Office of Clinical Pharmacology Review

NDA or BLA Number	NDA215256 (SDN221)
Link to EDR	\\CDSESUB1\evsprod\NDA215256\0217
Submission Date	06/29/2022
Submission Type	Efficacy supplement (S-005)
Brand Name	Wegovy
Generic Name	Semaglutide
Dosage Form and Strength	Pre-filled, single-dose pen that delivers doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg
Route of Administration	Subcutaneous (SC) Injection
Proposed Indication	Adjunct to a reduced calorie diet and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with an initial BMI at the: • 95th percentile or greater for age and sex (obesity) (b) (4) (b) (4) [redacted]
Applicant	Novo Nordisk Inc.
Associated INDs	IND126360, IND114464
OCP Review Team	Mohamed Ismail Nounou, *Ph.D.* (Clin. Pharm.), Edwin C.Y. Chow, *Ph.D.* (TL, Clin. Pharm.), Elyes Dahmane, *Ph.D.* (PM) & Justin C. Earp, *Ph.D.* (TL, PM)
OCP Final Signatory	Jayabharathi Vaidyanathan, *Ph.D.*

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1. EXECUTIVE SUMMARY

Semaglutide is a long-acting analog of human glucagon-like peptide-1 (GLP-1). It was approved in 2021 as an adjunct treatment to reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition. The recommended dosage is to initiate SC dose of 0.25 mg once weekly for 4 weeks, followed by multiple dose increment increases up to 2.4 mg at 4-weeks intervals. The drug product is supplied as a solution in a pre-filled, disposable, single-patient-use, single dose pen-injector. June 4, 2021 NDA approval letter for NDA 215256, Wegovy® (semaglutide) injection included a post-marketing requirement PMR 4081-1 to "Complete the ongoing 68-week randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of semaglutide for the treatment of obesity in pediatric patients ages 12 to less than 18" On July 26, 2021, a pediatric Written Request – Amendment 1 for semaglutide included the requirements for "Study 2: Efficacy and safety of semaglutide on weight management in adolescents with overweight or obesity." In this supplement 005, Novo Nordisk is hereby submitting the results from the adolescent clinical trial, STEP TEENS (NN9536-4451) in support of a label update.

In this efficacy supplement (S-005), Novo Nordisk Inc. (applicant) submitted clinical efficacy and safety data in Study NN9536-4451 (STEP TEENS) to fulfill the PMR and support the following indication.

Adjunct to a reduced calorie diet and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with an initial BMI at the:

- 95th percentile or greater for age and sex (obesity) (b) (4)

(b) (4)

The proposed dosing regimen of semaglutide used in Study 4451 is the same as that used in the previous adult trial (Study 4373) in the original NDA submission. However, Study 4451 allowed pediatric patients to reduce the dose < 2.4 mg in the event of adverse events related to tolerability. The clinical pharmacology review focused on the dose selection, pharmacometrics analyses, and dose modification in Study 4451 and determine whether the proposed dosing recommendation is appropriate in the target pediatric population.

Based on the results from Study 4451, the Applicant has fulfilled all requirement for PMR 4081-1 from a clinical pharmacology perspective. The results from the study in this submission are updated to the currently approved package insert.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed information submitted in sNDA 215256 (S-005) and recommends approval from a clinical pharmacology perspective. Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	In Study 4451 (STEP TEENS), mean BMI (%) change from baseline to week 68 was -16.1% with semaglutide 2.4 mg compared to 0.6% with placebo. Greater proportions of subjects achieved ≥5% (72.5%), ≥10% (61.8%), ≥15 (53.4%) and ≥20% (37.4%) body weight reduction with semaglutide 2.4 mg compared to placebo (17.7%, 8.1%, 4.8% and 3.2%, respectively). Greater improvements in weight category, from a higher obesity class to a lower obesity class or to overweight or normal weight, was seen with semaglutide 2.4 mg vs placebo (Odds Ratio (OR) = 14.66). The safety and tolerability data from Study 4451 are comparable with the safety profile established in the adult clinical development program with semaglutide 2.4 mg. The most common adverse event (AE) was gastrointestinal AEs. There were no new or unexpected safety observations.
General dosing instructions	The therapeutic and maintenance dose is 2.4 mg once weekly. Dose-escalation is used to mitigate gastrointestinal (GI) adverse event (AE). The starting SC dose is 0.25 mg and then following a dose escalation regimen with dose increment increases every 4 weeks (to doses of 0.5, 1.0, and 1.7 mg once weekly) until 2.4 mg once weekly is reached. be administered subcutaneously into the abdomen, thigh or upper arm with change of the injection sites.
Dosing in patient subgroups (intrinsic and extrinsic factors)	In adolescents aged 12 years and older (12-18 years of age) with an initial BMI at the 95th percentile or greater for age and sex (obesity) (b) (4) , dose can be decreased to 1.7 mg weekly if patients do not tolerate the maintenance 2.4 mg dose. This is different from adult population dosing. If adult (>18 years old) patients do not tolerate the maintenance 2.4 mg once-weekly dose, the dose can be temporarily decreased to 1.7 mg once-weekly, for a maximum of 4 weeks. After 4 weeks, WEGOVY can be increased to the maintenance 2.4 mg once weekly. WEGOVY is discontinued if the adult patient cannot tolerate the 2.4 mg dose. In cased of adolescents aged 12 years and older (12-18 years of age) not tolerating the 2.4 mg, the patient may stay at a 1.7 mg weekly.

Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label (b) (4). Clinical pharmacology labeling recommendations are detailed in Section 2.4. Immunogenicity data (b) (4) was moved to Section 12.6, in concordance with FDA guidance "Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format", published in Feb 2022.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Semaglutide is a long-acting GLP-1 receptor agonist (GLP-1 RA), which consists of human GLP-1 analog, C18 fatty di-acid and a hydrophilic spacer. Semaglutide has a long half-life (i.e., 155 hours) supporting once weekly injection. Semaglutide has a prolonged plasma half-life as compared to endogenous GLP-1 due to the increased stability of GLP-1 against DPP-4 enzyme with amino acid substitution from endogenous GLP-1 and increased protein binding from both the fatty acid side chain and spacer.

Pooled PK data from the adult (Study 4373) and pediatric (Study 4451) study was used to conduct population pharmacokinetic (PK) analyses (See Appendix for FDA assessment). The results showed that exposure was inversely correlated with body weight. Age (≥ 12 years) is not associated to clinically relevant change in semaglutide exposure C_{avg}. Other covariates such as sex, race, ethnicity, and glycemic status had no effects on semaglutide concentrations C_{avg}. The estimates for apparent clearance and exposure (CL/F and C_{avg}) were comparable between adolescent and adult subjects with obesity. The exposure levels (C_{avg}, average steady state semaglutide concentrations) 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. Hence, it is expected that adolescent patients (aged 12 to <18 years) with obesity will have a similar exposure as adults with obesity.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The therapeutic and maintenance dose is 2.4 mg once weekly, starting with 0.25 mg once weekly and then following a dose escalation regimen with dose increases every 4 weeks (to doses of 0.5, 1.0, and 1.7 mg once weekly) till 2.4 mg once weekly is reached.

2.2.2 Therapeutic individualization

No separate dose/dosing regimen is recommended in adolescent patients. Dose-escalation was used to mitigate GI AEs (e.g., nausea and/or vomiting), based on the Phase 2 dose-finding information, and prior experience from semaglutide for T2DM and GLP-1 RA drug class. The dose can be decreased to 1.7 mg weekly if patients do not tolerate the maintenance 2.4 mg dose.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The Applicant is proposing a dosage for pediatrics in section 2.3 as follows:

Pediatric Patients

• Patients should aim at reaching the maintenance 2.4 mg once-weekly dose following the dose escalation schedule in Table 2.

• If patients cannot reach the 2.4 mg dose or do not tolerate 2.4 mg, the patient may stay at a lower dose level.

Reviewer's comment: Based on FDA's pharmacometrics analyses (See ***Appendix 4.1***), FDA recommends, if patients cannot reach the 2.4 mg dose or do not tolerate 2.4 mg, the patient may stay 1.7 mg dose. If patients do not tolerate the maintenance 2.4 mg once-weekly dose, the dose can be decreased to 1.7 mg once-weekly. Discontinue WEGOVY® if the patient cannot tolerate the 1.7 mg dose.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1. Overview of the Product and Regulatory Background Relevant to The Current Submission

Semaglutide has been approved for T2DM as follows:

• Once weekly SC administration (NDA 209637 for Ozempic®) on December 5, 2015, with the starting dose of 0.25 mg and then increasing to 0.5 mg once weekly after 4 weeks of 0.25 mg dosing and further to 1 mg once weekly if additional glycemic control is needed after 4 weeks on 0.5 mg dose.

• Once daily oral administration (NDA 213051 for Rybelsus®) on September 20, 2019, with the starting dose of 3 mg once daily and then increase to 7 mg once daily after 30 days of 3 mg dosing and further to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.

NDA 215256 consisted of two Phase 1 trials (Trial 4590 for the pivotal PK bridge and Trial 4455 for gastric emptying assessment), one Phase 2 trial (Trial 4135 for dose-finding), two Phase 3 trials (Trial 4373 to support weight management and Trial 4374 to support weight management in T2DM), and population analysis on PK and exposure-response analyses for efficacy and safety.

NDA 215256, Wegovy® (semaglutide) injection was approved on June 4, 2021, as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

On June 4, 2021, the NDA approval letter included a post-marketing requirement 4081-1 to "Complete the ongoing 68-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of semaglutide for the treatment of obesity in pediatric patients ages 12 to less than 18". On July 26, 2021, in a pediatric Written Request – Amendment 1 for Semaglutide, "Study 2: Efficacy and safety of semaglutide on weight management in adolescents with overweight or obesity." was issued. Subsequently, the sponsor submitted the clinical results from the adolescent clinical trial, STEP TEENS (NN9536-4451) in this efficacy supplement to fulfill PMR 4081-1 from the June 4, 2021, NDA 215256 approval letter and to support label update for adolescent patients.

3.2. General Pharmacology and Pharmacokinetic Characteristics

Please refer to the Clinical Pharmacology review of the original NDA (215256) by ***Dr. Sang Chung*** **in DARRTS (dated 05/21/2021) for complete details of previous human experience in adults.**

3.3 Clinical Pharmacology Review Questions

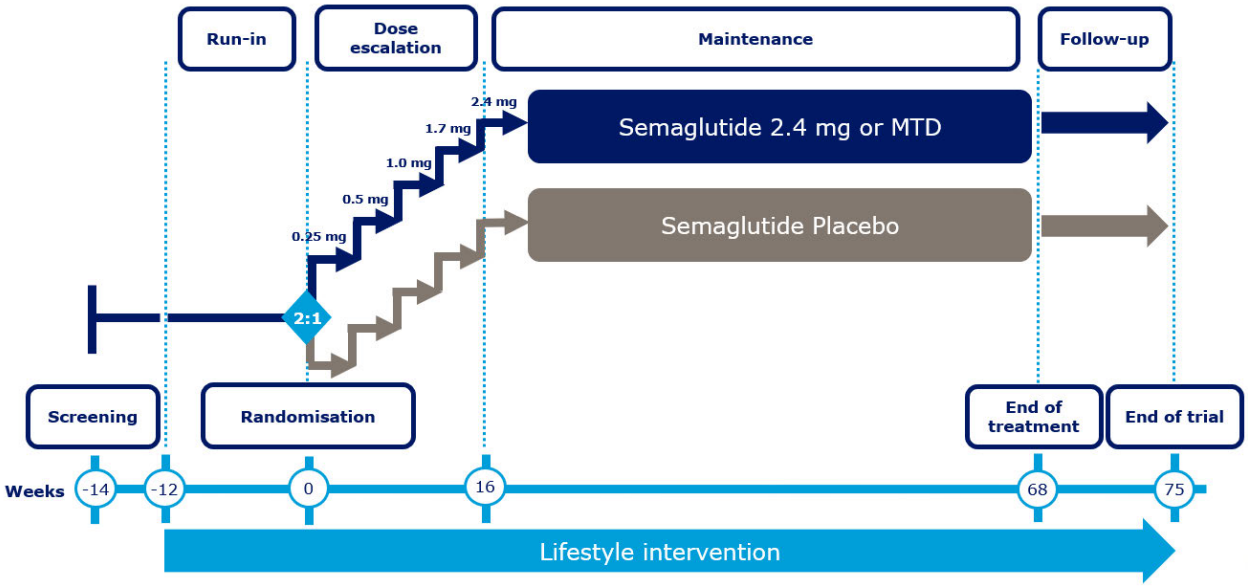
3.3.1 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the adolescent patient population (aged 12 to <18 years) based on the clinical trial STEP TEENS (NN9536-4451) results. The Applicant's population PK and exposure-response analyses support the semaglutide SC 2.4 mg once weekly for weight management in adolescents aged 12-18 years of age. The population PK and exposure-response 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 data from study has been previously submitted to the NDA).

The NN9536–4451 (STEP TEENS) trial was conducted to assess the effectiveness and safety of semaglutide for treatment of adolescents ages 12 to <18 years with obesity. The primary objective was to compare the effect of semaglutide SC 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. The primary endpoint was change in BMI from baseline (week 0) to week 68 (%). The secondary endpoint was subjects achieving ≥5% reduction of body weight from baseline (week 0) to week 68.

This trial was a multinational, multi-center, randomized, 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. The trial design is outlined in **Figure 1**.

Figure 1: Trial design



Source: Clinical Trial Report, Module 5.3.5.1. NN9536-4451, Sequence 217

The trial included a screening visit to assess the subject's eligibility. Subjects fulfilling the eligibility criteria commenced with a 12-week non-pharmacological lifestyle intervention run-in period before randomization. The lifestyle intervention consisted of diet and physical activity counselling and continued throughout the trial until 'end of trial' (week 75). Subjects, who fulfilled the randomization criteria, were randomized 2:1 to receive either semaglutide s.c. once weekly or semaglutide placebo s.c. once weekly for a dose escalation period of 16 weeks and a maintenance period of 52 weeks. This was followed by a 7-week follow-up period after 'end of treatment' due to the long half-life of semaglutide. Approximately 237 subjects were planned to be screened to achieve 213 subjects to be included in the run-in period to reach the anticipated 192 subjects randomly assigned to trial product.

The population PK analyses, comparing exposure for adolescent subjects in STEP Teens and adult subjects in STEP 1, appeared to show that the major clinically relevant influence on exposure (C_{avg}) was body weight (See Appendix for FDA's assessment). Age does not appear to have any clinically relevant changes to semaglutide exposure. At week 68, the exposure-response relationship for efficacy appeared slightly steeper in adolescents compared to adults; however, there was a large overlap in exposure and response in adolescents and adults, with no statistically significant difference is slope between the STEP TEENS and STEP 1 trial (p value=0.11) according to the FDA assessment. The Applicant's model-based analyses, reviewed by the FDA, supports the use of the same dose escalating scheme with semaglutide 2.4 mg as target dose for adolescents as in adults, without the need for dose adjustment based on age or body weight. Decreases in BMI with increasing semaglutide exposure were observed in both adults (STEP 1) and adolescents (STEP Teens).

The Applicant proposes the following semaglutide SC dosage for pediatric patients (aged 12 to <18 years):

- Patients should aim at reaching the maintenance 2.4 mg once-weekly dose following the dose escalation schedule in **Table 1**.

Table 1: Dose escalation scheme

Weeks	**Weekly Dose**	
1 through 4	0.25 mg	Dose escalation
5 through 8	0.5 mg	
9 through 12	1 mg	
13 through 16	1.7 mg	
Week 17 and onward	2.4 mg	Maintenance dose

If patients do not tolerate the maintenance 2.4 mg once-weekly dosage, the maintenance dosage may be reduced to 1.7 mg daily. WEGOVY should be discontinued if the patient cannot tolerate the 1.7 mg dose. The sponsor did not specify the lower dose in down-titration scheme if WEGOVY is not tolerated.

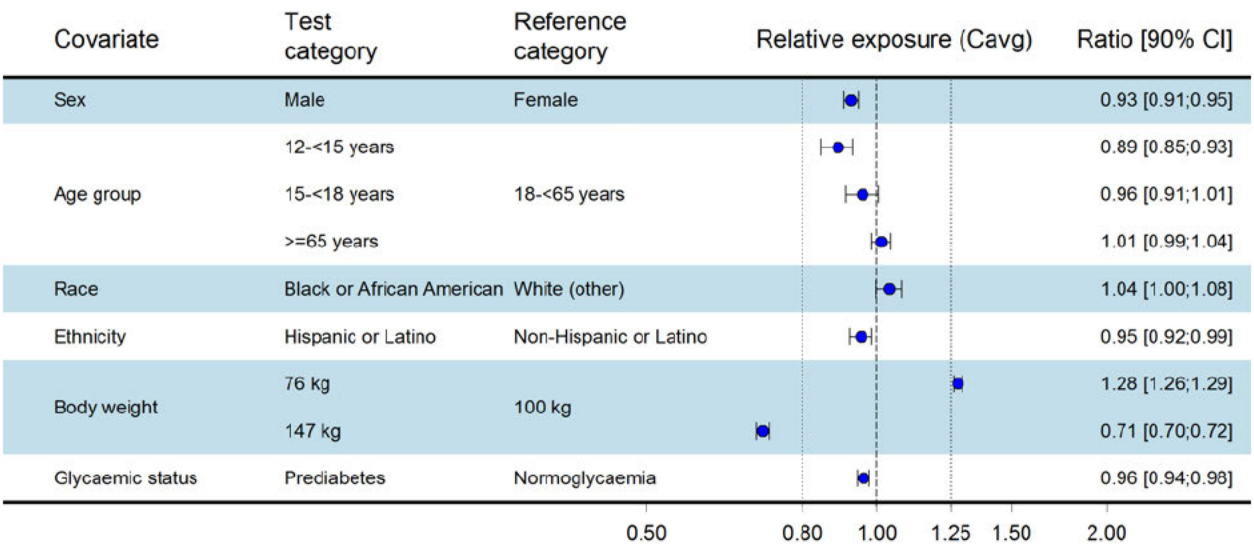
The proposed pediatric dose reduction plan is different than the that for adult patients in which the drug is discontinued for adult patients who cannot tolerated the 2.4 mg dose.

3.3.2 Is the SC maintenance dose of 2.4 mg once weekly acceptable based on exposure-response relationship in the pediatric population?

Yes. Exposure-response relationship in pediatric population supports the proposed dosing regimen. The Pharmacometrics modeling report (PopPK and E-R report, Module 5.3.3.5) presents the population PK and exposure-response analyses of semaglutide SC 2.4 mg once weekly for weight management in adolescents to support regulatory evaluation of this population and to support the dose selection in children (aged 6 to <12 years). The population PK and exposure-response 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 exposure of semaglutide (C_{avg}) was similar in adolescents and adults with respect to BMI (**Figure 4**). Consistent with adults (STEP 1), analysis of adolescents (STEP TEENS) showed that the most important covariate for exposure is body weight. Moreover, age does not appear to have clinically relevant change in semaglutide exposure with a ratio (90%CI) of 0.89 (0.85, 0.93) between adolescents and adults (**Figure 2**).

