U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 215256
Supplement #:	005
Drug Name:	Wegovy (semaglutide 2.4 mg injection)
Indication(s):	Adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management in pediatric patients ages 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity) (b) (4) [redacted]
Applicant:	Novo Nordisk, Inc
Date(s):	Submitted: 6/29/2022 Filing Meeting: 8/15/2022 Review Due: 12/6/2022 PDUFA: 12/29/2022
Review Priority:	Priority
Biometrics Division:	DBII
Statistical Reviewer:	Kyunghee K. Song, PhD
Concurring Reviewers:	Feng Li, PhD, Team Leader
Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity Products
Clinical Team:	Julie Golden, MD, Reviewer Laura Higginbotham, MD, Team Leader
Project Manager:	Martin White

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Novo Nordisk submitted an NDA supplement for Wegovy (semaglutide 2.4 mg injection) to add a pediatric indication for adolescents ages 12 years or older with an initial Body Mass Index (BMI) at the 95th percentile or greater for age and sex (obesity) (b) (4) , as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management. The product was approved in 2021 for weight management in adults.

The submission consists of one phase 3 clinical trial (STEP Teens). The trial was a 68-week, multinational, multicenter, randomized, double-blind, placebo-controlled trial and the study subjects received either semaglutide 2.4 mg or placebo subcutaneous (s.c.) once weekly.

The primary endpoint was the percent change from baseline to Week 68 in BMI. The primary efficacy results demonstrated the efficacy for BMI reduction at Week 68, and the results are shown in Table 1. Missing values were handled using retrieved-dropout multiple imputation approach for the primary analysis.

Table 1: Percent Change in Body Mass Index from Baseline to Week 68

	N (obs)	LS mean[1] (SE)	Treatment Difference [95% CI]; p-value
Semaglutide 2.4 mg	134 (131)	-16.14 (1.01)	-16.75 [-20.27, -13.23]; <0.0001
Placebo	67 (62)	0.61 (1.48)	

Abbreviations: N=number of subjects randomized; obs=number of observed; LS mean= least squares mean; SE: standard error; CI=confidence interval; [1]Model based estimates and standard error, the analysis of covariance model included treatment, stratification factors as fixed effects and baseline BMI value as a covariate; Missing observations were multiple imputed (1000 times) from retrieved dropouts in the same randomized treatment.

There were no major statistical issues found during the review of this submission. Efficacy in comparison to placebo for the primary endpoint was further supported by the confirmatory secondary endpoint, proportion of subjects achieving ≥5% reduction of body weight from baseline to Week 68. Based on information from the clinical reviewer, it seems there were no major safety concerns identified that could impact the approval of the product.

The study provided evidence of a robust treatment effect for the study population. Based on findings from this efficacy study, I recommend approval for the proposed indication.

2 INTRODUCTION

2.1 Overview

Semaglutide, a long-acting glucagon-like peptide -1 (GLP-1) analogue, has a 94% homology to human GLP-1 and a long half-life suitable for once weekly dosing. GLP-1 is a known physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation.

The trial NN9536-4451 (STEP Teens) was conducted to assess the effect and safety of semaglutide in the pediatric population for treatment of adolescents ages 12 to <18 years with obesity.

The applicant complied with the statistical comments conveyed during the IND stage of this submission (IND 126360).

2.2 Data Sources

Materials for this statistical review, including the data and a clinical trial report (CTR), were submitted electronically under the network path location:
\\CDSESUB1\evsprod\NDA215256\0217\m5

The information necessary for the statistical review was contained in Module 1 (cover letter and labeling) and Module 5 (clinical study report, study protocol, statistical analysis plan, datasets, and programs).

In addition, the Data Monitoring Committee meeting minutes were located under the network path:
\\CDSESUB1\evsprod\NDA215256\0217\m5\53-clin-stud-rep\535-rep-effic-safety-stud\weight-management\5354-other-stud-rep\step-teens-nn9536-4451

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted efficacy data and analyses are generally acceptable in quality and documentation. The statistical reviewer was able to reproduce the results of primary and important secondary analyses and performed additional analysis as needed.

Blinding procedures were described in the study reports and acceptable.

3.2 Evaluation of Efficacy

Efficacy analysis procedures were pre-specified in the protocol and these analysis procedures were followed generally according to the protocol.

