CLINICAL REVIEW

Application Type	NDA
Application Number	215256
Priority or Standard	Priority
Submit Date	June 29, 2022
Received Date	June 29, 2022
PDUFA Goal Date	December 29, 2022
Division/Office	DDLO/OCHEN
Reviewer Names	Julie Golden and Iffat Chowdhury
Review Completion Date	December 22, 2022
Established/Proper Name	Semaglutide
Trade Name	Wegovy
Applicant	Novo Nordisk Inc.
Dosage Form	Injection
Applicant Proposed Dosing Regimen	Patients should aim at reaching the maintenance 2.4 mg once-weekly dose following the weekly dose escalation schedule [weeks 1-4: 0.25 mg, weeks 5-8: 0.5 mg, weeks 9-12: 1 mg, weeks 13-16: 1.7 mg]. 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.
Applicant Proposed Indication/Population	Pediatric patients aged 12 years and older with an initial BMI at the: • 95th percentile or greater for age and sex (obesity) or • (b) (4)
Recommendation on Regulatory Action	Approve
Recommended Indication/Population	Pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater standardized for age and sex (obesity)

Table of Contents

Table of Tables

Table of Figures

Glossary

AC advisory committee
AE adverse event
AR adverse reaction
BLA biologics license application
BPCA Best Pharmaceuticals for Children Act
BRF Benefit Risk Framework
CBER Center for Biologics Evaluation and Research
CDER Center for Drug Evaluation and Research
CDRH Center for Devices and Radiological Health
CDTL Cross-Discipline Team Leader
CFR Code of Federal Regulations
CMC chemistry, manufacturing, and controls
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF case report form
CRO contract research organization
CRT clinical review template
CSR clinical study report
CSS Controlled Substance Staff
DMC data monitoring committee
ECG electrocardiogram
eCTD electronic common technical document
ETASU elements to assure safe use
FDA Food and Drug Administration
FDAAA Food and Drug Administration Amendments Act of 2007
FDASIA Food and Drug Administration Safety and Innovation Act
GCP good clinical practice
GRMP good review management practice
ICH International Council for Harmonization
IND Investigational New Drug Application
ISE integrated summary of effectiveness
ISS integrated summary of safety
ITT intent to treat
MedDRA Medical Dictionary for Regulatory Activities
mITT modified intent to treat
NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA new drug application

NME new molecular entity
OCS Office of Computational Science
OPQ Office of Pharmaceutical Quality
ORA Office of Regulatory Affairs
OSE Office of Surveillance and Epidemiology
OSI Office of Scientific Investigation
PBRER Periodic Benefit-Risk Evaluation Report
PD pharmacodynamics
PI prescribing information or package insert
PK pharmacokinetics
PMC postmarketing commitment
PMR postmarketing requirement
PP per protocol
PPI patient package insert
PREA Pediatric Research Equity Act
PRO patient reported outcome
PSUR Periodic Safety Update report
REMS risk evaluation and mitigation strategy
SAE serious adverse event
SAP statistical analysis plan
SGE special government employee
SOC standard of care
TEAE treatment emergent adverse event

1. Executive Summary

1.1 Product Introduction

Semaglutide is a glucagon-like peptide 1 (GLP1) receptor agonist approved for chronic weight management in adults with obesity and overweight with weight-related comorbidities (Wegovy, 2.4 mg weekly as a subcutaneous injection).

Semaglutide injection is also approved for the treatment of type 2 diabetes (T2D) in adults, as well as to reduce the risk of major cardiovascular events in adults with T2D and established cardiovascular disease (Ozempic, NDA 209637). The maintenance dosages of Ozempic are 0.5 mg, 1.0 mg, and 2.0 mg weekly.

Oral semaglutide is also approved in the US at daily maintenance doses of 7 mg and 14 mg for treatment of T2D (NDA 213051, Rybelsus).

At the time of the original Wegovy approval in 2021, two pediatric PMR clinical trials were required:

- 4081-1: 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.

- 4081-2: Conduct a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy after 68 weeks of semaglutide for the treatment of obesity in pediatric patients ages 6 to less than 12. Compare the long-term (at least 2 years) safety and tolerability of semaglutide versus placebo for the treatment of obesity in both children and adolescents (ages 6 to less than 18 years). The trial may not be initiated until results from the semaglutide adolescent trial have been submitted to and reviewed by the Agency.

This supplement is intended to fulfill PMR 4081-1.

Semaglutide is also the subject of a written request (WR), and this trial will fulfill the first of the three trials included in the WR. The other two trials are 1) the second pediatric trial listed above (PMR 4081-2) and (b) (4)

1.2 Conclusions on the Substantial Evidence of Effectiveness

This supplemental application contains substantial evidence that Wegovy (semaglutide) is

effective for chronic weight management in adolescents (ages 12-17 years) with obesity (BMI ≥ 95th percentile). Adolescent subjects with obesity treated with semaglutide in this adequate and well-controlled trial (placebo-controlled and 68-weeks in duration) lost a clinically and statistically significant amount of weight versus placebo, expressed as percent change in BMI (primary endpoint) and in the proportions of subjects who lost at least 5% baseline body weight (key secondary endpoint). Additional efficacy endpoints supported the primary endpoint, including changes in waist circumference, glycemic parameters, and lipids.

Although there is only one trial conducted in this adolescent population, the results were highly consistent with the large chronic weight management program conducted in adults that supported the original approval of Wegovy. The adult program provides confirmatory evidence of benefit.

Uncertainties include: (b) (4) the long-term benefits of treatment beyond the study duration, whether Wegovy treatment in adolescents impacts the trajectory of obesity and comorbidities into adulthood, the effectiveness of remaining on lower doses due to tolerability, and the treatment effect in certain minority racial and ethnic populations, given the relatively higher enrollment of individuals who were white and/or non-Hispanic. These uncertainties did not ultimately impact the approval decision.

1.3 **Benefit-Ri**sk Asses**sme**nt

Benefit-Risk Integrated Assessment

Semaglutide is a glucagon-like peptide 1 (GLP1) receptor agonist approved for chronic weight management in adults with obesity and overweight with weight-related comorbidities (Wegovy, 2.4 mg weekly as a subcutaneous injection). The clinical trial submitted to support this supplemental application (NN9536-4451, STEP Teens) demonstrated substantial evidence of effectiveness to support an indication for chronic weight management in the adolescent population with obesity. The trial demonstrated a statistically significant change in the primary endpoint, percent change in BMI, with a placebo-subtracted difference of -16.75% (95% CI -20.27, -13.23, p<0.001) and the confirmatory secondary endpoint, the odds ratio of the proportions of participants achieving at least 5% weight loss, 14.02 (95% CI 6.34, 31.02), p<0.001. Other secondary analyses of weight and BMI change over the course of the trial and associated cardiometabolic endpoints (waist circumference, blood pressure, glycemic parameters, lipids) are relevant to interpreting the clinical significance of the primary endpoint. All were nominally statistically significant or trended in favor of semaglutide.

In STEP TEENS, adverse reactions with semaglutide treatment in pediatric patients 12 years of age and older were generally similar to those reported in adults. However, subjects treated with semaglutide had greater incidences of cholelithiasis, cholecystitis, hypotension, rash, and urticaria compared to adults treated with semaglutide.

In this trial in adolescents, there were no deaths reported. The most frequently reported SAEs were related to gallbladder adverse events. No events of pancreatitis or acute kidney injury occurred during the trial. The proportion of subjects with AEs related to hepatic events was higher in the semaglutide group than in placebo; however, most of the events were non-serious, mild to moderate in severity, and subjects recovered. When both central and local labs are considered, four subjects on semaglutide compared to 0 subjects on placebo had elevated liver enzymes ≥5x ULN. Cholelithiasis may have contributed to liver enzyme elevations in 3 of the 4 subjects on semaglutide; however, the chronology of the liver enzyme elevation in relation to the gallstones is not clear in those cases. Therefore, liver enzyme elevations will be described in the semaglutide label. Rash and urticaria were seen at higher frequency with semaglutide than with placebo. Hypotension was reported as an AE in 2.3% of subjects on semaglutide compared to none on placebo. Suicidality and depression are safety concerns for all centrally acting obesity drugs. In this trial, there was no imbalance of events against semaglutide for psychiatric related AEs. Similar to adults, mean heart rate

increases of 3-4 beats/min were observed with subjects on semaglutide compared to placebo. The most frequently reported AEs were gastrointestinal disorders such as nausea, vomiting, and abdominal pain, which were also the most common AEs leading to discontinuation.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Obesity (excess in adiposity) in children is defined as BMI ≥ 95th percentile for age and sex on growth charts; (b) (4) • According to the CDC, obesity prevalence was 22.2% among adolescents ages 12 to 19 years in 2017-2020[1] • As in adults, obesity in adolescents can be associated with metabolic abnormalities such as dysglycemia and steatohepatitis, as well as cardiovascular, gastrointestinal, orthopedic, pulmonary, psychosocial, and other long-term health consequences • It remains unclear to what extent intervening in childhood obesity will prevent significant obesity-related consequences throughout adulthood • (b) (4)	Obesity and its comorbidities in children and adolescents are rising problems in the U.S. and globally. The goal of treating childhood obesity is to prevent long-term consequences in adulthood.
Current Treatment Options	• Diet and exercise are the mainstay of weight management in patients of all ages, but weight loss is notoriously difficult to maintain • Currently approved drug treatments for adolescents with obesity include Qsymia (phentermine/topiramate), Saxenda (liraglutide), and Xenical (orlistat)	Obesity in adolescence may be difficult to treat and often requires a multidisciplinary approach. Despite recent drug approvals for this

[1] https://stacks.cdc.gov/view/cdc/106273

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Bariatric surgery is used to treat adolescents whose obesity has been refractory to other interventions	population (Qsymia, Saxenda), highly effective treatment options are still needed.
Benefit	• At week 68, the mean change from baseline in BMI was -16.14% in the semaglutide group and +0.61% in the placebo group, with a difference in LS means of -16.75% (95% CI -20.27, -13.23), p<0.0001. • The confirmatory secondary endpoint was the odds of achieving at least 5% body weight loss at week 68 (semaglutide/placebo). The proportions of participants achieving at least 5% weight loss were 72.5% and 17.7% for semaglutide and placebo groups, respectively; odds ratio 14.02 (95% CI: 6.34, 31.02), p<0.0001. • Other secondary analyses of weight and BMI change over the course of the trial and associated cardiometabolic endpoints (waist circumference, blood pressure, glycemic parameters, lipids) are relevant to interpreting the clinical significance of the primary endpoint. All were nominally statistically significant or trended in favor of semaglutide. • The heights in some subjects may not have been accurate (loss of height or unchanged heights over time); however, based on Tanner staging, bone age, and epiphyseal closure most of these subjects likely had reached full or near-full height prior to or during the trial. • Most participants were non-Hispanic and/or white, which does not fully reflect the racial and ethnic diversity of adolescents with obesity in the U.S. • (b) (4).	Despite some concerns about the accuracy of height measurements, mean changes across a variety of supportive endpoints, such as weight and waist circumference, as well as cardiometabolic endpoints, support the efficacy of semaglutide in this population of adolescents with obesity for the duration studied. Efficacy results for BMI/weight were highly consistent with the adult program. Weight change is clinically relevant in the studied pediatric population as most participants had achieved the majority of final adult height. The limited number of participants in some race and ethnicity subgroups complicates the interpretation of efficacy in these subgroups. More research is needed regarding the use of semaglutide in a more diverse pediatric population with obesity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Labeling should reflect the population studied (i.e., adolescents with BMI ≥ 95th percentile).
Risk and Risk Management	• Adverse events with semaglutide treatment in pediatric patients 12 years of age and older were similar to those reported in adults. • Cholelithiasis was reported by 3.8% of subjects on semaglutide compared to 0% of subjects on placebo. • Liver enzyme elevations ≥5x ULN (detected by central and local labs) were reported in 4 (3%) of subjects on semaglutide compared to 0% on placebo. • Rash (3.0%) and urticaria (3.0%) were reported by subjects on semaglutide with higher frequency than subjects on placebo (0%). • Mean heart rate increases of 3-4 beats/min were observed with subjects on semaglutide compared to placebo. • Approximately 2.3% of subjects on semaglutide reported hypotension as compared to 0% on placebo. • The most common AEs on semaglutide were gastrointestinal disorders (62% vs 42%) such as nausea (42% vs.18%), diarrhea (22% vs. 19%), abdominal pain (15% vs. 6%), and vomiting (36% vs. 10%). • Gastrointestinal AEs were the most common reason (2.3% vs. 1.5%) for study drug discontinuation.	There were 5 (3.8%) subjects with 6 gallbladder-related events in the semaglutide group compared to none in the placebo group. Although gallbladder disease is already labeled, the adolescent population experienced a higher frequency of these events than the adult population (1.2%). The adolescent population's incidence of gallbladder disease will be described in the label. Liver enzyme elevations ≥5x ULN may have been confounded by the presence of gallstones; however, not all cases were related to gallstones. Liver enzyme elevations will be described in the label. Approximately 23 (17.3%) subjects on semaglutide and 6 (9.0%) of subjects on placebo reported an AE in the Skin and Subcutaneous Tissue System Organ Class (SOC). Rash (3.0%) and urticaria (3.0%) were seen at higher frequency with semaglutide than with placebo (0%). One subject on

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		semaglutide discontinued treatment due to rash. Currently rash is listed in Section 6.3 Post-marketing Experience. The adolescent population's incidence of rash and urticaria will be described in the label in Section 6.1. An FDA Medical Query on Tachycardia showed that approximately 2.3% of subjects on semaglutide reported an AE compared to none on placebo. A shift table analysis showed that a greater proportion of subjects (54%) in the semaglutide group with an average baseline pulse had a maximum increase of at least 20 beats/min compared to placebo subjects (39%). Increase in heart rate is described in the current label. Three (2.3%) of subjects on semaglutide versus none on placebo reported an AE of hypotension. These reports were not clearly demonstrated to be due to gastrointestinal AEs or volume depletion. The frequency of hypotension will be described in the semaglutide label. Semaglutide is associated with gastrointestinal

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		AEs. The risk for GI AEs is monitorable and can be adequately addressed through labeling. In summary, risks associated with semaglutide use in the pediatric population can be adequately addressed with labeling.

1.4 Patient Experience Data

Patient experience data in the form of quality-of-life questionnaires (Impact of Weight and Quality of Life Kids; IWQOL-Kids) were collected as exploratory secondary endpoints to support the benefits of weight loss in this population of adolescents with obesity. Similar to the adult studies, mean changes in the tested domains of quality-of-life appeared to be favorable for semaglutide-treated subjects (the overall score and the physical functioning domain), but the clinical relevance at this time is unclear. See discussion in Section 6.1.2.

Table 1. Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
✓	☒		Patient reported outcome (PRO)	Sec 6.1.2 Study results
	☐		Observer reported outcome (ObsRO)	
	☐		Clinician reported outcome (ClinRO)	
	☐		Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

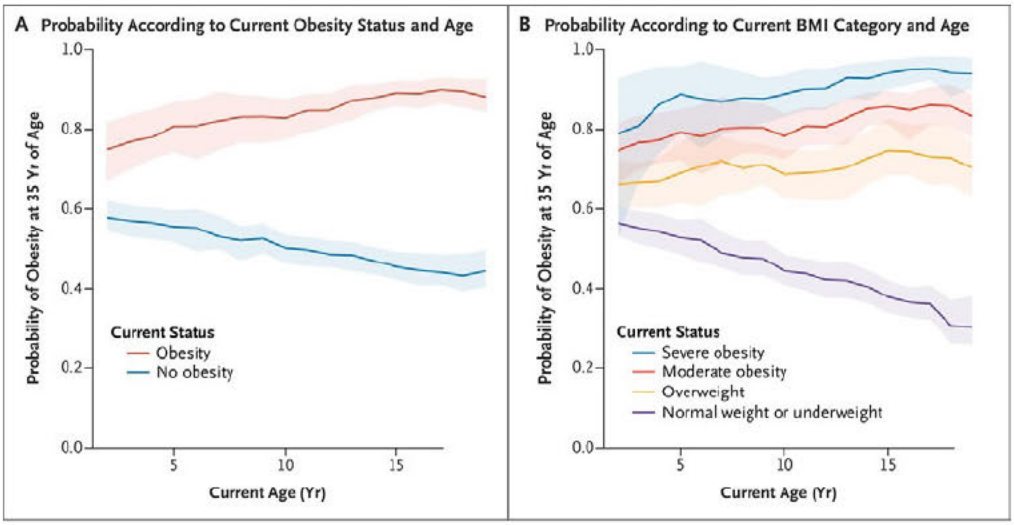
2.1 Analysis of Condition

Obesity in children and adolescents is a rising problem in the U.S. and globally with a current U.S. prevalence of ~8.9% of adolescents considered to have class I obesity (defined as BMI ≥95th to <120 percent of the 95th and BMI <35 kg/m^2) and ~10.1% of adolescent girls and ~13.2% of adolescent boys considered to have class II or III obesity (defined as BMI ≥120 percent of the 95th percentile or ≥35 kg/m^2).[2]

Medical sequelae of obesity can be significant in this population, with some adolescents exhibiting evidence of metabolic abnormalities such as dysglycemia and steatohepatitis, as well as cardiovascular, gastrointestinal, orthopedic, pulmonary, psychosocial, and other health consequences.[3]

The occurrence of obesity in adolescence, and its severity, may predict development of obesity in adulthood (Figure 1).[4]

Figure 1. Predicted Probability of Obesity at the Age of 35 Years, According to Current Age, Obesity Status, and BMI Category



[2] https://www.uptodate.com/contents/definition-epidemiology-and-etiology-of-obesity-in-children-and-adolescents Accessed 24 Oct 2022.
[3] Kumar S and Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin Proc. 2017;92(2):251-265.
[4] Ward ZJ, et al. Simulation of growth trajectories of childhood obesity into adulthood. N Engl J Med 2017; 377:2145-53.

Source: Reference 4

In the U.S., prevalence of obesity is particularly high among non-Hispanic black and Hispanic children and adolescents compared those of other racial or ethnic backgrounds.[5]

Effective treatment options for childhood obesity are needed.

2.2 Analysis of Current Treatment Options

The mainstay of obesity management in patients of all ages is a comprehensive lifestyle program including healthy eating, physical activity, and behavioral management.

Despite several recent drug approvals for adolescent obesity (Qsymia and Saxenda, see Table 2), treatment options for this age group are still somewhat limited. Change in BMI for Saxenda (liraglutide) vs. placebo in the 56-week adolescent trial was -4.6%. Acknowledging the limitations of cross-study comparisons, Qsymia (phentermine/topiramate extended-release, PHEN/TPM) may have greater effectiveness for weight loss (BMI for mid-dose PHEN/TPM vs. placebo -8.1% and high-dose PHEN/TPM vs. placebo -10.4% at 56 weeks) but is associated with a number of safety and tolerability issues, including the newly described decrease in linear growth. Neither Qsymia nor Saxenda was associated with substantial improvements in cardiometabolic parameters. Xenical (orlistat) has data from an adolescent trial in labeling but no formal indication. Its weight loss efficacy is marginal, and it is associated with alterations in bowel patterns that limit its use.

[5] Fryar CD, et al. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats. 2020

Table 2: Summary of Available Drug Treatments for Adolescents with Obesity

Product Name	Relevant Indication	Year of Approval (pediatric labeling)	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
QSYMIA (phentermine and topiramate extended-release capsules)	Pediatric patients aged 12 years and older with BMI in the 95th percentile or greater standardized for age and sex.	2022	Oral, once daily	Change in BMI (%) at week 56: Qsymia 15/92 = -7.1 Qsymia 7.5/46 = -4.8 Placebo = +3.3	• Embryo/fetal toxicity • Increase in heart rate • Suicidality • Depression/anxiety, insomnia • Cognitive dysfunction • Slowing of linear growth • Metabolic acidosis • Decrease in bone mineral density • Decrease in renal function • Hypoglycemia • Seizure risk with discontinuation • Kidney stones • Oligohidrosis and hyperthermia • Hypokalemia • Serious skin reactions
SAXENDA (liraglutide) injection	Pediatric patients aged 12 years and older with: • body weight above 60 kg and • an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cut-offs	2020	Subcutaneous injection, once daily	Change in BMI (%) at week 56: Saxenda = -4.29 Placebo = +0.35	• Thyroid C-cell tumors • Acute pancreatitis • Acute gallbladder disease • Hypoglycemia • Heart rate increase • Renal impairment • Hypersensitivity • Suicidality • Gastrointestinal AEs
XENICAL (orlistat) capsules	N/A (pediatric information in 8.4)	2003	Oral, three times daily	Change in BMI (kg/m^2) at week 52: Xenical = -0.55 Placebo = +0.31	• Drug and vitamin interactions • Liver injury • Oxalate nephropathy • Cholelithiasis • Gastrointestinal AEs

Source: Qsymia, Saxenda, Xenical prescribing information

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Semaglutide (Wegovy, NDA 215256) was approved in the U.S. on June 4, 2021, for chronic weight management in adults with obesity. The dosage of Wegovy is 2.4 mg administered weekly as a subcutaneous injection.

Semaglutide is also marketed in the U.S. as Ozempic (NDA 209637) at doses of 0.5 and 1 mg once weekly subcutaneously (SC), and Rybelsus (NDA 213051) at doses of 7 and 14 mg once daily orally (PO), for glycemic control in patients with T2D. Ozempic also has an indication to reduce major adverse cardiovascular (CV) events in patients with T2D and established CV disease.

3.2 Summary of Presubmission/Submission Regulatory Activity

At the time of Wegovy's initial U.S. approval, two pediatric PMRs were issued under the Pediatric Research Equity Act (PREA):

Table 3. Pediatric PMRs Under PREA

4081-1	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.
4081-2	Conduct a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy after 68 weeks of semaglutide for the treatment of obesity in pediatric patients ages 6 to less than 12. Compare the long-term (at least 2 years) safety and tolerability of semaglutide versus placebo for the treatment of obesity in both children and adolescents (ages 6 to less than 18 years). The trial may not be initiated until results from the semaglutide adolescent trial have been submitted to and reviewed by the Agency.

Source: NDA 215256 approval letter

The pediatric study requirement for ages under 6 years old was waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

The submission of the second study was deferred because the product was ready for approval for use in adults and the first pediatric study (the focus of this review) was not completed at the time.

FDA has also issued a pediatric written request for semaglutide (July 26, 2021), which requires completion of the following studies:

- Study 1: Efficacy and safety of oral semaglutide versus placebo both in combination with metformin and/or basal insulin in children and adolescents with type 2 diabetes

- Study 2: Efficacy and safety of semaglutide on weight management in adolescents with overweight or obesity

(b) (4)

Study 1 (trial NN9924-4437) is currently ongoing under IND 114464. Study 2 is fulfilled with this submission (trial NN9536-4451, STEP Teens), (b) (4)

3.3 Foreign Regulatory Actions and Marketing History

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

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

An OSI audit was requested for this application. Two domestic sites were selected for clinical inspections based on relatively high enrollment.

- Silva A. Arslanian, M.D. (Site 501): Screened and enrolled 7 subjects; 6 subjects completed the trial. Data from this site were considered adequate, and Form 483 was not issued.
- Rachel Edelen, M.D. (Site 509): Screened 6 subjects and enrolled 4 subjects; all 4 subjects completed the trial. Data from this site were considered adequate, and Form 483 was not issued.

See Dr. Ling Yang's clinical inspection summary for more details.

In addition to the scheduled inspections for this application, an additional foreign site [Margarita Barrientos (Site 701)] was partially inspected at the time of another application's

inspection. The clinical review team shared some concerns with OSI regarding height measurements at this site (see further discussion in the Data Quality and Integrity subsection under Section 6). The ORA investigator confirmed that subjects' height, weight, and BMI values were able to be verified and did not identify any major discrepancies (internal communication).

4.2 **Product** Quality

There are no proposed changes to the drug product quality information or to the CMC sections of labeling.

4.3 Clinical **Microbi**ology

There is no new drug product or drug substance microbiology information.

4.4 **Noncl**inical Pharma**cology/Toxico**logy

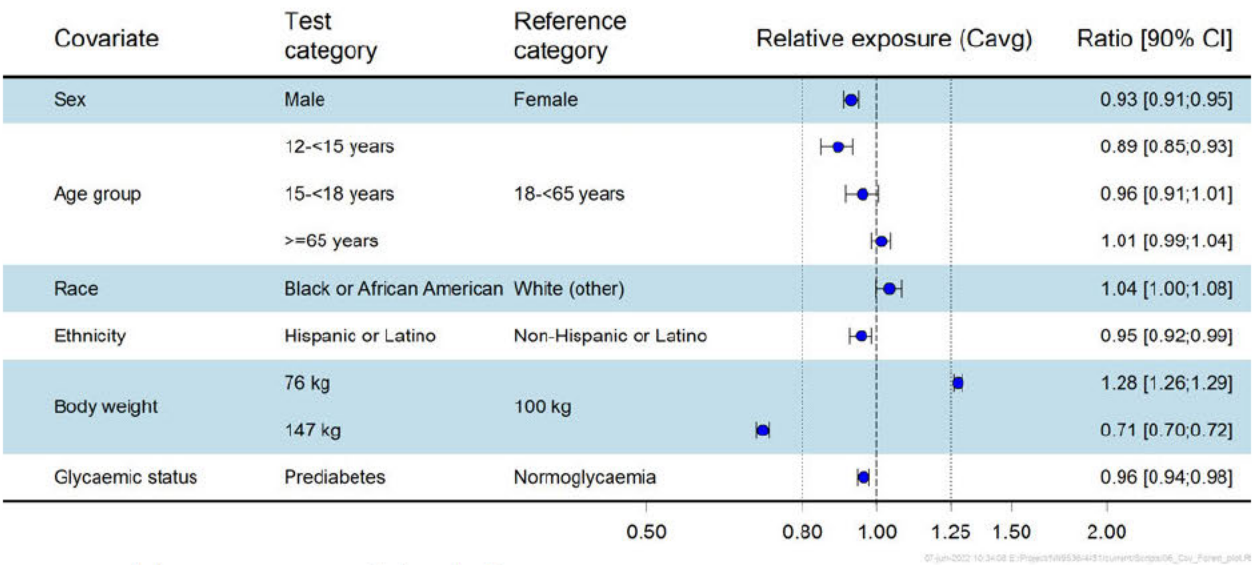
No pharmacology/toxicology review was done for this supplement. A juvenile rat toxicology study was conducted under the Ozempic NDA 209637. The iPSP notes that once daily SC administration of semaglutide to juvenile Sprague Dawley rats for 11 weeks caused reduced food consumption, body weight gain, a delay in sexual maturation, and higher body weight at attainment of sexual maturation. Delays in attainment of sexual maturation were not considered to be adverse, and the NOAEL was considered to be 0.6 mg/kg/day (highest dose tested), corresponding to 11-fold the clinical exposure at 2.4 mg/week based on AUC in adults. These conclusions appear consistent with the pharmacology/toxicology review of this trial under the Ozempic NDA.[6]

4.5 Clinical **Pharmacolo**gy

The clinical pharmacology team reviewed the relevant clinical pharmacology information for this supplement. Body weight is the most important covariate for semaglutide exposure (Figure 2). Body weight was similar for the adolescent and adult populations, and therefore exposure was similar for the adolescent and adult populations. The sponsor notes that the exposure-response relationship appeared slightly steeper in adolescents compared to adults; however, there is a large overlap in exposure and response in adolescents and adults.

[6] NDA 209637, Dr. Federica Basso, dated 2 August 2017

Figure 2. Forest Plot of Covariate Effects for Semaglutide Exposure, STEP Teens and STEP 1 (adults)



Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 4-1

The clinical pharmacology team also evaluated the applicant's proposed dosing recommendations, which stated that 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. This recommendation was based on the dosing recommendations in the trial, which allowed for dose flexibility based on tolerability. Notably, most participants remained on the 2.4 mg dose throughout the maintenance period of the trial.

According to the clinical pharmacology team, an exposure-response model predicted that a dose above 1 mg is predicted to decrease BMI by at least 5% in treated patients. At the 1 mg dose level, there was more uncertainty; in male patients the upper bound of the confidence interval for predicted weight loss was less than 5%. The clinical pharmacology team is accepting 1.7 mg as a viable down-titration (internal communication). See the clinical pharmacology review for more details.

4.6 Devices and Companion Diagnostic Issues

The Division of Medication Error Prevention and Analysis 1 (DMEPA) reviewed the results of a human factors (HF) validation study for pediatrics that was included in this supplement. The DMEPA review noted that the results of the study demonstrated several use errors/close calls/use difficulties with critical tasks, but that the risks have been acceptably mitigated and no further changes are recommended. See DMEPA review dated December 2, 2022, for further

details.

4.7 Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

Table 4. Clinical Trial Supporting this NDA Supplement

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpts	Duration/ Follow Up	No. of pts enrolled	Study Population	No. of Centers and Countries
NN9536-4451	NCT04102189	Randomized, double-blind, placebo-controlled, multi-center, multi-national trial assessing the effect and safety of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to reduced calorie diet and increased physical activity	Semaglutide s.c. 2.4 mg once weekly versus placebo	Percent change in BMI	68 weeks	201	Adolescents aged 12 to <18 years with obesity (BMI ≥ 95th percentile) or with overweight (BMI ≥ 85th percentile) and at least 1 weight related comorbidity	37 sites in 8 countries

5.2 Review Strategy

The clinical review for this supplement consisted of the review of the single efficacy and safety trial in adolescents, NN9536-4451 (STEP Teens). Dr. Golden reviewed efficacy and Dr. Chowdhury reviewed safety. Both reviews are incorporated into this document.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1 NN9536-4451 (STEP Teens)

6.1.1 Study Design

Overview and Objective

STEP Teens evaluated the effect of semaglutide SC once weekly versus placebo as an adjunct to diet and exercise on weight management (percent change in BMI) in adolescents with overweight and obesity. Secondary objectives were to evaluate the effect on cardiovascular risk factors and glucose metabolism, as well as safety and tolerability.

Trial Design

STEP Teens was a 68-week double-blind, randomized, parallel group, placebo-controlled trial in pubertal adolescents ages 12 to <18 with overweight and obesity. The trial was conducted at 37 sites in 8 countries, including the US.

Key inclusion criteria included BMI ≥95th percentile, or 85th percentile with ≥1 weight-related comorbidity (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or type 2 diabetes). Subjects with T2D were either to be treated with diet and exercise alone or on stable treatment with metformin and have an HbA1c ≤10%.

Key exclusion criteria included uncontrolled thyroid disease, secondary causes of obesity, major depressive disorder within 2 years, other severe psychiatric disorder, PHQ-9 ≥15, history of suicide attempt, suicidal behavior or ideation within 30 days, bulimia nervosa, prepuberty (Tanner 1), history of pancreatitis, personal or first degree relative with MEN2 or MTC, type 1 diabetes, impaired renal function, history of heart disease, pregnancy, and breastfeeding. Subjects with or without T2D were not to be treated with a glucose-lowering agent within 90 days (except for metformin) or with a GLP-1 RA within 180 days. Subjects with T2D were excluded with uncontrolled and potentially unstable diabetic retinopathy or maculopathy.

Subjects fulfilling the eligibility criteria entered a 12-week run-in period before randomization

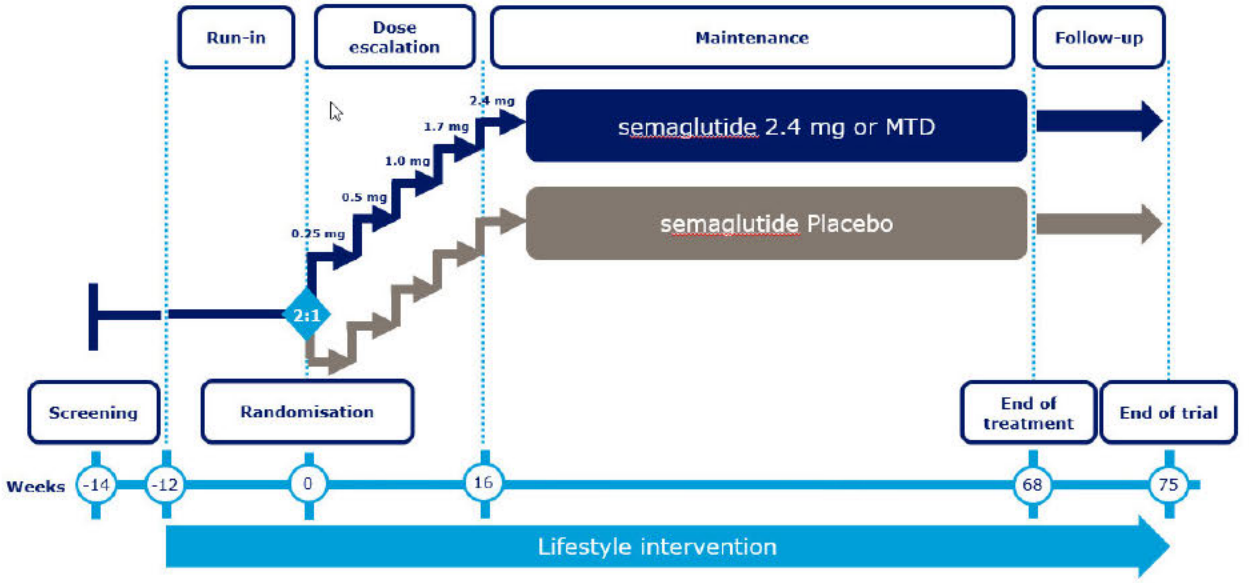
to ensure that lifestyle intervention (diet and physical activity counseling) was insufficient.

