbpit.png



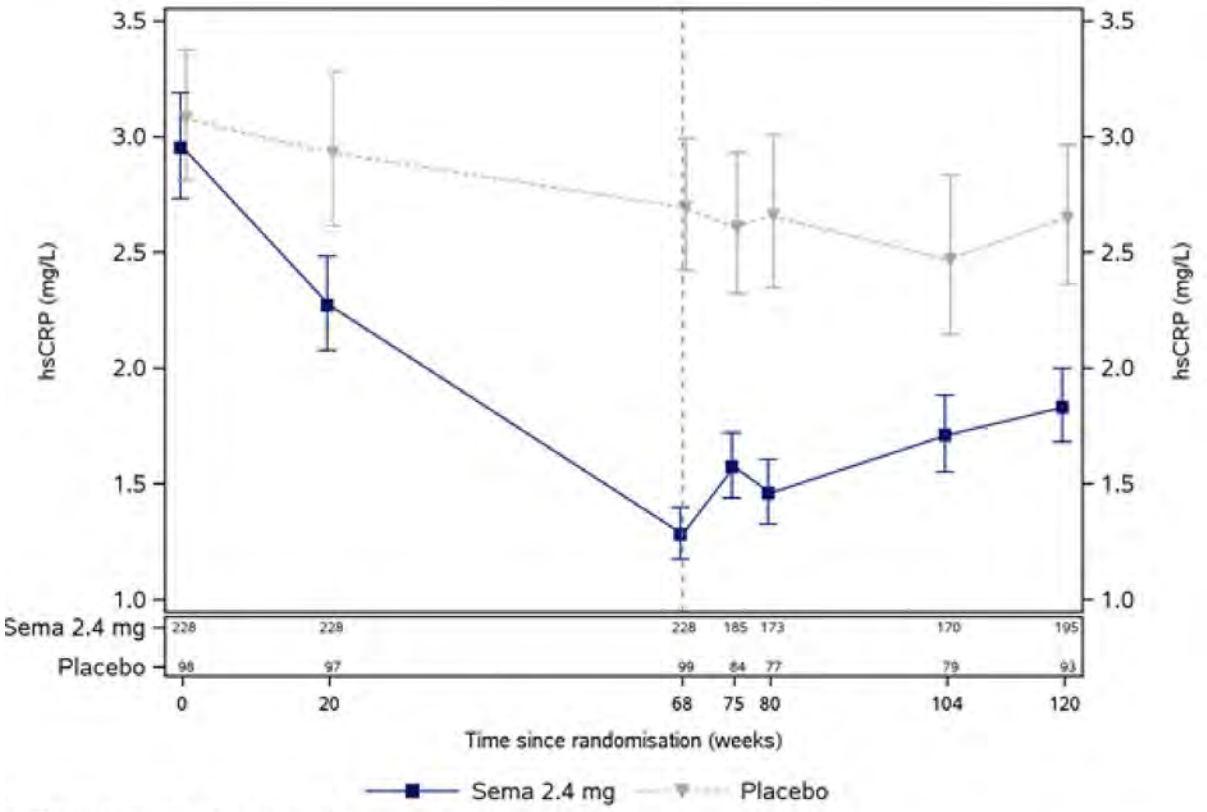
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

Figure 7.3.3.5 Lipids (mmol/L) from baseline to week 120 by week - geometric mean plot - in-trial - extension analysis set (copied from Figure 11-7, Study NN9546-4373 Extension)



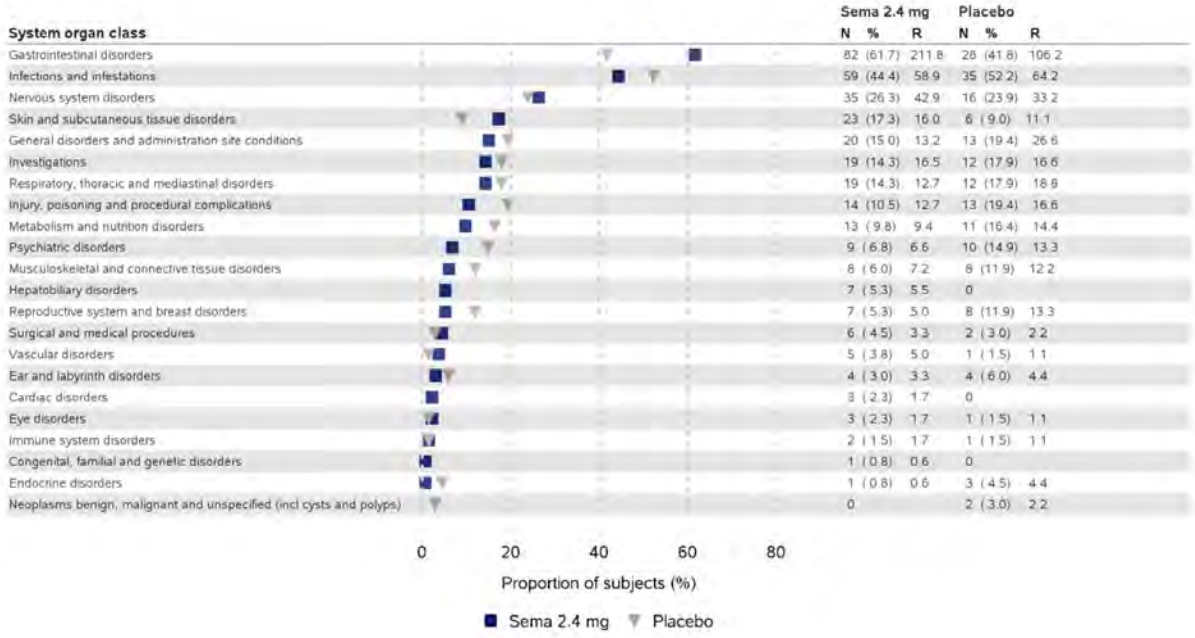
HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Observed data from in-trial period. Error bars are +/- standard error of the mean calculated on logarithmic scale and back-transformed to linear scale. Numbers shown in the lower panel are subjects contributing to the mean. Free fatty acids are not shown due to different fasting requirements in the main phase (weeks 0-68) and the extension phase (weeks 75-120). Treatment arms refer to the main phase of the trial.

Figure 7.3.3.6 C-Reactive Protein from baseline to week 120 by week - geometric mean plot - in-trial - extension analysis set (copied from Figure 11-8, Study NN9536-4373 Extension)



hsCRP: High sensitivity C-reactive protein.
Observed data from in-trial period. Error bars are +/- standard error of the mean calculated on logarithmic scale and back-transformed to linear scale. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.

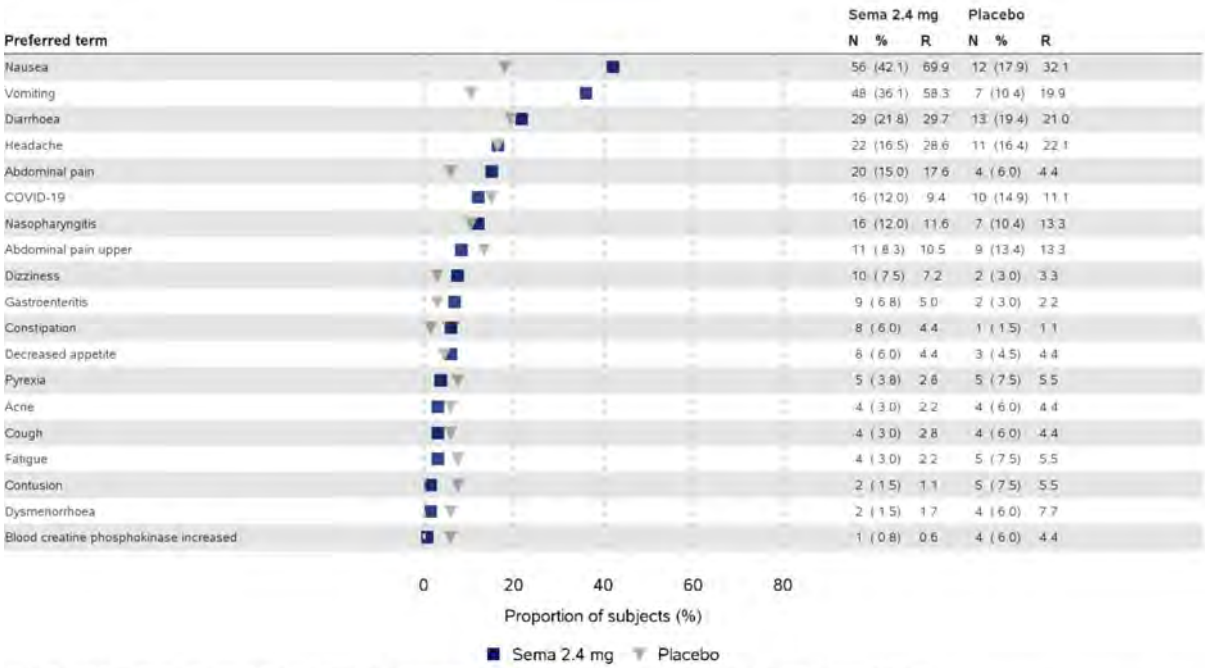
Figure 8.4.1.3.1 Adverse events by system organ class - summary plot - on-treatment (copied from Figure 12-2, Study NN9536-4451)



System organ class	Sema 2.4 mg N	%	R	Placebo N	%	R
Gastrointestinal disorders	82	(61.7)	211.8	28	(41.8)	106.2
Infections and infestations	59	(44.4)	58.9	35	(52.2)	64.2
Nervous system disorders	35	(26.3)	42.9	16	(23.9)	33.2
Skin and subcutaneous tissue disorders	23	(17.3)	16.0	6	(9.0)	11.1
General disorders and administration site conditions	20	(15.0)	13.2	13	(19.4)	26.6
Investigations	19	(14.3)	16.5	12	(17.9)	16.6
Respiratory, thoracic and mediastinal disorders	19	(14.3)	12.7	12	(17.9)	18.8
Injury, poisoning and procedural complications	14	(10.5)	12.7	13	(19.4)	16.6
Metabolism and nutrition disorders	13	(9.8)	9.4	11	(16.4)	14.4
Psychiatric disorders	9	(6.8)	6.6	10	(14.9)	13.3
Musculoskeletal and connective tissue disorders	8	(6.0)	7.2	8	(11.9)	12.2
Hepatobiliary disorders	7	(5.3)	5.5	0		
Reproductive system and breast disorders	7	(5.3)	5.0	8	(11.9)	13.3
Surgical and medical procedures	6	(4.5)	3.3	2	(3.0)	2.2
Vascular disorders	5	(3.8)	5.0	1	(1.5)	1.1
Ear and labyrinth disorders	4	(3.0)	3.3	4	(6.0)	4.4
Cardiac disorders	3	(2.3)	1.7	0		
Eye disorders	3	(2.3)	1.7	1	(1.5)	1.1
Immune system disorders	2	(1.5)	1.7	1	(1.5)	1.1
Congenital, familial and genetic disorders	1	(0.8)	0.6	0		
Endocrine disorders	1	(0.8)	0.6	3	(4.5)	4.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0			2	(3.0)	2.2

N: Number of subjects experiencing at least one event. %: Percentage of subjects experiencing at least one event. R: Event rate per 100 years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days.
Sorted in descending order by system organ class based on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

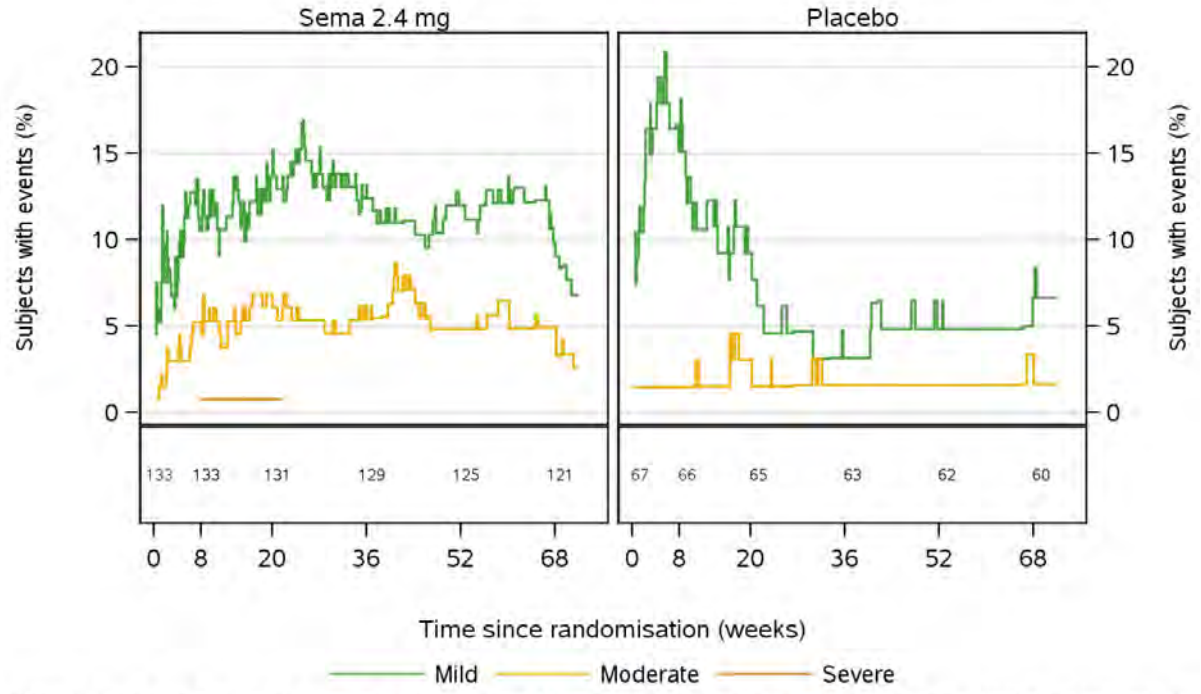
Figure 8.4.1.3.2 Adverse events by preferred term - most frequent (>=5%) - summary plot – on-treatment (copied from Figure 12-3, Study NN36-4451)