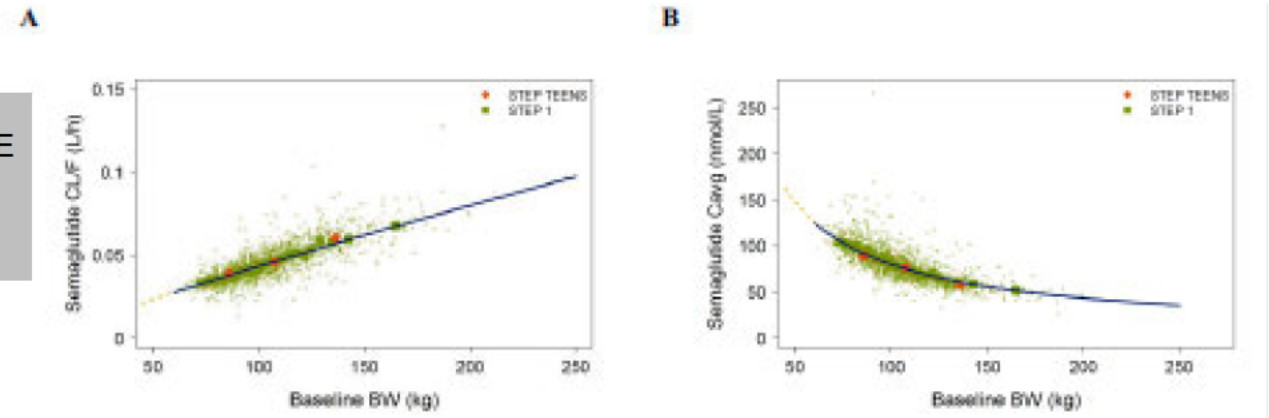
Figure 2: Forest plot of covariate effects for semaglutide exposure



Source: PopPK and E-R report, Figure 1-1, Module 5.3.3.5, Sequence 217

Adolescent and adult trials enrolled subjects down to 60 kg and therefore only a minor part of the body weight (BW) range was extrapolated (as indicated by the dotted yellow line). From **Figure 3**, it can be observed that at similar baseline BWs similar semaglutide exposure levels are expected in adults, adolescents and children for the 2.4 mg dose.

Figure 3: Apparent clearance (CL/F) (A) and semaglutide exposure for the 2.4 mg dose (B) versus baseline body weight stratified by trial

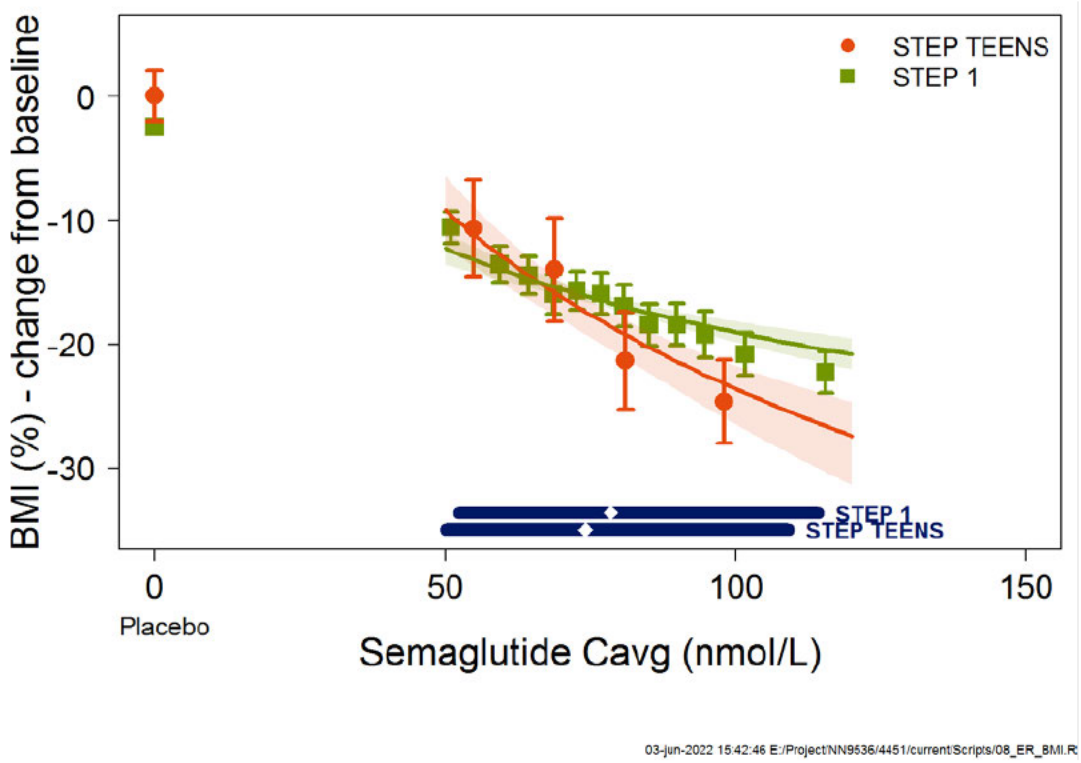


Data are model derived individual apparent clearance (CL/F) or average semaglutide concentrations (Cavg) versus baseline body weight (small symbols) and geometric mean estimates versus body weight or age presented in quantiles by trial (large symbols).

Source: PopPK and E-R report, Figure 1-2, Module 5.3.3.5, Sequence 217

An increasing improvement in BMI with increasing semaglutide exposure in adolescents (STEP TEENS) was observed (**Figure 4**) at Week 68. The exposure-response relationship was comparable in adolescents and adults, with a large overlap in exposure and response between the two populations (see FDA assessment in section 4.1.2.3).

Figure 4: Percent change in BMI from baseline versus semaglutide exposure by trial at week 68

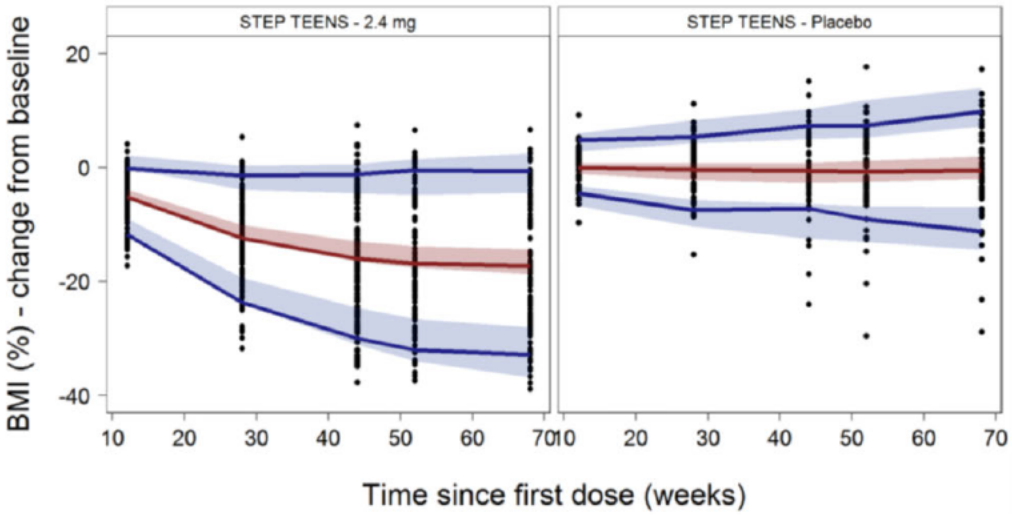


Source: PopPK and E-R report, Figure 1-3, Module 5.3.3.5, Sequence 217

In this analysis, the $C_{average}$ did not correspond to the actual maintenance doses at week 68. The Applicant analysis did not account for dose reductions or actual maintenance dose at week 68.

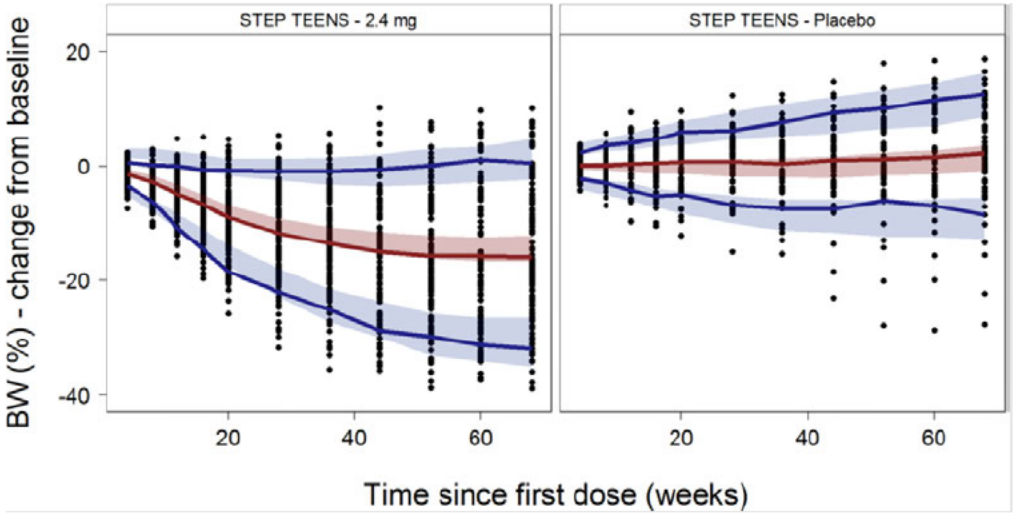
Reanalyzing the longitudinal weight-loss model appropriately described the observed data from STEP-TEENS study (as well as STEP 1 study, **Figures 5 and 6**).

Figure 5: Predicted BMI (%) change from baseline versus placebo (data are observed (lines) and simulated (Shaded area, n=500) medians and 10th and 90th weight loss percentiles after the first dose).



Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Figures 2-3 and 2-6, pages 8 and 12.

Figure 6: Predicted Body Weight BW (%) change from baseline versus placebo (data are observed (lines) and simulated (Shaded area, n=500) medians and 10th and 90th weight loss percentiles after the first dose).



Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Figures 2-3 and 2-6, pages 8 and 12.

Table 2: Model-predicted average percent change from baseline in BMI by dose for males and females in STEP TEENS population (FDA analysis)

Maintenance Dose	Mean (95%CI) %CFB in ***BMI*** ***Female***	Mean (95%CI) %CFB in ***BMI*** ***Male***
Placebo	-0.181(-1.56 - 1.11)	-0.209(-1.85 - 1.66)
0.25 mg	-4.92(-7.31 - -2.11)	-2.83(-5.53 - 0.0921)
0.5 mg	-7.8(-10.4 - -5.25)	**-4.76**(-7.78 - -1.51)
1 mg	**-12.2(-15.2 - -9.23)**	-7.56(-10.9 - **-4.32**)
1.7 mg	-16.3(-19.4 - -13.2)	-10.1(-14.5 - -6.71)
2.4 mg	-19.1(-22.2 - -15.8)	-12.3(-16.3 - -8.37)

Source: FDA's assessment (**Appendix 4.1**)

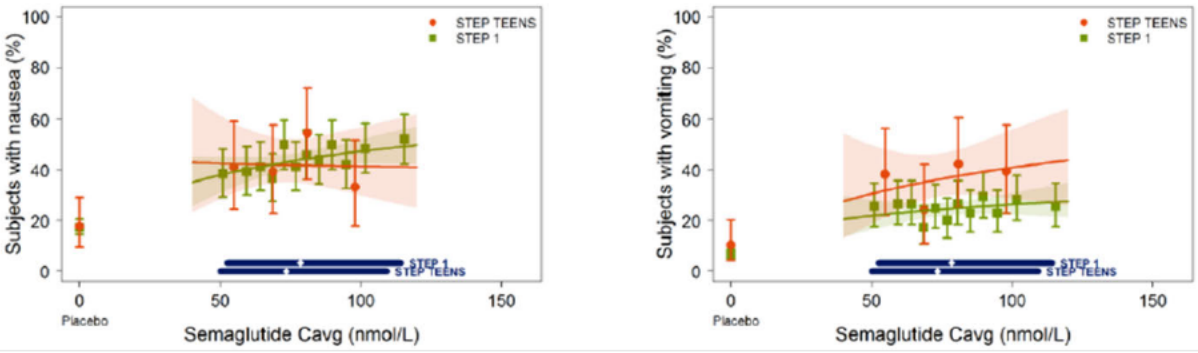
Reanalyzing the sponsor's data, the model-prediction % change in BMI based on pediatric virtual populations (population simulations, 500 replicates of STEP TEENS demographics) in the 1 mg dose level was -4.32% in males. Based on the longitudinal model predictions, a reduced maintenance of 1.7 mg once-weekly is predicted to maintain efficacy (with a minimum of 5% decrease in BMI) in all patients. However, when considering the difference in response between male and female, male subjects are predicted to derive less benefit from a 1 mg maintenance dose compared to female, with the lower bound of the 95% CI for the mean PCFB (percent change from baseline) in BMI of -4.5%. In comparison, a maintenance dose of 1.7 mg is predicted to provide a mean reduction in BMI of at least 5%, regardless of patients' sex. (b) (4) This analysis supports the 1.7 mg dose for down-titration (b) (4).

3.3.3 Is the safety profile of proposed dosing regimen for pediatric comparable to the adult population?

Yes, based on the safety data collected in the trial, semaglutide 2.4 mg administered once weekly, as an adjunct to a reduced-calorie diet and increased physical activity, was well tolerated in the target population of adolescents with obesity. No new or unexpected findings were reported. Overall, the safety profile of semaglutide 2.4 mg resembles that of GLP-1 RA class.

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 patient years of exposure (PYE) in semaglutide 2.4 mg vs 362.9 events per 100 PYE in placebo), driven primarily by gastrointestinal AEs. 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.

Figure 7: Proportion of subjects reporting nausea (A) and vomiting (B) of any severity versus semaglutide exposure stratified by trial

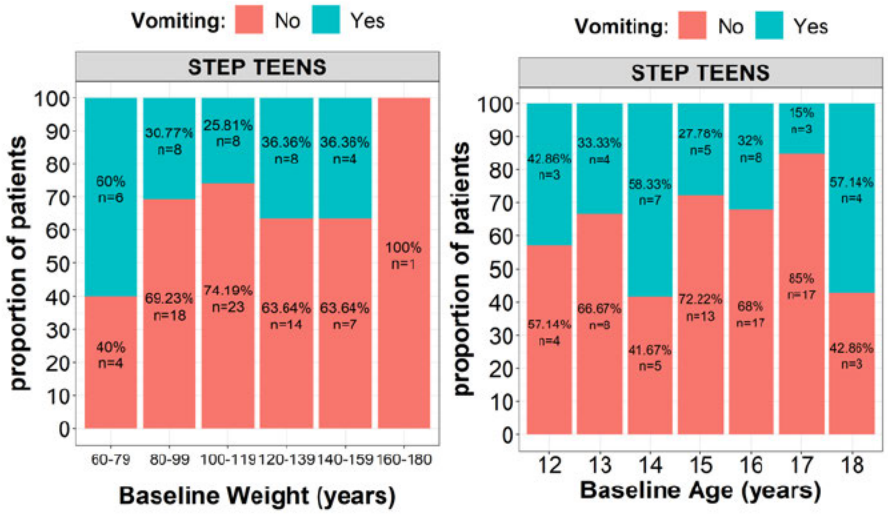


Source: PopPK and E-R report, Figure 1-4, Module 5.3.3.5, Sequence 217

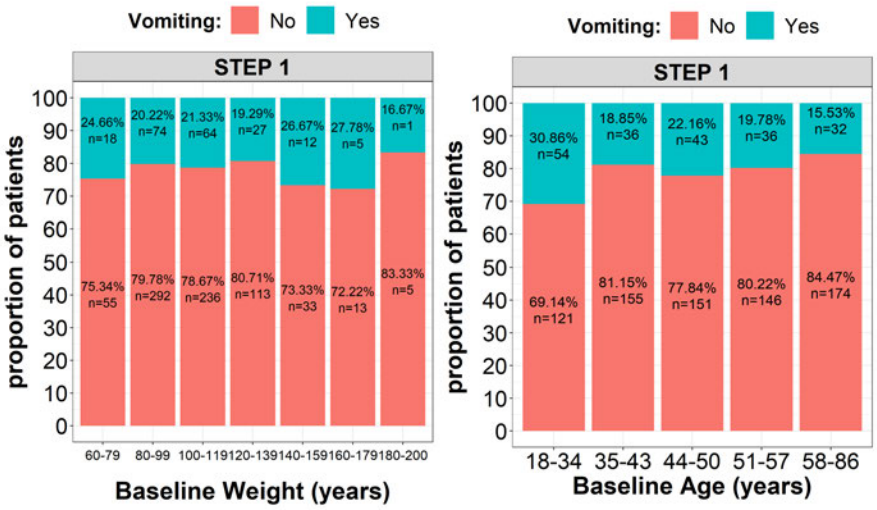
The exposure-response relationship for the proportion of subjects reporting nausea was comparable in adults and adolescents (**Figure 7**). In adults, there was a trend of higher proportion of nausea with increasing exposure that was not found to be statistically significant, according to the Applicant analysis (Applicant's Pharmacometrics Modelling Report, Table 9-10, *page 56*, with 95%CI of the STEP1: slope parameter included zero). There was no apparent exposure-response relationship in adolescents. The proportion of subjects reporting vomiting of any severity during treatment increased to a minor extent with semaglutide exposure with the trend being similar in both populations (**Figure 7**). At similar exposure levels, higher proportions of subjects reporting vomiting was observed in STEP TEENS compared to STEP 1. **Figure 8** shows, no clear trend for effect of age or weight on vomiting was observed.

Figure 8: Proportion of subjects reporting vomiting in STEP TEENS (A) and STEP 1 (B) with respect to age groups and baseline weight groups of any severity

(A)



(B)



Source: FDA's assessment **(Appendix 4.1)**

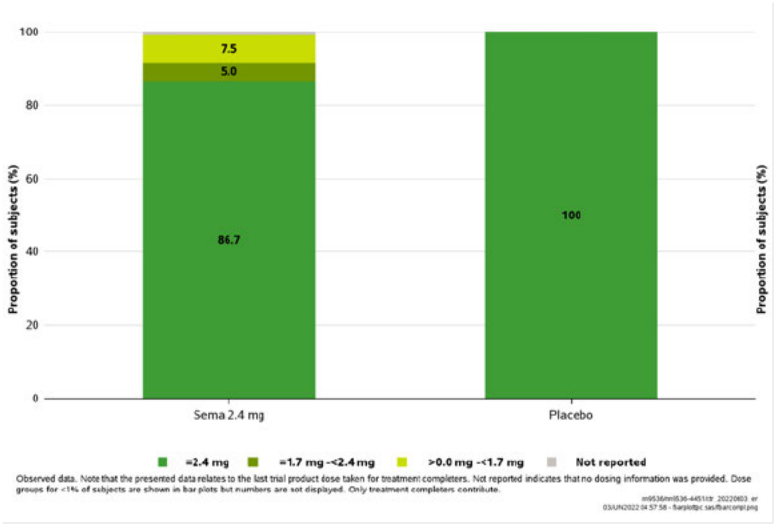
Higher exposure appears to have higher reduction in BMI, but also increases the risk of GI AEs. See clinical review on risk-benefit assessment. The model-based analyses support the use of the same dose regimen and 2.4 mg as target dose as in adults for adolescents.