Subjects who fulfilled randomization criteria (eligible BMI criteria, no suicidal behavior or ideation, PHQ-9 ≤15) were randomized 2:1 to receive semaglutide SC or placebo once weekly. Randomization was stratified according to sex and Tanner stage (2-3 vs. 4-5).

The dose escalation period was 16 weeks and the maintenance period 52 weeks. The follow-up period was 7 weeks after end-of-treatment due to the long half-life of semaglutide.

The following figure illustrates the study design including the semaglutide dosing regimen with titration; i.e., 0.25 mg, 0.5 mg, 1 mg, and 1.7 mg, and the maintenance dosage of 2.4 mg weekly.

Figure 3. STEP Teens Study Design



MTD, Maximum Tolerated Dose

Source: STEP Teens protocol, Figure 5-1

The sponsor acknowledged in the protocol that some participants might not tolerate the 2.4 mg dose; the following are instructions regarding alternative dosing:

- *If a subject does not tolerate the designated target dose (2.4 mg once-weekly), the subject may stay at a lower dose level. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue on trial product, as per the investigator's discretion. It is recommended that the subject makes at least one attempt to re-escalate to the designated target dose (2.4 mg once-weekly), as per the*

investigator's discretion

- *In case the subject needs to be on a lower dose level than 1.0 mg after V12, the site must advise the subject how to administer the 0.25 or 0.50 mg dose using the 3 mg/mL pen*
- *It is recommended that the investigator consults Novo Nordisk in case the subject should be on a lower dose than 1.0 mg using the 3.0 mg/mL pen or in case of persistent deviation from the planned escalation regimen*

Study Endpoints

The primary endpoint was percent change in BMI from baseline to week 68.

Medical Officer Comment: BMI is an accepted measure of the weight status of growing children, and its change (decrease) is associated with improvements in metabolic endpoints, such as triglycerides and blood pressure.[7] Because BMI increases with age through childhood and adolescence, percent change in BMI is used to evaluate for clinically relevant changes over one year.

The confirmatory secondary endpoint was the proportion of subjects achieving ≥5% reduction of body weight from baseline to week 68.

Medical Officer Comment: A reduction of 5% body weight is considered clinically relevant in adults and is considered relevant in an adolescent population that has achieved most of their adult height (see discussion further below).

Only the primary endpoint and confirmatory secondary endpoint were controlled for multiplicity.

Supportive secondary endpoints (not controlled for type I error) include:

- Mean change in:
    - Body weight (kg)
    - Body weight (%)
    - BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) (%)
    - BMI (standard deviation score) (WHO.int)
    - Waist circumference (cm)
    - Systolic blood pressure (mmHg)
    - Diastolic blood pressure (mmHg)

[7] Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, Yanovski JA. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Mar 1;102(3):709-757.

  - HbA1c (% point)
- Subjects achieving ≥10, 15, 20% reduction of weight (yes/no)
- Subjects achieving ≥5% reduction of BMI (yes/no)

Medical Officer Comment: Irrespective of type I error control, chronic weight management drug labels include a number of standard cardiometabolic endpoints, including for the pediatric population: waist circumference, blood pressure, heart rate, HbA1c, and lipids (see: Saxenda (liraglutide) and Qsymia (phentermine/topiramate)).

Statistical Analysis Plan

The statistical analysis plan (SAP) was dated December 16, 2021 and submitted to FDA December 21, 2021. The statistical team found information in the SAP acceptable.

Efficacy analyses were performed using the full analysis set (FAS), which includes all randomized subjects according to the intent-to-treat principle.

The tests of superiority of semaglutide 2.4 mg to placebo for the primary and confirmatory secondary endpoints were performed using a fixed-sequence statistical strategy that tested the endpoints in a predefined hierarchical order. First, the primary endpoint of change in BMI (%) from baseline to week 68 was tested at a significance level of 5%. Once superiority was confirmed (two-sided p-value <5%), the test of the confirmatory secondary endpoint, subjects achieving ≥5% reduction of body weight, was performed. No other endpoints were controlled for multiplicity.

To address missing data, the primary imputation approach for the primary estimand used a multiple imputation approach using retrieved subjects (RD-MI), which has been previously recommended by FDA.[8]

Sensitivity analyses for the primary endpoint included: a jump to reference multiple imputation approach (J2R-MI), which samples all available BMI assessments for imputation; a tipping-point multiple imputation analysis (TP-MI), which evaluates the robustness of the superiority conclusions to departures from the observed change in body weight in both treatment groups; a mixed model for repeated measurements (MMRM), which uses all assessments regardless of adherence to randomized treatment; and ANCOVA assuming unequal variances, which is similar to the primary imputation but assesses unequal variances instead of equal variances.

In the SAP, changes to the protocol relevant to clinical efficacy analyses included:

- Fasting plasma glucose and lipids were promoted from exploratory endpoints to supportive

[8] McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.

secondary endpoints in order to align with the other semaglutide pediatric trial for chronic weight management (STEP Young).

- Based on feedback from authorities, ALT was promoted to a supportive secondary endpoint.

Medical Officer Comment: (b) (4)

- Due to the stadiometer not being calibrated at site 402, a sensitivity analysis of the primary endpoint was added.

Medical Officer Comment: This protocol deviation is discussed further below.

Protocol Amendments

Protocol version 2.0, dated January 6, 2021, was implemented to allow co-participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19.

6.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

A total of 142 investigators participated in this trial. None disclosed financial conflicts of interest. See Appendix 13.2.

Patient Disposition

Out of 229 subjects screened, 21 failed screening, including 13 due to depression and suicidality-related exclusion criteria.

Medical Officer Comment: The substantial number of subjects who failed screening due to significant mental health concerns is notable and to some extent may limit the

generalizability of the study.

Seven additional participants withdrew prior to randomization; these subjects were from 5 sites outside of the US (United Kingdom, Belgium, and Russian Federation). Two subjects were male, 6 were non-Hispanic white and 1 was Asian, and ages ranged from 12 to 16 years.

Subjects entered a 12-week non-pharmacological lifestyle intervention run-in period prior to randomization. The lifestyle intervention consisted of diet and physical activity counselling and continued throughout the trial until 'end of trial' (week 75). There was no significant difference in mean weight or BMI from screening (week -14) to randomization (week 0) [mean body weight, week -14: 106.3 kg, week 0: 107.5 kg; mean BMI, week -14: 36.9 kg/m^2, week 0: 37.0 kg/m^2].

Of the 201 randomized subjects (134 semaglutide, 67 placebo), 200 were exposed to trial product. One subject who was randomized to the semaglutide group in violation of eligibility criteria related to mental health never received trial product. The subject remained in the trial, off-treatment.

Table 5. Subject Disposition

	Semaglutide N (%)	**Placebo N (%)**
Screened	229	
Screening failures	21	
Withdrawn before randomization[a]	7	
Randomized (FAS)	134 (100)	67 (100)
Randomized in violation of inclusion, exclusion criteria	2 (1.5)	1 (1.5)
Exposed (SAS)	133 (99.3)	67 (100)
Treatment completers	120 (89.6)	60 (89.6)
After at least one temporary interruption	11 (8.2)	4 (6.0)
Attended end-of-treatment visit without permanent discontinuation	120 (89.6)	59 (88.1)
Trial product permanently discontinued	14 (10.4)	7 (10.4)
Primary reason		
Adverse event	6 (4.5)	4 (6.0)
Protocol violation[b]	2 (1.5)	1 (1.5)
Pregnancy	1 (0.7)	0
Lack of efficacy	0	0
Investigator-initiated	0	0
Withdrawal of consent	1 (0.7)	1 (1.5)
Lost to follow-up	0	0
Other	4 (3.0)	1 (1.5)
Attended end-of-treatment visit after permanent discontinuation	13 (9.7)	5 (7.5)

Trial completers	132 (98.5)	64 (95.5)
Withdrawn from trial	2 (1.5)	3 (4.5)
Primary reason		
Withdrawal by subject	1 (0.7)	2 (3.0)
Withdrawal by parent/guardian	0	1 (1.5)
Lost to follow-up	1 (0.7)	0
Withdrawn from trial before week 68	2 (1.5)	2 (3.0)
Withdrawn from trial without prior permanent discontinuation of trial product	0	0

[a] Includes two subjects who were withdrawn before the run-in period started
[b] All protocol violations leading to discontinuation were in the category 'randomized in violation of inclusion, exclusion criteria'
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).

Source: STEP Teens CSR, Table 10-1

Protocol Violations/Deviations

Other Important Protocol Deviations

According to the sponsor, important protocol deviations (PDs) were deviations that could significantly impact the completeness, accuracy, and/or reliability of the trial data or that could significantly affect the subject's rights, safety, or well-being. There were 217 important PDs in the trial: 2 trial-level, 49 site-level, and 166 subject-level PDs.

The 2 trial-level deviations were:

- Trial procedures/assessment: A software problem in the eCRF system caused the auto-calculation of BMI not to work, impacting 154 subjects. The sponsor stated that the malfunctioning of the BMI auto-calculation field had no impact on study conduct, quality control, data integrity, or the interpretation of the data.

- Privacy and data protection: A vendor ((b) (4)) used for collection of electronic clinical outcome assessments (b) (4) certain network systems making them unavailable to site staff and the sponsor from (b) (4). Data collection was still possible on another device. According to the sponsor, the (b) (4) had no impact on subject safety, data reliability, and conduct of the trial as no data were affected or lost. "(b) (4)

The summary of site-level and subject-level PDs is as follows:

Table 6. Summary of Site- and Subject-Level Important Protocol Deviations, By Category

Protocol deviation category	Site level	Subject level				Total
		Sema	Placebo	Not allocated	Total	
Total	49	91	68	7	166	215
Informed consent	2	13	10	2	25	27
Inclusion/exclusion criteria	1	5	1	2	8	9
Treatment administration	1	10	6	0	16	17
Trial procedures/assessment	22	24	31	1	56	78
Concomitant medication	0	0	0	0	0	0
Subject visit schedule	23	34	19	2	55	78
SAE notification/safety procedure	0	4	0	0	4	4
Privacy and data protection	0	0	1	0	1	1

Source: STEP Teens CSR, Appendix 16.2.2, Table 16.2.2.1

The high numbers of PDs in the categories, 'subject visit schedule' and, 'trial procedures/assessments', were related to COVID-19. The primary impact of COVID-19 was on visit attendance. Nine visits where important assessments should have been taken were missed; however, according to the sponsor the missing data do not impact primary or confirmatory endpoints.

Table 7. COVID-19 Impact

	Semaglutide N=134 n (%)	Placebo N=67 n (%)	Total N=201 n (%)
Impacted subjects	64 (47.8)	27 (40.3)	91 (45.3)
Number of visits impacted			
Site visit converted to phone visit	90	49	139
Visit out of window	40	18	58
Visit with missed important assessments			
Calcitonin	0	1	1
C-SSRS questionnaire	0	1	1
Pregnancy test	0	6	6
PHQ-9 questionnaire	0	1	1

Source: STEP Teens CSR, Table 10-6

See the section below on data quality and integrity for a discussion of protocol deviations related to heights, specifically at site 402, as part of a further discussion of subject height quality in the trial.

Table of Demographic Characteristics

Generally, demographic characteristics were well-balanced among groups. Because only approximately 25% of participants were enrolled from U.S. sites, total Black or African American representation was relatively low (8% overall; 24% from U.S. sites vs. 3% from non-U.S. sites). Other racial groups also had limited representation; see Table 8.

Table 8. Demographics

	Semaglutide N=134 n (%)	**Placebo N=67 n (%)**
Sex		
Male	50 (37.3)	26 (38.8)
Female	84 (62.7)	41 (61.2)
Age		
Mean years (SD)	15.5 (1.5)	15.3 (1.6)
Median (years)	15.8	15.4
Min, max (years)	12, 18	12, 18
Age Group		
12 - < 15 years	47 (35.1)	25 (37.3)
15 - < 18 years	87 (64.9)	42 (62.7)
Race		
White	104 (77.6)	55 (82.1)
Black or African American	11 (8.2)	5 (7.5)
Asian	3 (2.2)	1 (1.5)
American Indian or Alaska Native	2 (1.5)	0
Native Hawaiian or Other Pacific Islander	0	0
Other[1]	14 (10.4)	6 (9.0)
Ethnicity		
Hispanic or Latino	14 (10.4)	8 (11.9)
Not Hispanic or Latino	120 (89.6)	59 (88.1)
Region		
United States	35 (26.1)	16 (23.9)
Rest of the World	99 (73.9)	51 (76.1)
Austria	4 (3.0)	7 (10.4)
Belgium	15 (11.2)	9 (13.4)
Croatia	12 (9.0)	4 (6.0)
Ireland	3 (2.2)	1 (1.5)
Mexico	13 (9.7)	5 (7.5)
Russian Federation	37 (27.6)	18 (16.9)
United Kingdom	15 (11.2)	7 (10.4)

[1] Other as defined in the ADSL dataset = 'Mexican' (sema 13, placebo 5); 'Roma' (sema 0, placebo 1); 'White/Black Caribbean' (sema 1, placebo 0)

Source: STEP Teens CSR, Tables 10-2 and 10-3

Other Baseline Characteristics

Table 9 summarizes the baseline characteristics related to weight and relevant comorbidities. Subjects randomized to semaglutide tended to have higher baseline body weight and BMI than those randomized to placebo. Only one participant had a baseline BMI in the 85th to 95th percentile range (overweight). A limited number of participants in either group were Tanner stage 2 or 3 (approximately 11%).

Table 9. Baseline Characteristics

	Semaglutide N=134 n (%)	**Placebo N=67 n (%)**
Height (cm)		
Mean (SD)	170.1 (9.4)	168.8 (10.6)
Median	170.1	167.8
Min, max	145.5, 193.0	146.6, 192.1
Body weight (kg)		
Mean (SD)	109.9 (25.2)	102.6 (22.3)
Median	106.4	97.8
Min, max	61.6, 211.9	61.0, 147.4
BMI (kg/m^2)		
Mean (SD)	37.7 (6.7)	35.7 (5.4)
Median	36.7	34.9
Min, max	26.8, 60.0	26.6, 49.9
HbA1c (%)		
Mean (SD)	5.5 (0.4)	5.5 (0.4)
Median	5.5	5.4
Min, max	4.8, 9.0	4.8, 7.0
Weight class		
Overweight (≥85th – <95th percentile)	1 (0.7)	0
Obesity class I (≥95th - <120% of the 95th percentile)	42 (31.3)	27 (40.3)
Obesity class II (≥120% - <140% of the 95th percentile)	44 (32.8)	25 (37.3)
Obesity class III (≥140% of the 95th percentile)	47 (35.1)	15 (22.4)
Tanner stage		
Female, Tanner 2-3	4 (3.0)	1 (1.5)
Female, Tanner 4-5	80 (59.7)	40 (59.7)
Male, Tanner 2-3	10 (7.5)	7 (10.4)
Male, Tanner 4-5	40 (29.9)	19 (28.4)
Epiphyseal closure		
All epiphyses closed	69 (51.5)	34 (50.7)
Weight-related comorbidities		
At least 1 comorbidity	41 (30.6)	21 (31.3)
Dyslipidemia	27 (20.1)	10 (14.9)
Hypertension	18 (13.4)	9 (13.4)
Type 2 diabetes	5 (3.7)	3 (4.5)

Obstructive sleep apnea	2 (1.5)	1 (1.5)
Glycemic status		
Type 2 diabetes	5 (3.7)	3 (4.5)
Pre-diabetes	19 (14.2)	8 (11.9)
Normoglycemia	110 (82.1)	56 (83.6)
Pre-existing hepatic disorders (by SOC, PT)		
At least 1, Hepatobiliary disorders SOC	25 (18.7)	8 (11.9)
Hepatic steatosis	13 (9.7)	6 (9.0)
Nonalcoholic fatty liver disease	4 (3.0)	1 (1.5)
Hepatomegaly	3 (2.2)	1 (1.5)
Non-alcoholic steatohepatitis	3 (2.2)	0
ALT (U/L)		
Geometric mean (CV)	23 (69.9)	20 (70.8)
Median	21	19
Min, max	8, 261	3, 155
Systolic blood pressure (mmHg)		
Mean (SD)	120 (11)	120 (12)
Median	120	120
Min, max	95, 149	98, 150
Diastolic blood pressure (mmHg)		
Mean (SD)	73 (9)	73 (9)
Median	72	72
Min, max	52, 100	56, 93

Source: STEP Teens CSR, Tables 10-2, 10-3, 10-4, 14.1.13, 14.1.14, 14.2.90, 14.2.96, 14.2.134; reviewer assessment of ADVS (weight class), ADSL (glycemic status), ADSC (epiphyseal closure)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance of trial product was assessed by asking the subject about missed doses. Two participants on semaglutide and 1 participant on placebo were reported as having important treatment non-compliance protocol deviations.[9]

At baseline, use of concomitant medication was either balanced among groups, or slightly more frequently used in the semaglutide group. The following is a summary of the most frequent concomitant medications by indication or type:[10]

- Diabetes drugs – biguanides (semaglutide 21.6%, placebo 19.4%)
- Sex hormones and modulators of the genital system (semaglutide 9.0%, placebo 6.0%)
- Drugs for obstructive airway disease (semaglutide 7.5%, placebo 4.5%)
- Thyroid hormones (6.0% in both groups)
- Psychoanaleptics (semaglutide 6.7%, placebo 3.0%)
- Agents acting on the renin-angiotensin system (4.5% in both groups)

[9] STEP Teens CSR Appendix 16.2.2, Table 16.2.2.2
[10] STEP Teens CSR, Table 14.1.16

- Psycholeptics (semaglutide 6.0%, placebo 1.5%)

There were no important protocol deviations under the category of concomitant medications.

Some concomitant mediations of note initiated at or after randomization included:
- Drugs for functional gastrointestinal disorders (semaglutide 10.4%, placebo 6.0%); antidiarrheals (4.5%, 3.0%), antiemetics (3.7%, 1.5%), drugs for constipation (3.7%, 0)
- Diabetes drugs – biguanides (semaglutide 3.0%, placebo 1.5%)
- Lipid modifying agents (semaglutide 2.2%, placebo 0)
- Antihypertensives – imidolazine receptor agonists (semaglutide 0.7%, placebo 0)
- Beta-blocking agents (semaglutide 3.0%, placebo 1.5%)
- Vaccines (semaglutide 21.6%, placebo 10.4%)

Medical Officer Comment: The small differential in concomitant medication use is noted for biguanides, lipid-modifying drugs, imidolazine receptor agonists, and beta-blocking agents (i.e., drugs that are specifically relevant to the efficacy endpoints). The indications for their use are unknown in these cases (for example, metformin can be used for off-label purposes such as polycystic ovarian syndrome, and clonidine can be used for attention-deficit hyperactivity disorder). Furthermore, differences in weight and dyslipidemia at baseline might have affected concomitant medication use. The small differences between groups are unlikely to change the conclusions of the overall effectiveness of semaglutide.

Efficacy Results – Primary Endpoint

The primary endpoint in this trial was percent change in BMI from baseline to week 68.[11] The superiority of semaglutide was confirmed versus placebo, with a percent difference in BMI between groups of -16.8, p <0.0001 (Table 10).

[11] This clinical review focuses on the primary estimand, which quantifies the treatment effect in all randomized subjects regardless of adherence to treatment or initiation of other anti-obesity therapies. The hypothetical estimand (treatment effect in all randomized subjects and had they remained on their randomized treatment for the entire planned duration of the trial had not initiated other anti-obesity therapies) resulted in an estimated treatment difference of -18.6 (95% CI -22.1, -15.1).

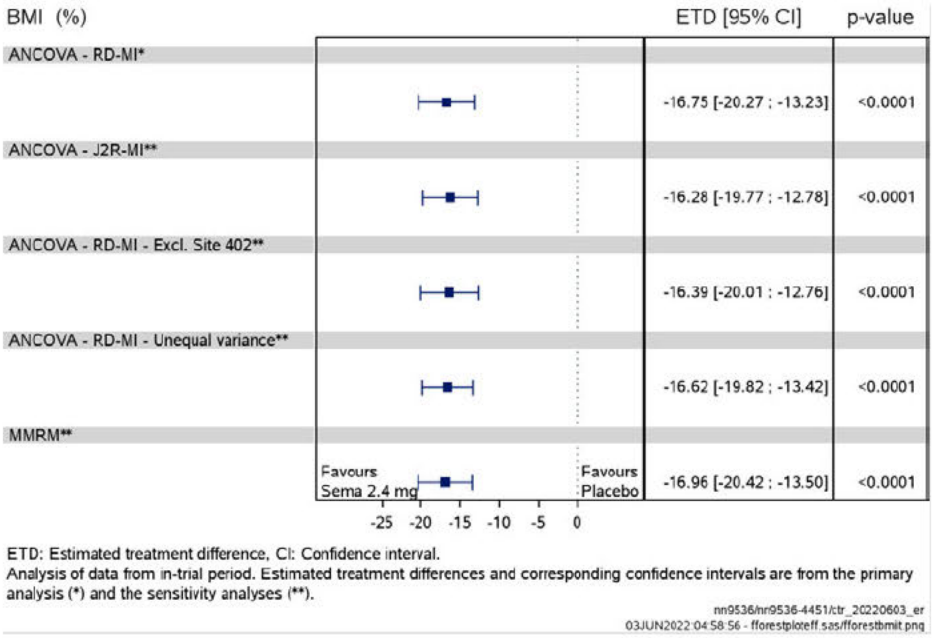
Table 10. Primary Efficacy Analysis: Percent BMI Change from Baseline to Week 68

Treatment	N	Baseline Mean BMI (SD)	Percent Change from Baseline
Semaglutide	134	37.7 (6.7)	-16.14
Placebo	67	35.7 (5.4)	+0.61
Between treatment difference		**Difference in LS means (95% CI)**	**p value**
Semaglutide vs. Placebo		-16.75 (-20.27, -13.23)	<0.0001

Source: STEP Teens CSR, Tables 14.2.2 and 14.2.11

Several sensitivity analyses as described in the statistical analysis plan subsection of Section 6.1.1 were conducted (Figure 4). All results were consistent with the primary analysis.

Figure 4. Mean Percent Change in BMI at Week 68, Primary and Sensitivity Analyses



Source: STEP Teens CSR, Figure 11-6

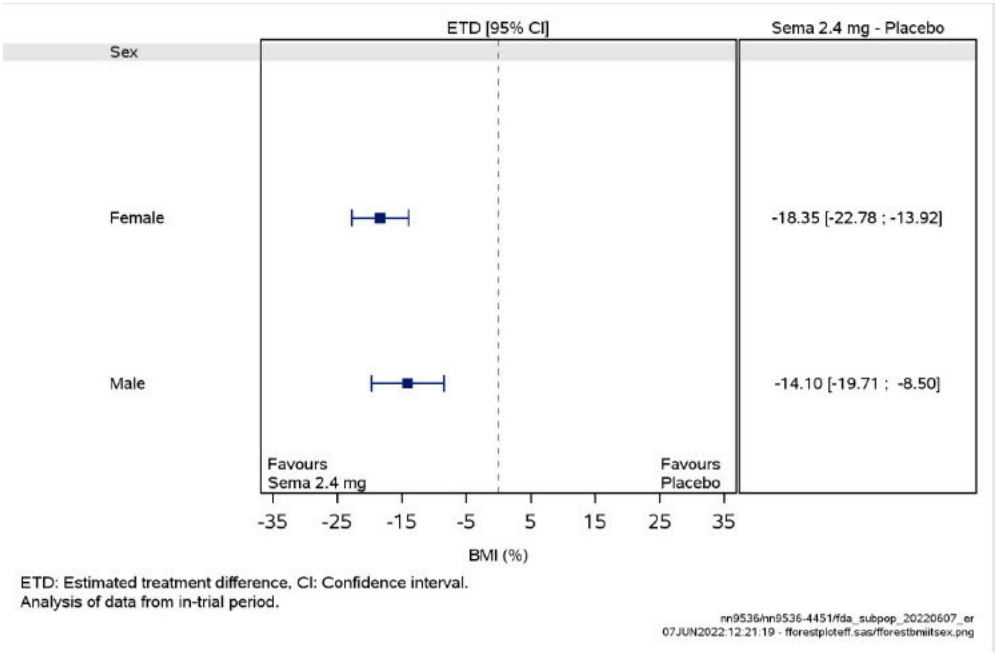
Subgroup Analyses

The treatment effect of the percent change in BMI primary endpoint was generally consistent across the various subgroups evaluated with no significant subgroup interactions. Forest plots are shown below.

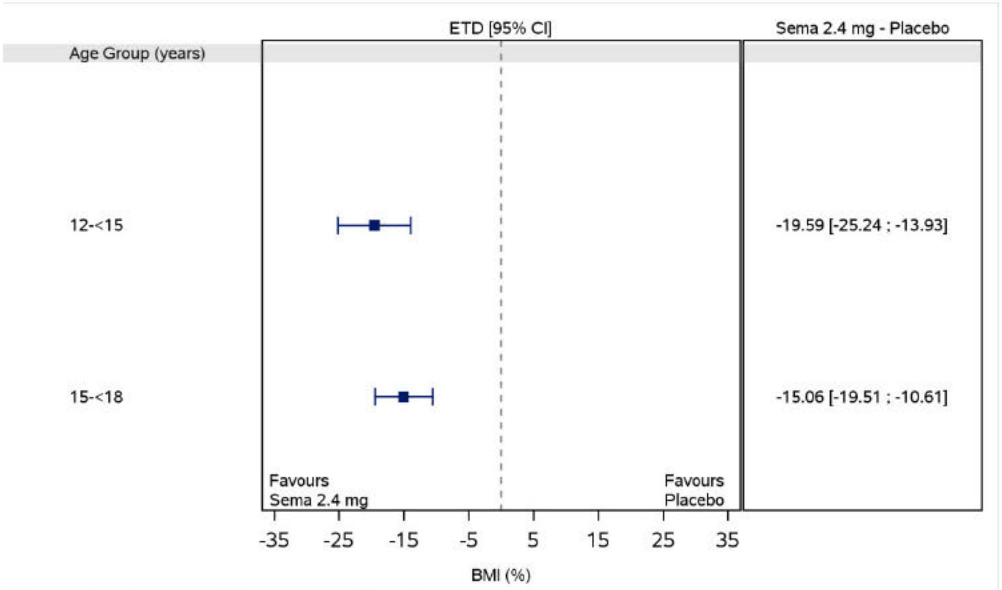
There was some attenuation of the point estimate of the treatment effect in "South America" (Figure 5); the test for treatment-by-subgroup interaction was p=0.0625. "South America" is

actually a description of a single site in Mexico.[12] At this site, the 13 subjects randomized to semaglutide had a mean change in BMI of -14.2% and the 5 subjects randomized to placebo had a mean change in BMI of -11.0%.[13] By contrast, the placebo groups in the "Europe" and "North America" sites had mean change in BMI of +1.1% and 0, respectively. Note also that the single site 701 in Mexico contributed 18 of the 21 subjects who were reported as Hispanic/Latino ethnicity in the trial.

Figure 5. Subgroup Analyses of Primary Endpoint (% Change in BMI from Baseline to Week 68)

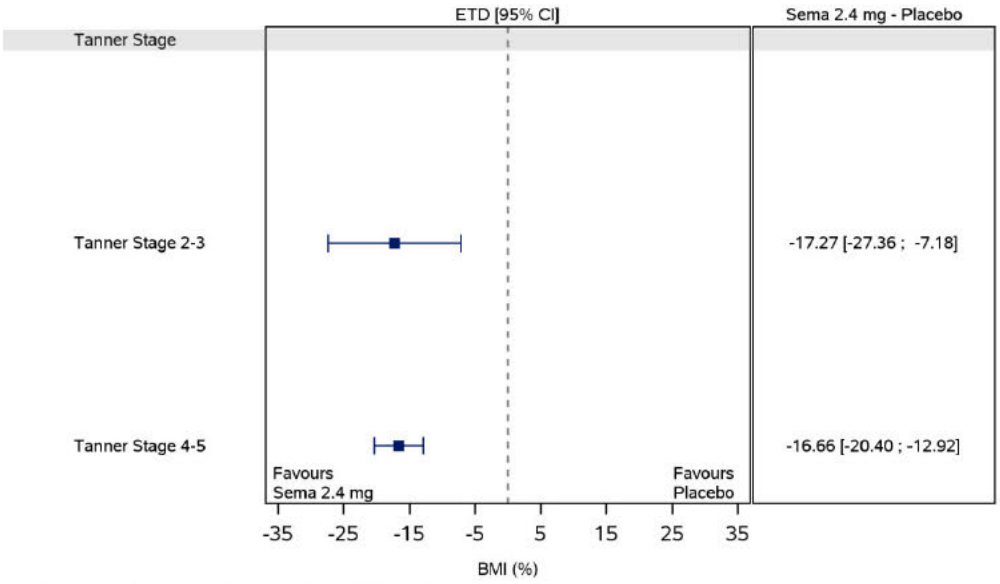


[12] This is site 701, which is discussed under the Heights subsection of Data Quality and Integrity.
[13] This mean change appears to be particularly driven by a single participant who lost approximately 23% of baseline BMI.