Preferred term	Sema 2.4 mg N	%	R	Placebo N	%	R
Nausea	56	(42.1)	69.9	12	(17.9)	32.1
Vomiting	48	(36.1)	58.3	7	(10.4)	19.9
Diarrhoea	29	(21.8)	29.7	13	(19.4)	21.0
Headache	22	(16.5)	28.6	11	(16.4)	22.1
Abdominal pain	20	(15.0)	17.6	4	(6.0)	4.4
COVID-19	16	(12.0)	9.4	10	(14.9)	11.1
Nasopharyngitis	16	(12.0)	11.6	7	(10.4)	13.3
Abdominal pain upper	11	(8.3)	10.5	9	(13.4)	13.3
Dizziness	10	(7.5)	7.2	2	(3.0)	3.3
Gastroenteritis	9	(6.8)	5.0	2	(3.0)	2.2
Constipation	8	(6.0)	4.4	1	(1.5)	1.1
Decreased appetite	8	(6.0)	4.4	3	(4.5)	4.4
Pyrexia	5	(3.8)	2.6	5	(7.5)	5.5
Acne	4	(3.0)	2.2	4	(6.0)	4.4
Cough	4	(3.0)	2.8	4	(6.0)	4.4
Fatigue	4	(3.0)	2.2	5	(7.5)	5.5
Contusion	2	(1.5)	1.1	5	(7.5)	5.5
Dysmenorrhoea	2	(1.5)	1.7	4	(6.0)	7.7
Blood creatine phosphokinase increased	1	(0.8)	0.6	4	(6.0)	4.4

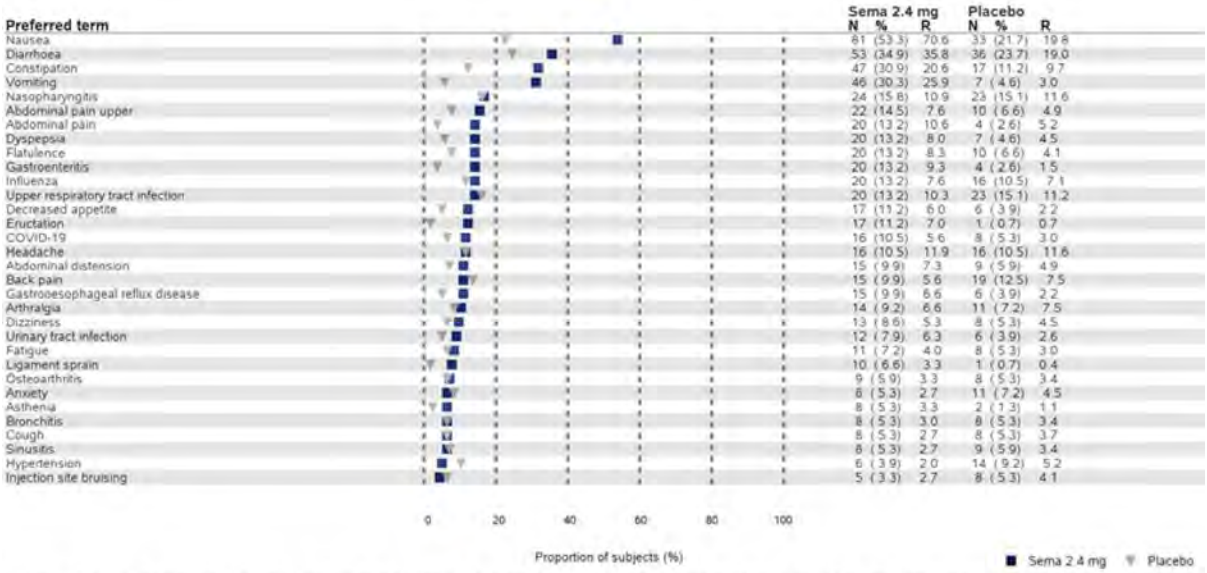
N: Number of subjects experiencing at least one event. %: Percentage of subjects experiencing at least one event. R: Event rate per 100 years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days.
Adverse events with preferred terms reported for at least 5% of subjects in any arm. Sorted in descending order by preferred term based on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 24.1

Figure 8.4.1.3.3 Gastrointestinal adverse events by severity - pre-defined MedDRA search - prevalence plot - on-treatment - safety analysis set (copied from 14.3.1.29, Study NN9536-4451)



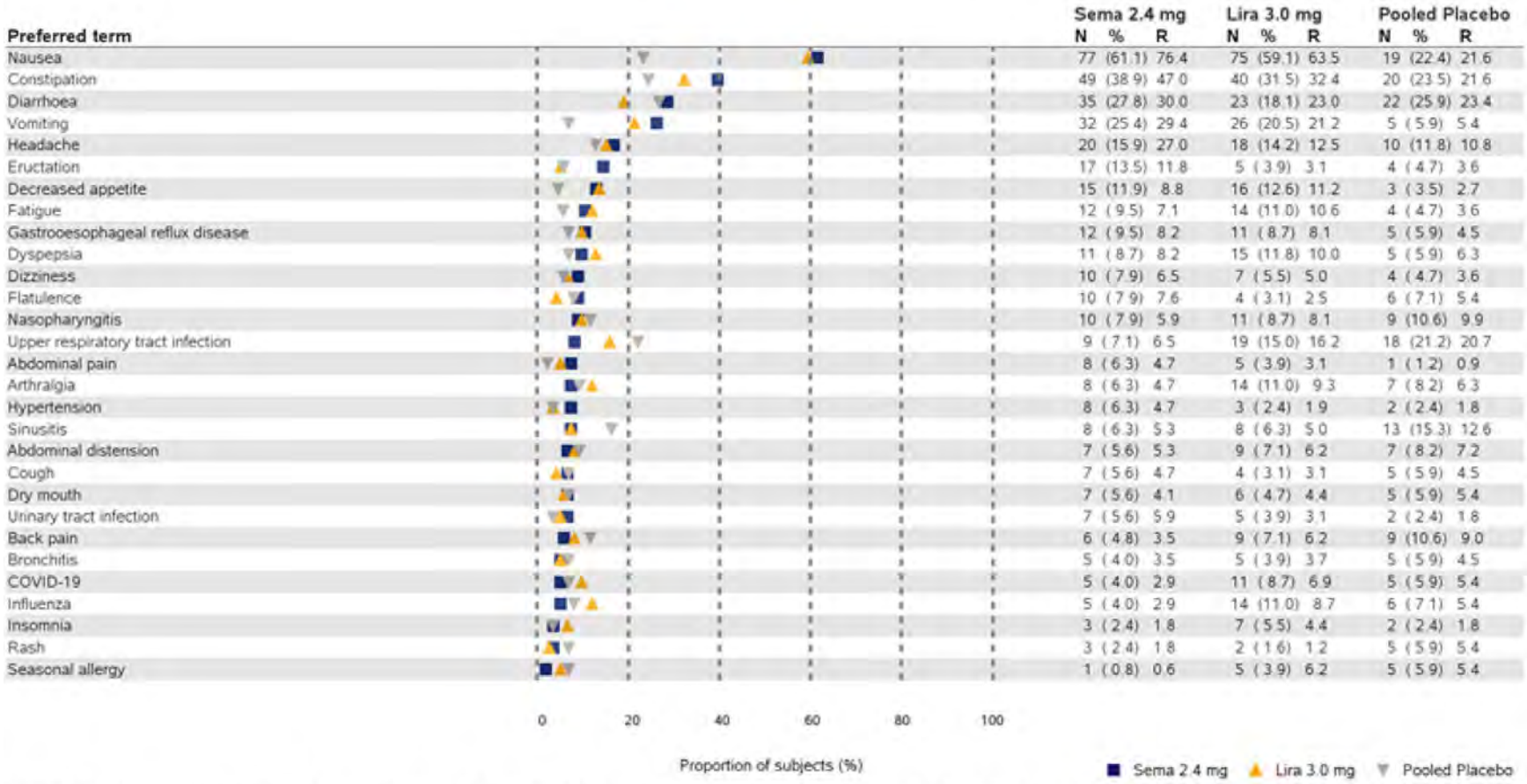
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Lower panel: Number of subjects at risk.
MedDRA version 24.1

Figure 8.4.1.4.1 Adverse events by preferred term - most frequent (>=5%) - summary plot – on-treatment (copied from Figure 12-3, Study NN9536-4378)



N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, R: Event rate per 100 years, NEC: Not elsewhere classified.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days.
Adverse events with preferred terms reported for at least 5% of subjects in any arm. Sorted in descending order by preferred term based on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

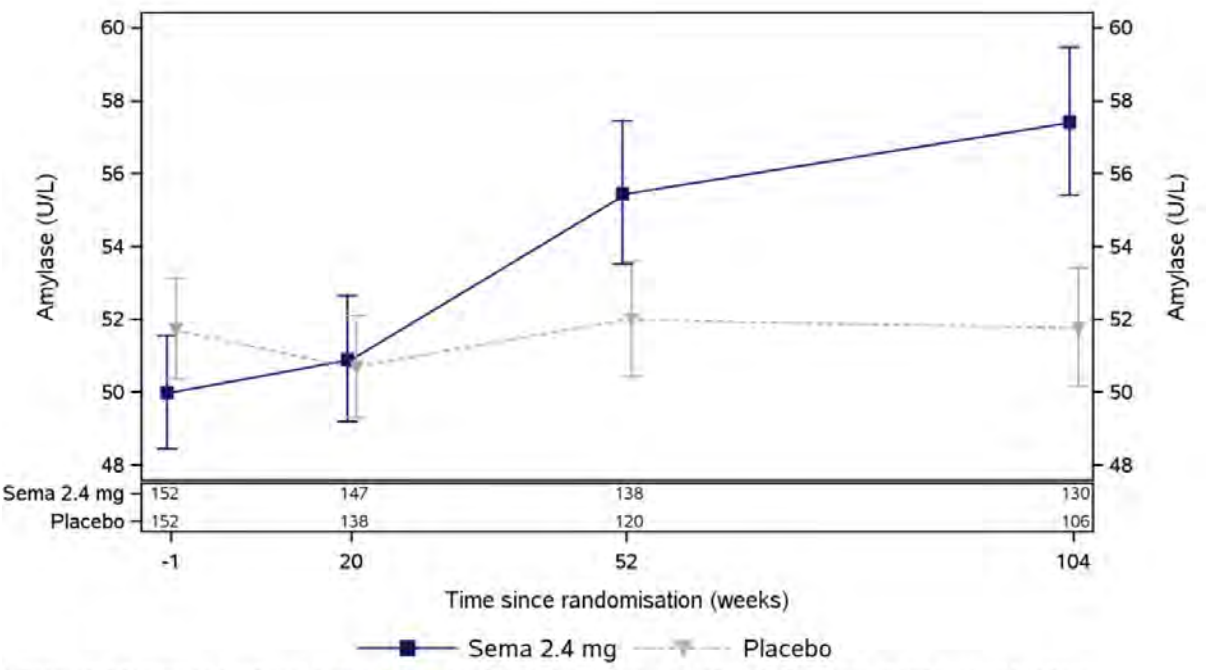
Figure 8.4.1.4.2 Adverse events by preferred term - most frequent (>=5%) - summary plot - on-treatment - safety analysis set (copied from Figure 12-3, Study NN9536-4376)