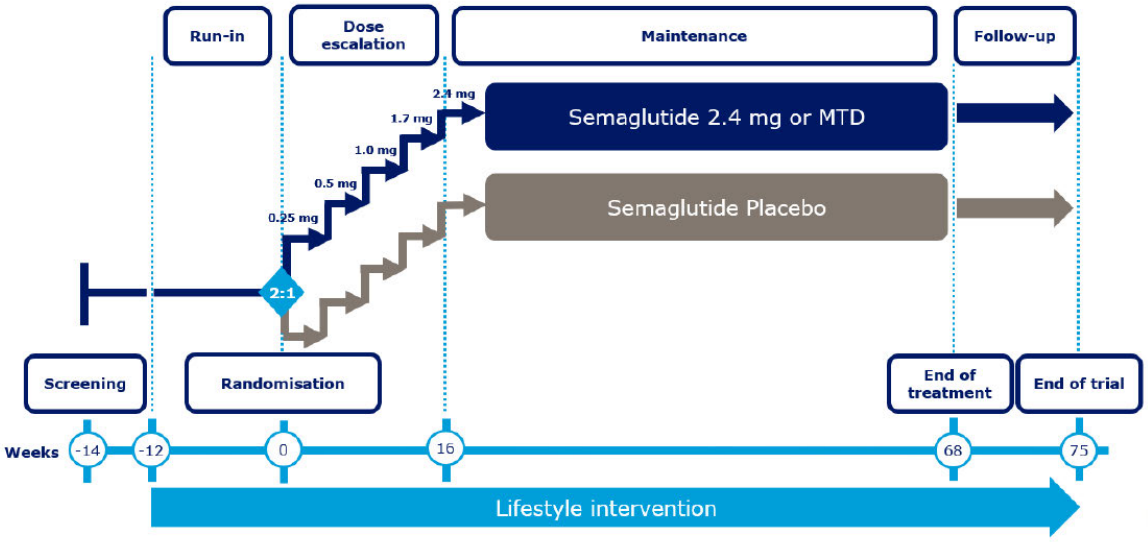
3.2.1 Study Design and Endpoints

The trial was a multinational, multicenter, randomized, double-blind, two-armed, placebo-controlled trial with a 68-week trial period comparing semaglutide s.c. 2.4 mg once weekly with placebo in pubertal adolescents, 12 to <18 years of age, with obesity or with overweight and at least one weight-related comorbidity.

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 the end of the trial (Week 75).

The trial design used for this study is shown in Figure 1.

Figure 1: Trial Design



MTD: maximum tolerated dose

[Source: page 35 of Clinical Trial Report (CTR)]

Subjects were randomized in a 2:1 ratio to receive either semaglutide 2.4 mg or 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.

The study population consisted of pubertal adolescents, 12 to <18 years of age at the time of signing informed consent, male or female, with:

- Obesity (BMI ≥95th percentile on CDC's gender and age-specific growth charts) or
- Overweight (BMI≥85th percentile on CDC's gender and age-specific growth charts) and at least one weight-related comorbidity
- History of at least one self-reported unsuccessful dietary efforts to lose weight on gender and age-specific growth charts (CDC.gov)

For subjects with Type 2 diabetes at screening:

- HbA_{1c} ≤10.0% (86 mmol/mol) as measured by central laboratory at screening

A total of 229 subjects were screened, and 201 subjects were randomized in a 2:1 ratio to receive either semaglutide 2.4 mg (n=134) or placebo (n=67). Of the 201 randomized subjects, 200 were exposed to trial product. One subject who was initially randomized to the semaglutide group in violation of eligibility criteria related to mental health never received trial product. This subject remained in the trial, off-treatment, to ensure continuity of care. Thus, the full analysis set (FAS) consisted of 201 subjects and the safety analysis set (SAS) consisted of 200 subjects.

The trial was conducted at 37 sites in 8 countries including United States.

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

Primary endpoint

- Percent change in BMI from baseline (Week 0) to Week 68, which is defined as:

$$\%\ \text{change in BMI} = \frac{(\text{BMI at week 68} - \text{BMI at baseline})}{\text{BMI at baseline}} \times 100.$$

Confirmatory secondary endpoint

- Subjects achieving ≥5% reduction of body weight from baseline (Week 0) to Week 68

The tests of superiority of semaglutide 2.4 mg to placebo for the primary and confirmatory endpoints were, 1) first the primary endpoint was tested at a significance level of 5% (2-sided). 2) if superiority was confirmed, then the test of the confirmatory secondary endpoint was to be performed.

3.2.2 Statistical Methodologies

The primary estimand quantified the average treatment difference of semaglutide relative to placebo after 68 weeks, in all randomized subjects regardless of adherence to treatment or initiation of rescue interventions, and this estimand covered efficacy related objectives.

The in-trial period was defined as the uninterrupted time interval from randomization to last contact with trial site, and the in-trial period was used for efficacy (observed values) and safety (death and events with potential long latency to diagnosis).

The on-treatment period was defined as the interval from first to last trial product administration plus 2 or 7 weeks of follow-up and excluding any period of temporary treatment interruption defined as >2 or >7 consecutive missed doses (corresponding to >2 or >7 weeks off-treatment). The on-treatment period (+2 weeks) was used for efficacy (observed values) and safety (ECG, laboratory assessments, physical examination, and pulse) and the on-treatment period (+7 weeks) was used for safety (adverse events and hypoglycemic episodes).

The last available and eligible observation at or before randomization was used as the baseline value. If no assessments were available, the mean value at randomization across all subjects was used as the baseline value.

Analysis sets
The full analysis set (FAS) included all randomized subjects according to the intention-to-treat principle.

The safety analysis set (SAS) included all randomized subjects exposed to at least one dose of randomized treatment.