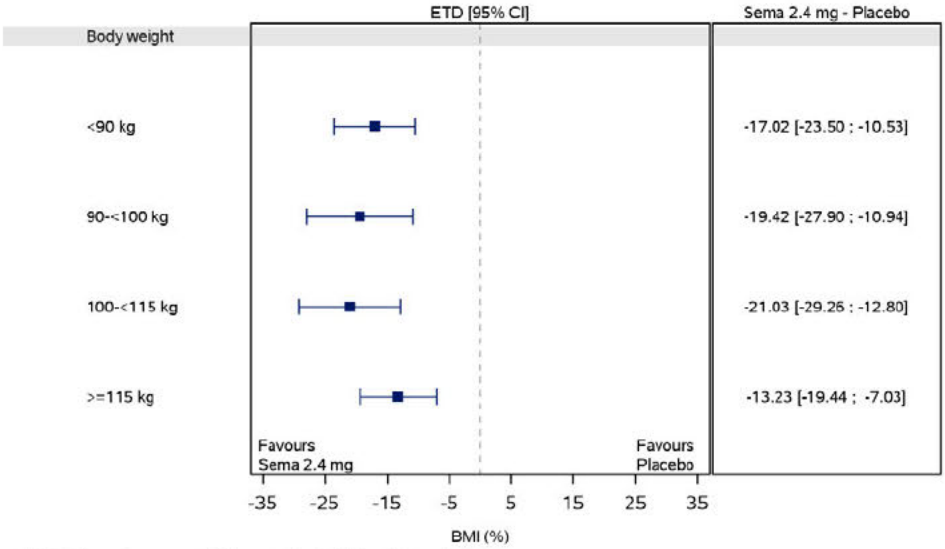
ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-4451/fda_subpop_20220607_er
07JUN2022:12:21:24 - fforestploteff.sas/fforestbmiitage.png



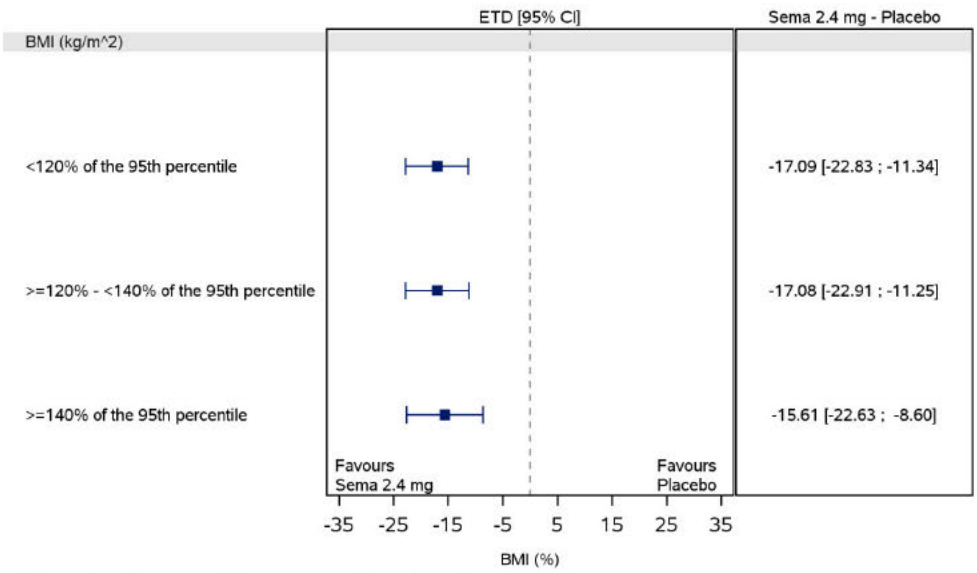
ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-4451/fda_subpop_20220607_er
07JUN2022:12:21:25 - fforestploteff.sas/fforestbmiittan.png



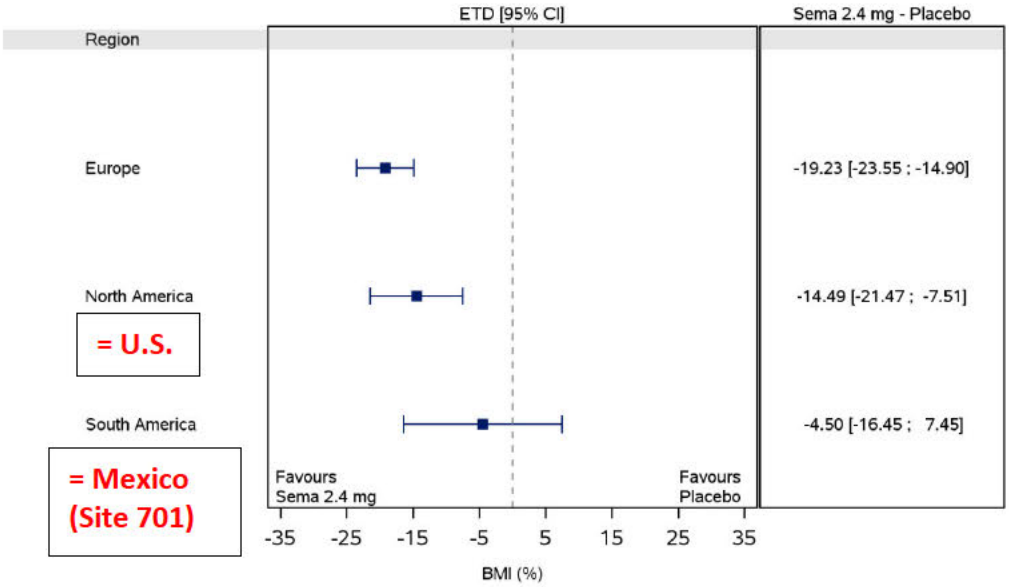
ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-4451/fda_subpop_20220607_er
07JUN2022:12:21:26 - fforestploteff.sas/fforestbmiitbwcat.png



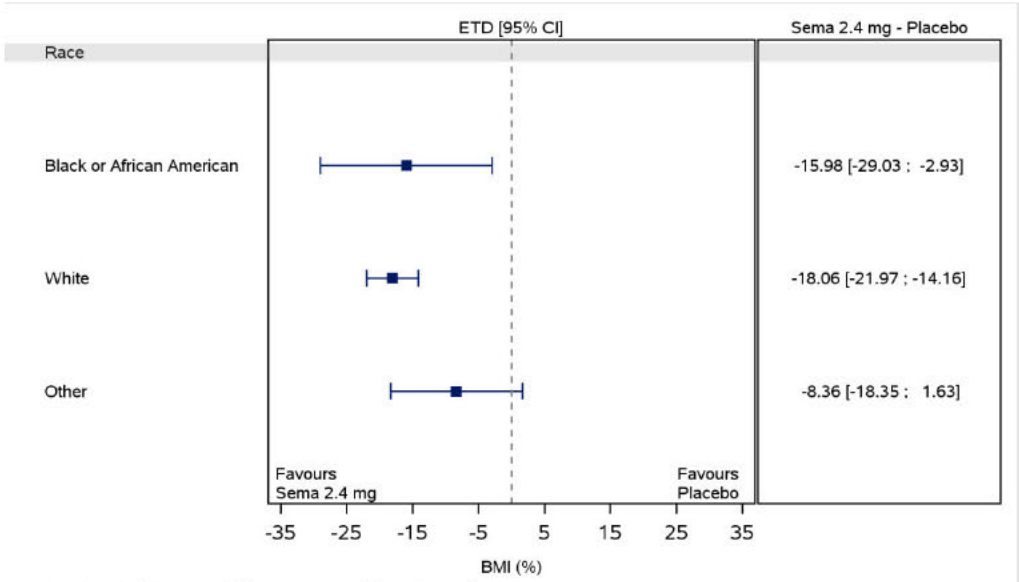
ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-4451/fda_subpop_20220607_er
07JUN2022:12:21:26 - fforestploteff.sas/fforestbmiitwgtcat.png



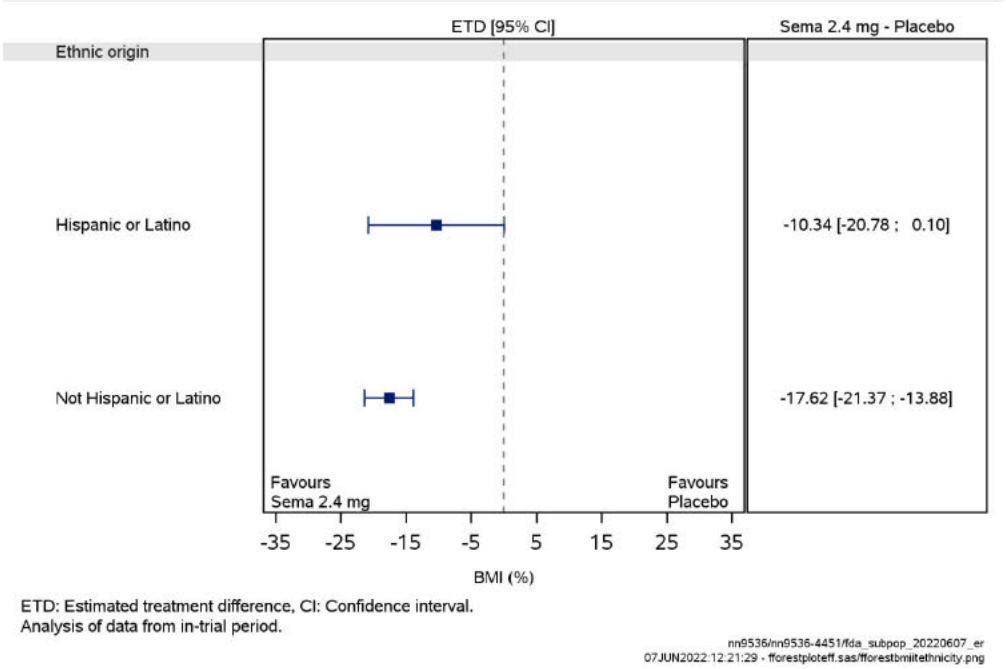
ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

nn9536/nn9536-4451/fda_subpop_20220607_er
07JUN2022:12:21:27 - fforestploteff.sas/fforestbmiitregion.png



ETD: Estimated treatment difference, CI: Confidence interval.
Category Other includes: Asian, American Indian or Alaska native, Other. Analysis of data from in-trial period.

nn9536/nn9536-exploratory/qaus022_20221027_er
27OCT2022:22:24:35 - fforestploteff.sas/fforestbmiitrace.png



Source: Module 2.7.3 Summary of clinical efficacy, Figures 6.4.33 to 6.4.40, modified by reviewer; response to information request[14] dated 27 October 2022, Figure 5

Because of an attenuated treatment effect of semaglutide noted in adult subjects with diabetes versus without diabetes (see Wegovy USPI, Table 4 Study 1 and Study 2), an exploratory analysis was requested of the applicant to evaluate the primary and key secondary endpoints by glycemic status subgroups. Pre-diabetes and type 2 diabetes subgroups were combined.

For the primary endpoint of percent change from baseline to week 68 (semaglutide vs. placebo), the normoglycemic subgroup treatment difference was -17.09 (95% CI -20.92, -13.25) and the pre-diabetes or T2D treatment difference was -15.79 (-24.07, -7.52), with a test for treatment by subgroup interaction p=0.7797.

Data Quality and Integrity

Heights

Height changes over time in growing children and is a component of the primary endpoint (percent change in BMI). Challenges in its measurement and accurate data collection have

[14] This IR was to update the race subgroup analysis to include separate subgroup for "Black or African American"; the prespecified subgroup analysis was "White" and "Other"

been discussed in other pediatric obesity trial reviews.[15]

As described in the protocol, heights were to be measured as follows:

Height should be measured (centimetres or inches, one decimal) without shoes as two individual measurements performed by a single observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject should be repositioned between the two measurements.

In response to an information request by FDA, the sponsor clarified[16] their procedures for height quality control checks. This included automatic queries in the electronic data capture to ensure any decreases in height of >2 cm would notify the site staff. These queries were supplemented by manual review of the height data every 3-4 months to flag decreases in height of >1 cm.

In interpreting the height data, it is relevant to note that the adolescents in this trial had, on average, advanced bone age (semaglutide 16.9 years, placebo 16.8 years) as compared to chronological age (semaglutide 15.8 years, placebo 15.6 years); accelerated skeletal maturation has been described to occur with pediatric obesity.[17]

There were several observations about the height data of note. No requirement for calibration of wall stadiometers was noted in the protocol. Improperly affixed stadiometers were reported at the following sites:

- Site 402 (6 subjects)
- Site 606 (2 subjects at Visit 14)
- Site 603 (6 screening heights taken using a non-wall mounted stadiometer)

Site 402 was of particular concern because the stadiometer issue potentially impacted all 6 subjects' height measurements. Although information in the protocol deviations' descriptions suggested this was an incidental finding that was discovered because a subject alerted the site to an incorrect height measurement (Section 16.2.2; page 15 of 520), the sponsor stated in an information request[16] that issues with height measurements at site 402 were "queried repeatedly" presumably due to automatic and/or manual height data reviews and was finally reported after medical monitoring contacted the site.

Height measurement issues, including those of site 402 and "decreasing height measurements

[15] See: Saxenda NDA 206321 S12 (Golden, J.) and Qsymia NDA 022580 S21 (Roberts, M.)
[16] NDA 215256 response to Sep 8 FDA IR, dated 14 Sep 2022
[17] www.uptodate.com, Clinical evaluation of the child or adolescent with obesity; accessed 21 Sept 2022.

in 34 subjects,"[18] was also discussed at the DMC meeting (b) (4).[19] Two of the DMC members (b) (4) "raised the issue that subjects with obesity are not always able to stand completely straight against the stadiometer. This issue was also observed in the TODAY study."[20] (b) (4) "also raised that the biggest concern is where the height measurements do not change over time as this may imply that the height has been carried over from the last visit." After the DMC meeting, an email followed by 2 newsletters were sent to the sites emphasizing the importance of accurate height measurements.

The applicant was also queried further about this DMC discussion and the clinical impact of errors in height measurement.

Regarding the observation regarding height decreases, the applicant notes that of the 201 subjects in the study, each with an average of 6 heights taken from randomization to end of treatment, 33 subjects had height measurements that decreased by ≥1 cm from the previous height taken (Table 11). The applicant acknowledges that "several of these decreases may have been avoidable by better equipment and better practice."

In addition to site 402 discussed above (which was removed for the primary efficacy endpoint evaluation in a sensitivity analysis, see results in Figure 4), site 801 had 4 subjects with height decreases; 3 had full epiphyseal closure at randomization and the fourth had full epiphyseal closure by end of treatment.

In total, of the 33 subjects listed, 19 had full epiphyseal closure at randomization, 8 had full closure at end of treatment, 4 had partial epiphyseal closure both a randomization and endpoint treatment, and 2 had no x-ray data.

Table 11. Subjects with Height Decrease >1 cm Since Last Visit by Site

Site	Semaglutide	Placebo	Total
101		1	1
102		1	1
201	1		1
203	1		1
204	1	1	2
205	1	1	2
206	1		1

[18] Included height decreases reported between screening and randomization.
[19] NDA 220415256 STEP TEENS Data Monitoring Committee (DMC) minutes
[20] Adolescent and youth study in T2D sponsored by the NIDDK, NCT00081328

301	1		1
402	3	2	5
501	2	1	3
502	1		1
504		1	1
505	1		1
506	2		2
508	1		1
509	1		1
510	1		1
511	1		1
514	1		1
801	2	2	4
802		1	1
Total	22	11	33

Source: Response to IR dated 30 Sep 2022, Table 1

Medical Officer Comment: Given the 2:1 randomization, this issue affected semaglutide and placebo subjects in a similar proportion (approximately 16%).

Regarding the concern raised by (b) (4) that some height measurements were noted not to change over time, the applicant stated that processes had been implemented prior to the DMC meeting in (b) (4) to screen for consecutive, identical heights. The medical monitoring plan was amended on 20 April 2020 to ensure that if there was no change in height (defined as <1cm change in 3 consecutive measurements, or in 2 consecutive measurements if the heights were taken 6 or more months apart), a query would be generated to have the site confirm if the subject was assumed to have reached final height. Review of the data led to the identification of one site (701) where a stadiometer that lacked sufficient gradation had been installed. The heights of 4 subjects at site 701 were affected; all 4 subjects had full epiphyseal closure at randomization. The stadiometer at the site was reportedly replaced.

Table 12 lists the sites with subjects with the same height at 4 or more consecutive visits. In total, there were 7 subjects in the semaglutide group and 3 in the placebo group. Four instances were due to the stadiometer issue in site 701 as discussed above. For the other 6 subjects, 5 occurred in subjects where all epiphyses were closed at randomization. The hand/wrist x-ray for Subject (b) (6), where partial epiphyseal closure was reported at randomization was not provided at end of treatment. However, in the medical monitoring issue log, it was noted that the patient may have reached final height.

Table 12. Subjects with Same Height at 4 Consecutive Visits (or More) by Site

Site	Semaglutide	Placebo	Total
103	1		1
511		1	1

603	2		2
606	2		2
701	2	2	4
Total	7	3	10

Source: Response to IR dated 30 Sep 2022, Table 1

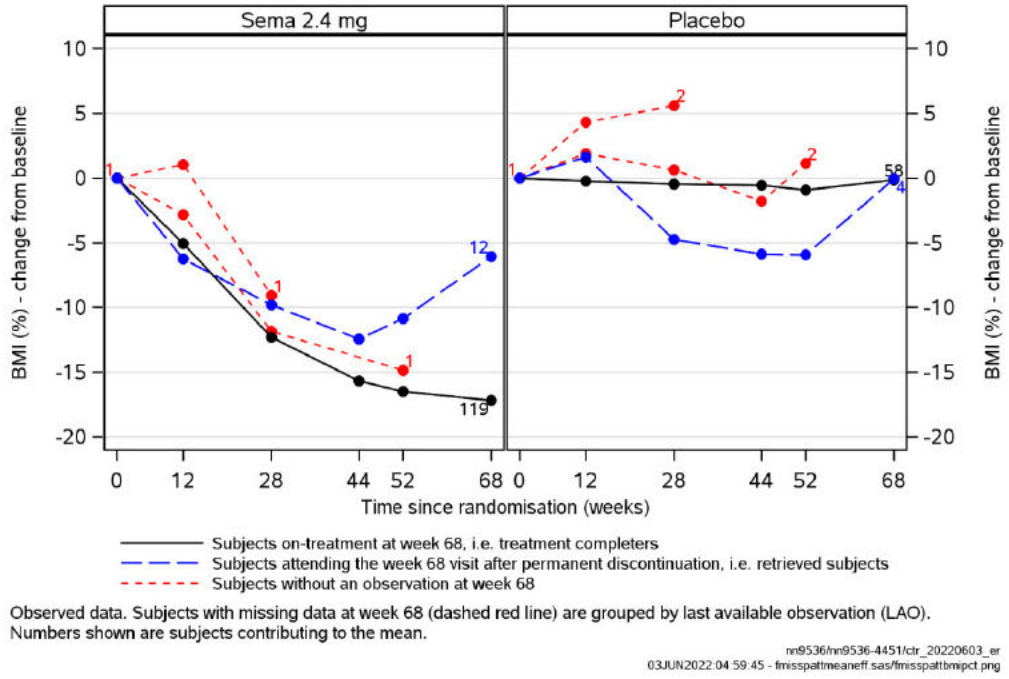
The Office of Clinical Investigations inspected site 701 and was able to verify the primary efficacy endpoints as well as the height, weight, and BMI values and did not identify any major discrepancies. Furthermore, site 701 is shown as the entirety of the subgroup called "South America" in Figure 5 and Figure 8. These analyses obviate the need for a sensitivity analysis removing that site, given that the point estimate is in fact smaller than the sites in "Europe" and "North America" (i.e., the U.S.).

Medical Officer Comment: In summary, given that most participants were at full height, these discrepancies are unlikely to affect the final conclusions of the trial.

Missing Data

Missing data were kept to a minimum in this trial, as most participants who discontinued treatment returned for a week 68 visit. Data from these "retrieved" subjects were used to impute the primary endpoint intent-to-treat result. Retrieved subjects randomized to semaglutide tended to regain weight, whereas retrieved subjects randomized to placebo had similar results at the end of the trial as placebo participants who remained on-treatment.

Figure 6. Percent BMI Change by Week, Missing Data Pattern Plot



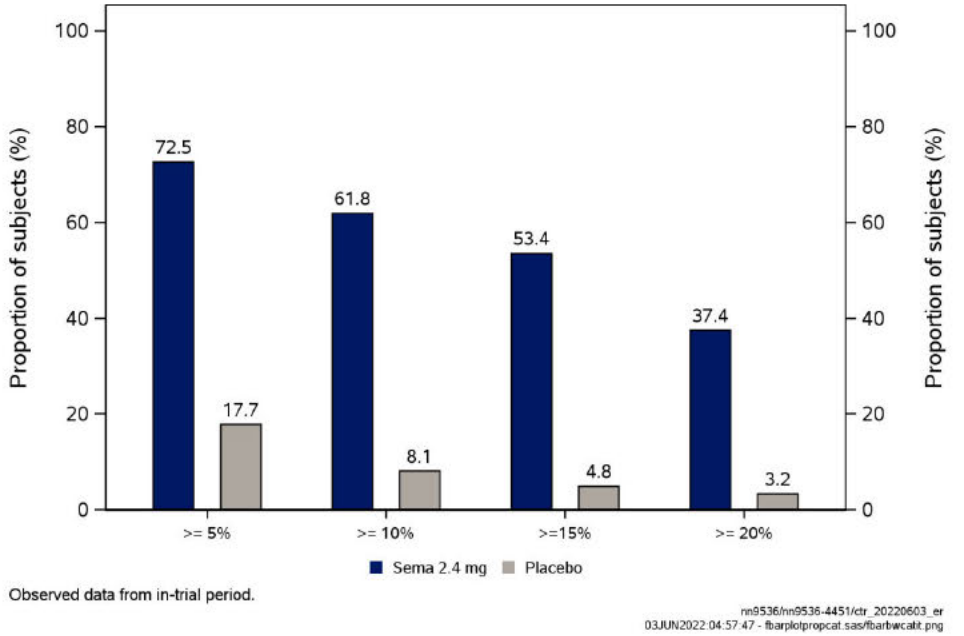
Source: STEP Teens CSR, Figure 14.2.9

Efficacy Results – Secondary and other relevant endpoints

The confirmatory secondary endpoint was the odds of achieving ≥5% body weight loss at week 68 (semaglutide/placebo). The superiority of this endpoint was confirmed. The proportions of participants achieving at least 5% weight loss were 72.5% and 17.7% for semaglutide and placebo groups, respectively; odds ratio 14.02 (95% CI: 6.34, 31.02), p<0.0001.

The proportions of subjects achieving at least 5%, 10%, 15%, and 20% weight loss is illustrated in the following figure:

Figure 7. Proportion of Subjects Achieving Body Weight Loss Response Criteria at Week 68



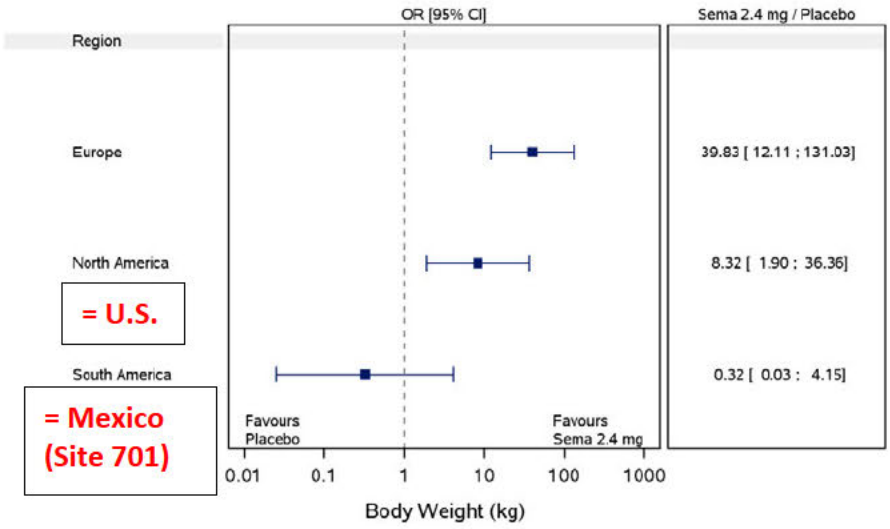
Source: STEP Teens CSR, Figure 11-7

All treatment odds ratios (semaglutide/placebo) for the above proportions represented in Figure 7 were nominally statistically significant.

For the secondary confirmatory endpoint – odds of achieving ≥5% body weight loss from baseline to week 68 – a statistically significant interaction, or trend for an interaction, was identified for region (Europe compared to North America and South America, p=0.003), race (White, Black or African American, and Other; p=0.08[21]), and ethnicity (non-Hispanic compared to Hispanic, p=0.01).[22]

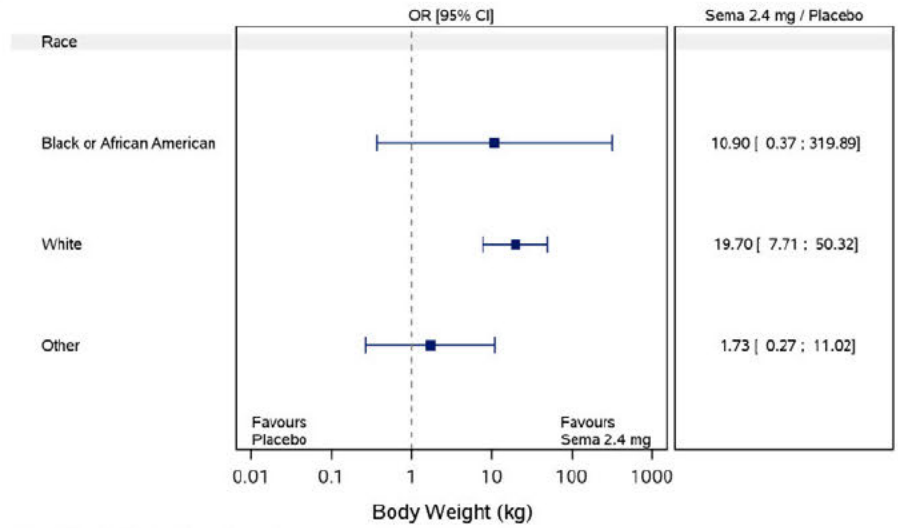
[21] Note that the prespecified race subgroups were "White" and "Other", with an interaction p-value for the secondary endpoint of 0.048. FDA requested an additional analysis to evaluate "White," "Black or African American," and "Other" as described in the text.
[22] The site 701 from Mexico may be somewhat influencing these results, as it makes up the entirety of the "South America" region, and all participants at that site were reported as "other" race and "Hispanic/Latino" ethnicity.

Figure 8. Summary of Significant Subgroup Interactions, Secondary Confirmatory Endpoint (Odds of Achieving ≥5% Baseline Body Weight Loss at Week 68)



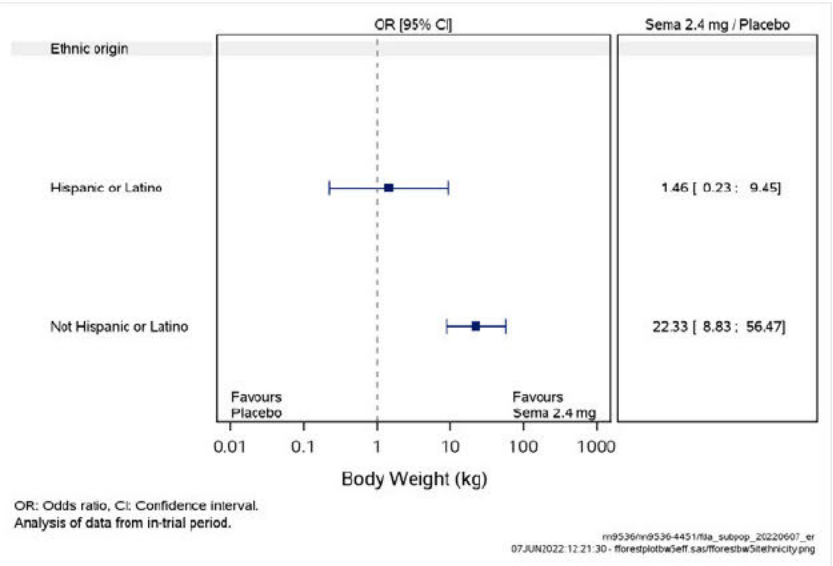
OR: Odds ratio, CI: Confidence interval.
Analysis of data from in-trial period.

rm9536/rm9536-4451/fda_subpop_20220607_er
07JUN2022:12:21:28 - fforestplotbw5eff.sas/fforestbw5itregion.png



OR: Odds ratio, CI: Confidence interval.
Category Other includes: Asian, American Indian or Alaska native, Other. Analysis of data from in-trial period.

rm9536/rm9536-exploratory/rqaus022_20221027_er
27OCT2022:22:24:29 - fforestplotbw5eff.sas/fforestbw5itrace.png



Source: Module 2.7.3 Summary of clinical efficacy, Figures 6.4.46 to 6.4.48, modified by reviewer; response to information request dated 27 October 2022 (updated race subgroup analysis to include separate subgroup for Black or African American), Figure 6

Medical Officer Comment: The unfavorable point estimate for secondary endpoint for the region "South America" is noted. However, as highlighted in the reviewer modified figures above, "South America" consists of a single site in Mexico – site 701 with 18 participants – for which there were questions about accuracy of height measurements (see heights discussion above), and for which the placebo weight change was -9.5% at this subgroup/site (largely driven by significant weight/BMI change in a single patient), as compared to other subgroups that demonstrated small mean weight gain (Europe: +3.8%, North America: +2.1%). Because this is a single site with a relatively small sample size, it is difficult to draw conclusions about any potential treatment effect by region. Many (18/21) of these participants also contributed to the "Hispanic/Latino" subgroup in the figure showing ethnicity subgroups and to the "Other" subgroup in the figure showing race subgroups.

In the adult program (evaluating % body weight loss), subgroup analyses including by race and ethnicity did not demonstrate significant interactions. In this pediatric trial, some of the numbers of participants contributing to a particular subgroup are relatively small and are therefore challenging to interpret.

The exploratory analysis of glycemic status subgroups (normoglycemic and pre-diabetes/T2D) for the key secondary endpoint showed a treatment odds ratio (semaglutide/placebo) of normoglycemic: 17.05 (95% CI 7.06, 41.20) and pre-diabetes or T2D: 6.93 (1.17, 41.05); p for interaction=0.3677.

Other secondary analyses of weight and BMI change and the associated cardiometabolic

endpoints that were observed over the course of the trial are relevant to interpreting the clinical significance of the primary endpoint despite not being controlled for type I error. As shown in Table 13 and Table 14, all were nominally statistically significant with the exception of blood pressure (SBP and DBP). Note that only descriptive changes for HbA1c were included for all subjects and subjects with T2D (a group with very few subjects). An estimated treatment difference was calculated for subjects without T2D.

Table 13. Body Weight (kg and %) Change from Baseline to Week 68

Treatment	N	Baseline Mean Weight (kg)	Change from Baseline	Percent Change from Baseline
Semaglutide	134	109.9	-15.34	-14.67
Placebo	67	102.6	+2.39	+2.75
Between treatment difference			**Difference in LS means (kg) (95% CI)**	**Difference in LS means (%) (95% CI)**
Semaglutide vs. Placebo			-17.73 (-21.76, -13.70)	-17.42 (-21.08, -13.75)

Source: STEP Teens CSR, Tables 14.1.4, 14.2.53, and 14.2.34

Medical Officer Comment: The results of weight change in this patient population, for which many subjects have reached full or near-full linear growth, supports the primary endpoint.

Table 14. Additional Supportive Secondary Efficacy Endpoints

	Semaglutide N=134		Placebo N=67		
	Baseline	**Change from BL**	**Baseline**	**Change from BL**	**ETD (95% CI)**
BMI percentage of the 95th percentile[a]	133.8	-24.58	127.8	-4.18	-20.40 (-25.01, -15.79)
BMI standard deviation score (SDS)[b]	3.4	-1.09	3.1	-0.06	-1.03 (-1.27, -0.80)
Waist circumference[c]	111.9	-12.69	107.3	-0.55	-12.14 (-15.59, -8.69)
Systolic blood pressure[d]	120	-2.70	120	-0.79	-1.91 (-4.96, +1.15)
Diastolic blood pressure[d]	73	-1.43	73	-0.83	-0.60 (-2.98, +1.77)
HbA1c[a]	5.5	-0.4[e]	5.5	-0.1[e]	ND
	n=129		n=64		
HbA1c[a] – without T2D	5.5	-0.35	5.4	-0.14	-0.22 (-0.29, -0.14)
	n=5		n=3		
HbA1c[a] – with T2D	6.7	-1.0[e]	6.1	+0.3[e]	ND

ND=not done
Units:
[a] mean: %, change from BL: percentage points, treatment difference: percentage points
[b] all units are 'score'
[c] all units are cm

[d] all units are mmHg
[e] descriptive statistics

Source: STEP Teens CSR, Tables 14.2.61, 14.2.64, 14.2.71, 14.2.74, 14.2.81, 14.2.84, 14.2.90, 14.2.96, 14.2.99, 14.2.102, 14.2.103, 14.2.104, 14.2.106, 14.2.109

Medical Officer Comment: The point estimates for the estimated treatment effects for the BMI analyses, waist circumference, and systolic blood pressure, and change from baseline in HbA1c in the subgroup of subjects with T2D, are all clinically meaningful and support the observed weight/BMI loss in this population.

Similar to the categorical weight analysis, the proportion of subjects on semaglutide who lost 5% of baseline BMI was 77.1% versus 19.7% in those on placebo, with a treatment difference of 57.4 percentage points (95% CI 44.6, 70.2) and treatment odds ratio (sema/placebo) of 13.76 (6.31, 30.02).

In addition, improvement in weight category (normal weight, overweight, obesity class I, II, and III) was seen for a larger proportion of subjects on semaglutide (71.8%) compared to placebo (21.0%). The table below also indicates that more subjects on semaglutide improved more than 1 category, and more subjects on placebo moved to a higher obesity category.

Table 15. Weight Category Shifts

		Baseline			
		Overweight	**Obesity class I**	**Obesity class II**	**Obesity class III**
	N	n (%)	n (%)	n (%)	n (%)
Week 68					
Sema	131				
Normal weight		1 (100)	22 (53.7)	6 (14.0)	3 (6.5)
Overweight		0	9 (22.0)	13 (30.2)	2 (4.3)
Obesity class I		0	10 (24.4)	13 (30.2)	9 (19.6)
Obesity class II		0	0	9 (20.9)	16 (34.8)
Obesity class III		0	0	2 (4.7)	16 (34.8)
Placebo	62				
Normal weight		0	1 (3.8)	0	0
Overweight		0	6 (23.1)	1 (4.2)	0
Obesity class I		0	17 (65.4)	3 (12.5)	0
Obesity class II		0	2 (7.7)	17 (70.8)	2 (16.7)
Obesity class III		0	0	3 (12.5)	10 (83.3)

Source: STEP Teens CSR, Table 11-2

Additional exploratory endpoints included the evaluation of changes in BMI, fasting glucose and insulin, lipids, homeostasis model assessment, the Impact of Weight on Quality-of-Life Kids

(IWQOL-Kids), alanine aminotransferase, and body weight reduction of ≥10%, 15%, and 20% from baseline (described above with proportions of subjects losing ≥5% body weight from baseline).