3.3.4 What are the key study highlights and results from pediatric population in study NN9536-4451?

The NN9536–4451 (STEP Teens) trial was conducted to assess the effect and safety of semaglutide in the pediatric population ages 12 to <18 years with obesity. The trial design is outlined in **Figure 1**. A summary of the study methodology is mentioned under section 3.3.1.

Dose escalation occurred comparably in both treatment groups to week 16. At week 28, a slightly lower proportion of subjects in the semaglutide 2.4 mg group (90.2%) were at the target dose of 2.4 mg than the placebo group (98.4%). Most subjects in both treatment groups remained at target dose through the remainder of the trial (week 68). Based on the last doses of subjects completing treatment, 86.7% of subjects in the semaglutide group were on 2.4 mg of semaglutide, and 100% of placebo subjects reached the equivalent volume of placebo (**Figure 9**).

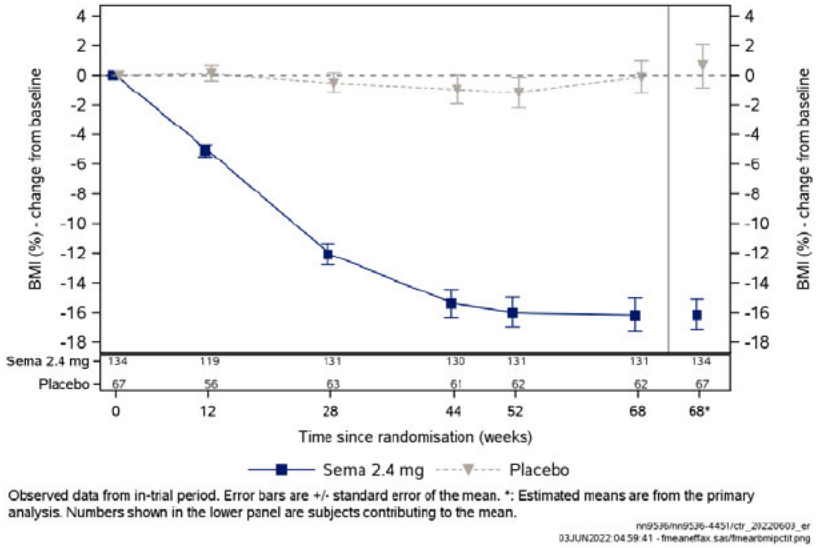
Figure 9: Last dose for treatment completers - bar plot - in-trial - full analysis set



Source: Clinical Trial Report, Module 5.3.5.1. NN9536-4451, Sequence 217

The BMI (%) change from baseline occurred during the first 52 weeks with semaglutide 2.4 mg treatment after which a plateau was reached (**Figure 10**). With placebo, mean BMI (%) change from baseline was very limited and the BMI remained close to the baseline level throughout the trial (**Figure 10**).

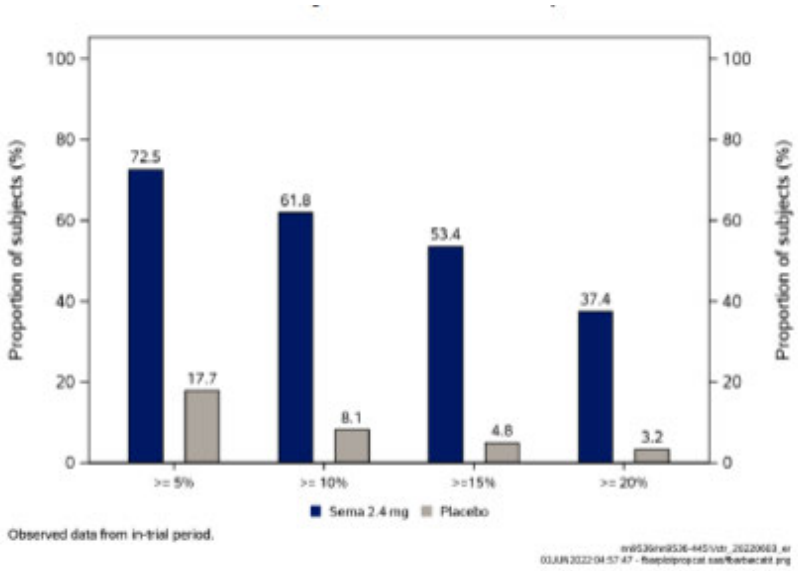
Figure 10: BMI (%) change from baseline by week - mean plot - treatment policy estimand - full analysis set



Source: Clinical Trial Report, Module 5.3.5.1. NN9536-4451, Sequence 217

At week 68, the observed proportion of subjects achieving a weight loss of ≥10%, ≥15%, or ≥20% were also greater with semaglutide 2.4 mg compared to placebo (**Figure 11**).

Figure 11: Proportion of subjects achieving body weight loss response criteria since baseline at week 68 - bar plot - in-trial - full analysis set



Source: Clinical Trial Report, Module 5.3.5.1. NN9536-4451, Sequence 217

Single blood samples for measuring plasma concentration of semaglutide were drawn for both semaglutide and placebo subjects at specific visits, as specified in the protocol. The dual purpose of measuring plasma semaglutide levels was for population PK analyses and to assess the level of drug interference in the anti-semaglutide antibody analyses. Subjects were instructed to withhold trial product until blood sampling had been performed. The population PK analysis is reported in the modelling report. Results related to the prespecified PK endpoints are summarized in **Section 3.3**.

As reported by the applicant for STEP TEENS, from baseline to week 75, one (1) of the 133 subjects tested positive for anti-drug antibody at week 68. The subject's sample was negative at week 75. No subjects tested positive for either anti-semaglutide neutralizing antibodies or anti-semaglutide antibodies cross-reacting with endogenous GLP-1 (*Clinical Trial Report, Module 5.3.5.1. NN9536-4451, Sequence 217, Table 14.3.5.17, Page 1013*). The data are consistent with STEP 1-2 studies. For STEP 1-2 studies, the proportion for subjects with positive anti-drug antibody (ADA) at any time post-baseline was 2.9% (N=50) in STEP 1-2, and approximately half of positive ADA measures was transient. Neutralizing antibody cross-reacting with endogenous GLP-1 (NAb) was 1.6% for Semaglutide treatment arm. In general, ADA and NAb detection rates are low and its impact on PK was not significant as concluded in Clinical Pharmacology review of the original NDA (215256) by *Dr. Sang Chung* in DARRTS (dated 05/21/2021).

4. APPENDIX

4.1. Pharmacometrics Review

The Applicant's population pharmacokinetic (PK) and longitudinal exposure-response analyses are considered acceptable for 1) describing semaglutide average exposure under different maintenances doses, 2) for capturing the effect of different semaglutide maintenance doses, as well as 3) capturing the placebo effect (diet and exercise), on the body weight and BMI reduction over time. Therefore, the developed PK and pharmacodynamic (PD) models were considered acceptable for performing simulations (within the studied dose range) and PD predictions to support semaglutide labeling and reduced dosage in case of lack of tolerability in adolescents. More specifically, the developed longitudinal weight and BMI loss model was utilized to support the current submission as outlined below:

Table 4.1.1. Utility of the Population PK Modeling

Utility of the final model		**Reviewer's Comments**
Derive exposure metrics and PK parameters	• The PK model was used to characterize the PK of semaglutide under a once-weekly subcutaneous (SC) dosing regimen in adults (STEP 1 trial) and adolescents (STEP TEENS trial). • The PK model was used to identify and quantify the effect of various covariates on semaglutide exposure, where body weight (BW) was found to be the was the most clinically relevant covariate on semaglutide exposure. • The PK model was used to derive the individual PK parameters and predict the average semaglutide concentrations (C_{avg}) under different dosage,	• No dose adjustment is needed based on body weight or age in adolescents, as comparable semaglutide exposure was observed between adults and adolescent at different weight groups.

	used to support the exposure-response analyses.	
Exposure-response **Analyses to support labeling**	• The final PK model was used to predict the semaglutide C_{avg} used in the sequential PK-PD modeling for the following models: The longitudinal BW and BMI loss model, the exposure-BMI reduction analysis at Week 68, and logistic regression models to assess the relationship between semaglutide exposure and nausea or vomiting (of any severity).	• The longitudinal BW and BMI loss model was considered acceptable to perform simulations and predict the percent change from baseline (PCFB) in BW and particularly in PCFB in BMI (primary endpoint). • Based on the longitudinal model predictions, a reduced maintenance of 1.7 mg once-weekly is predicted to maintain efficacy (with a minimum of 5% decrease in BMI) in all patients, if patients cannot reach the 2.4 mg dose or do not tolerate 2.4 mg. (b) (4) [redacted] • No significant relationship was found between semaglutide C_{avg} and the proportion of subjects developing nausea or vomiting of any severity.

The current pharmacometrics review evaluates the following:

a. The adequacy of the PK model in describing semaglutide PK in adults (STEP 1 trial) and adolescents (STEP TEENS) and predict semaglutide exposure.

b. The adequacy of the sequential longitudinal exposure-BW and -BMI loss model in describing the effect of semaglutide doses on BMI reduction, and the reliability of the model to perform simulations and predict the ability of reduced semaglutide maintenance doses to maintain efficacy (minimum of 5% decrease in BMI).

c. Relationship between semaglutide exposure and the occurrence of nausea or vomiting of any severity.

4.1.1 Applicant's Population PK Analysis

The population PK (popPK) analysis was based on PK data from 2 phase 3a trials: the STEP 1 trial in adults (NN9536-4373) and the STEP TEENS trails conducted in adolescents (NN9536-4451). The current popPK model was built on the previously develop PK model from STEP 1 data. In both studies, semaglutide was administered as a subcutaneous (SC) injection, once-weekly subcutaneous (SC), following the same dosing and dose escalation schedule.

The final PK dataset used for the analysis comprised a total of 1419 subjects (n=1295 from STEP 1 and 124 from STEP TEENS), and 8395 quantifiable concentrations (n=7775 from STEP 1 and 620 from STEP TEENS), excluding samples below the limit of quantification (BLQ). The limit of quantification (LLOQ) was 0.729 nmol/L (nM). BLQ samples represented about 2% and 7% of the PK data in STEP 1 (n=162) and SETP TEEN (n=44) respectively, and therefore were excluded from the analysis. **Table 4.1.2** summarizes the PK sampling schedule from both trials.

Table 4.1.3 summarizes the demographic characteristics of the subjects from the STEP 1 and STEP TEENS trials included in the PK analysis.

Table 4.1.2. Planned PK Sampling Schedule in STEP 1 and STEP TEENS trials

Trial/sampling timepoint[a]		Week 2	Week 4	Week 8	Week 12	Week 16	Week 28	Week 36	Week 52	Week 68
STEP 1	Planned dose	0.25 mg	0.25 mg	0.50 mg	1.0 mg	1.7 mg	2.4 mg	2.4 mg	2.4 mg	2.4 mg
	#samples	1300	1300	1300	1300	---	1300	---	1300	1300
STEP TEENS	Planned dose	0.25 mg	0.25 mg	0.50 mg	1.0 mg	1.7 mg	2.4 mg	2.4 mg	2.4 mg	2.4 mg
	#samples	---	---	128	---	128	128	128	128	128

a. The planned number of samples are based on the planned number of randomised subjects. However, it is expected that less PK data is available for the population PK analysis, due to treatment discontinuation, subject withdrawal or missing data. In addition, semaglutide concentrations were collected at the follow-up visit (week 75) in both trials; These samples were excluded from the population PK analysis.

Source: Applicant's Pharmacometrics Modelling Report, Table 4-1, page 14.

Table 4.1.3. Demographic Characteristics of Subjects for the Population PK Analysis

Category	Group	STEP 1	STEP TEENS	Total
All	N	1306	134	1440
Age (years)	12-<15	0	47	47
	15-<18	0	87	87
	18-<65	1198	0	1198
	>=65	108	0	108
Sex	Female	955	84	1039
	Male	351	50	401
Race[a]	White (other)	1234	123	1357
	Black or African American	72	11	83
Ethnicity[b]	Hispanic or Latino	150	14	164
	Not Hispanic or Latino	1156	120	1276
Glycaemic status[c]	Normoglycaemia	713	110	823
	Prediabetes	593	24	617
Body mass index groups	<30	81	12	93
	30-<35	436	45	481
	35-<40	406	33	439
	>=40	383	44	427
With PK data[d]	Subjects with PK	1295	124	1419
	Subjects without PK	11	10	21
Body weight (kg)	Mean (SD)	105.4 (22.1)	109.9 (25.2)	105.8 (22.4)
	Range	[61.8-245.6]	[61.6-211.9]	[61.6-245.6]
Body mass index (kg/m2)	Mean (SD)	37.8 (6.7)	37.7 (6.7)	37.8 (6.7)
	Range	[26.5-83]	[26.8-60]	[26.5-83]

a. Race categories: Other, not applicable, Native Hawaiian or Other Pacific Islander, Asian and American Indian or Alaska Native are pooled with white in the population PK analysis.

b. Ethnicity categories: Not applicable are pooled with Not Hispanic or Latino in the population PK analysis.

c. Glycaemic status: There were 5 subjects in STEP TEENS with diabetes (at screening) included in the prediabetes group.

d. Subjects without PK data in STEP TEENS: 6 of 10 subjects without PK data were from the same site and the missing PK data was caused by a sample collection error at the site. This was reported as protocol deviation.

Source: Applicant's Pharmacometrics Modelling Report, Table 6-1, page 23.

Structural and Base PK model

The PK of semaglutide was described by a one-compartment model, with first order absorption and elimination. The PK model was parameterized in terms of apparent clearance (CL/F), apparent central volume of distribution (V/F), and the absorption rate constant (K_a). Inter-individual variability (IIV) was included for semaglutide CL/F, V/F. No IIV was included for Ka due to the

sparse sampling of semaglutide concentrations. The residual variability was described by a proportional error model with trial specific variances.

Covariate analysis

The following covariates were included in the final PK model:

- Body weight on CL/F and V/F, using a power function standardized to a weight of 100 kg.
- Binary variables on CL/F: sex (with female as reference), ethnicity (Not Hispanic or Latino as reference), and glycemic status (normoglycemic as reference), coded as multiplicative (fold) effect.

Final model

The parameter estimates from the final PK model describing semaglutide PK in adults (STEP 1 trail) and adolescents (STEP TEENS trial) are listed in Table 4.1.4.

Table 4.1.4. Parameter Estimates from the Final Population PK Model

Parameter	Labels	Estimate [95% CI]
KA [1/h]	Absorption rate constant	0.0331 [0.023;0.043]
CL/F [L/h]	Apparent clearance	0.0457 [0.045;0.047]
V/F [L]	Apparent volume of distribution	10.6 [10;11.2]
CL.sex	Sex factor on CL/F	1.08 [1.05;1.1]
CL.hisp	Ethnicity factor on CL/F (Hispanic or Latino)	1.05 [1;1.09]
CL.BW	Body weight exponent on CL/F	0.799 [0.754;0.844]
CL.predia	Glycaemic status factor on CL/F (Prediabetes)	1.03 [1.01;1.05]
V.BW	Body weight exponent on V/F	0.6 [0.447;0.753]
IIV.CV CL/F [%]	Interindividual variability of CL/F	17.5
IIV.CV V/F [%]	Interindividual variability of V/F	38
Prop. Error STEP 1 [%]	Proportional residual error STEP 1	26
Prop. Error STEP TEENS [%]	Proportional residual error STEP TEENS	30.3

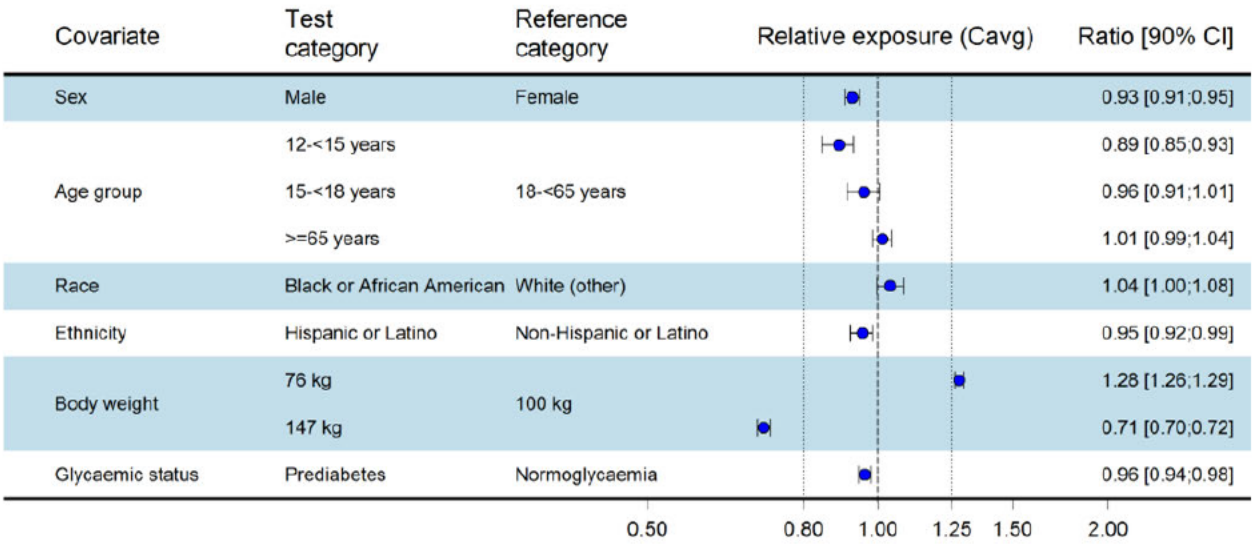
Note: the 95% confidence interval (CI) derived from non-parametric bootstrap (500 datasets), using the percentiles method.

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Tables 2-2, page 8.

The interindividual random effect (ETA) shrinkage was low for CL/F (16.6%). However, the ETA shrinkage was relatively higher (43.8%) for V/F, likely due to the sparse PK sampling scheme implemented in both STEP 1 and STEP TEENS trials.

Body weight was the most clinically relevant covariate on semaglutide exposure with lower exposures at larger body weights. Other covariates such as sex, ethnicity, and glycemic status were estimated to have minor effects on exposure (Figure 4.1.1).