Primary endpoint

Primary analysis
The analysis model for %change in BMI was an analysis of covariance model (ANCOVA) with treatment and stratification group (gender and Tanner stage) as factors, and baseline BMI as a covariate. The estimated treatment difference between semaglutide 2.4 mg and placebo was reported with the associated 2-sided 95% confidence interval (CI) and corresponding p-value.

Handling of missing Week 68 values

All available data at Week 68 were used and missing values at Week 68 were imputed. To describe the imputation, subjects were categorized as below:

- AT: Subjects who completed the trial on randomized treatment with an assessment at Week 68. It included those who stopped and restarted trial product.
- AD: Subjects who discontinued randomized treatment prematurely but returned to have an assessment at Week 68. These were called retrieved dropouts.
- MT: Subjects who completed the trial on randomized treatment without an assessment at Week 68. It included those who stopped and restarted trial product.
- MD: Subjects who discontinued randomized treatment prematurely and did not return to have an assessment at Week 68. There were called non-retrieved dropouts.

The primary imputation approach for the primary estimand was a multiple imputation using retrieved dropouts (RD-MI or retrieved-dropouts multiple imputation)). Missing BMI measurements at Week 68 for MD were imputed using assessments from AD in each randomized treatment arm. Missing BMI measurements at Week 68 for MT were imputed by sampling from available measurements at Week 68 from AT in the relevant treatment arm. This was done according to the timing of last available observation during the on-treatment period of BMI.

A total of 1000 complete datasets were generated for the analysis and the final results were integrated using Rubin's rule.

Sensitivity and supplementary analyses

- Jump to reference multiple imputation approach (J2R-MI): Missing values of BMI at Week 68 for both treatment groups (MT and MD) were imputed by sampling among all available assessments at Week 68 in the placebo group (AT and AD). This approach assumed that subjects instantly after discontinuation lost any effect of randomized treatment beyond what could be expected from placebo as adjunct to diet and physical activity
- Tipping point multiple imputation analysis (TP-MI): Missing data were imputed according to the primary multiple imputation approach. Then, a penalty was added to the imputed values at Week 68. The approach was to explore a range of penalties for both treatment groups, and to assess the impact these would have on the study conclusions. The 2-dimensional space of penalties covering the range from -30% to 30% was explored for both treatment groups
- Excluding subjects from site 402: Six subjects were randomized in Belgium site 402. After six subjects had been randomized it was discovered that the stadiometer was not calibrated. A sensitivity analysis was performed excluding these six subjects
- Mixed model for repeated measurements (MMRM): The MMRM was fitted using the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject was employed, assuming that measurements for different subjects were independent
- ANCOVA assuming unequal variances: The primary analysis model using a primary imputation approach (RD-MI) was conducted assuming unequal variances

Confirmatory secondary endpoint

Primary analysis

The ≥5% change in body weight responder endpoint was analyzed using the same imputation approach as used for the primary endpoint. The imputation model was the same as for the primary endpoint, with BMI replaced by body weight, and the resulting imputed values were dichotomized to derive the responder endpoint. The statistical model for a responder endpoint was a logistic regression model using randomized treatment and stratification group (gender and Tanner stage) as factors, and baseline body weight as a covariate. The estimated odds ratio between semaglutide 2.4 mg and placebo was reported with the associated 2-sided 95% CI and corresponding p-value.

Sensitivity analysis
A sensitivity analysis considering non-retrieved dropouts as non-responders was carried out.

Subgroup analysis of the primary endpoint
Subgroup analysis was carried out addressing the primary estimand using the same imputation approach and statistical model used in the analysis of the primary endpoint. The results of the subgroup analysis were presented with treatment contrasts and treatment-by-subgroup interaction p-values.

Analysis of safety endpoints
Adverse events were defined as "treatment-emergent" (TEAE) if the onset of the event occurred in the on-treatment period. TEAEs and Serious adverse events (SAEs) were summarized by descriptive statistics.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition
The summary of the subject disposition is given in

Table 2. The proportion of subjects who completed treatment were 89.6% in both groups. Main reason for discontinuing treatment was adverse event in both groups followed by "other" and protocol violation. The proportion of subjects who withdrew from the trial was 1.5% in the semaglutide group and 4.5% in the placebo group.

Table 2: Patient Disposition

	Sema 2.4 mg	Placebo	Total
Randomized	134	67	201
Completed treatment	**120 (89.6%)**	**60 (89.6%)**	**180 (89.6%)**
discontinued treatment	14 (10.4%)	7 (10.4%)	21 (10.4%)
adverse event	6 (4.5%)	4 (6.0%)	10 (5.0%)
protocol violation	2 (1.5%)	1 (1.5%)	3 (1.5%)
pregnancy	1 (0.7%)	0	1 (0.5%)
withdrawal of consent	1 (0.7%)	1 (1.5%)	2 (1.0%)
other	4 (3.0%)	1 (1.5%)	5 (2.5%)
Completed trial (attended end-of-trial visit)	**132 (98.5%)**	**64 (95.5%)**	**196 (97.5%)**
withdrawal from the trial	2 (1.5%)	3 (4.5%)	5 (2.5%)
withdrawal by subject/parent/guardian	1 (0.7%)	3 (4.5%)	4 (2.0%)
lost to follow-up	1 (0.7%)	0	1 (0.5%)

[Source: excerpted from Table 10-1 of CTR]

Summary of COVID-19 Impact

This trial was conducted between 7 October 2019 and 28 March 2022. The trial was primarily impacted by COVID-19 due to lock-down restrictions imposed at trial sites, and both treatment groups were impacted comparably. If sites were closed or subjects would not come to the clinic, sites supplied subjects with trial product by alternative methods. When necessary, on-site monitoring was replaced by additional off-site monitoring activities and centralized monitoring.

