30 March 2023
EMA/CHMP/141429/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Wegovy

International non-proprietary name: Semaglutide

Procedure No. EMEA/H/C/005422/II/0009

Note

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

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List of abbreviations

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BMI	body mass index
C_{avg}	average steady-state concentrations
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent clearance
Cmax	maximum observed drug concentration
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
EMA	European Medicines Agency
ETD	estimated treatment difference
ETR	estimated treatment ratio
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GOF	goodness of fit
GSPRs	general safety and performance requirements
HbA1c	haemoglobin A1c
HDL	high-density lipoprotein
IIV	inter-individual variability
IOTF	international obesity task force
KA	absorption rate constant
LDL	low-density lipoprotein
PD	pharmacodynamic(s)
PI	product information
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PT	preferred term
PYE	patient years exposure
PYO	person-years of observation
RA	receptor agonist
RMP	Risk Management Plan

SAE	serious adverse event
SBP	systolic blood pressure
s.c.	subcutaneous
SDS	standard deviation score
SmPC	summary of product characteristics
T2D	type 2 diabetes
T2DM	type 2 diabetes mellitus
V/F	apparent volume of distribution
VLDL	very low-density lipoprotein
VPC	visual predictive check
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 30 August 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescents for weight management based on the final results from study NN9536-4451; this trial was conducted to assess the efficacy and safety of semaglutide in the paediatric population.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.2.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0461/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0461/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Thalia Marie Estrup Blicher

Timetable	Actual dates
Submission date:	30 August 2022
Start of procedure:	17 September 2022
CHMP Rapporteur Assessment Report circulated on:	11 November 2022
PRAC Rapporteur Assessment Report circulated on:	17 November 2022
CHMP Co-Rapporteur Assessment circulated on:	24 November 2022
Updated PRAC Rapporteur Assessment Report circulated on:	24 November 2022
PRAC Outcome:	1 December 2022
CHMP members comments:	5 December 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report circulated on:	8 December 2022
1st Request for supplementary information (RSI) adopted by the CHMP on:	15 December 2022
MAH's responses submitted on:	21 December 2022
Restart of procedure:	26 December 2022
CHMP Rapporteur Assessment Report circulated on:	3 February 2023
CHMP members comments:	n/a
Updated CHMP Rapporteur Assessment Report circulated on:	n/a
2nd Request for supplementary information (RSI) adopted by the CHMP on:	23 February 2023
MAH's responses submitted on:	27 February 2023
Restart of procedure:	1 March 2023
CHMP Rapporteur Assessment Report circulated on:	15 March 2023
CHMP members comments:	20 March 2023
Updated CHMP Rapporteur Assessment Report circulated on:	24 March 2023
CHMP Opinion:	30 March 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Adolescent obesity and the need for more treatment options

The prevalence of obesity in children and adolescents has been increasing steadily during the past decades and has reached alarming proportions. It is expected that more than 250 million children and adolescents worldwide will be living with obesity by 2030.

More than 70% of children suffering from obesity before puberty will also suffer from obesity as adults. Childhood obesity increases the risk of an earlier development of obesity-related comorbidities during adulthood. These comorbidities, as in the adult population, are associated with a wide range of severe health-related and psychosocial consequences, including a higher risk of disability in adulthood and premature death.

State the claimed therapeutic indication

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 (Centers for Disease Control and Prevention (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*

Management

Current international treatment guidelines for childhood obesity suggest community/environment-based prevention, behaviour-oriented, and family-centred lifestyle modification as first-line treatment and standard of care, to help patients adopt healthier eating habits, increase physical activity and decrease sedentary time.

Bariatric surgery is primarily restricted to adolescents with unsuccessful weight loss and comorbidities after implementing lifestyle modifications and/or pharmacotherapy. There remains a treatment gap for children and adolescents who have failed lifestyle modifications but do not meet the criteria for bariatric surgery. As in adults, most children and adolescents with obesity, especially those with severe obesity, struggle to achieve and maintain weight loss.

Currently, there is an unmet medical need for safer, more effective therapeutic options for the treatment of obesity in children and adolescents.

Therefore, pharmacotherapy may serve as a valuable adjunct to lifestyle modification for children and adolescents with obesity or overweight. Pharmacotherapy has the potential to help this population to achieve and to sustain clinically relevant weight loss, as well as to improve or prevent comorbid conditions and facilitate a healthier lifestyle.

2.1.2. About the product

Semaglutide subcutaneous (s.c.) 2.4 mg once weekly (Wegovy) has been approved as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance in adults with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) and at least one weight-related comorbidity. It was initially approved in the US (June 2021) and hereafter in the UK (September 2021), Canada (November 2021), EU (January 2022), Switzerland (February 2022) and India (April 2022).

The initial marketing authorisation application was based on 4 phase 3a trials (STEP 1–4), 1 phase 2 dose-finding trial and 3 clinical pharmacology trials. These trials demonstrated that the balance between the benefits and risks of semaglutide s.c. 2.4 mg once weekly (hereafter referred to as semaglutide 2.4 mg) was favourable when the magnitude and range of benefits, the manageable and well-characterised risks, the substantial and increasing burden of obesity and the unmet medical need was taken into account.

The 4 phase 3a trials in the original application were conducted worldwide. All 4 trials were 68-week randomised, double-blind, placebo-controlled trials evaluating the efficacy, safety and tolerability of semaglutide 2.4 mg compared to placebo in adult subjects with obesity or overweight and at least one weight-related comorbidity (including type 2 diabetes [T2D] in STEP 2). A total of 4585 subjects were enrolled and randomised in these 4 trials, and all trials showed the superiority of semaglutide 2.4 mg compared to placebo.

With the increasing prevalence of adolescents living with obesity, there is a need for effective and safe pharmacotherapy for weight management in the adolescent population. To address this, Trial NN9536-4451 (hereafter referred to as STEP Teens) was conducted to evaluate the efficacy and safety of semaglutide 2.4 mg once weekly as an adjunct to calorie-reduced diet and increased physical activity in adolescents (age 12 to <18 years). This trial forms the basis of this label update.

Rationale for the proposed label update

This variation application aims at extending the current Wegovy label with results from STEP Teens demonstrating the efficacy and safety of semaglutide 2.4 mg in an adolescent population (ages 12 to <18 years) with obesity or with overweight and at least one weight-related comorbidity.

Overview of included trials

An overview of details for the trial included in this variation application is available in the table below. The trial included in this variation application followed accepted industry and regulatory requirements for developing weight management products and were conducted according to ICH Good Clinical Practice.

Table Overview of completed phase 3a trial included in the variation application

Trial	Subjects	Brief description
Trial 4451 (STEP Teens) Adolescent population (ages 12 to <18 years)	N=201	68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide 2.4 mg once weekly in adolescents with obesity (BMI corresponding to ≥95th percentile*) or with overweight (BMI corresponding to ≥85th percentile*) and at least one weight-related comorbidity.

*on gender and age-specific growth charts (CDC.gov).

- Body mass index (BMI) 85th and 95th percentiles on gender and age-specific growth charts (CDC.gov)

These adolescents with overweight or obesity represent a clinically relevant population for pharmacotherapeutic weight management as they are at significant risk for weight-related comorbidities and have increased long-term mortality.

Impact of COVID-19

Although restrictions due to COVID-19 led to some changes in trial conduct, subject safety and trial integrity were maintained in the trial. The primary impact of COVID-19 was on visit attendance; however, both treatment groups were impacted comparably. Five subjects withdrew from the study, primarily due to personal or unstated reasons. Overall, treatment and trial completion were at a high level 89.6% and 97.5%, respectively.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The development programme

The global clinical development programme for semaglutide s.c. 2.4 mg for weight management, forming the basis for the initial application, comprised of 8 completed clinical trials:

- clinical pharmacology trials (of which two bioequivalence trials)
- 1 phase 2 dose-finding trial
- 4 phase 3a therapeutic confirmatory trials (referred to as the STEP 1-4 trials)

Compliance with CHMP guidance

Compliance with CHMP guidelines is discussed in the respective paragraphs below; no issues were identified.

Paediatric Investigation Plan

A Paediatric Investigation Plan has been agreed upon with the Paediatric Committee (PDCO).

Indication targeted by the PIP: Treatment of obesity.

Subset of the paediatric population concerned by the paediatric development: from 6 years to less than 18 years of age.

The PIP involves four clinical studies:

Study 1 (NN9536-4451) is a randomised, double-blind, placebo-controlled multi-centre trial to evaluate the tolerability, safety and efficacy on weight management of semaglutide once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity, in adolescents (aged 12 to less than 18 years) with overweight or obesity. *Completed.*

Study 2 (NN9536-4512) is a randomised, double-blind, placebo-controlled trial to evaluate the tolerability, safety and efficacy on weight management of semaglutide once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in children (aged 6 to less than 12 years) with obesity. *Planned.*

Study 3 involves population PK modelling analysis to support dose selection in the adolescent population (12 to < 18 years), and to support dose selection in a subsequent trial in children (6 to < 12 years) with obesity. *Completed.*

Study 4 involves population PK modelling analysis to support dose selection in children (6 to < 12 years). *Planned.*

Date of completion of the paediatric investigation plan: June 2027.

A waiver was granted for the paediatric population from birth to less than 6 years of age.

Scientific advice

No Scientific Advice was requested for the current application.

2.1.4. General comments on compliance with GCP

GCP

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

2.2. Quality

Dose

The maintenance dose of semaglutide 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:

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

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. No dose adjustment is required for adolescents ages 12 years and above.

To cover this range of doses, the following products are approved:

- Wegovy 0.25 mg solution for injection in pre-filled pen, 0.5 ml
- Wegovy 0.5 mg solution for injection in pre-filled pen, 0.5 ml
- Wegovy 1 mg solution for injection in pre-filled pen, 0.5 ml
- Wegovy 1.7 mg solution for injection in pre-filled pen, 0.75 ml
- Wegovy 2.4 mg solution for injection in pre-filled pen, 0.75 ml
- Wegovy 0.25 mg FlexTouch solution for injection in pre-filled pen, 1.5 ml per pen (4 doses)
- Wegovy 0.5 mg FlexTouch solution for injection in pre-filled pen, 1.5 ml per pen (4 doses)
- Wegovy 1 mg FlexTouch solution for injection in pre-filled pen, 3 ml per pen (4 doses)
- Wegovy 1.7 mg FlexTouch solution for injection in pre-filled pen, 3 ml per pen (4 doses)
- Wegovy 2.4 mg FlexTouch solution for injection in pre-filled pen, 3 ml per pen (4 doses)

Methods of administration

Wegovy is administered subcutaneously once weekly at any time of the day, with or without meals.

Pre-filled pen, single-dose

The semaglutide finished products comprise the following commonly used excipients: disodium phosphate dihydrate (buffering agent), sodium chloride (tonicity agent), hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment), and water for injections (solvent).

Pre-filled pen, FlexTouch (This pen is for multi-use. It contains 4 doses.)

The semaglutide finished products comprise the following commonly used excipients: disodium phosphate dihydrate (buffering agent), propylene glycol (tonicity agent), phenol (preservative), hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment), and water for injections (solvent).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say, essentially 'sodium-free'.

Dose delivery system

Pre-filled pen, single-dose

1 mL glass syringe (type I glass) with an attached stainless steel needle, rigid needle shield (type II/polyisoprene) and a rubber plunger (type I/chlorobutyl).

Pre-filled pen, FlexTouch (0.25, 0.5 mg)

1.5 mL glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Pre-filled pen, FlexTouch (1, 1.7 and 2.4 mg)

3 mL glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

For the multidose FlexTouch pen 4 NovoFine Plus needles are provided in the product package.

2.2.1. Discussion on chemical, pharmaceutical and biological aspects

Excipients

No direct safety issues are foreseen with regard to the excipients disodium phosphate, dihydrate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injections, and phenol.

Propylene glycol is present in the 3 ml FlexTouch pen. The thresholds mentioned in EMA/CHMP/302620/2017 Rev. 1* (Annex to the European Commission guideline on 'Excipients in the

labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668)) are 1 mg/kg/day and higher. Therefore, propylene glycol is not considered an issue for children aged 12 years and older and no warning is necessary in the product information.

Dosing

The foreseen doses and injection volumes seem acceptable for use of the product in children from 12 - 18 years (see also Clinical part below).

Other relevant aspects

Container Closure System

Editorial changes to the wording related to the user group are made. No actual changes to the container closure system are made.

Regional Information

Notified body opinion has been updated with the evaluation of the revised human factor engineering reports. The notified body concludes that "the function of the device is identical to the assessed single dose pen injector for semaglutide in the notified body Opinion Review 713201094; some documents have been updated regarding the revised population group. In the updated notified body Opinion report 713260955 it has been assessed that the revised documents also show compliance to the relevant general safety and performance requirements (GSPRs)."

As the notified body has concluded that the submitted changes are in compliance with the relevant GSPRs, a further quality review is not required.

2.2.2. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data provided, the application is considered approvable from the quality point of view.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The Applicant has justified that semaglutide is exempt from an environmental risk assessment by its protein nature, which is agreed. As there is no expected environmental exposure and because there is no concern that semaglutide (a recombinant protein) is persistent, bioaccumulative and toxic, a Phase II assessment is not necessary and environmental studies with semaglutide are not required. The logKow of semaglutide will be lower than the cut-off value of 4.5. The results of Phase I assessment yielded a PECsw of 0.002 µg/L, which is below the limit triggering Phase II. The use of semaglutide in humans will not result in a risk to environmental organisms.

2.3.2. Conclusion on the non-clinical aspects

A Phase II environmental risk assessment is not required. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of semaglutide.

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This variation application aims at extending the current Wegovy label with results from STEP Teens demonstrating the efficacy and safety of semaglutide 2.4 mg in an adolescent population (ages 12 to <18 years) with obesity or with overweight and at least one weight-related comorbidity.

To support this application one clinical trial has been conducted.

GCP

The Clinical trials (see table below) were performed in accordance with GCP as claimed by the MAH.

Table Overview of completed phase 3a trial included in the variation application

Trial	Subjects	Brief description
Trial 4451 (STEP Teens) Adolescent population (ages 12 to <18 years)	N=201	68-week, randomised, double-blind, placebo-controlled trial investigating effect and safety of semaglutide 2.4 mg once weekly in adolescents with obesity (BMI corresponding to ≥95th percentile*) or with overweight (BMI corresponding to ≥85th percentile*) and at least one weight-related comorbidity.

*on gender and age-specific growth charts (CDC.gov)

2.4.2. Pharmacokinetics

Population PK and exposure-response analyses of semaglutide s.c. 2.4 mg once weekly for weight management in adolescents were presented. The meta-analyses were based on data from 2 trials: STEP TEENS (aged 12 to <18 years; NN9536-4451) and STEP 1 (aged ≥18 years; NN9536-4373). The baseline characteristics of the paediatric population are provided in Table. Sparse PK samples were collected in both studies. In STEP TEENS, sampling was done in Weeks 8,16, 28,36, 52, and 68.

The STEP 1 trial, with adult patients, has been previously submitted and assessed in the initial application for Wegovy, solution for injection in pre-filled pen, for weight management, procedure EMEA/H/C/005422/0000. In this initial application, population pharmacokinetic analyses and exposure-response analyses using data from the STEP 1 (N=1306; semaglutide s.c. 2.4 mg) and STEP 2 (N=403; semaglutide s.c. 1.0mg, N= 404;semaglutide 2.4mg) trials were presented. In STEP 1 and 2 trials, only sparse (trough) samples were collected. A one-compartment structural model with first-order absorption and elimination was used to describe the pharmacokinetics of semaglutide. Bodyweight was the most influential covariate that influenced semaglutide plasma exposure in adults.

PK modelling

Population pharmacokinetic (PK) analyses comparing the adolescent subjects in STEP Teens to the adult subjects in STEP 1. The final PK dataset comprised a total of 1419 subjects and 8395 concentration samples from STEP TEENS (N=134) and STEP 1 (N=1306). A one-compartment model

with first-order absorption and elimination was used to describe the semaglutide PK in adults and adolescents. The structural models were parameterized in terms of the following parameters:

- Absorption rate constant: ka
- Apparent clearance: CL/F
- Apparent volume of distribution: V/F

Between-subject variability was included for CL/F and V/F, assuming a bivariate log-normal distribution. No between-subject variability was included for ka as only a typical value for ka was estimated due to the sparse sampling of semaglutide concentrations. Within-subject variability (residual) was described by a proportional error model with trial specific variances.

A confirmatory model approach was applied for the evaluation of covariate effects. This comprised estimation of a full covariate model, a reduced covariate model and a base model. A reduced list of covariates were included in the full model; these include: Sex, Age, Race, Ethnicity, Baseline body weight, and Glycaemic status.

