CLINICAL REVIEW

Application Type	NDA
Application Number	206321
Priority or Standard	Standard
Submit Date	February 6, 2020
Received Date	February 6, 2020
PDUFA Goal Date	December 6, 2020
Division/Office	DDLO/OCHEN
Reviewer Name	Julie Golden
Review Completion Date	December 3, 2020
Established/Proper Name	liraglutide
Trade Name	Saxenda
Applicant	Novo Nordisk Inc
Dosage Form	Subcutaneous injection
Applicant Proposed Dosing Regimen	3 mg once daily
Applicant Proposed Indication/Population	SAXENDA is indicated as an adjunct to (b) (4) increased physical activity for chronic weight management in pediatric patients aged 12 years and older with • body weight above 60 kg (b) (4) and • an initial body mass index (BMI) corresponding to ≥30 kg/m^2 for adults (obese) by international cut-offs (Cole criteria)
Recommendation on Regulatory Action	Approve
Recommended Indication/Population	SAXENDA is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with: ▪ body weight above 60 kg and ▪ an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs (Cole criteria)

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
ATC	Anatomical Therapeutic Chemical classification
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
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

Liraglutide is a glucagon-like peptide 1 (GLP1) receptor agonist approved for chronic weight management in adults with obesity with and without type 2 diabetes (Saxenda, 3 mg daily). At the time of the original Saxenda approval in 2014 (NDA 206321), four pediatric PMR clinical trials were required:

- 2802-2: A clinical pharmacology study (Trial NN8022-3967) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive).

- 2802-3: A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).

- 2802-4: A clinical pharmacology study to assess pharmacokinetic and pharmacodynamics parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive).

- 2802-5: A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). The trial may not be initiated until results from the Saxenda adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

This supplement is intended to fulfill PMR 2802-3. This clinical review includes a summary of the safety and pharmacokinetics of 2802-2 and a full safety and efficacy review of 2802-3.

Liraglutide is also approved for the treatment of type 2 diabetes in adults and children and adolescents ages 10 and over, as well as to reduce the risk of major cardiovascular events in adults with type 2 diabetes and established cardiovascular disease (Victoza, NDA 22341). The pediatric indication was approved in June of 2019 and the trial fulfilled a written request. The dosages of Victoza are 0.6 mg (pediatric only), 1.2 mg, and 1.8 mg administered as a daily subcutaneous injection.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary endpoint was change in BMI SDS from baseline to week 56. A BMI SDS score of at least 0.20 has been suggested to be clinically meaningful.[1]

Statistical significance in this trial was met, with the estimated mean change in BMI SDS from baseline to week 56 of -0.23 in the liraglutide group and -0.00 in the placebo group and an estimated mean treatment difference (ETD) between groups of -0.22 (95% CI -0.37, -0.08), p=0.0022.

Despite some concerns about the BMI SDS primary endpoint given its ceiling effect in severely obese adolescents, mean changes across a variety of supportive endpoints, such as BMI, weight, and waist circumference, support the efficacy of liraglutide in the study population for the duration studied. Furthermore, missing data were reasonably low (particularly in the liraglutide group) and the primary analysis was supported by a number of sensitivity analyses, supporting the robustness of the estimated treatment effect.

There are some limitations to the efficacy evaluation. Cardiometabolic parameters that are expected to improve with weight loss (e.g., lipids, glycemic parameters, and blood pressure) were essentially unchanged. It should be noted that a lack of improvement in these parameters was also observed in the orlistat pediatric trial,[2] and might reflect the lack of metabolic decompensation in the adolescent population despite significant obesity.

Unsurprisingly, once liraglutide was discontinued, patients regained body weight. This phenomenon has been described in adults with this drug and others,[3] supporting the chronic nature of obesity treatment.

In the postmarket setting, the weight loss benefit of Saxenda in this population will likely be similar to that in the adult population but will depend – at least in part – on drug availability, patient willingness to take a daily injectable medication on a chronic basis, adherence to lifestyle changes, and labeling (e.g., the stopping rule). Furthermore, although not observed in this trial, cardiometabolic improvements that are expected with Saxenda in adult patients with obesity could potentially occur in the adolescent population to the extent there is significant metabolic derangement. It is possible that adolescent patients have not had the degree of metabolic decompensation due to their obesity that adults have. The treatment paradigm in

[1] Kelly AS, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med 2020; 382: 2117-28.
[2] Kehoe T, clinical review of NDA 20766 S-018, 12 Dec 2003
[3] See original clinical reviews for Saxenda (liraglutide, NDA 206321), Belviq (lorcaserin NDA 22529), and Xenical (orlistat NDA 20766)

adolescents is generally one of prevention (i.e., treat adolescent obesity in order to prevent future adverse health effects).

1.3. Benefit-Risk Assessment

Liraglutide has a well-characterized safety profile in adults in type 2 diabetes and obesity, and this trial did not identify new safety concerns. Mitigation of safety concerns can be addressed with labeling. In a population of adolescents with significant obesity, the benefits of the efficacy of liraglutide outweigh the potential risks.

There was one fatal adverse event in this trial, in the liraglutide group (1/125, 0.8%); a suicide, which is discussed further below.

A total of 4 patients (3.2%) in the liraglutide arm and 9 patients (7.1%) in the placebo arm reported an SAE during the trial; during the 'on-treatment' period, 3 SAEs occurred in 3 patients in the liraglutide group (myositis, post-procedural hemorrhage, and completed suicide) and 6 SAEs occurred in 5 patients in the placebo group (appendicitis, pneumonia, cholecystitis acute, cholelithiasis, hemorrhagic ovarian cyst, and thrombophlebitis).

Approximately 10% of patients treated with liraglutide and no patients randomized to placebo discontinued study drug due to an adverse event. Most AEs leading to discontinuation were because of gastrointestinal disorders (nausea, vomiting, and abdominal pain).

Although adverse events associated with liraglutide in this trial of obese adolescents were generally consistent with its known safety profile, there are a number of findings that are worth highlighting and should be considered in labeling and future pediatric trials (listed below). Of note, there were no thyroid neoplasms (including no medullary thyroid carcinoma, c-cell hyperplasia, or significant calcitonin increases).

- Suicidality and depression

There was one completed suicide in the liraglutide group. There was not enough information to make a causality determination about the completed suicide, but other suicidality events were observed in both groups. One patient in each group (liraglutide and placebo) experienced an AE of suicidal ideation on-treatment (the liraglutide patient had a negative rechallenge to liraglutide), and one patient in each group (liraglutide and placebo) reported a suicide attempt in-trial but off-treatment (the liraglutide patient had multiple confounders). There was no imbalance of psychiatric events overall in this trial, although one event of depression led to discontinuation in a liraglutide patient. This population may be at high risk for suicidality and depression.