The primary impact of COVID-19 was on visit attendance. There were 91 subjects reported as impacted subjects. For those subjects, site visits were converted to phone visit or visit out of window. There were 9 visits with missing assessments, however, these assessments were not for the primary or confirmatory endpoints.

Demographic and other baseline characteristics

Baseline demographics and baseline characteristics are shown in Table 3. In both treatment groups, most of the subjects were females (62.2%) and in Tanner stage 4 or 5 (89.1%). The study population was largely white (79.1%). The mean age was 15.4 years of age, with 35.8% in the 12 to <15 years old stratum and 64.2% in the 15 to <18 years old stratum. Baseline body weight and BMI (kg/m^2) were slightly higher in the semaglutide group compared to the placebo group. There was only one subject in the 85^{th} to $<95^{th}$ BMI percentile stratum.

Table 3: Baseline Demographics and Characteristics of Subjects

		Semaglutide 2 4 mg (N=134)	Placebo (N=67)	Total (N=201)
Age (years)	12- <15	47 (35 1%)	25 (37 3%)	72 (35 8%)
	15 -<18	87 (64 9%)	42 (62 7%)	129 (64 2%)
Sex	Female	84 (62 7%)	41 (61 2%)	125 (62 2%)
	Male	50 (37 3%)	26 (38 8%)	76 (37 8%)
Ethnic Origin	Not Hispanic or Latino	120 (89 6%)	59 (88 1%)	179 (89 1%)
	Hispanic or Latino	14 (10 4%)	8 (11 9%)	22 (10 9%)
Race	White	104 (77 6%)	55 (82 1%)	159 (79 1%)
	Other	14 (10 4%)	6 (9 0%)	20 (10 0%)
	Black or African American	11 (8 2%)	5 (7 5%)	16 (8 0%)
	Asian	3 (2 2%)	1 (1 5%)	4 (2 0%)
	American Indian or Alaska Native	2 (1 5%)	0	2 (1 0%)
Country	Austria	4 (3 0%)	7 (10 4%)	11 (5 5%)
	Belgium	15 (11 2%)	9 (13 4%)	24 (11 9%)
	Croatia	12 (9 0%)	4 (6 0%)	16 (8 0%)
	Ireland	3 (2 2%)	1 (1 5%)	4 (2 0%)
	Mexico	13 (9 7%)	5 (7 5%)	18 (9 0%)
	Russian Federation	37 (27 6%)	18 (26 9%)	55 (27 4%)
	United Kingdom	15 (11 2%)	7 (10 4%)	22 (10 9%)
	United States	35 (26 1%)	16 (23 9%)	51 (25 4%)
BMI (kg/m^2)	<30	12 (9 0%)	8 (11 9%)	20 (10 0%)
	30 -<35	45 (33 6%)	26 (38 8%)	71 (35 3%)
	35 -<40	33 (24 6%)	19 (28 4%)	52 (25 9%)
	40 or greater	44 (32 8%)	14 (20 9%)	58 (28 9%)
BMI group*	≥85th to <95th percentile	1 (0 7%)	0	1 (0 5%)
	≥95th percentile to <120% of 95th percentile	42 (31 3%)	27 (40 3%)	69 (34 3%)
	≥120% to <140% of 95th percentile	44 (32 8%)	25 (37 3%)	69 (34 3%)
	≥140% of 95th percentile	47 (35 1%)	15 (22 4%)	62 (30 8%)
Tanner Stage and Sex	Female with Tanner Stage 2-3	4 (3 0%)	1 (1 5%)	5 (2 5%)
	Female with Tanner Stage 4-5	80 (59 7%)	40 (59 7%)	120 (59 7%)
	Male with Tanner Stage 2-3	10 (7 5%)	7 (10 4%)	17 (8 5%)
	Male with Tanner Stage 4-5	40 (29 9%)	19 (28 4%)	59 (29 4%)
Age (years): Mean (SD)		15 5 (1 5)	15 3 (1 6)	15 4 (1 6)
Height (cm): Mean (SD)		170 1 (9 4)	168 8 (10 6)	169 7 (9 8)
Body Weight (kg): Mean (SD)		109 9 (25 2)	102 6 (22 3)	107 5 (24 5)
BMI (kg/m^2): Mean (SD)		37 7 (6 7)	35 7 (5 4)	37 0 (6 4)
Waist Circumference (cm): Mean (SD)		111 9 (16 9)	107 3 (13 4)	110 4 (16 0)
HbA_{1c} (%): Mean (SD)		5 5 (0 4)	5 5 (0 4)	5 5 (0 4)