Figure 4.1.1. Forest Plot of Covariate Effects on Semaglutide Average Steady-State Concentration

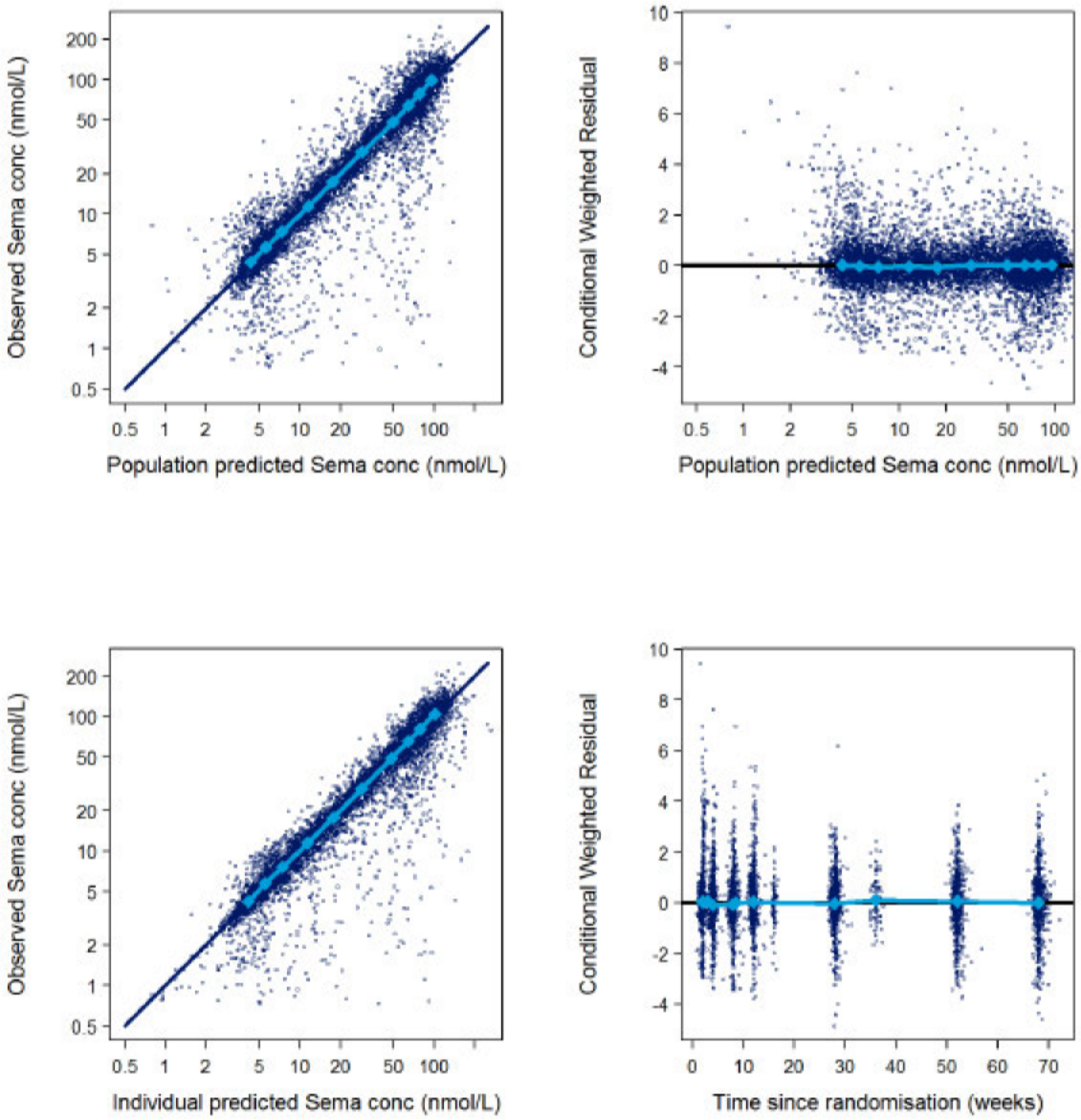


Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino, normoglycaemic white female aged 18-<65 years (STEP 1) and with a body weight of 100 kg). The forest plot and the column to the right show means and 90% CI for the relative 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).

Source: Applicant's Pharmacometrics Modelling Report, Figure 6-2, page 27.

Figure 4.1.2 shows the goodness-of-fit (GOF) plots from the final PK model. The GOF plots were showing a reasonable fit and there were no critical trends in the observed versus the individual predicted concentrations, and in the conditional weighted residuals (CWRES) versus either semaglutide concentration or time. The visual predictive check for the final model stratified by trial (**Figure 4.1.3**) showed that the models could adequately predict the median and variability in the observed data.

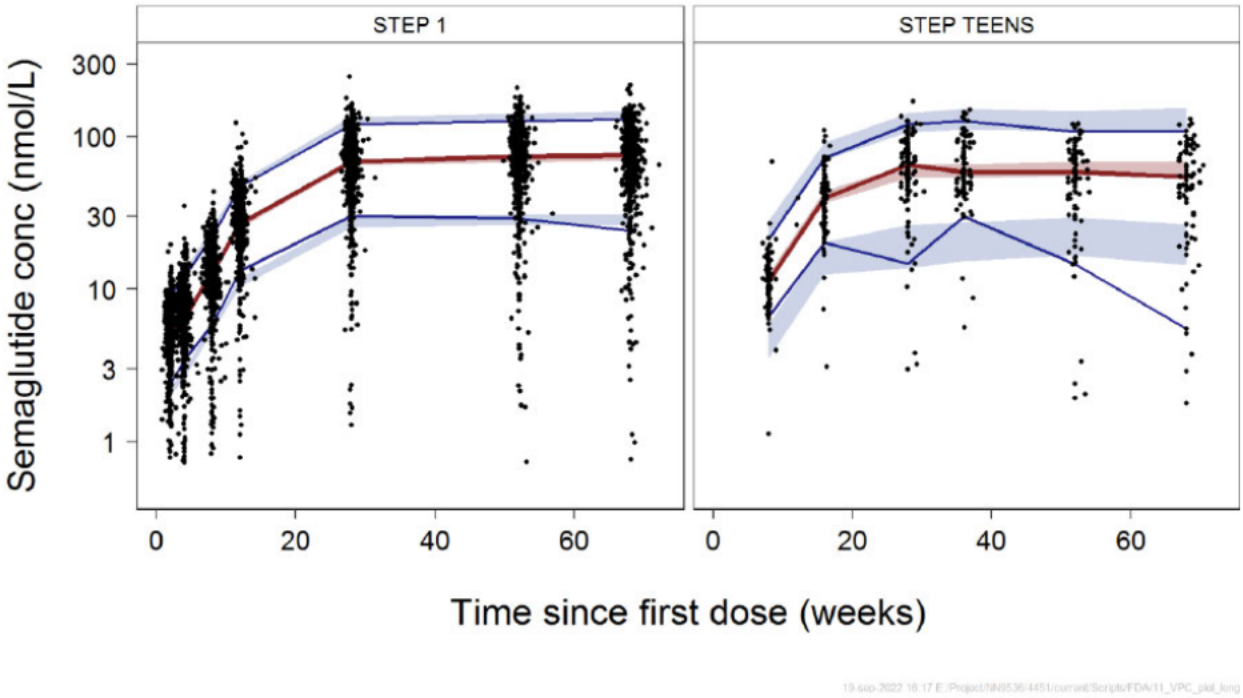
Figure 4.1.2. Goodness of Fit Plot from the Final PK Model



Note: Light blue lines are median values for quantiles of concentration or time.

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Figure 1-8, page 56.

Figure 4.1.3. Visual Predictive Check Plots from the Final PK Model



Data are observed (lines) and simulated (shaded area, n=500) medians and 5th and 95th concentration percentiles after the first dose. Black dots represent individual observed concentrations.

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Figure 1-7, page 55.

Reviewer's Assessment of the Population PK Analysis

- The Applicant's PK model adequately describes the observed concentrations from both studies.
- The PK parameter from the final model were estimated with a good precision (RSE ≤ 15%). The residual error (Epsilon) shrinkage was low (< 10%), indicating the informativeness of the GOF plots to diagnose structural and residual error model misspecifications.
- The GOF plots stratified by study are showing a reasonable fit and do not show major trends or bias for the majority of PK data (**Figure 4.1.4**).
- Similar exposure was observed between adults and pediatrics (12 to <18 years old) in different body weight groups. Therefore, no dose adjustment is needed based on age or weight (**Figure 4.1.5**).
- **Figure 4.1.6** and **Table 4.1.5** show the model-predicted steady-state average concentrations ($C_{avg,ss}$) of semaglutide under each dose level.

Figure 4.1.4. Goodness of Fit Plot from the Final PK Model, Stratified by Trial

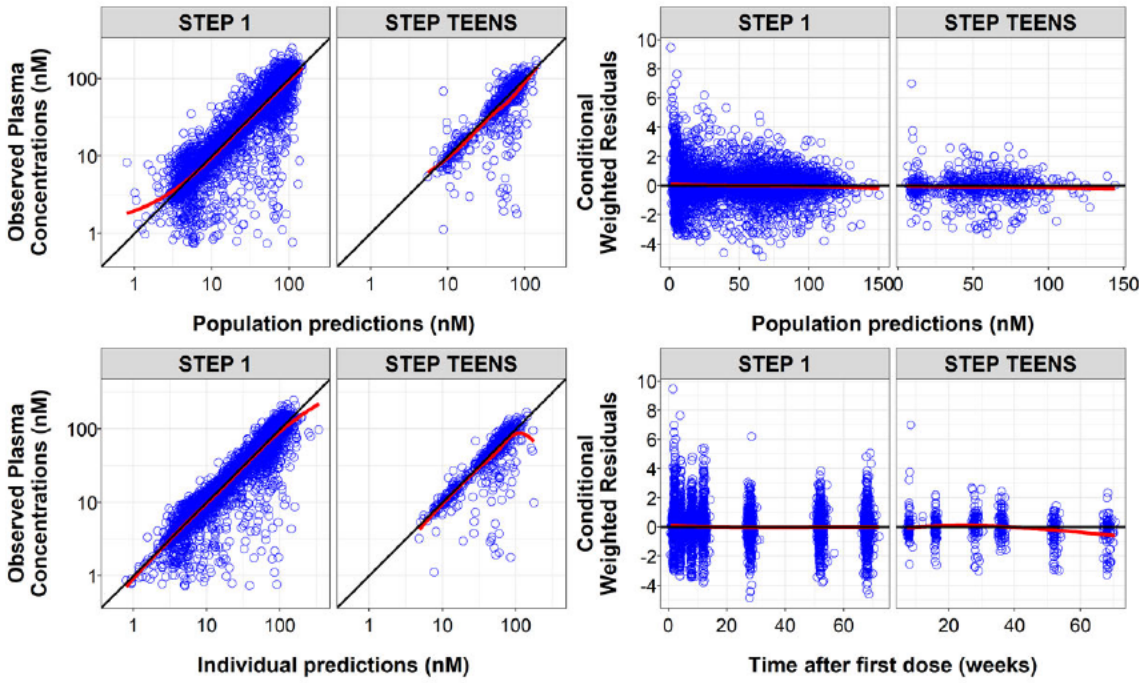
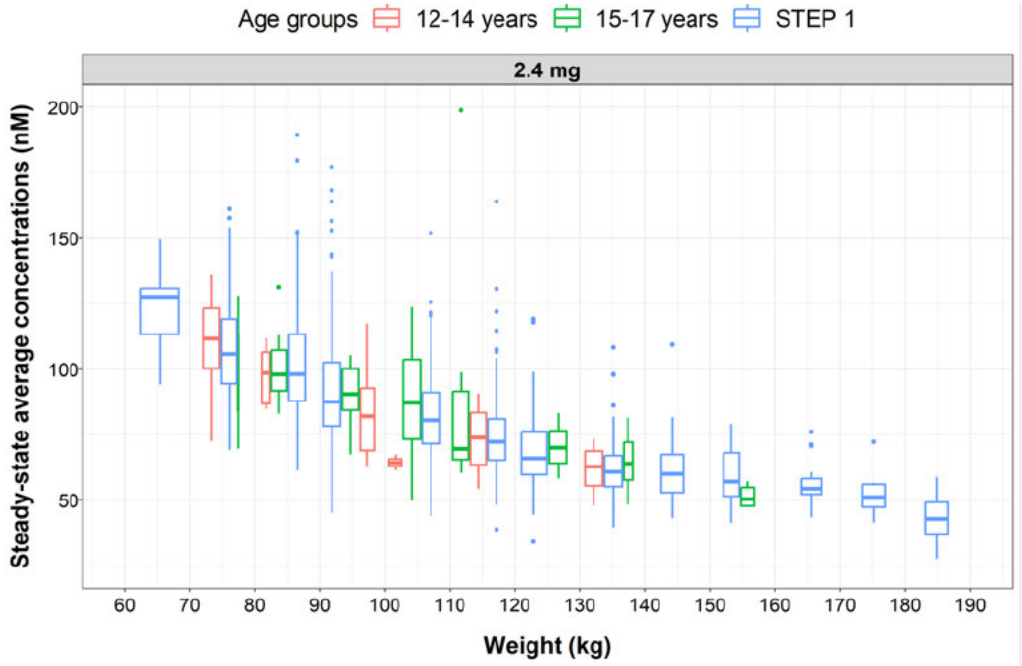


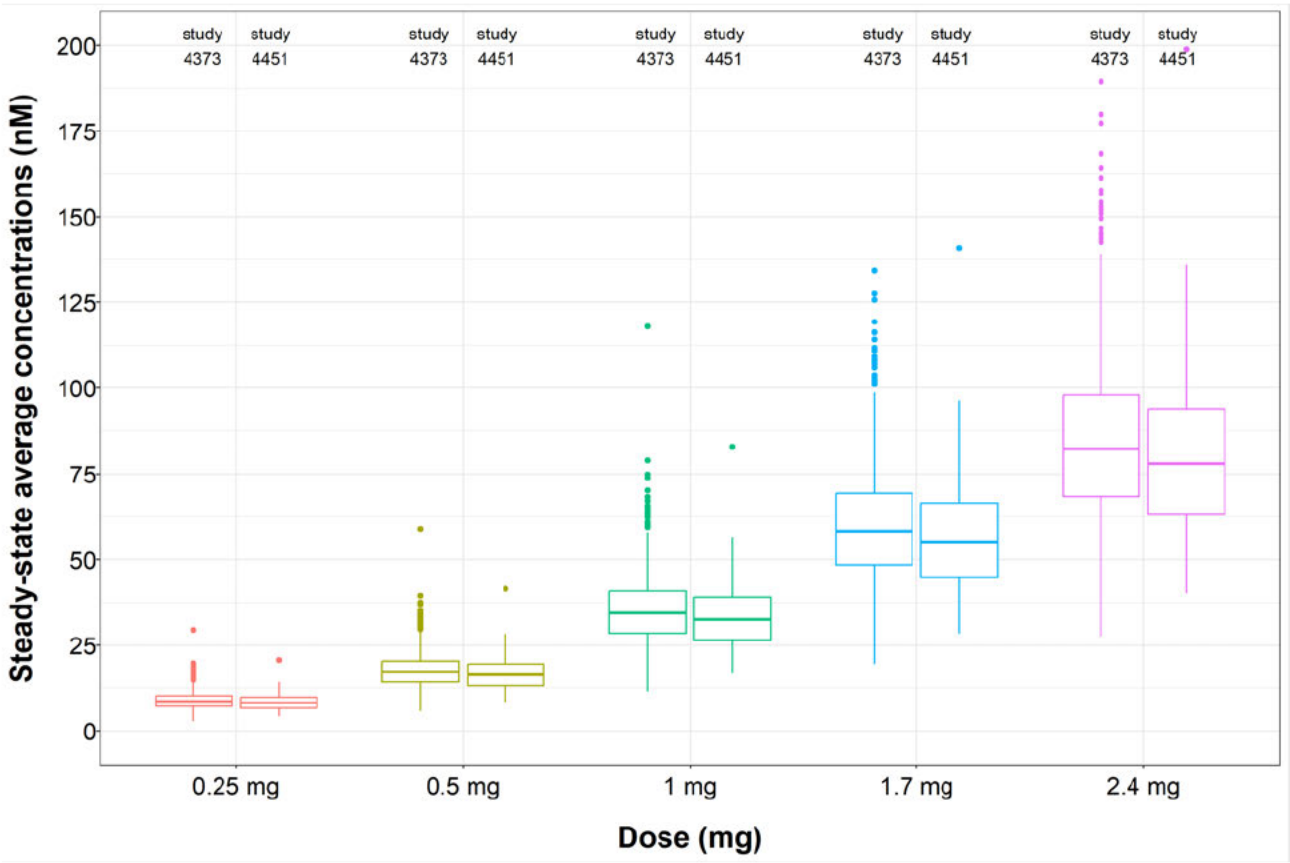
Figure 4.1.5. Distribution of the Model-Predicted Average Steady-State Concentrations by Weight and Age groups in STEP TEENS and STEP 1 Population Under a Maintenance Dose of 2.4 mg



Note: the steady-state average concentrations are in nanomole/L (nmol/L or nM), calculated as Dose [nmol] /(168 [h] * individual CL [L/h]). Semaglutide molecular weight is 4113.6 g/mol.

Source: FDA assessment

Figure 4.1.6. Model-Predicted Average Steady-State Concentrations Under Different Semaglutide Maintenance Doses



Note: the steady-state average concentration in nanomole/L (nmol/L or nM) was calculated as Dose [nmol] /(168 [h] * individual CL [L/h]). Semaglutide molecular weight is 4113.6 g/mol. Study 4373: STEP 1 trial. Study 4451: STEP TEENS trial.

Source: FDA assessment

Table 4.1.5. Summary of the Model-Predicted Average Steady-State Concentrations Under Different Semaglutide Maintenance Doses

Dose	$C_{avg,ss}$ (nM)	
	median (25^{th} - 75^{th} percentile)	Geometric mean (%CV)
0.25 mg	8.12 (6.57 - 9.78)	8.04 (29.4%)
0.5 mg	16.2 (13.1 - 19.6)	16.1 (29.4%)
1 mg	32.5 (26.3 - 39.1)	32.2 (29.4%)
1.7 mg	55.2 (44.7 - 66.5)	54.7 (29.4%)
2.4 mg	78 (63.1 - 93.9)	77.2 (29.4%)

$C_{avg,ss}$: steady-state average concentrations in nM.

