Office of Clinical Pharmacology Review

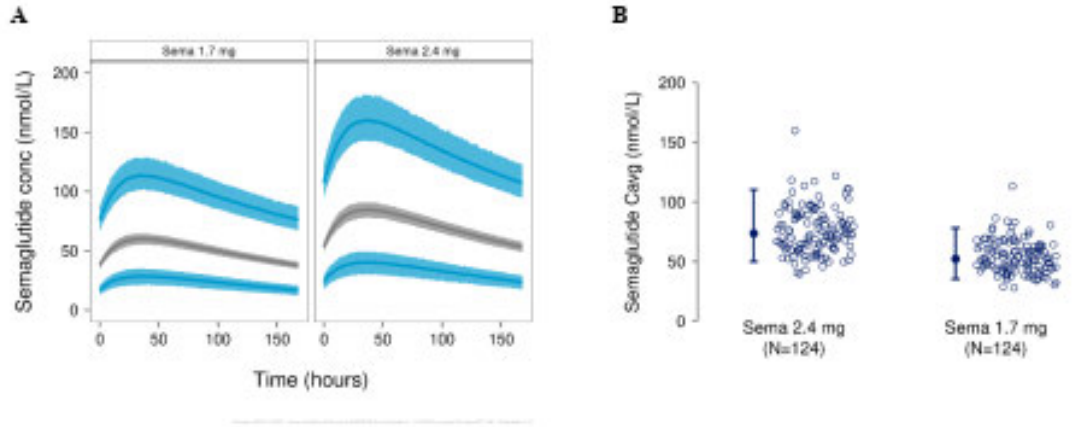
<table>
<tr><td>NDA Number</td><td>215256 (Supplement S-015) (SDN 533/ eCTD 0518)</td></tr>
<tr><td>Link to EDR</td><td>\\CDSESUB1\evsprod\NDA215256\0518</td></tr>
<tr><td>Submission Date</td><td>01/29/2024</td></tr>
<tr><td>Submission Type</td><td>Efficacy supplement (S-015)</td></tr>
<tr><td>Brand Name</td><td>Wegovy®</td></tr>
<tr><td>Generic Name</td><td>Semaglutide</td></tr>
<tr><td>Dosage Form and Strength</td><td>Pre-filled, single-dose pen that delivers doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous (SC) Injection</td></tr>
<tr><td>Indication</td><td>Wegovy® is indicated in combination with a reduced calorie diet and increased physical activity:
to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
to reduce excess body weight and maintain weight reduction long term in:
Adults and pediatric patients aged 12 years and older with obesity.
Adults with overweight in the presence of at least one weight-related comorbid condition.</td></tr>
<tr><td>Dosage Regimen (Current)</td><td>Initial Wegovy® dose of 0.25 mg injected subcutaneously once weekly and follow the dose escalation schedule in Table to minimize gastrointestinal adverse reactions.
<table>
<tr><th>Treatment</th><th>Weeks</th><th>Once weekly SC Dose</th></tr>
<tr><td>Initiation</td><td>1 through 4</td><td>0.25 mg</td></tr>
<tr><td rowspan="3">Escalation</td><td>5 through 8</td><td>0.5 mg</td></tr>
<tr><td>9 through 12</td><td>1 mg</td></tr>
<tr><td>13 through 16</td><td>1.7 mg</td></tr>
<tr><td>Maintenance</td><td>17 and onward</td><td>1.7 mg or 2.4 mg (Adult)
2.4 mg (Pediatric)</td></tr>
</table>
If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.
The maintenance dosage of Wegovy® in adults is either 2.4 mg (recommended) or 1.7 mg once weekly.
The maintenance dosage of Wegovy® in pediatric patients aged 12 years and older is 2.4 mg once weekly.</td></tr>
<tr><td>Applicant</td><td>Novo Nordisk Inc.</td></tr>
<tr><td>Associated INDs</td><td>IND126360, IND114464</td></tr>
<tr><td>OCP Review Team</td><td>Mohamed Ismail Nounou, Ph.D. (Clin. Pharm), Jiajun Liu, PharmD., MSc (PM) & Justin C. Earp, Ph.D. (TL, PM)</td></tr>
<tr><td>OCP Final Signatory</td><td>Jayabharathi Vaidyanathan, Ph.D. (TL & Signatory)</td></tr>
</table>

Table of Contents

1. EXECUTIVE SUMMARY

- Semaglutide is a long-acting analog of human glucagon-like peptide-1 (GLP-1).
- 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 adults 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 T2DM, or dyslipidemia). Dose is initially initiated at 0.25 mg once weekly (QW) for 4 weeks. The dose is then titrated every 4 weeks to achieve the maintenance dosage (**2.4 mg QW**).
- NDA 215256 Wegovy® (semaglutide) injection Supplement S-007 was approved on July 21, 2023, for an **additional maintenance dose** of 1.7 mg QW for adults. The approval of Supplement S-007 included the following post-marketing requirement (*PMR*): *PMR 4472-1: Conduct exposure and exposure-response analyses to evaluate the efficacy and safety of semaglutide to support the 1.7 mg dose for the treatment of chronic weight management in pediatric patients with obesity ages 12 to less than 18 years. In addition to pharmacokinetic and pharmacodynamic data from STEP 1 and STEP TEENS, include data from STEP 6 in your analyses.*
- NDA 215256 Wegovy® (semaglutide) injection Supplement S-011 was approved on March 08, 2024, for an **additional indication** to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke) in adults with an initial BMI of 27 kg/m^2 or greater).
- In the current efficacy supplement, Novo Nordisk is submitting the final PMR report in response to Supplement S-007 and proposing prescribing information updates for an additional maintenance dose of 1.7 mg in pediatric patients aged 12 years and older with obesity based on extrapolation. No new clinical data has been submitted in the current efficacy supplement (S-015).
- According to the Applicant's modeling and simulation analyses, the efficacy of 1.7 mg QW as a maintenance dose was supported for adolescents aged 12 years and older with obesity in regard to percent change from baseline in body weight (BW), BMI, and additional BMI related responder endpoints. Overall, the proposed maintenance dose of 1.7 mg QW provided differentiation from placebo and clinical benefits in the target pediatric patients with obesity.
- The predicted exposure for semaglutide 1.7 mg was extrapolated from semaglutide 2.4 mg by a dose ratio of 1.7/2.4 (**Figure 1**, *Source: **Figure 6-1**, NN9536 STEP TEENS Extrapolation Study, Population PK and Exposure- Response Meta-Analysis Report Version: 1.0, 16 January 2024, eCTD 0518, M5.3.3.5*). The average semaglutide exposure reduced from 74.0 nmol/L for semaglutide 2.4 mg to 52.4 nmol/L for semaglutide 1.7 mg.