Abbreviations: N=number of patients randomized; BMI=Body Mass Index; SD=Standard Deviation; cell contents for Age (years), Sex, Ethnic Origin, Race, Country, BMI (kg/m^2), and Tanner Stage and Sex are frequencies with relative frequencies in parentheses; For all other characteristics are mean and the standard deviation in parentheses; [Source: excerpted from Table 10-2 and Table 10-3 of CTR and Statistical Reviewer*]

3.2.4 Results and Conclusions

Missing Data

The amount of missing data at Week 68 are shown in Table 4. The proportion of missing data was 3% for semaglutide 2.4 mg and 7.5% for placebo. As noted in Table 4, the number of observed values is the sum of the number of observed values from subjects who completed treatment (A) and the number of retrieved values from subjects who discontinued treatment (B). For the primary efficacy analysis, missing values at Week 68 were imputed using assessment from retrieved dropouts in each randomized treatment arm. Missing values at Week 68 for subjects on treatment were imputed from available measurements at Week 68 from subjects on treatment in the relevant randomized treatment arm (Section 3.2.2 of this review).

Table 4: Summary of Missing Data

	N	Observed (A+B)	On treatment at Week 68 (A)	Retrieved dropouts (B)	Missing
Semaglutide 2.4 mg	134	131 (97.8%)	119 (88.8%)	12 (9.0%)	3 (2.2%): complete trt: 1 discontinue trt: 2
Placebo	67	62 (92.5%)	58 (86.6%)	4 (6.0%)	5 (7.5%): complete trt: 2 discontinue trt: 3

Abbreviations: N=number of subjects randomized; cell content shows frequency and percentage relative to N in the parentheses; trt=treatment; [Source: Statistical Reviewer]

Primary endpoint results

Treatment with semaglutide 2.4 mg resulted in a statistically significant greater reduction in BMI compared to placebo supporting the efficacy of active treatment (Table 5). The treatment effect of active treatment on percent change in BMI at Week 68 was -16.75%.

Table 5: Percent Change in BMI from Baseline to Week 68: Primary Endpoint

Primary endpoint: %change in BMI			
	N (obs)	LS mean[1] (SE)	Treatment Difference [95% CI]; p-value
Semaglutide 2.4 mg	134 (131)	-16.14 (1.01)	-16.75 [-20.27, -13.23]; <0.0001
Placebo	67 (62)	0.61 (1.48)	

Abbreviations: N=number of subjects randomized; BMI=body mass index (kg/m^2); obs=number of observed; LS mean= least squares mean; SE: standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment, stratification factors as fixed effects and baseline BMI value as a covariate; Missing observations were multiple imputed (1000 times) from retrieved dropouts of the same randomized treatment; [Source: Statistical Reviewer]

Pre-specified sensitivity analyses using different imputation approaches (J2R-MI, analysis excluding a site 402, ANCOVA assuming unequal variance) were conducted to evaluate the robustness of the conclusions based on the primary analysis. All sensitivity analyses yielded results that were consistent with the primary analysis results.

Two-dimensional tipping point analyses with incremental changes ranging from -30% to 30% applied to imputed values at Week 68 were performed. The conclusion of the primary analysis was not overturned in the range of the incremental changes explored, supporting the robustness of the conclusion based on the primary analysis.

Additional analysis
The primary analysis excluding subjects from site 701 (in Mexico) was conducted (This was a request from the clinical reviewer due to concerns on height measurements at site 701). The results were consistent with the primary results.

Key secondary endpoint results
The proportion of subjects who had at least 5% body weight loss from baseline to Week 68 was statistically significant (Table 6). The results indicated that the proportion of subjects who had at least 5% body weight loss was greater in the semaglutide group compared to the placebo group.

Table 6: Key Secondary Endpoint

Key secondary endpoint: ≥5% body weight loss			
	N (obs)	Proportion[1] (%)	Treatment difference [95% CI]; p-value
Semaglutide 2.4 mg	134 (131)	73.2%	56.9% [44.8%, 69.0%]; <0.0001
Placebo	67 (62)	16.3%	

Abbreviations: N=number of subjects randomized; obs=number of observed; CI=confidence interval; [1]Estimates using a logistic regression with terms of treatment and stratification factors and baseline body weight (kg); Missing observations were multiple imputed (1000 times) from retrieved dropouts of the same randomized treatment; [Source: Statistical Reviewer]

Pre-specified sensitivity analysis using non-responders was conducted to evaluate the robustness of the primary results, and this analysis yielded results that were consistent with the primary results.

3.3 Evaluation of Safety

All safety analyses were conducted on the safety analysis set (N=200), which was defined as all randomized subjects who were treated with at least one dose of randomized treatment. The results are summarized in Table 7. Adverse events were primarily driven by gastrointestinal (GI) events, infections, and infestations. More severe or mild adverse events were observed in the semaglutide group compared to the placebo. Most adverse events were non-serious and of mild or moderate in severity and reported as recovered. There was no death during the trial.