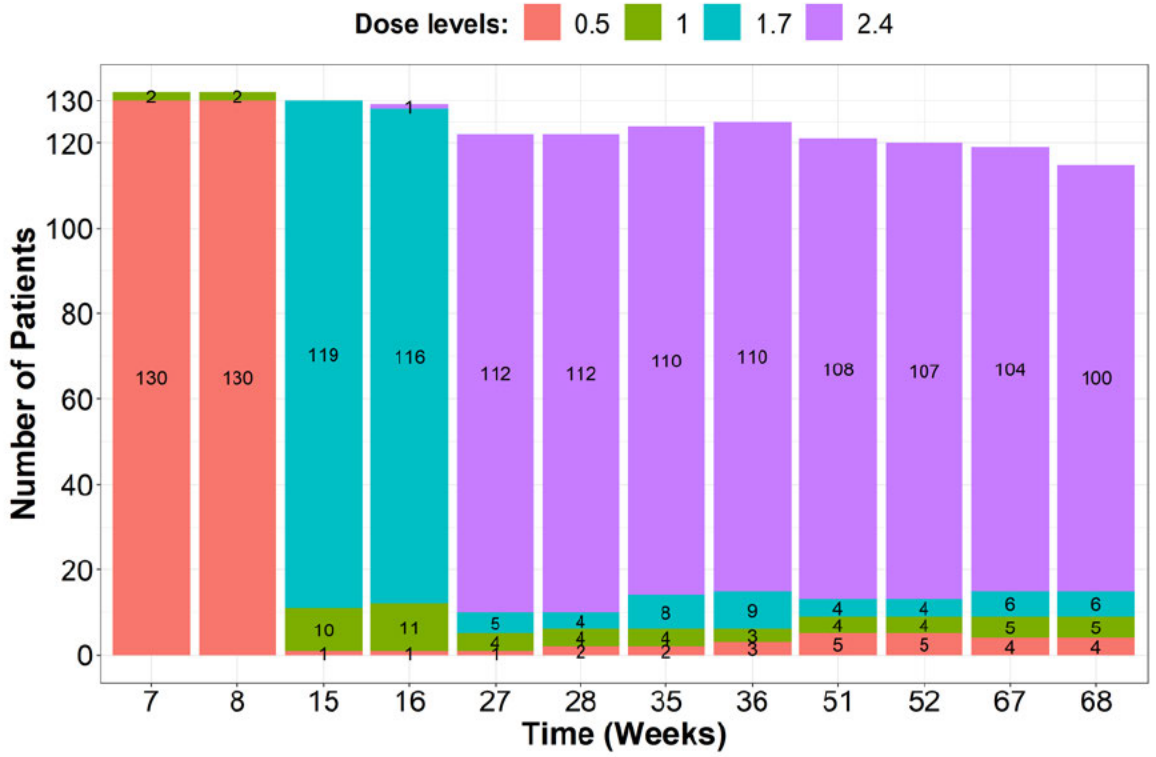
Source: FDA assessment

4.1.2 Applicant's Exposure-Response Analyses for Efficacy

In STEP TEENS, subjects were permitted to escalate semaglutide dose to their maximum tolerated dose (resulting in a maintenance of up to 2.4 mg or lower). Fifteen of the 120 subjects randomized to the semaglutide arm, who completed treatment, had a maintenance dose below the suggested 2.4 mg dose at the end of the treatment period (**Figure 4.1.7**). Fourteen of the 15 subjects (93%) who reduced their dose lost more than 10% of their baseline body weight (BW), and 53% of subjects who reduced their dose lost more than 20% of their baseline BW at end of treatment.

In the adult population, the proposed dosing regimen for weight management for semaglutide does not allow patients to remain at a maintenance dose below 2.4 mg. In contrast, based on STEP TEENS observations in 15 patients, the Applicant proposes that adolescent patients may remain at lower maintenance doses other than 2.4 mg. Upon the FDA review team request, the Applicant performed a longitudinal exposure-response analysis (longitudinal weight loss modeling) in order to predict the average change from baseline in BMI and BW at different maintenance doses below 2.4 mg at week 68, and therefore support his new dosing recommendations in adolescents and provide justifications showing that, in case of intolerance, a lower maintenance dose in adolescents is expected to remain efficacious.

Figure 4.1.7. Number of Adolescents with PK and PD data at Each Dose Level by Week, in STEP TEENS trial



Source: FDA assessment

4.1.2.1 Longitudinal Weight Loss Model

The exposure-response analysis characterizing the time-course of semaglutide effect on lowering body weight (BW) and body mass index (BMI) was based on PK and PD observations from 4 trials: 3 trials in adults (STEP 1 [NN9536-4373], STEP 2 [NN9536-4374] and a phase 2 trial NN9536-4153) and 1 trial in adolescents (STEP TEENS [NN9536-4451]). Table 4.1.6 summarizes the study designs for the trials included in the longitudinal weight loss model analysis. In the phase2 trial NN9536-4153, semaglutide was administered as a once-daily SC injection instead of once-weekly SC dosing. The study arms included in the analysis had the same dose escalation frequency (i.e., every 4 weeks). Diet and exercise were included in all trials and followed a regimen that was aligned across the trials.

All trials employed sparse PK sampling of semaglutide, including the STEP 2 trial and trial 4153. The PK data from these two trials have previously been reviewed by the FDA, where a one-compartment PK model with first-order absorption and elimination was used to describe the semaglutide PK. The exposure metric used in the exposure-response analyses was the weekly average concentrations (C_{avg}). For subjects randomized to placebo, C_{avg} was set to 0 nmol/L (nM) at all time points.

The final dataset for exposure-response analysis included 43035 observations for the percent change from baseline (PCFB) in body weight from 3968 patients (n=1954 in STEP 1, n=1179 in STEP 2, n=642 in trial 4153 and n=193 in STEP TEENS), and 44146 observations for PCFB in BMI over time from 3973 patients (n=1954 in STEP 1, n=1179 in STEP 2, n=642 in trial 4153 and n=198 in STEP TEENS).

Table 4.1.7 summarizes the demographic characteristics of the adult patients included in the longitudinal exposure-response model. The demographic characteristics of subjects from STEP TEENS trial were summarized in **Table 4.1.3**.

Table 4.1.6. Summary of the trials included in the Longitudinal Weight Loss Model

Phase	Trial ID	Description	Population	N[a]	Duration	Maintenance doses[b]
2	4153	Phase 2 trial of once-daily semaglutide with liraglutide 3.0 mg as active comparator	Subjects with obesity (BMI ≥30 kg/m^2), without T2D.	957	52 weeks	0.05, 0.1, 0.2, 0.3 or 0.4 mg once daily Placebo once daily
3a	4373	STEP 1	Subjects with overweight (BMI ≥27 kg/m^2) and weight-related co-morbidities, or subjects with obesity (BMI ≥30 kg/m^2). Normoglycaemic or prediabetes (HbA_{1c} <6.5%)	1961	68 weeks	2.4 mg once weekly Placebo once weekly
	4374	STEP 2	Overweight (BMI ≥27 kg/m^2) with T2D	1210	68 weeks	1.0 or 2.4 mg once weekly Placebo once weekly

a. N is the number of subjects randomised to semaglutide, liraglutide 3.0 mg (4153), or placebo
b. Dose escalation happened every 4 weeks, except for the 2 excluded semaglutide arms in the phase 2 trial 4153 with fast escalation (every 2 weeks). Dosing frequency was once weekly for all trials, except for the phase 2 trial 4153, where subjects dosed once daily.

Source: Response to FDA Request, 09 September 2022 (SN 0244), Table 4-1, page 28.

Table 4.1.7. Demographic Characteristics of Adult Subjects included in the Weight Loss Modelling

Category	Group	4153	4373	4374	Total
All	N	647	1961	1210	3818
Sex	Female	418	1453	616	2487
	Male	229	508	594	1331
Age	18-<65 years	603	1831	986	3420
	> 65 years	44	130	224	398
Race	White	476	1472	751	2699
	Asian	4	261	317	582
	Black or African American	45	111	100	256
	Other	117	88	35	240
	American Indian or Alaska Native	3	27	6	36
	Native Hawaiian or Other Pacific Islander	2	2	1	5
Ethnicity	Not Hispanic or Latino	607	1725	1055	3387
	Hispanic or Latino	40	236	155	431
Treatment	Sema 2.4 mg	-	1306	404	1710
	Placebo	-	655	403	1058
	Sema 1.0 mg	-	-	403	403
	Placebo Pool	134	-	-	134
	Sema 0.05 mg	103	-	-	103
	Sema 0.2 mg	103	-	-	103
	Sema 0.3 mg	103	-	-	103
	Sema 0.1 mg	102	-	-	102
	Sema 0.4 mg	102	-	-	102
Body weight (kg)	Mean (SD)	112.7 (24)	105.3 (21.9)	99.8 (21.5)	104.8 (22.6)
	Range	[73.3-243.7]	[61.8-245.6]	[54.4-199.2]	[54.4-245.6]
Age (years)	Mean (SD)	46.3 (12.5)	46.5 (12.7)	55.3 (10.6)	49.3 (12.7)
	Range	[18-77]	[18-86]	[19-84]	[18-86]
HbA1c (%)	Mean (SD)	5.5 (0.4)	5.7 (0.3)	8.1 (0.8)	6.4 (1.3)
	Range	[4.2-7]	[4.1-6.6]	[5.7-10.6]	[4.1-10.6]
BMI (kg/m^2)	Mean (SD)	39.7 (7.3)	37.9 (6.7)	35.7 (6.3)	37.5 (6.8)
	Range	[29.8-80.3]	[26.5-83]	[26.5-66.2]	[26.5-83]

[a]Trial 4153 employed once-daily dosing, as opposed to once-weekly dosing used in other trials of semaglutide s.c.

[b]'Other' and 'not applicable' were pooled 'Other'

[c]'Not applicable' were pooled with Not Hispanic or Latino

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Table 7-1, page 37.

Base PK-PD model

A sequential modeling approach was used to characterize the effect of semaglutide weekly Cavg on BW reduction over time. Individual weekly Cavg values from week 0 to end-of-treatment were derived from individual PK parameters and dosing history, including information on treatment pauses. The derived weekly Cavg were then integrated with the BW and BMI observations for the PD modeling.

The time course of body weight (in kg) was modelled as a sum of the baseline body weight (BW_0), an immediate effect on BW (BWi), a slow effect on BW (BWs) and a placebo effect (BWpl):

$$BW(t) = BW_0 - BW_s(t) - BW_i(t) - BW_{pl}(t)$$

- *Placebo effect model (encompassing diet and exercise effect):*

The placebo effect on BW change over time was modeled using an indirect response model with inhibitory effect on the formation rate on BW. The placebo model was parameterized as:

$$\frac{dBW_{pl.dynamic}}{dt} = -k_{outPl} \cdot \left(BW_{pl.dynamic}(t) - BW_0 \cdot PL \cdot e^{-TFAC \cdot t}\right)$$

where:

- k_{outPL}: Body weight rate constant for placebo (1/week)
- k_{out}: Body weight rate constant shared for placebo and active (1/week)
- PL: Placebo effect magnitude (%)
- TFAC: Placebo rate constant (1/week)

- *Semaglutide effect model:*

The longitudinal effect of semaglutide was described as combined direct (immediate) and indirect (slow) treatment effect models. The expected BW and weight loss was computed as the sum of the direct and indirect responses of semaglutide.

The direct effect component reflects a low fraction of the effect on body weight that is expected to occur quickly compared to the time interval between body weight assessments. The direct (immediate) effect component was concentration-dependent through a standard E_{max}-model. The direct effect was parameterized as:

$$BW_I = 0.01 * BW_0 \frac{Emax_I * C_{avg}}{EC_{50} + C_{avg}}$$

where:

- EC_{50}: Semaglutide concentration achieving half of maximal effect (nmol/L)
- $E_{max,I}$: Maximum effect of semaglutide (%) on the direct effect component

The indirect (slow) treatment effect component had a slower, but greater effect on weight loss. Consistent with the mode-of-action of semaglutide (semaglutide inhibiting body weight gain through the downregulation of food intake), the drug effect was placed on kin. The indirect response model was parameterized as:

$$\frac{dBW_s}{dt} = k_{in}\left(\frac{0.01 * Emax_s * C_{avg}}{EC_{50} + C_{avg}}\right) - k_{out}BW_s(t)$$

where:

- k_{in}: Body weight input rate, parameterised as $k_{in} = BW_0 \cdot k_{out} \cdot NEW_{ss}$. Where NEW_{ss}. is the ratio between the new steady state body weight that will be obtained for placebo treatments and the baseline body weight. This part of the model reflects that stationarity was not assumed for this model, because BW begins at baseline value, changes with time following drug administration, and eventually returns to a new steady-state level. The parameter NEW_{ss} was introduced to allow for subject-specific steady-state body weights.
- k_{out}: Body weight elimination rate constant for semaglutide (1/week)
- $E_{max,S}$: Maximum effect of semaglutide (%) on the indirect effect component
- EC50: The semaglutide concentration responsible for half of the maximum effect was considered the same as for the direct (immediate) treatment effect component.

Inter-individual variability (IIV) was included for semaglutide E_{max},I, E_{max},S, EC50 with a full omega matrix. The IIV was incorporated as exponential random error model on EC50 and as an additive random error model on E_{max},I, E_{max},S, assuming a normal distribution for the Emax parameters. The residual variability was described by an additive error model. The longitudinal weight loss model was first developed on adult data, then the adolescent population (STEP TEENS trial) parameters were conditioned on model parameters estimated in the adult population.

The Applicant also developed a longitudinal BMI reduction model, using the same structural and covariate model as the weight loss model and where the dependent variable was modified from BW to BMI. In adults, the BW and BMI loss model and the percent change from baseline in BW and BMI are similar, as the height is adults was constant.

Covariate analysis

The following covariates were included in the final PD model, coded as a proportional change relative to the typical value:

- Sex (with female as reference) on E_{max},I and E_{max},S.
- Additional binary variables on E_{max},S: ethnicity (Not-Hispanic or Latino as reference), Asian (Not Asian as reference), and Type 2 diabetes (T2D) population or STEP 2 trial (trials other than STEP2 as reference).
- Continuous variables on E_{max},S: baseline HbA1c, baseline age and baseline BMI.
- STEP 2 trial (T2D population) on the placebo effect magnitude (PL).

Final PK-PD model

The longitudinal weight loss model was first developed on adult data, then the adult weight loss model parameters were fixed, and the adolescent population (STEP TEENS trial) parameters were adjusted by including STEP TEENS trial as a covariate on the adult model parameters. Table 4.1.8 shows the longitudinal weight loss model parameters in adults population determined from (Trial STEP 1, STEP 2 and 4153).

Table 4.1.8. Parameter Estimates from the Final Weight Loss Model in Adults

Parameter	Label	Units	Estimates	SIR 95% CI	Shrinkage
KOUT	Elimination rate constant	1/week	0.0319	[0.0307; 0.0332]	NA
EMAXI	Emax Semaglutide, direct	%	3.99	[3.50; 4.42]	NA
KOUTP	placebo elimination rate constant	1/week	0.00885	[0.00716; 0.0111]	NA
PLBMAX	Maximum placebo response	%	34.4	[26.2; 43.1]	NA
TFAC	Placebo time factor	1/week	0.0794	[0.0694; 0.0909]	NA
EMAXS	Emax Semaglutide, indirect	%	26.2	[24.8; 27.6]	NA
EC50	EC50 Semaglutide	nM	48.0	[43.3; 53.5]	NA
NEWSS	New steady state	NA	0.990	[0.983; 0.996]	NA
COV_EMAXI_SEX	Sex (male) factor on EMAXI	NA	0.332	[0.153; 0.514]	NA
COV_EMAXS_AGE	Age factor on EMAXS	NA	-0.00588	[-0.00893; -0.00267]	NA
COV_EMAXS_BMI	BMI factor on EMAXS	NA	-0.0169	[-0.0217; -0.0124]	NA
COV_EMAXS_ETHN	Ethnicity (hispanic) factor on EMAXS	NA	-0.191	[-0.297; -0.0839]	NA
COV_EMAXS_HBA1CBL	HbA1c factor on EMAXS	NA	-0.0790	[-0.144; -0.00783]	NA
COV_EMAXS_SEX	Sex (male) factor on EMAXS	NA	-0.445	[-0.503; -0.382]	NA
COV_EMAXS_ASIAN	Race (Asian) factor on EMAXS	NA	-0.323	[-0.414; -0.236]	NA
COV_EMAXS_T2D	T2D factor on EMAXS	NA	-0.203	[-0.379; -0.0298]	NA
COV_PLACEBO_T2D	T2D factor on PLACEBO	NA	-0.270	[-0.335; -0.197]	NA
NEWSS.IIV	IIV on NEWSS (Var)	NA	0.00473	[0.00432; 0.00519]	20.5
EMAXS.IIV	IIV on EMAXS (Var)	NA	282	[250; 320]	34.6
EC50.IIV	IIV on EC50 (CV%)	%	71.1	[62.7; 77.8]	22.9
EMAXI.IIV	IIV on EMAXI (Var)	NA	54.9	[48.9; 62.3]	32.2
AddErr	Additive error (SD)	%	1.44	[1.43; 1.45]	7.68

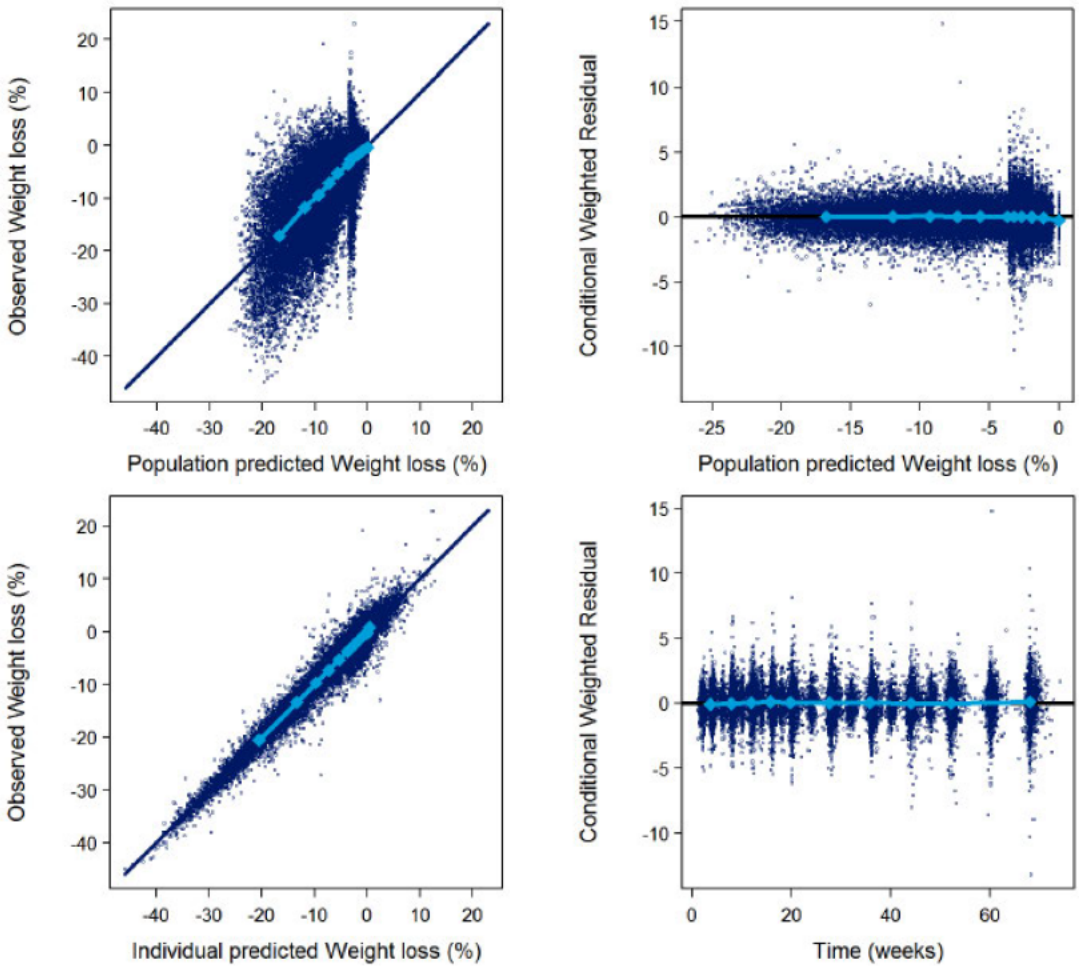
Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Table 7-2, page 38.