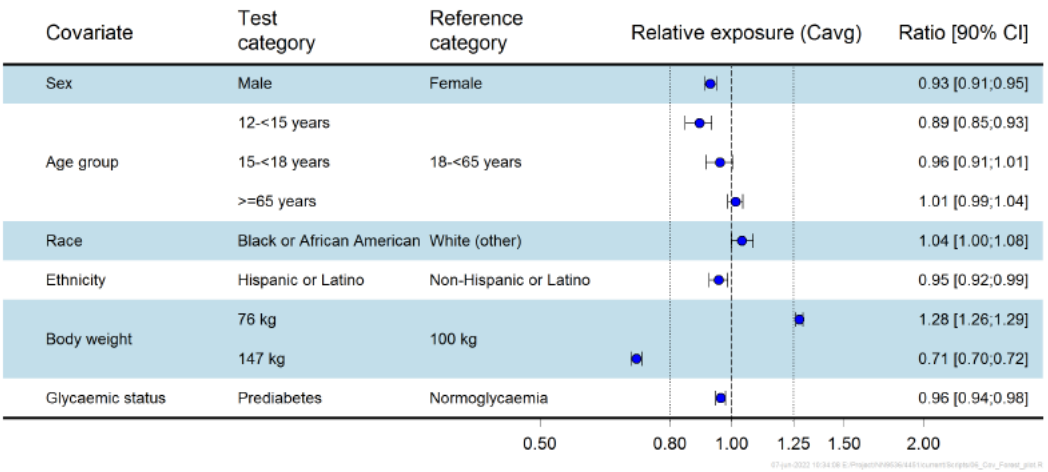
Table Parameter estimates for final reduced PK model

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

The population PK analysis showed that exposure was inversely correlated with body weight (Figure 1). 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.

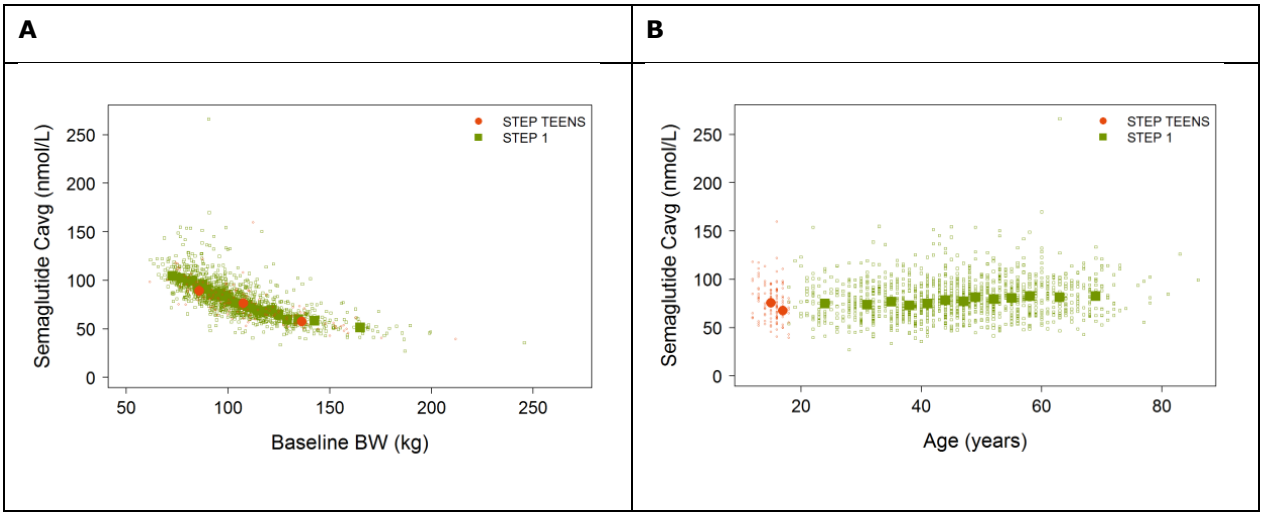
Figure 1: Semaglutide steady-state exposure (Cavg) across trials in subjects treated with semaglutide 2.4 mg



C_{avg}: average steady-state semaglutide concentrations; CI confidence interval.
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).

The exposure levels in adolescent subjects with obesity were comparable to exposure levels in adult subjects with obesity as a result of the similar baseline body weights in these trials. (see Figure 2)

Figure 2 Exposure versus baseline body weight (A) and Exposure versus age (B)

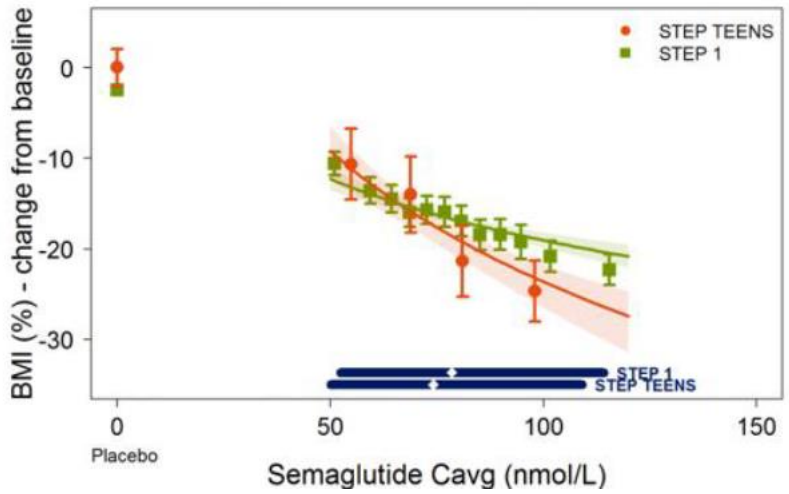


2.4.3. Pharmacodynamics

▪ PK/PD modelling

The exposure/response analyses showed a larger reduction in BMI (%) with higher exposure for both the adolescent population in STEP Teens and the adult population in STEP 1 (Figure 3). The exposure-response relationship appeared slightly steeper in adolescents compared to adults; however, with a large overlap in exposure and response in adolescents and adults.

Figure 3: BMI (%) change from baseline vs semaglutide exposure for adolescents (STEP Teens) compared to adults (STEP 1)



BMI: body mass index; Cavg: average steady-state semaglutide concentrations, CI: confidence interval.
Data points with error bars are mean BMI changes with 95% CI obtained after 68 weeks of treatment vs 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.

The exposure-response relationship for the proportion of subjects reporting nausea appeared similar in adults and adolescents (Figure 4). The proportion of subjects reporting vomiting increased to a minor extent with semaglutide exposure, with similar trends in the adolescent and adult populations (Figure 5). At similar exposure levels, higher proportions of vomiting were seen in subjects in STEP Teens compared to STEP 1; however, this difference was also evident in the placebo groups.

Figure 4 Proportion of subjects reporting nausea of any severity versus semaglutide exposure by age group

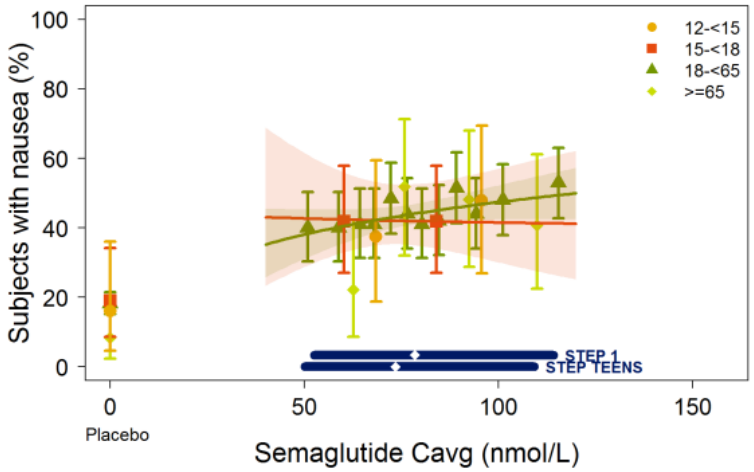
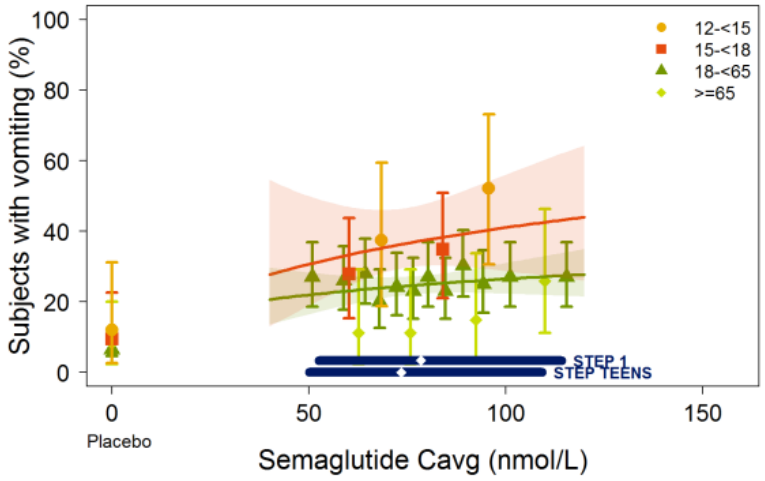


Figure 5 Proportion of subjects reporting vomiting of any severity versus semaglutide exposure by trial (A) and by age group



2.4.4. Discussion on clinical pharmacology

Population PK

Overall, the population PK objectives were clear and with an appropriate description of the nature of the data to be analysed. The general modelling aspects, including software, estimation methods and diagnostics, were properly reported. The population PK analyses compared PK/exposure in the adult population of phase 3 trial STEP 1 (NN9536-4373) to that of the target adolescent population of STEP Teens (NN9536-4451). The final dataset comprised of a total of 1419 patients, of which 1295 were adult patients, and 124 were adolescent patients (~9%), with a total of 8395 concentration samples.

A one-compartment model parameterized with KA, CL/F and V/F was used to describe semaglutide PK with inter-individual variability (IIV) terms included on CL/F and V/F. IIV was not included on KA due to the sparse (trough) sampling scheme. Covariates were tested using a confirmatory approach, and the final reduced model included sex, ethnicity and glycaemic status on CL/F and body weight on CL/F and V/F, which is a reduced number of covariates as compared to the adult-only model. Age was not a statistically significant covariate. IIV was 17.9 %CV and 35 %CV on CL/F and V/F, respectively. As indicated by the forest plot, body weight was the most important covariate for predicting semaglutide exposure (C_{avg}) whilst the other covariates were not clinically relevant. Model-derived PK endpoints (C_{avg}, AUC0-168h and CL/F) for the adolescent population (12 to <18 years) were comparable to that of the adult model-derived PK endpoints. Residual unexplained variability was described by a proportional error model and was comparable between the adolescent and adult population (31.2% and 26.6%, respectively). Sensitivity analyses did not indicate any major impact on PK parameters due to data exclusions. All fixed and random effects were estimated with good precision (<13%RSE). Shrinkage was relatively low on CL/F (16.3%) but high on V/F (44.6%); hence the information for this effect is less informative.

No critical model misspecifications were indicated by goodness of fit (GOF)-plots. Trial-stratified visual predictive checks (VPCs) indicated that the model could adequately capture the tendency of the data in the adolescent population as the median observed percentile was not systematically different from the corresponding confidence interval. However, some concentration overprediction was noted in the 5^{th} percentile towards the end of the trial in the adolescent population.

Only trough concentrations were used in the model development, so the absorption characteristics could not be estimated very accurately. The applicant estimated a typical value for KA but could not include an estimate of between-subject variability on KA. This is acceptable as the model has not been used for extrapolations, and the pharmacokinetics of semaglutide was comparable in the adolescent and adult groups.

Approximately 10% of the subjects is aged 12 to <18 years, so the population PK model is mainly driven by adult data. However, body weight, the most important factor affecting the pharmacokinetics of semaglutide was comparable in the adolescent and adult groups. Based on VPC, pharmacokinetics was sufficiently well described in adolescents. Population PK analysis showed that exposure was inversely correlated with body weight. Age did not appear to be a clinically relevant covariate for semaglutide exposure, as well as any of the other tested covariates.

Exposure-response

C_{avg} was chosen as the exposure-metric for exposure-response analyses, which may not be ideal for exposure-safety analyses. Linear regression modelling was applied for exposure-efficacy with percent change in BMI (change from baseline to week 68 in BMI) as efficacy endpoint. Percent change in BMI increased in an exposure-dependent manner, and the relationship appeared steeper in the adolescent population as compared to the adult population but with an overlap in the exposure-efficacy relationship of the two populations. Nausea events of any severity and vomiting events of any severity were chosen as safety endpoints and analysed using logistic regression modelling. The proportion of patients with nausea appeared similar in adults and adolescents, whereas the proportion of patients with vomiting was slightly higher in adolescents as compared to adults.

The exposure/response relationship appeared slightly steeper in adolescents compared to adults; however, with a large overlap in exposure and response in adolescents and adults. Further, the number of adolescent subjects reporting vomiting was slightly higher than for adult subjects, but also with a large overlap. The PKPD modelling is only used for descriptive purposes; the clinical efficacy and safety of semaglutide in adolescents are discussed in the paragraph.

The applicant proposes the following Changes in SmPC 5.2 (additions in bold, deletion in strikethrough):

> *Paediatrics*
> **Pharmacokinetic properties for semaglutide were assessed in a clinical trial for adolescent patients with obesity or overweight and at least one weight-related comorbidity ages 12 to <18 years (124 patients, body weight 61.6.-211.9 kg). The semaglutide exposure in adolescents was similar to that in adults with obesity or overweight.**
> Safety and efficacy of semaglutide in children ~~and adolescents~~ below ~~18~~ **12** years of age have not been studied.

No other changes based on PK or PKPD modelling are proposed.

Although the population PK an PKPD dataset mainly consists of adult data, the data are sufficient to support the changes of the SmPC section 5.2. No clear differences were observed between adolescents and adults based on the presented exposure-response data.

2.4.5. Conclusions on clinical pharmacology

Population PK analysis showed that exposure was inversely correlated with body weight in adolescents. This is in line with adult data. The updated text of SmPC section 5.2 is considered acceptable. No clear differences were observed between adolescents and adults based on the presented exposure-response data (BMI) or exposure-safety data (nausea and vomiting).

2.5. Clinical efficacy

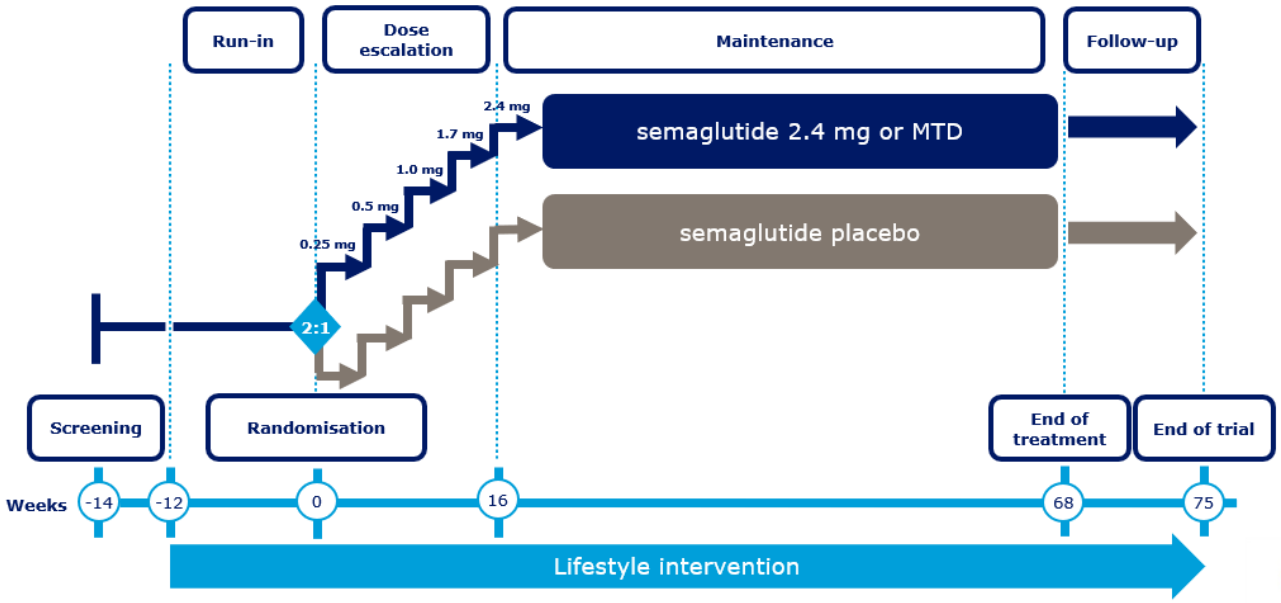
2.5.1. Main study(ies)

3.5.1.1 Trial design

Study STEP Teens was a multinational, randomised, double-blind, two-armed, placebo-controlled trial with a 68-week trial period comparing semaglutide s.c. 2.4 mg once weekly with placebo in pubertal adolescents, ages 12 to <18 years, with obesity or with overweight and ≥1 weight-related comorbidity. A schematic overview of the trial design is shown in Figure 6.