Table 7: Overview of Adverse Events

	Semaglutide 2.4 mg (N=133)	Placebo (N=67)
Adverse event (AE)	106 (79.7%)	56 (83.6%)
Serious AE	15 (11.3%)	6 (9.0%)
Severe	4 (3.0%)	0
Moderate	9 (6.8%)	3 (4.5%)
Mild	2 (1.5%)	3 (4.5%)

Abbreviations: N=number of subjects; cell content shows the number of subjects experiencing at least one event; [Source: excerpted from Section 12. Safety evaluation of CTR]

For more details regarding the safety findings, refer to the review from the Medical Reviewer, Dr. Iffat Chowdhury.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analysis using an ANCOVA model compared %change from baseline at Week 68 in BMI across treatment groups within subgroups. The LS mean differences and the corresponding 95% CIs are shown in Figure 2 to Figure 3.

There were some random highs and random lows in sample estimates of subgroup treatment effect due to small sample size and large variability for some subgroups. Therefore, we also calculated shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For i=1, 2,..., Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Yi \sim N(\mu_i, \sigma_i^2)$ where

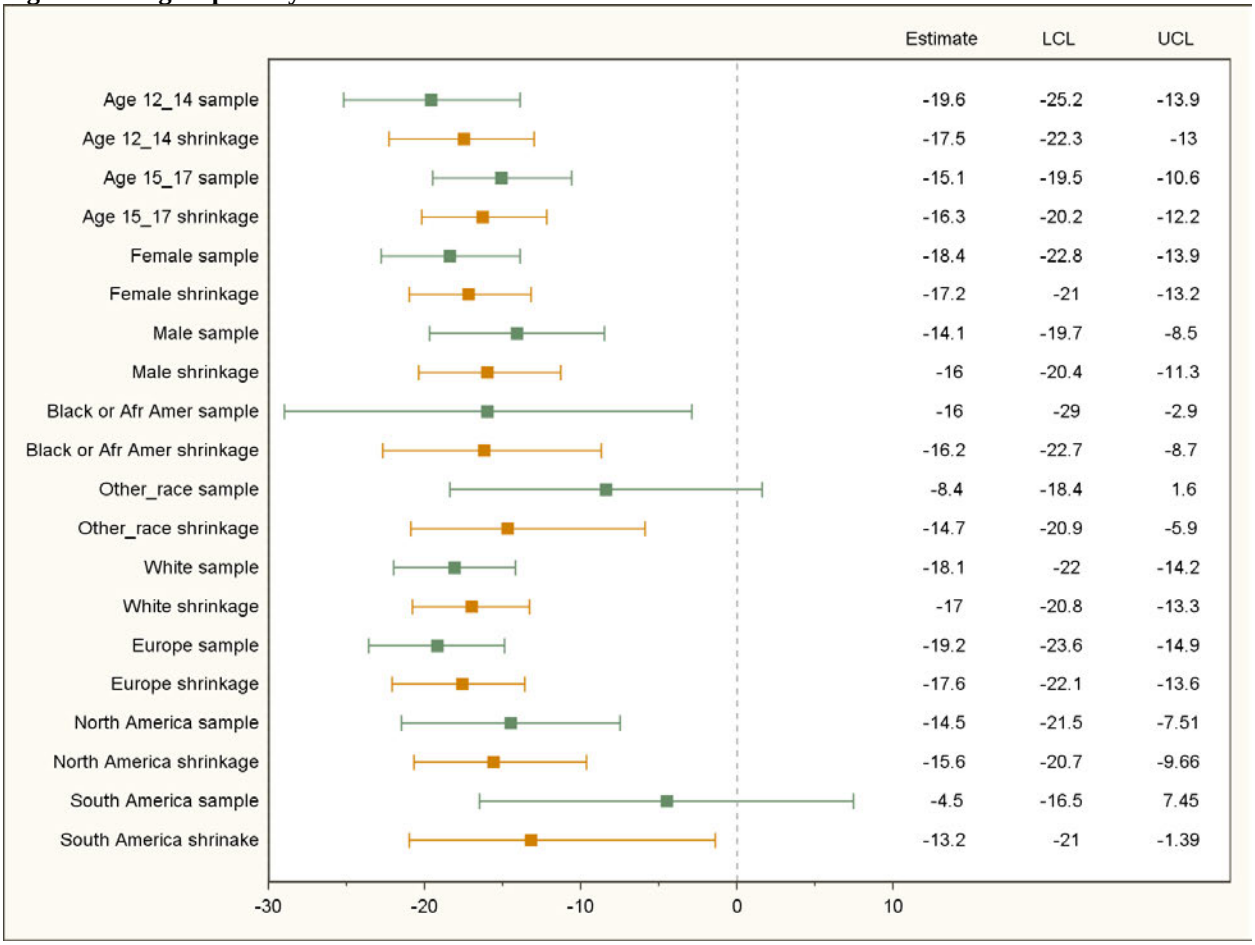
- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 45^2)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

A standard deviation of 45% was chosen so that the standard deviation was approximately 4 times subject-level standard deviation. Results from both the sample and shrinkage estimates of the treatment effects for the subgroups are presented in Figure 2 to Figure 3.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed for age, gender, race, and region (Figure 2). For subgroup analysis, "Other" category in race consisted of several race categories combined (Asian or American Indian or Alaskan Native or Other; see Section 3.2.3 of this review). All subgroups reported the upper limit of the 95% confidence interval less than zero, in favor of semaglutide, except for Other race and South America. However, with shrinkage estimates, the upper limits of the 95% credible intervals for Other race and South America were less than zero, in favor of semaglutide.