Figure 1: A) Simulated steady state concentrations versus time since latest doses 1.7 and 2.4 mg and B) Average individual steady-state semaglutide concentrations (C_{avg}) predicted from empirical Bayes estimates of apparent clearance from STEP TEENS.



A) The 95% CI for the model simulated median (grey) and 5th /95th (blue) percentiles are shown by the coloured ribbons from 1000 trial simulations.

B) Error bars are geometric mean with 5th and 95th percentiles. N is the number of subjects contributing with PK data.

The model-predicted changes from baseline in BW and BMI after 68 weeks of placebo and semaglutide treatments are presented in **Table 1** and **Table 2** *(Source: **Tables 6-1 & 6-2,** NN9536 STEP TEENS Extrapolation Study, Population PK and Exposure- Response Meta-Analysis Report Version: 1.0, 16 January 2024, eCTD 0518, M5.3.3.5).*

Table 1: Model-predicted Changes from Baseline in BW at Week 68 in Adolescent Patients with Obesity.

Treatment	Endpoint	Prediction[a]	Lower	Upper	Treatment policy estimand[b]	Hypothetical estimand[c]
Placebo	% change from baseline in BW	1.44	-3.68	5.65	2.7	2.6
Sema 1.7 mg	% change from baseline in BW	-13.4	-17.7	-8.96		
Sema 2.4 mg	% change from baseline in BW	-15.6	-20.0	-10.8	-14.7	-16.3

Table 2: Model-predicted Changes from Baseline in BMI at Week 68 in Adolescent Patients with Obesity.

Treatment	Endpoint	Prediction[a]	Lower	Upper	Treatment policy estimand[b]	Hypothetical estimand[c]
Placebo	% change from baseline in BMI	-0.00458	-4.01	3.79	-0.6	0.6
Sema 1.7 mg	% change from baseline in BMI	-15.2	-18.8	-11.4		
Sema 2.4 mg	% change from baseline in BMI	-17.4	-21.4	-13.4	-16.1	-17.9

- **Review questions are as follows:**
  - How does the expected semaglutide exposure levels following administration of 1.7 mg QW compare to 2.4 mg QW?
  - Is the exposure-response (E-R) analysis results from STEP adult and STEP TEENS studies provide sufficient evidence of efficacy for the proposed 1.7 mg maintenance dose in adolescents?
  - Is the E-R analysis results from STEP adult and STEP TEENS studies provide sufficient evidence of safety for the proposed 1.7 mg maintenance dose in adolescents?

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed information submitted in sNDA 215256 (S-015) 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	The Pharmacometrics Study Report (*Version: 1.0, Jan 16, 2024, M5.3.3.5 eCTD 0518/SDN533*) entitled "*Extrapolation of pharmacokinetics, efficacy and safety from 2.4 mg to 1.7 mg semaglutide in adolescents, using population PK and exposure-response analysis*" supports the proposed prescribing information for the additional maintenance dose of 1.7 mg for pediatric population with obesity aged 12 and above. The efficacy of 1.7 mg QW based on modeling and simulation was supported for percent change from baseline in BW, BMI, and additional BMI related responder endpoints (i.e. proportion of patients that achieved 5%, 10%, and 15% change in BMI).
General dosing instructions	The therapeutic and maintenance doses is 2.4 mg or 1.7 mg QW. 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. Administration is SC into the abdomen, thigh or upper arm with change of the injection sites.
Dosing in patient subgroups	In adult and pediatric populations, maintenance dose can be decreased to 1.7 mg QW if patients do not tolerate the 2.4 mg maintenance dose.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label regarding allowing dose reduction no lower than 1.7 mg. We disagree with the sponsor's proposal deleting the following language: *"Discontinue WEGOVY if the patient cannot tolerate the 1.7 mg once-weekly dosage."*

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 Glucagon-like peptide-1 (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 Dipeptidyl peptidase 4 (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 pharmacokinetic (PK) data from 3 adult (Studies 4153, 4373 (STEP 1) & 4374 (STEP-2)) and one pediatric (Study 4451) studies was used by the Applicant to conduct population PK and extrapolation analyses (Population PK and Exposure-Response Meta-Analysis Report Version: 1.0, 16 January 2024, *eCTD 0518, M5.3.3.5*). STEP 6 (Study 4382) trial was used to evaluate the predictive capabilities of the E-R model. The results showed the average semaglutide exposure was reduced from 74.0 nmol/L for semaglutide 2.4 mg to 52.4 nmol/L for semaglutide 1.7 mg at steady state with overlapping exposures. Based on the population PK and exposure-efficacy weight loss model, the efficacy of 1.7 mg was supported for adolescents aged 12 years and older with obesity, for percent change from baseline in BW, BMI, and additional BMI related responder endpoints (i.e., proportion of patients achieving 5%, 10%, and 15% reductions in BMI). Across these endpoints 1.7 mg provided sufficient differentiation from placebo, and incremental clinical benefits were predicted with semaglutide 2.4 mg and semaglutide 1.7 mg as maintenance dosages. Model-based exposure-safety simulations showed similar proportions of nausea and vomiting for semaglutide 1.7 mg and 2.4 mg, and the results are in line with the known safety profile observed in adults. No other safety concerns would be expected when extrapolating the safety established at 2.4 mg QW to the reduced dose of 1.7 mg QW as a maintenance dose. The results provided in this report are considered adequate to document the pharmacokinetics, efficacy, and safety of semaglutide 1.7 mg as a maintenance dose in adolescents with obesity aged 12 years and older.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