Preferred term	Sema 2.4 mg N	%	R	Lira 3.0 mg N	%	R	Pooled Placebo N	%	R
Nausea	77	(61.1)	76.4	75	(59.1)	63.5	19	(22.4)	21.6
Constipation	49	(38.9)	47.0	40	(31.5)	32.4	20	(23.5)	21.6
Diarrhoea	35	(27.8)	30.0	23	(18.1)	23.0	22	(25.9)	23.4
Vomiting	32	(25.4)	29.4	26	(20.5)	21.2	5	(5.9)	5.4
Headache	20	(15.9)	27.0	18	(14.2)	12.5	10	(11.8)	10.8
Eructation	17	(13.5)	11.8	5	(3.9)	3.1	4	(4.7)	3.6
Decreased appetite	15	(11.9)	8.8	16	(12.6)	11.2	3	(3.5)	2.7
Fatigue	12	(9.5)	7.1	14	(11.0)	10.6	4	(4.7)	3.6
Gastrooesophageal reflux disease	12	(9.5)	8.2	11	(8.7)	8.1	5	(5.9)	4.5
Dyspepsia	11	(8.7)	8.2	15	(11.8)	10.0	5	(5.9)	6.3
Dizziness	10	(7.9)	6.5	7	(5.5)	5.0	4	(4.7)	3.6
Flatulence	10	(7.9)	7.6	4	(3.1)	2.5	6	(7.1)	5.4
Nasopharyngitis	10	(7.9)	5.9	11	(8.7)	8.1	9	(10.6)	9.9
Upper respiratory tract infection	9	(7.1)	6.5	19	(15.0)	16.2	18	(21.2)	20.7
Abdominal pain	8	(6.3)	4.7	5	(3.9)	3.1	1	(1.2)	0.9
Arthralgia	8	(6.3)	4.7	14	(11.0)	9.3	7	(8.2)	6.3
Hypertension	8	(6.3)	4.7	3	(2.4)	1.9	2	(2.4)	1.8
Sinusitis	8	(6.3)	5.3	8	(6.3)	5.0	13	(15.3)	12.6
Abdominal distension	7	(5.6)	5.3	9	(7.1)	6.2	7	(8.2)	7.2
Cough	7	(5.6)	4.7	4	(3.1)	3.1	5	(5.9)	4.5
Dry mouth	7	(5.6)	4.1	6	(4.7)	4.4	5	(5.9)	5.4
Urinary tract infection	7	(5.6)	5.9	5	(3.9)	3.1	2	(2.4)	1.8
Back pain	6	(4.8)	3.5	9	(7.1)	6.2	9	(10.6)	9.0
Bronchitis	5	(4.0)	3.5	5	(3.9)	3.7	5	(5.9)	4.5
COVID-19	5	(4.0)	2.9	11	(8.7)	6.9	5	(5.9)	5.4
Influenza	5	(4.0)	2.9	14	(11.0)	8.7	6	(7.1)	5.4
Insomnia	3	(2.4)	1.8	7	(5.5)	4.4	2	(2.4)	1.8
Rash	3	(2.4)	1.8	2	(1.6)	1.2	5	(5.9)	5.4
Seasonal allergy	1	(0.8)	0.6	5	(3.9)	6.2	5	(5.9)	5.4

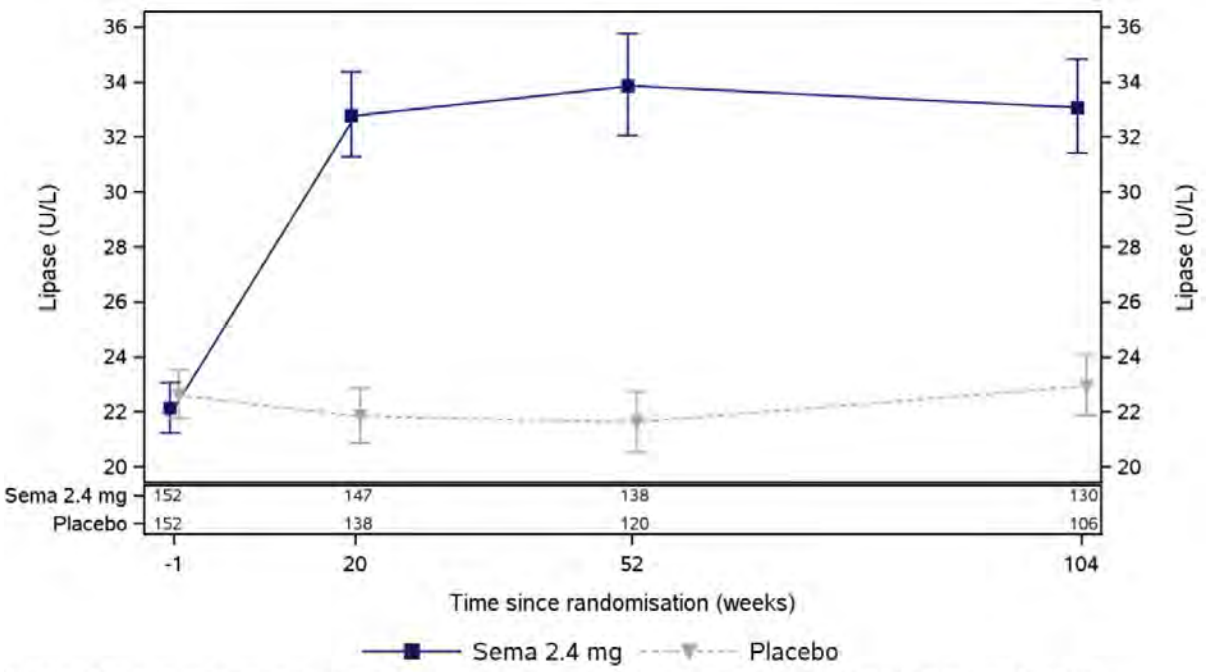
N: Number of subjects experiencing at least one event. %: Percentage of subjects experiencing at least one event. R: Event rate per 100 years.
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Adverse events with preferred terms reported for at least 5% of subjects in any arm. Sorted in descending order by preferred term based on the percentage of subjects in the Sema 2.4 mg arm experiencing at least one event.
MedDRA version 23.1

Figure 8.5.3.4.1 Amylase by week - geometric mean plot - on-treatment - safety analysis set (copied from 14.3.5.10, Study NN9536-4478)



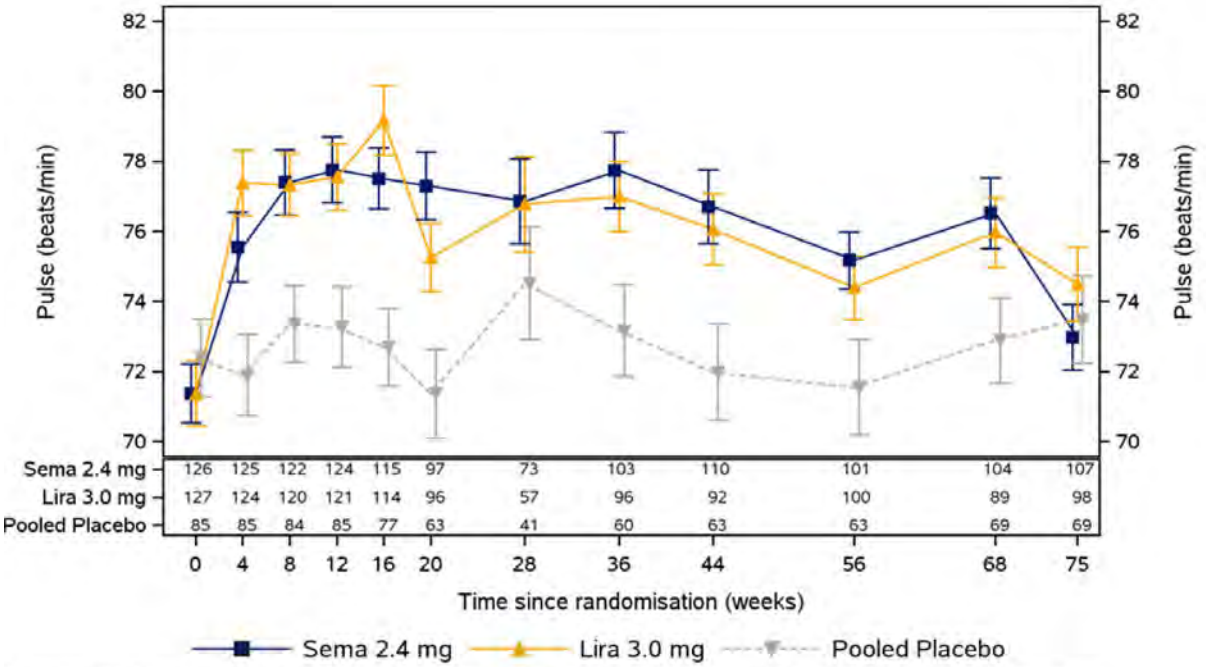
Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days.
Error bars are +/- standard error of the mean calculated on logarithmic scale and back-transformed to linear scale.
Numbers shown in the lower panel are subjects contributing to the mean.

Figure 8.5.3.4.2 Lipase by week - geometric mean plot - on-treatment - safety analysis set (copied from 14.3.5.19, Study NN9536-4378)



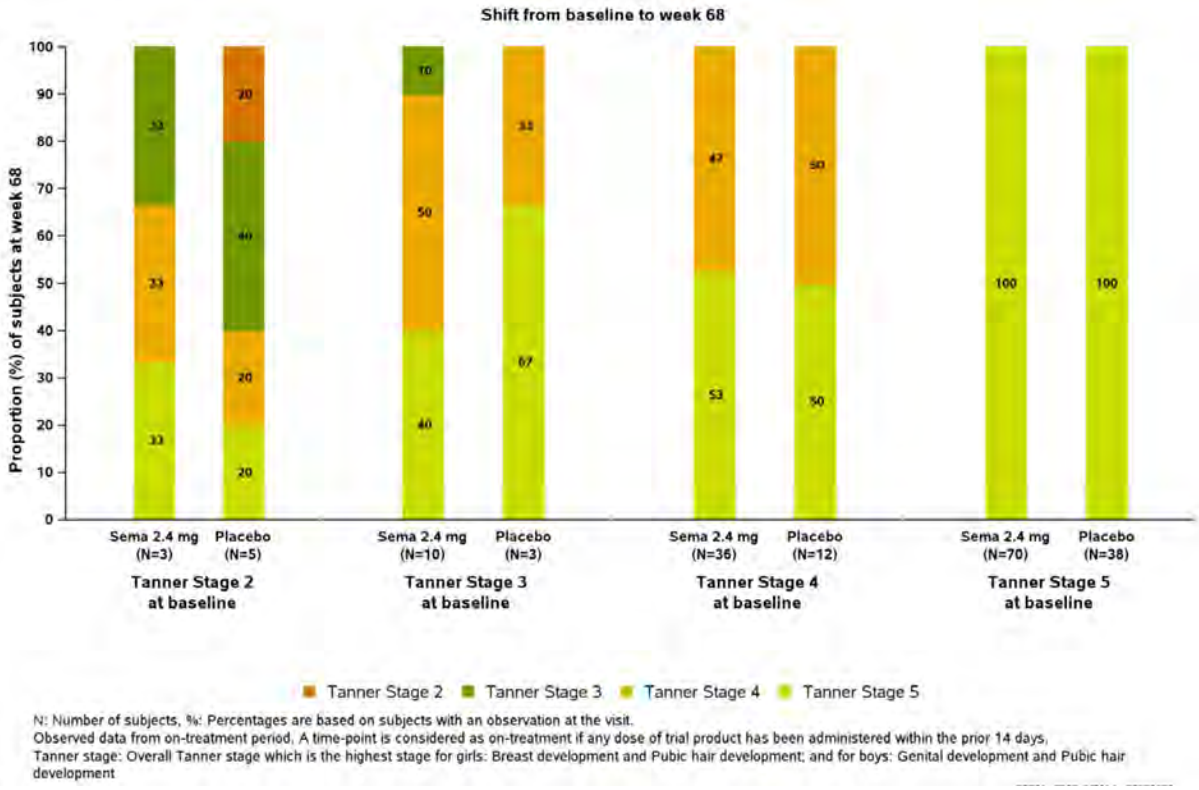
Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days.
Error bars are +/- standard error of the mean calculated on logarithmic scale and back-transformed to linear scale.
Numbers shown in the lower panel are subjects contributing to the mean.