Figure 2: Subgroup Analysis

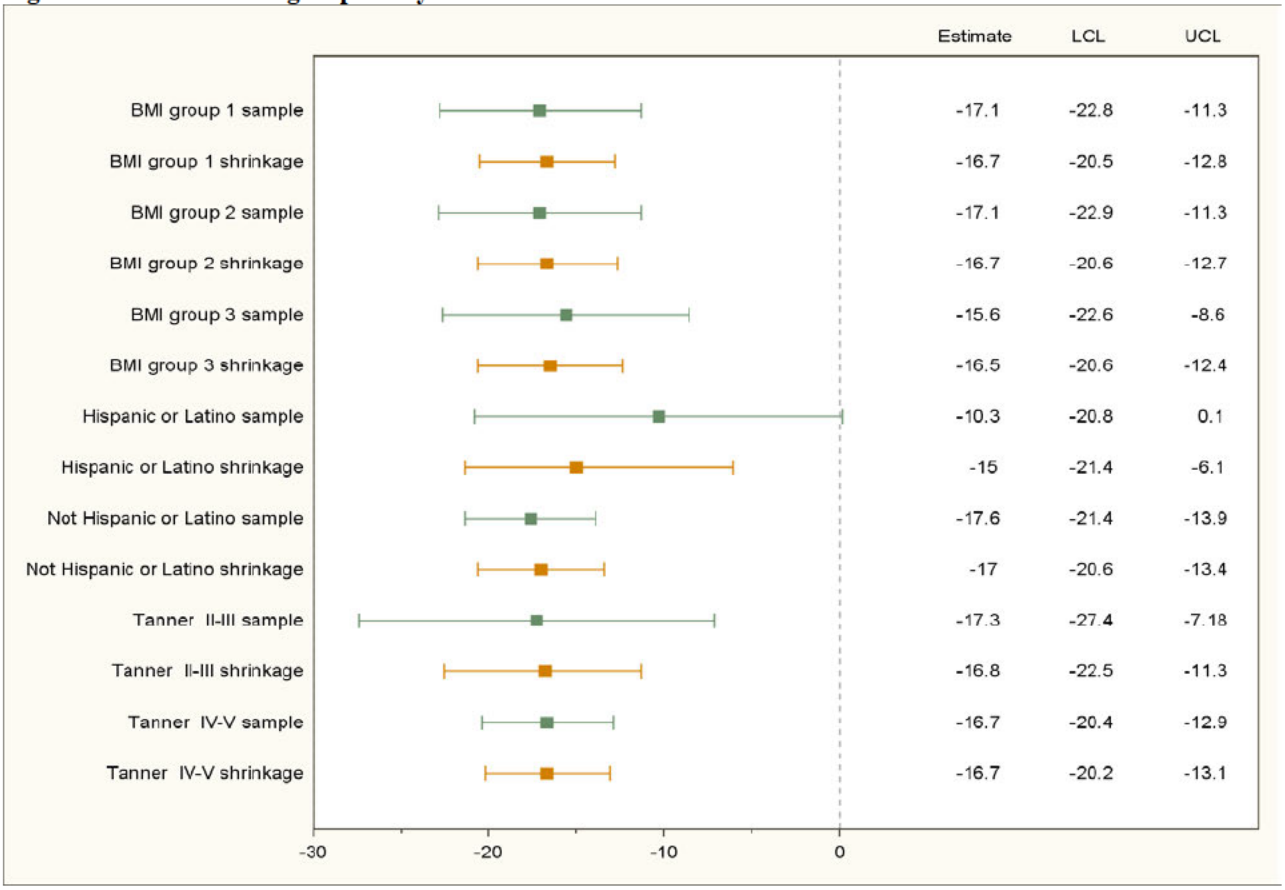


Sample estimates are shown with the corresponding 95% confidence interval (in green) and shrinkage estimates are shown with the corresponding 95% credible interval (in orange); LCL: lower confidence (or credible) limit; UCL: upper confidence (or credible) limit; Dotted vertical line indicates zero; [Source: Statistical Reviewer]

4.2 Other Special/Subgroup Populations

Additional subgroup analyses were performed for baseline BMI group (<120% of 95th percentile, ≥120 to <140% of 95th percentile and ≥140% of 95th percentile), ethnicity (Hispanic or Latino and not Hispanic or Latino) and baseline Tanner stage (Tanner stage II/III and Tanner stage IV/V). All subgroups reported the upper limits of intervals less than zero, in favor of semaglutide except for Hispanic or Latino. However, with shrinkage estimates, the upper limit of the 95% credible interval was less than zero, in favor of semaglutide.