Table 16. Selected Exploratory Efficacy Endpoints

	Semaglutide N=134		Placebo N=67		
	Baseline	**Change from BL**	**Baseline**	**Change from BL**	**ETD (95% CI)**
BMI	37.7	-5.85	35.7	+0.11	-5.96 (-7.29, -4.62)
Fasting plasma glucose[b]	90.8	-4.2[c]	90.5	0.0[c]	
	n=129		n=64		
Fasting plasma glucose[b] – without T2D	89.5	-3.46	89.6	-0.39	-3.07 (-5.62, -0.52)
	n=5		n=3		
Fasting plasma glucose[b] – with T2D	124.4	-18.8[c]	110.3	+2.0[c]	ND
	n=129		n=64		
Fasting insulin[d] – without T2D	21.1	-33.61	18.1	-10.06	-26.19 (-38.55, -11.34)
Lipids[e]					
TC	159.4	-8.31	160.1	-1.35	-7.06 (-10.49, -3.50)
HDL-C	43.7	+8.01	43.3	+3.18	+4.68 (-1.04, +10.74)
LDL-C	89.79	-9.91	91.72	-3.58	-6.57 (-11.29, -1.59)
VLDL-C	21.7	-28.38	21.1	+1.65	-29.54 (-37.28, -20.84)
TG	111.29	-28.38	108.05	+2.62	-30.20 (-37.95, -21.49)
HOMA[g]					
HOMA-B – without T2D	ND[h]	-16.42	ND[h]	-0.61	-15.90 (-31.77, +3.65)
HOMA-IR – without T2D	ND[i]	-35.03	ND[i]	-5.32	-31.38 (-43.87, -16.12)
IWQOL-Kids					
Physical function score	84.4	+6.6	86.2	+1.6	+6.60 (+1.99, +11.21)
Body esteem score	72.2	+9.0	69.5	+5.6	+3.92 (-1.94, +9.77)
Social life score	90.0	+2.3	89.9	-0.3	+3.08 (-1.76, +7.92)
Family relations score	96.2	+0.7	95.2	-1.8	+3.42 (-0.26, +7.11)
Total score	84.2	+5.1	83.5	+1.7	+4.27 (+0.23, +8.32)
ALT[f]	23	-18.26	20	-4.85	-14.09 (-25.15, -1.39)

ND=not done
Units:
[a] all units are kg/m^2
[b] all units are mg/dL

[c] descriptive statistics
[d] mean: U/L, change from BL: percentage points, treatment difference: percentage points
[e] baseline: geometric means mg/dL, change from BL: percentage points, treatment difference: percentage points
[f] baseline: geometric means U/L, change from BL: percentage points, treatment difference: percentage points
[g] change from BL: percent
[h] geometric means at BL for the FAS: sema 296.5, placebo 259.4
[i] geometric means at BL for the FAS: sema 4.77, placebo 4.03

Source: STEP Teens CSR, Tables 14.2.2, 14.2.79, 14.2.111, 14.2.112, 14.2.113, 14.2.115, 14.2.117, 14.2.118, 14.2.120, 14.2.121, 14.2.122, 14.2.124, 14.2.127, 14.2.129, 14.2.131, 14.2.134, 14.2.137, 14.2.146, 14.2.142, 14.2.148, 14.2.149, Figure 11-20

Glycemic Endpoints

As seen in the tables above, mean changes in fasting glucose and HbA1c, as well as fasting insulin and HOMA-IR were favorable (decreased) in the semaglutide group versus placebo, in subjects without T2D at screening. Figure 9 (mean HbA1c),
Figure 10 (mean fasting glucose), and

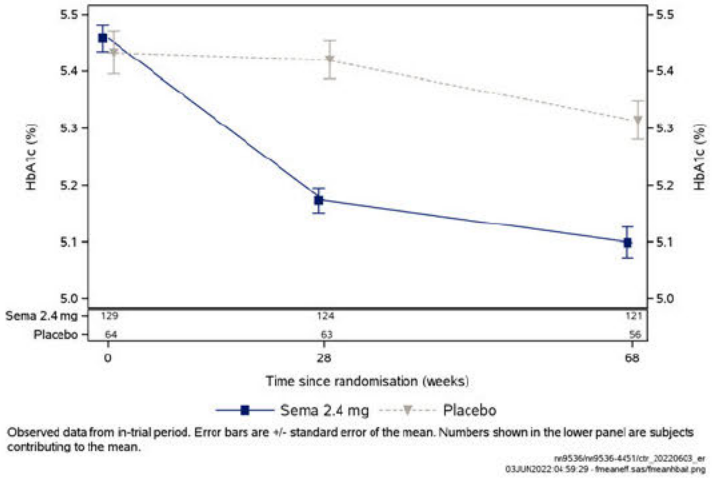
Figure 11 (mean fasting insulin) similarly illustrate the favorable decreases in glycemic parameters in subjects without T2D.

There were too few subjects with T2D to conduct statistical analyses (n=8), but descriptive statistics suggested favorable changes in HbA1c (Table 14) and glucose (Table 16).

Mean HOMA-B also decreased (unfavorable change) throughout the trial in semaglutide-treated subjects without T2D (Table 16), although changes versus placebo were not nominally statistically significant and the clinical significance is unclear given the favorable changes in the other parameters.[23]

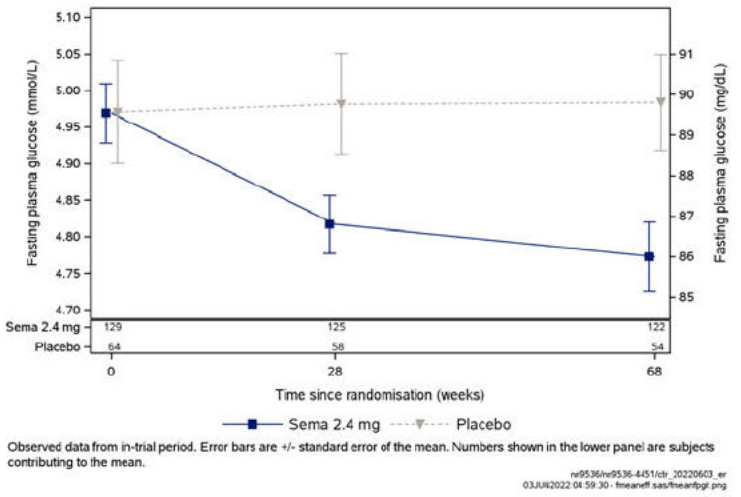
[23] The sponsor was queried on the HOMA-B interpretation, and they indicated that in this population where the vast majority do not have T2D and have normal FPG values, the "marked reduction in insulin resistance (as measured by HOMA-IR) leads to an expected greater decrease in HOMA-B with semaglutide versus placebo". They note that sufficient beta cell activity in the semaglutide treated group is reflected by the greater decrease in HbA1c and FPG versus placebo. This reviewer agrees with this interpretation, as the HOMA-B is not a direct measure of beta cell function.

Figure 9. Mean HbA1c by Week, Subjects without Type 2 Diabetes at Screening



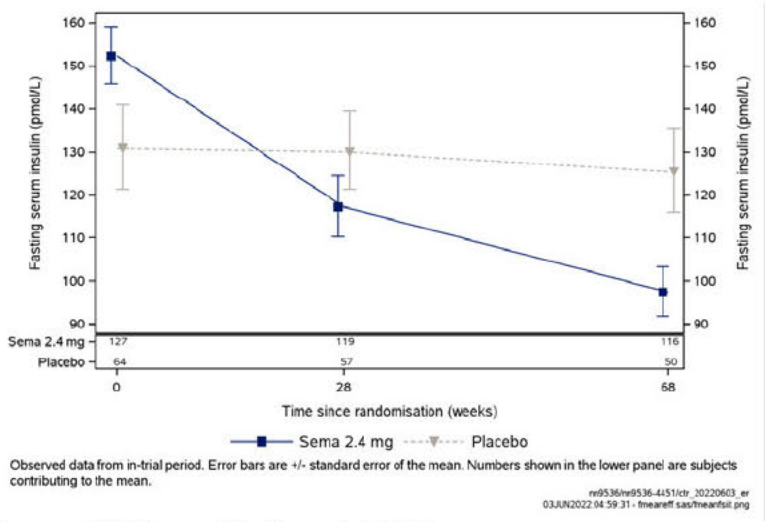
Source: STEP Teens CSR, Figure 14.2.105

Figure 10. Mean Fasting Glucose by Weeks, Subjects without Type 2 Diabetes at Screening



Source: STEP Teens CSR, Figure 14.2.114

Figure 11. Mean Fasting Serum Insulin by Week, Subjects without Type 2 Diabetes at Screening



Source: STEP Teens CSR, Figure 14.2.123

Table 17 is a table of shifts from normoglycemia and pre-diabetes status at baseline. The majority of subjects in both groups were normoglycemic at baseline and remained in that category. Other shifts were based on relatively small numbers of subjects and should be interpreted with caution.

Table 17. Glycemic Category Shifts

		Normoglycemia at Baseline		Pre-diabetes at Baseline	
	N	Normoglycemia n (%)	Pre-diabetes n (%)	Normoglycemia n (%)	Pre-diabetes n (%)
Week 28					
Sema	127	102 (94.4)	6 (5.6)	9 (47.4)	10 (52.6)
Placebo	62	53 (98.1)	1 (1.9)	3 (37.5)	5 (62.5)
Week 68					
Sema	126	107 (99.1)	1 (0.9)	7 (38.9)	11 (61.1)
Placebo	59	48 (94.1)	3 (5.9)	3 (37.5)	5 (62.5)

Source: STEP Teens CSR, Table 14.2.153

Blood Pressure

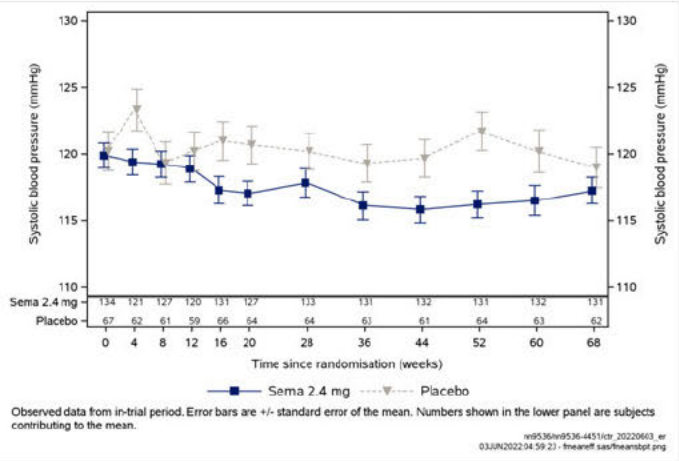
In the Wegovy clinical program in adults, systolic blood pressure (SBP) decreased by 3 to 5 mmHg versus placebo, and diastolic blood pressure (DBP) by 1 to 2 mmHg over the course of

the 68-week trial. By contrast, in a trial evaluating Saxenda (liraglutide) in adolescents with obesity, blood pressure changes were mixed, with SBP decreasing by 2 mmHg and DBP increasing by 1 mmHg versus placebo.[24] Only SBP in the Wegovy adult trials was included in the pre-specified hierarchical testing.

In STEP Teens, mean baseline blood pressure was similar among groups: 120/73, and as shown in Table 14, there was a trend for mean decreases (SBP: -2 mmHg, DBP: -1 mmHg) at week 68. Blood pressure was not included in the pre-specified testing hierarchy.

The figures below illustrate the mean SBP and DBP trajectory in both treatment groups over time.

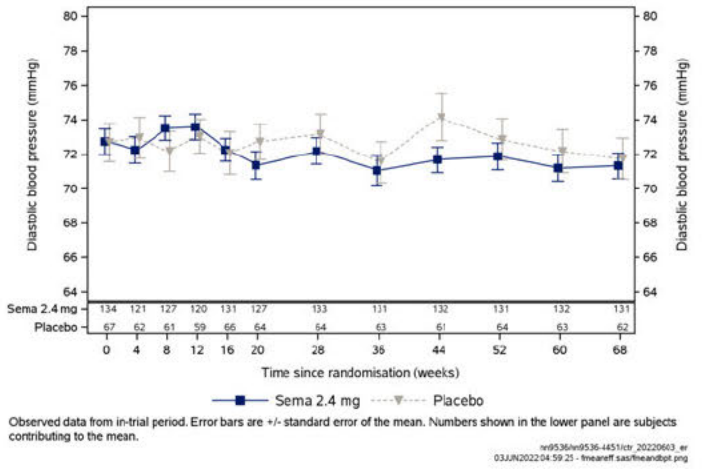
Figure 12. Systolic Blood Pressure by Visit



Source: STEP Teens CSR, Figure 14.2.91

[24] Saxenda (liraglutide) USPI

Figure 13. Diastolic Blood Pressure by Visit



Source: STEP Teens CSR, Figure 14.2.97

Table 18. Blood Pressure Category Shifts

		Baseline			
Week 68	**N**	**Normal n (%)**	**Elevated n (%)**	**Stage 1 n (%)**	**Stage 2 n (%)**
Sema	131				
Normal		43 (71.7)	11 (44.0)	14 (31.8)	1 (50.0)
Elevated		11 (18.3)	8 (32.0)	9 (20.5)	0
Stage 1		6 (10.0)	6 (24.0)	20 (45.5)	1 (50.0)
Stage 2		0	0	1 (2.3)	0
Placebo	62				
Normal		23 (74.2)	2 (20.0)	4 (21.1)	0
Elevated		7 (22.6)	4 (40.0)	5 (26.3)	0
Stage 1		1 (3.2)	3 (30.0)	9 (47.4)	2 (100)
Stage 2		0	1 (10.0)	1 (5.3)	0

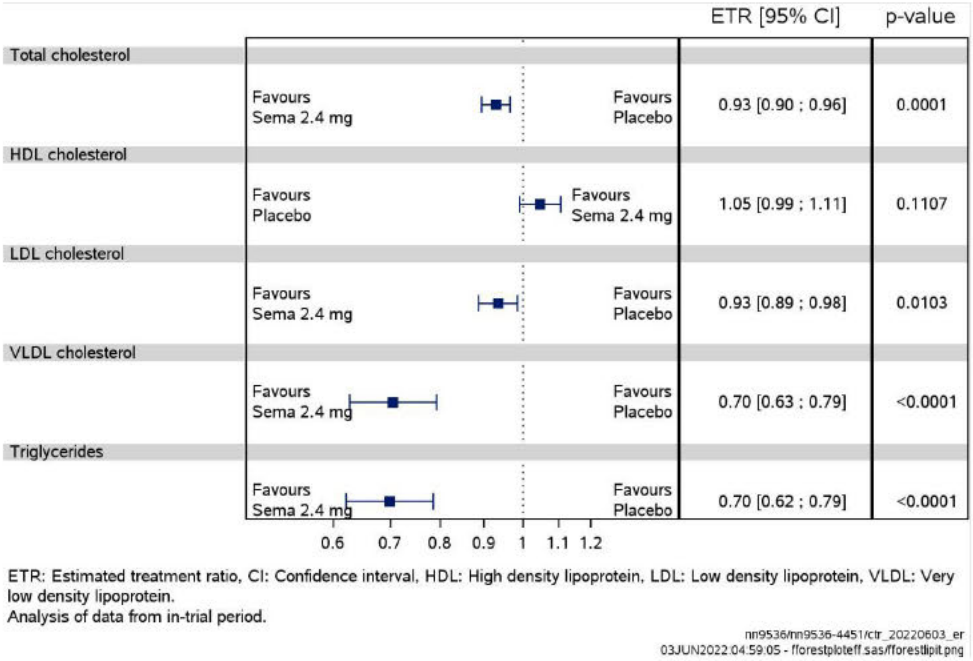
Source: Response to FDA IR 17 Oct 2022, Table 1

Lipids

The baseline lipid profile of the STEP Teens population was similar among semaglutide and placebo groups, and also similar to the adolescent population studied with Saxenda (liraglutide).[24] Although not included in the testing hierarchy, the mean changes in lipids were notable in this trial. Semaglutide was associated with a substantial decrease (~30%) in VLDL cholesterol and triglycerides and more modest, yet still favorable, decreases in total and LDL cholesterol. The increase observed with HDL cholesterol in the semaglutide versus placebo groups was not nominally statistically significant, however, the percent change from baseline and relative difference from placebo was at least similar to, if not greater in magnitude than,

the adult population.

Figure 14. Lipids Ratio to Baseline at Week 68



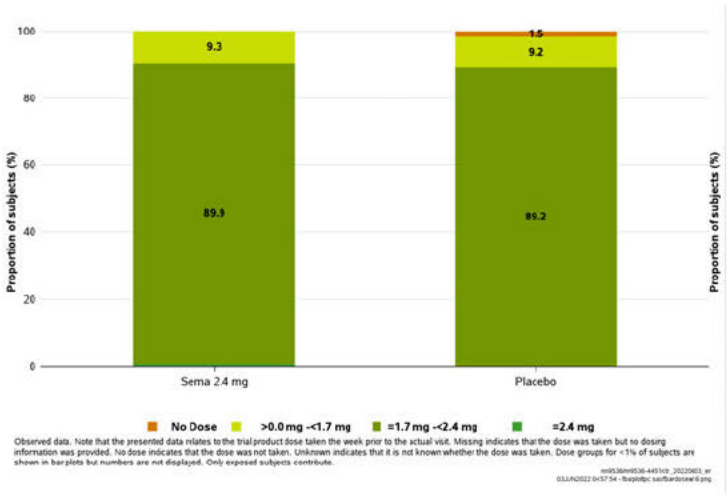
Source: STEP Teens CSR, Figure 14.2.132

Dose/Dose Response

A single dose and dosing strategy was tested in this trial: subjects were initiated at a once-weekly dose of 0.25 mg and followed a fixed-dose escalation regimen with dose increases every 4 weeks to doses of 0.5, 1.0, 1.7 and 2.4 mg/week. If a subject did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose level.

In the semaglutide group, 89.9% of subjects followed the planned dose escalation regimen and escalated to semaglutide 1.7 mg by week 16.

Figure 15. Dose at Week 16



Source: STEP Teens CSR, Figure 14.2.155

At the end-of-treatment visit (week 68), 86.7% of subjects were on the maintenance dose of semaglutide 2.4 mg. In comparison, 89.6% of the adult subjects in STEP 1 (original NDA) were on the maintenance dose of semaglutide 2.4 mg at the end-of-treatment visit (Figure 16).

Figure 16. Last Dose for Treatment Completers, STEP Teens and STEP 1 (adults)

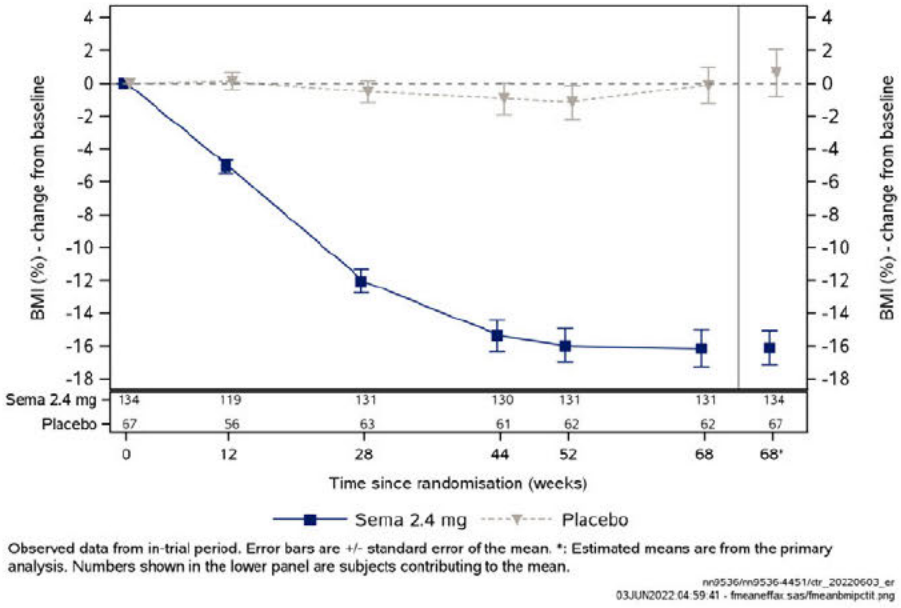
Source: STEP Teens CSR, Figure 14.2.156 and STEP 1 CSR, Figure 14.2.149

Medical Officer Comment: See the discussion in Section 4.5 regarding the clinical pharmacology team's assessment of dosing recommendations based on exposure-response modeling. Their analysis supports a reduction to the 1.7 mg dose if needed for tolerability. Given the limited number of participants who were downtitrated in the trial (i.e., did not tolerate 2.4 mg), there is less confidence in doses less than 1.7 mg for efficacy. Although it seems reasonable to allow for flexibility to the 1.7 mg dose as needed for tolerability in the adolescent population based on the data, a substantially different dosing regimen for adolescents than what is currently recommended for the adult population is not supported, given the similarity in proportions of patients who completed treatment at the semaglutide 2.4 mg dose.

Durability of Response

Figure 17 presents the mean percent change in BMI over time, including the escalation period (first 16 weeks) and 1-year maintenance period (week 16 to week 68). Separation in percent change in BMI is observed at the first datapoint (12 weeks), and the effect of semaglutide appears to plateau by week 52. By contrast, mean percent change in BMI is relatively unchanged throughout the trial in the placebo group.

Figure 17. Mean Percent Change in BMI from Baseline by Week



Source: STEP Teens CSR, Figure 14.2.10

Persistence of Effect

Semaglutide has a relatively long half-life (approximately 1 week[25]), and participants were kept in-trial until week 75, despite the end-of-treatment being at week 68. Percent change in BMI was evaluated as an exploratory endpoint from baseline to week 75. Some attenuation of effect versus the week 68 result was observed, but participants continued to have clinically significant mean % BMI change at week 75: semaglutide -13.20, placebo +1.24; treatment difference -14.43 (95% CI: -17.82, -11.05). A persistence of effect beyond week 75 (off-drug) was not evaluated.

Additional Analyses Conducted on the Individual Trial

Quality-of-Life

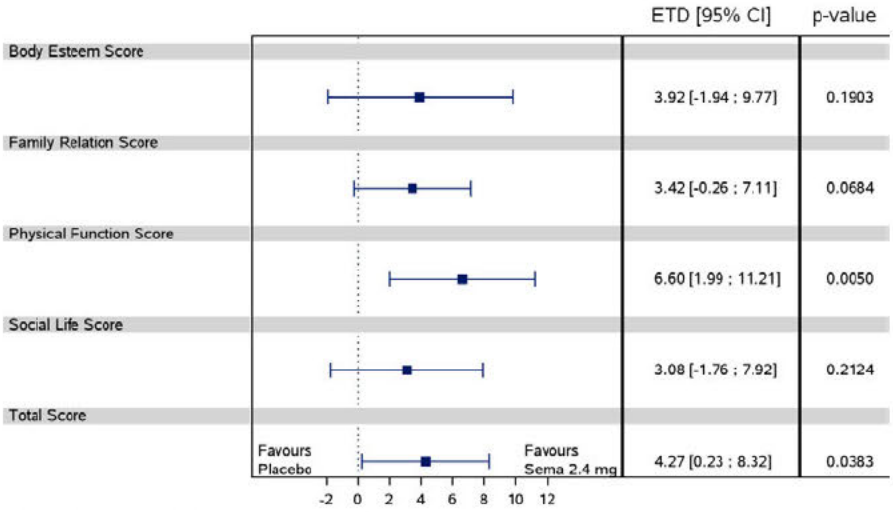
Quality-of-life was evaluated as an exploratory endpoint (Table 16) utilizing the Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire, which has been evaluated for use in pediatric patients with obesity ages 11 to 19 years of age.[26] The IWQOL-Kids has 27 items and 4 domains ranging from 1-5: the impact of weight on an individual's physical mobility and comfort (Physical Comfort), how an individual feels about themselves and their body (Body Esteem), how an individual is treated in their social environment (Social Life), and the individual's perception of what family members may think and feel about them (Family Relations). Total and domain-specific scores are derived, and higher scores represent better health-related quality-of-life.

Baseline mean domain and total scores were similar among groups and relatively high (see Table 16).

The figure below illustrates a trend toward improved scores by domain and overall, particularly in the physical function score. To the reviewer's knowledge, clinically meaningful changes have not been established.

[25] Wegovy (semaglutide) USPI
[26] Kolotkin RL, et al. Assessing weight-related quality of life in adolescents. Obesity (Silver Spring). 2006;14(3):448-57.

Figure 18. IWQOL-Kids Change from Baseline to Week 68



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

Source: STEP Teens CSR, Figure 14.2.151

Medical Officer Comment: The sponsor has not requested labeling of these items. Although mean changes are favorable, and generally consistent with the adult findings, the clinical relevance of the changes is uncertain, especially in the setting of relatively high baseline values (indicating higher baseline health-related quality of life). More research is needed, particularly in patients with obesity (of all ages) who have quality-of-life or daily functioning limitations due to their obesity.

Alanine Transaminase (ALT)

(b) (4)

As shown in Table 16 above, mean ALT decreased with semaglutide and remained unchanged with placebo. The estimated treatment ratio was in favor of semaglutide (0.86 (95% CI: 0.75, 0.99)).

Applicability of Foreign Data to the U.S. Population

The sponsor provided a separate analysis of the U.S. versus non-U.S. populations in this trial under module 5.3.5.3. For a complete discussion regarding pre-specified subgroups for the primary and confirmatory secondary endpoints, see the relevant subsections under discussion of the results for the primary and confirmatory secondary endpoints.

Of the 201 subjects randomized in this trial, 51 (25.4%) were from sites in the U.S. Although a lower proportion of subjects in the semaglutide arm from the U.S. discontinued treatment prematurely than those from non-U.S. sites, the proportions completing the trial were similar.

Table 19. Subject Disposition, U.S. vs. Non-U.S. Population

	Semaglutide		Placebo	
	U.S.	**Non-U.S.**	**U.S.**	**Non-U.S.**
Randomized	35	99	16	51
Exposed	35 (100)	98 (99.0)	16 (100)	51 (100)
Treatment completers	27 (77.1)	93 (93.9)	14 (87.5)	46 (90.2)
Trial product permanently discontinued	8 (22.9)	6 (6.1)	2 (12.5)	5 (9.8)
Primary reason:				
Adverse event	4 (11.4)	2 (2.0)	1 (6.3)	3 (5.9)
Protocol violation	1 (2.9)	1 (1.0)	1 (6.3)	0
Pregnancy	0	1 (1.0)	0	0
Withdrawal of consent	1 (2.9)	0	0	1 (2.0)
Other	2 (5.7)	2 (2.0)	0	1 (2.0)
Trial completers	34 (97.1)	98 (99.0)	15 (93.8)	49 (96.1)
Withdrawn from trial	1 (2.9)	1 (1.0)	1 (6.3)	2 (3.9)
Primary reason:				
Withdrawal by subject	1 (2.9)	0	0	2 (3.9)
Withdrawal by parent/guardian	0	0	1 (6.3)	0
Lost to follow-up	0	1 (1.0)	0	0

Source: Module 5.3.5.3, Applicability of non-US data for US population, Table 2-1

In the U.S. population, slightly higher proportions of subjects were female as well as Tanner stage 5. Many more subjects from the U.S. population vs. non-U.S. were 'Black or African American' (24% vs. 3%), and 2 participants of 'American Indian or Alaska Native' descent were enrolled, both from the U.S. The majority of participants of Hispanic or Latino ethnicity were from a single site in Mexico.

Age and weight categories were similar among U.S. and non-U.S. populations.

Table 20. Demographics and Baseline Characteristics, U.S. vs. Non-U.S. Population

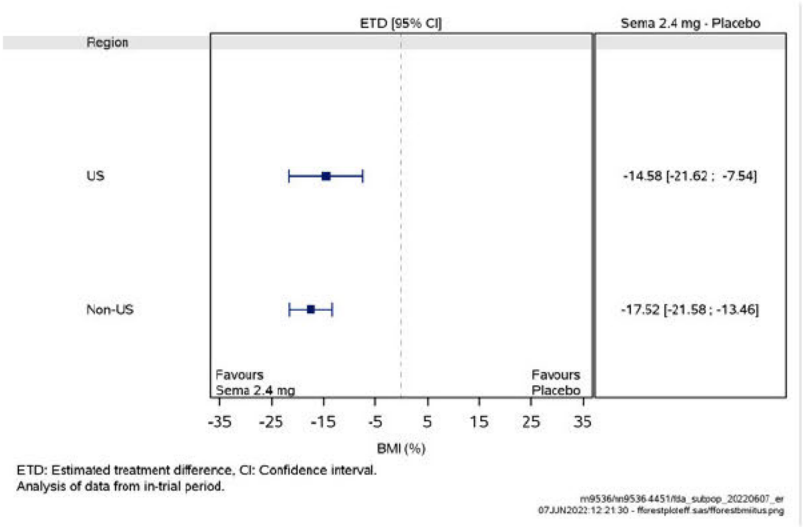
	U.S. N=51	Non-U.S. N=150
Age (years)		
12-<15	17 (33.3)	55 (36.7)
15-<18	34 (66.7)	95 (63.3)
Sex		
Female	37 (72.5)	88 (58.7)
Male	14 (27.5)	62 (41.3)
Ethnic origin		
Not Hispanic or Latino	48 (94.1)	131 (87.3)
Hispanic or Latino	3 (5.9)	19 (12.7)
Race		
White	36 (70.6)	123 (82.0)
Other[1]	0	20 (13.3)
Black or African American	12 (23.5)	4 (2.7)
Asian	1 (2.0)	3 (2.0)
American Indian or Alaska Native	2 (3.9)	0
Native Hawaiian or Other Pacific Islander	0	0
Tanner Stage		
Stage 2	1 (2.0)	7 (4.7)
Stage 3	3 (5.9)	11 (7.3)
Stage 4	10 (19.6)	44 (29.3)
Stage 5	37 (72.5)	88 (58.7)
Glycemic category		
Normoglycemia	43 (84.3)	123 (82.0)
Pre-diabetes	5 (9.8)	22 (14.7)
Type 2 diabetes	3 (5.9)	5 (3.3)
Weight category		
Overweight	0	1 (0.7)
Obesity class I	16 (31.4)	53 (35.3)
Obesity class II	18 (35.3)	51 (34.0)
Obesity class III	17 (33.3)	45 (30.0)

[1] Other as defined in the ADSL dataset = 'Mexican' (n=18); 'Roma' (n=1); 'White/Black Caribbean' (n=1)

Source: Module 5.3.5.3, Applicability of non-US data for US population, Table 2-2

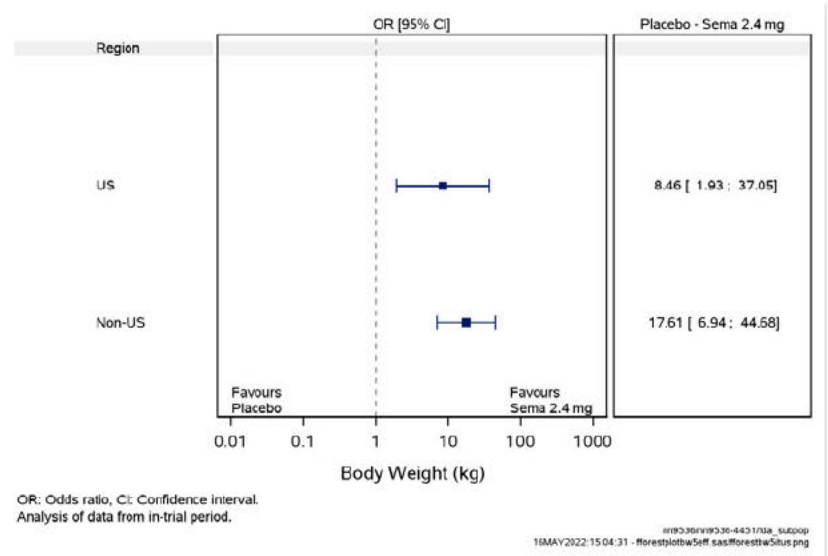
For the primary (percent change in BMI) and key secondary (odds of achieving 5% body weight loss) endpoints, no significant interaction was observed for the U.S. and non-U.S. subgroups.