Figure 8.5.7.4.1 Pulse by week - mean plot - on-treatment and planned follow-up visit – safety analysis set (copied from Figure 12-7, Study NN9536-4376)



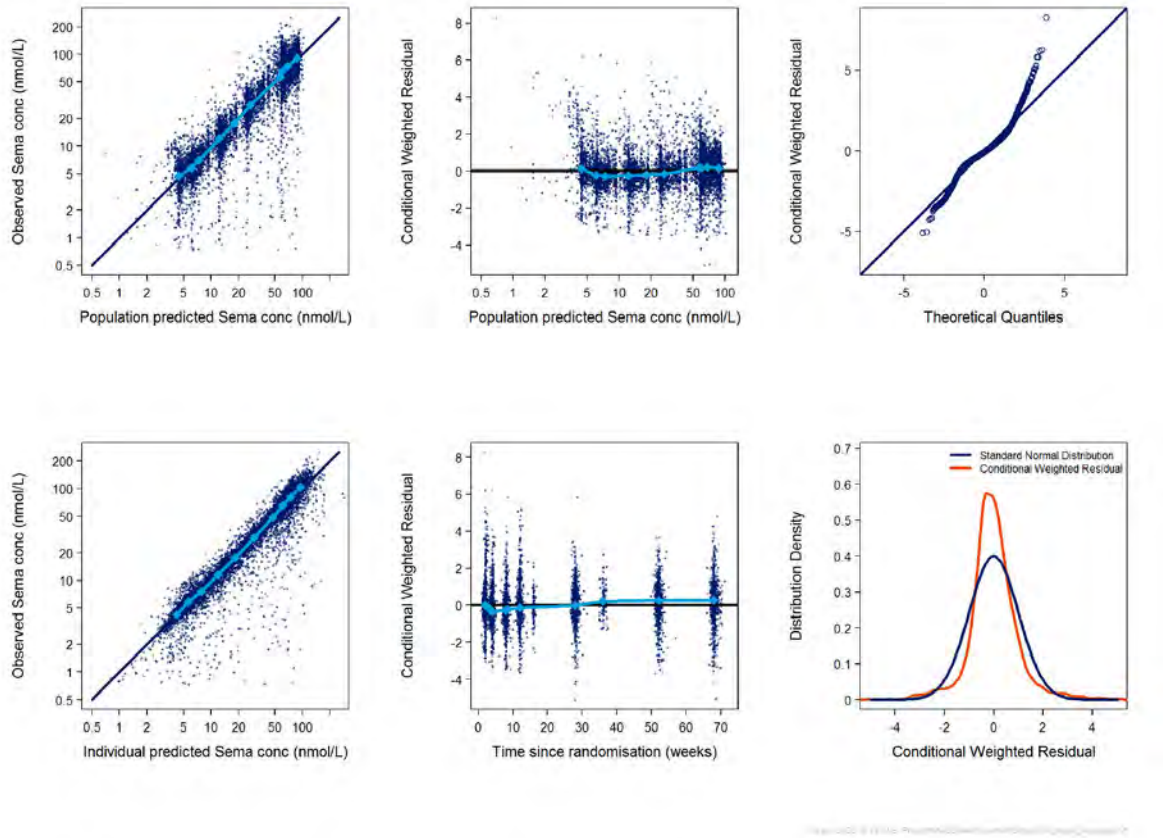
Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 8.5.12.3.1 Tanner Stage - shift plot - on-treatment - safety analysis set (copied from Figure 12-15, Study NN9536-4451)



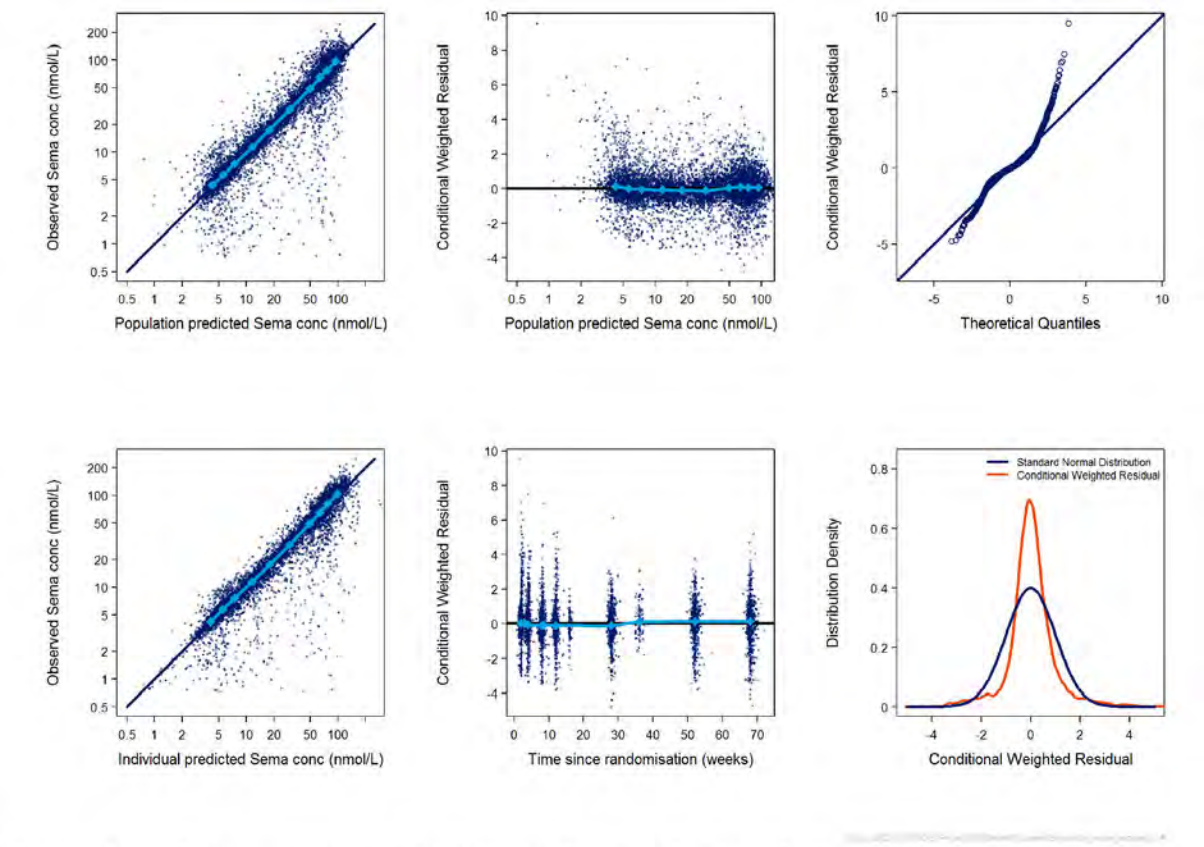
N: Number of subjects, %: Percentages are based on subjects with an observation at the visit.
Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days.
Tanner stage: Overall Tanner stage which is the highest stage for girls: Breast development and Pubic hair development; and for boys: Genital development and Pubic hair development

Figure 19.1.3.1.1 Standard goodness-of-fit plot for the base PK model without covariates (copied from Figure 9-2, Study NN9536-4451 Modelling Report)



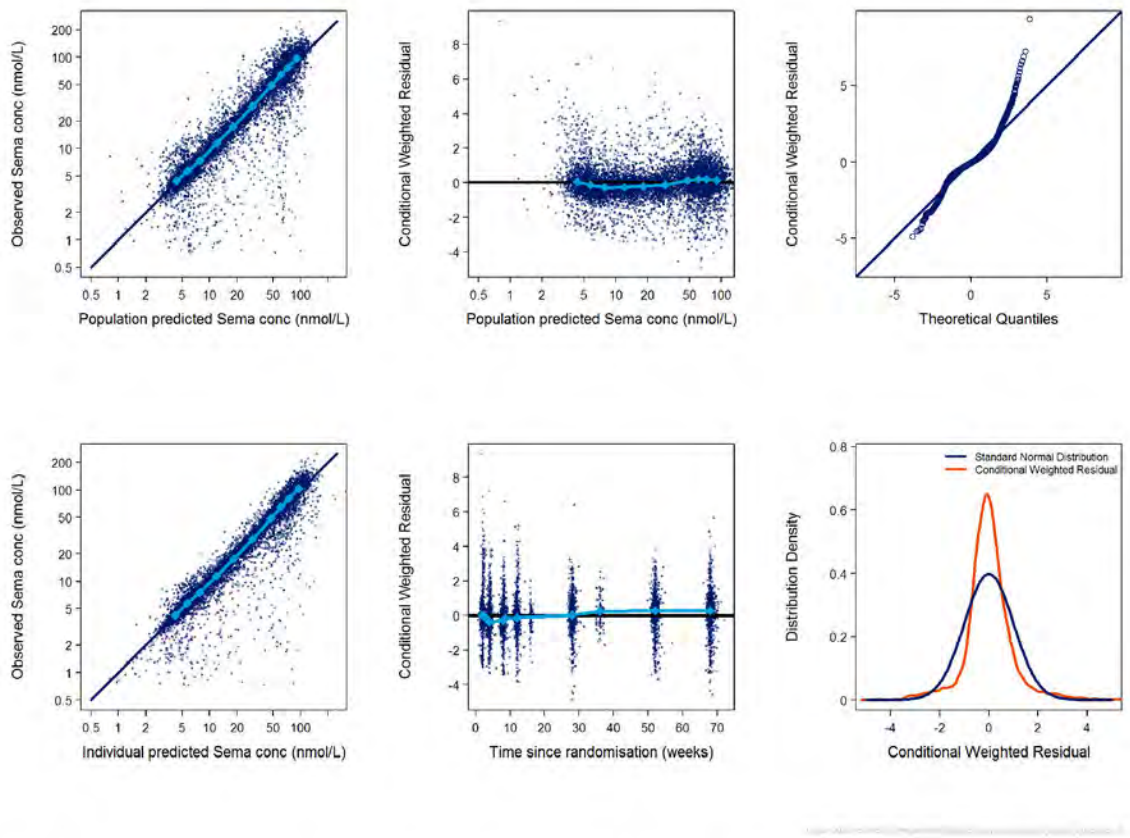
Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Light blue lines are median values for quantiles of concentration or time.

Figure 19.1.3.1.2 Standard goodness-of-fit plot for the full PK model including all the covariates (copied from Figure 9-4, Study NN9536-4451 Modelling Report)



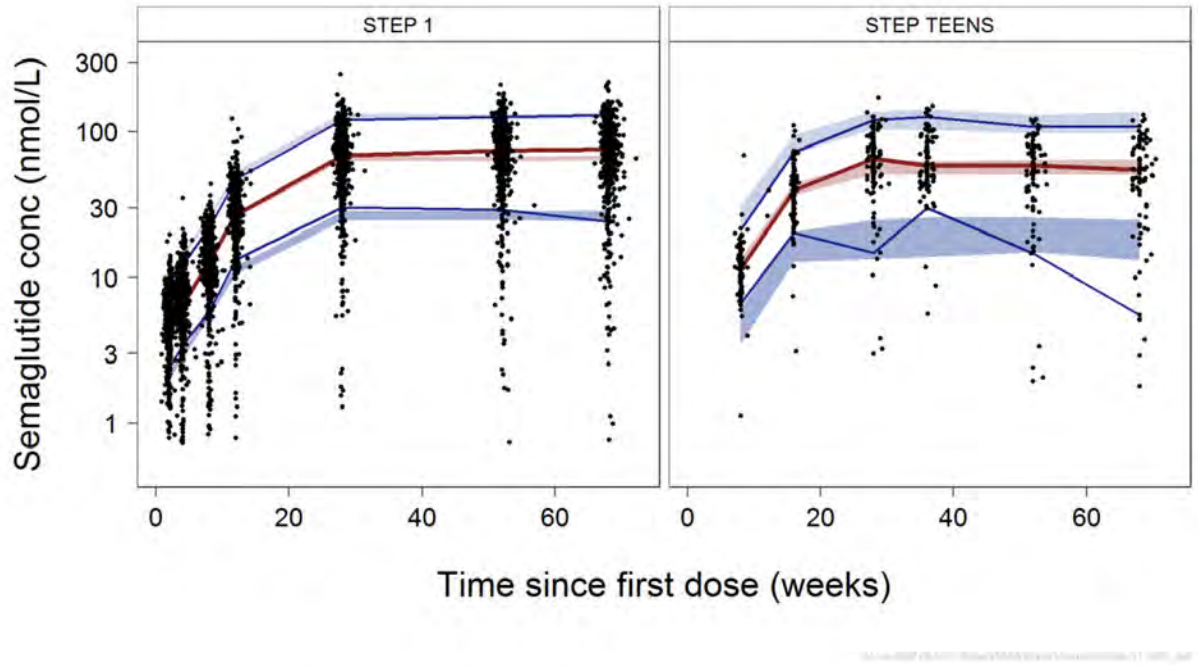
Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Light blue lines are median values for quantiles of concentration or time.