- Hypoglycemia

Self-monitored plasma glucose was measured throughout the trial and was required prior to dose escalation and anytime patients had symptoms of suspected hypoglycemia. No severe hypoglycemic events, defined as events requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, were reported in the liraglutide- or placebo-treated patients during the trial. No hypoglycemia SAEs were reported. No hypoglycemia events led to treatment discontinuation. Documented symptomatic hypoglycemia was reported more frequently in liraglutide patients (19 patients [15%], 31 events) versus placebo patients (5 patients [4%], 6 events). Events were reported throughout the trial. Two (2) liraglutide patients reported 4 events of blood glucose less than 54 mg/dL with or without symptoms versus 1 placebo patient who reported 1 event.

- Pancreatitis

There were 2 AEs with the preferred term of 'Pancreatitis': 1 AE of 'Clinically confirmed pancreatitis' was reported in 1 patient in the liraglutide group (and led to drug discontinuation) and 1 AE of 'Suspicion of pancreatitis' reported by the physician that was not confirmed by laboratory results in 1 patient in the placebo group. Another patient randomized to liraglutide discontinued treatment due to AEs of 'Pancreatic enzymes increased', 'Retching', and 'Vomiting'. Small elevations in mean amylase and lipase, compared to baseline and to placebo, were observed during treatment with liraglutide. More patients with liraglutide than placebo experienced amylase and particularly lipase greater than the upper limit of normal during the trial.

- Immunogenicity

Fourteen (14) liraglutide-treated patients (12.0%) had at least 1 post-baseline positive anti-liraglutide antibody sample; most were transient. Five patients (4.3%) had persistent antibodies as defined by more than 2 antibody-positive visits at least 16 weeks apart. Two (2) patients (1.7%) remained positive throughout the follow-up period.

- Bone metabolism

Median decreases from baseline were seen in all bone marker parameters, consistent with typical adolescence. There was a numerically greater median decrease in the markers of bone resorption type 1 collagen N-telopeptide crosslinks (NTX1) and type 1 C-telopeptide crosslinks (CTX1) in the placebo arm, compared to a slightly greater median decrease in the marker of bone formation bone-specific alkaline phosphate (BSAP) in the liraglutide arm. Mean changes in height and bone age were similar among groups.

- Urinary lithiasis

There were two events of urinary lithiasis in patients treated with liraglutide. Adequate hydration while on liraglutide should be reinforced in the adolescent population.

- Increased heart rate

Mean increase in heart rate in the liraglutide group ranged from +3 to +7 bpm during the trial. More patients in the liraglutide group had increases of greater than 10 and 20 beats/min and heart rate of 100 beats/min or greater at 2 consecutive visits.

- Common AEs

Gastrointestinal (GI) AEs were more frequently reported with liraglutide (65% reported at least one GI AE) than placebo (37%). Other common AEs of noted imbalance not in favor of liraglutide included dizziness, lipase increased, and rash. Other AEs of incidence greater than 3% with numerical imbalances (e.g., depression, fatigue) greater with liraglutide than placebo should be included in labeling.

Benefit-Risk Integrated Assessment

The clinical trial submitted to support this supplemental application demonstrated substantial evidence of effectiveness to support an indication for weight loss in the intended population. The trial demonstrated a statistically significant change in the primary endpoint, the change in BMI SDS from baseline to week 56, of -0.23 in the liraglutide group versus -0.00 in the placebo group, resulting in an estimated mean treatment difference between groups of -0.22 (95% CI -0.37, -0.08), p=0.0022. A change in BMI SDS score of at least 0.20 is considered clinically meaningful.

Supportive endpoints, such as changes in BMI, weight, and waist circumference, support the efficacy of liraglutide in this the study population for the duration studied. Missing data were reasonably low and sensitivity analyses support the robustness of the estimated treatment effect.

Although cardiometabolic parameters, such as lipids, glycemic parameters, and blood pressure, were essentially unchanged during the trial, the absence of meaningful changes in these parameters is unclear given the general absence of metabolic decompensation in the study population at baseline.

Liraglutide has a well-characterized safety profile in adults in type 2 diabetes and obesity, and this trial did not identify new safety concerns. Mitigation of safety concerns can be addressed with labeling. The most frequently reported adverse events were gastrointestinal disorders, such as nausea, vomiting, and abdominal pain.

There was one completed suicide in the liraglutide group, although there were no imbalances in suicidal behavior or ideation overall. Suicidal behavior and ideation are already included in Section 5 (Warnings and Precautions) of the US Prescribing Information, but this event should be added to current to the section.

Self-monitored plasma glucose was measured throughout the trial and was required prior to dose escalation and for symptoms of suspected hypoglycemia. Documented symptomatic hypoglycemia (<70 mg/dL) occurred more frequently with liraglutide than placebo and should be addressed in labeling.

Overall, the benefits of liraglutide on weight loss outweigh the potential risks in adolescents with obesity.

Reviews provided by all disciplines involved in this supplementary application support approval, including the statistical review by Dr. Kiya Hamilton and the clinical pharmacology review by Dr. Suryanarayana Sista and Dr. Justin Earp. The OPQ reviewer, Dr. Pallaiah Thannana, granted the applicant's request for categorical exclusion for an Environmental Assessment. A safety evaluation of the revisions to the Prescribing Information and Medication Guide was conducted by DMEPA (reviewer: Melina Fanari) and no medication error vulnerabilities were identified. Clinical site inspections were not conducted for this supplement, and there was no new CMC or nonclinical information submitted with this supplementary application.