Figure 19. Percent Change in BMI from Baseline to Week 68, U.S. vs. Non-U.S. Population



Source: Module 5.3.5.3, Applicability of non-US data for US population, Figure 2-1

Figure 20. Odds of Achieving at Least 5% Baseline Body Weight Loss at Week 68, U.S. vs. Non-U.S. Population



Source: Module 5.3.5.3, Applicability of non-US data for US population, Figure 2-2

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

7. Integrated Review of Effectiveness

7.1 Assessment of Efficacy Across Trials

Not applicable; this supplement is based on a single trial.

7.2 Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Postmarket Setting

In the postmarket setting, the weight loss benefit of Wegovy in this population will likely be similar to the adult population.

Cardiometabolic improvements that are expected with Wegovy in adult patients with obesity could potentially occur in the adolescent population to the extent there is significant metabolic derangement. The treatment paradigm in adolescents is generally one of prevention.

7.2.2 Other Relevant Benefits

Not applicable.

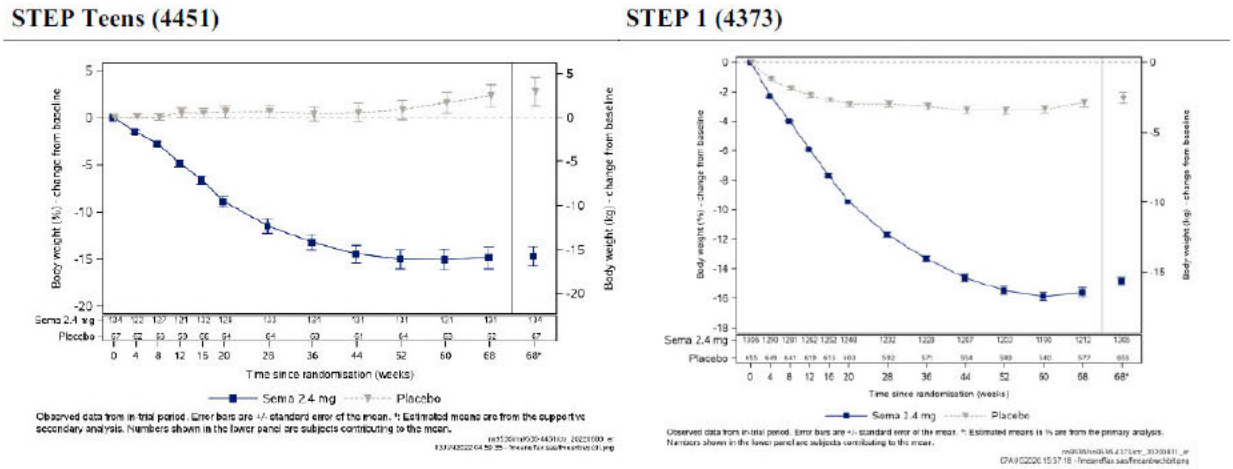
7.3 Integrated Assessment of Effectiveness

The primary efficacy endpoint, mean percent change in BMI, is consistent with recommendations by practice guidelines[28] and FDA draft guidance[29] that describe the effectiveness of weight loss interventions in adolescents with obesity. Akin to the evaluation of the clinical meaningfulness of efficacy in adult obesity – weight loss of 5% or more from baseline after 1 year – clinical evidence of efficacy in pediatric patients is often defined as BMI decrease of 5% or more versus placebo. The treatment effect in this trial, Wegovy versus placebo after 68 weeks of treatment of -16.75%, is robust and clinically meaningful.

This supplemental NDA meets the evidentiary standard of substantial evidence of effectiveness based on a single adequate and well-controlled trial [NN9536-4451 (STEP Teens)] and confirmatory evidence, i.e., a large and highly consistent clinical program in adult patients with obesity.[30] See Figure 22 for a graphical comparison of the results of the adolescent and adult trials; STEP 1 was the largest phase 3 trial in the Wegovy adult program.

[28] Styne DM, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Mar 1;102(3):709-757.
[29] FDA 2007 draft Guidance for Industry: Developing Products for Weight Management
[30] See the original clinical review for NDA 215256 and approved Wegovy labeling.

Figure 22. Percent Body Weight Change by Week, STEP Teens (Left) and STEP 1 (Right)



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

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

Source: Module 2.7.3 Summary of clinical efficacy, Figure 3-1

8. Review of Safety

8.1 Safety Review Approach

There was only one randomized, placebo-controlled phase 3 trial of semaglutide submitted for the target population of adolescents 12 to <18 years of age with overweight/obesity. However, the safety review was informed by the well characterized safety profile of semaglutide and other GLP1 RAs in the adult population and liraglutide in the pediatric population.

The safety evaluation is based on the Safety Analysis Set (safety population), which includes all subjects exposed to at least one dose of randomized treatment and analyzed according to treatment received.

The Applicant defined three observation periods for adverse event categorization:

- The run-in period: events with onset date between Visit 2 (Week -12) and the first day of study drug administration. This review does not focus on AEs observed in the run-in period.
- The in-trial period: events with onset date between the first day of study drug administration and the last study visit.

- The on-treatment period: events with onset date from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

A treatment emergent adverse event (TEAE) was defined as an event that occurred in the on-treatment period. This review generally presents TEAEs/events that occurred during the on-treatment period unless otherwise identified as occurring during the in-trial period.

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively. Subjects were randomized 2:1 to receive semaglutide 2.4 mg or placebo treatment, so evaluation of the safety data focuses on proportional comparisons.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

The following table summarizes the duration of exposure to study drug during the on-treatment period as well as the in-trial period. The mean duration of exposure was 71.3 weeks in the semaglutide group and 70.4 weeks in the placebo group during the "on-treatment" period with a 49-day ascertainment window after drug discontinuation used for the safety evaluation of adverse events.

Table 21: Duration of Exposure -Various Observation Periods- Safety Population

	Semaglutide N=133	Placebo N=67
*On Treatment Period (49 day ascertainment window), weeks of duration		
Mean (SD)	71.3 (11.0)	70.4 (13.7)
Median	74.1	74.1
Min; Max	8.1; 77.1	7.1; 76.1
Total (years)	181.8	90.4
In-Trial Period, weeks of duration		
Mean (SD)	75.3 (3.4)	73.2 (10.9)
Median	75.1	75.1
Min; Max	42.1; 86.0	12.6; 83.1
Total (years)	192.0	94.0

Source: STEP TEENS CSR; Table 14.1.19; *A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 (49) days. An ascertainment window of 14 days is used for the safety evaluation of laboratory parameters, pulse, ECG and physical examination; an ascertainment window of 49 days is

used for the safety evaluation of adverse events only. In-trial: The uninterrupted time interval from date of randomization to date of last contact with trial site.

The following table summarizes the number (%) of subjects exposed to the study drug at different time intervals during the study.

Table 22: Number of Subjects (%) Exposed to Study Drug-On Treatment-49 Day Ascertainment Window-Safety Population

	Number (%) of subjects exposed to the study drug				
	≥ 0 month	≥1 month	≥6 months	≥12 months	≥ 17 months
Semaglutide	133 (100%)	133 (100%)	130 (97.7%)	125 (94%)	99 (74.4%)
Placebo	67 (100%)	67 (100%)	65 (97.0%)	62 (92.5%)	50 (74.6%)

Source: STEP TEENS CSR; Table 14.1.27

Medical Officer Comment: The proportion of subjects in the two treatment groups exposed to study drug was similar at various time points throughout the trial. The mean exposure duration was also similar, regardless of the chosen observation period (on-treatment or in-trial), suggesting that results of safety analyses would be similar regardless of the observation period used.

8.2.2 Relevant characteristics of the safety population:

Refer to the baseline characteristics table in the efficacy section. In brief, the mean age was 15.4 years, mean body weight was 107.5 kg, mean weight circumference was 110.4 cm, and mean BMI was 37 kg/m^2. Most of the subjects, in both treatment groups, were white, female and had a Tanner Stage of 4 or 5 pubertal. A total of 25% of subjects were from the United States.

8.2.3 Adequacy of the safety database:

The number of adolescents and extent of exposure to semaglutide in this trial meets the expectations of the Division. The trial was not powered for any specific safety finding and is, therefore, descriptive for safety.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

Review of trial data showed possible height measurement issues at one site. An OSI reviewer was able to conduct an inspection at the site. According to the inspector, no major discrepancies were identified with height, weight, or BMI values. (See efficacy section for more details).

8.3.2 Categorization of Adverse Events

This reviewer utilized the Adverse Events Coding Quality Report by the Office of Computational Science to assess the quality of the study data. The algorithm uses approximate string matching, and the score represents similarity between the reported term and either the MedDRA PT (preferred term) or MedDRA LLT (lower level term) in the submitted data. A score of 100 means the strings are identical, while a score of 0 means the algorithm was unable to determine sufficient similarity. All adverse events were presented in the STEP TEENS study with Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

On review, the majority of reported terms matched the MedDRA PT or MedDRA LLT with a score of 100 (see figure below). There were a few terms that were not a direct match from reported term to LLT or PT. Terms that had a lower score did not match primarily due to an "alternate spelling" or "partial word match". However, this reviewer determined that the coding was appropriate in most cases, even though the algorithm had flagged the term due to the string match algorithm.

Table 23: Sample Adverse Events Coding Quality Report, Safety Population

Reported Term (AETERM)	MedDRA LLT (AELLT)	MedDRA PT (AEDECOD)	Match Details	Score	Number of Rows
UPPER RESPIRATORY INFECTION	Upper respiratory infection	Upper respiratory tract infection	Direct match to LLT	100	5
VIRAL SYNDROME	Viral syndrome	Viral infection	Direct match to LLT	100	1
EMESIS	Emesis	Vomiting	Direct match to LLT	100	19
POSTPRANDIAL EMESIS	Postprandial emesis	Vomiting	Direct match to LLT	100	1
ABDOMINAL PAIN	Abdominal pain	Abdominal pain	Direct match to PT	100	22
ACNE	Acne	Acne	Direct match to PT	100	4
ALOPECIA	Alopecia	Alopecia	Direct match to PT	100	2
ANAL FISSURE	Anal fissure	Anal fissure	Direct match to PT	100	1

Reported Term (AETERM)	MedDRA LLT (AELLT)	MedDRA PT (AEDECOD)	Match Details	Score	Number of Rows
BURNED RIGHT HAND WITH HOT OIL	Thermal burn	Thermal burn	Could not match	0	1
RINGWORM	Tinea	Tinea infection	Could not match	0	1
ALT/AST > 3XUNL	Transaminases increased	Transaminases increased	Could not match	0	1
BILATERAL HAND SHAKING	Shaking of hands	Tremor	Could not match	0	1
BODERLINE IMPAIRED FASTING GLUCOSE - T2DM	Type 2 diabetes mellitus	Type 2 diabetes mellitus	Could not match	0	1
FLU LIKE SYMPTOMS AFTER 2ND SHOT OF COVID :	Vaccination adverse reaction	Vaccination complication	Could not match	0	1
HEADACHE DUE TO COVID VACCINATION	Vaccination adverse reaction	Vaccination complication	Could not match	0	1

Source: Reviewer Analysis, Office of Computational Science.

Medical Officer Comment: Terms that did not match were primarily due to an alternate spelling or partial word match. This reviewer determined that the coding was appropriate in most cases, even though the algorithm had flagged the term due to the string match algorithm. Based on the Adverse Events Coding Quality Report and my review, I believe that AEs were generally categorized appropriately and do not impact the overall conclusions.

8.3.3 Routine Clinical Tests

The following table lists the schedule and parameters of routine clinical laboratory assessments.

Table 24: List and Schedule of Safety Laboratory Assessments

Scheduled Assessments	Parameters
Hematology-V1, V8, V20, V30	Hemoglobin, Hematocrit, Thrombocytes, Erythrocytes, Leucocytes, Eosinophils, Neutrophils, Basophils, Lymphocytes, Monocytes
Biochemistry-V1, V8, V20, V30	Creatinine, Creatinine kinase, Urea (BUN), Albumin, Bilirubin (total), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), sodium, Potassium, Calcium total, Calcium (albumin corrected), gamma-glutamyl transferase (GGT), calcitonin, amylase, lipase
Hormones- V8, V20, V30	Thyroid stimulating hormone, (TSH, also at V1), Free thyroxine (Free T4, also at V1), Dehydroepiandrosterone sulfate (DHEAS), Luteinising hormone (LH), Follicle stimulating hormone (FSH), Estradiol (females), Testosterone (males), Prolactin
Bone metabolism- V8, V30	Type 1 collagen N-telopeptide (NTX1), Type 1 C-telopeptide (CTX1), Procollagen 1 N-terminal propeptide (P1NP), Alkaline phosphatase (bone)
Biomarkers- V8, V20, V30	Carcinoembryonic antigen, insulin-like growth factor1
Antibodies (V8, V12, V16, V20, V26, V30, V31)	Anti-semaglutide antibodies, Antibodies cross-reacting native GLP-1, Semaglutide AB (neutralizing effect), semaglutide antibody titer
Antibodies (unscheduled)[1]	Anti-semaglutide antibodies, anti-semaglutide IgE antibodies
PK (V12, V16, V20, V22, V26, V30,V31)	Semaglutide PK

Source: STEP TEEN CSR, Table 9-6.

Medical Officer Comment: The safety laboratory assessments and scheduled lab collection time points are reasonable for this pediatric trial.

8.4 Safety Results

8.4.1 Deaths

No deaths were reported in this trial.

8.4.2 Serious Adverse Events

The review of serious adverse events (SAEs) is based on all treatment emergent SAEs that occurred in the drug development program without regard to causality. The treatment emergent period is represented by the on-treatment period.

During the lifestyle intervention run-in period (before drug randomization), three SAEs were reported by two subjects who were later randomized to treatment. One event was an ovarian cyst, and two events (in one subject) were a fall and related upper limb fracture. Both subjects recovered from these events.

Overall, 24 SAEs were reported during the on-treatment period, 17 (9.4%) in the semaglutide group and 7 (7.7%) in the placebo group. The following table summarizes the treatment emergent SAEs in the safety population.

Table 25: Summary of Serious Adverse Events- On Treatment- Safety Population

	Semaglutide 2.4 mg		Placebo	
	N (%)	Events (rate)	N (%)	Events (rate)
Number of patients	133		67	
Patient-years of exposure	181.8		90.4	
Total number of subjects with SAEs	15 (11.3)	17 (9.4)	6 (9.0)	7 (7.7)
Hepatobiliary disorders	4 (3.0)	5 (2.8)	0	
Cholelithiasis	3 (2.3)	3 (1.7)	0	
Cholecystitis acute	1 (0.8)	1 (0.6)	0	
Hepatic function abnormal	1 (0.8)	1 (0.6)	0	
Infections and infestations	4 (3.0)	4 (2.2)	0	
Appendicitis	2 (1.5)	2 (1.1)	0	
COVID-19	1 (0.8)	1 (0.6)	0	
COVID-19 pneumonia	1 (0.8)	1 (0.6)	0	
Gastrointestinal disorders	3 (2.3)	3 (1.7)	1 (1.5)	1 (1.1)

	Semaglutide 2.4 mg		Placebo	
	N (%)	Events (rate)	N (%)	Events (rate)
Abdominal pain	1 (0.8)	1 (0.6)	0	
Gastritis	1 (0.8)	1 (0.6)	0	
Vomiting	1 (0.8)	1 (0.6)	0	
Abdominal pain upper	0		1 (1.5)	1 (1.1)
Injury, poisoning, and procedural complications	1 (0.8)	2 (1.1)	2 (3.0)	2 (2.2)
Post procedural constipation	1 (0.8)	1 (0.6)	0	
Urinary retention postoperative	1 (0.8)	1 (0.6)	0	
Clavicle fracture	0		1 (1.5)	1 (1.1)
Contusion	0		1 (1.5)	1 (1.1)
Investigations	1 (0.8)	1 (0.6)	1 (1.5)	1 (1.1)
Transaminase increased	1 (0.8)	1 (0.6)	1 (1.5)	1 (1.1)
Psychiatric disorders	1 (0.8)	1 (0.6)	0	
Depression	1 (0.8)	1 (0.6)	0	
Respiratory, thoracic and mediastinal disorders	1 (0.8)	1 (0.6)	0	
Sleep apnea syndrome	1 (0.8)	1 (0.6)	0	
Neoplasms benign, malignant and unspecified (incl cycts and polyps)	0		1 (1.5)	1 (1.1)
Ovarian germ cell teratoma benign	0		1 (1.5)	1 (1.1)
Nervous system disorders	0		2 (3.0)	2 (2.2)
Loss of consciousness	0		1 (1.5)	1 (1.1)
Tension headache	0		1 (1.5)	1 (1.1)

Source: STEP TEEN CSR; Table 12-3; 14.3.1.17

Medical Officer Comment: The frequency of SAEs in the semaglutide group at 11.3% was higher than placebo at 9.0%. The leading System Organ Class (SOC) of SAEs were in Hepatobiliary disorders, Infections, and Gastrointestinal disorders. The most frequently reported preferred terms (PTs) for SAEs were related to gallbladder disease.

Selected Serious Adverse Event Narratives

Medical Officer Comment: This medical officer reviewed a few SAE narratives to ensure agreement with the diagnosis and to make sure there were no additional SAEs described within the narrative.

Subject ID # (b) (6) SAE for cholelithiasis: This is a 14 yo female patient with a BMI of 33 who was treated with blinded semaglutide from (b) (6) to (b) (6) and again from (b) (6) at a reduced dose. Current Condition: Obesity, Polycystic Ovarian Syndrome, Vitamin D Deficiency, Acanthosis Nigricans, Impaired Fasting Glucose, Abnormal Thyroid Lab, Chronic Headaches, Elevated Liver Enzymes, Never smoked.

On (b) (6), onset date, the patient started to have right upper quadrant stomach pain with nausea. The patient went to the ER (Emergency Room) where the following tests were performed: ALT: 45.0 U/L, (Norm High: 69.0 Norm Low: 13.0); AST: 36.0 U/L, (Norm High: 36.0 Norm Low: 14.0); Lipase: 100.0 U/L, (Norm High: 300.0 Norm Low: 23.0);Total bilirubin: 0.6 mg/dL, (Norm High: 1.3 Norm Low): 0.2; White blood count: 9.3 10*3/µL, (Norm High: 10.5 Norm Low: 3.9)
Ultrasound with Primary indication for imaging: Suspicion of gallbladder disease (including gallstones and cholecystitis), showed abnormal findings: Gallstone(s) in the gallbladder (non-serious adverse event), indicating acute cholecystitis, indicating chronic cholecystitis. On (b) (6) outpatient laparoscopic cholecystectomy was performed. The patient recovered. Action taken to blinded semaglutide was reported as drug discontinued temporarily.

Subject ID # (b) (6): This is a 15 yo female with a BMI of 30 who was treated with blinded semaglutide from (b) (6) to (b) (6) and again from (b) (6). Current Condition: Acne, Overweight/Obesity, Irregular Periods, Premenstrual Migraines, Restless Legs, Never smoked.

On (b) (6) the patient presented with abdominal pain which lasted for multiple days. The following tests were performed: ALT: 12.0 U/L (Norm High: 55.0)
AST: 13.0 U/L (Norm High: 35.0); Lipase: 82.0 U/L (Norm High: 80.0, Norm Low: 5.0); Total bilirubin: 0.3 mg/dL (Norm High: 1.2, Norm Low: 0.2); White blood count (WBC): 8.9 unit/ul (Lower normal: 4.0, Upper normal: 11.0); Ultrasound: imaging abnormal: Gallstone(s) in the gallbladder. On an unknown date the patient came to the ER (emergency room) with gallstones. On (b) (6) the patient met with surgeon. On (b) (6) the patient had elective outpatient surgery of cholecystectomy performed (not hospitalized). Action taken to blinded semaglutide was reported as drug discontinued temporarily.

Subject ID # (b) (6): This is a 14 yo female who was treated with blinded semaglutide from (b) (6) to (b) (6) and again from (b) (6). Patient's height: 157 cm, weight: 75 kg,

BMI: 30.42. Current conditions: Obesity, Epilepsy, Sulfate and dust allergy, Hypothyroidism, Insulin resistance, Never smoked.

On (b) (6) the patient was diagnosed with asymptomatic gallbladder disease. The disease was a finding in an ultrasonography study, without clinical acute or chronic manifestations.

The parents decided to carry out the elective surgery as treatment. On (b) (6) lipase and amylase were within normal values. On (b) (6) the patient was admitted to the hospital and had laparoscopic cholecystectomy performed. As per investigator the event was considered severe as it required hospitalization for one day but the patient did not have any signs or symptoms, it was considered as mild. The patient did not have significant weight loss during the last 3 months (only 2 kg). Gallstones were only found in gallbladder. The surgeon did not send an anatomopathological study of gallbladder, nor determination of the composition of gallstones.

Medical Officer Comment: No other SAE or AE were identified within the patient narratives. This medical officer assesses the potential drug-relatedness of cholelithiasis/acute cholecystitis as well as abdominal pain, gastritis, and vomiting under gastrointestinal disorders SOC as highly likely related to semaglutide administration. Acute gallbladder disease is listed under the Warning & Precautions section of the current semaglutide labeling. Gastrointestinal AEs such as vomiting and abdominal pain are also identified as common adverse events in the label.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

There were 6 (4.5%) subjects on semaglutide and 3 (4.5%) subjects on placebo who permanently discontinued study drug due to an adverse event. In the semaglutide group, most AEs leading to discontinuation were due to gastrointestinal disorders (abdominal discomfort, gastritis, and vomiting). For example, of the 6 subjects in the semaglutide group who had an AE leading to permanent drug discontinuation, 3 (2.3%) subjects did so because of a gastrointestinal-related AE. The other 3 study drug discontinuations in the semaglutide group were due to malaise, rash, and decreased appetite. Placebo study drug discontinuations were due to nausea (1), injection site pruritis (1), and mental disorder (1).

Table 26: Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug- On Treatment - Safety Population

	Semaglutide 2.4 mg		Placebo	
Number of patients	133		67	
Patient-years of exposure	181.8		90.4	
	N (%)	Events (rate)	N (%)	Events (rate)
Total study drug permanent discontinuations	6 (4.5)	6 (3.3)	3 (4.5)	3 (3.3)
Gastrointestinal disorders	3 (2.3)	3 (1.7)	1 (1.5)	1 (1.1)
Abdominal discomfort	1 (0.8)	1 (0.6)	0	
Gastritis	1 (0.8)	1 (0.6)	0	
Vomiting	1 (0.8)	1 (0.6)	0	
Nausea	0		1 (1.5)	1 (1.1)
General disorders and administration site conditions	1 (0.8)	1 (0.6)	1 (1.5)	1 (1.1)
Malaise	1 (0.8)	1 (0.6)	0	
Injection site pruritus	0		1 (1.5)	1 (1.1)
Metabolism and nutrition disorders	1 (0.8)	1 (0.6)	0	
Decreased appetite	1 (0.8)	1 (0.6)	0	
Skin and subcutaneous tissue disorders	1 (0.8)	1 (0.6)	0	
Rash	1 (0.8)	1 (0.6)		
Psychiatric disorders	0		1 (1.5)	1 (1.1)
Mental disorder			1 (1.5)	1 (1.1)

Source: STEP TEEN CSR, Table 12-5; 14.3.1.23

Medical Officer Comment: This medical officer reviewed patient listings for all subjects who permanently discontinued trial product or withdrew from the trial to confirm the number of subjects who discontinued study drug/study due to an adverse event. On review, there was one subject (Subject ID# (b) (6)) who discontinued study drug due to an event of acute pancreatitis; she was not counted by the sponsor, as her event occurred on Day 16, prior to study drug randomization. Subject ID# (b) (6), who was in the placebo group, reportedly discontinued due to a "mixed behavioral and emotional disorder" which the sponsor described as "mental disorder".

8.4.4 Significant Adverse Events

Significant AEs of interest are reviewed in depth in Section 8.5. The following table gives an overview of AEs in the safety population.

Table 27: Summary of Adverse Events- Overview of Categories - Safety Population

	Semaglutide N (%)	Placebo N(%)
Number of subjects	133	67
All adverse events	105 (78.9)	55 (82.1)
Serious adverse events	15 (11.3)	6 (9.0)
Severe	6 (4.5)	1 (1.5)
Relationship to study drug-Probable	46 (34.6)	15 (22.4)
Outcome-Not recovered	32 (24.1)	20 (29.9)
Leading to:		
Permanent treatment discontinuation	6 (4.5)	3 (4.5)
Temporary interruption of trial product	14 (10.5)	5 (7.5)
Dose reduction of trial product	16 (12.0)	1 (1.5)

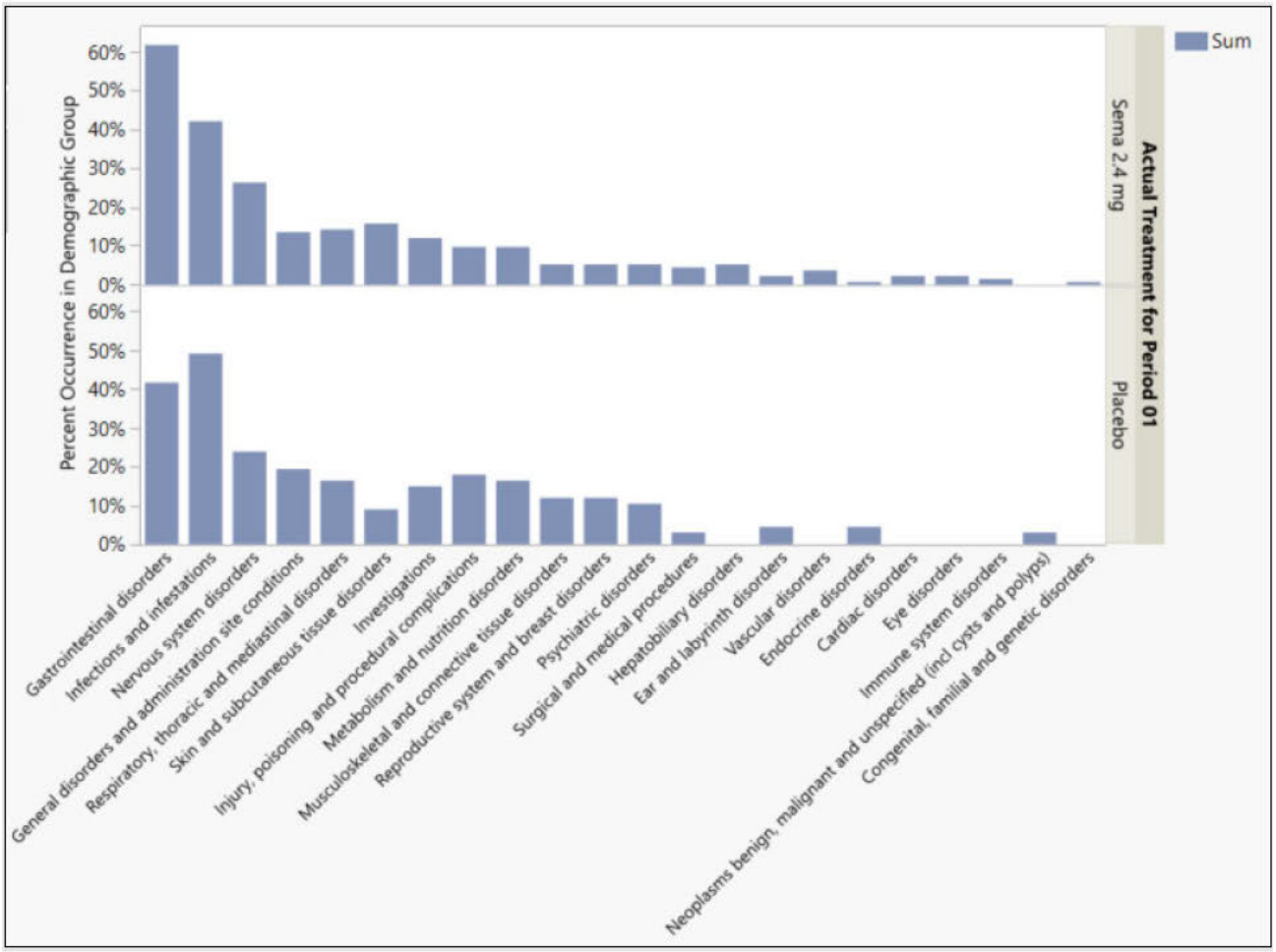
Source: STEP TEEN CSR, Table 12-1; 14.3.1.1.

Medical Officer Comment: More subjects on semaglutide versus placebo reported SAEs, severe AEs, AEs considered "probably" related to the drug, and AEs leading to temporary treatment discontinuation and to dose reduction.

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

To give a broader understanding of the type of AEs reported by subjects, the following figure and table show the most frequently reported AEs by System Organ Class (SOC) in the two treatment groups during the on-treatment period. In the semaglutide group, most AEs occurred in the SOCs Gastrointestinal disorders, Infections and infestations, and Nervous system disorders. In the placebo group, most AEs were within the SOCs Infections and infestations, Gastrointestinal disorders, and Nervous system disorders.

Figure 23: Treatment Emergent Adverse Event by System Organ Class, Safety Population



Source: Reviewer Analysis with Applicant submitted datasets.

Table 28: Overall Frequency of Adverse Events by System Organ Class, On Treatment, Safety Population

System Organ Class	Semaglutide	Placebo
	N=133	N=67
	n (%)	n (%)
Gastrointestinal disorders	82 (61.7)	28 (41.8)
Infections and infestations	59 (44.4)	35 (52.2)
Nervous system disorders	35 (26.3)	16 (23.9)
Skin and subcutaneous tissue disorders	23 (17.3)	6 (9.0)
General disorders and administration site conditions	20 (15.0)	13 (19.4)
Investigations	19 (14.3)	12 (17.9)
Respiratory, thoracic and mediastinal disorders	19 (14.3)	12 (17.9)

System Organ Class	Semaglutide	Placebo
	N=133	N=67
	n (%)	n (%)
Injury, poisoning and procedural complications	14 (10.5)	13 (19.4)
Metabolism and nutrition disorders	13 (9.8)	11 (16.4)
Psychiatric disorders	9 (6.8)	10 (14.9)
Musculoskeletal and connective tissue disorders	8 (6.0)	8 (11.9)
Hepatobiliary disorders	7 (5.3)	0
Reproductive system and breast disorders	7 (5.3)	8 (11.9)
Surgical and medical procedures	6 (4.5)	2 (3.0)
Vascular disorders	5 (3.8)	1 (1.5)
Ear and labyrinth	4 (3.0)	4 (6.0)
Cardiac disorders	3 (2.3)	0
Eye disorders	3 (2.3)	1 (1.5)
Immune system disorders	2 (1.5)	1 (1.5)
Congenital, familial and genetic disorders	1 (0.8)	0
Endocrine disorders	1 (0.8)	3 (4.5)
Neoplasms benign, malignant and unspecified	0	2 (3.0)

Source: STEP TEENS CSR, Figure 12-2

Overall by SOC, approximately 62% of semaglutide-treated subjects versus 42% of placebo-treated subjects reported at least one gastrointestinal (GI) AE. In the semaglutide group, the most frequent preferred terms under GI disorders were nausea (42.1%), vomiting (36.1%), diarrhea (21.8%), and abdominal pain (15.0%).

AEs in the Infections and infestations SOC were the most frequently reported events in the placebo group, led by events of COVID-19 and nasopharyngitis. Infections and infestations SOC was the second-most commonly reported SOC in the semaglutide group. Comparable proportions of most PTs included in this SOC were seen in both treatment groups.

In the Nervous systems disorders SOC, the proportion of events reported related to neurological disorders (primarily dizziness) was higher in the semaglutide group than in the placebo group.

In the Skin and subcutaneous tissue disorders SOC, there was a greater proportion of events in the semaglutide group related to rash, alopecia, and urticaria than in the placebo group.

Imbalances in the Hepatobiliary disorders SOC were also observed, with events only reported in the semaglutide group. These events were primarily related to cholelithiasis. Refer to Section 8.5 Acute Gallbladder Disease for more details on these events

Medical Officer Comment: This medical officer requested the sponsor to conduct a MedDRA Hypersensitivity SMQ analysis based on the higher proportion of PTs that mapped to the Skin

and subcutaneous disorders SOC. See further details in the Hypersensitivity Reactions sections.

The following table summarizes treatment emergent adverse events by SOC and PT with a frequency ≥3% in the semaglutide group and greater than placebo. The most common AEs are still in GI, Infections, Nervous system, and Skin and subcutaneous disorders categories.