Figure 19.1.3.1.3 Standard goodness-of-fit plot for the final PK model including reduced number of covariates (copied from Figure 9-6, Study NN9536-4451 Modelling Report)



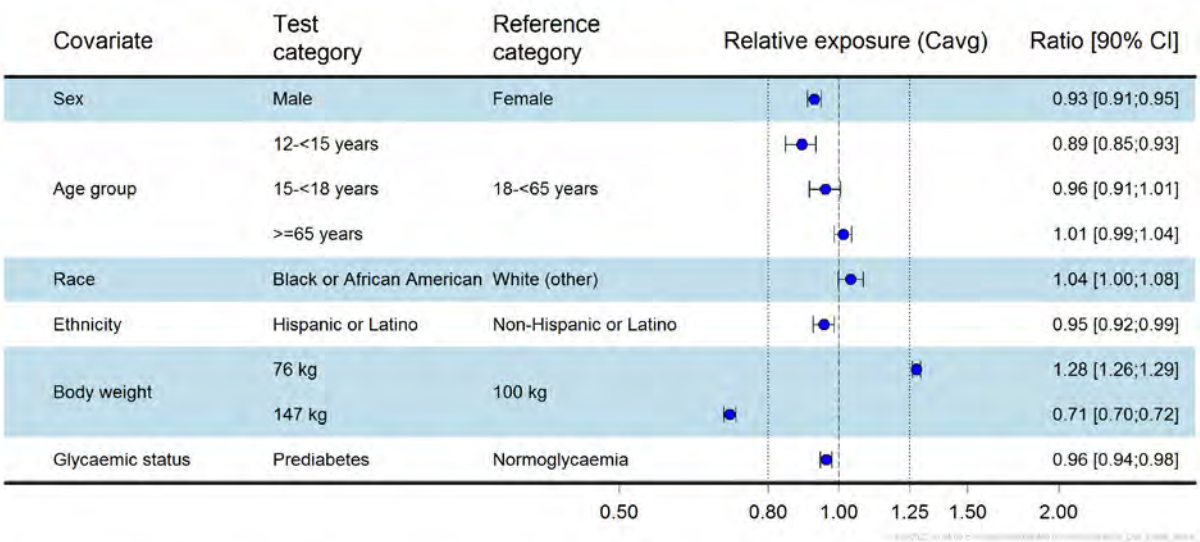
Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Light blue lines are median values for quantiles of concentration or time.

Figure 19.1.3.1.4 Visual predictive check for the final reduced PK model of semaglutide stratified by trial (copied from Figure 9-9, Study NN9536-4451 Modelling Report)



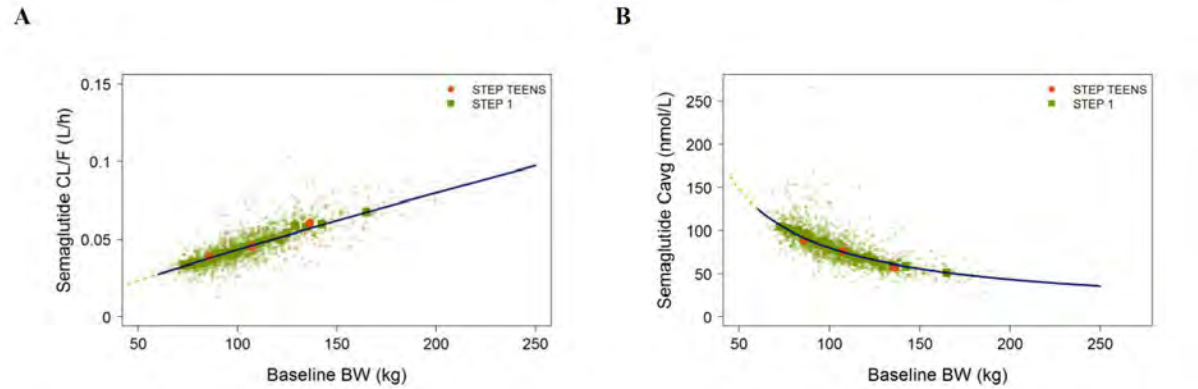
Data are observed (lines) and simulated (shaded area, n=500) medians and 5th and 95th concentration percentiles after the first dose. Black dots represents individual observed concentrations

Figure 19.1.3.1.5 Forest plot of covariate effects for semaglutide exposure (copied from Figure 6-2, Study NN9536-4451 Modelling Report)



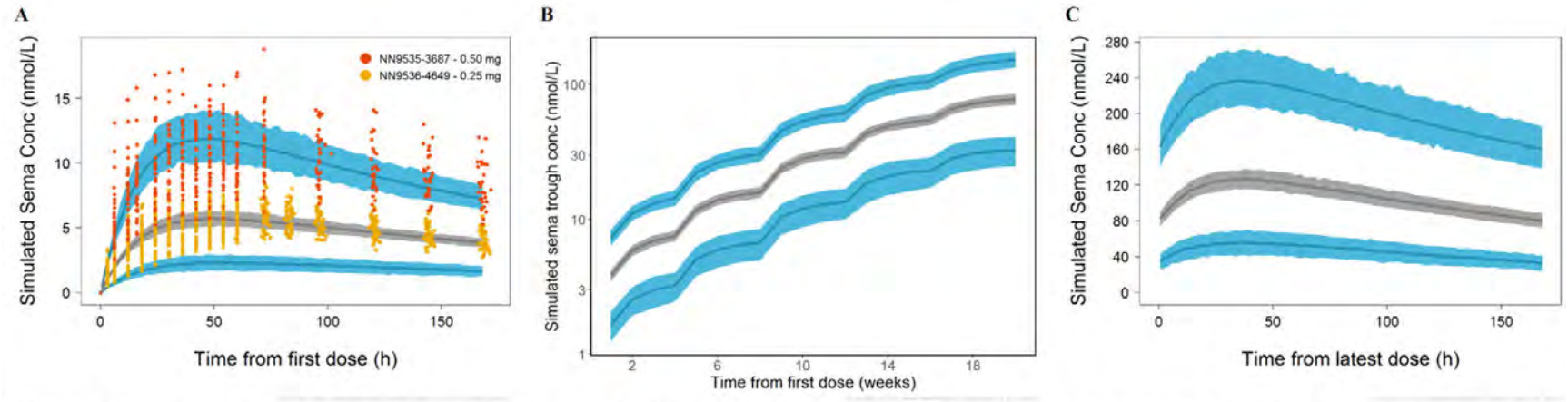
Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino, normoglycaemic white female aged 18-<65 years (STEP 1) and with a body weight of 100 kg). The forest plot and the column to the right show means and 90% CI for the relative exposures. Body weight test categories (76 and 147 kg) represent the 5% and 95% percentiles, respectively in the data set. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80;1.25).

Figure 19.1.3.1.6 Apparent clearance (CL/F) (A) and semaglutide exposure for a 2.4 mg dose (B) versus baseline body weight by trial (copied from Figure 6-5, Study NN9536-4451 Modelling Report)



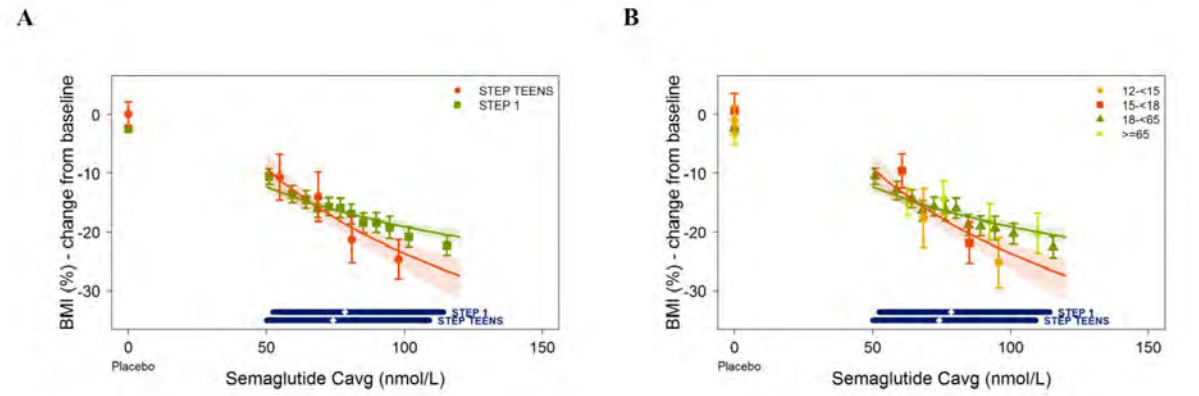
Data are model derived individual apparent clearance (CL/F) or average semaglutide concentrations (C_{avg}) versus baseline body weight (small symbols). Geometric mean estimates versus body weight are presented in quantiles by trial (large symbols). Trend lines are derived from the final population PK model.

Figure 19.1.3.1.7 Simulated concentrations in children a single dose of 0.25 mg and observed concentrations in adults versus time since first dose (A), simulated trough concentrations from first dose of 0.25 mg to steady state of 2.4 mg during dose escalation (B) and simulated steady state concentrations versus time since latest dose of 2.4 mg (C) (copied from Figure 6-6, Study NN9536-4451 Modelling Report)



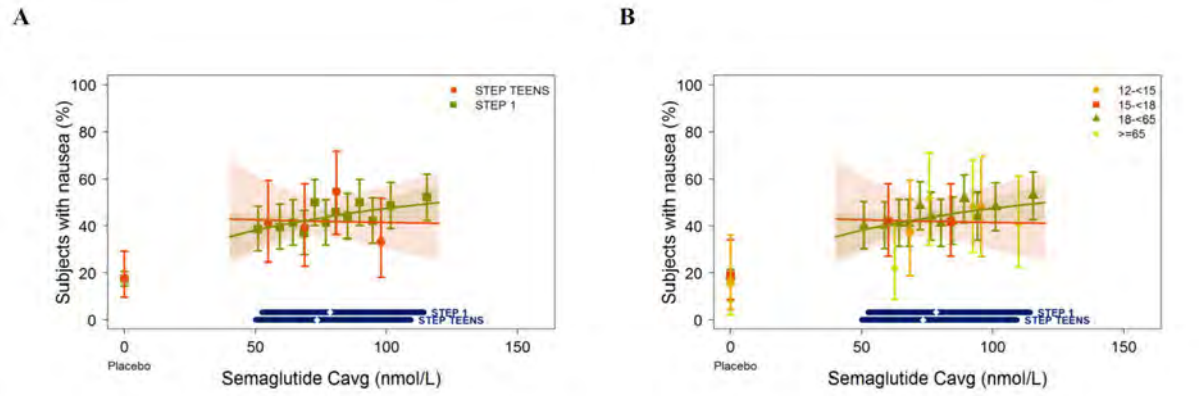
A virtual trial population with a mean body weight of 72.5 kg and range 47.2-114.1 kg (N=110). The 95% CI for the model simulated median (grey) and 5th /95th (blue) percentiles are shown by the coloured ribbons from 500 trial simulations. Observed semaglutide concentrations from trials NN9535-3687 and NN9536-4649.

Figure 19.1.3.1.8 Percent change in BMI from baseline versus semaglutide exposure by trial (A) and by age group (B) (copied from Figure 6-7, Study NN9536-4451 Modelling Report)



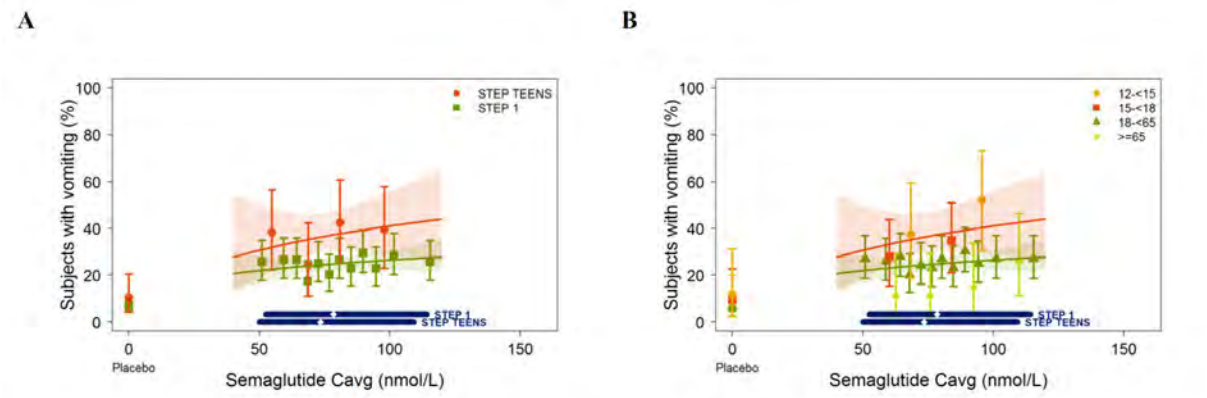
Data points with error bars are mean BMI changes with 95% CI obtained after 68 weeks of treatment versus exposure expressed as quantiles of Cavg, where STEP 1 is divided into 12 and STEP TEENS into 4 quantiles (plus placebo at Cavg of 0 nmol/L). Lines through data are covariate-adjusted model-derived exposure-response relations with shaded areas being 95% point-wise CIs. Horizontal lines with diamonds represent the median and 90% exposure range. Missing data at week 68 were predicted using trial specific mixed model for repeated measures. Data from trials STEP 1 and STEP TEENS from the full analysis set.