In the currently approved USPI (Reference ID: 5342984, Revised: 03/2024), the maintenance dose is 2.4 mg (recommended) or 1.7 mg once weekly for adult patients and 2.4 mg once weekly for pediatric patients aged 12 years and older, 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) until 2.4 mg once weekly is reached.

The proposed language update in the labeling states that maintenance dosage is either 2.4 mg (recommended) or 1.7 mg once weekly for the indicated patient population.

2.2.2 Therapeutic individualization

No separate dose/dosing regimen is recommended in adolescent patients. Dose-escalation is 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 QW dose.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The Applicant is proposing a unified maintenance dosage for pediatrics and adult population in section 2.3 as follows:

The maintenance dosage of WEGOVY in adults is either 2.4 mg (recommended) or 1.7 mg once weekly. Consider treatment response and tolerability when selecting the maintenance dosage.

The sponsor is proposing to delete section 2.4 "*Recommended Dosage in Pediatric Patients Aged 12 Years and Older*", as follows:

~~Dosage Initiation and Escalation~~

- ~~Initiate WEGOVY according to the dosage escalation schedule in Table 4 to minimize gastrointestinal adverse reactions [see Adverse Reactions (6.1)].~~
- ~~If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.~~
- ~~The 0.25 mg, 0.5 mg, and 1 mg once-weekly dosages are initiation and escalation dosages and are not approved as maintenance dosages for~~ (b) (4) ~~weight management.~~

~~Table 4~~~~: Recommended Dosage Regimen for Pediatric Patients Aged 12 Years and Older~~

~~Treatment~~	~~Weeks~~	~~Once-weekly Subcutaneous Dosage~~
~~Initiation~~	~~1 through 4~~	~~0.25 mg[a]~~
~~Escalation~~	~~5 through 8~~	~~0.5 mg[a]~~
	~~9 through 12~~	~~1 mg[a]~~
	~~13 through 16~~	~~1.7 mg[b]~~
~~Maintenance~~	~~17 and onward~~	~~2.4 mg~~

~~[a]~~ (b) (4) ~~not approved as maintenance~~ (b) (4)

~~[b]See Dosage Modifications for Adverse Reactions~~

~~Maintenance Dosage~~

- ~~The maintenance dosage of WEGOVY in pediatric patients aged 12 years and older is 2.4 mg once weekly.~~

~~Dosage Modifications for Adverse Reactions~~

- ~~If patients do not tolerate the 2.4 mg once-weekly maintenance dosage, the maintenance dosage may be reduced to 1.7 mg once weekly.~~
- ~~Discontinue WEGOVY if the patient cannot tolerate the 1.7 mg once-weekly dosage.~~

We disagree with the sponsor's proposal deleting the following language: *"Discontinue WEGOVY if the patient cannot tolerate the 1.7 mg once-weekly dosage."*

Reviewer's comment: Based on FDA's pharmacometrics analyses (See ***Appendix 4.1***), FDA recommends, if patients (i.e., adults and pediatrics) cannot reach the 2.4 mg dose or do not tolerate 2.4 mg, the patient can decrease to 1.7 mg dose. Discontinue WEGOVY® if the patient cannot tolerate the 1.7 mg dose.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1. 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.**

3.2 Clinical Pharmacology Review Questions

3.2.1 How does the expected semaglutide exposure levels following administration of 1.7 mg Once Weekly (QW) compare to 2.4 mg QW?

The predicted exposure for semaglutide 1.7 mg was extrapolated from semaglutide 2.4 mg by a dose ratio of 1.7/2.4 (**Figure 1**, Source: *Figure 6-1, NN9536 STEP TEENS Extrapolation Study, Population PK and Exposure- Response Meta-Analysis Report Version: 1.0, 16 January 2024, eCTD 0518, M5.3.3.5*). The results showed the average semaglutide exposure was reduced from 74.0 nmol/L for semaglutide 2.4 mg to 52.4 nmol/L for semaglutide 1.7 mg, but with some overlap in exposure between the 2 doses.

3.2.2 Does the Exposure-Response analysis from STEP adult and STEP TEENS studies provide sufficient evidence of efficacy for the proposed 1.7 mg maintenance dose in adolescents?

Yes, E-R efficacy analysis in pooled adult and adolescent patients provide sufficient evidence of efficacy for the 1.7 mg QW maintenance dose based on extrapolation. No new or unexpected findings were reported. Because there is no new clinical data and the E-R efficacy model (i.e., weight loss model) remains the same, the reviewer agrees with the previous FDA assessment that the 1.7 mg once-weekly dose is predicted to maintain efficacy, and the model predictions support the reduced 1.7 mg maintenance dose in adolescent patients (*See Pharmacometrics Review, Section 4.1.; 4.1.2.1 E-R Efficacy Extrapolation*). Overall, the 1.7 mg dose is predicted to maintain efficacy in all patients.

3.2.3 Is the E-R analysis results from STEP adult and STEP TEENS studies provide sufficient evidence of safety for the proposed 1.7 mg maintenance dose in adolescents?