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; other definitions can be used • 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 the significant consequences throughout adulthood	Obesity and its co-morbidities in children and adolescents are rising problems in the U.S. and globally. The goal in 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 • Orlistat is currently the only obesity drug that is labeled for use in adolescents • Other drugs (e.g., amphetamines, metformin) are used off-label or in research settings • Bariatric surgery is being utilized to treat obesity in adolescents refractory to other interventions	Obesity is difficult to treat and there is a paucity of treatment options, particularly in children. Treatment often requires a multidisciplinary approach.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The observed mean change in BMI SDS from baseline to week 56 was -0.23 in the liraglutide group and -0.00 in the placebo group. The estimated treatment difference in BMI SDS reduction from baseline between liraglutide and placebo was -0.22 with a 95% confidence interval of -0.37, -0.08; p=0.0022 • Changes in BMI SDS of ~0.20 have been cited in the literature as clinically meaningful in children who are treated with diet and exercise • BMI SDS has limitations in very obese adolescents and children (ceiling effect) • Improvements were also seen with liraglutide vs. placebo in percent body weight change, percent BMI change, the proportions who experienced a decrease in at least 5% and 10% BMI from baseline, waist circumference, and systolic blood pressure • No beneficial changes were observed in glycemic parameters, lipids, or diastolic blood pressure	Despite some concerns about the BMI SDS primary endpoint, mean changes across a variety of supportive endpoints, such as BMI, weight, and waist circumference, support the efficacy of liraglutide in this population for the duration studied. Lack of improvement in cardiometabolic parameters might reflect the lack of metabolic decompensation in the adolescent population despite significant obesity.
Risk and Risk Management	• There was one fatal adverse event in this trial, a completed suicide, in the liraglutide group (1/125, 0.8%) • Other serious adverse events (AEs) that occurred on-treatment with liraglutide were myositis and post-procedural hemorrhage; neither of which were clearly attributable to drug • Approximately 10% of patients treated with liraglutide and no patients randomized to placebo discontinued study drug due to an AE; most due to gastrointestinal disorders (nausea, vomiting, and abdominal pain) • Other safety items of interest included: o Hypoglycemia: Self-monitored plasma glucose was	Liraglutide has a well-characterized safety profile in adults in type 2 diabetes and obesity, and this trial did not identify new safety concerns. Mitigation of safety concerns can be addressed with labeling. Adolescents with obesity seeking weight loss may be at high risk for depression, suicidality, and other mood disorders.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	measured throughout the trial and was required prior to dose escalation and anytime patients had symptoms of suspected hypoglycemia. No severe hypoglycemic events were reported in the liraglutide- or placebo-treated patients during the trial. No hypoglycemia SAEs were reported. No hypoglycemia events led to treatment discontinuation. Documented symptomatic hypoglycemia was reported more frequently in liraglutide patients (19 patients (15%), 31 events) versus placebo patients (5 patients (4%), 6 events). o Pancreatitis: one event of pancreatitis was reported in a liraglutide-treated patient o Immunogenicity: anti-liraglutide antibodies were detected in 14 liraglutide-treated patients; 5 had persistent antibodies as defined by more than 2 antibody visits at least 16 weeks apart; 2 remained positive throughout the follow-up period; 1 had antibodies cross reactive to native GLP-1; no patients had neutralizing antibodies o Increased heart rate: mean increases from baseline in resting heart rate ranged from 3 to 7 beats per minute in liraglutide-treated patients	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

x	The patient experience data that was submitted as part of the application include:					Section where discussed
	x	Clinical outcome assessment (COA) data, such as				
		x	Patient reported outcome (PRO)			Section 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 ~20.6% of adolescents considered to have obesity (BMI ≥ 95th percentile) and ~7% of adolescent girls and ~9.7% of adolescent boys considered to have severe obesity (BMI ≥ 120 percent of the 95th percentile or ≥ 35 kg/m^2).[4] 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.

The definition for severe obesity noted above corresponds to the approximately the 99th percentile or BMI Z-score ≥ 2.33. The BMI Z-score (or standard-deviation score, SDS) was used as the primary endpoint in the trial that is the subject of this supplement. The advantage of BMI SDS is that it accounts for sex and age; its limitations are apparent at higher BMI values as it has a ceiling effect.

The applicant has proposed the following indication:

SAXENDA is indicated as an adjunct to (b) (4) *increased physical activity for chronic weight management in pediatric patients aged 12 years and older with*

- *body weight above 60 kg* (b) (4) *and*
- *an initial body mass index (BMI) corresponding to ≥30 kg/m^2 for adults (obese) by international cut-offs (Cole criteria)*

[4] https://www.uptodate.com/contents/definition-epidemiology-and-etiology-of-obesity-in-children-and-adolescents Accessed 14 Oct 2020.

Table 1: International Obesity Task Force (IOTF) BMI Cut-offs for Overweight and Obesity by Sex between 12 to 18 Years (Cole Criteria)

Age (years)	Body mass index 30 kg/m^2	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16.0	28.88	29.43
16.5	29.14	29.56
17.0	29.41	29.69
17.5	29.70	29.84
18.0	30.00	30.00

Source: Annotated draft pediatric label

The Cole criteria defines overweight and obesity in childhood based on pooled international data for BMI, linked to the commonly accepted adult obesity BMI cut-off of 30 kg/m^2. It is more conservative (corresponds to higher BMIs) than the 95th percentile BMI cut-off commonly used in the U.S., with the exception of girls approximately 16 years and older, where it is similar to or slightly less than the 95th BMI percentile.

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. Medications are generally considered when other attempts at weight management have failed. Bariatric surgery is also an option in certain clinical scenarios.

Currently approved drugs for weight management, chronic and short-term, are used off-label in pediatric patients. Prescription orlistat (Xenical) does not have a formal pediatric indication, but results of an adolescent trial were added to product labeling in 2003. In the orlistat trial, the primary endpoint was change in BMI, with orlistat -0.55 kg/m^2 and placebo +0.31 kg/m^2 after 54 weeks of treatment, p=0.001. Other medications reported in the literature for

treatment of adolescent obesity include metformin and exenatide[5] (both off-label).

[5] Axon E, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database of Systematic Reviews 2016, Issue 11.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Liraglutide (Saxenda, NDA 206321) was approved in the U.S. on December 23, 2014 for chronic weight management in adults with obesity. The dosage of Saxenda is 3 mg administered as a daily subcutaneous injection.

Liraglutide (Victoza, NDA 22341) is also approved for the treatment of type 2 diabetes in adults and children and adolescents ages 10 and over, as well as to reduce the risk of major cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. The pediatric indication was approved in June of 2019 and the trial fulfilled a written request. The dosages of Victoza are 0.6 mg (pediatric only), 1.2 mg, and 1.8 mg administered as a daily subcutaneous injection.

3.2. Summary of Presubmission/Submission Regulatory Activity

A proposed Pediatric Study Plan (PSP) was submitted to FDA on December 20, 2013 with the initial NDA but was not formally agreed to before the NDA was approved on December 23, 2014. The proposed studies from the PSP were required as PMRs under PREA.

3.3. Foreign Regulatory Actions and Marketing History

To date, Saxenda has been approved in at least 68 countries and launched in at least 43 countries, including the US, EU, Australia, Brazil, Canada, Mexico, and Russia. The trial that is the subject of this supplement (NN8022-4180) was conducted to fulfill a regulatory requirement for pediatric trials in the US and the EU. This trial is also currently under review by the EMA.

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

4.1. Office of Scientific Investigations (OSI)

Because of travel restrictions due to the current coronavirus pandemic, site inspections were not conducted for this supplement.

4.2. Product Quality

No new product quality information was submitted with this supplement.