Figure 19.1.3.1.9 Proportion of subjects reporting nausea of any severity versus semaglutide exposure by trial (A) and by age group (B) (copied from Figure 6-8, Study NN9536-4451 Modelling Report)



Data are proportions with 95% CI versus exposure expressed as quantiles of model-derived C_{avg} values, where STEP 1 is divided into 12 and STEP TEENS into 4 quantiles plus placebo (at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-derived estimates for each trial population with shaded areas being 95% point-wise CIs. Horizontal lines with diamonds represent the median and 90% exposure range. Data from trials STEP 1 and STEP TEENS from the on-treatment safety analysis set.

Figure 19.1.3.1.10 Proportion of subjects reporting vomiting of any severity versus semaglutide exposure by trial (A) and by age group (B) (copied from Figure 6-9, Study NN9536-4451 Modelling Report)



Data are proportions with 95% CI versus exposure expressed as quantiles of model-derived C_{avg} values, where STEP 1 is divided into 12 and STEP TEENS into 4 quantiles plus placebo (at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-derived estimates for each trial population with shaded areas being 95% point-wise CIs. Horizontal lines with diamonds represent the median and 90% exposure range. Data from trials STEP 1 and STEP TEENS from the on-treatment safety analysis set.

20. Attachment: additional evaluation material

NA.

21. Information about the evaluator

Removed by the TGA.

Appendix: study summary and commentary

NA.

Therapeutic Goods Administration

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Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au

NONCLINICAL EVALUATION REPORT

Product:	Semaglutide (WEGOVY)		
Dose form & strength:	Solution for Injection; 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.27 mg/mL, 3.2 mg/mL	**Tox File No.:**	E18-318244
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd	**TRIM Reference:**	D23-5203115
Submission No.:	PM-2022-04980-1-5	**Evaluator:**	s22
Submission Type:	Extension of indication	**Date:**	11 August 2023

This submission proposes to extend the indication for the use of WEGOVY (semaglutide) as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity or
- overweight and with at least one weight-related comorbidity.

WEGOVY is currently approved for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.

The proposed dosing regimen for the new indication is identical to that approved for use in the adult patient group.

In population PK studies comparing adolescents and adults, exposure was inversely correlated with bodyweight and age caused on clinically relevant change in semaglutide exposure (Module 2.5 Clinical Overview). Exposure levels in adolescent subjects with obesity were comparable to exposure levels in adult subjects with obesity. From the model (Population PK study [STEP TEENS], page 29), in the adolescent population aged 12 to <18 years with bodyweight of 62–212 kg the geometric mean for C_{avg} was 74 nM and $AUC_{0\text{-}168h}$ was 12.4 µM·h. This is similar to the C_{avg} and $AUC_{0\text{–}168h}$ previously used to support the indication in adult patients (59.4 nM and 14.7 µM.h, respectively; PM-2021-00612-1-5 [D21-2820164]).

No new module 4 data were submitted in support of the extension of indication.

In previously evaluated juvenile animal studies (evaluated in submission PM-2018-02748-1-5 [D18-11164343]; 2 studies; identical doses), when rats were treated directly with semaglutide, delayed sexual maturation likely secondary to suppressed body weight gain was observed in both sexes. No adverse effects on development were observed at doses up to 600 µg/kg/day SC. At this

dose, semaglutide exposures achieved were moderate (ER_{AUC} 9) compared to the clinical AUC at the maximum clinical dose of 2.4 mg/week SC (see Table I below). These studies did not raise any safety concerns for the proposed patient group.

Table I. Relative exposure in juvenile animal toxicity studies

Species	Study duration [Study no.]	Dose (µg/kg/day SC)	AUC_{0-168h}^ (µM·h)	Exposure ratio#
Rat (SD)	Juvenile study 11 weeks Study 214479*	20	3.2	0.3
		130	25.3	2.0
		600	105	9
Human (Adolescence patients)	steady state [STEP TEENS]	[2.4 mg]	12.4	–

= animal:human plasma $AUC_{0-168\ h}$; ^ = data are for the sexes combined at the last sampling occasion; AUC_{0-24h} data from rodents were ×7. *Study 214479 was previously evaluated in submission PM-2018-02748-1-5

No nonclinical PI changes are proposed, and none are necessary.

Overall, there are no nonclinical objections to registration of WEGOVY for the proposed indication in adolescence.

Australian Government
Department of Health
Therapeutic Goods Administration

Nonclinical Evaluation Report

Semaglutide [WEGOVY®]

Submission No: PM-2021-00612-1-5
Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

27 October 2021

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type:	Extension of indications New indication, new strengths & new dosage delivery system
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd
Generic name:	**Semaglutide**
Trade name:	**WEGOVY®**
Dose form and strength:	Solution for Injection; 0.5 mg/mL; 1.0 mg/mL; 2.0 mg/mL; 2.27 mg/mL; 3.2 mg/mL
Drug class:	GLP-1 receptor agonist
Submission No:	PM-2021-00612-1-5
Tox file No:	E18-318244
TRIM reference:	D21-2820164
Date authorised:	27 October 2021

Note: This evaluation report has been peer-reviewed and is authorised for release to the sponsor.

TABLE OF CONTENTS

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

- Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indications for semaglutide to be used as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of ≥30 kg/m^2 (obesity), or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. For the new indication, the Sponsor is proposing a new trade name (WEGOVY®), new strengths (up to 3.2 mg/mL), an increase in the maximum dose (from 1 mg/week, SC to 2.4 mg/week, SC) and a new dosage delivery system.
- The submitted Module 4 dossier was generally acceptable. No major deficiencies were identified.
- Two primary pharmacology studies were submitted. Semaglutide is a GLP-1 receptor agonist, which is a physiological regulator of appetite and caloric intake. The GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies showed that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake, and therefore support the new indication.
- There are no new safety concerns associated with the higher systemic exposures expected with the higher strength formulation of semaglutide (as WEGOVY®), and overall no nonclinical objections to registration.
- The draft Product Information should be amended as directed on pages 10–14.

ASSESSMENT

Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indication of recombinant human glucagon-like peptide-1 (GLP-1) analogue semaglutide (under trade name WEGOVY®) to be used for chronic weight management. Semaglutide is currently approved (as OZEMPIC®) as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and for the prevention of cardiovascular events in adults with type 2 diabetes mellitus and high cardiovascular risk. The new submission also concerns increased strength of semaglutide (up to 3.2 mg/mL solution for injection), an increase in the maximum weekly dose (from 1 mg to 2.4 mg) and use of a new dosage delivery system (single use prefilled pen with pre-assembled needle).

The proposed dosing regimen for WEGOVY® involves a fixed dose escalation regimen to reduce the likelihood of gastrointestinal symptoms, with an initiation dose of 0.25 mg once weekly from week 1–4. Thereafter, the dose is increased to 0.5 mg (week 5–8), 1 mg (week 9–12) and 1.7 mg (week 13–16) once weekly. After at least 16 weeks, the dose may be increased to 2.4 mg once weekly for additional glycaemic control. Treatment is expected to be ongoing.

The Sponsor indicated that nonclinical studies conducted to support the approval of OZEMPIC® for the Type 2 Diabetes (T2D) indication are also sufficient to support the new indication of weight management. In addition to these, the Sponsor also submitted two new pharmacology studies in mice that further explored the effects of semaglutide in the brain in relation to its effects on body weight.

Pharmacology

Primary pharmacology

GLP-1 is an intestinally-derived peptide hormone that is secreted after ingestion of glucose or a mixed meal. GLP-1 receptor agonists, such as semaglutide, are expected to lower post-prandial glucose levels *via* retardation of gastric emptying, a stimulation of insulin biosynthesis and secretion by pancreatic β cells and inhibition of glucagon secretion from pancreatic α cells[1]. Published studies indicate GLP-1 receptor agonists may have beneficial effects on cardiovascular outcomes[2] and have an appetite suppressant action[3].

Semaglutide has been previously shown to reduce bodyweight gain and food consumption in mice, normal and obese rats, and minipigs (see NER for OZEMPIC® D18-11164343).The two new pharmacology studies that were provided in this submission examined the *ex vivo* effects of semaglutide on neuronal activity and distribution in mouse brain.

In mice dosed with fluorescently-labelled semaglutide (0.5 mg/kg/day, SC for 5 weeks), semaglutide was detected in brain regions expressing the GLP-1 receptor, including several of the circumventricular organs (CVO) devoid of a blood brain barrier (area postrema (AP), the median eminence (ME) and subfornical organ (SFO)). Semaglutide was also measured in brain regions protected by the blood brain barrier in the brain stem (AP, the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus nerve (DMX)), the hypothalamus (arcuate hypothalamic nucleus (ARH), ME, dorsomedial hypothalamic nucleus (DMH), and the paraventricular nucleus

[1] Meier, J.J. (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **8:** 728–742.

[2] Marso S.P., Holst A.G. and Vilsbøll T. (2017) Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N. Engl. J. Med.* **376:** 891–892.

[3] Friedrichsen M., Breitschaft A., Tadayon S., Wizert A. and Skovgaard D. (2021) The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes. Obes. Metab.* **23:** 754–762.

(PVH)), and in the septum (triangular nucleus of septum (TRS), the caudal part of the lateral septal nucleus (LS), and the septofimbrial nucleus (SF)). These areas have been shown to express GLP-1 receptors in mouse and Rhesus monkey brains[4] [5], and stimulation of receptors in the LS has been associated with modification of dopamine-related reward pathways[6], suggesting that semaglutide has access to select GLP-1R populations in brain regions associated with homeostatic and reward related regulation of food intake.

In the second study peripheral administration of semaglutide to diet-induced obese mice (0.1 mg/kg, SC) activated neurons (measured by monitoring cFos expression) in several sites that express GLP-1 receptors (accessed from the periphery such as in the CVO and the brain stem), while acute administration with semaglutide activated neurons in the parabrachial nucleus (PB) and the midline group of the dorsal thalamus (MTN). PB and MTN are regions important for homeostatic and hedonic aspects of food intake and, which were not directly accessible to semaglutide. Semaglutide also activated neurons in brain regions that are part of the circuits to and from the PB and MTN (the bed nuclei of the stria terminalis (BST) and the central amygdala (CeA)).

Overall, the primary pharmacology studies showed that semaglutide can access and target areas of the brain associated with food intake and reward-processes, and therefore support the proposed indication for chronic weight management, including weight loss and weight maintenance, in adults.

Toxicity

Repeat dose toxicity

Previously assessed repeat-dose toxicity studies of up to 13, 26 and 52 weeks duration were conducted in mice, rats and monkeys, respectively, using the clinical route (subcutaneous injection). Semaglutide exposures achieved in these studies were moderate to high multiples of the clinical AUC at the maximum clinical dose of 2.4 mg/week SC (7.4–55 times the clinical AUC; see Table I).

Semaglutide was generally well-tolerated in all repeat-dose studies. Transient effects on activity, body weight and food consumption (all species) were observed, which are relevant to the pharmacological actions of semaglutide.

Other notable findings included:

- ↑ incidence of proliferative lesions in thyroids of mice and rats seen at low relative exposures (**1.2×** and **0.14×** the clinical AUC at 2.4 mg/week SC, respectively), which were likely rodent specific, as GLP-1 receptor expression is ↑ in thyroids of rodents *cf*. humans, and mechanism for tumour development is present in rodent but not human thyroid.

- Minimal to moderate dilatation and/or hypertrophy of Brunner's glands in the duodenum were also seen in rodents at low systemic exposures (**1.2×** and **0.14×** the clinical AUC at 2.4 mg/week SC, respectively), but not in monkeys treated for 52 weeks (up to **7.4×** the clinical AUC), and therefore the toxicological significance is uncertain but likely to be minimal.

[4] Jensen C.B., Pyke C., Rasch M.G., Dahl A.B., Knudsen L.B. and Secher A. (2018) Characterization of the Glucagonlike Peptide-1 Receptor in Male Mouse Brain Using a Novel Antibody and In Situ Hybridization. *Endocrinology* **159:** 665–675.

[5] Heppner K.M., Kirigiti M., Secher A., Paulsen S.J., Buckingham R., Pyke C. *et al.* (2015) Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (Macaca mulatta) brain. *Endocrinology* **156:** 255–267.

[6] Harasta A.E., Power J.M., von Jonquieres G., Karl T., Drucker D.J., Housley G.D. *et al.* (2015) Septal Glucagon-Like Peptide 1 Receptor Expression Determines Suppression of Cocaine-Induced Behavior. *Neuropsychopharmacology* **40:** 1969–1978.

- Uterine luminal dilatation seen in female rats at doses that achieved systemic exposures **8.6×** the clinical AUC at 2.4 mg/week SC was likely a secondary effect of lower body weight gain related to altered oestrus cycling.

- ECG abnormalities (bigeminal rhythm. sinus tachycardia, chronic left bundle block) observed in one female monkey (360 µg/kg SC, Q2W; **7.4×** the clinical AUC) from the 52 week study, were likely an isolated finding as there were no correlative cardiac lesions post-mortem.

Although exposure margins associated with these toxicity findings are lower at the higher clinical dose, none of these raise new concerns of toxicities.