Figure 3: Additional Subgroup Analysis



Sample estimates are shown with the corresponding 95% confidence interval (in green) and shrinkage estimates are shown with the corresponding 95% credible interval (in orange); LCL: lower confidence (or credible) limit; UCL: upper confidence (or credible) limit; Dotted vertical line indicates zero; BMI group 1: <120% of 95th percentile BMI; BMI group 2: >=120 to <140% of 95th percentile BMI; BMI group 3: >=140% of 95th percentile BMI; [Source: Statistical Reviewer]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues that would impact or change the overall conclusions. The amount of missing data was not large (4%) and the sensitivity analyses using the pre-specified approaches supported the robustness of the primary efficacy results. Both primary and confirmatory secondary efficacy endpoints were statistically significant, in favor of the semaglutide group.

The study primarily consisted of subjects in ≥95th BMI percentile and included only one subject in the 85th to <95th BMI percentile stratum. (b) (4)

[redacted] (b) (4)

5.2 Collective Evidence

The primary analysis showed statistically significant treatment effect in body mass index (BMI) reduction (%) at Week 68. The proportion of subjects achieved at least 5% body weight reduction was also statistically significant, in favor of semaglutide. Sensitivity analyses supported the robustness of the primary efficacy results.

5.3 Conclusions and Recommendations

The collective evidence from the submitted data demonstrated efficacy of semaglutide in the study population. I recommend approval for the proposed indication based on findings from the submitted results. [redacted] (b) (4)

5.4 Labeling Recommendations (as applicable)

Reviewing of labeling is still ongoing while this statistical review is finalized.

Table 8 and Table 9 present results from endpoints that were not prespecified in the hierarchical testing. However, these endpoints are considered clinically relevant and have been included in labeling for adult population.

Table 8: Parameters related to Body Weight

	N	Proportion[1] (%)	Treatment difference [95% CI]
≥10% body weight loss			
Semaglutide 2.4 mg	134	62.8%	55.9% [45.5%, 66.4%]
Placebo	67	6.8%	
≥15% body weight loss			
Semaglutide 2.4 mg	134	53.2%	49.0% [39.0%, 58.9%]
Placebo	67	4.2%	
		LS mean[2]	
Body weight: %change from baseline			
Semaglutide 2.4 mg	134	-14.7	-17.4 [-21.1, -13.7]
Placebo	67	2.7	

Abbreviations: N=number of subjects randomized; LS mean= least squares mean; CI=confidence interval;
[1]Estimates using a logistic regression with terms of treatment and stratification factors and baseline body weight;
[2]Model based estimates, the ANCOVA model included treatment, stratification factors as fixed effects and baseline body weight as a covariate; Missing observations were multiple imputed (1000 times) from retrieved dropouts of the same randomized treatment; [Source: Statistical Reviewer]

Table 9: Waist Circumference and Cardiometabolic Parameters

	N	LS mean[1]	Treatment difference [95% CI]
Waist circumference (cm)			
Semaglutide 2.4 mg	134	-12.69	-12.14 [-15.59, -8.69]**
Placebo	67	-0.55	
Systolic blood pressure (mmHg)			
Semaglutide 2.4 mg	134	-2.70	-1.91 [-4.96, 1.15]
Placebo	67	-0.79	
Diastolic blood pressure (mmHg)			
Semaglutide 2.4 mg	134	-1.43	-0.60 [-2.98, 1.77]
Placebo	67	-0.83	
Heart rate*			
Semaglutide 2.4 mg	133	1.19	3.50 [0.34, 6.66]**
Placebo	67	-2.31	
HbA1c (%)[2]			
Semaglutide 2.4 mg	129	-0.35	-0.22 [-0.29, -0.14]**
Placebo	64	-0.14	
Total cholesterol (mg/dL): %change from baseline			
Semaglutide 2.4 mg	134	-8.31	-7.06 [-10.5, -3.50]**
Placebo	67	-1.35	
LDL cholesterol (mg/dL): %change from baseline			
Semaglutide 2.4 mg	134	-9.91	-6.57 [-11.29, -1.59]**
Placebo	67	-3.58	
HDL (mg/dL): %change from baseline			
Semaglutide 2.4 mg	134	8.01	4.68 [-1.04, 10.74]
Placebo	67	3.18	
Triglycerides (mg/dL): %change from baseline			
Semaglutide 2.4 mg	134	-28.38	-30.20 [-37.95, -21.49]**
Placebo	67	2.62	

Abbreviations: N=number of subjects randomized; LS mean= least squares mean; CI=confidence interval; [1]Model based estimates, the ANCOVA model included treatment, stratification factors as fixed effects and baseline value as a covariate;[2]Subjects without Type 2 diabetes were included in the analysis; Missing observations were multiple imputed (1000 times) from retrieved dropouts of the same randomized treatment; *Heart rate was analyzed using a mixed model repeated measures approach with treatment as a factor and baseline body weight as a covariate, nested within visit, in a safety analysis set; **nominally statistically significant; [Source: Statistical Reviewer]

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/

KYUNGHEE K SONG
11/29/2022 01:03:57 PM

FENG LI
11/29/2022 01:34:35 PM