According to regulatory guidelines, the trial included a run-in period of 12 weeks non-pharmacological lifestyle intervention before randomisation. Lifestyle intervention consisted of diet and physical activity counselling for weight loss and continued throughout the trial until the 'end of trial' (week 75). At randomisation, subjects were stratified by gender and Tanner stage (2-3 vs 4-5) to ensure an even distribution of males vs females and early vs late pubertal development. A comparator group, receiving placebo as well as lifestyle intervention, was included in the trial design to allow for evaluation of the effect of semaglutide 2.4 mg on weight management.

Figure 6 Overview of trial design



- MTD: maximum tolerated dose

3.5.1.2 Objectives, estimands and efficacy endpoints

3.5.1.2.1 Objectives and endpoints

This efficacy summary addendum summarises results for the efficacy endpoints from STEP Teens presented in the table below.

Table Efficacy endpoints presented in addendum – STEP Teens

Objectives	Endpoints	STEP Teens (4451) Adolescent population (ages 12 to <18 years)
	Body weight related endpoints	
Primary objective: To compare the effect of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity on weight management in adolescents (ages 12 to <18 years) with overweight or obesity.	**Change from baseline (week 0) to week 68 in:**	
	BMI (%)	Primary endpoint
	Body weight (kg)	Supportive secondary endpoint
	BMI (kg/m^2)	Supportive secondary endpoint
	BMI percentage of the 95th percentile* (%-points)	Supportive secondary endpoint
	BMI SDS[a]	Supportive secondary endpoint
	Waist circumference (cm)	Supportive secondary endpoint
	Subjects who achieve at week 68 (y/n):	
	≥5% body weight reduction from week 0	Confirmatory secondary endpoint
	≥10% body weight reduction from week 0	Supportive secondary endpoint
	≥15% body weight reduction from week 0	Supportive secondary endpoint
	≥20% body weight reduction from week 0	Supportive secondary endpoint
	≥5% reduction of BMI from week 0	Supportive secondary endpoint
	Improvement in weight category	Supportive secondary endpoint
Secondary objectives: To compare the effect of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents (ages 12 to <18 years) with overweight or obesity on: Cardiovascular risk factors Glucose metabolism	**Cardiovascular-related endpoints**	
	Change from baseline (week 0) to week 68 in:	
	Systolic blood pressure (mmHg)	Supportive secondary endpoint
	Lipids (mmol/L) • Total cholesterol • HDL • LDL • VLDL • Triglycerides	Supportive secondary endpoints
	ALT (U/L)	Supportive secondary endpoint
	Glucose metabolism-related endpoints	
	Change from baseline (week 0) to week 68 in:	
	HbA_{1c} (%-points)[b]	Supportive secondary endpoint
	Patient-reported outcomes	
Exploratory objective: To compare the effect of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents (ages 12 to <18 years) with overweight or obesity on: Clinical Outcome Assessments (COAs)	IWQOL-Kids	Exploratory endpoint

- ALT: alanine aminotransferase; BMI: body mass index; HDL: high-density lipoprotein; IWQOL-Kids: Impact of weight on quality of life-kids; LDL: low-density lipoprotein; SDS: standard deviation score; VLDL: very low-density lipoprotein.
- * on gender- and age-specific growth charts (CDC.gov)
- [a] BMI SDS: calculated using growth reference data for children and adolescents (5-19 years) from WHO.int[13]
- [b] HbA_{1c} for subjects without type 2 diabetes (T2D) at baseline

3.5.1.2.2 Estimands

The efficacy-related endpoints are evaluated for two pre-specified estimands (treatment policy and hypothetical estimand), which are used to address the trial objectives in terms of two different aspects of the treatment effect of semaglutide 2.4 mg. This efficacy summary addendum only summarises results for the primary estimand (i.e., the treatment policy estimand).

Primary estimand (treatment policy estimand)

This estimand will quantify the average treatment effect of semaglutide 2.4 mg relative to placebo after 68 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies (weight management drugs or bariatric surgery).

3.5.1.3 Trial subjects

3.5.1.3.1 Key inclusion criteria

- Informed consent of the parent(s) or legally acceptable representative of the subject and child assent, as appropriate, obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male or female, ages 12 to <18 years at the time of signing the informed consent
- BMI ≥95th percentile* OR ≥85th percentile* with ≥1 weight-related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or T2D
- History of at least one self-reported unsuccessful dietary effort to lose weight

* on gender and age-specific growth charts (CDC.gov).

- For subjects with T2D at screening, the following inclusion criteria apply in addition:
HbA_{1c} ≤10.0% (86 mmol/mol) as measured by central laboratory at screening

3.5.1.3.2 Key exclusion criteria

- Prepubertal subjects (Tanner stage 1)
- History of type 1 diabetes
- A self-reported (or by parent(s)/legally acceptable representative where applicable) 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 T2D only: Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening

(Visit 1). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

3.5.1.3.3 Randomisation criteria

- BMI corresponding to:
  ≥95th percentile* *OR*
  ≥85th percentile* with ≥1 weight-related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or T2D
- Compliance with trial procedures and visit schedule as judged by the investigator
- A PHQ-9 score of <15 at randomisation
- No suicidal behaviour in the period between screening and randomisation
- No suicidal ideation corresponding to type 4 or 5 on the C-SSRS in the period between screening and randomisation
- Absence of uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 30 days prior to randomisation (Visit 8)**. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

*On gender and age-specific growth charts (CDC.gov).
**Diabetes related for subjects with T2D only (at screening or if diagnosed during the trial).

3.5.1.3.4 Withdrawal criteria

Efforts were made to ensure treatment compliance and that subjects attended and completed all scheduled visit procedures. Randomised subjects were to stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only if a subject or a subject's legally acceptable representative (LAR) declined any further contact with the site in relation to the trial, were they to be considered as withdrawn from the trial.

A subject could withdraw consent at will at any time, either by the subject and/or by the subject's LAR. The subject's request to withdraw from the trial was always respected.

The subject could be prematurely discontinued from the trial product due to a safety concern, at the discretion of the investigator and/or if any of the criteria specified applied.

3.5.1.3.5 Dosing strategy

Subjects were initiated at a once-weekly dose of 0.25 mg and followed a fixed-dose escalation regimen, with dose intended increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week). 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 the trial product completely and if it was considered safe to continue on trial product.

Statistical methods

3.5.1.3.6 Sample size

The trial was designed with an effective power of 90% and 72% to detect differences in the primary and confirmatory secondary endpoints, respectively. All statistical tests were conducted at a significance level of 5%.

3.5.1.3.7 Analysis sets and observation periods

Efficacy endpoints were analysed in the full analysis set (FAS), including all randomised subjects.

Observation periods included the in-trial period (the time from randomisation to last contact with a trial site, regardless of treatment discontinuation or rescue intervention) and the on-treatment period.

3.5.1.3.8 Analysis of endpoints

Primary and confirmatory secondary endpoints were tested in a prespecified hierarchical order. All results from statistical analyses were accompanied by a two-sided 95% confidence interval and corresponding P values (with significance defined as $P<0.05$).

3.5.1.2 Subject disposition

The trial enrolled 201 adolescent subjects (ages 12 to <18 years) with obesity or with overweight and at least one weight-related comorbidity. Subjects were randomised 2:1 to receive either semaglutide 2.4 mg or placebo.

The proportion of treatment completers (subjects on treatment at week 68) and trial completers (subjects who attended the end-of-trial visit) was similar between the semaglutide 2.4 mg and placebo groups.

In the FDA semaglutide Written Request, it was required that at least 150 patients should have an assessment of BMI at week 68, regardless of whether the subject remained on the study drug or completed other study assessments. As seen in the tables below, this requirement was met in the trial.

Permanent discontinuation of trial product due to AEs was reported by 4.5% of subjects with semaglutide 2.4 mg vs 6.0% with placebo.

Table Subject disposition – summary – all subjects

	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)
Attended end-of-treatment visit after permanent discontinuation of trial product	13 (9.7)	5 (7.5)	18 (9.0)

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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.

3.5.1.3 Demographics and baseline characteristics

Overall, the demographic and baseline characteristics were well-balanced between the semaglutide 2.4 mg and placebo groups, although baseline BMI and body weight were higher in the semaglutide 2.4 mg group, as shown in the tables below.

In the FDA semaglutide Written Request, it was required that the population in STEP Teens included a minimum of 30% of subjects between ages 12 to 14, and 30% of subjects needed to be male. As seen in the table belwo, both these requirements were met.

Table Demographics and baseline characteristics - summary - full analysis set

	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)
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 Baseline characteristics – descriptive statistics - full analysis set

	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

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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.

3.5.1.4 Efficacy results

3.5.1.4.1 Summary of results for the primary and confirmatory secondary endpoints

Superiority of semaglutide 2.4 mg vs placebo was confirmed for the primary and the confirmatory secondary endpoints.

Table Error! No text of specified style in document. **STEP Teens – key efficacy results – treatment policy estimand**

Endpoint	Est.	95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoint						
BMI (%) change from baseline to week 68						
Sema 2.4 mg - Placebo	-16.75	[-20.27; -13.23]	<.0001	0.05	Superiority	Confirmed
Confirmatory secondary endpoint						
Odds of achieving baseline body weight loss >=5% at week 68						
Sema 2.4 mg / Placebo	14.02	[6.34; 31.02]	<.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.

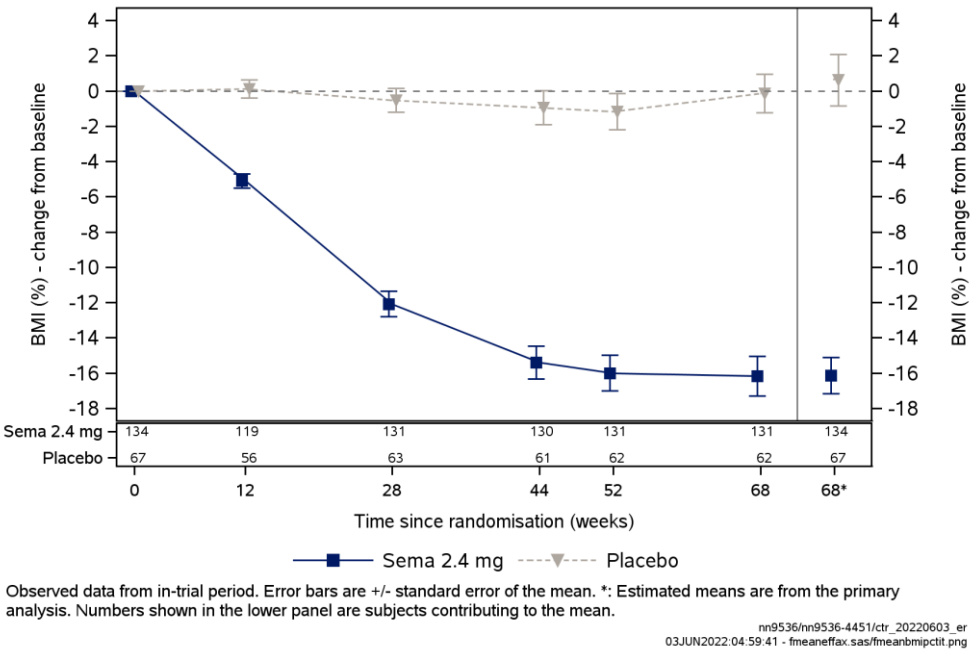
The estimated change from baseline BMI (%) at week 68 was -16.14% with semaglutide 2.4 mg and 0.61% with placebo. With semaglutide 2.4 mg, 72.5% of subjects achieved ≥5% weight loss vs 17.7% with placebo.

3.5.1.4.2 BMI (%) change from baseline

The superiority of semaglutide 2.4 mg vs placebo was confirmed for the primary endpoint; change in BMI (%) from baseline (week 0) to week 68.

The BMI (%) change from baseline occurred during the first 52 weeks with semaglutide 2.4 mg treatment, after which a plateau was reached. With placebo, mean BMI (%) change from baseline was very limited and the BMI remained close to the baseline level throughout the trial.

Figure BMI (%) change from baseline by week - mean plot - treatment policy estimand – STEP Teens



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

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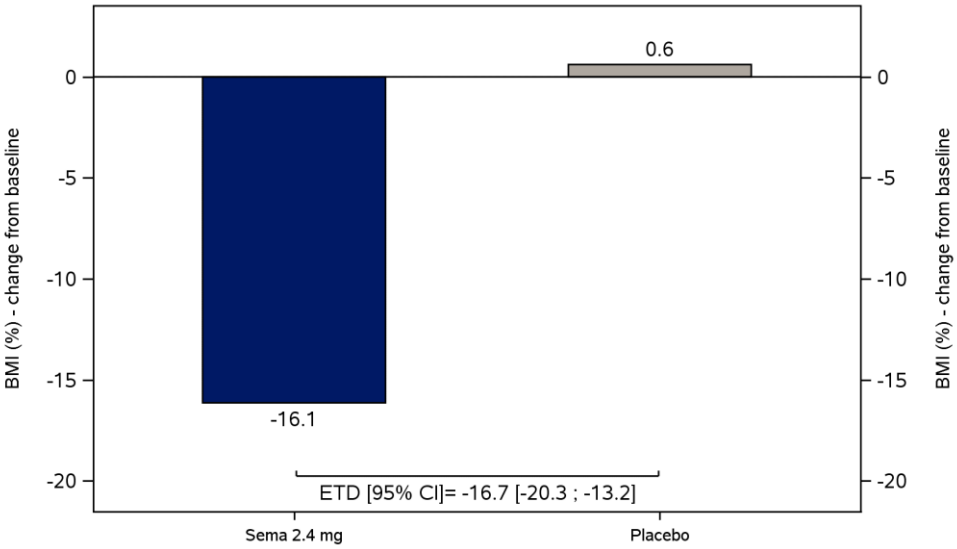
The estimated change in BMI (%) from baseline to week 68 was greater with semaglutide 2.4 mg (-16.14%) compared to placebo (0.61%); with an estimated treatment difference (ETD) of -16.75 %-points $[-20.27; -13.23]_{95\%\ CI}$.

Figure BMI (%) change from baseline to week 68 – bar plot – treatment policy estimand - STEP Teens



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

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3.5.1.4.3 Body weight – categorical response

Body weight reduction of ≥5% from baseline (week 0) to week 68 was a confirmatory secondary endpoint in STEP Teens. The superiority of semaglutide 2.4 mg vs placebo was demonstrated in terms of the proportion of subjects achieving ≥5% body weight reduction from baseline to week 68, with odds ratios (ORs) in favour of semaglutide 2.4 mg.

The proportions of subjects achieving ≥10%, ≥15% or ≥20% body weight reduction from baseline to week 68 were also greater with semaglutide 2.4 mg compared to placebo, with more than half of the subjects achieving a weight loss of at least 15%.