Table I. Relative exposure in previously evaluated repeat-dose toxicity and carcinogenicity studies[7]

Species	Study duration [Study no.]	Dose (µg/kg SC)	AUC_{0-168h}^ (µM·h)	Exposure ratio#
Mouse (CD-1)	13 weeks [Study 200663]	1000	79.8	5.4
		3000	268	18
		10000	815	55
	104 weeks Carcinogenicity [Study 207362]	100	17.4 (♀ only)	1.2
		300	21.6	1.5
		1000	80.0	5.4
		3000	277 (♂ only)	19
Rat (SD)	13 weeks [Study 206662]	4	0.511	0.04
		82	8.44	0.6
		784	65.8	4.5
	26 weeks [Study 207377]	30	6.31	0.4
		130	27.0	1.8
		600	127	8.6
	104 weeks Carcinogenicity [Study 207363][a]	10	2.05	0.14
		25	4.49	0.3
		100	26.7	1.8
Monkey (Cynomolgus)	13 weeks Study 206450	4	1.61	0.11
		86	25.3	1.7
		977/467§	130	8.8
	12 months [Study 207288]	10	2.92	0.2
		60	18.5	1.25
		360	109	7.4
Human (Overweight to obese subjects)	steady state [Trial NN9535-4590]	[2.4 mg]	14.7	–

= animal:human plasma AUC_{0-168h}; Human AUC value for 2.4 mg was from Trial NN9535-4590 (2.7.2. Summary of Clinical Pharmacology Studies); ^ = data are for the sexes combined at the last sampling occasion unless otherwise indicated; AUC_{0-24h} data from rodents were ×7, AUC_{0-72h} data from monkeys were ×2; ; § = ♀ switched to lower dose wk 4; ♂, wk 5.

[7] Nonclinical Evaluation Report for semaglutide (OZEMPIC®) (D18-11164343)

Reproductive toxicity

Previously evaluated reproductive toxicity studies covered all stages of reproduction and development (fertility, early embryonic development, embryofetal development, and pre-/postnatal development). Studies were conducted by the SC route and used daily dosing in rats and rabbits and dosing every three days in monkeys. A dose escalation period was included in the rat and monkey studies. Exposures achieved in rats and rabbits were subclinical, but limited by pharmacological effects on body weight. Exposures in monkeys were subclinical to low in the pivotal embryofetal development study and in the pre-/postnatal study (see Table II).

Main treatment-related findings:

- Fertility:
    - no effect on fertility in male rats (NOAEL 828 µg/kg/day SC in the pilot study; **4.5×** the clinical AUC at 2.4 mg/week SC);
    - abnormal oestrus cycling & ↓ corpora lutea seen in females (NOEL 10 µg/kg/day; **0.03×** the clinical AUC), was likely secondary to effects on body weight and an effect seen with another GLP-1 agonist**Error! Bookmark not defined.**;
- Embryofetal development:
    - Embryofetal lethality & toxicity, e.g. embryonic death, ↓ live fetuses/infants, ↑ developmental abnormalities (NOAELs: rats 10 µg/kg/day SC or **0.03×** the clinical AUC; rabbits 1 µg/kg/day SC or **0.01×** the clinical AUC; monkeys 15 µg/kg SC every 3 days or **0.2×** the clinical AUC)
- Postnatal development:
    - ↓ infant body weights in monkeys (at maternal exposures of 150 µg/kg SC every 3 days or 2× the clinical AUC), which normalised by day 91
    - Delayed sexual maturation in rats of both sexes seen at all dose levels which was likely secondary to lower body weight gain (at 20–600 µg/kg/day, SC or **0.22–7×** the clinical AUC). No other adverse effects on development were observed.

Table II. Relative exposure in previously evaluated reproductive toxicity studies[7]

Species	Study [Study no.]	Dose (µg/kg SC)	AUC_{0-168h} (µM·h)	Exposure ratio#
Rat (SD)	Fertility/ embryofetal development [Study 207361]	10	0.5	0.03
		30	1.5	0.1
		90	4.1	0.3
Rabbit (NZW)	Embryofetal development [Study 207360]	1	0.14	0.01
		2.5	1.5	0.1
		7.5	10.7	0.7
Monkey (Cynomolgus)	Embryofetal development [Study 208486]	15	4.0	0.3
		75	20.8	1.4
		15	60.0	4.1
	Embryofetal+pre/post-natal development [Study 210061]	15§	2.6	0.2
		75§	13.4	0.9
		150§	28.8	2
Human (Overweight to obese subjects)	steady state [Trial NN9535-4590]	[2.4 mg]	14.7	–

= animal:human plasma AUC_{0-168h}; Human AUC value for 2.4 mg was from Trial NN9535-4590 (2.7.2. Summary of Clinical Pharmacology Studies); ^ = data are for the sexes combined at the last sampling occasion unless otherwise indicated; AUC_{0-24h} data from rodents were ×7, AUC_{0-72h} data from monkeys were ×2. § Mothers were not dosed during lactation.

Pregnancy classification

The sponsor is maintaining a **Pregnancy Category D**, which is considered appropriate, given the embryofetal lethality and toxicity (including malformations) previously observed at subclinical to low exposure margins in three species.

Local tolerance

In the original submission, injection site reactions to semaglutide in repeat dose toxicity studies were generally well-tolerated and were minimal to slight in severity. Although no new studies were submitted to support the higher strength semaglutide formulation *cf*. Ozempic® (i.e. 2.0–3.2 mg/mL *cf*. 1.34 mg/mL, respectively), the Sponsor referred to previously evaluated local tolerance studies conducted in rabbits and pigs where there were no notable local effects at the site of semaglutide administration. In rabbits, intramuscular, intraarterial and intravenous injections of semaglutide of up to 1.35 mg/mL were well tolerated with mild changes that were comparable to vehicle. Similarly subcutaneous injections of semaglutide at 10 mg/mL were well-tolerated in pigs, with injection site reactions comparable to saline vehicle-treated areas. Although the formulation that was used varied from the one proposed for WEGOVY®, the removal of propylene glycol and phenol from the WEGOVY® formulation is unlikely to negatively affect its tolerability. Injection site reactions have been observed with clinical use of semaglutide.

PRODUCT INFORMATION

The following comments refer to the draft Product Information document (Wegovy-pi-v0.3-annotated) accompanying the sponsor's letter of application dated 24 September 2021. Where changes are suggested, text proposed to be inserted is underlined and text to be deleted is shown struck-through. The Sponsor has proposed a separate Product Information document for WEGOVY® based on the existing OZEMPIC® Product Information document.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The text should be revised to more closely match that used in the existing PI for OZEMPIC®:

"*In vitro* studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

~~As with other GLP-1 receptor agonists, semaglutide may delay~~ The delay of gastric emptying with semaglutide may ~~and could potentially~~ influence the absorption of concomitantly administered oral medicinal products, therefore semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption."

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The exposure margins should be included to more closely match the text used in the existing PI for OZEMPIC®:

"The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats at daily SC doses of 828 µg/kg, resulting in exposures approximately 4.5 times the clinical AUC. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (≥30 µg/kg/day SC, resulting in subclinical exposures)."

Use in pregnancy

The sponsor proposes Pregnancy Category D and the following statement (the text second paragraph onwards appears erroneously under the "genotoxicity" heading:

"*Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2 Pharmacokinetic properties)*."

(from section 5.3)

"In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight, and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity

involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to lack of GLP-1 receptor expression in the yolk sac of non-human primates, this mechanism is considered unlikely to be of relevance to humans.

In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery but recovered during the lactation period."

As outlined in the assessment, the proposed Pregnancy Category D is considered appropriate for this product based on the embryofetal lethality and toxicity seen in three species, rats, rabbits and monkeys. As the submitted embryofetal development studies and mechanistic studies did not confirm a species-specific effect for these adverse embryofetal development effects, the role of GLP-1 receptor expression on the yolk sac to the adverse effects should be phrased appropriately. Findings from the rabbit embryofetal development studies should be included. The changes in the text are recommended to more closely match the text used in the existing PI for OZEMPIC®:

"~~Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). There are limited data from the use of semaglutide in pregnant women. Therefore, s~~Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2 Pharmacokinetic properties).

Studies in animals have shown reproductive toxicity ~~(see section 5.3 Preclinical safety data)~~ when semaglutide was administered during organogenesis. In pregnant rats, embryofetal toxicity (lethality, impaired growth and an increased incidence of fetal abnormalities) was observed at subclinical plasma exposures. Mechanistic studies suggest a direct GLP-1 receptor mediated role of semaglutide on some of the effects in rats (species specific). In pregnant rabbits, pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures. In pregnant cynomolgus monkeys, pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) and with an increase in early pregnancy losses at ≥0.075 mg/kg twice weekly (>1.4- fold clinical exposure at 2.4 mg/week). Exposures at the NOAEL in all species were subclinical and a direct effect of semaglutide on the fetus cannot be excluded."

Use in lactation

The proposed text is acceptable.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The text below is generally acceptable and supported by submitted or published data. Minor changes are recommended to specify pharmacological actions that are relevant to the indication (i.e. glucose and appetite regulation).Data referring to clinical studies require comments from the Clinical Evaluator.

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

GLP-1 is a physiological regulator and has multiple actions in glucose and ~~of~~ appetite regulation. ~~and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.~~ The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly s.c. administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fulness and control of eating, and reduces feelings of hunger, and frequency and intensity of cravings.

Animal studies show that semaglutide works in the brain through the GLP-1 receptor. Semaglutide have direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem. Semaglutide affects the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala. Semaglutide has shown an effect to change food intake in animals away from more rewarding high fat, sweet items.

Semaglutide orchestrates the homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice. In addition, in clinical studies semaglutide have shown to reduce blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

~~Furthermore, animal studies have shown that semaglutide attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular system.~~"

5.2 PHARMACOKINETIC PROPERTIES

Distribution

The following statement is supported by submitted nonclinical data. The remaining statement requires clinical comment.

"Semaglutide was extensively bound to plasma albumin (>99%)."

Metabolism

The following statement is supported by submitted nonclinical data.

"Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain."

Excretion

The following statement is supported by submitted nonclinical data.

"The primary excretion routes of semaglutide related material were via the urine and faeces."

5.3 PRECLINICAL SAFETY DATA

The following text should be deleted because it is not completely correct:

"~~Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.~~"

Genotoxicity

The sponsor has proposed the following text:

"In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight, and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to lack of GLP-1 receptor expression in the yolk sac of non-human primates, this mechanism is considered unlikely to be of relevance to humans.

In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery but recovered during the lactation period."

None of this information relates to genotoxicity and should be deleted with the relevant information placed in the "**Effects on fertility**", "**Use in pregnancy**" and "**Use in lactation**" sections.

The following text is recommended as an alternative:

"Semaglutide was not mutagenic in the bacterial reverse mutation assay, and was not clastogenic *in vitro* (cytogenetic assay in human lymphocytes), or *in vivo* (rat bone marrow micronucleus test)."

Carcinogenicity

The text proposed by the sponsor is generally acceptable. The exposure margins should be included. Thus, the following changes are recommended:

"Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures (at ≥ 1.2× the clinical AUC in mice [based on the plasma AUC at the maximum recommended human dose of 2.4 mg/week and subclinical exposures in rats; a no effect level was not established in either species). No other treatment-related tumours were observed. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded."

Juvenile toxicity

The proposed text is acceptable.

MAIN BODY OF REPORT

1. INTRODUCTION

Novo Nordisk Pharmaceuticals Pty Ltd has applied to extend the indication of recombinant human glucagon-like peptide-1 (GLP-1) analogue semaglutide (as WEGOVY®) to be used for chronic weight management. This submission relates to change in strength (up to 3.2 mg/mL), an increase in the maximum weekly dose (from 1 mg to 2.4 mg) and a new dosage delivery system (solution for injection in pre-filled pens).

1.1. EXISTING AND PROPOSED CLINICAL USE

Semaglutide (registered as OZEMPIC®) is currently approved to be used as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and for the prevention of cardiovascular events in adults with type 2 diabetes mellitus and high cardiovascular risk, as an adjunct to standard treatment of cardiovascular risk factors. Patients are required to follow a fixed dose escalation regimen, with an initiation dose of 0.25 mg once weekly. After 4 weeks, the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose may be increased to 1.0 mg once weekly for additional glycaemic control. The maximum recommended dose is 1.0 mg once weekly. OZEMPIC® is provided in a pre-filled multidose disposable pen, which contains semaglutide in a 1.5 mL or 3 mL cartridge.

WEGOVY® is proposed to be used as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of ≥30 kg/m^2 (obesity), or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. The proposed dosing regimen involves a fixed dose escalation regimen to reduce the likelihood of gastrointestinal symptoms, with an initiation dose of 0.25 mg once weekly from week 1–4. Thereafter, the dose should be increased to 0.5 mg (week 5–8), 1 mg (week 9–12) and 1.7 mg (week 13–16) once weekly. After at least 16 weeks, the dose may be increased to 2.4 mg once weekly for additional glycaemic control. Treatment is expected to be ongoing. The proposed presentation is a solution for injection in pre-filled pen with pre-assembled needle.