Table 29: Common Adverse Events ≥3% in the Semaglutide Group and Greater Than Placebo, On Treatment, Safety Population

	Semaglutide		**Placebo**	
Number of patients	**N=133**		**N=67**	
Patient-years of exposure	181.8		90.4	
	n (%)	Events (rate)	n (%)	Events (rate)
Number of subjects with adverse events	89 (67)	484 (266)	31 (46)	117 (129)
Gastrointestinal signs and symptoms (HLGT)	78 (59)	338 (186)	22 (33)	72 (80)
Nausea	56 (42)	127 (70)	12 (18)	29 (32)
Vomiting	48 (36)	106 (58)	7 (10)	18 (20)
Diarrhea	29 (22)	54 (30)	13 (19)	19 (21)
Abdominal pain	20 (15)	32 (18)	4 (6)	4 (4)
Constipation	8 (6)	8 (4)	1 (2)	1 (1)
Eructation	5 (4)	6 (3)	0	
Gastroesophageal reflux disease	5 (4)	5 (3)	1 (2)	1 (1)
Infections and infestations	31 (23)	44 (24)	11 (16)	16 (18)
Nasopharyngitis	16 (12)	21 (12)	7 (10)	12 (13)
Gastroenteritis	9 (7)	9 (5)	2 (3)	2 (2)
Sinusitis	5 (4)	5 (3)	1 (2)	1 (1)
Urinary tract infection	5 (4)	5 (3)	1 (2)	1 (1)
Influenza	4 (3)	4 (2)	0	
Nervous system disorders	27 (20)	65 (36)	12 (18)	23 (25)
Headache	22 (17)	52 (29)	11 (16)	20 (22)
Dizziness	10 (8)	13 (7)	2 (3)	3 (3)
Skin and subcutaneous tissue disorders	11 (8)	14 (8)	0	
Alopecia	5 (4)	5 (3)	0	
Rash	4 (3)	5 (3)	0	
Urticaria	4 (3)	4 (2)	0	
Metabolism and nutrition disorders	8 (6)	8 (4)	3 (5)	4 (4)
Decreased appetite	8 (6)	8 (4)	3 (5)	4 (4)
Hepatobiliary disorders	5 (4)	5 (3)	0	

	Semaglutide		Placebo	
Number of patients	N=133		N=67	
Patient-years of exposure	181.8		90.4	
	n (%)	Events (rate)	n (%)	Events (rate)
Cholelithiasis	5 (4)	5 (3)	0	
Injury, poisonings and procedural complications	5 (4)	5 (3)	1 (2)	1 (1)
Ligament sprain	5 (4)	5 (3)	1 (2)	1 (1)
Psychiatric disorders	5 (4)	5 (3)	1 (2)	1 (1)
Anxiety	5 (4)	5 (3)	1 (2)	1 (1)

Source: Applicant response to information request.

8.4.6 Laboratory Findings

Amylase, lipase, calcitonin, liver, and renal-related laboratory values are discussed in the respective subsections in Section 8.5. Hypoglycemia is also discussed separately in Section 8.5, Analysis of Submission Specific Safety Issues.

Most laboratory parameters measured were within normal limits during the trial, with similar proportions of subjects experiencing out of range values for biochemistry and hematological parameters.

Bone metabolism biomarkers
Bone metabolism markers type 1 collagen N-telopeptide (NTX1), type 1 C-telopeptide (CTX1), procollagen 1 N-terminal propeptide (P1NP), and bone-specific alkaline phosphatase (BSAP) were measured at Week 0 and Week 68.

Baseline values for bone metabolism markers were comparable across both treatment groups. No clinically relevant treatment differences between the treatment groups were evident at end of treatment.

Table 30: Bone Metabolism Markers-Baseline Levels and Ratio to Baseline at Week 68, On-Treatment, Safety Population

	Semaglutide N=133	Placebo N=67
Bone Specific Alkaline Phosphatase (U/)		
Mean level at Baseline (CV)	38.0 (69.2)	43.2 (74.3)
Ratio to Baseline at Week 68 (CV)	0.65 (30.8)	0.76 (35.9)
CTX1 serum (pg/mL)		
Mean level at Baseline (CV)	1009 (62.0)	1077 (65.8)

	Semaglutide N=133	Placebo N=67
Ratio to Baseline at Week 68 (CV)	0.87 (38.9)	0.81 (46.2)
Type I Collagen N-Telopeptides (nmol BCE/L)		
Mean level at Baseline (CV)	31.8 (64.4)	35.3 (68.5)
Ratio to Baseline at Week 68 (CV)	0.80 (39.5)	0.80 (33.8)
Procollagen ! N-Terminal Propeptide (ng/mL)		
Mean level at Baseline (CV)	155 (86.1)	179 (106.4)
Ratio to Baseline at Week 68 (CV)	0.68 (48.3)	0.70 (44.9)

Source: STEP TEENS CSR, Table 14.3.5.3 *CV= Coefficient of variation in percent.

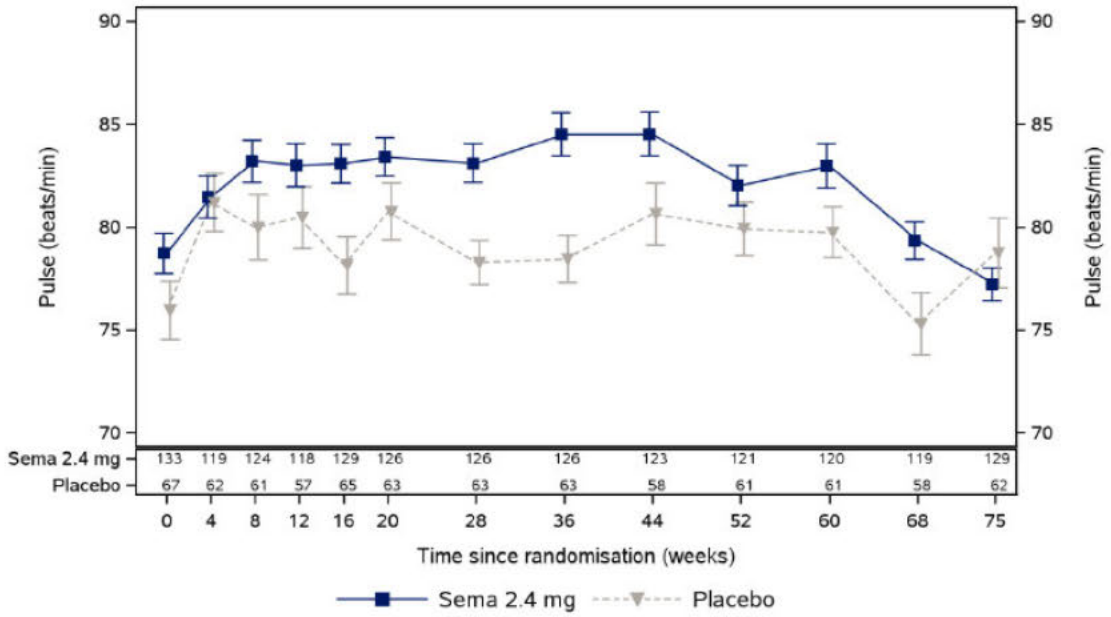
Sex Hormones
No notable differences between groups were observed in sex hormones: LH, FSH, estradiol (females), or testosterone (males).

8.4.7 Vital Signs

Heart Rate
Semaglutide was associated with an increase in heart rate of 1-4 beats per minute greater than placebo in the adult phase 3 clinical trial. Increases in heart rate is currently described in the Warnings and Precautions section of the label.

In the STEP TEENS study, at Baseline, the mean heart rate was 79 beats/min in the semaglutide group and 76 beats/min in the placebo group. At Week 28, mean heart rate was 83 beats/min in the semaglutide group and 78 beats/min in the placebo group. At Week 68, mean heart rate was 79 beats/min in the semaglutide group and 75 beats/min in the placebo group; the estimated treatment difference between the semaglutide and placebo groups at Week 68 was statistically significant (3.50 beats/min [0.34; 6.66]95% CI).

Figure 24: Mean Heart Rate by Week, On Treatment, Safety Population



In a shift table analysis by baseline pulse rate groups [low (<60 beats/min), average (between 60 and 80 beats/min), high (>80 beats/min)], a greater proportion of subjects in the semaglutide group with an average baseline pulse rate had a maximum increase of at least 20 beats/min compared to placebo, 54% versus 39%, respectively. The following table summarizes the shift table pulse rate findings.

Table 31: Maximum Change in Heart Rate from Baseline, On Treatment, Safety Population

	Sema 2.4 mg N (%)	Placebo N (%)
Number of subjects	133	67
All subjects		
N	132	66
Maximum pulse change from baseline		
(< -20 beats/min)	0	0
(-20 to <-10 beats/min)	1 (0.8)	0
(-10 to < 0 beats/min)	8 (6.1)	4 (6.1)
(0 to < 10 beats/min)	34 (25.8)	17 (25.8)
(10 to < 20 beats/min)	41 (31.1)	23 (34.8)
(>= 20 beats/min)	48 (36.4)	22 (33.3)
Baseline pulse <60 beats/min		
N	3	3
Maximum pulse change from baseline		
(< -20 beats/min)	0	0
(-20 to <-10 beats/min)	0	0
(-10 to < 0 beats/min)	0	0
(0 to < 10 beats/min)	0	0
(10 to < 20 beats/min)	0	0
(>= 20 beats/min)	3 (100)	3 (100)
Baseline pulse >=60 to <80 beats/min		
N	71	39
Maximum pulse change from baseline		
(< -20 beats/min)	0	0
(-20 to <-10 beats/min)	0	0
(-10 to < 0 beats/min)	2 (2.8)	1 (2.6)
(0 to < 10 beats/min)	10 (14.1)	6 (15.4)
(10 to < 20 beats/min)	21 (29.6)	17 (43.6)
(>= 20 beats/min)	38 (53.5)	15 (38.5)
Baseline pulse >=80 beats/min		
N	58	24
Maximum pulse change from baseline		
(< -20 beats/min)	0	0
(-20 to <-10 beats/min)	1 (1.7)	0
(-10 to < 0 beats/min)	6 (10.3)	3 (12.5)
(0 to < 10 beats/min)	24 (41.4)	11 (45.8)
(10 to < 20 beats/min)	20 (34.5)	6 (25.0)
(>= 20 beats/min)	7 (12.1)	4 (16.7)

Source: STEP TEENS CSR, Table 14.3.6.5

To analyze heart rate-related reported AEs, this medical officer conducted an FDA Medical Query for Tachycardia (Narrow) and summarized the findings in the following table.

Table 32: FDA Medical Query, Tachycardia (Narrow), Safety Population

FDA Medical Query	Semaglutide N=133	Placebo N=67	Risk Difference for Semaglutide over Placebo
Tachycardia	3 (2.3%)	0	0.02 (0, 0.05)
Tachycardia	2 (1.5%)	0	0.02 (-0.01, 0.04)
Heart rate increased	1 (0.8%)	0	0.01 (-0.01, 0.02)

Source: Reviewer Analysis

Medical Officer Comments: There were 3 (2.3%) heart-rate related AEs reported for semaglutide, compared to none on placebo. Mean heart rate increases in adolescents from this study will be described in the label.

Blood Pressure
Blood pressure was assessed as an efficacy endpoint and is discussed in Section 6. There were reported AEs of hypotension in the semaglutide group and one AE of hypertension in both treatment groups in the safety database.

Table 33: Reported Adverse Events Related to Hypotension or Hypertension, Safety Population

	Semaglutide N=133	Placebo N=67
Vascular disorders		
Hypotension	3 (2.3%)	0
Hypertension	1 (0.8%)	1 (1.5%)

Source: Reviewer Analysis

Medical Officer Comment: The frequency of hypotension will be described in the semaglutide label. See Section 8.5.3 on hypotension, syncope, and dizziness for analyses on AEs related to blood pressure.

8.4.8 Electrocardiograms (ECGs)

ECG assessments were performed at screening, Week 0 (Baseline) and Week 68/End of Treatment. The findings were categorized as "normal", "abnormal, not clinically significant", or "abnormal, clinically significant" by the investigator. One subject in the semaglutide group was diagnosed with a clinically significant ECG result at Baseline; this AE of left atrial enlargement was reported as non-serious, mild in severity, unlikely related to trial product. The remaining ECGs at Baseline and at Week 68 were reported as normal, or abnormal, not clinically significant.

8.4.9 QT

Potential for QT effect was evaluated in the adult population. There is no QT signal described with semaglutide.

There were no AEs related to QT prolongation (Investigations SOC) nor were there any AEs of Torsades de pointes in the trial.

8.4.10 Immunogenicity

Blood samples for determination of serum antibodies against semaglutide, including cross-reactivity to endogenous GLP-1, were taken during the trial at specific visits. Samples which were positive for anti-semaglutide antibodies were further characterized for cross-reactivity to endogenous GLP-1, titer, and *in vitro* neutralizing effect.

From baseline to week 75, one of the 133 subjects (0.75%) tested positive for anti-semaglutide antibodies at week 68. The subject's sample was negative at week 75, thus the positive result was likely a transient antibody response. No subjects tested positive for either anti-semaglutide neutralizing antibodies or anti-semaglutide antibodies cross-reacting with endogenous GLP-1.

8.5 Analysis of Submission-Specific Safety Issues

8.5.1 Gallbladder-Related Disorders

Obesity and rapid weight loss are associated with an increased risk for gallstone formation; however, in adult clinical trials, even after accounting for the degree of weight loss, the incidence of acute gallbladder disease was greater in subjects treated with semaglutide than placebo. The current semaglutide labeling lists acute gallbladder disease under the Warnings and Precautions Section.

The sponsor conducted a predefined MedDRA search based on the on-treatment period and identified 6 events of gallbladder related AEs in 5 subjects, all in the semaglutide treatment group. The following table summarizes those AEs.

Table 34: Gallbladder Related Disorders, On Treatment, Safety Population

Subject ID/ Age/Sex/ BMI	Preferred Term	Trial day of onset	Seriousness/ Severity/Risk factors	Relation/ Action	Outcome/ Treatment Given
(b) (6)/ 16/ F/ 34.9	Cholelithiasis	Day 114	Non-serious/Mild/None	Unlikely? /Dose not changed	Not recovered/ Not stated
(b) (6)/ 14/ F/30.5	Cholelithiasis	Day 241	Non-serious /Moderate/None	Unlikely/ Dose not changed	Recovered/ Cholecystectomy, urgent surgery
	Cholecystitis acute	Day 241	Serious/ Moderate/ None	Probable/ Temporary interruption	Recovered
(b) (6)/ 15/F/40.1	Cholelithiasis	Day 392	Serious/Severe/Family history of gallstones, rapid weight loss	Unlikely? /Temporary interruption	Recovered/ Other (not specified)
(b) (6)/ 15/F/30.2	Cholelithiasis	Day 191	Serious/Moderate/ Prior experience of similar pain; rapid weight loss	Possible/ Temporary interruption	Recovered/ Cholecystectomy elective surgery
(b) (6)/ 13/F/31.9	Cholelithiasis	Day 251	Serious/ Mild/ Not reported	Possible/ Temporary interruption	Recovered/ Cholecystectomy elective surgery

Source: STEP TEENS CSR, Table 12-17.

Medical Officer Comment: There were approximately 3.8% of subjects with cholelithiasis in the semaglutide group compared to none in the placebo group. This incidence of cholelithiasis in adolescents is slightly higher than that seen in the adult clinical trial population of 1.6% on semaglutide and will be described in the proposed label.

8.5.2 Acute Pancreatitis

In adult clinical trials, acute pancreatitis was observed in subjects treated with semaglutide, and has been observed with other GLP-1 receptor agonists. In Study NN9536-4451 (STEP TEENS), subjects with a history of chronic or acute pancreatitis were excluded from the trial. Furthermore, diagnosis of acute pancreatitis was a reason for premature study drug discontinuation. The diagnosis of acute pancreatitis required two of the following three features (Atlanta Criteria):

1. abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
2. serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
3. characteristic findings of acute pancreatitis on imaging.

One event of acute pancreatitis (Subject ID# (b) (6)) occurred prior to randomization during the run-in period. The event was reported as moderate and the subject recovered. Although the investigator reported that the subject permanently discontinued trial product, the subject did continue in the study and was randomized to placebo treatment.

This medical officer reviewed subjects who were reported to have amylase or lipase elevations as an adverse event to ensure that a diagnosis of pancreatitis was not missed. One subject (Subject ID# (b) (6)) on semaglutide had an AE of amylase increase, and two subjects (Subject ID# (b) (6) and # (b) (6)) on semaglutide had an AE of lipase increase. Two subjects on placebo (Subject ID# (b) (6) and (b) (6)) also had AEs of lipase increase. Although not reported as an AE, Subject ID # (b) (6) on semaglutide, had multiple amylase elevations that were >3x ULN.

Medical Officer Comment: None of the subjects with AE of elevated amylase or lipase met the Atlanta criteria for pancreatitis.

The following figures show the percent change from Baseline for amylase and lipase during the course of the study.

Figure 25: Percent Change from Baseline for Amylase U/L Over Time, Safety Population

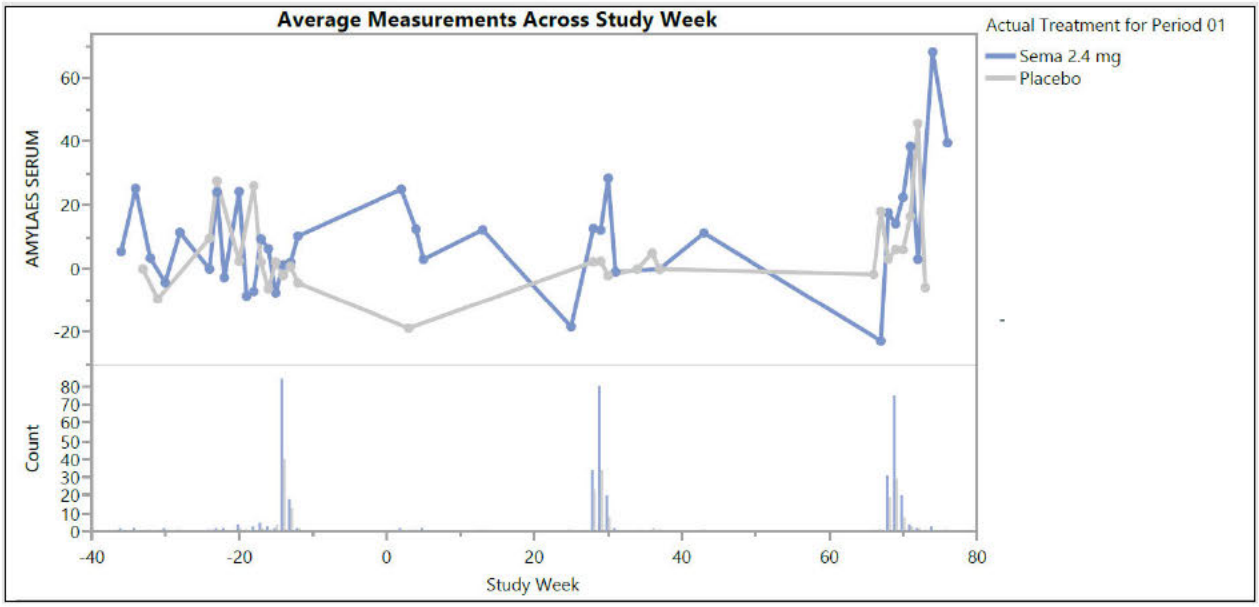
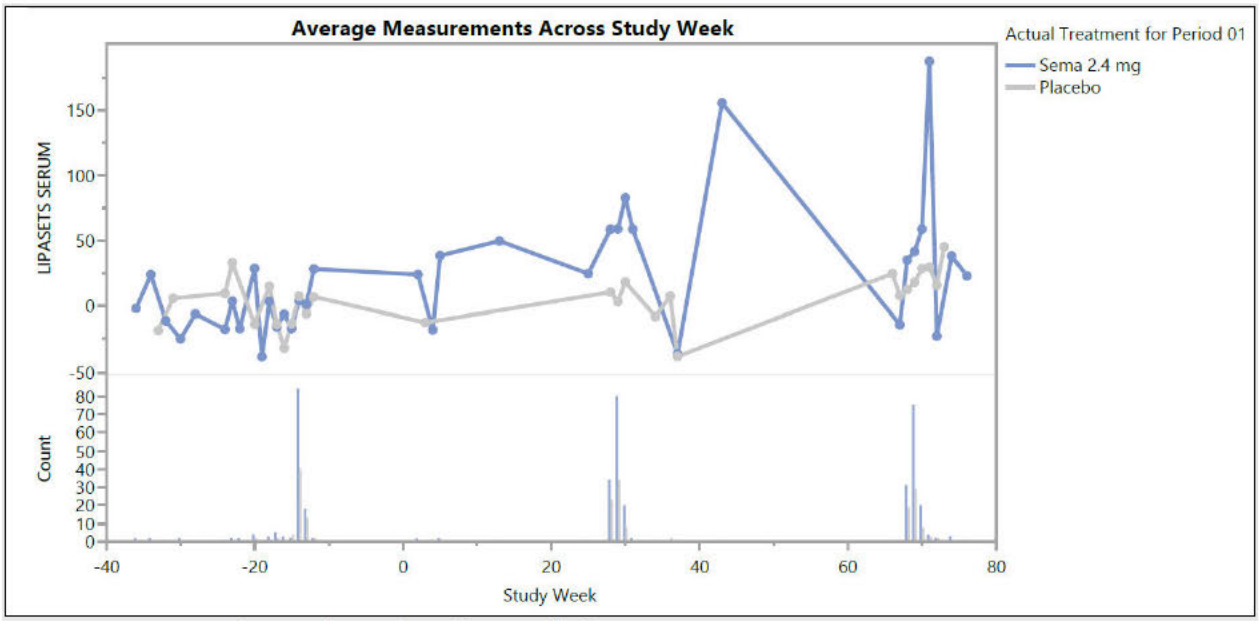


Figure 26: Percent Change from Baseline for Lipase U/L Over Time, Safety Population



Source: Reviewer Analysis, Submitted Applicant adlb datasets.

There were greater increases from baseline in the semaglutide group compared to placebo for both amylase and lipase. Amylase increased by approximately 15% compared to baseline and lipase increased by 39% compared to baseline in the semaglutide group. In the placebo group, amylase increased by 4% compared to baseline and lipase increased by 12% compared to

baseline.

Table 35: Amylase and Lipase, Baseline Levels and Ratio to Baseline at Week 68, On-Treatment, Safety Population

	Semaglutide N=133	Placebo N=67
Amylase (U/L)		
Mean* level at Baseline	46 (35.9)	44 (38.5)
Ratio to Baseline at Week 68	1.15 (17.4)	1.04 (18.2)
Lipase (U/L)		
Mean* level at Baseline	18 (43.2)	18 (52.7)
Ratio to Baseline at Week 68	1.39 (37.3)	1.12 (37.0)

Source: STEP TEENS CSR, Table 12-20. *Geometric mean: Coefficient of variation in %.

Medical Officer Comment: GLP-1 RAs are associated with elevations in pancreatic enzymes of unclear clinical significance in the absence of other signs and symptoms of pancreatitis. This increase in amylase and lipase will be described in the label.

8.5.3 Hypotension, Syncope and Dizziness

Adverse events related to hypotension and syncope under the FDA Medical Query of "Syncope, Broad" were reported in 12% of semaglutide treated subjects versus 6% of placebo treated subjects. The specific preferred term "hypotension" was reported in 3 (2.3%) of subjects on semaglutide versus none on placebo. Combining the terms "syncope, presyncope, and loss of consciousness" resulted in 4 (3.0%) subjects on semaglutide and 2 (2.98%) subjects on placebo who had these events.

Table 36: FDA Medical Query, Syncope (Broad), Safety Population

	Semaglutide N=133 n (%)	**Placebo N=67 n (%)**	**Risk Difference for Semaglutide over Placebo**
Syncope	16 (12.0%)	4 (6.0%)	0.06 (-0.02, 0.14)
Dizziness	10 (7.5%)	2 (3.0%)	0.05 (-0.02, 0.11)
Hypotension	3 (2.3%)	0	0.02 (0.0, 0.05)
Syncope	3 (2.3%)	1 (1.5%)	0.01 (-0.03, 0.05)
Presyncope	1 (0.8%)	0	0.01 (-0.01, 0.02)
Loss of Consciousness	0	1 (1.5%)	-0.01 (-0.04, 0.01)

Source: Reviewer Analysis

Medical Officer Comment: This medical officer reviewed subjects on semaglutide who reported either "hypotension" or "syncope" to see if gastrointestinal adverse reactions (and

possible volume loss) associated with semaglutide occurred within +/- 3 days of the hypotensive/syncopal event. Of the 6 subjects reviewed, only 2 (Subject ID# (b) (6) and # (b) (6)) had either a hypotensive or syncopal episode with GI symptoms. Subject ID # (b) (6) also reported influenza during the episode. Therefore, in this small sample of adolescents, hypotension and syncope did not seem to be associated with GI adverse events and subsequent volume loss (see table below).

Table 37: Subjects on Semaglutide with Hypotension/Syncope and Other Adverse Events in Close Proximity

Subject ID	Hypotensive/Syncopal Adverse Event	Other Adverse Events reported in close proximity	Dates of Adverse Events
Subject ID# (b) (6)	Syncope		(b) (6)
		Vomiting	
		Hyperventilation	
		Tachycardia	
		Malaise	
Subject ID # (b) (6)	Syncope		
		Vomiting	
		Diarrhea	
		Nausea	
Subject ID# (b) (6)	Syncope		
Subject ID# (b) (6)	Hypotension		
		Vertigo	
Subject ID# (b) (6)	Hypotension		
		Hematemesis	
		Influenza	
		Vertigo	
Subject ID# (b) (6)	Hypotension		
		Nausea	
		Lymph gland infection	

Source: Reviewer Analysis

This medical officer conducted an analysis with the FDA Medical Query "Dizziness, Narrow" to evaluate other AE terms that may be associated with low blood pressure and obtained results summarized in the following table.

Table 38: FDA Medical Query, Dizziness, Narrow, Safety Population

	Semaglutide N=133	Placebo N=67	Risk Difference for Semaglutide over Placebo
Dizziness	13 (9.8%)	3 (4.5%)	0.05 (-0.02, 0.12)
Dizziness	10 (7.5%)	2 (3.0%)	0.05 (-0.02, 0.11)
Dizziness postural	1 (0.8%)	0	0.01 (-0.01,0.02)

Presyncope	1 (0.8%)	0	0.01 (-0.01,0.02)
Vertigo	2 (1.5%)	1 (1.5%)	0 (-0.04, 0.04)

Source: Reviewer Analysis, JMP Clinical

Medical Officer Comment: The FDA Medical Query for "Dizziness, Narrow", shows there is a nominal increase in the frequency of dizziness as well as a nominal increase in the PT dizziness by itself 7.5% on semaglutide vs. 3.0% on placebo. This medical reviewer will list the frequency of dizziness in an adverse reactions table in Section 6.1 "Clinical Trial Experience" of the semaglutide label to better inform the healthcare provider and consumer.

The Applicant conducted an analysis based on a predefined MedDRA search to identify events related to cardiovascular safety. The evaluation of cardiovascular safety was based on the in-trial period due to potentially long latencies prior to diagnosis. The findings are summarized below.

Table 39: Cardiovascular Related Adverse Events, In Trial, Safety Population

	Semaglutide		Placebo	
Number of patients	133		67	
	N (%)	Events (rate)	N (%)	Events (rate)
Number of subjects with adverse events	10 (7.5)	13 (6.8)	7 (10.4)	7 (7.4)
Cardiac disorders	3 (2.3)	3 (1.6)	0	
Tachycardia	2 (1.5)	2 (1.0)	0	
Left atrial enlargement	1 (0.8)	1 (0.5)	0	
Nervous system disorders	3 (2.3)	4 (2.1)	2 (3.0)	2 (2.1)
Syncope	3 (2.3)	4 (2.1)	1 (1.5)	1 (1.1)
Loss of consciousness	0		1 (1.5)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	3 (2.3)	3 (1.6)	1 (1.5)	1 (1.1)
Dyspnea	3 (2.3)	3 (1.6)	0	
Pulmonary congestion	0		1 (1.5)	1 (1.1)
Investigations	2 (1.5)	2 (1.0)	4 (6.0)	4 (4.3)
Blood creatine phosphokinase increased	1 (0.8)	1 (0.5)	4 (6.0)	4 (4.3)
Heart rate increased	1 (0.8)	1 (0.5)	0	
General disorders and administration site conditions	1 (0.8)	1 (0.5)	0	
Chest pain	1 (0.8)	1 (0.5)	0	

Source: STEP TEENS CSR, Table 12-10, Table 14.3.1.59

Medical Officer Comment: Both the proportion and rate of subjects reporting AEs related to the Applicant's predefined cardiovascular safety search were comparable across both

treatment groups.

8.5.4 Neoplasms

The sponsor conducted a predefined MedDRA search to assess the risk of neoplasms across multiple SOC hierarchies. Both treatment groups reported 3 AEs in 3 subjects, across a range of terms that mostly included benign cysts and polyps. One of the six events was reported as an SAE (ovarian germ cell teratoma, benign) in the placebo treatment group. No events related to malignant neoplasms was reported.

Table 40: Neoplasm Adverse Events, Pre-defined MedDRA search, In-Trial Safety Population

	Semaglutide		**Placebo**	
Number of subjects	133		67	
Patient years of observation	192.0		94.0	
	n (%)	Event (rate)	n (%)	Event (rate)
Reproductive system and breast disorders	1 (0.8)	1 (0.5)	0	
Ovarian cyst	1 (0.8)	1 (0.5)	0	
Respiratory, thoracic and mediastinal disorders	1 (0.8)	1 (0.5)	0	
Nasal polyps	1 (0.8)	1 (0.5)	0	
Skin and subcutaneous tissue disorders	1 (0.8)	1 (0.5)	0	
Dermal cyst	1 (0.8)	1 (0.5)	0	
Gastrointestinal disorders	0		1 (1.5)	1 (1.1)
Abdominal wall cyst	0		1 (1.5)	1 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0		2 (3.0)	2 (2.1)
Ovarian germ cell teratoma benign	0		1 (1.5)	1 (1.1)
Prolactin-producing pituitary tumor	0		1 (1.5)	1 (1.1)

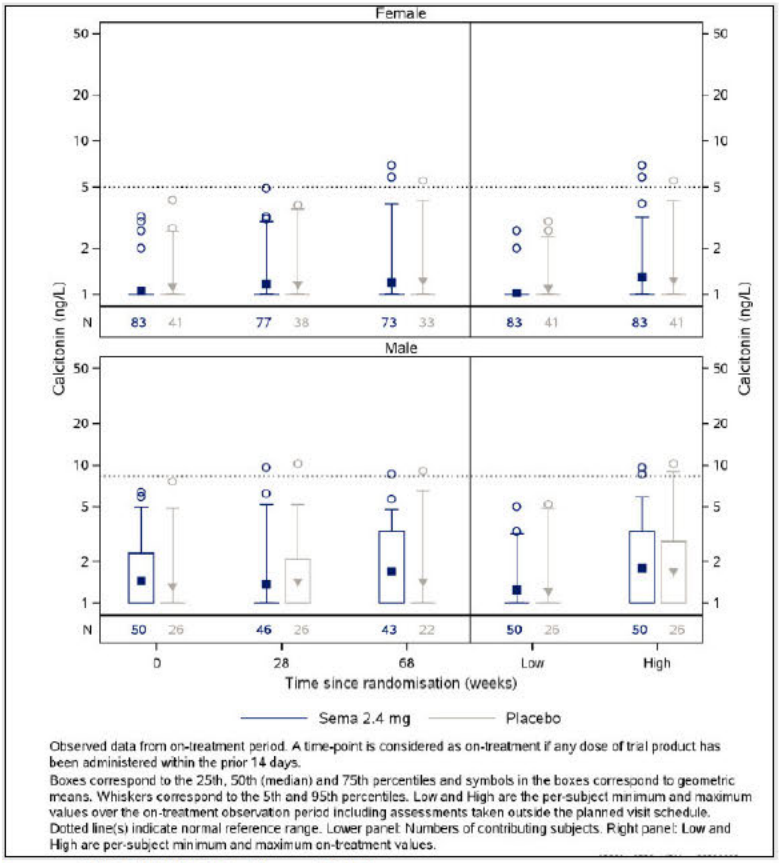
Source: STEP TEENS CSR, Table 12-18; 14.3.1.64

Labeling for GLP1-RAs includes a black box warning for risk of thyroid C-cell tumors. However, in this study there were no thyroid neoplasms (medullary thyroid carcinoma or c-cell hyperplasia).