Considering the clinical experience with 2.4 mg QW maintenance dose in both adult and adolescent patients, a reduced maintenance dose of 1.7 mg QW is expected to be safe in adolescent patients. Furthermore, the E-R safety analyses in the pooled adult and adolescent patients provide additional supportive evidence of safety for the 1.7 mg QW maintenance dose (*See Pharmacometrics Review, Section 4.1.; 4.1.2.2 E-R Safety Extrapolation*). The E-R safety model for nausea suggests that there is no statistically significant difference in E-R relationship between adult and adolescent patients, and similar proportions of nausea are expected at both 1.7 mg and 2.4 mg QW (**Figure 5**). Based on the E-R safety model for vomiting, STEP TEENS effect is statistically significant (odds ratio of 1.8), indicating that the adolescent patients are expected to have higher proportions of vomiting than adult patients. This is also evident based on **Figure 5**. For the 1.7 mg reduced maintenance dose, however, the proportion of vomiting is expected to be similar or lower than those of the 2.4 mg maintenance dose (**Table 10**). Overall, the E-R analysis results for nausea and vomiting support the reduced 1.7 mg maintenance dose for adolescent patients.

4. APPENDIX

4.1. Pharmacometrics Review

4.1.1. Population PK analysis

4.1.1.1. Review Summary

The Applicant submitted population pharmacokinetic (popPK) and exposure-response (E-R) analyses for safety and efficacy to support extrapolation of semaglutide PK, efficacy, and safety from 2.4 mg once weekly in adults and adolescents and 1.7 mg once weekly in adults to an additional maintenance dose of 1.7 mg once weekly in adolescents (i.e., 12 to less than 18 years of age). The extrapolation approach utilized a previously developed semaglutide popPK model to characterize semaglutide PK in adult and adolescent patients and to support subsequent E-R analyses for safety and efficacy. The popPK analysis was reviewed previously. Briefly, the popPK model is a one-compartment model that adequately describes the pooled semaglutide concentrations for adult (STEP 1, NN9536-4373) and adolescent (STEP TEENS, NN9536-4451) patients, and based on FDA assessment, no dose adjustment is needed based on age or weight. For details on popPK model development, refer to the Clinical Pharmacology review of NDA 215256 efficacy supplement 005 (*DARRTS: link; Reference ID: 5098541*). The E-R models are also considered acceptable for capturing the effects of different semaglutide maintenance doses (i.e., 2.4 mg and 1.7 mg) and placebo effect (i.e., diet and exercise) on body weight and BMI reductions from baseline and additional BMI related responder endpoints (i.e., proportion of patients that achieved 5%, 10%, and 15% change in BMI) over time. Overall, the popPK and the E-R models (efficacy and safety) are considered acceptable for performing simulations within the studied dose levels and predicting pharmacodynamic (PD) endpoints to support semaglutide labeling update of a reduced maintenance dosage of 1.7 mg for adolescent patients (in cases where 2.4 mg once weekly cannot be reached or tolerated).

4.1.1.2. Introduction

The Applicant aims to extrapolate semaglutide PK, efficacy and safety from available clinical PK and outcomes data, leveraging developed models based on data from completed phase 2 and phase 3 weight management trials in adults and adolescents with obesity, with additional model evaluation for the 1.7 mg dose in adults (trial STEP 6). Following administration of 1.7 mg once weekly in adolescents, the Applicant's objectives are to:

- Characterize semaglutide exposure levels
- Quantify the percent change from baseline in body weight and BMI, as well as additional BMI related responder endpoints (i.e., proportion of patients that achieved 5%, 10%, and 15% change in BMI), to Week 68
- Quantify the expected proportion of patient's reported nausea or vomiting from baseline to Week 75

4.1.1.3. Model Development

PopPK model analysis (for STEP 1 and STEP TEENS) and the similarity of model-predicted exposures of 1.7 mg once weekly maintenance dose between STEP 1 and STEP TEENS patients were previously reviewed in efficacy supplement 005. For semaglutide popPK model assessment, refer to Clinical Pharmacology review of NDA 215256 efficacy supplement 005 (*DARRTS: link; Reference ID: 5098541*).

4.1.2. E-R Analyses

The E-R analysis population (for safety and efficacy) were pooled from 4 clinical studies, including placebo patients (Study 4153, STEP 1, STEP 2, and STEP TEENS), and semaglutide concentrations

were set to zero. A summary of clinical studies is provided in **Table 3**. Of note, STEP 6 (NN9536-4382) included placebo and 1.7 mg and 2.4 mg semaglutide doses, where pharmacokinetics, efficacy and safety were assessed in East-Asian patients, of whom 24.7% having type 2 diabetes at baseline. STEP 6 trial was used to evaluate the predictive capabilities of the E-R model.