4.3. Clinical Microbiology

Not applicable; Saxenda is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

As Dr. Anthony Parola noted in his memo dated 17 March 2020, PMR 2802-1 was fulfilled by conducting a toxicity study with liraglutide in juvenile rats. This study demonstrated (as noted by Dr. Lee Elmore's secondary review dated 22 May 2019 under the Victoza NDA) general developmental delay (slightly reduced ulna length) and delayed sexual development (reduced ovary weights in the absence of correlative histopathology, delayed vaginal opening) in female rats. However, these findings are contrary to a signal observed in earlier studies in monkeys of *accelerated* sexual development. The clinical significance of the dichotomous sexual development findings is unclear, and these juvenile animal study results are therefore not currently described in Victoza or Saxenda labeling. (See the referenced memo by Dr. Parola and review by Dr. Elmore.) No new nonclinical data was submitted with this supplement.

4.5. Clinical Pharmacology

The clinical pharmacology team reviewed the population PK meta-analysis and relevant clinical pharmacology information for this supplement. Liraglutide exposure in adolescents was as expected; body weight was the only covariate with an impact on liraglutide exposure. However, liraglutide 3 mg provided similar exposures in adolescents and adults, even without adjusting for baseline body weights, supporting the 3 mg dose for this population. The liraglutide exposure-response was similar in adolescents and adults.

The clinical information in the PK study in adolescents, trial NN8022-3967, was also reviewed. Trial 3967 was a randomized, double-blind, placebo-controlled trial to assess safety, tolerability, and pharmacokinetics of liraglutide in obese adolescents aged 12 to 17 years, Tanner stage 2 to 5. This trial was conducted to support the dosing in trial 4180.

The trial consisted of a screening phase, a 5- to 6-week treatment phase, and a 5- to 14-day follow-up phase. Patients were randomized 2:1 with either liraglutide or placebo; the liraglutide schedule started at a dose of 0.6 mg/day and was increased by 0.6 mg weekly until the maximum dose of 3 mg. If during dose-escalation the higher dose was not tolerated, the dose was de-escalated to the previous level. Patients could remain on this dose for the remainder of the treatment period or take a given dose for 2 weeks before escalating to the next dose. The total treatment period was for a maximum of 6 weeks.

A total of 21 patients were randomized and exposed to treatment: 14 to liraglutide and 7 to placebo. One patient – (b) (6) from the liraglutide group – withdrew from the trial for a reason categorized as 'other' (withdrawn 4 days after treatment due to a storage temperature deviation of trial product at site).

In the liraglutide group, 79% were female and 21% were male; in the placebo group, 43% were female and 57% were male. Patients were mostly white (95%), with a mean age of 15 years, mean weight of 105.5 kg, mean BMI 36.2 kg/m^2, and mean BMI z-score 3.20. Most patients were Tanner 4 or 5; none were Tanner 2.

Regarding safety:

- There were no deaths, SAEs, or AEs leading to withdrawal.
- All 14 patients in the liraglutide group and 4 patients (57%) in the placebo group reported at least one TEAE during the trial.
- A total of 93 TEAEs were reported during the trial; 86 (92%) of these were reported in the liraglutide group and 7 (8%) were reported in the placebo group.
- No severe TEAEs were reported and the majority were mild.
- GI disorders were more frequent with liraglutide than placebo; the most frequent PTs were abdominal pain, nausea, vomiting, and diarrhea.
- Other frequently reported AEs in the liraglutide group included headache and injection site pain.
- More hypoglycemic episodes were reported with liraglutide than placebo; 12 hypoglycemic episodes occurred in 8 patients in the liraglutide group compared to 2 episodes in 1 placebo patient. Subject (b) (6) from the liraglutide group was treated with 1.2 mg for 2 weeks due to a low glucose concentration and only reached a maximum dose of 2.4 mg.
- No liraglutide antibodies were detected.

4.6. Devices and Companion Diagnostic Issues

None; the marketed product was used for the pivotal trial.

4.7. Consumer Study Reviews

None.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Tabular Listing of Studies to Support Pediatric Indication

Trial ID Country	Type of study	Trial design and type of control	Test drugs and route of administration	Number of subjects (FAS) (M/F)	Healthy subjects or population	Duration of treatment	Study status Type of report Location
NN8022-3967 DE	Clinical pharmacology	Single-centre, randomised, double blind, parallel-group, Placebo-controlled trial to assess safety, tolerability and pharmacokinetics of liraglutide in adolescent subjects with obesity	Once-daily s.c. doses of liraglutide or placebo. Starting at 0.6 mg and the dose was escalated in weekly increments of 0.6 mg to a maximum of 3.0 mg/day for liraglutide (or volume corresponding to these doses for placebo)	21 FAS (7 M/14 F) Liraglutide 3.0 mg: 14 (3 M/11 F) Placebo: 7 (4 M/3 F)	Adolescent subjects with obesity, Tanner stage 2 −5 pubertal development	5–6 weeks	Completed; Full; EU: M 5.3.5.1 seq 0005; US: M 5.3.3.2 seq 0062
NN8022-4180 BE, SE, RU, MX, US	Efficacy and safety	Double-blind, randomised, parallel-group, placebo-controlled multi-national 56-week trial followed by a 26-week period off study-drug for weight management in pubertal adolescent subjects with obesity	Once daily s.c. doses of liraglutide or placebo. Starting at 0.6 mg, the dose was escalated weekly to 1.2, 1.8, 2.4 mg or 3.0 mg or MTD for liraglutide (or volume corresponding to these doses for placebo equivalent) based on safety and tolerability.	251 (FAS) (102 M/149 F) Liraglutide 3.0 mg: 125 (54 M/71 F) Placebo: 126 (48 M/78 F)	Pubertal adolescent subjects with obesity, Tanner stage 2−5 pubertal development	56 weeks	Completed; Full; M 5.3.5.1

Source: Module 5.2, Tabular Listing of Clinical Studies

5.2. Review Strategy

The clinical review for this supplement consisted of the review of the single efficacy and safety trial in adolescents, NN8022-4180. A summary of the safety for the PK trial 3967 is in Section 4.5, Clinical Pharmacology.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NN8022-4180: Effect of Liraglutide for Weight Management in Pubertal Adolescent Subjects with Obesity

6.1.1. Study Design

Overview and Objective

The primary objective of this trial was to compare the efficacy of liraglutide versus placebo on weight loss in adolescent patients with obesity after 56 weeks of treatment. Secondary objectives were to assess the effect of liraglutide versus placebo on glycemic control, cardiovascular risk factors, Impact of Weight on Quality of Life-Kids (IWQOL-Kids), and safety after 30 and 56 weeks, and to examine the potential rebound effect after drug discontinuation.

Trial Design

This was a 56-week double-blind, randomized, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug. The trial was conducted in pubertal adolescents with obesity aged 12 to less than 18 years.