Figure Proportion of subjects achieving body weight loss response criteria since baseline at week 68 – bar plot – observed in-trial data – STEP Teens

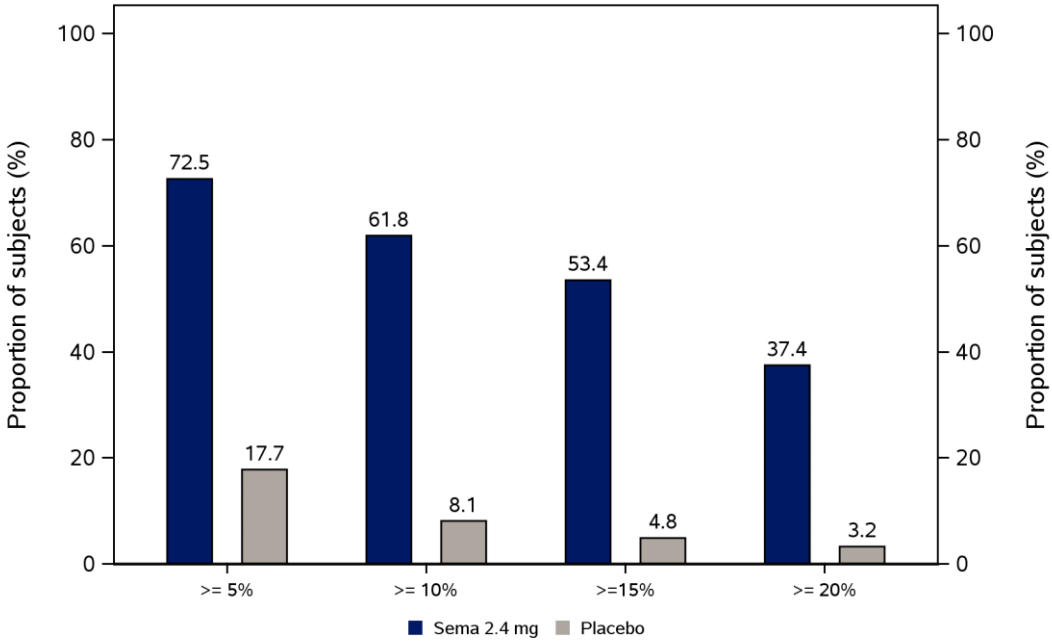
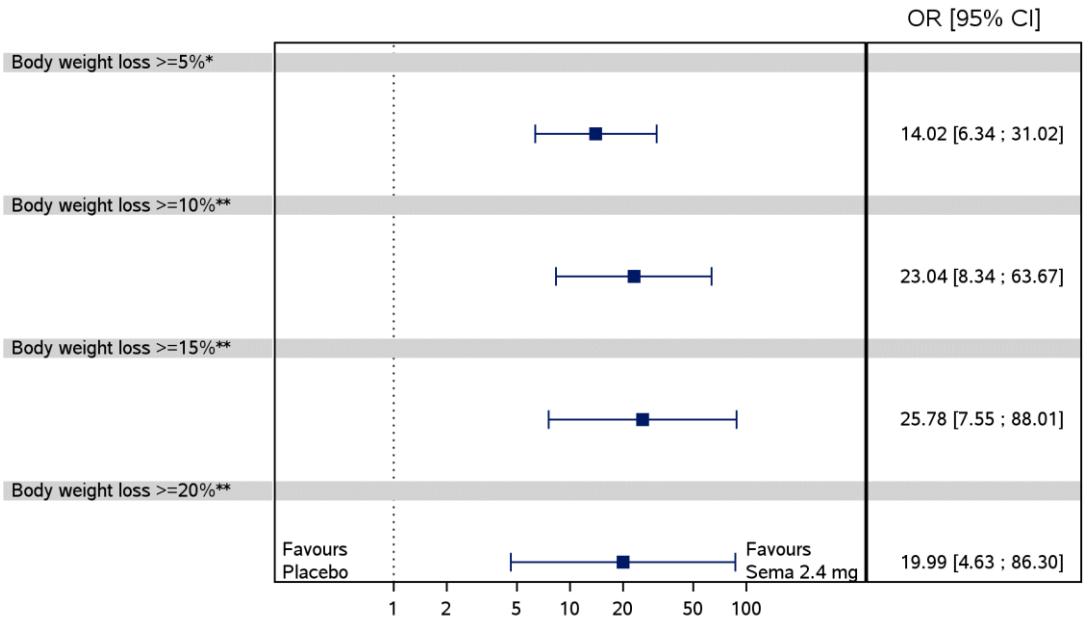


Figure Odds of achieving body weight loss response criteria since baseline at week 68 - forest plot - treatment policy estimand - STEP Teens



OR: Odds ratio, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment differences and corresponding confidence intervals are from the confirmatory secondary analysis (*) and the supportive secondary analyses (**).

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3.5.1.4.4 BMI – categorical response

The estimated proportion of subjects with ≥5% reduction in BMI from baseline to week 68 was greater with semaglutide 2.4 mg (77.1%) compared to placebo (19.7 %). The OR was 13.76 [6.31; 30.02]$_{95\% CI}$, favouring semaglutide 2.4 mg.

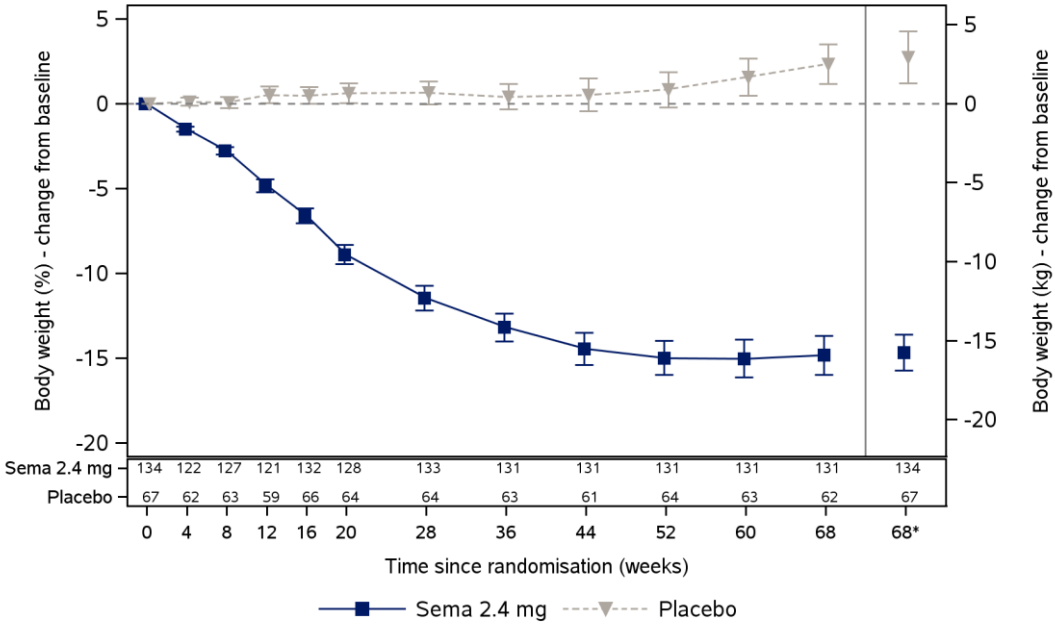
3.5.1.4.5 Body weight (kg, %)

At baseline, the mean body weight (kg) was slightly higher with semaglutide 2.4 mg compared to placebo. Mean decrease in body weight (kg, %) was greater with semaglutide 2.4 mg compared to placebo. The decrease with semaglutide 2.4 mg reached a plateau around week 52. With placebo, a slight increase in body weight occurred towards the end of the trial.

The estimated treatment differences (ETDs) for change in body weight were in favour of semaglutide 2.4 mg vs placebo:

- Body weight (kg): ETD: -17.73 kg [-21.76; -13.70]$_{95\% CI}$
- Body weight (%): ETD: -17.42% [-21.08; -13.75]$_{95\% CI}$

Figure Body weight (kg, %) change from baseline by week - mean plot - treatment policy estimand - STEP Teens



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.

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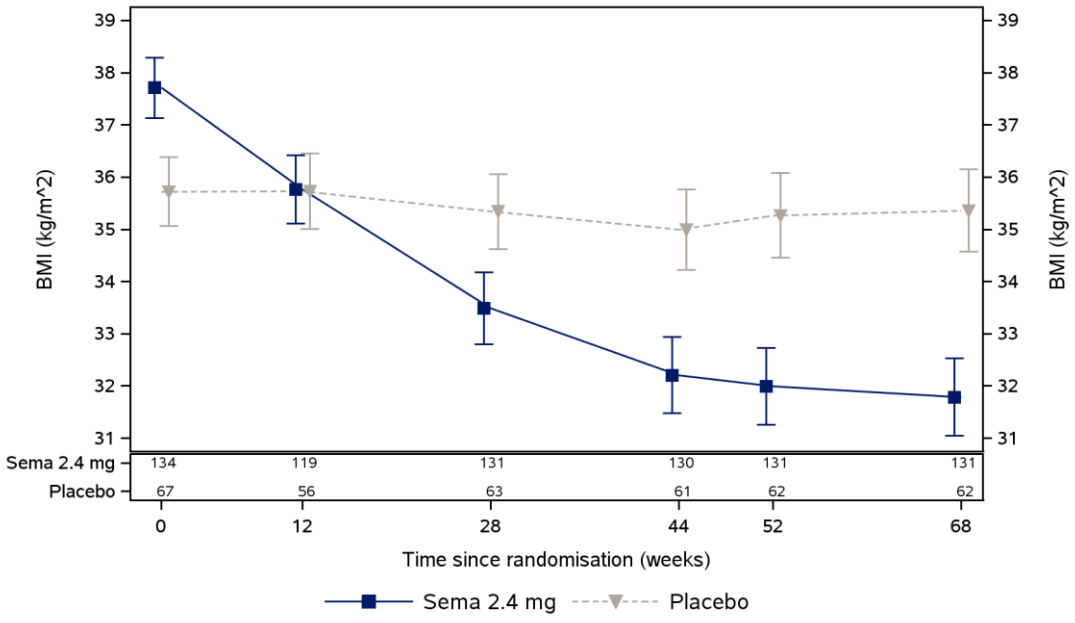
3.5.1.4.6 BMI (kg/m^2)

At baseline (week 0) mean BMI (kg/m^2) was slightly higher for the semaglutide 2.4 mg group compared to the placebo group. For the semaglutide 2.4 mg group, mean BMI decreased from baseline to week 68. With placebo, the mean BMI remained at the same level throughout the trial, even though there was a slight increase in body weight. The estimated mean change in BMI from baseline to week 68 was -5.85 kg/m^2 for the semaglutide 2.4 mg group and 0.11 kg/m^2 for the placebo group, resulting in an ETD of -5.96 kg/m^2 [-7.29; -4.62]$_{95\% \text{ CI}}$ in favour of semaglutide 2.4 mg.

Figure 7 BMI (kg/m^2) by week - mean plot - in-trial - full analysis set – STEP Teens



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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3.5.1.4.7 BMI percentage of the 95th percentile

In STEP Teens, the BMI cut-off for obesity for adolescents was defined as the 95th percentile on gender- and age-specific growth charts, according to CDC.gov.

From baseline to week 68, the estimated mean BMI percentage of the 95th percentile on gender and age-specific growth charts decreased more with semaglutide 2.4 mg (-24.58 %-points) than with placebo (-4.18 %-points), ETD: -20.40 %-points $[-25.01; -15.79]_{95\% \text{ CI}}$.

3.5.1.4.8 BMI SDS

In STEP Teens, the BMI SDS were calculated using growth reference data for children and adolescents (5-19 years) from WHO.int.

From baseline to week 68, the estimated mean BMI SDS decreased considerably more with semaglutide 2.4 mg (-1.09) than with placebo (-0.06), with an ETD of -1.03 $[-1.27; -0.80]_{95\% \text{ CI}}$.

3.5.1.4.9 Improvement in weight category

In STEP Teens, improvements in weight category from baseline to week 68 was a supportive secondary endpoint. Weight categories for the adolescent population were defined based on CDC's gender- and age-specific BMI growth charts, as presented in the table below.

Table Weight categories

Obesity class	BMI
Normal	BMI <85th percentile
Overweight	BMI >85th to <95th percentile
Obesity	BMI >95th percentile
Obesity class I	BMI >95th to <120% of the 95th percentile
Obesity class II	BMI ≥120% of the 95th percentile to <140% of the 95th percentile
Obesity class III	BMI ≥140% of the 95th percentile

- Weight categories for adolescent population, defined based on gender and age-specific BMI growth charts (CDC.gov).

From baseline to week 68, improvement in weight category was seen for a larger proportion of subjects with semaglutide 2.4 mg (71.8%) compared to placebo (21.0%). In the semaglutide 2.4 mg group, a considerable proportion of subjects shifted more than one level in the weight category. The odds of achieving improvement in the weight category at week 68 was greater with semaglutide 2.4 mg than with placebo.

3.5.1.4.10 Waist circumference

The estimated decreases in waist circumference (cm) from baseline to week 68 were -12.69 cm with semaglutide 2.4 mg and -0.55 cm with placebo and the ETD was statistically significant in favour of semaglutide 2.4 mg (-12.14 cm [-15.59; -8.69]$_{95\% CI}$

3.5.1.4.11 Glucose metabolism

HbA_{1c}

The adolescent population in STEP Teens included subjects with and without T2D.

For subjects without T2D at baseline, the mean HbA_{1c} levels at baseline were 5.5% with semaglutide 2.4 mg and 5.4% with placebo. The estimated mean change in HbA_{1c} from baseline to week 68 was -0.35 %-points with semaglutide 2.4 mg compared to -0.14 %-points with placebo, with a statistically significant ETD in favour of semaglutide 2.4 mg (-0.22 %-points [-0.29; -0.14]$_{95\%CI}$.

For subjects with T2D at baseline (n=8), mean HbA_{1c} levels at baseline were 6.7% with semaglutide 2.4 mg and 6.1% with placebo.

3.5.1.4.12 Cardiovascular efficacy results

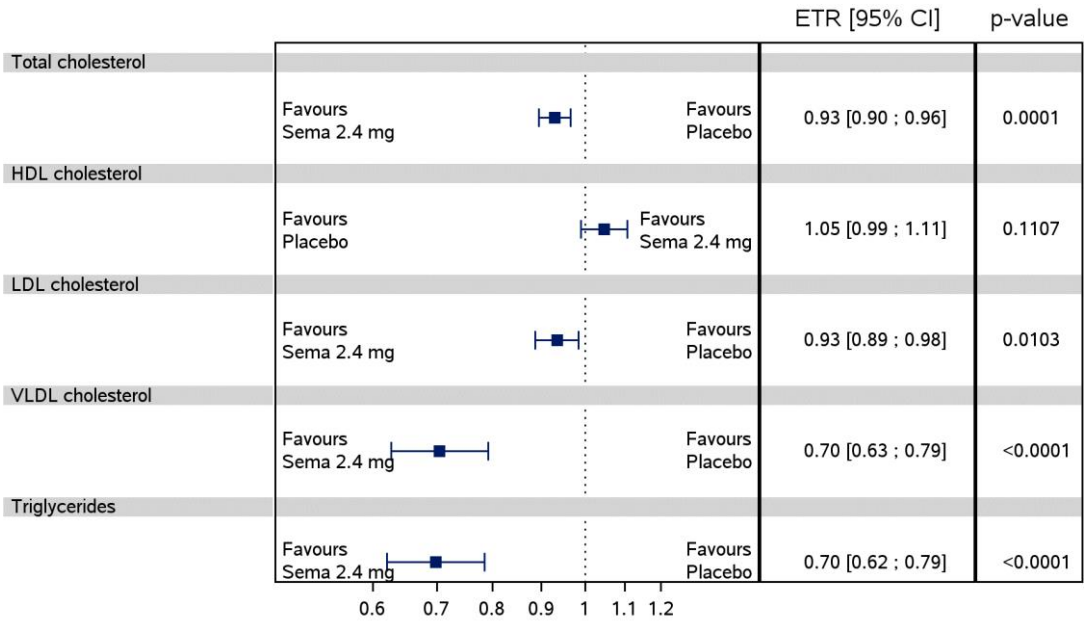
Blood pressure

At baseline, the observed mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) were the same in both treatment groups (SBP: 120 mmHg; DBP: 73mmHg). A minor decrease in SBP and DBP were seen in both groups with no statistically significant difference between the groups.

Lipids

Beneficial effects of semaglutide 2.4 mg vs placebo were observed for all lipid parameters from baseline to week 68. The estimated treatment ratios (ETRs) were statistically significant in favour of semaglutide 2.4 mg for total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides.

Figure Lipids ratio to baseline at week 68 - forest plot - treatment policy estimand - full analysis set – STEP Teens



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.

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Alanine aminotransferase

In STEP Teens, ALT (U/L) change from baseline to week 68 with semaglutide 2.4 mg vs placebo was a supportive secondary endpoint. In week 68, mean ALT levels decreased with semaglutide 2.4 mg, whereas it remained at the same level with placebo. The ETR was statistically significant in favour of semaglutide 2.4 mg (ETR: 0.86 $[0.75;0.99]_{95\%\ CI}$).