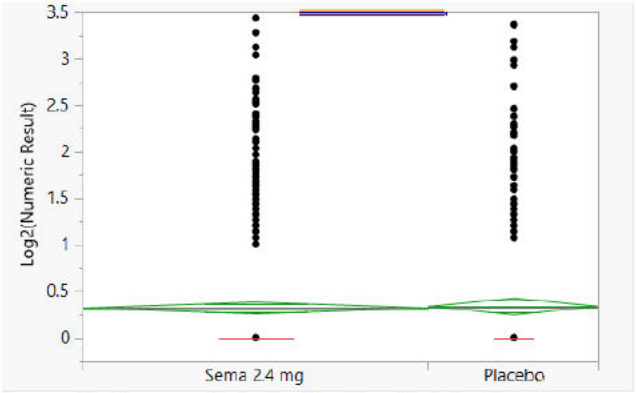
Calcitonin levels were assessed as part of the evaluation of neoplasms as it is used as a marker to monitor for potential medullary thyroid cancer (MTC). At baseline, geometric mean levels of calcitonin were comparable across both treatment groups.

The following figure shows calcitonin levels by gender and treatment arm during the trial.

Figure 27: Calcitonin Levels by Week, On Treatment, Safety Population



Source: STEP TEENS CSR, Figure 12-14.



Source: Reviewer analysis, Applicant's adlb dataset.

Medical Officer Comment: No treatment differences in calcitonin levels were evident during the trial period. No clinically relevant elevations in calcitonin were reported in either treatment group.

8.5.5 Hepatic events and related laboratory values

The most specific indicator of a possible drug-induced liver injury signal in a clinical trial database is believed to be the occurrence of subjects experiencing drug-associated elevations in both serum ALT and serum total bilirubin (TB) without a significant elevation in serum alkaline phosphatase (ALP), otherwise known as Hy's Law. In this study, no patient fulfilled Hy's law. The table below summarizes the elevation in ALT, AST, ALP, TB, and GGT seen in labs analyzed at the Applicant's central laboratory.

Table 41: Frequency of Central Hepatic Safety Laboratory Parameters at Any Post-Baseline Visit, Safety Population

Laboratory Parameter	Semaglutide N=133	Placebo N=67
ALT		
n	132	66
<3xULN	126 (95.5%)	64 (97.0%)
3 to <5xULN	4 (3.0%)	2 (3.0%)
5 to <10xULN	1 (0.8%)	0
10 to <20xULN	1 (0.8%)	0
AST		
n	132	66
<3xULN	131 (99.2%)	65 (98.5%)
5 to <10xULN	1 (0.8%)	1 (1.5%)
Alkaline Phosphatase		
n	132	66
<2xULN	131 (99.2%)	66 (100%)
2 to <3xULN	1 (0.8%)	0
Bilirubin		
n	132	66
<2xULN	131 (99.2%)	65 (98.5%)
2 to <5xULN	1 (0.8%)	1 (1.5%)
GGT		
n	132	66
<2xULN	125 (94.7%)	63 (95.5%)
≥2xULN	7 (5.3%)	3 (4.5%)

Source: Applicant Response to FDA Information Request.

Medical Officer Comment: A review of hepatic safety laboratory parameters (central laboratory measurements) showed similar proportions of subjects in each treatment group had AST, ALP, TB and GGT elevations. Imbalances in ALT elevations >5x ULN were observed (1.5% semaglutide versus 0% placebo). There was 1 subject (Subject ID# (b) (6)) in the semaglutide group with ALT 5 to <10xULN and 1 subject (Subject ID# (b) (6)) in the

semaglutide group with ALT 10 to < 20xULN compared to none on placebo for these two categories. A brief narrative of these two subjects is below.

Subject ID# (b) (6): This is a 14 yo female with a BMI of 32.7 kg/m^2 on semaglutide. At Week 0 (Baseline) (b) (6), subject's ALT was 90 U/L (4.5XULN) (5-20 U/L normal range), AST was 30 U/L, GGT was 21 U/L; repeat testing 1 month later ((b) (6)) ALT was 103 U/L (>5xULN), AST was 32 U/L. Two months later ((b) (6)) ALT was 240 U/L (>10XULN) and AST was 62 U/L. Subject reported postural dizziness on (b) (6), and dose of study medication was reduced. Postural dizziness was subsequently reported as recovered. Testing on (b) (6) showed an ALT level of 41 U/L (5-20 U/L normal range) and AST was 28 U/L (0-31 U/L normal range). On (b) (6), an SAE of cholecystitis acute, and an AE of cholelithiasis, were reported for this subject. Subject had right upper quadrant abdominal pain with nausea. ALT was 45 U/L, AST was 36 U/L, Lipase was 100 U/L, and ultrasound showed gallstones in the gallbladder. On (b) (6), outpatient laparoscopic cholecystectomy was performed. The SAE resulted in temporary interruption of treatment. The subject recovered and treatment was restarted on (b) (6). At the end of study, ALT level was 14 U/L.

Medical Officer Comment: This subject had elevated ALT of approximately 4.5X ULN at Baseline, which subsequently increased to >10XULN and then decreased to 2XULN on Day 206. (The Applicant states that the ALT value of 240 U/L was an unscheduled "retest value" and does not include this value in their analysis.) A month later, the subject was diagnosed with cholelithiasis and acute cholecystitis and had cholecystectomy. Of note, during an acute episode of right upper quadrant pain, her liver enzymes were within normal limits. It is possible that her Baseline ALT elevation and increased ALT levels during the study were due to undiagnosed gallstones leading to obstruction and increased ALT levels. Obesity is an independent risk factor for developing gallstones. Development of gallstones is also a well-known adverse effect of treatment with semaglutide. Therefore, it is possible that cholelithiasis confounded the ALT increase in this subject.

Subject ID# (b) (6): This is a 13 y.o. female with a BMI of 31.9 kg/m^2 on semaglutide. At Week 0 (Baseline) (b) (6), subject's ALT was 45 U/L. On Day 193, AE of gastritis was reported and on Day 196 ALT was 127 U/L, AST was 166 U/L and GGT was 98 U/L. Repeat bloodwork 1 month later (b) (6) showed an ALT of 12 U/L, AST of 10 U/L Study drug dose was not changed for liver enzyme elevations. Almost 2 months later, subject reported cholelithiasis on Day 251, and had elective cholecystectomy. Cholelithiasis was diagnosed by ultrasound; however, subject was asymptomatic. Study drug was temporarily interrupted for the surgery. Subject recovered and end of treatment ALT was 9 U/L, AST was 10 U/L, GGT was 7 U/L.

Medical Officer Comment: This subject may have had undiagnosed cholelithiasis earlier in the study which may have contributed to in the increase in ALT, although "gastritis" was reported as an etiology of the liver enzyme increase.

The increase in liver enzymes will be described in the semaglutide label.

Medical Officer Comment: This medical officer requested that the Applicant tabulate ALT/AST elevations of >3XULN alone, >5XULN, and >3XULN concurrent with a total bilirubin of >2XULN detected by local laboratories to ensure all liver enzyme elevations (whether analyzed by central or local labs) were considered. The Applicant submitted the following summary table for 2 subjects on semaglutide and 1 subject on placebo.

Table 42: Liver Enzyme Elevations -Local Laboratory Elevations, Safety Population

Subject ID/Treatment Arm	Related Medical History	Date of Lab Elevation	ALT/AST Elevation >3XULN	ALT/AST Elevation >5XULN	ALT> 3XULN and Bilirubin >2XULN
# (b) (6) / Semaglutide	Transaminase increased likely due to transient hepatic injury due to gastrointestinal infection Hypertension, dyslipidemia, insulin resistance, non-alcoholic fatty liver disease	(b) (6)	ALT=373 U/L (ULN =29 U/L)	ALT=373 U/L (ULN =29 U/L)	None
			AST=168 U/L (ULN=32 U/L)	AST=168 U/L (ULN=32 U/L)	
# (b) (6) / Semaglutide	Hepatic function decreased, cholelithiasis Non-alcoholic fatty liver disease, polycystic ovaries, family history of gallstones		ALT=634 U/L (ULN= 37 U/L)	ALT=634 U/L (ULN= 37 U/L)	
			ALT= 522 U/L	ALT= 522 U/L	Bilirubin=92 umol/L
			ALT=314 U/L		Bilirubin=26 umol/L
			ALT=699 U/L AST=354 U/L		Bilirubin=57 umol/L
			ALT=71 U/L AST=16 U/L		
			ALT=101 U/L AST=45 U/L		
# (b) (6) / Placebo	Transaminase increased; Nonalcoholic fatty liver disease, hypertriglyceridemia		ALT=98 U/L (ULN=35 U/L) AST=155 U/L (ULN=35 U/L)		

Subject ID/Treatment Arm	Related Medical History	Date of Lab Elevation	ALT/AST Elevation >3XULN	ALT/AST Elevation >5XULN	ALT> 3XULN and Bilirubin >2XULN

Source: Applicant response to information request. ULN= Upper Limit of Normal.

Narratives for subjects on semaglutide who had liver enzyme elevations measured at local laboratories are as follows:

Subject ID # (b) (6): This is a 16 y.o. female on semaglutide from (b) (6) to (b) (6) and again from (b) (6)-to end of trial. Due to frequent menstruation the subject was advised to consult a gynecologist who planned to introduce contraceptive therapy to regulate her menstrual cycle. Transaminase levels were checked prior to contraceptive initiation. Prior to event, the following laboratory tests were performed: (b) (6), AST was 20.0 U/L (Norm High: 30) and GGT was 22.0 U/L (Norm High: 24, Norm Low: 4). On (b) (6) ALT was 26.0 U/L (Norm High: 20, Norm Low: 5). On (b) (6) ALT was 35.0 U/L (Norm High: 20, Norm Low: 5), AST was 25.0 U/L (Norm High: 30).

According to the CSR, on (b) (6), AEs of nausea and vomiting were reported. (The subject narrative also reported that subject had no complaints at the time of reporting; therefore, there is some discrepancy on the issue of symptoms.) On (b) (6) (reported as onset date) the transaminase result indicated elevated values. Laboratory tests performed on this date: **ALT 373.0 U/L**, (Norm High: 29 Norm Low: 10); **AST 168.0 U/**L, Norm High: 32 Norm Low: 14.; GGT 282 U/L, Norm High: 24 Norm Low: 10 ;Total Bilirubin/bilirubin 25.0 µmol/L, (Norm High: 26 Norm Low: 6). The patient had an Ultrasound performed which showed hepatic, biliary, and pancreas morphology was normal. Viral hepatitis serology did not reveal acute viral hepatitis. On (b) (6) tests for autoimmune hepatitis; ANA (Test Name: Antinuclear antibody), AGLM (Test Name: Smooth muscle antibody) and LKM (Test Name: Autoantibody test) were done and came negative on (b) (6).

On (b) (6) the following laboratory tests were performed:
-ALT: 63 U/L, Norm High: 29 Norm Low: 10
-Alkaline phosphatase: 106.0 U/L, Norm High: 193 Norm Low: 79
- AST: 26 U/L, Norm High: 32 Norm Low: 14
-GGT: 120 U/L, Norm High: 24 Norm Low: 10
-INR: 1.1 INR, Norm High: 3.5 Norm Low: 2

Action taken to Blinded Semaglutide was reported as Drug discontinued temporarily. Trial drug treatment was re-initiated on (b) (6). On (b) (6) ALT (was 28 U/L (Norm High: 29, Norm Low: 10) and AST was 18 U/L (Norm High: 32, Norm Low: 14). After the reintroduction of trial drug the patient had no complaints. On (b) (6) the outcome for the event "increased hepatic transaminases (Transaminases increased)" was Recovered.

Medical Officer Comment: This case concerns a 16 year old female subject who was diagnosed with "increased hepatic transaminases" after being treated with semaglutide for approximately 5½ months. No etiology of the transaminase elevation was identified. Laboratory tests revealed no viral or autoimmune hepatitis, there were no gallstones detected on ultrasound, and no history of binge alcohol consumption. According to the investigator the most likely cause of the transient acute hepatic injury was gastro-enteral infection. Eight days after the temporary discontinuation of trial drug treatment, the level of transaminases decreased significantly to normal (AST) or only 2xUNL (ALT) values. In addition, the level of transaminases did not increase again after re-initiation of trial drug treatment (negative rechallenge). Given the positive dechallenge, but negative rechallenge, the association with semaglutide is unclear.

Subject ID # (b) (6): This is a 16 y.o. female subject on semaglutide from (b) (6) to end of trial. Week 0 (Baseline) ALT level was 40 U/L (5-20 U/L normal range), and on Week 28 ((b) (6)) ALT level was 22 U/L. Prior to the reported events, subject had multiple nausea and vomiting non-serious events. On (b) (6), subject had increasing abdominal pain and vomiting. On (b) (6) subject was admitted to the hospital. The following tests were performed:
Alanine aminotransferase (ALT) Results: **634.0 U/L**, Norm High: 37.0
- Albumin Results: 51.0 mg/L, Norm High: 45.0, Norm Low: 32.0
- Amylase Results: 53.0 U/L, Norm High: 100.0, Norm Low: 28.0
- C Reactive Protein (CRP) Results: 1.0 mg/L, Norm High: 5.0
- Total bilirubin Results: 97.0 µmol/L, Norm High: 21.0
- White blood count (WBC) Results: 5.0 10*9/L, Norm High: 12.0, Norm Low: 3.5

On (b) (6) Ultrasound showed: Abnormal findings. Gallstone(s) in the gallbladder/Multiple gallstones. Also showed lesion on liver. On the same day bloodwork were repeated (no units or reference ranges provided):
- ALT Results: 314
- Bilirubin Results: 26
On (b) (6), the patient was discharged, awaiting surgical review. Dose (trial product) delayed until well.

On (b) (6) the patient reattended (b) (6) with Gallstone pain. Not admitted, but given dihydrocodeine for pain. Referral to surgeons completed and the following test were performed. Bloods (no units or reference ranges provided):
- ALT Results: 699
- Alk Phosphate Results: 129
- Bilirubin total Results: 57
- GGT Results: 317

- Lipase Results: 71
- AST Results: 354

On (b) (6) the patient obtained bloodwork (no units or reference ranges provided) with marked improvement in hepatic function.
- ALT Results: 71
- ALK Phosphate Results: 63
- GGT Results: 114
- Lipase Results: 26
- AST Results: 16

On (b) (6), the patient had repeated bloodwork, which showed function improved:
- ALT: 28
- Bilirubin (conjugated): 7

Gallbladder event: Abdominal pain, right upper quadrant, nausea, vomiting and jaundice/ Icterus were present during the course of event. Family history of gallstones and rapid weight loss were identified as relevant risk/confounding factors.
Hepatic event: Hepatic laboratory finding leading to request and date of finding; gallstones, (b) (6) . Nausea, Vomiting, Abdominal Pain and Jaundice were present during the course of event. There had been no episodes of excessive (binge) drinking in the last 30 days prior to the event.

Medical Officer Comment: This case concerns a 16 year old female patient who had been treated with semaglutide for approximately 13 months, when she experienced the reported events "Gallstones" and "Deranged Liver Function". The narrative history, including labs and imaging results, is consistent with obstructive cholelithiasis. Some confounding factors for developing gallstones were present including family history of gallstones and rapid weight loss. However, as gallstones are a well-known side effect of treatment with semaglutide and as obstructive gallstones can cause deranged liver function, a causal relationship between trial drug and both events cannot be dismissed.

The sponsor conducted a predefined MedDRA search in the evaluation of hepatic events. A hepatic event was defined as:

- Disorders of the liver including cholestatic conditions and liver related signs and symptoms
- ALT or AST > 3X UNL and total bilirubin > 2X ULN*
- ALT or AST > 3X UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia

*In case of a hepatic event defined as ALT/AST > 3XULN and total bilirubin >2XULN, where no other alternative etiology exists (Hy's Law), this must be reported as an SAE.

The proportion of subjects with AEs related to hepatic events was higher in the semaglutide group 10 (7.5%) vs. 1 (1.5%) in the placebo group. Hepatic events were distributed across both Investigations SOC and Hepatobiliary SOC.

Table 43: Hepatic Adverse Events by System Organ Class and Preferred Term, On Treatment, Safety Population

	Semaglutide		Placebo	
Number of total subjects	133		67	
Patient years of exposure	181.8		90.4	
	N(%)	Event (rate)	N(%)	Event (rate)
Number of subjects with hepatic events	10 (7.5)	13 (7.2)	1 (1.5)	1 (1.1)
Investigations	7 (5.3)	9 (5.0)	1 (1.5)	1 (1.1)
Alanine aminotransferase increased Subject ID#: (b) (6)	3 (2.3)	3 (1.7)	0	
Gamma-glutamyl transferase increased Subject ID#: (b) (6)	2 (1.5)	2 (1.1)	0	
Hepatic enzyme increased Subject ID#: (b) (6)	2 (1.5)	2 (1.1)	0	
Aspartate aminotransferase increased Subject ID# (b) (6)	1 (0.8)	1 (0.6)	0	
Transaminases increased Semaglutide Subject ID#: (b) (6) also reported as SAE; Placebo Subject ID# (b) (6), also reported as SAE	1 (0.8)	1 (0.6)	1 (1.5)	1 (1.1)
Hepatobiliary disorders	3 (2.3)	4 (2.2)	0	
Hepatic function abnormal Subject ID#: (b) (6) Also reported as SAE	1 (0.8)	1 (0.6)	0	
Hepatic lesion Subject ID# (b) (6)	1 (0.8)	1 (0.6)	0	
Hepatic steatosis Subject ID#: (b) (6)	1 (0.8)	1 (0.6)	0	
Non-alcoholic steatohepatitis Subject ID# (b) (6)	1 (0.8)	1 (0.6)	0	

Source: STEP TEENS CSR, Table 12-11; 14.3.1.45

Medical Officer Comment: Liver-related AEs were not evenly distributed between treatment groups, as more AEs were reported with semaglutide than with placebo.

The following table briefly summarizes the reported hepatic AEs in the Investigations SOC.

Table 44: Brief Narratives for Hepatic Adverse Events under Investigations SOC, Safety Population

Subject ID/Age/Sex/BMI	Reported Adverse Event/ Lab Value	Trial Day of Onset	Seriousness/ Severity/ Related AEs	Action/ Outcome	Medical history/ Baseline (Week 0) Labs
(b) (6) / 16/F/42.9	ALT increased/ 29 U/L	Day 197	Non-serious/ Mild/Abdominal pain	Dose not changed/Recovered	ALT 23 U/L
(b) (6) / 15/F/37.5	ALT increased 90 U/L	Day 1	Non-serious/ Mild/HbA1c increased (Day1)	Not provided/ Recovered	Pre-diabetes/ALT 90 U/L
(b) (6) / 13/F/31.9	ALT increased/ 127 U/L AST increased 166 U/L GGT increased 98 U/L	Day 196	Non-serious/ Moderate/ Gastritis (Day 193) Cholelithiasis (Day 251)	Dose not changed/ Recovered	Hypothyroidism/ ALT 45 U/L AST 25 U/L GGT 41 U/L
(b) (6) / 16/F/60.0	GGT increased/ 79 U/L	Day 478	Non-serios/Mild	Dose not changed/ Not recovered	Hepatic steatosis Pancreatic steatosis/ GGT 98 U/L
(b) (6) / 13/F/45.6	Hepatic enzymes increased/ ALT 50 U/L AST 35 U/L	Day 1	Non-serious/Mild/ Nausea, vomiting, abdominal pain upper(Day 2)	Dose not changed/ Recovered	ALT 50 U/L AST 35 U/L
(b) (6) / 14/F/30.5	Hepatic enzymes increased/ ALT 90 U/L AST 30 U/L GGT 21 U/L	Day 1	Non-serious/Moderate/ Gastroenteritis (Day -77) Cholelithiasis, Acute cholecystitis (Day 241)	Not provided/ Recovered	Hepatic enzymes elevated, Impaired fasting glucose, PCOS/ ALT 90 U/L AST 30 U/L GGT 21 U/L
(b) (6) / 16/F/41.0	Transaminases increased ALT 62 U/L GGT 95 U/L	Day 197	Serious/Mild/ Acute viral hepatitis (not reported as AE)	Unlikely/Temporary interruption of trial product/ Recovered	Insulin resistance, NAFLD, Thyroiditis/ ALT 35 U/L GGT 32 U/L
Placebo (b) (6) / 16/F/40.8	Transaminases increased ALT 98 U/L AST 98 U/L GGT 73 U/L	Day 472	Serious/Mild	Probable/NA/ Not recovered	NAFLD, Hypercholesterolemia Hyperuricemia/ ALT 52 U/L AST 89 U/L GGT 54 U/L

Source: STEP TEENS CSR Table 12-12; Table 14.3.1.45

Medical Officer Comment: In STEP TEENS, there were 4 subjects on semaglutide versus 0 subjects on placebo with elevated ALT (including both central and local laboratory values)

that were at least ≥5XULN. Three of the 4 subjects on semaglutide had gallstones diagnosed at some point during the study, which may have been a confounding factor.

Additionally on October 2021, the Division of Pharmacovigilance investigated for the association of drug induced liver injury (DILI) with the GLP-1 RA class. Overall, the review did not identify information to support a direct mechanism for liver injury with the GLP-1 RA drug class or any individual GLP-1 RA drug. However, rare idiosyncratic reactions have been reported for liraglutide and dulaglutide and are labeled in the post marketing section.

This medical officer recommends describing liver enzyme elevations in the semaglutide label to alert health care providers of the possibility of its occurrence with semaglutide treatment.

8.5.6 Psychiatric Adverse Events Including Suicidality

Suicidality and depression are safety issues of concern for all the centrally acting obesity drugs. For this trial, subjects with a history of major depressive disorder, suicidal attempt/ ideation, or other severe psychiatric disorders were excluded, and mental health well-being questionnaires, the PHQ-9 and C-SSRS, were administered during study.

The following table summarizes AEs related to psychiatric disorders identified by a pre-defined MedDRA search. The proportion and rate of subjects reporting AEs related to psychiatric disorders was lower in the semaglutide group than the placebo group. The events in both groups were distributed across a broad range of preferred terms.

Table 45: Psychiatric Disorders Adverse Events, On-Treatment, Safety Population

	Semaglutide		Placebo	
Number of total subjects	133		67	
Patient years of exposure	181.8		90.4	
	n(%)	Event (rate)	n(%)	Event (rate)
Number of subjects with psychiatric disorders adverse events	9 (6.8)	12 (6.6)	10 (14.9)	12 (13.3)
Psychiatric disorders	9 (6.8)	12 (6.6)	10 (14.9)	12 (13.3)
Anxiety	5 (3.8)	5 (2.8)	1 (2.5)	1 (1.1)
Depression	2 (1.5)	2 (1.1)	0	
Insomnia	2 (1.5)	2 (1.1)	1(1.5)	1 (1.1)
Adjustment disorder with depressed mood	1 (0.8)	1 (0.6)	0	
Affective disorder	1 (0.8)	1 (0.6)	0	
Depressed mood	1 (0.8)	1 (0.6)	2 (3.0)	2 (2.2)
Aggression	0		1 (1.5)	1 (1.1)

	Semaglutide		Placebo	
Behavior disorder	0		1 (1.5)	1 (1.1)
Enuresis	0		1 (1.5)	1 (1.1)
Intentional self-injury	0		1 (1.5)	1 (1.1)
Mental disorder	0		1 (1.5)	1 (1.1)
Persistent depressive disorder	0		1 (1.5)	1 (1.1)
Sleep disorder	0		1 (1.5)	1 (1.1)
Suicidal ideation	0		1 (1.5)	1 (1.1)

Source: STEP TEENS CSR, Table 12-4; Table 14.3.1.61

Medical Officer Comment: This medical officer combined the preferred terms depression, depressed mood, and persistent depressive disorder as well as combined the terms insomnia and sleep disorder to better understand the frequency of closely related AEs. The following table summarizes the new results.

Table 46: Some Combined Psychiatric Adverse Events, On Treatment, Safety Population

	Semaglutide	Placebo
Number of total subjects	133	67
	n (%)	n (%)
Number of subjects with psychiatric disorders adverse events	9 (6.8)	10 (14.9)
Psychiatric disorders	9 (6.8)	10 (14.9)
Anxiety	5 (3.8)	1 (2.5)
Depression/depressed mood/persistent depressive disorder	2 (1.5)	3 (4.5)
Insomnia/ sleep disorder	2 (1.5)	2 (3.0)
Adjustment disorder with depressed mood	1 (0.8)	0
Affective disorder	1 (0.8)	0
Aggression	0	1 (1.5)
Behavior disorder	0	1 (1.5)
Enuresis	0	1 (1.5)
Intentional self-injury	0	1 (1.5)
Mental disorder	0	1 (1.5)
Suicidal ideation	0	1 (1.5)

Source: Reviewer Analysis

Medical Officer Comment: Overall, in this clinical trial, there was no imbalance of psychiatric adverse events against semaglutide with the exception of "anxiety" which will be described in the label.

Most of the events, in both treatment groups, were nonserious and mild to moderate in severity. One event, mental disorder, in the placebo group led to permanent discontinuation of treatment. One event of suicidal ideation in the placebo group was reported as non-serious, moderate, unlikely related to treatment, and recovered.

One SAE of depression (Subject ID# (b) (6)) was reported in the semaglutide group. This event was reported as severe, possibly related to trial product, and not recovered. The following is a summary of the serious case of depression:

Subject ID# (b) (6): This is an 18 y.o. female, in the semaglutide group (from (b) (6) to (b) (6)), who had an SAE of depression on (b) (6) and was admitted to the hospital. The subject received treatment medications: ABILIFY(ARIPIPRAZOLE), NESTROLAN(TRAZODONE HYDROCHLORIDE), SERLAIN SERTRALINE, ETUMINE(CLOTIAPINE), FOLAVIT(FOLIC ACID. She denied history of previous diagnosis of depression, anxiety, suicidal ideation, or hospitalizations for psychiatric disorder. The outcome of the event, depression, was not recovered at the end of the trial.

PHQ-9
Mental health was prospectively monitored in this adolescent trial using questionnaires recommended by FDA for suicidality (Columbia-Suicide Severity Rating Scale, C-SSRS) and mood (Patient Health Questionnaire-9, PHQ-9). These questionnaires were completed at V1, V8, V20, and V30.

For the PHQ-9, total score ranges from 0 to 27. Total scores of 0–4 represent no to minimal depression, 5–9 represent mild depression, 10–14 represent moderate depression, 15–19 represent moderately severe depression, and 20–27 represent severe depression. Major depression is diagnosed if 5 or more of the 9 criteria have been present at least “more than half the days” in the past 2 weeks and one of the symptoms is depressed mood or anhedonia. The symptom criterion in Question 9, “thoughts that you would be better off dead or hurting yourself in some way,” is a single screening question on suicide risk. A patient who answers yes to Question 9 needs further assessment for suicide risk.

At Week 0 (Baseline), there was a similar proportion of subjects in the PHQ-9 score categories corresponding to no to minimal, mild, moderate, moderately severe, and severe depression. At Week 68, most subjects remained within the overall score categories that do not indicate depression or increased suicidality risk.

Table 47: PHQ-9 Week 0 and Week 68 Scores, Safety Population

	Semaglutide N 133 n (%)	Placebo N 67 n (%)
Visit 8 (Week 0), n	133 (100)	67 (100)
Total Score		
0-4	103 (77.4)	49 (73.1)
5-9	25 (18.8)	13 (19.4)

	Semaglutide N=133 n (%)	Placebo N=67 n (%)
10-14	4 (3.0)	5 (7.5)
15-19	1 (0.8)	0
>=20	0	0
Visit 30 (Week 68), n	130 (100)	62 (100)
Total Score		
0-4	100 (76.9)	43 (69.4)
5-9	23 (17.7)	14 (22.6)
10-14	5 (3.8)	4 (6.5)
15-19	2 (1.5)	1 (1.6)
>=20	0	0

Source: STEP TEENS CSR, Table 14.3.6.16

Table 48: PHQ-9 Question 9 Responses, Safety Population

	Semaglutide N=133 n (%)	Placebo N=67 n (%)
Question 9: Thoughts that you would be better off dead or of hurting yourself in some way		
Visit 8 (Week 0), n	133 (100)	67 (100)
Not at all	131 (98.5)	62 (92.5)
Several days	1 (0.8)	4 (6.0)
More than half the days	0	1 (1.5)
Nearly every day	1 (0.8)	0
Visit 20 (Week 28), n	132 (100)	66 (100)
Not at all	131 (99.2)	62 (93.9)
Several days	1 (0.8)	2 (3.0)
More than half the days	0	1 (1.5)
Nearly every day	0	1 (1.5)
Visit 30 (Week 68), n	130 (100)	62 (100)
Not at all	128 (98.5)	58 (93.5)
Several days	2 (1.5)	2 (3.2)
More than half the days	0	1 (1.6)
Nearly every day	0	1 (1.6)

Source: STEP TEENS CSR, Table 14.3.6.16

Medical Officer Comment: In regards to Question 9, there did not seem to be an increased suicidality risk as measured by this question in the semaglutide group compared to placebo.

C-SSRS

The C-SSRS was completed at V1, V8, V20, and V30. The C-SSRS is a detailed questionnaire assessing both suicidal behavior and suicidal ideation. Subjects reporting active suicidal ideation on the C-SSRS at screening and randomization were excluded from the trial. The lifetime C-SSRS assessment identified a total of 4 (3.0%) subjects with lifetime suicidal behavior and/or ideation in the semaglutide group and 7 (10.4%) subjects on placebo. At Week 28, there were no subjects in the semaglutide group and 2 patients (3.1%) in the placebo group who had reported suicidal ideation or suicidal behavior. At Week 68, there were no subjects in the semaglutide group and 3 (4.8%) subjects in the placebo group who had reported suicidal ideation or suicidal behavior.

Table 49: Summary of C-SSRS, Proportion of Subjects with Suicidal Ideation and/or Behavior, Safety Population

	Semaglutide N=133 n (%)	Placebo N=67 n (%)
Lifetime Assessment (Baseline)		
Number of subjects answering the C-SSRS	133	67
Subjects with suicidal ideation and/or behavior	4 (3.0)	7 (10.4)
Subjects with suicidal ideation	2 (50.0)	4 (57.1)
Subjects with suicidal behavior	2 (50.0)	3 (42.9)
Visit 20 (Week 28)		
Number of subjects answering C-SSRS	132	65
Subjects with suicidal ideation and/or behavior	0	2 (3.1)
Subjects with suicidal ideation	0	2 (100)
Subjects with suicidal behavior	0	0
End of treatment	130	62
Subjects with suicidal ideation and/or behavior	0	3 (4.8)
Subjects with suicidal ideation	0	2 (66.7)
Subjects with suicidal behavior	0	2 (66.7)

Source: STEP TEENS CSR, Table 14.3.6.14

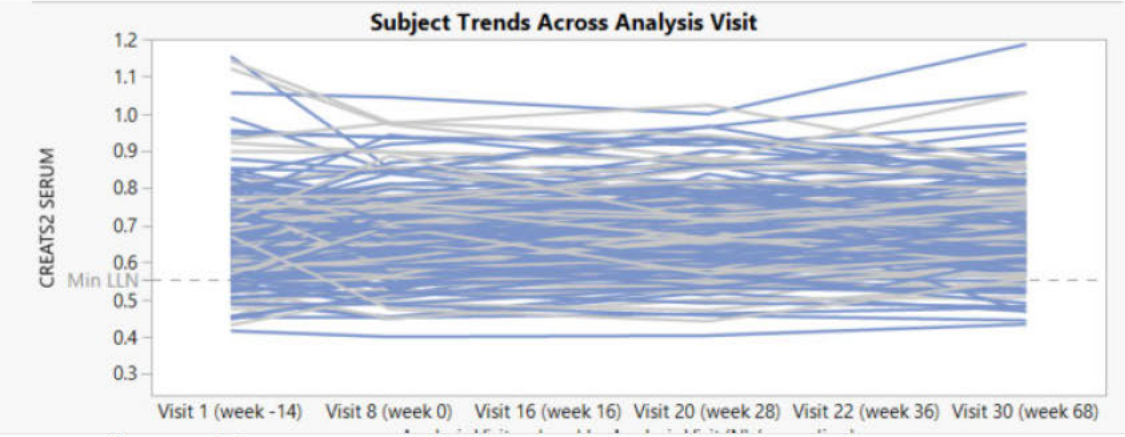
8.5.7 Renal Events and Related Laboratory Values

Acute kidney injury is listed as in the Warnings and Precautions section of the semaglutide labelling due to post-marketing reports. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea leading to volume depletion.

No cases of acute renal failure were reported during the study. One subject (Subject ID# (b) (6)) in the semaglutide group reported an episode of mild hematuria from which he recovered.

There were no AEs related to abnormal renal laboratory tests. Creatinine levels were similar between the two treatment groups during the study.