Table 3: Summary of Clinical Studies

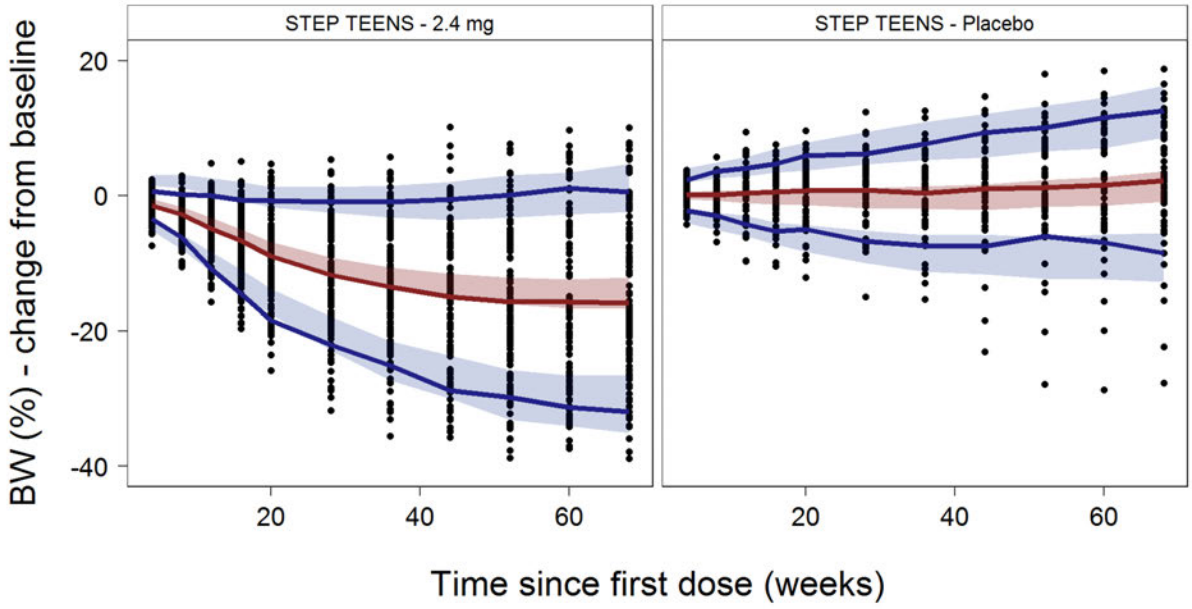
Trial	Description	Randomization	Population	Analyses included in analysis of adult data	Analyses included in analysis of paediatric data	Date of completion
Phase 2 dose-ranging trial (NN9536-4153)	52-week, placebo-controlled, phase 2 trial of once-daily semaglutide with liraglutide 3.0 mg as active comparator	6:1 to each active treatment group (semaglutide doses of 0.05, 0.1, 0.2, 0.3 or 0.4 mg once daily; liraglutide 3.0 mg daily) or matching placebo (52 weeks)	Adults with a BMI ≥30 kg/m^2 without T2D N = 957	Population PK E-R development for efficacy		October-2017
STEP 1 (NN9536-4373)	68-week, placebo-controlled, phase 3 trial of once-weekly semaglutide	2:1 to semaglutide 2.4 mg once weekly or matching placebo (68 weeks)	Adults without T2D† with a BMI ≥27 kg/m^2 and ≥1 weight-related co-morbidity or a BMI ≥30 kg/m^2 N = 1961	Population PK E-R development for efficacy and gastrointestinal AE	Population PK E-R development for gastrointestinal AE	June-2020
STEP 2 (NN9536-4374)	68-week, placebo-controlled, phase 3 trial of once-weekly semaglutide	1:1:1 to semaglutide 2.4 mg once weekly, semaglutide 1.0 mg once weekly or matching placebo (68 weeks)	Adults with T2D with a BMI ≥27 kg/m^2 N = 1210	Population PK E-R development for efficacy and gastrointestinal AE	E-R development for gastrointestinal AE	August-2020
STEP 6 (NN9536-4382)	68-week, placebo-controlled, phase 3 trial of once-weekly semaglutide	4:1:2:1 to semaglutide 2.4 mg once weekly, semaglutide 1.7 mg once weekly or matching placebo groups (68 weeks)	Adults without or with T2D with a BMI ≥27 kg/m^2 and ≥2 weight-related co-morbidity or a BMI ≥35 kg/m^2 and ≥1 weight-related co-morbidity N=401	Population PK E-R development for efficacy and gastrointestinal AE	E-R development for gastrointestinal AE	April-2021
STEP TEENS (NN9536-4451)	68-week, placebo-controlled, paediatric trial of once-weekly semaglutide	2:1 to semaglutide 2.4 mg once weekly (or MTD**) or matching placebo (68 weeks)	Adolescents (ages 12 to <18) with BMI ≥95th percentile* OR adolescents (ages 12 to <18) with BMI ≥85th percentile* with ≥1 weight related comorbidity (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or T2D N = 201		Population PK E-R extension for efficacy and development for gastrointestinal AE	June-2022

**sex-specific or age-specific growth charts (CDC.gov)*
***Maximum tolerated dose*
AE, adverse event
Source: Applicant's popPK and E-R extrapolation report, Table 4-1, page 12