1.2. CHEMISTRY AND FORMULATION

The formulation of WEGOVY® solutions for injection is shown in **Error! Reference source not found.**. A comparison with the currently registered OZEMPIC® solution is shown. In addition the amounts, differences in the composition of the new formulation *cf.* the old formulation includes the use of sodium chloride as a tonicity agent instead of propylene glycol, and the removal of phenol (preservative).

Table 1.1. Product formulation

Ingredient	Function	Quantity (mg) per mL		
		WEGOVY®		OZEMPIC®
Semaglutide	Active ingredient	WEGOVY® 0.25 mg [a]	0.5	1.34
		WEGOVY® 0.5 mg [a]	1.0	
		WEGOVY® 1.0 mg [a]	2.0	
		WEGOVY® 1.7 mg [b]	2.27	
		WEGOVY® 2.4 mg [b]	3.2	
Disodium phosphate, dehydrate	Buffer	1.42		1.42
Propylene glycol	Tonicity agent	—		14
Phenol	Preservative	—		5.5
Sodium chloride	Tonicity agent	8.25		—
Hydrochloric acid	pH adjustment	q.s. [c]		
Sodium hydroxide	pH adjustment	q.s. [c]		
Water for injection	Solvent	To make 1.0 mL		

[a] Semaglutide 0.5 mg/ml, 1.0 mg/ml and 2.0 mg/ml in single dose pen-injector for semaglutide supplied as 0.5 mL volume;

[b] Semaglutide 2.27 mg/ml and 3.2 mg/ml in single dose pen-injector for semaglutide supplied as 0.75 mL volume;

[c] To reach pH 7.4

1.3. INTERNATIONAL REGULATORY STATUS

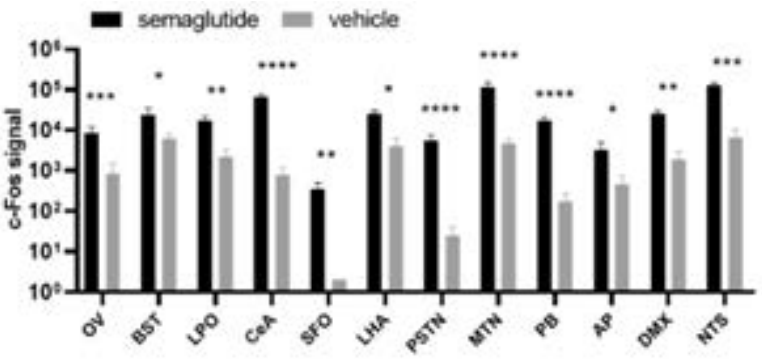
A similar application has been made in the USA (04 December 2020), the EU (4 January 2021), Canada (8 December 2020) and in the UK (5 January 2021). Semaglutide under the tradename WEGOVY® was approved in the USA on 4 June 2020, for an indication comparable to the proposed indication in the current application.

1.4. SCOPE OF NONCLINICAL DATA

Nonclinical studies conducted for semaglutide to support the Type 2 Diabetes indication also support the indication for weight management. Two new pharmacology studies in mice, investigating the effects of semaglutide in the brain were submitted and are evaluated in this report for WEGOVY® to further support the understanding of mode of action n in weight management.

2. PRIMARY PHARMACOLOGY

The following additional studies were submitted:

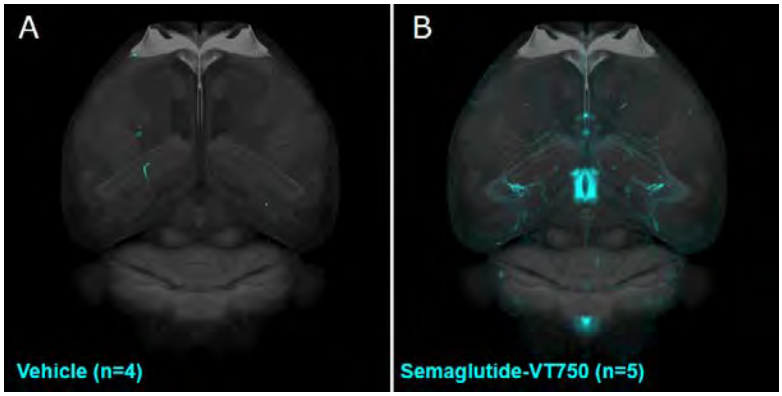
Study details	Main findings
Study 321410 **Mouse** (C57BL/6J, Diet induced obese ♂) *n*= 8/group Semaglutide 0, 0.1 mg/kg SC for 4 hours Examinations: Brain – Immunohistochemistry for cFos (proto-oncogene expressed within some neurons following depolarization) microscopy (LSFM). Follow up by co-staining for cFos (selected brain regions) and calcitonin gene-related peptide (CGRP)	• c-Fos expression was used as a marker for neuronal activity. • Activation of cFos was seen in regions of mouse brain following semaglutide administration. • cFos activity was observed in several brain areas: brain stem in the area postrema (AP) and the nucleus of the solitary tract (NTS). • Increased cFos activity was also observed in the central amygdala nucleus (CeA), the parabrachial nucleus (PB) and the midline group of the dorsal thalamus (MTN). Effects of semaglutide on cFos induction in different brain areas is shown below.  *p<0.05, **p<0.01, ***p<0.001, ****p<0.00001 *cf.* vehicle OV: Vascular organ of the lamina terminalis, BST: Bed nuclei of the stria terminalis, LPO: Lateral preoptic area, CeA: Central amygdala nucleus, SFO: Subfornical organ, LHA: Lateral hypothalamic area, PSTN: Parasubthalamic nucleus, MTN: Midline group of the dorsal thalamus, PB: Parabrachial nucleus, AP: Area postrema, DMX: Dorsal motor nucleus of the vagus nerve, NTS: Nucleus of the solitary tract • Subset of cFos positive cells were identified as CGRP positive cells within the Parabrachial nucleus (PB).

Study 321411
Mouse (C57BL/6J, ♂)
n= 5 (test), 4 (vehicle)
0, 0.5 mg/kg total (Semaglutide VT750 – fluorescently labelled) SC daily for 5 weeks

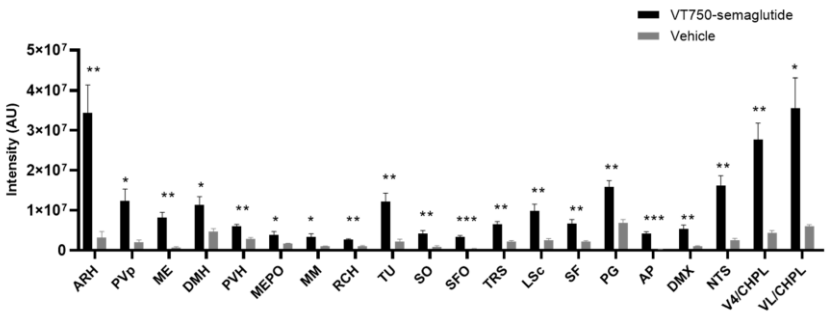
Group	Day	Dose (mg/kg)
Vehicle	1-5	–
Semaglutide VT750	1	0.04
	2	0.07
	3-5	0.15

Examinations:
Whole brain by scanning with a laser sheet to determine the distribution of the fluorescently labelled peptide

Distribution of semaglutide-VT750 in the mouse brain was observed following peripheral administration (SC) of semaglutide VT750 as shown below.



- Strong fluorescent signal was observed in the meninges and the choroid plexus (CHPL)
- Strong signal was observed in the brain regions devoid of a blood brain barrier: circumventricular organs (CVO's –), including the area postrema (AP) and the median eminence (ME)
- Signal was observed in brain regions protected by the blood-brain barrier: hypothalamus including the arcuate hypothalamic nucleus (ARH) and the brainstem including the nucleus of the solitary tract (NTS)
- Semaglutide-VT750 was observed in the septum (caudal part of the lateral septal nucleus (LSc)
- Steady-state distribution of semaglutide-VT750 in mouse brain is shown below with average intensity of total fluorescence signal in all brain regions that showed 2-fold enrichment and were significant



*p<0.5, **p<0.01, ***p<0.001 *cf.* vehicle

ARH – Arcuate hypothalamic nucleus, PVp – Arcuate nucleus, posterior part, ME – Median eminence, DMH – Dorsomedial hypothalamic nucleus, PVH – Paraventricular nucleus of the hypothalamus, MEPO – Median preoptic nucleus, MM – Medial mammillary nucleus, RCH – Retrochiasmatic area, TU – Tuberal nucleus, SO – Supraoptic nucleus, SFO – Subfornical organ, TRS – Triangular nucleus of septum, LSc – Caudal part of the lateral septal nucleus, SF – Septofimbrial nucleus, PG – Pontine gray, AP – Area postrema, DMX – Dorsal motor nucleus of the vagus nerve, NTS – Nucleus of the solitary tract, V4/CHPL – Choroid plexus, VL/CHPL – Choroid plexus.

3. PHARMACOKINETICS

3.1.1. Plasma kinetics in human subjects

The steady-state exposure of semaglutide 2.4 mg for weight management was evaluated by standard PK endpoints in Bioequivalence study (Trial 4590) in overweight or obese individuals. Steady-state PK endpoints for semaglutide 2.4 mg are shown in Table 3-1 below.

Table 3-1. Pharmacokinetic parameters in humans

Study details	Dose (mg)	C_{max} (nM)	C_{avg} (nM)**	Vss/F (L)	t_{max} (h)	$AUC_{0-168\,h}$ (nM·h)*	$t_{½}$ (h)
Bioequivalence study – Trial 4590 ****NN9536 Phase 3a Meta Analysis Modelling report** Overweight or obese individuals NN9536-4373 and overweight or obese individuals with T2D NN9536-4374	2.4	119	59.4	9.8	24	14698	155 (~1 week)

* AUC value is for a dosing interval (168 h) at steady-state.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

NONCLINICAL EVALUATION REPORT

Product:	Semaglutide (WEGOVY)		
Dose form & strength:	Solution for Injection; 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 2.27 mg/mL, 3.2 mg/mL	**Tox File No.:**	E18-318244
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd	**TRIM Reference:**	D23-5203115
Submission No.:	PM-2022-04980-1-5		
Submission Type:	Extension of indication	**Date:**	11 August 2023

This submission proposes to extend the indication for the use of WEGOVY (semaglutide) as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity or
- overweight and with at least one weight-related comorbidity.

WEGOVY is currently approved for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.

The proposed dosing regimen for the new indication is identical to that approved for use in the adult patient group.

In population PK studies comparing adolescents and adults, exposure was inversely correlated with bodyweight and age caused on clinically relevant change in semaglutide exposure (Module 2.5 Clinical Overview). Exposure levels in adolescent subjects with obesity were comparable to exposure levels in adult subjects with obesity. From the model (Population PK study [STEP TEENS], page 29), in the adolescent population aged 12 to <18 years with bodyweight of 62–212 kg the geometric mean for C_{avg} was 74 nM and $AUC_{0\text{-}168h}$ was 12.4 µM·h. This is similar to the C_{avg} and $AUC_{0\text{–}168h}$ previously used to support the indication in adult patients (59.4 nM and 14.7 µM.h, respectively; PM-2021-00612-1-5 [ ).

No new module 4 data were submitted in support of the extension of indication.

In previously evaluated juvenile animal studies (evaluated in submission PM-2018-02748-1-5 [ ]; 2 studies; identical doses), when rats were treated directly with semaglutide, delayed sexual maturation likely secondary to suppressed body weight gain was observed in both sexes. No adverse effects on development were observed at doses up to 600 µg/kg/day SC. At this dose,

semaglutide exposures achieved were moderate (ER_{AUC} 9) compared to the clinical AUC at the maximum clinical dose of 2.4 mg/week SC (see Table I below). These studies did not raise any safety concerns for the proposed patient group.

Table I. Relative exposure in juvenile animal toxicity studies

Species	Study duration [Study no.]	Dose (µg/kg/day SC)	AUC_{0-168h}^ (µM·h)	Exposure ratio#
Rat (SD)	Juvenile study 11 weeks Study 214479*	20	3.2	0.3
		130	25.3	2.0
		600	105	9
Human (Adolescence patients)	steady state [STEP TEENS]	[2.4 mg]	12.4	–

= animal:human plasma $AUC_{0-168\,h}$; ^ = data are for the sexes combined at the last sampling occasion; AUC_{0-24h} data from rodents were ×7. *Study 214479 was previously evaluated in submission PM-2018-02748-1-5

No nonclinical PI changes are proposed, and none are necessary.

Overall, there are no nonclinical objections to registration of WEGOVY for the proposed indication in adolescence.