Key inclusion criteria included BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points and ≥ 95^{th} percentile for age and sex, stable body weight within 90 days, and history of failing to lose sufficient weight by lifestyle modification. Key exclusion criteria included Tanner stage 1 at screening, body weight ≤ 60 kg, type 1 diabetes mellitus, calcitonin ≥ 50 ng/L, family or personal history of multiple endocrine neoplasia type 2 (MEN2), medullary thyroid carcinoma (MTC), history of pancreatitis, secondary causes of obesity, treatment with medications that could significantly impact weight, anti-diabetic treatment other than metformin, bariatric surgery, major depressive disorder within 2 years, any severe psychiatric disorder, PHQ-9 score ≥ 15, suicidal ideation at screening, suicidal behavior within 30 days, or any suicide attempt. Female patients must have been using adequate contraception if sexually active.

After a 12-week lifestyle run-in period, patients were randomized 1:1 to liraglutide or placebo, and the randomization was stratified according to pubertal[6] and glycemic status (normoglycemia versus dysglycemia [pre-diabetes and T2DM], Table 3).

[6] Tanner JM. Normal growth and techniques of growth assessment. Clin Endocrinol Metab. 1986;15(3):411-51.

Table 3: Glycemic Categories

Normoglycaemia	FPG <5.6 mmol/L (<100 mg/dL) and/or HbA_{1c} <5.7%
Pre-diabetes	FPG 5.6–6.9 mmol/L (both inclusive), FPG 100–125 mg/dL (both inclusive) or HbA_{1c} 5.7–6.4% (both inclusive)
Type 2 diabetes (T2DM)	FPG ≥7.0 mmol/L (≥126 mg/dL) and/or HbA_{1c} ≥6.5%

Source: Study 4180 Protocol, Table 5-1

Table 4: Strata

Tanner 2 or 3	Dysglycaemia yes
Tanner 2 or 3	Dysglycaemia no
Tanner 4 or 5	Dysglycaemia yes
Tanner 4 or 5	Dysglycaemia no

Source: Study 4180 Protocol, Table 11-1

Treatment with liraglutide was initiated with 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a maximum tolerated dose (MTD) or the 3.0 mg dose of liraglutide (highest allowed liraglutide dose) was reached over 4-8 weeks.

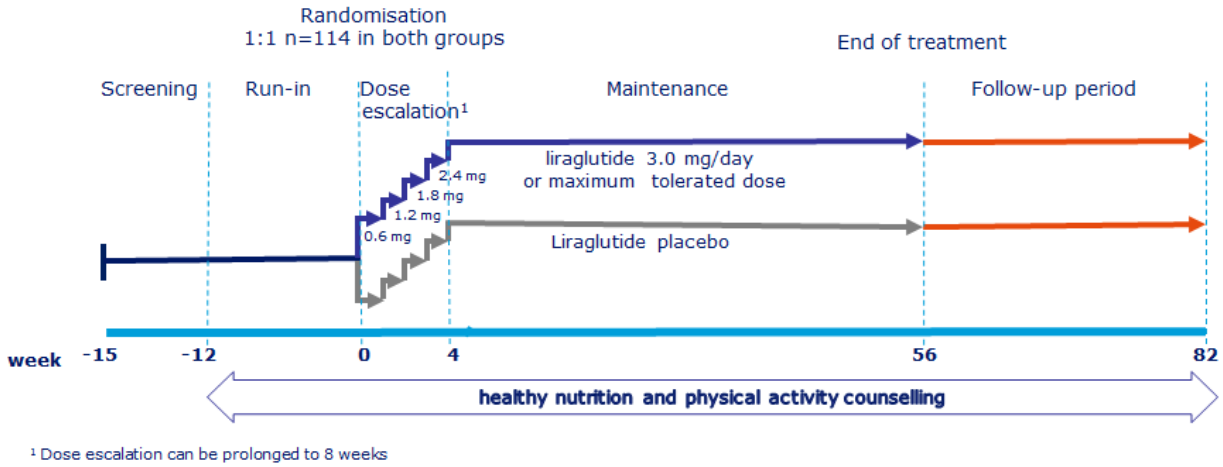
Dose escalation was based on tolerability as judged by the investigator. If, after increasing to next dose level, the dose was poorly tolerated, it could be lowered to the previously dose level. If a patient had tolerability issues with a given dose level, he or she could remain at that dose level for a maximum of 2 weeks. This extended time of one additional week was allowed at each dose level (i.e., the dose escalation process could take up to 8 weeks in total). It was at the discretion of the investigators to judge when the patient had reached MTD.

The self-monitored plasma glucose (SMPG) measurement performed during dose escalation visits was required before instructing the patient in dose escalation. Escalation of the trial product was not allowed if the patient had a SMPG < 56 mg/dL or < 70 mg/dL in the presence of symptoms of hypoglycemia during the week prior to or during the dose escalation visits, or during contacts (i.e., telephone visits).

Visits to the clinic occurred weekly during the first 4 weeks of dose escalation (V10-V13). Ideally, patients would reach the maximum dose of 3.0 mg at V13. In those cases where more than one week was needed at any dose escalation step, the patient was to follow the visit schedule (V10-V13). For the remaining dose escalation step(s) after V13, it was at the discretion of the investigator to be in frequent contact (e.g., by phone) with the patient to

ensure correct dose settings. The dose escalation process must have been finalized no later than V14.

Figure 1: Trial Design



Source: Study 4180 protocol, Figure 5-1

Study Endpoints

The primary endpoint was change in body mass index (BMI) standard deviation score (SDS) from baseline to 56 weeks.

Analyses of other endpoints were not adjusted for Type I error. Additional study endpoints and the study flowchart can be found in the Appendix (Section 13.3).

Statistical Analysis Plan

Results from the statistical analysis were presented by two-sided confidence intervals (CIs) with a confidence level of 95%. Superiority was to be claimed if the two-sided p-value is less than 5% and the treatment estimate favors liraglutide. If the upper limit was below 0, superiority of liraglutide against placebo could be concluded.

The full analysis set (FAS) population includes all randomized patients who have received at least one dose of trial product and have any post-randomization data. The statistical evaluation of the FAS follows the intention-to-treat (ITT) principle and patients contribute to the evaluation "as randomized".

The safety analysis set (SAS) population includes all patients exposed to at least one dose of trial product. Patients in the SAS contribute to the evaluation "as treated".

The hypothesis was tested using an analysis of covariance (ANCOVA) model using including

the factors, covariates and interaction term listed in the table below.

Table 5: Factors and Covariates for the Analysis of the Primary Endpoint

Factors and covariates at baseline	Type	Categories
Randomised treatment	Factors	Liraglutide 3.0 mg, Placebo
Sex	Factors	Female, Male
Region	Factors	Europe, North America
Glycaemic category	Factors	Yes, No*
Tanner stage, Glycaemic category	Interaction factor	Not applicable
Tanner stage	Factors	Stage 2 and 3 together, Stage 4 and 5 together
Baseline BMI SDS	Covariate	Not applicable
Age	Covariate	Not applicable

*Yes: dysglycaemic, No: non-dysglycaemic.
Source: Study 4180 SAP, Table 2-1

Missing data in the main analysis was handled by the utilizing a multiple imputation (MI) method. A pattern mixture model approach was applied where withdrawn patients or treatment discontinued patients without a follow-up visit were assumed to respond as if treated with placebo for the entire trial. Sensitivity analyses include LOCF, BOCF, completers, and a mixed model for repeated measures (MMRM).