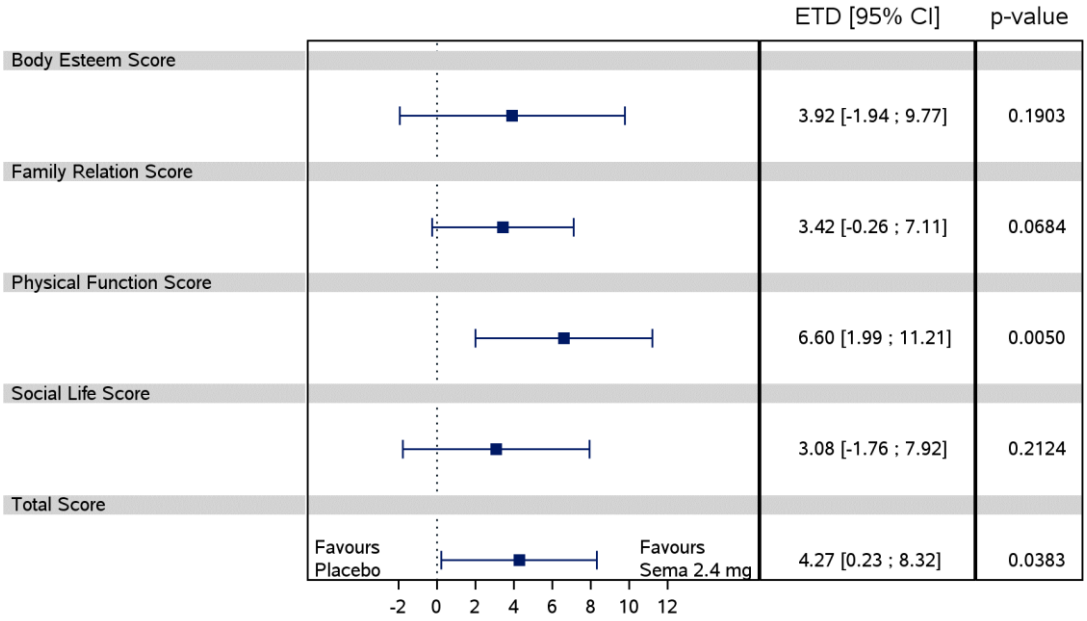
3.5.1.4.13 Patient reported outcome - Impact of Weight on Quality of Life-Kids (IWQOL-Kids)

The IWQOL-Kids questionnaire was used to assess weight-related quality of life in adolescents. The following four domain scores and a total score were calculated:
- Physical comfort
- Body esteem
- Social life
- Family relations

For all the individual domain scores, improvements in individual scores were seen with semaglutide 2.4 mg compared to placebo. The ETDs for the physical comfort score and the total score were statistically significant in favour of semaglutide 2.4 mg vs placebo:

Physical comfort score (change from baseline): 6.35 vs -0.25; ETD: 6.60 [1.99; 11.21]$_{95\%\ CI}$
Total score (change from baseline): 5.23 vs 0.98; ETD: 4.27 [0.23; 8.32]$_{95\%\ CI}$

Figure IWQOL-Kids change from baseline to week 68 – Forest plot - treatment policy estimand – STEP Teens



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.

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- In the TFL, Physical Comfort is denoted Physical Function.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Summary of efficacy for trial NN9536-4451 (STEP Teens)

Title	Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity	
Study identifier	Trial ID: NN9536-4451 UTN: U1111-1215-7560 www.clinicaltrials.gov identifier : NCT04102189 EudraCT number: 2018-002431-18	
Design	This trial was a multinational, multicentre, randomised, double-blind, two-armed, placebo-controlled trial with a 68-week trial period comparing semaglutide s.c. 2.4 mg once weekly with semaglutide placebo in pubertal adolescents, ages 12 to <18 years, with obesity or with overweight and ≥1 weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or T2D)	
	Duration of main phase: Duration of Run-in phase:	68 weeks 12 weeks
Hypotheses	**Primary objective:** • To compare the effect of semaglutide s.c. once-weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity on weight management in adolescents (ages 12 to <18 years) with overweight or obesity. **Secondary objective:** • To compare the effect of semaglutide s.c. once weekly versus semaglutide placebo as an adjunct to a reduced-calorie diet and increased physical activity in adolescents (ages 12 to <18 years) with overweight or obesity on: o Cardiovascular risk factors o Glucose metabolism	
Treatments groups	Semaglutide 2.4 mg	134 subjects
	Semaglutide placebo	67 subjects
Endpoints and definitions	**Primary endpoint:** Change in BMI from baseline (week 0) to week 68 (%)	
	Confirmatory secondary endpoint: Subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (yes/no)	

	Supportive secondary endpoints: Effect endpoints from baseline (week 0) to week 68: Change in: • Body weight (kg) • Body weight (%) • Subjects achieving ≥10% reduction of body weight (yes/no) • Subjects achieving ≥15% reduction of body weight (yes/no) • Subjects achieving ≥20% reduction of body weight (yes/no) • BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) (%-point) • Improvement in weight category (yes/no) • BMI (standard deviation score) (WHO.int) • BMI (kg/m^2) • Waist circumference (cm) • Subjects achieving ≥5% reduction of BMI (yes/no)		
Database lock	20 April 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis set	The full analysis set included all randomised subjects (n=201)		
Results	Treatment group	Semaglutide 2.4 mg	Semaglutide placebo
	Number of subject (FAS)	134	67
	Change in BMI from baseline (week 0) to week 68 (%)	-16.1	0.6
		ETD	-16.75
		95% CI	-20.3; -13.2
		p-value (ANCOVA)	<0.001
Analysis description	**Secondary confirmatory analysis**		
Analysis set	The full analysis set included all randomised subjects (n=201)		
Results	Treatment group	Semaglutide 2.4 mg	Semaglutide placebo
	Number of subjects (FAS)	134	67
	Proportion of subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (yes/no)	72.5	17.7
	Odds of achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (OR)	2.73	0.19
		Treatment OR	14.02
		95% CI	6.34; 31.02
		p-value (ANCOVA)	<0.0001

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Semaglutide s.c. 2.4 mg once weekly (Wegovy) has been approved as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance in adults with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) and at least one weight-related comorbidity. This variation application aims at extending the current Wegovy label with results from STEP Teens demonstrating the efficacy and safety of semaglutide 2.4 mg in an adolescent population.

This trial is a 68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide 2.4 mg once weekly in adolescents with obesity (BMI corresponding to ≥95th percentile*) or with overweight (BMI corresponding to ≥85th percentile*) and at least one weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or T2D).

The company initially proposed an extension of the indication in the adolescent population with overweight or obesity. However, the company subsequently acknowledged that only one subject was within the overweight with comorbidities category at baseline. Therefore, the benefit/risk ratio in individuals with overweight cannot be determined and an indication in overweight adolescents with comorbidities was not accepted. This is in line with the adolescent indication for Saxenda (liraglutide). Overweight adolescents with comorbidities were not included in the clinical trial with liraglutide, and liraglutide does not have an indication for overweight adolescents with comorbidities. The company removed the indication in overweight adolescents.

According to regulatory guidelines, the trial included a run-in period of 12 weeks non-pharmacological lifestyle intervention before randomisation. Lifestyle intervention consisted of diet and physical activity counselling for weight loss and continued throughout the trial.

Primary objective was to compare the effect of semaglutide s.c. once-weekly versus semaglutide placebo as an adjunct to a reduced- calorie diet and increased physical activity on weight management in adolescents (ages 12 to <18 years) with overweight or obesity.

Primary endpoint:

Change in BMI from baseline (week 0) to week 68 (%)

Confirmatory secondary endpoint:

Subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (yes/no).

The use of the treatment policy estimand as the primary estimand is acceptable.

For subjects with T2D only, uncontrolled and potentially unstable diabetic retinopathy or maculopathy was an exclusion criterion. This is clearly stated in the product information.

The inclusion criteria on BMI were based on CDC criteria instead of World Health Organization (WHO) criteria or international obesity task force (IOTF) criteria. Age and gender-specific BMI for inclusion is endorsed. The age-specific cut-offs for overweight and obesity are almost similar to the cut-off values defined by IOTF, which was used for Saxenda.

Regarding the WHO criteria, the cut-off values for overweight and obesity are generally lower for all age groups from 12-18 years and for both genders. Hence, the risk of overtreatment of the European population is not an issue when using the CDC criteria.

The trial enrolled 201 adolescent subjects (ages 12 to <18 years) with obesity or with overweight and at least one weight-related comorbidity. Subjects were randomised 2:1 to receive either semaglutide 2.4 mg or placebo.

Efficacy data and additional analyses

The proportions of treatment completers (subjects on treatment at week 68) and trial completers (subjects who attended the end-of-trial visit) were similar between the semaglutide 2.4 mg and placebo groups (89.6%).

Permanent discontinuation of trial product due to AEs was reported by 4.5% of subjects with semaglutide 2.4 mg vs 6.0% with placebo.

Overall, the demographic and baseline characteristics were well-balanced between the semaglutide 2.4 mg and placebo groups, although baseline BMI and body weight were higher in the semaglutide 2.4 mg group (37.7 vs 35.7 kg/m2; 109.9 vs 102.6 kg). However, the statistical analyses adjusted for this baseline difference.

Additionally, a higher frequency of dyslipidaemia was seen in the semaglutide arm, which is in line with the higher BMI in this group. On the other hand, a higher proportion of subjects with type 2 diabetes was seen in the placebo group, 4.5% vs. 3.7%; however, the numbers are very small (3 subjects in the placebo group and 5 subjects in the semaglutide group).

Effects on BMI and weight

The estimated change from baseline in BMI (%) at week 68 was -16.14% with semaglutide 2.4 mg and 0.61% with placebo. With semaglutide 2.4 mg, 72.5% of subjects achieved ≥5% weight loss vs 17.7% with placebo. 27.5% of the patients treated with semaglutide had a weight loss less than 5%. Almost 10% of the patients did not have a decrease in BMI or an increase. The ETDs for change in body weight were in favour of semaglutide 2.4 mg vs placebo: -17.73 kg (95% CI -21.76; -13.70) and -17.42% (95% CI -21.08; -13.75).

Of the subjects in STEP Teens, who were randomised to the semaglutide arm and completed treatment, 15 subjects were on a lower dose than semaglutide 2.4 mg by the end of the treatment period (week 68). 14 out of 15 subjects not ending on the maximum semaglutide dose had a relevant weight loss, and one subject had an increase in bodyweight (increase in 6.6%). The reduction in BMI ranges from 14.9% to 41.1%. Nine of the 15 subjects reached the maximum dose of 2.4 mg and thereafter decreased the dose stepwise to 1.7 mg, 1.0 mg or 0.5 mg. Based on these data no minimum dose should be stated in the SmPC and the proposed text in section 4.2 of the SmPC is acceptable.

Other endpoints

For subjects without T2D at baseline, the estimated mean change in HbA_{1c} from baseline to week 68 was -0.35 %-points with semaglutide 2.4 mg compared to -0.14 %-points with placebo, with a statistically significant ETD in favour of semaglutide 2.4 mg (-0.22 %-points [-0.29; -0.14].

For subjects with T2D at baseline (n=8), HbA1c decreased -1.0 %-point in the semaglutide 2.4 mg group (n=5), whereas the change was 0.3 %-point in the placebo group (n=3), but the groups were very small.

A minor decrease in SBP and DBP was seen in both groups, with no statistically significant difference between the groups.

Beneficial effects of semaglutide 2.4 mg vs placebo were observed for all lipid parameters from baseline to week 68. The estimated treatment ratios (ETRs) were statistically significant in favour of semaglutide 2.4 mg for total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides. However, the estimates

were not multiplicity adjusted; hence, the beneficial findings in terms of ETRs are regarded as exploratory only.

For all the individual domain scores, improvements in individual scores were seen with semaglutide 2.4 mg compared to placebo. The ETDs for the physical comfort score and the total score were statistically significant in favour of semaglutide 2.4 mg vs placebo.

2.5.3. Conclusions on the clinical efficacy

The effect of semaglutide on body weight and BMI was clinically relevant. However, 27.5% of the patients treated with semaglutide had a weight loss of less than 5%. Almost 10% of the patients did not have a decrease in BMI or an increase. A stopping rule is important in order to try to avoid unnecessary treatment of this subgroup.

2.6. Clinical safety

Patient exposure

Of the 201 subjects randomised 2:1 to treatment, 200 were exposed to the trial product: 133 subjects in the semaglutide 2.4 mg group (181.8 patient years exposure (PYE), 192.0 person-years of observation (PYO)); 67 subjects in the placebo group (90.4 PYE, 94.0 PYO).

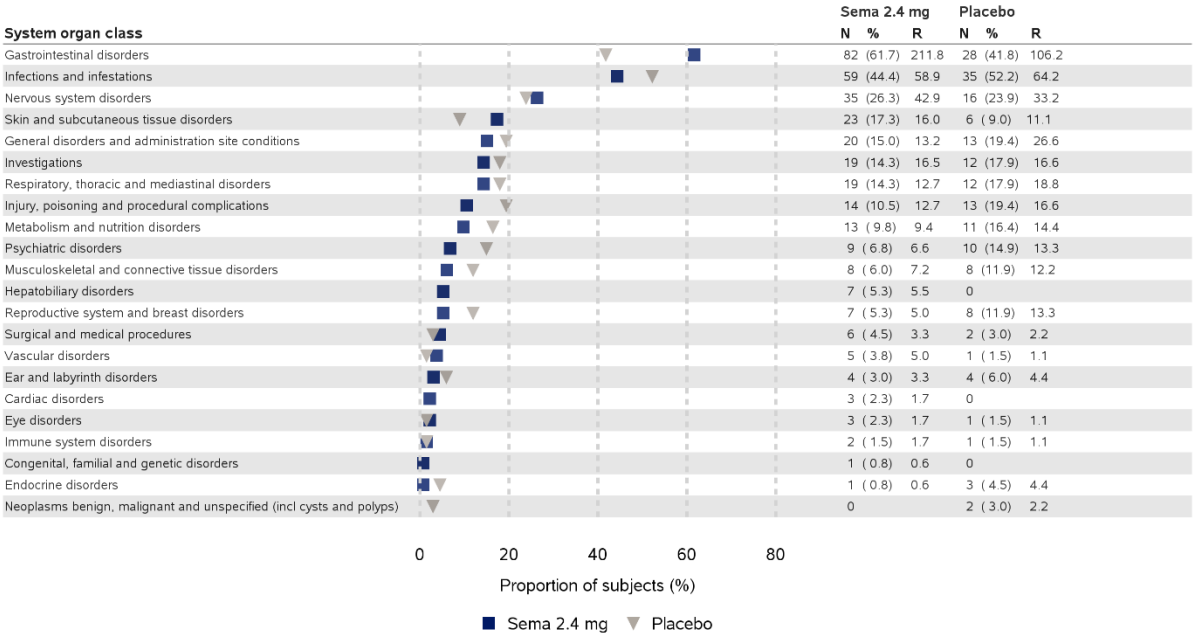
Overall, 89.6% completed treatment and 97.5% of subjects completed the trial. Comparable proportions of subjects in both treatment groups completed treatment (89.6% for both treatment groups) and completed the trial (98.5% semaglutide 2.4 mg group; 95.5% placebo group).

Dosing was initiated at 0.25 mg of semaglutide or the comparable volume of placebo. Both groups then escalated the dose every 4 weeks, over a period of 16 weeks, to 2.4 mg of semaglutide (or the comparable volume of placebo) or to the maximum tolerated dose. Dose escalation occurred comparably in both treatment groups to week 16. At week 28, 90.2% of subjects in the semaglutide 2.4 mg group, and 98.4% of subjects on placebo, were at the target dose of 2.4 mg. Most subjects in both treatment groups remained at the target dose through the remainder of the trial (week 68).

Adverse events

The proportion of subjects with AEs, was comparable between the treatment groups (78.9% in semaglutide 2.4 mg vs 82.1% in placebo). The rate of AEs reported, was higher with semaglutide 2.4 mg than with placebo (435.7 events per 100 PYE in semaglutide 2.4 mg vs 362.9 events per 100 PYE in placebo), driven primarily by gastro-intestinal (GI) AEs.