The most pronounced covariate for weight loss was sex; with females having a larger weight loss than males at the same exposure level. The differences in weight loss between subjects without and with T2D (corresponding to differences between STEP 1 and STEP 2 trials, respectively) were adequately captured by a trial effect and baseline HbA1c effect on E_{max},S. Other covariates, such

as age, race, ethnicity, BMI, BW, and region had no or only minor effects on weight loss, most being captured by differences in semaglutide exposure. For subjects without T2D, it appeared that the exposure-response was independent of dosing frequency (once daily in trial 4153 and once weekly in phase 3 trials).

Figure 4.1.8 show the GOF plots of the longitudinal weight loss model in adults. Figure 4.1.9 (for STEP 1, STEP 2 trials) and Figure 4.1.10 (for trial 4153) show the VPC plots in adults. These diagnostic plots show an adequate fit to the adults' data and the ability of the model to reproduce the observed variability in the data over the time-course of the studies, and under different dosing regimen.

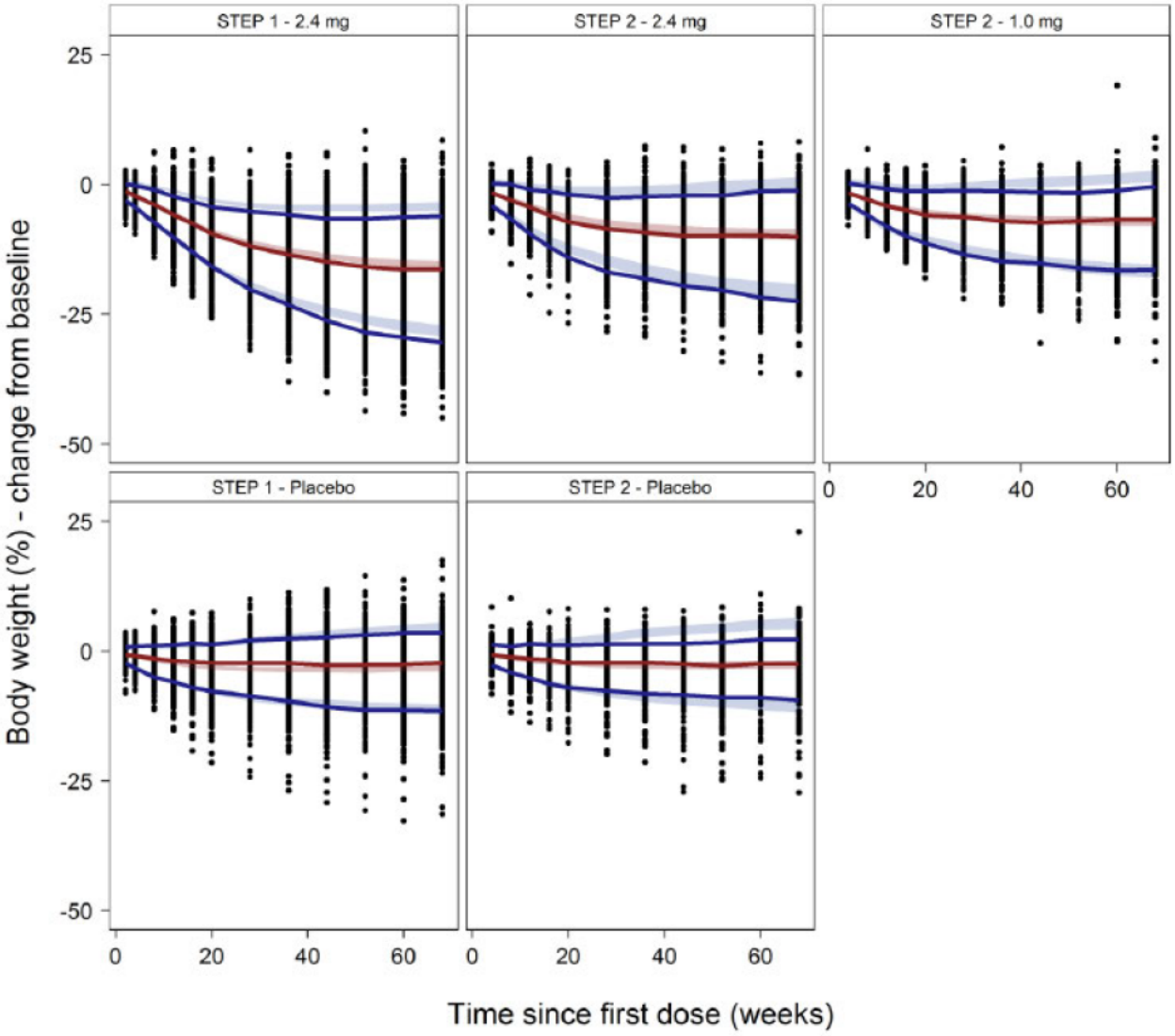
Figure 4.1.8. Goodness of Fit Plot from the Weight Loss Model in Adults



Note: Data are observed percent change in BW versus population predictions (left-top) and versus individual predictions (left-bottom), conditional weighted residuals versus population predictions (middle-top) and versus time (middle-bottom). Light blue lines are median values for quantiles of percent change in BW or time.

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Figure 7-4, page 42.

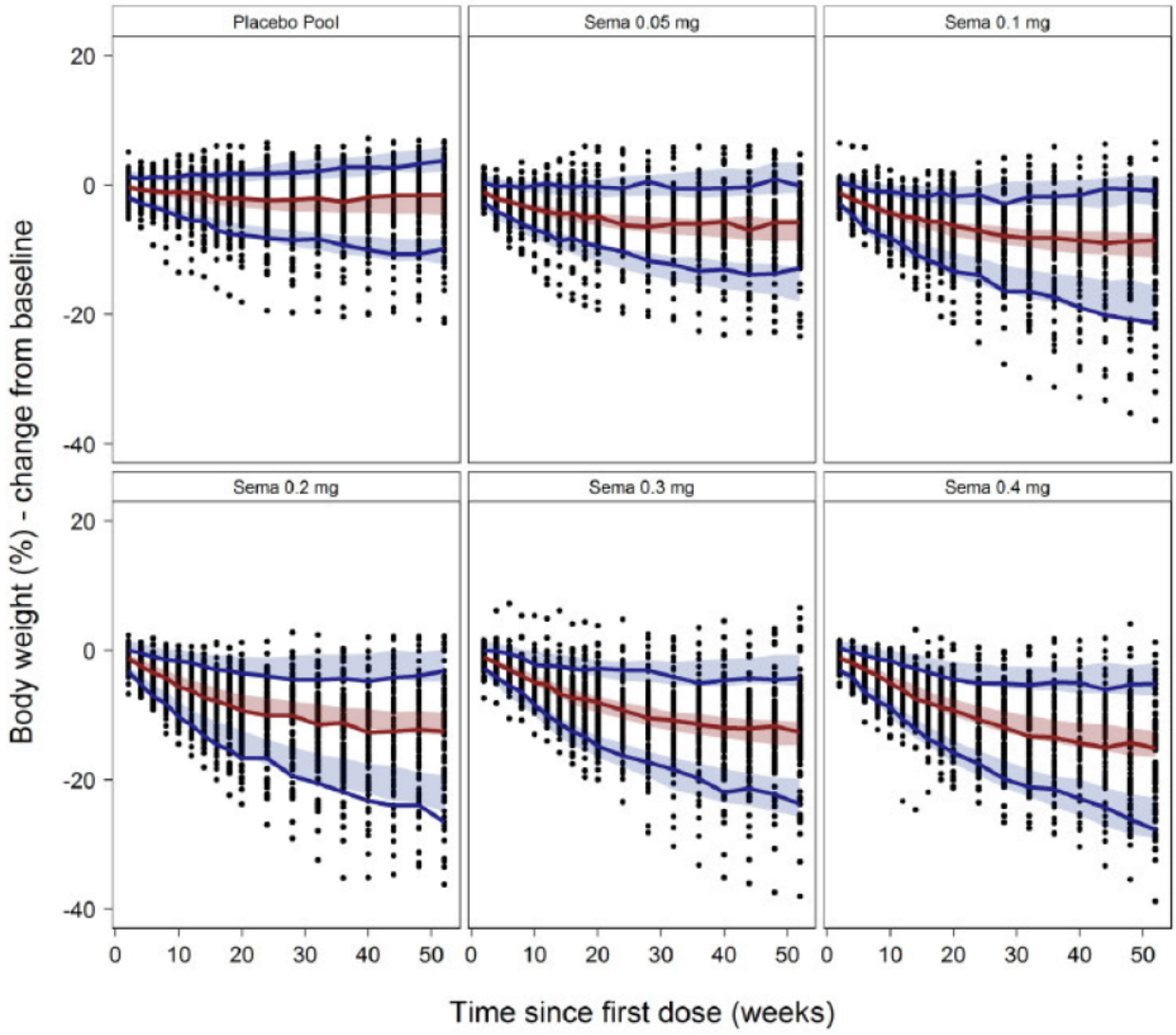
Figure 4.1.9. Visual Predictive Check Plots from the Final Weight Loss Model in Adults (STEP 1 and STEP 2 Trials)



Data are observed (lines) and simulated (shaded area, n=500) medians and 10th and 90th weight loss percentiles after the first dose.

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Figure 7-5, page 43.

Figure 4.1.10. Visual Predictive Check Plots from the Final Weight Loss Model in Adults (Trial 4153)



Data are observed (lines) and simulated (shaded area, n=500) medians and 10th and 90th weight loss percentiles after the first dose.

Source: Applicant's Response to FDA Request, 09 September 2022 (SN 0244), Figure 7-6, page 44.

Table 4.1.9 shows the estimated weight loss model parameters in adolescents (STEP TEENS trial). Table 4.1.10 shows the estimated longitudinal BMI reduction model parameters in adolescents, where the dependent variable in the weight loss model was modified from BW to BMI, using the same structural and covariate model as the weight loss model.

Table 4.1.9. Parameter Estimates from the Final Weight Loss Model in Adults and Adolescents

Parameter	Label	Units	Estimates	Bootstrap 95% CI	Shrinkage
KOUT	Elimination rate constant	1/week	0.0319	Fixed	
EMAXI	Emax Semaglutide,direct	%	3.99	Fixed	
KOUTP	placebo elimination rate constant	1/week	0.00885	Fixed	
PLBMAX	Maximum placebo response	%	34.4	Fixed	
TFAC	Placebo time factor		0.0794	Fixed	
EMAXS	Emax Semaglutide,indirect	%	26.2	Fixed	
EC50	EC50 Semaglutide	nM	48.0	Fixed	
NEWSS	New steady state		0.990	Fixed	
COV_EMAXI_SEX	Sex (male) factor on EMAXI		0.332	Fixed	
COV_EMAXS_AGE	Age factor on EMAXS		-0.00588	Fixed	
COV_EMAXS_BMI	BMI factor on EMAXS		-0.0169	Fixed	
COV_EMAXS_ETHN	Ethnicity (Hispanic) factor on EMAXS		-0.191	Fixed	
COV_EMAXS_HBA1CBL	HbA1c factor on EMAXS		-0.0790	Fixed	
COV_EMAXS_SEX	Sex (male) factor on EMAXS		-0.445	Fixed	
COV_EMAXS_ASIAN	Race (Asian) factor on EMAXS		-0.323	Fixed	
COV_EMAXS_T2D	T2D factor on EMAXS		-0.203	Fixed	
COV_PLACEBO_T2D	T2D factor on PLACEBO		-0.270	Fixed	
COV_NEWSS_TEENS	Adolescents factor on NEWSS		0.337	[0.198; 0.467]	
COV_PLACEBO_TEENS	Adolescents factor on PLACEBO		2.39	[0.937; 3.67]	
COV_TFAC_TEENS	Adolescents factor on TFAC		-0.754	[-0.793; -0.672]	
COV_EMAXS_TEENS	Adolescents factor on EMAXS		-0.145	[-0.371; 0.143]	
COV_EMAXI_TEENS	Adolescents factor on EMAXI		0.0901	[-0.363; 0.575]	
NEWSS.IIV	IIV on NEWSS (Var)		0.00473	Fixed	25.7
EMAXS.IIV	IIV on EMAXS (Var)		282	Fixed	26.6
EC50.IIV	IIV on EC50 (CV%)	%	71.2	Fixed	29.0
EMAXI.IIV	IIV on EMAXI (Var)		54.9	Fixed	31.8
AddErr	Additive error (SD)	%	2.10	[1.86; 2.34]	8.63

95% confidence intervals for the STEP TEENS parameters are derived from 500 replicates of a non-parametric bootstrap procedure, using the percentile method.

Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Table 2-1, page 9.

Table 4.1.10. Parameter Estimates from the Final BMI reduction Model in Adults and Adolescents

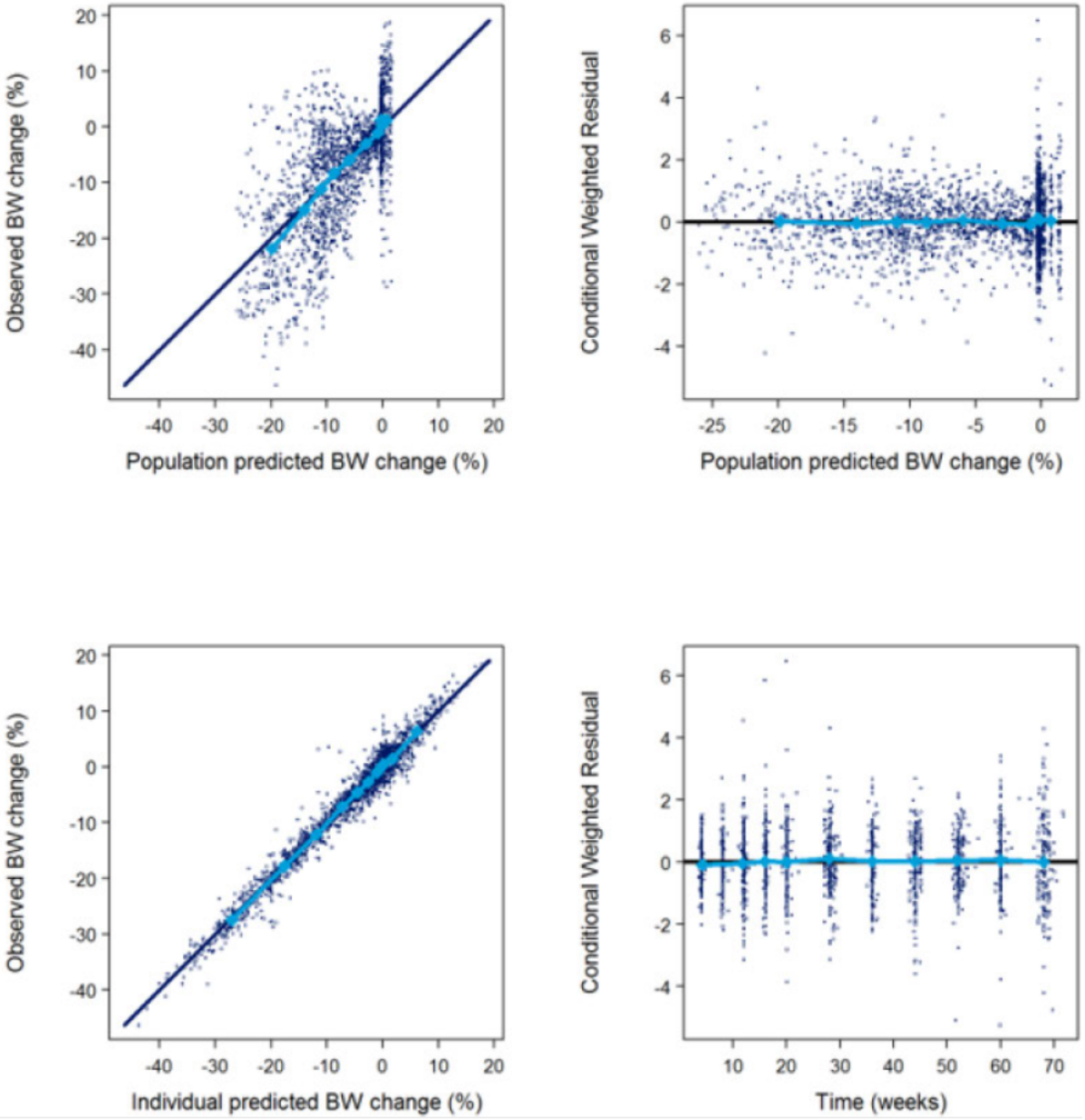
Parameter	Label	Units	Estimates	Bootstrap 95% CI	Shrinkage
KOUT	Elimination rate constant	1/week	0.0319	Fixed	
EMAXI	Emax Semaglutide,direct	%	3.99	Fixed	
KOUTP	placebo elimination rate constant	1/week	0.00885	Fixed	
PLBMAX	Maximum placebo response	%	34.4	Fixed	
TFAC	Placebo time factor		0.0794	Fixed	
EMAXS	Emax Semaglutide,indirect	%	26.2	Fixed	
EC50	EC50 Semaglutide	nM	48.0	Fixed	
NEWSS	New steady state		0.990	Fixed	
COV_EMAXI_SEX	Sex (male) factor on EMAXI		0.332	Fixed	
COV_EMAXS_AGE	Age factor on EMAXS		-0.00588	Fixed	
COV_EMAXS_BMI	BMI factor on EMAXS		-0.0169	Fixed	
COV_EMAXS_ETHN	Ethnicity (Hispanic) factor on EMAXS		-0.191	Fixed	
COV_EMAXS_HBA1CBL	HbA1c factor on EMAXS		-0.0790	Fixed	
COV_EMAXS_SEX	Sex (male) factor on EMAXS		-0.445	Fixed	
COV_EMAXS_ASIAN	Race (Asian) factor on EMAXS		-0.323	Fixed	
COV_EMAXS_T2D	T2D factor on EMAXS		-0.203	Fixed	
COV_PLACEBO_T2D	T2D factor on PLACEBO		-0.270	Fixed	
COV_NEWSS_TEENS	Adolescents factor on NEWSS		0.281	[0.139; 0.418]	
COV_PLACEBO_TEENS	Adolescents factor on PLACEBO		1.83	[0.442; 3.17]	
COV_TFAC_TEENS	Adolescents factor on TFAC		-0.773	[-0.810; -0.663]	
COV_EMAXS_TEENS	Adolescents factor on EMAXS		-0.137	[-0.387; 0.105]	
COV_EMAXI_TEENS	Adolescents factor on EMAXI		0.406	[-0.159; 1.02]	
NEWSS.IIV	IIV on NEWSS (Var)		0.00473	Fixed	23.9
EMAXS.IIV	IIV on EMAXS (Var)		282	Fixed	40.4
EC50.IIV	IIV on EC50 (CV%)	%	71.2	Fixed	25.4
EMAXI.IIV	IIV on EMAXI (Var)		54.9	Fixed	46.4
AddErr	Additive error (SD)	%	2.46	[2.14; 2.76]	16.8

95% confidence intervals for the STEP TEENS parameters are derived from 500 replicates of a non-parametric bootstrap procedure, using the percentile method.

Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Table 2-2, page 13.

Figure 4.1.11 and **Figure 4.1.12** show the GOF plots and Figure 4.1.13 shows the VPC plots of the longitudinal weight loss and BMI reduction model from the sequential modelling approach. The GOF plots shows an adequate fit to the STEP TEENS data and based on the visual predictive check it is assessed that the model can reproduce the observed variability in the data over the time-course of the study.

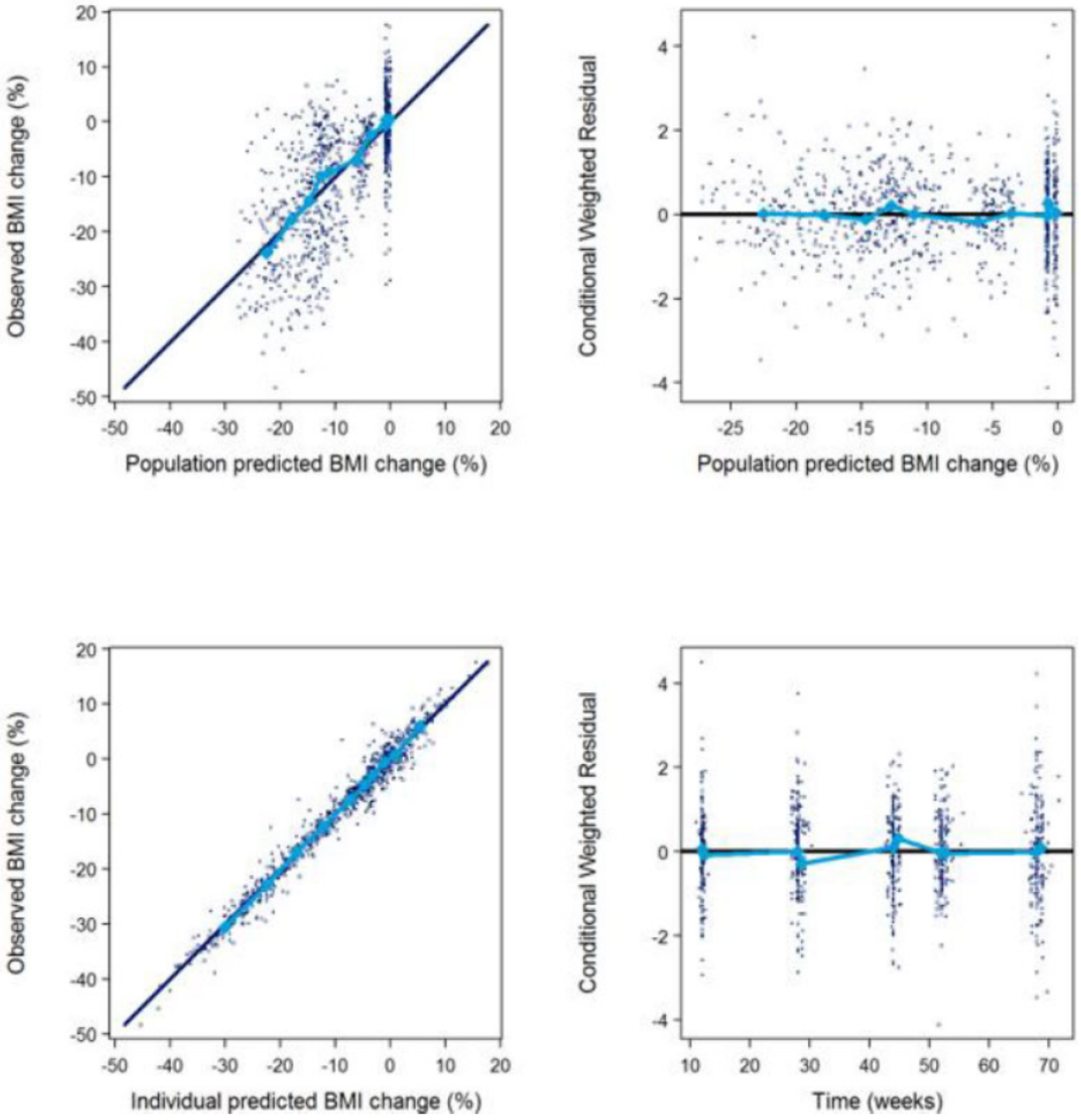
Figure 4.1.11. Goodness of Fit Plot for Pediatric data (STEP TEENS) from the Weight Loss Model



Note: Data are observed percent change in BW versus population predictions (left-top) and versus individual predictions (left-bottom), conditional weighted residuals versus population predictions (middle-top) and versus time (middle-bottom). Light blue lines are median values for quantiles of percent change in BW or time.

Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Figure 2-2, page 7.

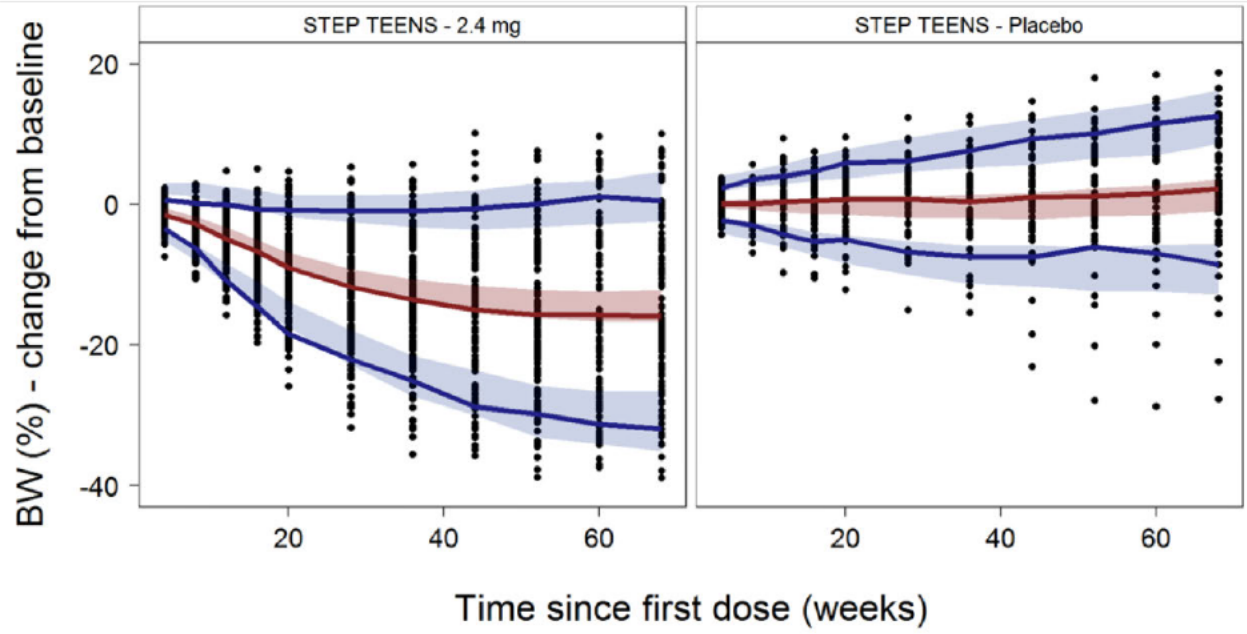
Figure 4.1.12. Goodness of Fit Plot for Pediatric data (STEP TEENS) from the BMI reduction Model



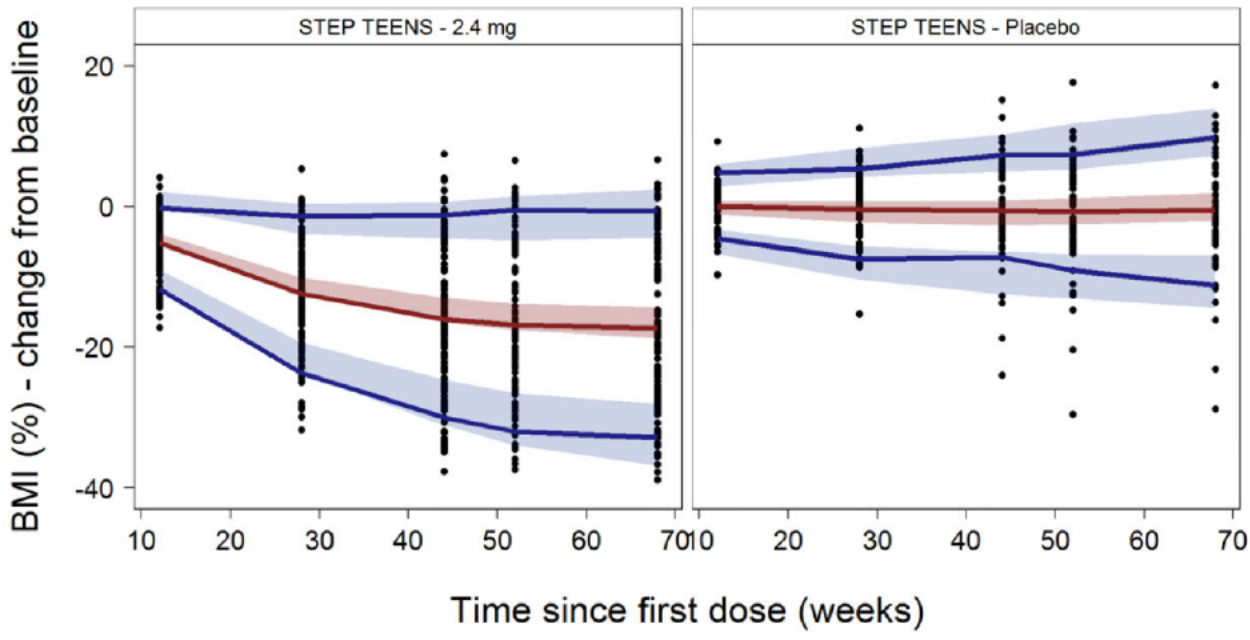
Note: Data are observed percent change in BW versus population predictions (left-top) and versus individual predictions (left-bottom), conditional weighted residuals versus population predictions (middle-top) and versus time (middle-bottom). Light blue lines are median values for quantiles of percent change in BW or time.

Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Figure 2-5, page 11.

Figure 4.1.13. Visual Predictive Check Plots from the Final Weight and BMI Loss Models



Data are observed (lines) and simulated (shaded area, n=500) means and 10th and 90th precent change BW percentiles after the first dose.



Data are observed (lines) and simulated (shaded area, n=500) means and 10th and 90th precent change BMI percentiles after the first dose.

Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Figures 2-3 and 2-6, pages 8 and 12.

Reviewer's Assessment of the Longitudinal Weight/BMI Loss Analyses

- The effect of STEP TEENS trial as a covariate on the maximum semaglutide effects ($E_{max,S}$ and $E_{max,I}$) were not precisely estimated and not significant (95% CI included zero), likely because the adult weight loss model already included the effect of Age on $E_{max,S}$.

- The GOF plots and VPC plots stratified by study show that the Applicant's longitudinal weight/BMI loss models adequately describes the observed PCFB in BW and BMI data across time in both adults (trials: STEP 1, STEP2 and trial 4153) and the pediatric population of interest (STEP TEENS trial), at different semaglutide dose levels and regimen (once daily versus once weekly).

Therefore, the longitudinal weight/BMI loss models can be used to perform simulations to predict the average PCFB in BMI and BW at different maintenance doses below 2.4 mg at week 68 and determine whether maintenance doses lower than 2.4 mg (in adolescents who cannot tolerate the highest maintenance dose) are expected to remain efficacious and provide a minimum of 5% decrease in BMI.

4.1.2.2 Application of the Longitudinal Weight Loss Models to Assess the Acceptability of Lowering the Maintenance Dose Below 2.4 mg, in Case of Intolerance.

The PCFB in BMI (primary endpoint) was considered most suited than PCFB in BW in assessing the efficacy various semaglutide maintenance doses in adolescent, as BMI takes into account the rapid change in height in adolescents. Table 4.1.11 shows the model-predicted response at Week 68 for various maintenance doses of 0.5, 1.0, 1.7 and 2.4 mg in a STEP TEENS population following the planned dose escalation. According to the Applicant's simulations (using the longitudinal weight and BMI loss models) substantial reductions of BMI can be realized with maintenance doses below 2.4 mg semaglutide (with average reductions of least 5%) and therefore support the proposal of allowing subjects to remain under lower maintenance doses, depending on individual's semaglutide treatment tolerance.

Table 4.1.11. Applicant's Model-Predicted Average Percent Change from Baseline in BMI or Weight by Dose for STEP TEENS Population

Dose	Steady state Cavg (nmol/L)	BMI (%) - change from baseline	BW (%) - change from baseline
Sema 2.4 mg	73.38	-17.99	-16.12
Sema 1.7 mg	51.98	-15.56	-13.75
Sema 1.0 mg	30.58	-11.71	-9.99
Sema 0.5 mg	15.29	-7.29	-5.66

Source: Applicant's Response to FDA Request, 25 October 2022 (SN 0262), Table 2-3, page 14.

The reviewer's evaluation of the ability of lower maintenance doses (below 2.4 mg) to provide a minimum of 5% decrease in BMI at Week 68, based on population simulations from the

longitudinal weight/BMI loss model, is summarized in Table 4.1.12. The reviewer's results show that under the regular maintenance of 2.4 mg, the model-predicted overall average PCFB in BMI is -16.4%, which is in line with the estimated 16.14% PCFB in BMI in STEP TEENS in semaglutide treatment arm. Under a maintenance of 1 mg, the overall mean (95%CI) predicted PCFB in BMI is -10.3% (-12.6%, -8.18%). However, when considering the difference in response between male and female, male subjects are predicted to derive less benefit from a 1 mg maintenance dose compared to female, with the lower bound of the 95% CI for the mean PCFB in BMI of -4.5%. In comparison, a maintenance dose of 1.7 mg is predicted to provide a mean reduction in BMI of at least 5%, regardless of patients' sex.

Based on the model prediction, a maintenance to 1.7 mg once-weekly is acceptable and is predicted to maintain efficacy (with a minimum of 5% decrease in BMI) in all patients, if patients cannot reach the 2.4 mg dose or do not tolerate 2.4 mg. (b) (4)

Table 4.1.12. Reviewer's Model-Predicted Average Percent Change from Baseline in BMI by Gender

Maintenance Dose	**Mean (95%CI)[a] %CFB in BMI at Week 68**		
	Overall	***Female***	***Male***
Placebo	-0.159 (-1.24, 0.874)	-0.181 (-1.56, 1.11)	-0.209 (-1.85, 1.66)
0.25 mg	-4 (-6.05, -2.09)	-4.92 (-7.31, -2.11)	-2.83 (-5.53, 0.0921)
0.5 mg	-6.64 (-8.86, -4.51)	-7.8 (-10.4, -5.25)	-4.76 (-7.78, -1.51)
1 mg	-10.3 (-12.6, -8.18)	-12.2 (-15.2, -9.23)	-7.56 (-10.9, ***-4.32***)
1.7 mg	-13.8 (-16.3, -11.5)	-16.3 (-19.4, -13.2)	-10.1 (-14.5, -6.71)
2.4 mg	-16.4 (-18.8, -13.8)	-19.1 (-22.2, -15.8)	-12.3 (-16.3, -8.37)

[a] Mean (95% CI) %CFB in BMI: mean (95% confidence interval) percent change from baseline (or PCFB) in BMI. The 95%CIs were derived using the percentiles method from Monte-Carlo simulations using the longitudinal BMI loss model, with 500 replicates of the STEP TEENS datasets. The population simulations were performed from day 0 up to Week 68 for all maintenance doses, with dose escalation every 4 weeks up to the maintenance dose of interest.

Source: FDA assessment

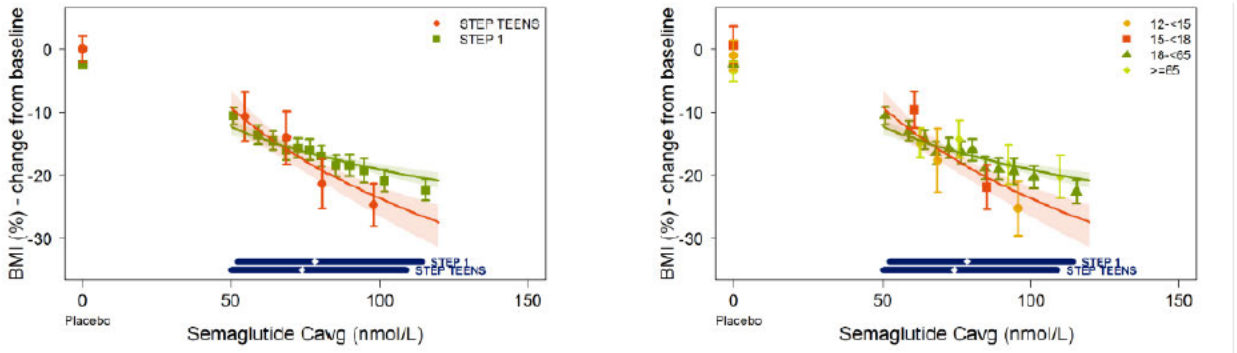
4.1.2.3 Exposure-response models for BMI reduction at Week 68

In addition to the longitudinal exposure-response model, the Applicant evaluated and compared the relationship between semaglutide exposure at Week 68 and the PCFB in BMI from STEP 1 and STEP TEENS trials.

The exposure-response analysis for the percent change in BMI was based on data from subjects randomized to the active semaglutide treatment only. The PCFB in BMI was analyzed using a linear regression model with trial, baseline BMI, sex, log-transformed C_{avg} [log(C_{avg})], [log(C_{avg})] by sex interaction and [log(C_{avg})] by trial interaction as covariates.