Protocol Amendments

There were no protocol amendments relevant to the US.

6.1.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (GCP). The trial was also conducted in accordance with the FDA 21 CFR 312.120.

Financial Disclosure

None of the 156 investigators in this trial had disclosable financial interests; see the Appendix, Section 13.2.

Patient Disposition

A total of 299 patients were screened, 259 entered the run-in period, and 251 were randomized (125 to liraglutide and 126 to placebo). All patients randomized were exposed (safety analysis set, SAS) and all patients were included in the full analysis set (FAS).

Of the 251 randomized patients, 201 (80%) remained on treatment and completed the week 56 visit. Approximately half of the liraglutide-treated patients who discontinued treatment remained in the trial for additional assessments. Reasons for premature discontinuation of trial product and/or withdrawing from trial during the treatment period are as follows:

Table 6: Subject Disposition, Trial and/or Treatment Discontinuation

	Liraglutide N=125 n (%)	Placebo N=126 n (%)
Premature discontinuation of trial product and/or withdrawn from trial during treatment period	24 (19.2)	26 (20.6)
Premature discontinuation of trial product		
Without withdrawing from trial	13 (10.4)	4 (3.2)
Adverse event	7 (5.6)	0
Other	6 (4.8)	4 (3.2)
Withdrawing from the trial	11 (8.8)	22 (17.5)
Adverse event	6 (4.8)	0
Protocol violation	1 (0.8)	0
Other	4 (3.2)	22 (17.5)
Withdrawn from trial*	13 (10.4)	23 (18.3)
Lost to follow-up	3 (2.4)	6 (4.8)
Withdrawal by patient	5 (4.0)	15 (11.9)
Withdrawal by parent/guardian	2 (1.6)	1 (0.8)
Other	3 (2.4)	1 (0.8)
* Note that 2 patients on liraglutide and 1 patient on placebo withdrew from the trial but completed treatment, which explains discrepancy of this row with the 'withdrawing from trial' under 'premature discontinuation of trial product' row		

Source: Study 4180 CSR, Table 10-1

Protocol Violations/Deviations

Table 7 enumerates the protocol deviations by category. The majority of informed consent violations involved conducting trial activities prior to informed consent and using an incorrect or incomplete informed consent form. The majority of eligibility criteria violations were due to missing screening results. The majority of trial product handling violations involved incorrectly story trial product dispensed. The majority of compliance violations involved administering the wrong dose due to patient non-compliance or error. The majority of assessment deviations were due to missing/late/incomplete efficacy or safety assessments, and the majority of other violations were due to documentation/delegation and source data missing.

Table 7: Summary of Site and Patient Level Protocol Deviations by Category

Protocol deviation category	Site level	Liraglutide	Placebo	Not allocated	Total patient level	Total site and patient PDs
Total	57	98	126	14	238	295
Informed consent	1	21	23	9	53	54
Inclusion/exclusion/randomization criteria	1	8	2	1	11	12
Trial product handling	6	2	4	0	6	12
Treatment compliance	1	12	19	0	31	32
Assessment deviations	8	35	54	3	92	100
Other	40	20	24	1	45	85

Source: Study 4180 CSR, Table 10-6

Of note, the missing safety assessments were brought to the attention of the external DMC, which concluded that the "missing data have a minor effect of subjects and robustness of the trial data." Corrective actions were taken by the IND sponsor.

Table of Demographic Characteristics

Demographic characteristics were generally well-balanced among groups. Approximately 59% of patients were female, mean age was 14.5 years, 88% were white and 8% were black, 22% were of Hispanic ethnicity, and 24% of patients were from the U.S.

Table 8: Demographic characteristics of the primary efficacy analysis

Demographic Parameters	Liraglutide N=125 n (%)	Placebo N=126 n (%)
Sex		
Male	54 (43.2)	48 (38.1)
Female	71 (56.8)	78 (61.9)
Age		
Mean years (SD)	14.6 (1.6)	14.5 (1.6)
Median (years)	15.0	14.0
Min, max (years)	12.0, 17.0	12.0, 17.0
Race		
White	105 (84.0)	115 (91.3)
Black or African American	14 (11.2)	6 (4.8)
Asian	2 (1.6)	0
American Indian or Alaska Native	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	0	0

Other	4 (3.2)	4 (3.2)
Ethnicity		
Hispanic or Latino	32 (25.6)	24 (19.0)
Not Hispanic or Latino	93 (74.4)	102 (81.0)
Region		
United States	35 (28.0)	25 (19.8)
Russian Federation	30 (24.0)	38 (30.2)
Mexico	26 (20.8)	20 (15.9)
Sweden	19 (15.2)	25 (19.8)
Belgium	15 (12.0)	18 (14.3)

Source: Study 4180 CSR, Table 10-3

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics were generally well-balanced among groups. The majority of adolescents (52%) were Tanner stage 5 at baseline, mean body weight was 101 kg, mean BMI was 35.6 kg/m^2, and mean BMI SDS was 3.17; therefore, the adolescents in this trial generally were in a class 2 obese category (i.e., greater than 120% of the 95th percentile).[7] Mean bone age was approximately 2 years older than mean chronological age; obesity in adolescents may be associated with accelerated bone age (see further discussion in Section 8.5). The table below enumerates other selected baseline characteristics.

[7] Racette SB, et al. BMI-for-age graphs with severe obesity percentile curves: tools for plotting cross-sectional and longitudinal youth BMI data. BMC Pediatrics, 2017; 17:130-136.