Figure Adverse events by system organ class - summary plot - on-treatment



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

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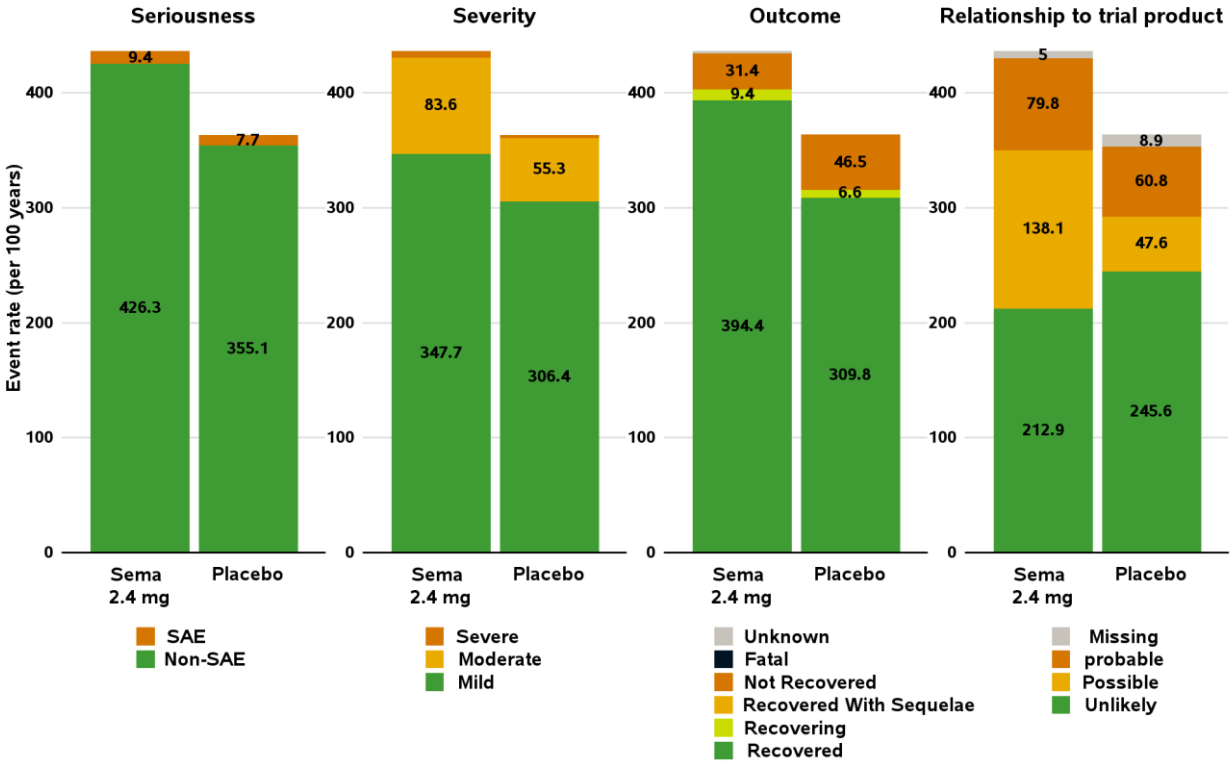
The relative distribution of AEs with respect to seriousness, severity and outcome were comparable across both groups, with most being non-serious, of mild or moderate severity, and reported as recovered.

A higher proportion of AEs in the semaglutide 2.4 mg group was considered probably or possibly related to the trial product compared with the placebo. This higher rate of attributing causality to the trial product in the semaglutide 2.4 mg group reflects the greater proportion of GI events in this group, as GI symptoms are a well-known side-effect of Glucagon-like peptide-1 receptor agonist (GLP-1 RA) treatment.

A higher proportion of subjects in the semaglutide 2.4 mg group compared to placebo reduced their dose (12.0% vs 1.5%) due to AEs. However, comparable proportions of subjects in both treatment groups temporarily interrupted treatment (10.5% vs 7.5%), or permanently discontinued treatment (4.5% vs 4.5%) due to AEs.

Figure Adverse events - overview plot - on-treatment



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. Event rate per 100 years based on patient years of exposure. Event rates <5.0 are shown in bar plots but numbers are not displayed.
MedDRA version 24.1

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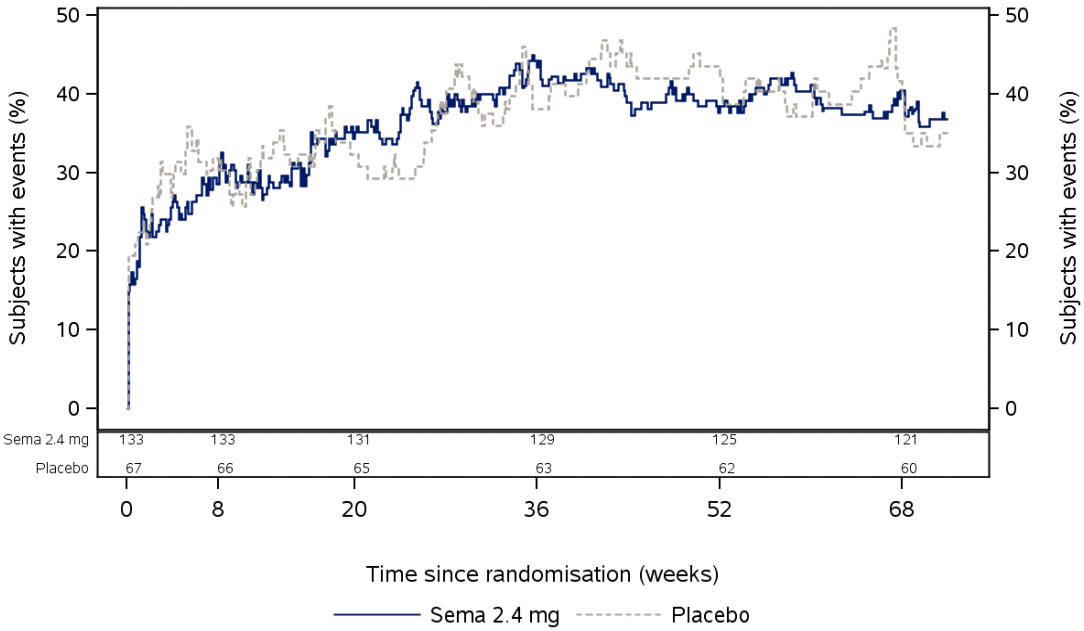
In both treatment groups, most AEs were reported within the first 20 weeks following randomisation, with comparably stable prevalence slopes for the remaining period of the study.

Figure Adverse events – prevalence plot – on-treatment – safety analysis set



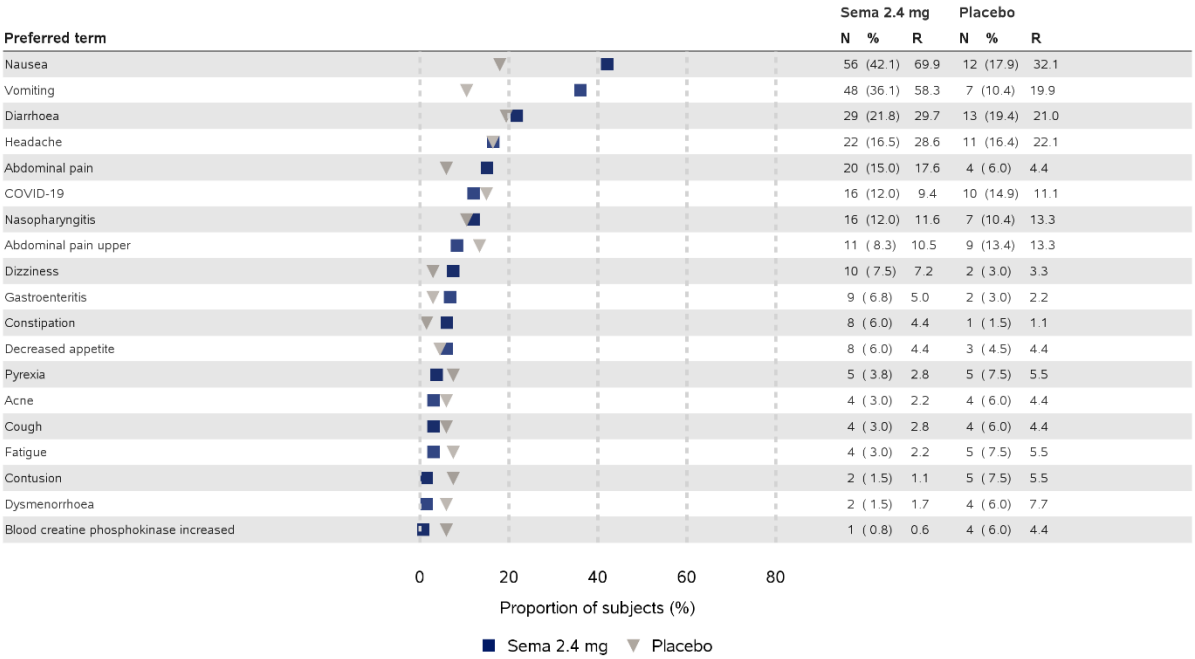
Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Lower panel: Number of subjects at risk.
MedDRA version 24.1

nn9536/nn9536-4451/ctr_20220603_er
03JUN2022:04:57:02 - faeprevalencetrt.sas/faeprevalot.png

Common adverse events

Greater proportions of subjects reported events of nausea and vomiting in the semaglutide 2.4 mg group than in the placebo group. Most of the common AEs were non-serious, of mild or moderate severity, and reported as recovered.

Figure Adverse events by preferred term - most frequent (>=5%) - summary plot - on-treatment



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

nn9536/nn9536-4451/ctr_20220603_er
03JUN2022:04:57:14 - faesummarysub.sas/faesummf5ptot.png

Serious adverse event/deaths/other significant events

Few (24) serious adverse events (SAEs) were reported during the on-treatment period, 17 in the semaglutide 2.4 mg group and 7 in the placebo group. Both the proportion of subjects with SAEs (11.3% vs 9.0%), and the rates of reporting SAEs (9.4 vs 7.7 events per 100 PYE) were comparable between semaglutide 2.4 mg and placebo. Most of the events, in both treatment groups, were moderate in severity, and the subjects recovered. The SAEs in both groups were distributed, in low numbers, across several preferred terms (PTs), with no evident patterning. In the semaglutide 2.4 mg group, there was a small concentration (5 events in 4 subjects) of SAEs in the system organ class (SOC) Hepatobiliary disorders, primarily related to events of cholelithiasis (see below).

No deaths were reported in this trial.

Other significant adverse events

Adverse events leading to withdrawal, discontinuation, and dose reductions

None of the 5 subjects, 2 in the semaglutide 2.4 mg group and 3 in the placebo group, who withdrew from the trial cited AEs as the reason for withdrawal.

Nine AEs led to permanent discontinuation of treatment, 6 in the semaglutide 2.4 mg group and 3 in placebo. The proportion of subjects (4.5%), and rates of reporting, were the same in both treatment groups. The AEs were distributed across a range of PTs, with 4 of the events (3 in the semaglutide 2.4 mg group and 1 in placebo) occurring in the GI disorders SOC.

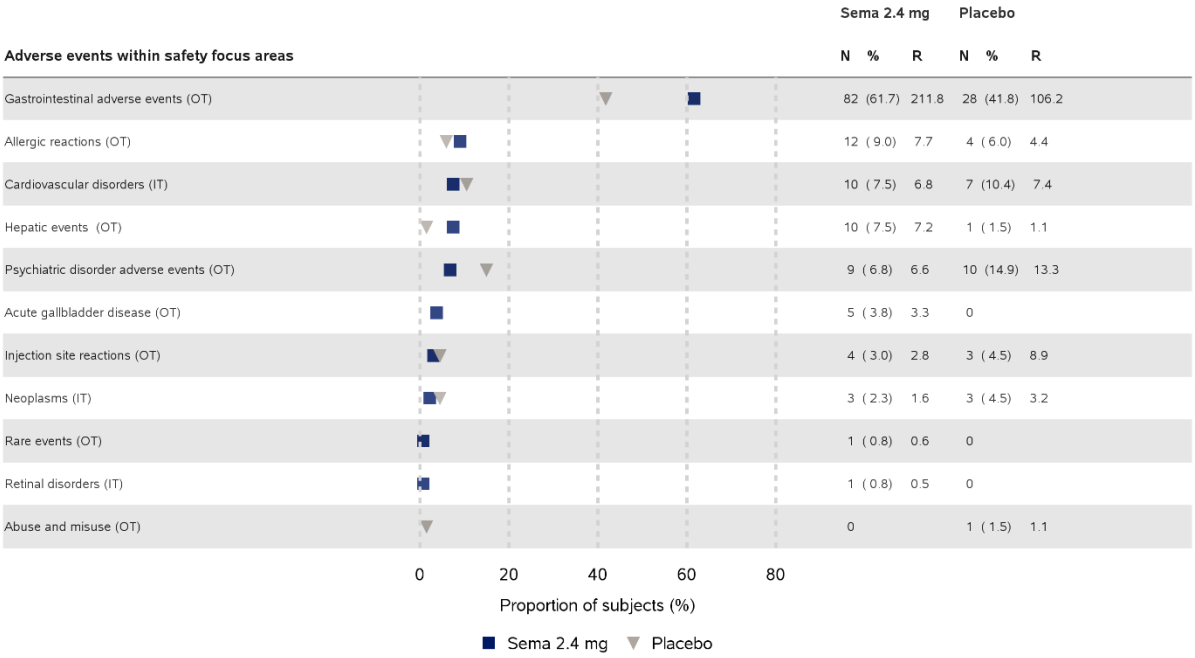
Comparable proportions of subjects in the semaglutide 2.4 mg group (10.5%) temporarily interrupted treatment with the trial product due to AEs compared to placebo (7.5%). Most of the events in both treatment groups occurred in the GI disorders SOC, led by vomiting, nausea, diarrhoea, and abdominal pain. Five AEs in 5 subjects (3.0%) in the semaglutide 2.4 mg group occurred in the Hepatobiliary disorders SOC.

Forty-six AEs, in 17 subjects led to dose reduction. All of the AEs leading to dose reduction occurred in the semaglutide 2.4 mg group, with the exception of 4 events in one subject in the placebo group. Most of the AEs in the semaglutide 2.4 mg group (29 events in 13 subjects) were related to GI disorders.

Safety focus areas

No events related to malignant neoplasms, acute pancreatitis, acute renal failure, diabetic retinopathy, medication errors, or suspected transmission of an infectious agent via trial product were reported .

Figure Safety focus areas - summary plot - safety analysis set



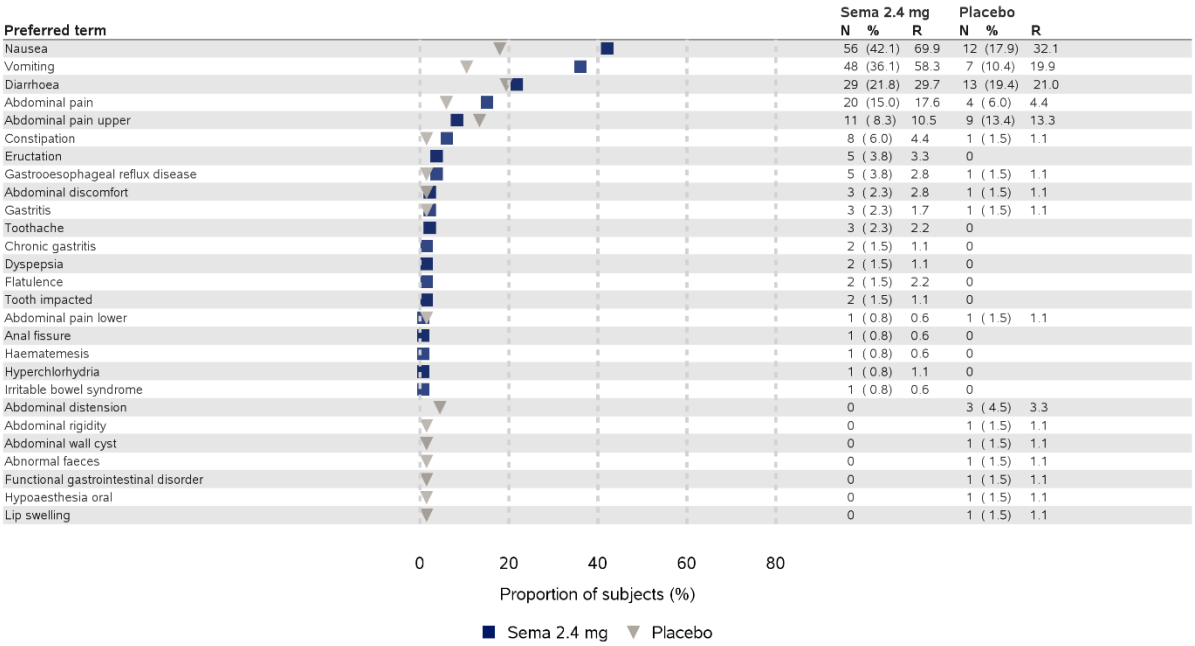
N: Number of subjects experiencing at least one event. %: Percentage of subjects experiencing at least one event. R: Event rate per 100 years. OT: On-treatment. IT: In-trial. Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product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

nn9536/nn9536-4451/ctr_20220603_er
03JUN2022:04:57:16 - faesummarysub.sas/faesummfocusot.png

Gastrointestinal disorders

GI disorders were reported by a higher proportion of subjects, and at a higher rate, in the semaglutide 2.4 mg group compared to placebo (61.7%, 211.8 events per 100 PYE vs 41.8%, 106.2 events per 100 PYE).