Figure 4.1.14 shows the exposure-response relationship for PCFB in BMI after 68 weeks of treatment. According to the Applicant analysis, the improvement in BMI increased in an exposure-dependent manner and the relationship was steeper in STEP TEENS compared to STEP 1. In addition, at similar exposure levels the response in teens aged 12 to <15 years and 15 to <18 years, appeared similar.

Figure 4.1.14. Percent Change from Baseline in BMI versus Semaglutide Exposure by Trial and by Age Groups



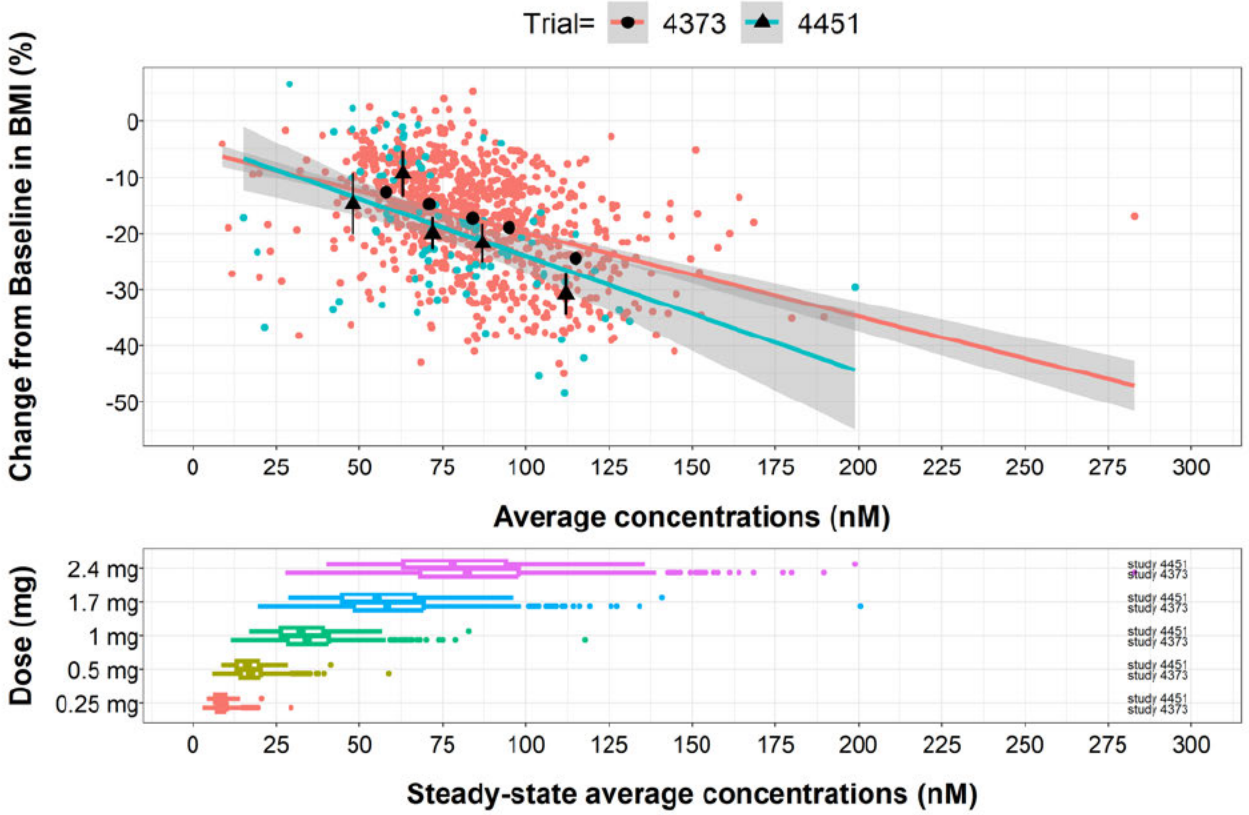
Data points with error bars are mean BMI changes with 95% CI obtained after 68 weeks of treatment versus exposure expressed as quantiles of Cavg, where STEP 1 is divided into 12 and STEP TEENS into 4 quantiles (plus placebo at Cavg of 0 nmol/L). Lines through data are covariate-adjusted model-derived exposure-response relations with shaded areas being 95% point-wise CIs. Horizontal lines with diamonds represent the median and 90% exposure range. Missing data at week 68 were predicted using trial specific mixed model for repeated measures. Data from trials STEP 1 and STEP TEENS from the full analysis set.

Source: Applicant's Pharmacometrics Modelling Report, Figure 6-7, page 35.

Reviewer's Assessment

The Applicant's C_{avg} calculation did not consider dose reductions and the actual maintenance dose at Week 68 and considered that all patients were receiving a dose of 2.4 mg at Week 68. Figure 4.1.15 shows the exposure-response relationship at Week 68 after accounting for dose reductions, when deriving the C_{avg} for each individual.

Figure 4.1.15. Observed and mean predicted Percent Change from Baseline in BMI versus Semaglutide Exposure at Week 68 (upper panel) and Distribution of Semaglutide Steady-State Average concentrations Under Different Maintenance Doses (lower panel)



Note: In the upper panel, the shared areas are the 95%CIs. Trial 4373 STEP 1 trial in adults and trial 4451 is STEP TEEN trial in adolescent.
Source: FDA assessment.

The reviewer's assessment of the relationship using C_{avg} instead of log (C_{avg}) as an independent variable, with adjustment for baseline BMI, trial, and sex as per the Applicant's model, provided a better fit of the data (with higher adjusted R-squared of 19%). No statistically significant difference in the steepness of the slope of the exposure-response relationship was identified between male and females, even after adjusting for age groups (12-<15 years old, 15-<18 years old and adults). However, males had a higher intercept compared to female. Age, age groups, or trials were not found to be statistically significant covariates.

Table 4.1.13 shows the predicted PCFB in BMI under different maintenance doses, based on the linear regression model. The results are in agreement with those obtained from the longitudinal BMI reduction model (**Table 4.1.12**), where a maintenance to 1.7 mg once-weekly is predicted to maintain efficacy (with a minimum of 5% decrease in BMI) in all patients, If patients cannot reach the 2.4 mg dose or do not tolerate 2.4 mg.

Table 4.1.13. Reviewer's Predicted Average Percent Change from Baseline in BMI by Gender

Maintenance Dose	**Mean (95%CI)[a] %CFB in BMI at Week 68**	
	Female	***Male***
0.25 mg	-8.87 (-14 - -3.7)	-4.27 (-9.76 - 1.21)
0.5 mg	-10.3 (-14.9 - -5.63)	-5.77 (-10.7 - -0.87)
1 mg	-13.1 (-16.8 - -9.45)	-8.75 (-12.5 - ***-4.99***)
1.7 mg	-17.1 (-19.6 - -14.6)	-12.9 (-15.4 - -10.5)
2.4 mg	-21.1 (-23 - -19.2)	-17.1 (-19.1 - -15.1)

[a] Mean (95% CI) %CFB in BMI: mean (95% confidence interval) percent change from baseline (or PCFB) in BMI, derived from the linear regression model.
Source: FDA assessment

4.1.3 Exposure-Response Analyses for Gastrointestinal Adverse Events

Most of the adverse events (AEs) that led to dose reduction or temporary interruption of treatment were related to a range of gastro-intestinal (GI) disorders common to the GLP-1 class. Nausea and vomiting were the most frequent GI AEs. The Applicant performed an exposure-response analysis to investigate whether there is an association between semaglutide exposure and nausea or vomiting events in adolescents and determine whether the exposure-response relationship was similar to adults.

The exposure-response analysis for GI AEs included only data from subjects randomized to active semaglutide treatment, who at any time experienced nausea or vomiting events of any severity. The data were analyzed using a logistic regression with trial, baseline BMI, sex and log-transformed C_{avg} [log(C_{avg})], log(C_{avg}) by sex interaction and log(C_{avg}) by trial interaction terms as covariates.

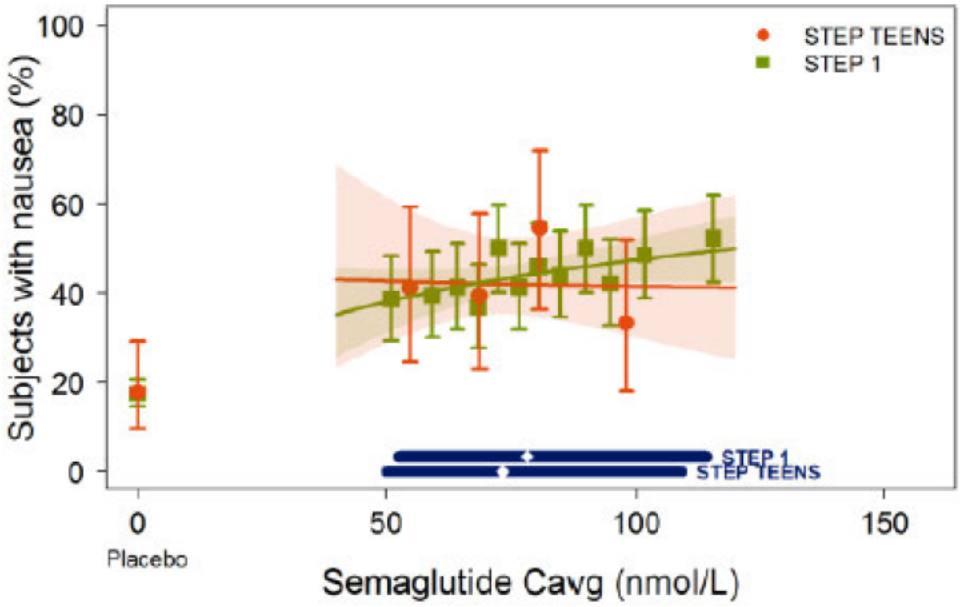
4.1.3.1 Exposure-Response Analysis for Nausea

The exposure-response relationship for the proportion of subjects reporting nausea was comparable in adults and adolescents (**Figure 4.1.16**,

Table 4.1.14). In adults, there was a trend of higher proportion of nausea with increasing exposure that was not found to be statistically significant, according to the Applicant analysis (**Table 4.1.14**

Table 4.1.14, with 95%CI of the STEP 1: slope parameter included zero). There was no apparent exposure-response relationship in adolescents.

Figure 4.1.16. Observed and Predicted Proportion of Subjects Reporting Nausea of Any Severity versus Semaglutide Exposure, Stratified by Trial



Note: Data are proportions with 95% CI versus exposure expressed as quantiles of model derived Cavg values, where STEP 1 is divided into 12 and STEP TEENS into 4 quantiles plus placebo (at Cavg of 0 nmol/L). The lines through data represent covariate-adjusted model-derived estimates for each trial population with shaded areas being 95% point-wise CIs. Horizontal lines with diamonds represent the median and 90% exposure range. Data from trials STEP 1 and STEP TEENS from the on-treatment safety analysis set.

Source: Applicant's Pharmacometrics Modelling Report, Figure 6-8, page 36.

Table 4.1.14. Parameter Estimates for the Exposure-Response Model for Nausea

Label	Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE
Intercept	(Intercept)	-0.064	-7.011	6.889	5514.7
Baseline BMI	bbmi	0.016	-0.005	0.037	65.7
Male	sexMale	-1.519	-6.131	3.062	154.1
STEP 1	TRIALSTEP 1	-2.796	-9.252	3.694	117.5
Slope	log(CAVG)	-0.142	-1.686	1.398	549.5
Male:slope	sexMale:log(CAVG)	0.190	-0.883	1.268	287.7
STEP1:slope	TRIALSTEP 1:log(CAVG)	0.644	-0.856	2.140	118.0

Estimated parameters are expressed on the underlying logit scale.

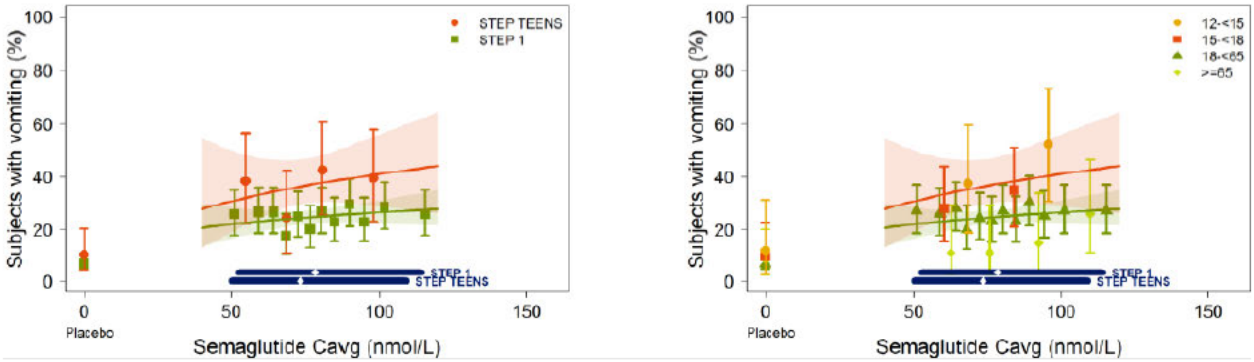
Source: Applicant's Pharmacometrics Modelling Report, Table 9-10, page 56.

The reviewer assessment of the relationship using C_{avg} instead of log (C_{avg}) as independent variable, with adjustment for baseline BMI, trial, and sex as per the Applicant's model, provided a better fit of the data (with lower AIC criterion). The reviewer assessment found that female patients had a statistically significant higher nausea compared to males (odd ratio [95%CI] of 3.1 [1.1 – 8.9]), regardless of exposure. The assessment of the exposure-response relationship after adjusting for age groups (12-<15 years old, 15-<18 years old and adults) did not find a difference in the slope of the exposure-vomiting relationship by age groups.

4.1.3.2 Exposure-Response Analysis for Vomiting

Figure 4.1.17 shows that the proportion of subjects reporting vomiting of any severity during treatment tend to increase with semaglutide exposure. However, this relationship was not found to be statistically significant (**Table 4.1.15**). Higher proportions of vomiting were seen in subjects in STEP TEENS compared to STEP 1, which was also evident from the placebo groups (STEP TEENS: 10.4% and STEP 1: 6.6%). However, this relationship was not found to be statistically significant according to the Applicant's analysis.

Figure 4.1.17. Observed and Predicted Proportion of Subjects Reporting Vomiting of Any Severity versus Semaglutide Exposure, Stratified by Trial and by Age Groups



Note: Data are proportions with 95% CI versus exposure expressed as quantiles of model derived Cavg, where STEP 1 is divided into 12 and STEP TEENS into 4 quantiles plus placebo (at Cavg of 0 nmol/L). The solid lines represent covariate-adjusted estimates for each trial with shaded areas being 95% CIs. Horizontal lines with diamonds represent the median and 90% exposure range. Data from trials STEP 1 and STEP TEENS from the on-treatment safety analysis set.

Source: Applicant's Pharmacometrics Modelling Report, Figure 6-9, page 37.

Table 4.1.15. Parameter Estimates for the Exposure-Response Model for Vomiting

Label	Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE
Intercept	(Intercept)	-3.003	-10.322	4.281	123.4
Baseline BMI	bbmi	0.031	0.008	0.054	38.2
Male	sexMale	-4.101	-9.438	1.203	66.1
STEP 1	TRIALSTEP 1	0.280	-6.468	7.131	1233.5
Slope	log(CAVG)	0.344	-1.264	1.957	237.4
Male:slope	sexMale:log(CAVG)	0.826	-0.419	2.071	76.8
STEP1:slope	TRIALSTEP 1:log(CAVG)	-0.211	-1.791	1.351	377.7

Estimated parameters are expressed on the underlying logit scale.

Source: Applicant's Pharmacometrics Modelling Report, Table 9-10, page 56.

The reviewer assessment of the relationship using C_{avg} instead of log (C_{avg}) as independent variable, with adjustment for baseline BMI, trial, and sex as per the Applicant's model, provided a better fit of the data (with lower AIC). The reviewer assessment found that female patients had a statistically significant higher vomiting compared to males (odd ratio [95%CI] of 5.6 [1.7 – 18.6]), regardless of exposure. The assessment of the exposure-response relationship after adjusting for age groups did not find a difference in the slope of the exposure-vomiting relationship by age groups.

4.2 Summary of Bioanalytical Method Validation

Semaglutide concentrations in human plasma were quantified using plasma protein precipitation followed by LC-MS/MS assays.

Table 4.2.1 Summary of bioanalytical method validation VCA11388

Analyte		Semaglutide (NNC0113-0000-0217)	
Matrix (Anticoagulant)		Human plasma (K_3EDTA)	
Preservative		N/AP	
SOP Number		SOP SM1-385A	
Assay Method		LC-MS/MS method following protein precipitation	
Detector		Applied Biosystems/MDS SCIEX API QTrap® 5500	
Assay Volume Required		0.10 mL	
Standard Curve Range		0.729 – 60.8 nmol/L (3.00 – 250 ng/mL)	
Regression Type		Linear (1/concentration^2)	
Quantification Method		Peak Area Ratio	
Quality Control Samples		Precision (%)	Accuracy (%)
Between-run	LLOQ (QC 3)	6.8	100.2
(Watson runs 2, 3, 4)	QC 9	3.9	99.9
	QC 40	3.3	99.7
	QC 200	3.3	98.0
Within-run	LLOQ (QC 3)	4.8	96.1
(Watson run 3)	QC 9	2.7	98.9
	QC 40	2.2	98.6
	QC 200	3.6	96.3
Sensitivity		Within acceptance	
Selectivity		No interference, 10 matrix lots investigated	
Matrix Effect		Within acceptance, 7 matrix lots investigated	
Carry-over		Within acceptance	
Stress test		No cross-well contamination	
Interference in haemolysed matrix		No interference observed	
Impact of haemolysis		No impact on precision and accuracy observed	
Processed Sample Integrity		Demonstrated for up to 172 hours at 5°C	
Performance of Acquity UPLC Iclass Binary Solvent Manager		Not demonstrated	
Stability of Semaglutide N15 C13 (IS):			
Short-term stability in solution		Demonstrated at room temperature for at least: • 20 hours at 1.20 mg/mL (as delivered by Sponsor) • 20 hours in methanol / water / formic acid (80:20:0.2 v/v/v) at 12.0 µg/mL • 29 hours in BSA / water (0.5:100 w/v) at 150 ng/mL	
Long-term stability in solution		Demonstrated at -20°C for at least 65 days in methanol / water / formic acid(80:20:0.2 v/v/v) at 12.0 µg/mL	
Stability of Semaglutide:			
Long-term stability in matrix		Demonstrated at -20°C for at least 463 days in matrix (at low QC, high QC and DQC level)	
Batch Size		Up to 192 injections	

(*Source*: Study report No. ACA27619-01, *"Determination of semaglutide in human plasma (EDTA) samples from "Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity" by LC-MS/MS*, Module 5.3.5.4, Sequence 0217; Trial ID: STEP TEENS NN9536-4451)

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JAYABHARATHI VAIDYANATHAN
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