Table 9. Baseline Characteristics

Baseline Characteristics	Liraglutide N=125 n (%)	Placebo N=126 n (%)
Tanner stage		
Stage 2	6 (4.8)	8 (6.3)
Stage 3	16 (12.8)	13 (10.3)
Stage 4	38 (30.4)	40 (31.7)
Stage 5	65 (52.0)	65 (51.6)
Height (m)		
Mean (SD)	1.67 (0.09)	1.68 (0.09)
Median	1.65	1.67
Min, max	1.51, 1.93	1.50, 1.96
Height SDS		
Mean (SD)	0.50 (1.02)	0.72 (1.04)
Median	0.39	0.65
Min, max	-1.91, 3.50	-1.92, 2.78
Body weight (kg)		
Mean (SD)	99.3 (19.7)	102.2 (21.6)
Median	96.0	97.6
Min, max	62.1, 178.2	70.6, 175.2
BMI (kg/m^2)		
Mean (SD)	35.3 (5.1)	35.8 (5.7)
Median	34.4	34.1
Min, max	26.6, 58.8	28.3, 53.4
BMI SDS		
Mean (SD)	3.14 (0.65)	3.20 (0.77)
Median	3.02	2.93
Min, max	2.07, 6.49	2.12, 5.55
HbA1c (%)		
Mean (SD)	5.3 (0.4)	5.3 (0.4)
Median	5.3	5.3
Min, max	4.4, 6.3	4.6, 8.6
Dysglycemia status		
Yes	32 (25.6)	33 (26.2)
No	93 (74.4)	93 (73.8)
Bone age (yr)		
Mean (SD)	16.55 (1.63)	16.44 (1.69)
Median	17.00	17.00
Min, max	12.00, 19.00	13.00, 19.00

Source: Study 4180 CSR, Tables 10-3, 10-4, and 14.3.6.23

Two patients, 1 randomized to liraglutide and 1 to placebo, had a history of type 2 diabetes at baseline; the rest of the patients with "dysglycemia" status had prediabetes.

At baseline, 24 patients (9.6%) reported a previous diagnosis of psychiatric disorder (positive response to a question asking if they had any psychiatric disorders), with the following conditions reported:

- 2 patients reported that they had experienced suicide behavior (1 patient in the liraglutide group and 1 patient in the placebo group)
- 9 patients were diagnosed with depression or other mood disorders (5 patients in the liraglutide group and 4 patients in the placebo group)
- 11 patients were diagnosed with anxiety (8 patients in the liraglutide group and 3 patients in the placebo group)
- 9 patients were diagnosed with sleep disorder (3 patients in the liraglutide group and 6 patients in the placebo group)

The most frequently used medications by ATC category were: biguanides – most commonly metformin (12.7%) (12 patients in the liraglutide group and 20 patients in the placebo group), propionic acid derivatives (10.0%) – most commonly ibuprofen (9 patients in the liraglutide group and 9 patients in the placebo group), and thyroid hormones (7.6%) (11 patients in the liraglutide group and 8 patients in the placebo group).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Deviations in treatment compliance were summarized in Table 7 (protocol deviations, PD): There was 1 site-level PD and 31 patient-level PDs in the 'treatment compliance' category. Most of the patient-level PDs (87.1%) were due to wrong dose due to patient's non-compliance or patient error.

Nutritional compliance was comparable among the liraglutide and placebo groups (or slightly better numerically for liraglutide) at each visit.

Notable concomitant medications started after randomization with imbalances by treatment were antiemetics, 12.0% liraglutide and 2.4% placebo; and loperamide, 8% and 4%, respectively.

Efficacy Results – Primary Endpoint

The primary endpoint was change in BMI SDS from baseline to week 56. This endpoint was discussed in the recent publication of this trial,[1] in which the authors note (based on their review of the limited literature) that a BMI SDS score of at least 0.20 has been suggested to be clinically meaningful.

Statistical significance in this trial was met, with the estimated mean change in BMI SDS from baseline to week 56 of -0.23 in the liraglutide group and -0.00 in the placebo group and an estimated mean treatment difference (ETD) between groups of -0.22 (95% CI -0.37, -0.08), p=0.0022.

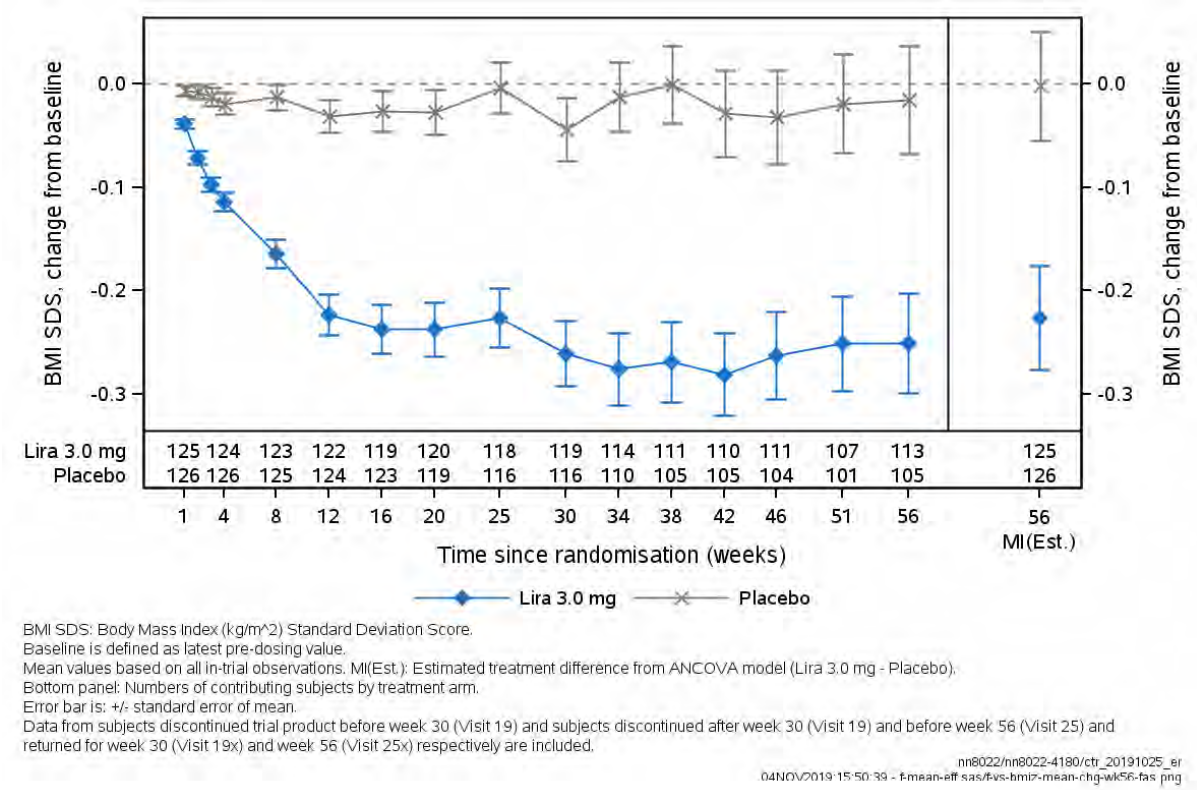
Table 10: Change in BMI SDS from Baseline to Week 56

Treatment	N	Baseline Mean (SD)	Week 56 Mean (SE)	Change from Baseline (SE)
Liraglutide	125	3.14 (0.65)	2.94 (0.05)	-0.23 (0.05)
Placebo	126	3.20 (0.77)	3.17 (0.05)	-0.00 (0.05)
Between treatment difference		Difference in LS means (95% CI)		p value
Liraglutide vs. Placebo		-0.22 (-0.37, -0.08)		0.0022