4.1.2.1. E-R Efficacy Extrapolation

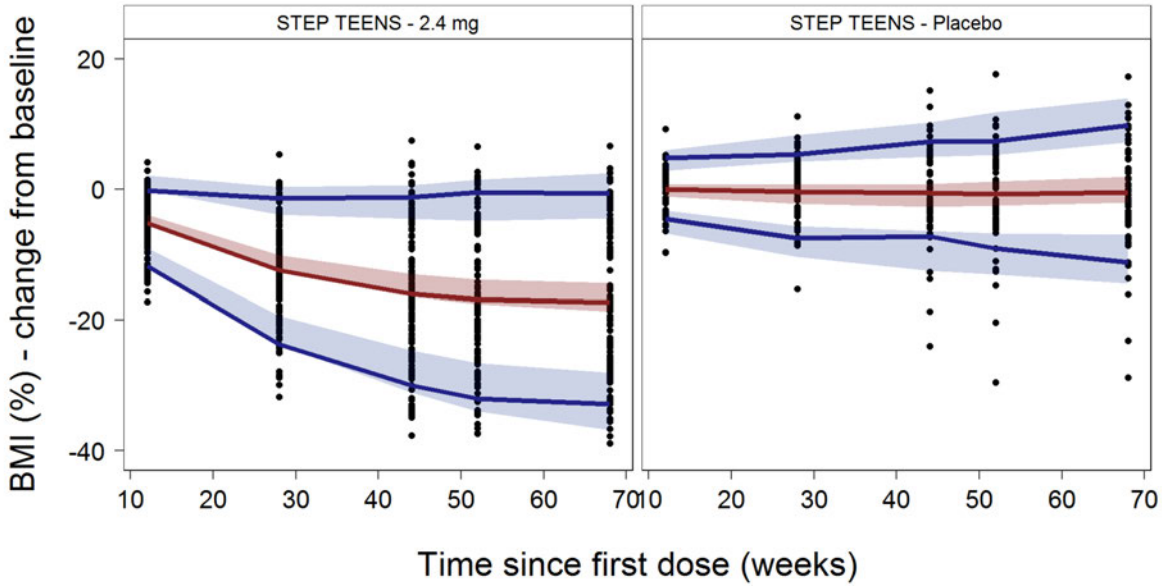
For the efficacy extrapolation analysis, a longitudinal weight loss model was used to characterize the time-course of semaglutide effect on the average body weight and BMI lowering from baseline at different maintenance doses (i.e., 1.7 mg and 2.4 mg) at Week 68. This E-R model and analysis results were previously reviewed, and the Applicant presented the same model output and E-R findings in this submission. Briefly, the longitudinal E-R model was first developed using STEP 1 data, and the weight loss parameters were fixed. Subsequently, the STEP TEENS data were included as a covariate on the adult model parameters. In the efficacy supplement S-005 review, the FDA review team concluded that the model can be used to perform simulations to predict the average percent change from baseline in body weight and BMI and determine whether maintenance doses lower than 2.4 mg (for adolescents who cannot tolerate the 2.4 mg maintenance dose) are expected to remain efficacious. Visual predictive check (VPC) plots for the final E-R model for placebo and 2.4 mg dose in adolescents are shown in **Figure 2** and **Figure 3**. Model-predicted percent changes in body weight, BMI, and additional BMI related responder endpoints (i.e., proportion of patients that achieved 5%, 10%, and 15% change in BMI) from baseline at Week 68 in adolescents are summarized in **Table 4** and **Table 5**, respectively. For the final E-R model development, parameter estimates, and evaluation, refer to Clinical Pharmacology review of NDA 215256 efficacy supplement 005 (*DARRTS: link; Reference ID: 5098541*).

Figure 2: VPCs of Longitudinal Body Weight Reduction in STEP TEENS



Lines, observed data at 10th, 50th and 90th percentiles of percent change of body weight; shaded area, simulated data of n=500 at 10th, 50th and 90th percentiles of percent change of body weight
Source: Applicant's popPK and E-R extrapolation report, Figure 9-12, page 46

Figure 3: VPCs of Longitudinal BMI Reduction in STEP TEENS



Lines, observed data at 10th, 50th and 90th percentiles of percent change of body weight; shaded area, simulated data of n=500 at 10th, 50th and 90th percentiles of percent change of body weight
Source: Applicant's popPK and E-R extrapolation report, Figure 9-11, page 45

Table 4: Model-predicted Changes in Body Weight at Week 68 in Adolescent Patients with Obesity

Treatment	Endpoint	Prediction[a]	Lower	Upper
Placebo	% change from baseline in BW	1.44	-3.68	5.65
Sema 1.7 mg	% change from baseline in BW	-13.4	-17.7	-8.96
Sema 2.4 mg	% change from baseline in BW	-15.6	-20.0	-10.8

[a]Prediction was mean of the 1000 simulated trials results. 95% confidence interval was presented as Lower, being 0.025 percentile and Upper, being 0.975 percentile from distribution of the 1000 simulated trials results.
Source: adapted from Applicant's popPK and E-R extrapolation report, Table 6-2, page 25

Table 5: Model-predicted Changes in BMI at Week 68 in Adolescent Patients with Obesity

Treatment	Endpoint	Prediction[a]	Lower	Upper
Placebo	% change from baseline in BMI	-0.00458	-4.01	3.79
Sema 1.7 mg	% change from baseline in BMI	-15.2	-18.8	-11.4
Sema 2.4 mg	% change from baseline in BMI	-17.4	-21.4	-13.4
Placebo	% of Patients with greater than or equal to 5% reduction in baseline BMI	27.2	10.4	46.3
Sema 1.7 mg	% of Patients with greater than or equal to 5% reduction in baseline BMI	79.6	68.7	88.8
Sema 2.4 mg	% of Patients with greater than or equal to 5% reduction in baseline BMI	83.7	73.9	91.8
Placebo	% of Patients with greater than or equal to 10% reduction in baseline BMI	11.3	2.99	26.9
Sema 1.7 mg	% of Patients with greater than or equal to 10% reduction in baseline BMI	65.2	52.2	77.6
Sema 2.4 mg	% of Patients with greater than or equal to 10% reduction in baseline BMI	71.1	58.2	82.8
Placebo	% of Patients with greater than or equal to 15% reduction in baseline BMI	3.64	0	11.9
Sema 1.7 mg	% of Patients with greater than or equal to 15% reduction in baseline BMI	49.0	35.8	61.9
Sema 2.4 mg	% of Patients with greater than or equal to 15% reduction in baseline BMI	56.2	42.5	68.7