Figure Gastrointestinal adverse events - by preferred term – summary plot - on-treatment - safety analysis set



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

nn9536/nn9536-4451/ctr_20220603_er
03JUN2022:04:57:18 - faesummarysub.sas/faesumgiot.png

In both the semaglutide 2.4 mg and the placebo groups, the majority of GI AEs were non-serious, mild or moderate in severity, and had a median duration of 2-3 days. Comparable proportions of events in both groups led to permanent treatment discontinuation (2.3% semaglutide 2.4 mg: 1.5% placebo) and temporary interruption of the trial product (5.3% semaglutide 2.4 mg: 4.5% placebo). A greater proportion of GI AEs in the semaglutide group (9.8%) compared to placebo (1.5%) led to dose reduction.

Treatment differences between semaglutide 2.4 mg and placebo for the most frequently reported GI disorders were comparable to those seen in the adult semaglutide 2.4 mg development programme for weight management.

Hepatic disorders

A total of 14 hepatic AEs were reported: 13 events in 10 subjects in the semaglutide 2.4 mg group and one event in one subject in the placebo group. The proportion of subjects reporting events, and the event rate, were higher in the semaglutide 2.4 mg group (7.5%, 7.2 per 100 PYE) than with placebo (1.5%, 1.1 per 100 PYE). Notably, a greater proportion of subjects with pre-existing hepatic disorders were randomised to the semaglutide 2.4 mg group (18.7%, 25 subjects) than with placebo (11.9%, 8 subjects) and 4 of the AEs were reported at randomisation.

In STEP Teens, mean levels of ALT decreased -23% in the semaglutide 2.4 mg group as opposed to a 4% increase in the placebo group. Mean AST levels decreased -13% in the semaglutide 2.4 mg group and -4.0% in the placebo group. In the semaglutide 2.4 mg adult weight management program, mean levels of ALT (-26% vs -13%) and AST (-12% vs -4%) similarly decreased to a greater extent with semaglutide 2.4 mg compared to placebo. As in the adult programme, overall improvements in liver function in STEP Teens, as assessed by the mean levels of liver enzymes, supports the beneficial effect of weight loss on

liver function in the general population with overweight or obesity, with or without evidence of liver disease.

The higher proportion of AEs reported in subjects in the semaglutide 2.4 mg group in STEP Teens is likely related to both the greater proportion of subjects in the semaglutide 2.4 mg group with hepatic disorders in their medical histories than in the placebo group, and the reporting of events occurring at randomisation (prior to treatment) as AEs rather than medical history.

Acute gall bladder disease

Six events of acute gall bladder disease were reported in 5 subjects (3.8%) in the semaglutide 2.4 mg group, which will be included in the paediatric section of the label. One event in one subject (0.8%) of acute cholecystitis was co-reported with one of the events of cholelithiasis. No events of gall bladder disease were reported in the placebo group.

Obesity is a well-established risk factor for acute gall bladder disease, including the adolescent population. Additionally, rapid, marked weight loss, in both adults and children with obesity, has also been associated with gallstone development.

Cholelithiasis is an identified risk for semaglutide 2.4 mg and is included as an adverse drug reaction (ADR) in the labelling for Wegovy.

Psychiatric disorders

In addition to AE reporting, mental health questionnaires, the PHQ-9 and C-SSRS, were administered at randomisation, and then periodically during the trial.

The proportion of subjects reporting events related to psychiatric disorders, and the event rate, was lower in the semaglutide 2.4 mg group than the placebo group. The events in both groups were distributed across a broad range of PTs. Most of the events, in both treatment groups, were non-serious, mild to moderate in severity, unlikely related to trial product, and recovering or not recovered. One event, Mental disorder, in the placebo group led to permanent discontinuation of treatment. One event of suicidal ideation in the placebo group was reported as non-serious, moderate, unlikely related to treatment and recovered.

One SAE of Depression in the semaglutide 2.4 mg group was reported as severe, possibly related to trial product, and not recovered. The event occurred on trial day 493, so the action taken to product was, 'Not Applicable' (the subject was already off-treatment).

Total scores for the PHQ-9 for both treatment groups were comparable at randomisation. Responses to Question 9, which directly addresses levels of suicidality, were also comparable. At end of treatment (visit 30, week 68), there were no notable changes in either total scores, or responses to Question 9. Most subjects in both treatment groups remained in categories that do not indicate increased suicidality risk or depression.

Baseline C-SSRS total mean scores indicated a slightly lower proportion of subjects with suicidal ideation/behaviour in the semaglutide group than in the placebo group. At end of trial, there was a reduction overall in the scores indicating suicidal ideation/behaviour; however, there were no notable treatment differences between the groups.

Laboratory findings

No clinically relevant safety findings were identified in relation to haematology, biochemistry, hormones, lipids, or calcitonin.

At baseline, mean levels of ALT, AST and GGT were comparable across both treatment groups. Mean reductions of all three liver enzymes were greater in the semaglutide 2.4 mg group than in the placebo group. Individual elevations in liver enzymes exceeding pre-defined safety thresholds primarily occurred in subjects with pre-existing liver disorders.

Although there were greater increases in both amylase and lipase from baseline in the semaglutide 2.4 mg group compared to placebo, the mean values remained within normal reference ranges throughout the treatment period. Increases in amylase and lipase are consistent with the safety profile of semaglutide 2.4 mg in adult populations, where they were similarly not seen as predictive of acute pancreatitis.

From baseline to week 75, one (1) of the 133 subjects tested positive for anti-semaglutide antibodies at week 68. The subject's sample was negative at week 75, thus, the positive result was likely a transient antibody response. No subjects tested positive for either anti-semaglutide neutralising antibodies or anti-semaglutide antibodies cross-reacting with endogenous GLP-1.

Vital signs and other observations related to safety

Pulse and ECG

At baseline, mean pulse was comparable in both treatment groups. During the treatment period, the mean pulse was higher in the semaglutide 2.4 mg compared with the placebo group; however, at the end of the trial, mean pulse rates in both treatment groups returned to near baseline levels.

No clinically relevant treatment difference was noted between the treatment groups in ECGs.

Growth and development assessments

In addition to body measurement, growth and development were evaluated by assessing height SDS, bone age, bone metabolism biomarkers, Tanner pubertal stage, and pituitary-gonadal hormones. No clinically relevant treatment differences were noted in any of the growth and development parameters.

Hypoglycaemic events (T2D subjects)

Hypoglycaemic episodes in the T2D population of the trial were reported using 3 methods of event classification: ADA/ISPAD 2014, ADA/ISPAD 2018, and Novo Nordisk Classification.

In the semaglutide 2.4 mg group, there were 5 subjects with T2D. Two hypoglycaemic events were reported in 2 subjects. Neither event was reported as severe. One event was symptomatic however the blood glucose (BG) level was not reported, and the second event was asymptomatic with a BG level ≤ 3.9 mmol/L (70 mg/dL).

In the placebo group, there were 3 subjects with T2D. Four hypoglycaemic events were reported in 3 subjects. One of the events was reported as a BG confirmed symptomatic event (BG level < 3.1 mmol/L (56 mg/dL)). Two of the events were symptomatic with BG levels ≤ 3.9 mmol/L (70 mg/dL). One event was symptomatic with a BG level > 3.9 mmol/L (70 mg/dL).

2.6.1. Discussion on clinical safety

Of the 201 subjects randomised 2:1 to treatment, 200 were exposed to the trial product: 133 subjects in the semaglutide 2.4 mg group (181.8 PYE, 192.0 PYO); 67 subjects in the placebo group (90.4 PYE, 94.0 PYO).

Overall, 89.6% completed treatment and 97.5% of subjects completed the trial. Comparable proportions of subjects in both treatment groups completed treatment (89.6% for both treatment groups) and completed the trial (98.5% semaglutide 2.4 mg group; 95.5% placebo group).

Adverse events

The proportion of subjects with AEs, was comparable between the treatment groups (78.9% in semaglutide 2.4 mg vs 82.1% in placebo). The rate of AEs reported was higher with semaglutide 2.4 mg than with placebo (435.7 events per 100 PYE in semaglutide 2.4 mg vs 362.9 events per 100 PYE in placebo). As expected, this was driven primarily by GI AEs.

In both treatment groups, most AEs were reported within the first 20 weeks following randomisation. Few (24) SAEs were reported during the on-treatment period, 17 in the semaglutide 2.4 mg group and 7 in the placebo group.

Serious adverse events

Both the proportion of subjects with SAEs (11.3% vs 9.0%), and the rates of reporting SAEs (9.4 vs 7.7 events per 100 PYE) were comparable between semaglutide 2.4 mg and placebo. Most of the events, in both treatment groups, were moderate in severity, and the subjects recovered.

GI adverse events

GI disorders were reported by a higher proportion of subjects, and at a higher rate, in the semaglutide 2.4 mg group compared to placebo (61.7%, 211.8 events per 100 PYE vs 41.8%, 106.2 events per 100 PYE). In both the semaglutide 2.4 mg and the placebo groups, the majority of GI AEs were non-serious, mild or moderate in severity, and had a median duration of 2-3 days. Comparable proportions of events in both groups led to permanent treatment discontinuation (2.3% semaglutide 2.4 mg: 1.5% placebo) and temporary interruption of trial product (5.3% semaglutide 2.4 mg: 4.5% placebo). A greater proportion of GI AEs in the semaglutide group (9.8%) compared to placebo (1.5%) led to dose reduction.

Hepatic adverse events

A total of 14 hepatic AEs were reported: 13 events in 10 subjects in the semaglutide 2.4 mg group and one event in one subject in the placebo group. The proportion of subjects reporting events, and the event rate, were higher in the semaglutide 2.4 mg group (7.5%, 7.2 per 100 PYE) than with placebo (1.5%, 1.1 per 100 PYE). Notably, a greater proportion of subjects with pre-existing hepatic disorders were randomised to the semaglutide 2.4 mg group (18.7%, 25 subjects) than with placebo (11.9%, 8 subjects) and 4 of the AEs were reported at randomisation.

In STEP Teens, mean levels of ALT decreased -23% in the semaglutide 2.4 mg group as opposed to a 4% increase in the placebo group. Mean AST levels decreased -13% in the semaglutide 2.4 mg group and -4.0% in the placebo group.

The higher proportion of hepatic AEs reported in subjects in the semaglutide 2.4 mg group in STEP Teens is maybe partly related to the greater proportion of subjects in the semaglutide 2.4 mg group with hepatic disorders in their medical histories than in the placebo group. In addition, there is an overall mean improvement in liver enzyme levels in subjects randomised to semaglutide 2.4 mg. In combination with the clinical and non-clinical evidence from both the adult semaglutide 2.4 mg programmes and the

GLP-1 RA drug class, there are no hepatic safety concerns related to the treatment with semaglutide 2.4 mg in the adolescent population.

Gall bladder

Six events of acute gall bladder disease were reported in 5 subjects (3.8%) in the semaglutide 2.4 mg group, and 0% patients treated with placebo, which is included in the paediatric section of the label. It should be noted that the frequency is numerically higher than what has been observed in the adult studies 3.8% in children and 1.6% in adults.

Other significant adverse events

Mental health questionnaires (the PHQ-9 and C-SSRS) showed no relevant differences between semaglutide and placebo.

No clinically relevant safety findings were identified in relation to haematology, biochemistry, hormones, lipids, or calcitonin. Although there were greater increases in both amylase and lipase from baseline in the semaglutide 2.4 mg group compared to placebo, the mean values remained within normal reference ranges throughout the treatment period. Increases in amylase and lipase are consistent with the safety profile of semaglutide 2.4 mg in adult populations, where they were similarly not seen as predictive of acute pancreatitis.

During the treatment period, mean pulse was higher in the semaglutide 2.4 mg compared with the placebo group. This is similar to the increase in pulse in adults.

There were no clinically relevant effects of semaglutide on hypoglycaemia in patients with diabetes.

In addition to body measurement, growth and development were evaluated by assessing height SDS, bone age, bone metabolism biomarkers, Tanner pubertal stage, and pituitary-gonadal hormones. No clinically relevant treatment differences were noted in any of the growth and development parameters.

2.6.2. Conclusions on clinical safety

In general, the safety and tolerability data from STEP Teens are comparable with the safety profile established in the adult clinical development programmes with semaglutide 2.4 mg and other GLP 1 RAs.

As expected, the most frequently reported AEs with semaglutide 2.4 mg in adolescent subjects were GI-related AEs. The higher incidence of cholelithiasis in populations with obesity, and rapid, significant weight loss is well known and is included in the appropriate sections of the product information.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.1 is acceptable.

Safety concerns

Summary of safety concerns	
Important identified risks	• Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer
Missing information	• Pregnancy and lactation • Patients with severe hepatic impairment

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk) **– semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM**				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk) **– semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM**				
None				
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA) **– semaglutide s.c. for T2D, oral semaglutide for T2D and semaglutide s.c. 2.4 mg for WM**				
MTC-22341 Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace.	Medullary thyroid cancer	**Semaglutide s.c. for T2D**	
			Submitted protocol	January 2019
			Final report	May 2035
			Oral semaglutide for T2D	
			Submitted protocol	November 2020
			Final report	February 2037
			Semaglutide s.c. 2.4 mg for WM	
			Submitted protocol	TBD
			Final report	TBD
		Pancreatic cancer	**Semaglutide s.c. for T2D**	
			Adopted protocol	20 Sep 2018

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes Ongoing	The study will evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D. (Results from the study will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for weight management)		Final report	**March 2026** ~~October 2025~~
			Oral semaglutide for T2D	
			Adopted protocol	12 Nov 2020
			Final report	**March 2026** ~~October 2025~~
NN9535-4352 Long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes (FOCUS). Ongoing	The study will assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy (Results from the trial will also be relevant for the ongoing evaluation of the risk for oral semaglutide for T2D and semaglutide s.c. 2.4 mg for weight management in patients with T2D.)	Diabetic retinopathy complications (only for patients with T2D)	**Semaglutide s.c. for T2D**	
			Adopted protocol	19 Nov 2018
			Final report	February 2028

Risk minimisation measures (semaglutide s.c. 2.4 mg for weight management)

Safety concern	Risk minimisation measures
Important identified risk Diabetic retinopathy complications (only for patients with T2D)	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. *Additional risk minimisation measures:* None
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None
Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Nonclinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None
Missing information: Pregnancy and lactation	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None
Missing information: Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None

3.1. Update of the Product information (PI)

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

Please refer to Attachment 1 which includes all agreed changes.

3.1.1. User consultation

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

- The changes to the patient leaflet are not considered significant
- A user consultation was made for semaglutide during the marketing authorisation application approved in 2022
- A user consultation was made for the additional pen-presentation (PDS290) approved in 2022.

4. Benefit-Risk Balance

4.1. Therapeutic Context

Semaglutide s.c. 2.4 mg once weekly (Wegovy) has been approved as an adjunct to a reduced-calorie diet and increased physical activity for weight management. This variation application aims at extending the current Wegovy label with results from STEP Teens demonstrating the efficacy and safety of semaglutide 2.4 mg in an adolescent population (ages 12 to <18 years) with obesity or with overweight and at least one weight-related comorbidity.

4.1.1. Disease or condition

The prevalence of obesity in children and adolescents has been increasing steadily during the past decades and has reached alarming proportions. It is expected that more than 250 million children and adolescents worldwide will be living with obesity by 2030.

4.1.2. Available therapies and unmet medical need

Pharmacotherapy may serve as a valuable adjunct to lifestyle modification for children and adolescents with obesity or overweight.

4.1.3. Main clinical studies

Semaglutide s.c. 2.4 mg once weekly (Wegovy) has been approved as an adjunct to a reduced calorie diet and increased physical activity for weight management, including weight loss and weight maintenance in adults with obesity (BMI ≥30 kg/m2) or overweight (BMI ≥27 kg/m2) and at least one weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or T2D). This variation application aims at extending the current Wegovy indication based on the results from STEP Teens demonstrating the efficacy and safety of semaglutide 2.4 mg in an adolescent population.

This trial (STEP Teens) was a 68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide 2.4 mg once weekly in adolescents with obesity (BMI corresponding to ≥95th percentile*) or with overweight (BMI corresponding to ≥85th percentile*) and at least one weight-related comorbidity.

According to regulatory guidelines, the trial included a run-in period of 12 weeks of non-pharmacological lifestyle intervention before randomisation. Lifestyle intervention consisted of diet and physical activity counselling for weight loss and continued throughout the trial.

Primary objective and endpoints

The primary objective was to compare the effect of semaglutide s.c. once-weekly versus semaglutide placebo as an adjunct to a reduced calorie diet and increased physical activity on weight management in adolescents (ages 12 to <18 years) with overweight or obesity.