Figure 28: Creatinine (mg/dL), Subject Trends Across Visits, Safety Population



Source: Reviewer Analysis

8.5.8 Hypoglycemia

In this trial, only subjects with type 2 diabetes mellitus (DM2) or those diagnosed during the trial with DM2 were provided with a diabetes diary to record self-measured plasma glucose and hypoglycemic events. Hypoglycemic episodes were classified according to International Society for Pediatric and Adolescent Diabetes (ISPAD)/ American Diabetes Association's (ADA) definition of severe hypoglycemia, as well as the Novo Nordisk classification of hypoglycemia.

In the semaglutide group, there were 5 subjects with DM2. Two hypoglycemic events were reported in 2 subjects. Neither event was reported as severe. One event was symptomatic however the blood glucose (BG) level was not reported, and the second event was asymptomatic with a BG level ≤70 mg/dL.

In the placebo group, there were 3 subjects with DM2. Four hypoglycemic events were reported in 3 subjects. One of the events was reported as a BG confirmed symptomatic event (BG level <56 mg/dL). Two of the events were symptomatic with BG levels ≤70 mg/dL. One event was symptomatic with a BG level >70 mg/dL.
Medical Officer Comment: The small number of subjects with diabetes enrolled in this trial makes it difficult to draw definitive conclusions, but the reported data do not suggest an imbalance in hypoglycemic events.

8.5.9 Injection Site Reactions

AEs related to injection site reactions were identified by a pre-defined MedDRA search and evaluated based on the on-treatment period. The following table summarizes the AEs related to injection site reactions.

Table 50: Summary of Adverse Events Related to Injection Site Reactions, On Treatment, Safety Population

	Semaglutide		Placebo	
Number of total subjects	133		67	
Patient years of exposure	181.8		90.4	
	N(%)	Event (rate)	N(%)	Event (rate)
Number of subjects with injection site related adverse events	4 (3.0)	5 (2.8)	3 (4.5)	8 (8.9)
General disorders and administration site conditions	4 (3.0)	5 (2.8)	3 (4.5)	8 (8.9)
Injection site hematoma	1 (0.8)	1 (0.6)	0	
Injection site induration	1 (0.8)	1 (0.6)	0	
Injection site nodule	1 (0.8)	1 (0.6)	0	
Injection site pain	1 (0.8)	1 (0.6)	1 (1.5)	3 (3.3)
Injection site pruritus	1 (0.8)	1 (0.6)	2 (3.0)	2 (2.2)
Injectate site erythema	0		1 (1.5)	1 (1.1)
Injection site urticaria	0		1 (1.5)	1 (1.1)
Puncture site pain	0		1 (1.5)	1 (1.1)

Source: STEP TEENS CSR, Table 12-3; Table 14.3.1.39

Medical Officer Comment: The proportion of subjects reporting AEs related to injection site reaction was comparable across both treatment groups.

8.5.10 Hypersensitivity Reactions

Anaphylaxis and angioedema have been reported with semaglutide and other GLP-1 receptor agonists. The current semaglutide label lists these AEs in the Warnings and Precautions section under Hypersensitivity. To investigate whether any anaphylaxis events occurred during the trial, this medical officer conducted an analysis with an algorithmic Anaphylactic Standardized MedDRA Query (SMQ) that resulted in 3 subjects who had 8 events on the semaglutide arm compared to none on placebo. This medical officer then drilled down on the 3 flagged subjects to understand more about the events. The following table summarizes the subjects and the events.

Table 51: Anaphylaxis SMQ: Subject Drill Down, Safety Population

Subject ID#/ Treatment Arm	Preferred Term/ (Number of Reports)	Reported Term	Date of event	Adverse Event Severity	Outcome
# (b) (6) Semaglutide	Hypotension (1)	Low blood pressure	(b) (6)	Mild	Not recovered
	Cough (1)	Tickling cough		Moderate	Recovered
# (b) (6) Semaglutide	Rash (1)	Rash Back and butt		Mild	Recovered
	Cough (3)	Pain in throat from cough/ Cough/ Cough		Mild	Recovered
# (b) (6) Semaglutide	Dyspnea (1)	Shortness of breath		Mild	Recovered
	Urticaria (1)	Hives on left and right forearms		Mild	Recovered

Source: Reviewer analysis of adae datasets with MAED software

Medical Officer Comment: On further review, the AEs that triggered the anaphylaxis SMQ were not actual anaphylactic events as the flagged AEs occurred separately in time and were not related to a single event. Thus, in this study there were no events of anaphylaxis.

Adverse events under the Skin and Subcutaneous Tissue Disorders were commonly reported during the study. Approximately 23 (17.3%) subjects on semaglutide and 6 (9.0%) of subjects on placebo reported an AE that mapped to this SOC. Considering that PTs under this SOC could also be related to hypersensitivity/allergic reactions, this medical officer analyzed the data using an FDA Medical Query with "Rash, narrow" grouping. The following table was obtained.

Table 52: FDA Medical Query, Rash (Narrow), Safety Population

FDA Medical Query	Semaglutide N=133	Placebo N=67	Risk Difference for Semaglutide over Placebo
Rash	11* (8.3%)	0	0.08 (0.04, 0.13)
Rash*	5 (3.8%)	0	0.04 (0.01, 0.07)
Urticaria	4 (3.0%)	0	0.03 (0, 0.06)
Dermatitis contact	1 (0.8%)	0	0.01 (-0.01, 0.02)
Skin exfoliation	1 (0.8%)	0	0.01 (-0.01, 0.02)
Toxic skin eruption	1 (0.8%)	0	0.01 (-0.01, 0.02)

Source: Reviewer analysis of adae datasets and JMP Clinical software *One subject with rash was not counted by the sponsor because of discontinuation due to protocol violation.

Medical Officer Comment: The "Rash, Narrow" FDA Medical Query resulted in approximately 8.3% of subjects on semaglutide compared to none on placebo. Additionally, rash and urticaria as separate PTs were reported at higher frequencies in the semaglutide group compared to no subjects on placebo.

The following table details the rash and urticaria events identified with the FDA Medical Query.

Table 53: Subjects with Adverse Events of Rash and Urticaria

Subject ID#/ Treatment Arm	Preferred Term/ (Number of Reports)	Reported Term	Study Start Day	Adverse Event Severity	Action Taken/ Outcome of Adverse Event	End of Treatment Status
# (b) (6) / Semaglutide	Rash (1)	Skin Rash	Day 523	Mild	Not applicable/ Recovered	Completed
# (b) (6) / Semaglutide	Rash(1)	Rash back and butt	Day 364	Mild	Dose not changed/ Recovered	Completed
# (b) (6) / Semaglutide	Rash (2)	Rash on skin of back	Day 52	Mild	Dose not changed/ Recovering	Discontinued treatment due to rash
		Worsening of rash on skin of back	Day 145	Moderate	Permanent treatment discontinuation /Recovering	
# (b) (6) / Semaglutide	Rash (1)	Rash	Day 412	Mild	Not applicable/ Recovered	Discontinued treatment due to protocol violation
# (b) (6) / Semaglutide	Rash (1)	Rash	Day 27	Mild	Dose not changed/ Recovered	Completed
# (b) (6) / Semaglutide	Urticaria (1)	Urticaria	Day 147	Moderate	Recovered	Completed
# (b) (6) / Semaglutide	Urticaria (1)	Urticaria	Day 367	Mild	Recovered	Completed
# (b) (6) / Semaglutide	Urticaria (1)	Urticaria lower legs after shower	Day 334	Mild	Not Recovered	Completed
# (b) (6) / Semaglutide	Urticaria (1)	Hives on left and right forearms	Day 72	Mild	Recovered	Completed

Source: Reviewer analysis; adae dataset and JMP software

Medical Officer Comment: In this subject-level review, rash, urticaria and other skin-related AEs occurred over a range of time, from Study Day 27 to Day 523. It is not possible to conclude with definitive certainty if semaglutide caused a delayed immunological response that led to

rash or urticaria presentation. However, given that the frequency of such events occurred more often in the semaglutide group (8.3%) when compared to placebo (0%), the incidence of rash and urticaria should be described in the drug label.

8.5.11 Retinal Disorders

No events of diabetic retinopathy were reported during the trial. One event of visual impairment (Subject ID# (b) (6)) was reported in the semaglutide group. The event was reported as "black dots for the eyes" and co-reported with AEs of alopecia, iron, and B1 deficiencies. Study drug dose was not changed, and the event was reported as recovered.

8.6 Safety Analyses by Demographic Subgroups

APPEARS THIS WAY ON ORIGINAL

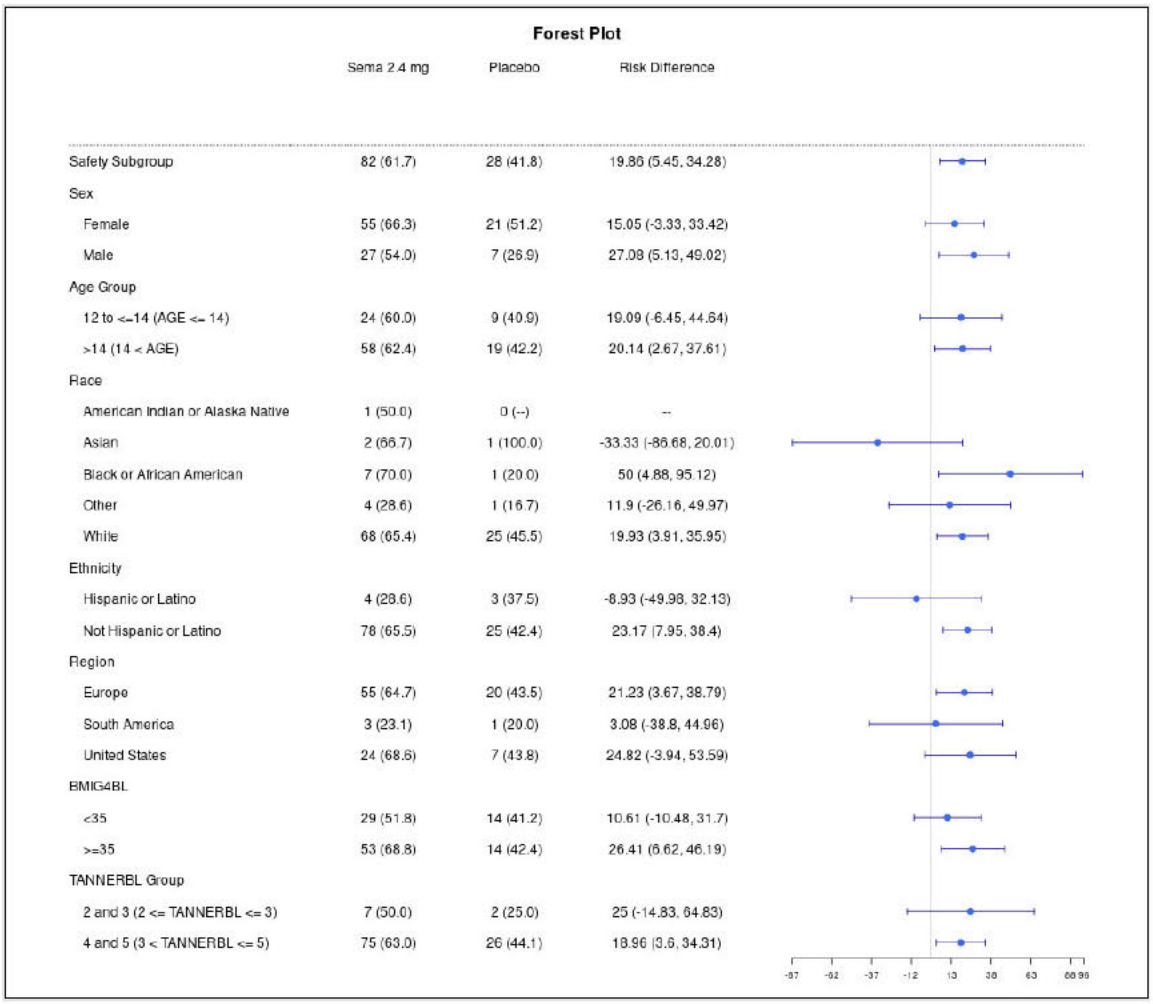
Gastrointestinal AEs were investigated for differences by demographic subgroups including sex, age group (12 to ≤14 years and 15 to ≤17 years), race, ethnicity, region, and BMI (<35 kg/m2 and ≥35 kg/m2).

Table 54: Gastrointestinal Adverse Events Demographic Subgroup Analysis by Treatment Arm, Safety Population

	Semaglutide		Placebo		Risk Difference
Subgroup	n (%)	N	n (%)	N	RD (95% CI)
Safety Subgroup	82 (61.7)	133	28 (41.8)	67	19.86 (5.45, 34.28)
Sex					
Female	55 (66.3)	83	21 (51.2)	41	15.05 (-3.33, 33.42)
Male	27 (54.0)	50	7 (26.9)	26	27.08 (5.13, 49.02)
Age Group					
12 to ≤14	24 (60.0)	40	9 (40.9)	22	19.09 (-6.45, 44.64)
15 to ≤17	58 (62.4)	93	19 (42.2)	45	20.14 (2.67, 37.61)
Race					
American Indian or Alaska Native	1 (50.0)	2	0 (--)	0	--
Asian	2 (66.7)	3	1 (100.0)	1	-33.33 (-86.68, 20.01)
Black or African American	7 (70.0)	10	1 (20.0)	5	50 (4.88, 95.12)
Other	4 (28.6)	14	1 (16.7)	6	11.9 (-26.16, 49.97)
White	68 (65.4)	104	25 (45.5)	55	19.93 (3.91, 35.95)
Ethnicity					
Hispanic or Latino	4 (28.6)	14	3 (37.5)	8	-8.93 (-49.98, 32.13)
Not Hispanic or Latino	78 (65.5)	119	25 (42.4)	59	23.17 (7.95, 38.4)
Region					
Europe	55 (64.7)	85	20 (43.5)	46	21.23 (3.67, 38.79)
South America	3 (23.1)	13	1 (20.0)	5	3.08 (-38.8, 44.96)
United States	24 (68.6)	35	7 (43.8)	16	24.82 (-3.94, 53.59)
BMI					
<35	29 (51.8)	56	14 (41.2)	34	10.61 (-10.48, 31.7)
>=35	53 (68.8)	77	14 (42.4)	33	26.41 (6.62, 46.19)
Tanner Group					
2 and 3	7 (50.0)	14	2 (25.0)	8	25 (-14.83, 64.83)
4 and 5	75 (63.0)	119	26 (44.1)	59	18.96 (3.6, 34.31)

Source: Reviewer Analysis

Figure 29: Gastrointestinal Adverse Events by Demographic Subgroup, Forest Plot, On-Treatment Safety Population



Source: Reviewer Analysis

Medical Officer Comment: Although there was a greater likelihood of having a GI AE for subjects on semaglutide as compared to placebo, the trial population does not show a markedly different GI AE profile when divided into demographic subgroups.

8.7 Specific Safety Studies/Clinical Trials

Not applicable.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

See discussion of neoplasms under Significant Adverse Events.

8.8.2 Human Reproduction and Pregnancy

One pregnancy occurred in the semaglutide group and none in the placebo group. The study drug was discontinued due to the pregnancy.

Subject ID# (b) (6): This was a 17 y.o. female from the Russian Federation who was treated with semaglutide from (b) (6) to (b) (6). On (b) (6), the subject had first day of last menstrual period. Product was discontinued on (b) (6), 7 weeks and 3 days after first day of last menstrual period. At gestational week 40 + 0 days (Full-term), the pregnancy resulted in a spontaneous vaginal birth of a live infant. The subject had non-serious events of 'rupture of the perineum in labor of 1 degree', 'hematometra after childbirth'. The subject had also a non-serious event of 'mild myopia'.

Regarding the infant: sex was female; weight and length at delivery were 2820 g (6.22 pounds) and 50.0 cm (19.69 inches), approximately 16th percentile for weight and 68th percentile for length[31]. A general Apgar score of 8/9 points was reported. At delivery, the newborn infant was not diagnosed with health problems or any congenital anomalies. However, the newborn infant was diagnosed with health problems in the period from birth to 1 month of age. On (b) (6) the newborn infant had onset of the events ''Intrauterine growth retardation, asymmetric variant' + 'Drug exposure in utero (Drug exposure in utero).

Medical Officer Comment*: *Wegovy labeling contains a warning that it may cause fetal harm and advises against use in pregnancy (Sections 8.1 and 8.3). A Pregnancy Exposure Registry exists to further monitor outcomes in pregnant patients exposed to semaglutide. At this time, no additional changes to labeling are warranted.

8.8.3 Pediatrics and Assessment of Effects on Growth

The Division of Diabetes, Lipids and Obesity (DDLO) consulted the Division of Pediatrics and Maternal Health (DPMH) to provide an assessment of the results of the STEP TEENS study in regard to evaluation of growth and sexual maturation (Tanner staging) in pubertal adolescents. The following is a summary of DPMH's evaluation and conclusion; please see DPMH's review for further details.

[31] Infant Growth Chart Calculator: Length Age WHO 0-2 Year (infantchart.com)

Changes in pubertal status:
120 (90%) of 134 trial patients randomized to treatment with semaglutide and 59 (88%) of 67 trial patients randomized to placebo were at Tanner stage 4 or 5 at baseline. Of the remaining trial patients, 14 were Tanner stage 3 and 8 were Tanner stage 2 at baseline. At the week 68 visit, approximately 50% of trial patients who were Tanner stage 4 at baseline were assessed to be at Tanner stage 5. At the week 68 visit, 12 (92%) of the 13 trial patients who were Tanner stage 3 at baseline were either Tanner stage 4 or 5. Of the 8 trial patients who were at Tanner stage 2 at baseline, 4 (50%) had progressed to Tanner stages 4 or 5 at the week 68 assessment. There was no difference noted in the proportion of trial patients who progressed from Tanner stages 2 – 4 at baseline to Tanner stage 5 at week 68 between trial patients randomized to semaglutide compared with placebo.

Changes in bone age:
At baseline, 103 (51%) trial patients had full epiphyseal closure on x-rays of the left hand. In addition, another 72 (36%) had partial epiphyseal closure at baseline. By the week 68 evaluation, 49 (50%) of the 98 trial patients without full epiphyseal closure at baseline had full epiphyseal closure on repeat x-rays of the left hand. Thirty-six (55%) of the 65 trial patients treated with semaglutide without full epiphyseal closure at baseline advanced to full closure and 13 (40%) of the 33 trial patients randomized to placebo without full epiphyseal closure at baseline advanced to full closure at the 68 week assessment. Comparison of chronological age to bone age at baseline in trial patients reveals that the mean bone age was 1.1 years higher than the mean chronological age (16.9 years vs. 15.8 years) in trial patients randomized to semaglutide and 1.2 years higher (16.8 years vs. 15.6 years) in trial patients randomized to placebo. At the 68 week measurement, the bone age and chronological age both increased by 1.3 years in trial patients treated with Wegovy while the bone age increased by 1.5 years and the chronological age increased by 1.3 years in trial patients randomized to placebo.

Changes in height:
At baseline, the height SDS (e.g. Z-score) score in trial patients randomized to semaglutide was 0.74 and those randomized to placebo was 0.61. The mean height Z score remained largely unchanged at 0.69 and 0.59 at 68 weeks of treatment in the semaglutide and placebo trial patients, respectively.

In conclusion, trial results suggest that the study population either largely completed linear growth upon trial entry or had deceleration in linear growth during the trial. The study population consisted of trial patients with a mean age of 15.4 years and the majority (89%) of trial patients were at either Tanner stage 4 or 5 at baseline, maturational stages at which linear growth either slows or stops altogether in adolescents. This was confirmed by the bone age assessment which showed that only 26 (13%) of the 201 trial patients did not have

either partial or full epiphyseal closure on hand x-ray at baseline and therefore still had the potential for continued significant linear growth at trial enrollment.

As a result, the ability to assess adverse effects of semaglutide on linear growth was limited to the 13% of trial patients who retained the potential for continued linear growth during the 68-week trial period. The assessments of changes in height in the limited number of study patients with remaining growth potential appeared acceptable during the trial, and the mean change in height Z-scores did not differ (-0.08 vs. -0.05) at the 68- week measurement between trial patients treated with Wegovy vs. placebo, respectively.

The STEP TEENS study protocol included adequate provisions for measuring height and assessing both pubertal maturation and bone age. The provisions included use of standardized equipment (e.g., stadiometers) to measure height and trained personnel to assess pubertal maturation and interpret hand x-rays for bone age and epiphyseal closure. However, the integrity and accuracy of the collected growth data relies on the fidelity by which the study staff used the standardized equipment, followed procedures as outlined in the trial protocol, and captured the results accurately in the CRFs.

The trial design minimized the likelihood of bias from errors due to inaccuracy in measurement and/or recording of height, and the methods for collecting growth parameters appeared adequate at all but three trial sites. Sensitivity analyses conducted by the Division to account for possible measurement errors in 6 patients due to incorrectly installed stadiometers did not change the overall results. However, the ability to draw firm conclusions about potential drug-related effects of Wegovy on linear growth are limited by a trial population that had largely completed or nearly completed their linear growth upon trial entry and a recruitment population spanning multiple study sites limiting the effect of measurement/data integrity issues from any one study site affecting the overall assessment.

8.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable; semaglutide is not a drug of abuse.

8.9 Safety in the Postmarket Setting

8.9.1 Safety Concerns Identified Through Postmarket Experience

Semaglutide has a well-known safety profile in adults with type 2 diabetes and obesity. Under Section 6.3 Postmarketing Experience, the current Wegovy label lists acute pancreatitis and necrotizing pancreatitis as well as hypersensitivity disorders such as anaphylaxis, angioedema, rash, and urticaria. Given the general similarity between the adult and pediatric safety profiles observed in clinical trials, it is expected that postmarketing safety in the adolescent population

will be consistent with the known safety profile in adults.

8.10 Integrated Assessment of Safety

Semaglutide has a well-characterized safety profile in the type 2 diabetes and obesity adult populations, having been first approved for the US market in 2017. Known safety concerns with GLP-1 receptor agonists and semaglutide include acute gallbladder disease, acute pancreatitis, acute kidney injury, heart rate increases, and suicidal behavior and ideation. Common adverse events include gastrointestinal events such as nausea, vomiting, abdominal pain, and diarrhea.

In general, the safety profile observed in this trial in obese adolescents was consistent with the known safety profile established in adults. Several new safety signals (LFT elevation, rash, urticaria) were observed in pediatrics, and several known adverse reactions (cholelithiasis, cholecystitis,) were observed with greater frequency in the pediatric population compared to adults. Adverse events with semaglutide in the adolescent population will be described in the drug label.

- Deaths/SAEs

There were no deaths in the study. The most frequently reported SAEs were related to hepatobiliary disorders 4 (3.0%) subjects compared to none on placebo. The second most common SAEs were related to infections and infestation with four (3.0%) subjects on semaglutide compared to no subjects on placebo. The third most common SAEs were in gastrointestinal disorders with 3 (2.3%) subjects on semaglutide and 1 (1.5%) of subject on placebo.

- AEs leading to discontinuations

There were 6 (4.5%) subjects on semaglutide and 3 (4.5%) subjects on placebo who permanently discontinued study drug due to an adverse event. In the semaglutide group, most AEs leading to discontinuation were due to gastrointestinal disorders (abdominal discomfort, gastritis, and vomiting).

- Common adverse events

Gastrointestinal disorders, especially nausea and vomiting were the most commonly reported AEs in the semaglutide group and were reported at much higher rates than placebo. After AEs related to Infections, Nervous system disorders such as headache were reported in 22 (17%) of subjects on semaglutide and 11 (16%) of subjects on placebo.

- Gastrointestinal adverse events

Similar to adults, the most common adverse events on semaglutide were gastrointestinal disorders (62% vs 42%) such as nausea (42% vs.18%), diarrhea (22% vs. 19%), abdominal pain (15% vs. 6%) and vomiting (36% vs. 10%). Gastrointestinal adverse events were also the most common reasons (2.3% vs. 1.5%) for study drug discontinuation.

- Acute gallbladder disease

There were 5 (3.8%) subjects with 6 gallbladder-related events in the semaglutide group compared to none in the placebo group. Although gallbladder disease is already labeled, the adolescent population seems to have a higher frequency of these events than in the adult population (1.6%). The adolescent population's incidence of gallbladder disease will be described in the label.

- Acute pancreatitis

There were no cases of acute pancreatitis during the treatment period, but the change from baseline in amylase and lipase was greater in semaglutide-treated subjects compared to placebo-treated. GLP1-RA are associated with increases in amylase and lipase levels of unknown significance in the absence of other signs/symptoms of pancreatitis.

- Liver enzyme elevations

The proportion of subjects with AEs related to hepatic events was higher in the semaglutide group than in placebo; however, most of the events were non-serious, mild to moderate in severity, and subjects recovered. The majority of subjects were observed to have ALT < 3xULN (96% on semaglutide and 97% on placebo). However, a total of 4 subjects on semaglutide (with lab results from central and local labs) had ALT elevations ≥ 5XULN compared to none on placebo. Some increases in ALT and AST were associated with other confounding factors (such as gallstones).

- Heart rate increases

Similar to adults, mean heart rate increases of 3-4 beats/min were observed with subjects on semaglutide compared to placebo. An FDA Medical Query on Tachycardia showed that approximately 2.3% of subjects on semaglutide reported an AE compared to none on placebo. A shift table analysis showed that a greater proportion of subjects (54%) in the semaglutide group with an average baseline pulse had a maximum increase of at least 20 beats/min compared to placebo subjects (39%).

- Rash and urticaria

Approximately 23 (17.3%) subjects on semaglutide and 6 (9.0%) of subjects on placebo reported an AE that mapped to Skin and Subcutaneous Tissue SOC. Rash (3.0%) and urticaria (3.0%) were seen at higher frequency with semaglutide than with placebo (0%). One subject on semaglutide discontinued treatment due to rash. Currently rash is listed in Section 6.3 Post marketing Experience. The adolescent population's incidence of rash and urticaria will be described in the label.

- Hypotension

Hypotension was reported in 2.3% of WEGOVY-treated subjects versus none on placebo.

- Suicidality and depression

Suicidality and depression are safety concerns for all centrally acting obesity drugs. In this trial, there was no imbalance of events against semaglutide for psychiatric related AEs. Overall, there were 9 (6.8%) on semaglutide and 10 (14.9%) on placebo with AEs under psychiatric disorders. Approximately, 3 (2.3%) on semaglutide and 3 (4.5%) on placebo were reported to have depressed mood disorders and disturbances. Two (3.0%) subjects on placebo reported suicidal and self-injurious behaviors compared to none on semaglutide.

- Acute kidney failure

There were no cases of acute renal failure and no AEs related to abnormal renal laboratory tests. Creatinine levels were similar between the two treatment groups.

- Injection site reactions

Injection site AEs were similar between the two treatment groups with approximately 4 (3.0%) subjects on semaglutide and 3 (4.5%) subjects on placebo who reported events such as (injection site hematoma, induration, nodule, pain, pruritus, and erythema).

- Growth and development

The Division of Pediatrics and Maternal Health concluded that the assessments of changes in height in the limited number of subjects with remaining growth potential appeared acceptable during the trial, and the mean change in height Z-scores did not differ (-0.08 vs. -0.05) at the 68-week measurement between trial patients treated with semaglutide vs. placebo, respectively. Additionally, there was no difference noted in the proportion of subjects who progressed from Tanner stages 2 – 4 at baseline to Tanner stage 5 at week 68 between subjects randomized to semaglutide compared with placebo. At the 68-week measurement, the bone age and chronological age both increased by 1.3 years subjects treated with semaglutide while the bone age increased by 1.5 years and the chronological age increased by 1.3 years in trial patients randomized to placebo.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee was not convened for this supplement.

10. Labeling Recommendations

Prescription Drug Labeling

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI and the applicant's draft PI (see the table below). The PI was reviewed to ensure it meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner. Additionally, there were minor formatting changes for clarity. A summary of major changes is presented below.

Full Prescribing Information Sections[1]	**Rationale for Major Changes to the Finalized Prescribing Information (PI)[2] Compared to the Currently Approved PI and Applicant's Draft PI**

BOXED WARNING	None
1 INDICATIONS AND USAGE	(b) (4) [redacted]
2 DOSAGE AND ADMINISTRATION	Included table of BMIs at the 95th percentile by age (in half year increments) and sex instead of the applicant's proposed figure. Included 1.7 mg as an alternate maintenance dose in pediatric patients that do not tolerate 2.4 mg.
4 CONTRAINDICATIONS	None
5 WARNINGS AND PRECAUTIONS	Generally, clarified relevant patient populations for listed Warnings and Precautions • 5.3 (Acute Gallbladder Disease) Included framing statement regarding overall risk and increased risk in pediatric patients. Similar to adults, provided rates of cholelithiasis and cholecystitis. • 5.6 (Hypersensitivity Reactions) Revised language for consistency with the contraindication and provided a cross reference to Section 6.2. • 5.8 (Heart Rate Increases) Included framing statement regarding overall risk and increased risk in pediatric patients. Provided the incidence of heart rate increases in pediatric patients and provided a cross reference to Section 6.1.
6 ADVERSE REACTIONS	• Generally, clarified relevant patient populations for reported adverse reactions, created an adverse reactions table for the pediatric population, described the incidence of adverse reactions in the pediatric population under new adverse reactions subheadings, and added the incidence of pediatric adverse reactions to already existing adverse reactions subheadings. • Under Acute Gallbladder Disease, added the incidence of cholelithiasis and cholecystitis. • Under Increase in Heart Rate, added the proportion of pediatric patients with a maximum change in heart rate of 20 beats per minute or more.

	• Under Hypotension and Syncope, added the incidence of hypotension. • Under Gastrointestinal Adverse Reactions, added the incidence of nausea, vomiting, diarrhea, as well as listed other gastrointestinal related reactions. Added the incidence of patient discontinuations due to gastrointestinal disorders. • Added a new adverse reaction subheading of Hypersensitivity Reactions and added the incidence of pediatric patients with rash, and urticaria, and the incidence of allergic reactions in adults who developed anti-semaglutide antibodies versus those that did not develop antibodies. • Added the incidence of pediatric patients with amylase and lipase increase (which was similar to adults). • Added a new adverse reactions subheading of Liver Enzymes and added the incidence of ALT increase greater than 5x ULN.
7 DRUG INTERACTIONS	None
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.4 (Pediatric Use) Generally added that the safety and effectiveness of WEGOVY as an adjunct to diet and increased physical activity for chronic weight management was established in pediatric patients aged 12 years and older with a BMI > 95th percentile standardized for age and sex with the support of a clinical trial in that population. Listed adverse reactions where the pediatric population had a greater incidence, or a new adverse reaction as compared to the adult population. Added that there is insufficient data in the pediatric population with type 2 diabetes treated with WEGOVY for obesity to determine if there is an increased risk of hypoglycemia. 8.5 (Geriatric Use)- Updated for consistency with current labeling guidance for this section.
9 DRUG ABUSE AND DEPENDENCE	None
10 OVERDOSAGE	None
12 CLINICAL PHARMACOLOGY	Relocated immunogenicity data from (b) (4), updated per Immunogenicity guidance to include the percentage of

	patients who developed anti-semaglutide antibodies and the percentage that developed anti-semaglutide antibodies that cross-reacted with native GLP-1. Provided summary of hypersensitivity reactions that occurred in a higher percentage of WEGOVY-treated patients with anti-semaglutide antibodies and a cross reference to the data in Section 6.1.
13 NONCLINICAL TOXICOLOGY	None
14 CLINICAL STUDIES	Reorganized adult and pediatric clinical trial data, including section, table, and figure headings for clarity. For the pediatric efficacy data: • Added the percent of patients that received 1.7 mg as the maximum tolerated dose. • Revised demographic information to approximate the total treatment population, as appropriate. • (b) (4) . • (b) (4) . • Added ≥5%, 10%, and 15% responder analysis for BMI. • Revised table and figure footnotes to disclose relevant statistical analyses.
17 PATIENT COUNSELING INFORMATION	None
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	None

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended for this supplement.

12. Postmarketing Requirements and Commitments

This supplement fulfills PREA PMR 4081-1: Effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with obesity (Trial ID: NN9536-4451 [STEP TEENS]).

No new PMRs or PMC are recommended. A separate trial to investigate semaglutide in children with obesity 6-11 years of age is being conducted by the sponsor as a PMR under PREA.

13. Appendices

References

Included in the body of the review as footnotes.

Financial Disclosure

No investigators who participated in this trial had disclosable financial interests.

Covered Clinical Study (Name and/or Number): Study NN9536-4451 (STEP TEENS)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 142		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

JULIE K GOLDEN
12/22/2022 02:28:18 PM

IFFAT N CHOWDHURY
12/22/2022 02:42:50 PM

LAURA B HIGGINBOTHAM
12/22/2022 02:46:02 PM