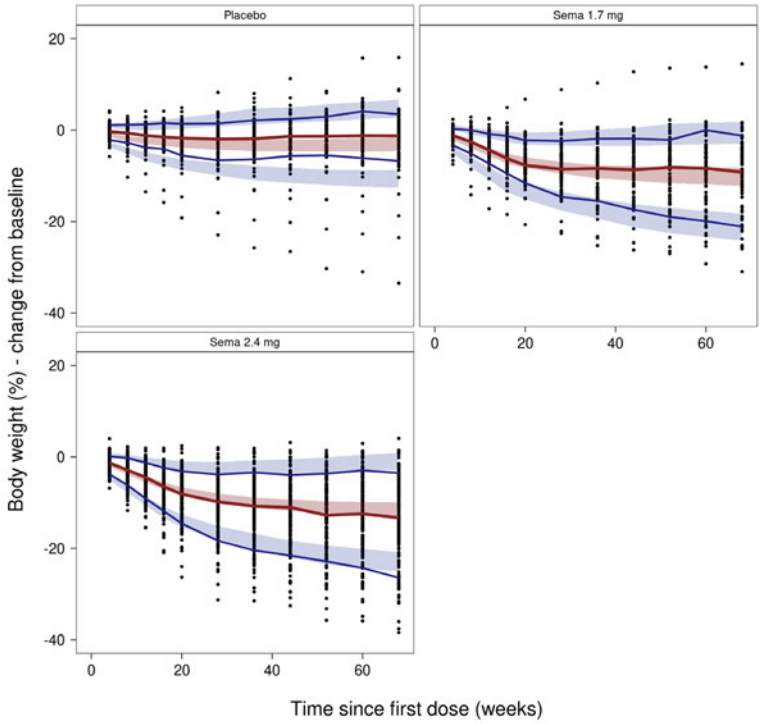
[a]Prediction was mean of the 1000 simulated trials results. 95% confidence interval was presented as Lower, being 0.025 percentile and Upper, being 0.975 percentile from distribution of the 1000 simulated trials results.
Source: adapted from Applicant's popPK and E-R extrapolation report, Table 6-1, page 24

Reviewer's comment: *because there is no new clinical data and the E-R efficacy model remains the same, the reviewer agrees with the previous FDA assessment (DARRTS: link; Reference ID: 5098541) that the 1.7 mg once-weekly dose is predicted to maintain efficacy, and the E-R weight loss model results support the reduced 1.7 mg maintenance dose in adolescent patients. This is also supported by the BMI changes from baseline. Refer to Applicant's popPK and E-R extrapolation report for more details.*

4.1.2.1.1. Prediction of Body Weight Changes in STEP 6

For model validation, data from STEP 6 was utilized to evaluate the predictive performance of the longitudinal E-R weight loss model. VPCs by treatment arms are shown in **Figure 4**.

Figure 4: VPCs of Longitudinal Body Weight Reduction in STEP 6



Lines, observed data at 10th, 50th and 90th percentiles of percent change of body weight; shaded area, simulated data of n=500 at 10th, 50th and 90th percentiles of percent change of body weight
Source: Applicant's popPK and E-R extrapolation report, Figure 9-7, page 41

Reviewer's comment: *the longitudinal E-R model adequately captures the central tendency of the observed percent weight loss from baseline in STEP 6 patients for both 1.7 mg and 2.4 mg once weekly dosing regimens. Overall, the 1.7 mg dose is predicted to maintain efficacy in all patients.*

4.1.2.2. E-R Safety Extrapolation

Based on safety clinical data from STEP TEENS, semaglutide 2.4 mg once weekly was overall well tolerated in adolescent patients with obesity. There were no unexpected safety findings, and the overall safety and tolerability profile reflected those of the adult studies and GLP-1 receptor agnostic class in general. Frequently reported types of gastrointestinal adverse events (AEs) for STEP 1 and STEP TEENS patients are summarized in **Table 6**. Proportions of patients experiencing any severity of nausea or vomiting across studied semaglutide exposure ranges in adult and adolescent patients are illustrated in **Figure 5**.

Table 6: Gastrointestinal AEs for STEP TEENS and STEP 1

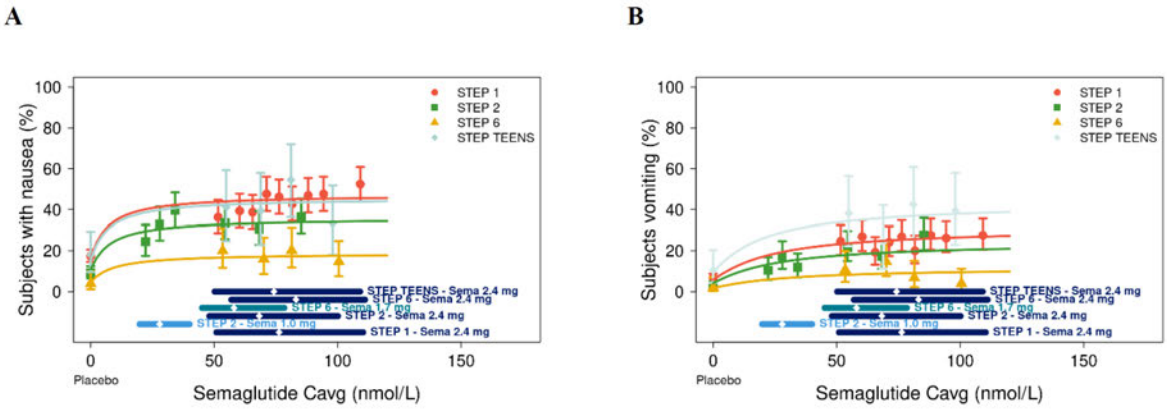
	STEP TEENS		STEP 1	
	Sema (% / R)	**Placebo (% / R)**	**Sema (% / R)**	**Placebo (% / R)**
Nausea	42.1% / 69.9	17.9% / 32.1	44.2% / 62.6	17.4% / 17.6
Vomiting	36.1% / 58.3	10.4% / 19.9	24.8% / 37.3	6.6% / 6.3
Diarrhoea	21.8% / 29.7	19.4% / 21.0	31.5% / 44.9	15.9% / 16.6
Constipation	6.0% / 4.4	1.5% / 1.1	23.4% / 22.9	9.5% / 8.8
Abdominal pain	15.0% / 17.6	6.0% / 4.4	10.0% / 10.3	5.5% / 4.9

%: proportion of subjects experiencing at least one event; R: event rate per 100 years. Data from on-treatment data from the safety analysis sets.