Primary endpoint:

Change in BMI from baseline (week 0) to week 68 (%).

Confirmatory secondary endpoint:

Subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68 (yes/no).

The use of the treatment policy estimand as the primary estimand is acceptable.

For subjects with T2D only, uncontrolled and potentially unstable diabetic retinopathy or maculopathy was an exclusion criterion. This is clearly stated in the product information.

The trial enrolled 201 adolescent subjects (ages 12 to <18 years) with obesity or with overweight and at least one weight-related comorbidity. Subjects were randomised 2:1 to receive either semaglutide 2.4 mg or placebo.

The proportions of treatment completers (subjects on treatment at week 68) and trial completers (subjects who attended the end-of-trial visit) were similar between the semaglutide 2.4 mg and placebo groups (89.6%).

Permanent discontinuation of trial product due to AEs was reported by 4.5% of subjects with semaglutide 2.4 mg vs 6.0% with placebo.

Overall, the demographic and baseline characteristics were well-balanced between the semaglutide 2.4 mg and placebo groups, although baseline BMI and body weight were higher in the semaglutide 2.4 mg group (37.7 vs 35.7 kg/m2; 109.9 vs 102.6 kg).

4.2. Favourable effects

Effects on BMI and weight

The estimated change from baseline in BMI (%) at week 68 was -16.14% with semaglutide 2.4 mg and 0.61% with placebo. With semaglutide 2.4 mg, 72.5% of subjects achieved ≥5% weight loss vs 17.7% with placebo. The ETDs for change in body weight were in favour of semaglutide 2.4 mg vs placebo: -17.73 kg (95% CI -21.76; -13.70) and -17.42% (95% CI -21.08; -13.75).

Other endpoints

For subjects without T2D at baseline, the estimated mean change in HbA1c from baseline to week 68 was 0.35 % points with semaglutide 2.4 mg compared to -0.14 % points with placebo, with a statistically significant ETD in favour of semaglutide 2.4 mg (0.22 % points [0.29; 0.14]).

For subjects with T2D at baseline (n=8), HbA1c decreased -1.0 %-point in the semaglutide 2.4 mg group (n=5), whereas the change was 0.3 %-point in the placebo group (n=3), but the groups were very small.

A minor decrease in SBP and DBP were seen in both groups, with no statistically significant difference between the groups.

For all the individual domain scores, improvements in individual scores were seen with semaglutide 2.4 mg compared to placebo. The ETDs for the physical comfort score and the total score were statistically significant in favour of semaglutide 2.4 mg vs placebo.

4.3. Uncertainties and limitations about favourable effects

On average, body weight loss was clinically relevant, but 27.5% of the patients treated with semaglutide had a weight loss of less than 5%. Almost 10% of the patients did not have a decrease in BMI or an increase. Other weight loss products such as Saxenda, Mysimba and Xenical have stopping rules included in the indication. For adolescents using Saxenda, treatment should be discontinued and re-evaluated if adolescents have not lost at least 4% of their BMI or BMI z score after 12 weeks on the maximum tolerated dose. For Wegovy, a stopping rule could not be defined in the adult population. In STEP 4, using a week 20 weight loss criterion of 5% for a stopping rule, it was demonstrated that a high proportion of early non-responders went on to achieve a clinically relevant weight loss by week 68. Among week 20

early non-responders, 51.6% of subjects randomised to continued semaglutide 2.4 mg treatment achieved a clinically significant weight loss by week 68. This is an important and relevant adult subgroup that would have been erroneously discontinued from treatment based on this stopping rule. The company also did early responder analyses for other percentages of early weight loss. Even if an early weight loss criterion of 1% was used, 47% of the adult early non-responders went on to achieve clinically relevant weight loss by week 68.

The company investigated a possible stopping rule for adolescents. The Applicant has provided data on various levels of BMI change at day 28, which is a BMI ≥ 3%, BMI ≥4 % and BMI ≥5 %.

4: Proportion of subjects achieving at least 5% BMI reduction at week 68 by week 28 BMI reduction (at least 3% to 5%) - summary - in-trial - full analysis set - Sema 2.4 mg arm

	Total N (%)	Week 28 responders N (%)	Week 28 non-responders N (%)
BMI reduction >=5% in-trial			
Sema 2.4 mg			
BMI reduction >=3% at week 28			
Total	122 (100)	106 (100)	16 (100)
Week 68 responders	94 (77.0)	91 (85.8)	3 (18.8)
Week 68 non-responders	28 (23.0)	15 (14.2)	13 (81.3)
BMI reduction >=4% at week 28			
Total	122 (100)	98 (100)	24 (100)
Week 68 responders	94 (77.0)	88 (89.8)	6 (25.0)
Week 68 non-responders	28 (23.0)	10 (10.2)	18 (75.0)
BMI reduction >=5% at week 28			
Total	122 (100)	93 (100)	29 (100)
Week 68 responders	94 (77.0)	86 (92.5)	8 (27.6)
Week 68 non-responders	28 (23.0)	7 (7.5)	21 (72.4)

BMI: Body mass index, N: Number of subjects, %: Percentages are based on total number of subjects with an observation at week 68 and an available on-treatment BMI at week 28.
Observed data from in-trial period.

nn9536/nn9536-exploratory/qaus016_20221212_er
14DEC2022:14:39:21 - tearlyresp.sas/tearlyresp.txt

With a stopping rule of BMI reduction of at least 5%, the positive predictive value is 86/93 (92%) and the negative predictive value is 21/29 (72%). In other words, 8% (7/93) of the initial responders continued treatment without a significant weight loss at study end, whereas 27.6% (8/29) of the initial non-responders had significant weight loss at study end. With a lower threshold, the positive predictive value decreases (91/106 =86% with a threshold of ≥3%) and the negative predictive value increases (13/16= 81% with a threshold of ≥3%). In other words, with a threshold of ≥3%, 14% (15/106) of the initial responders continued treatment without a significant weight loss at the study end, whereas 19% (3/16) of the initial non-responders had significant weight loss at the study end. It is considered very important to avoid the treatment of subjects who will not benefit from treatment. Therefore, the positive predictive value should be high. The lowest proportion of misclassified subjects (false responders and false non-responders) is seen with a threshold of ≥5%, where 7 subjects are misclassified as responders and 8 subjects are misclassified as non-responders. Hence, based on the data provided by the Applicant, it is suggested that a stopping rule of ≥ 5% should be added to the SmPC. The company first proposed a stopping rule stating that treatment should be re-evaluated if adolescent patients have not reduced their BMI by at least 5%. This proposed stopping rule did not contain the recommendation to discontinue treatment. Following the outcome of the CHMP assessment, the finally agreed stopping rule now states that treatment should be discontinued and re-evaluated if weight loss is not sufficient. This is in line with the stopping rule for Saxenda in paedicatric individuals

There is only experience with Wegovy in individuals with a body weight >60 kg. This is similar to the experience with Saxenda. The indication of Saxenda, therefore, states that Saxenda is only indicated for adolescents with a body weight above 60 kg. This lower bound of body weight is now included in the indication of Wegovy.

The number of overweight subjects included in the study could not be found in the clinical study report (CSR) and related documents. The company acknowledged that only one subject was within the overweight with comorbidities category at baseline. As only one subject was within the overweight with

comorbidities category at baseline, the benefit/risk ratio cannot be determined. Therefore, an indication in overweight adolescents with comorbidities is not acceptable. The final agreed indication is worded accordingly.

It was doubtful whether the submitted growth charts were well suited to determine the exact BMI that corresponds to overweight or obesity for a given age. The graphs were small and difficult to read. Now, tables are used instead of graphs.

Fourteen out of 15 subjects not ending on the maximum semaglutide dose had a relevant weight loss, and one subject had an increase in bodyweight (increase in 6.6%). The reduction in BMI ranges from 14.9% to 41.1%. Nine of the 15 subjects reached the maximum dose of 2.4 mg and thereafter decreased the dose stepwise to 1.7 mg, 1.0 mg or 0.5 mg. Based on those data no minimum dose should be stated in the SmPC.

Beneficial effects of semaglutide 2.4 mg vs placebo were observed for all lipid parameters from baseline to week 68. The estimated treatment ratios (ETRs) were statistically significant in favour of semaglutide 2.4 mg for total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides. However, the estimates were not multiplicity adjusted; hence, the beneficial findings in terms of ETRs are regarded as exploratory only.

4.4. Unfavourable effects

Of the 201 subjects randomised 2:1 to treatment, 200 were exposed to the trial product: 133 subjects in the semaglutide 2.4 mg group (181.8 PYE, 192.0 PYO); 67 subjects in the placebo group (90.4 PYE, 94.0 PYO).

Overall, 89.6% completed treatment and 97.5% of subjects completed the trial. Comparable proportions of subjects in both treatment groups completed treatment (89.6% for both treatment groups) and completed the trial (98.5% semaglutide 2.4 mg group; 95.5% placebo group).

Adverse events

The proportion of subjects with AEs, was comparable between the treatment groups (78.9% in semaglutide 2.4 mg vs 82.1% in placebo). The rate of AEs reported was higher with semaglutide 2.4 mg than with placebo (435.7 events per 100 PYE in semaglutide 2.4 mg vs 362.9 events per 100 PYE in placebo). As expected, this was driven primarily by GI AEs.

In both treatment groups, most AEs were reported within the first 20 weeks following randomisation. Few (24) SAEs were reported during the on-treatment period, 17 in the semaglutide 2.4 mg group and 7 in the placebo group.

Serious adverse events

Both the proportion of subjects with SAEs (11.3% vs 9.0%), and the rates of reporting SAEs (9.4 vs 7.7 events per 100 PYE) were comparable between semaglutide 2.4 mg and placebo. Most of the events, in both treatment groups, were moderate in severity, and the subjects recovered.

GI adverse events

GI disorders were reported by a higher proportion of subjects, and at a higher rate, in the semaglutide 2.4 mg group compared to placebo (61.7%, 211.8 events per 100 PYE vs 41.8%, 106.2 events per 100 PYE). In both the semaglutide 2.4 mg and the placebo groups, the majority of GI AEs were non-serious, mild or moderate in severity, and had a median duration of 2-3 days. Comparable proportions of events in both groups led to permanent treatment discontinuation (2.3% semaglutide 2.4 mg: 1.5% placebo)

and temporary interruption of trial product (5.3% semaglutide 2.4 mg: 4.5% placebo). A greater proportion of GI AEs in the semaglutide group (9.8%) compared to placebo (1.5%) led to dose reduction.

Gall bladder

Six events of acute gall bladder disease were reported in 5 subjects (3.8%) in the semaglutide 2.4 mg group, which is included in the paediatric section of the label. It should be noted that the frequency is numerically higher than what has been observed in adult studies, 3.8% in children and 1.6% in adults.

Other significant adverse events

Mental health questionnaires (the PHQ-9 and C-SSRS) showed no relevant differences between semaglutide and placebo.

No clinically relevant safety findings were identified in relation to haematology, biochemistry, hormones, lipids, or calcitonin. Although there were greater increases in both amylase and lipase from baseline in the semaglutide 2.4 mg group compared to placebo, the mean values remained within normal reference ranges throughout the treatment period. Increases in amylase and lipase are consistent with the safety profile of semaglutide 2.4 mg in adult populations, where they were similarly not seen as predictive of acute pancreatitis.

During the treatment period, the mean pulse was higher in the semaglutide 2.4 mg compared with the placebo group. This is similar to the increase in pulse in adults.

There were no clinically relevant effects of semaglutide on hypoglycaemia in patients with diabetes.

In addition to body measurement, growth and development were evaluated by assessing height SDS, bone age, bone metabolism biomarkers, Tanner pubertal stage, and pituitary-gonadal hormones. No clinically relevant treatment differences were noted in any of the growth and development parameters.

4.5. Uncertainties and limitations about unfavourable effects

Hepatic adverse events

A total of 14 hepatic AEs were reported: 13 events in 10 subjects in the semaglutide 2.4 mg group and one event in one subject in the placebo group. The proportion of subjects reporting events, and the event rate, were higher in the semaglutide 2.4 mg group (7.5%, 7.2 per 100 PYE) than with placebo (1.5%, 1.1 per 100 PYE). Notably, a greater proportion of subjects with pre-existing hepatic disorders were randomised to the semaglutide 2.4 mg group (18.7%, 25 subjects) than with placebo (11.9%, 8 subjects) and 4 of the AEs were reported at randomisation.

In STEP Teens, mean levels of ALT decreased -23% in the semaglutide 2.4 mg group as opposed to a 4% increase in the placebo group. Mean AST levels decreased -13% in the semaglutide 2.4 mg group and -4.0% in the placebo group. This was a supportive secondary end point.

The higher proportion of hepatic AEs reported in subjects in the semaglutide 2.4 mg group in STEP Teens is maybe partly related to the greater proportion of subjects in the semaglutide 2.4 mg group with hepatic disorders in their medical histories than in the placebo group.

In addition, there is an overall mean improvement in liver enzyme levels in subjects randomised to semaglutide 2.4 mg. In combination with the clinical and non-clinical evidence from both the adult semaglutide 2.4 mg programmes and the GLP-1 RA drug class, there are no hepatic safety concerns related to the treatment with semaglutide 2.4 mg in the adolescent population.

4.6. Effects Table

Effects Table for Semaglutide 2.4 mg: STEP Teens

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Change in BMI		%	-16.14%	0.61%	ETD of -16.75 %-points [-20.27; -13.23]95% CI BMI-SDS not primary endpoint?	STEP Teens
Subjects achieved ⩾5% weight loss		%	72.5%	17.7%		
Change in body weight		kg	-15.34 kg	2.39 kg	ETD: -17.73 kg[-21.76;-13.70]95% CI	
Unfavourable Effects						
Subjects with AEs		%	78.9%	82.1%		STEP Teens
SAEs		%	11.3%	9.0%		
GI disorders		%	61.7%	41.8%		
Hepatic adverse events		%	7.5%	1.5%		
Events of acute gall bladder disease		%	3.8%	0%		

Abbreviations: Abbreviations: AE, adverse event; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; GI, gastrointestinal; SAE, serious adverse event; SDS, standard deviation score

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The effect of semaglutide on body weight management in adolescents was clinically relevant. However, a large proportion of patients (27.5%) did not reach relevant body weight loss. In order to prevent unnecessary long-term treatment of this subgroup of young individuals, a stopping rule in adolescents of 5% is included as requested. With the 5% cut-off value, the lowest proportion of misclassified subjects (false responders and false non-responders) is observed, where 7 subjects are misclassified as responders and 8 subjects are misclassified as non-responders. It could be argued that a higher threshold could achieve a higher yield, but it is a threshold that is generally accepted in the professional domain.

As only one subject was within the overweight with comorbidities category at baseline, a positive benefit/risk could not be established in overweight subjects. Therefore, an indication in overweight adolescents with comorbidities is not acceptable. This is in line with the adolescent indication for Saxenda (liraglutide). Overweight adolescents with comorbidities were not included in the clinical trial with liraglutide, and liraglutide does not have an indication for overweight adolescents with comorbidities.

In general, the safety and tolerability data from STEP Teens are comparable with the safety profile established in the adult clinical development programmes with semaglutide 2.4 mg and other GLP 1 RAs.

As expected, the most frequently reported AEs with semaglutide 2.4 mg in adolescent subjects were GI-related AEs. The higher incidence of cholelithiasis in populations with obesity and rapid, significant weight loss is well known and is included in the appropriate sections of the product information.

4.7.2. Balance of benefits and risks

In general, the effect of semaglutide on body weight management in teens was clinically relevant. The safety and tolerability data from STEP Teens are comparable with the safety profile established in the adult clinical development programmes with semaglutide 2.4 mg and other GLP 1 RAs.

A large proportion of patients (27.5%) did not reach relevant body weight loss. Based on the data provided by the Applicant, inclusion of a stopping rule of 5% in the SmPC is warranted and is now implemented in the SmPC. In addition, as only one subject was within the overweight with comorbidities category at baseline, an indication in overweight adolescents with comorbidities is not acceptable and the indication has been worded accordingly.

The benefit-risk balance is positive.

4.7.3. Additional considerations on the benefit-risk balance

4.8. Conclusions

The overall benefit-risk balance of Wegovy is positive.

5. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescents for weight management based on the final results from study NN9536-4451; this trial was conducted to assess the efficacy and safety of semaglutide in paediatric patients of age 12 to <18 years with obesity. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP was agreed during the procedure. Furthermore, the PI is brought in line with the latest QRD template version 10.2.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

6. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Wegovy-H-C-005422-II-0009'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 30 March 2023.