Sema, semaglutide

Source: Applicant's popPK and E-R extrapolation report, Table 5-1, page 20

Figure 5: Proportion of Patients Reporting Nausea and Vomiting vs. Semaglutide Exposure



Symbols are proportions of patients, with 95% CI, versus exposure expressed as quantiles of model-derived Cavg values plus placebo (at Cavg of 0 nmol/L). Horizontal lines with diamonds represent the median and 90% exposure range. The lines through data represent covariate-adjusted model-derived estimates for each trial population, using on-treatment data from the safety analysis set.

Source: Applicant's popPK and E-R extrapolation report, Figure 9-14, page 48

4.1.2.2.1. E-R for Nausea

Nausea events are numerically similar between the treatment arms and placebo arms for STEP TEENS and STEP 1 patients. The model parameter estimates are provided in **Table 7.** Model-predicted nausea proportions are summarized by treatment groups in **Table 8**.

Table 7: Parameter Estimates of E-R for Nausea

Parameter	Estimate	pct.RSE	CI95.lower	CI95.upper
Emax	1.543	10.4	1.298	1.896
EC50 (nmol/L)	5.323	108.9	-1.559	20.918
E0, Placebo	-1.472	6.4	-1.662	-1.286
STEP 2 effect	-0.289	34.4	-0.490	-0.099
STEP 6 effect	-1.045	15.1	-1.350	-0.736
STEP TEENS effect	0.021	789.3	-0.306	0.353
Sex effect	-0.790	11.0	-0.964	-0.623
Baseline BW (kg)	0.003	63.1	-0.001	0.007

Parameters on logit scale

Source: Applicant's popPK and E-R extrapolation report, Table 9-7, page 37

Table 8: Proportion of Patients Reporting Nausea from Baseline to Week 75

Treatment	Semaglutide Cavg (nmol/L)	Prediction[a]	Lower	Upper	Observed[b]
Placebo	0	15.4	11.4	20.2	17.9
Sema 1.7 mg	52.4	42.4	35.3	50.1	
Sema 2.4 mg	74.0	43.4	36.5	50.8	42.1

[a]Prediction, mean of the 1000 simulated trials; 95% confidence interval was presented as 2.5th and 97.5th percentiles from distribution of the 1000 simulated trials results; [b]Observed, proportion (%) of patients in the safety analysis set, experiencing at least one event during on-treatment period
Source: Applicant's popPK and E-R extrapolation report, Table 6-3, page 26

Reviewer's comment: *based on the model parameter estimates and 95% confidence interval, the STEP TEENS effect included null effect. This suggest that the E-R relationship for nausea is not statistically different between STEP 1 and STEP TEENS patients. This is also supported by the comparable E-R relationships shown in* ***Figure* 5**. *Furthermore, the current result is consistent with the findings from the previously reviewed E-R model for nausea (DARRTS: link; Reference ID: 5098541). Overall, the model-based simulation demonstrates similar proportions of nausea at 1.7 mg and 2.4 mg, supporting the reduced 1.7 mg maintenance dose for adolescent patients.*

4.1.2.2.2. E-R for Vomiting

A higher proportion of STEP TEENS patients reporting vomiting is observed when compared to the STEP 1 patients (36.1% vs. 24.8%, respectively); however, STEP TEENS also had a higher rate of reporting vomiting in the placebo group vs. STEP 1 (10.4% vs. 6.6%, respectively). The model parameter estimates are provided in **Table 9.** Model-predicted vomiting proportions are summarized by treatment groups in **Table 10**.

Table 9: Parameter Estimates of E-R for Vomiting

Parameter	Estimate	pct.RSE	CI95.lower	CI95.upper
Emax	2.028	14.0	1.602	2.712
EC50 (nmol/L)	13.317	70.6	2.361	36.784
E0, Placebo	-2.664	5.4	-2.961	-2.410
STEP 2 effect	-0.141	88.9	-0.392	0.082
STEP 6 effect	-0.849	25.2	-1.306	-0.470
STEP TEENS effect	0.613	28.7	0.271	0.979
Sex effect	-0.786	15.0	-1.030	-0.569
Baseline BW (kg)	0.007	35.1	0.002	0.012

Parameters on logit scale
Source: Applicant's popPK and E-R extrapolation report, Table 9-8, page 37

Table 10: Proportion of Patients Reporting Vomiting from Baseline Week 75

Treatment	Semaglutide Cavg (nmol/L)	Prediction[a]	Lower	Upper	Observed[b]
Placebo	0	9.2	6.4	12.9	10.4
Sema 1.7 mg	52.4	34.4	27.5	42.1	
Sema 2.4 mg	74.0	36.7	29.4	44.3	36.1

[a]Prediction, mean of the 1000 simulated trials; 95% confidence interval was presented as 2.5th and 97.5th percentiles from distribution of the 1000 simulated trials results; [b]Observed, proportion (%) of patients in the safety analysis set, experiencing at least one event during on-treatment period
Source: Applicant's popPK and E-R extrapolation report, Table 6-4, page 26

Reviewer's comment: *based on the final* E-R *model for vomiting, STEP TEENS effect is statistically significant (odds ratio of 1.8 and not including null effect), indicating that the adolescent patients are expected to have higher proportions of vomiting than adult patients. This is also evident based on* ***Figure*** **5**. *For the 1.7 mg reduced maintenance dose, however, the proportion of vomiting is expected to be similar or lower than those of the 2.4 mg maintenance dose (****Table*** **10**). *Overall, the* E-R *relationship for vomiting also supports the reduced 1.7 mg maintenance dose for adolescent patients.*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAMED NOUNOU
10/25/2024 04:45:55 PM

JIAJUN LIU
10/25/2024 05:27:45 PM

JUSTIN C EARP
10/25/2024 05:37:35 PM

JAYABHARATHI VAIDYANATHAN
10/28/2024 10:22:11 AM