Source: Study 4180 CSR, Table 11-1

The figure below illustrates the change in BMI SDS from baseline over time:

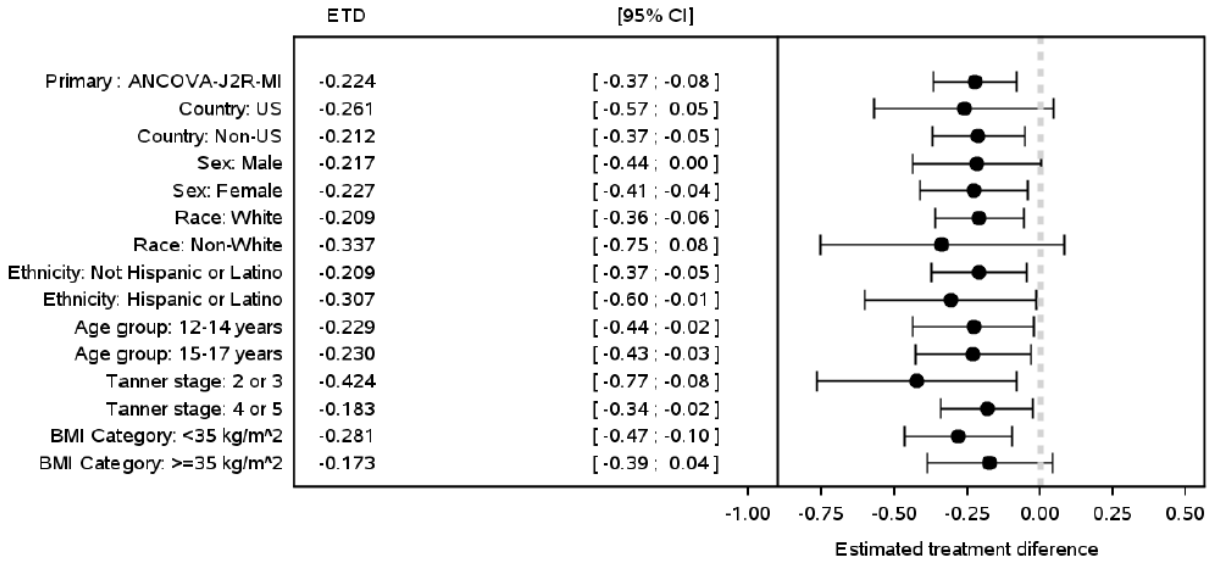
Figure 2: Change in BMI SDS by Treatment Week



Source: Study 4180 CSR, Figure 14.2.4

The estimated treatment difference of the primary efficacy endpoint was consistent across multiple subgroups:

Figure 3: Change in BMI SDS from Baseline, Subgroup Analysis



Source: Response to FDA Filing Review Letter Clinical Information Request #5 Dated April 8, 2020, Figure 17

A *post hoc* subgroup analysis was conducted on the primary endpoint to assess the impact of dysglycemia at baseline. Although the treatment effect appears numerically larger in the subgroup without dysglycemia, the p-value for interaction was not significant.

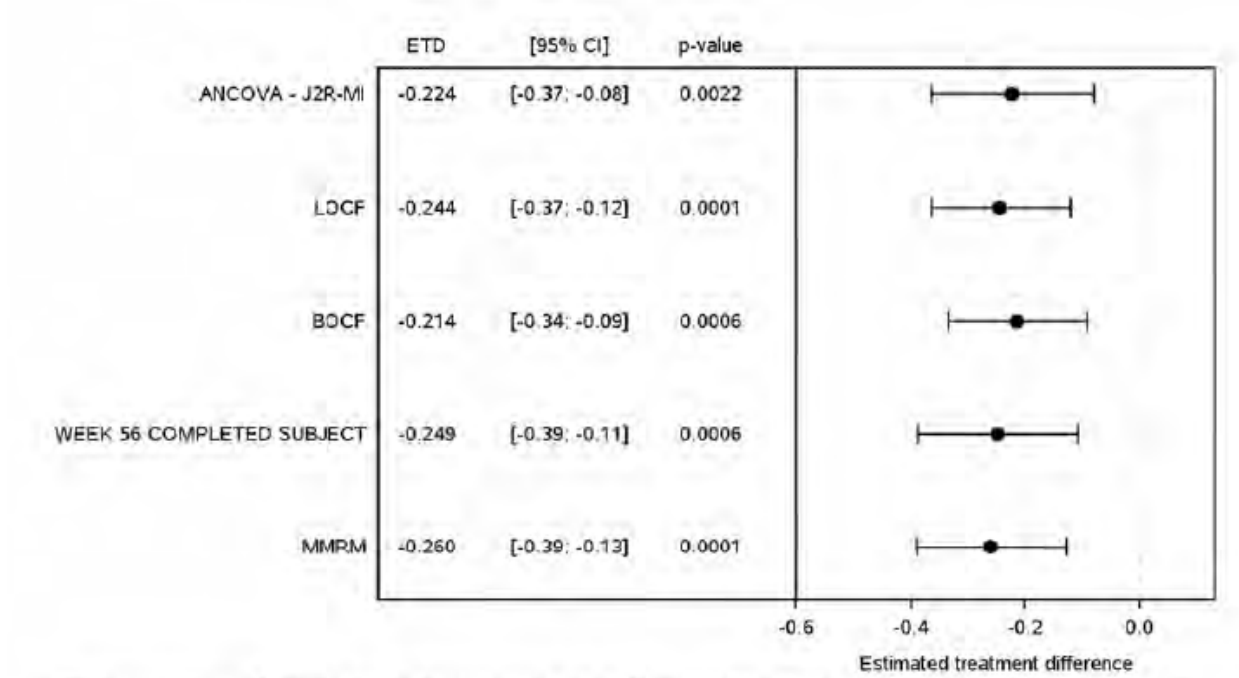
Table 11: BMI SDS by Baseline Glycemia Subgroup

Glycemia Subgroup	Liraglutide	Placebo
Normoglycemia		
n	93	93
Treatment Difference 95% CI	-0.24 -0.41, -0.08	
Prediabetes or diabetes		
n	32	33
Treatment Difference 95% CI	-0.09 -0.34, 0.16	

n: number of observations
Multiple imputation: Jump-to-reference
Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment sex, region, baseline glycemic category, stratification factor for Tanner stage and interaction between baseline glycemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, age as covariates.
Source: FDA Statistical Reviewer's Analysis

A number of sensitivity analyses were conducted to assess the robustness of the primary analysis for the impact of missing data. As shown below, the estimated treatment difference was robust to a number of sensitivity analyses.

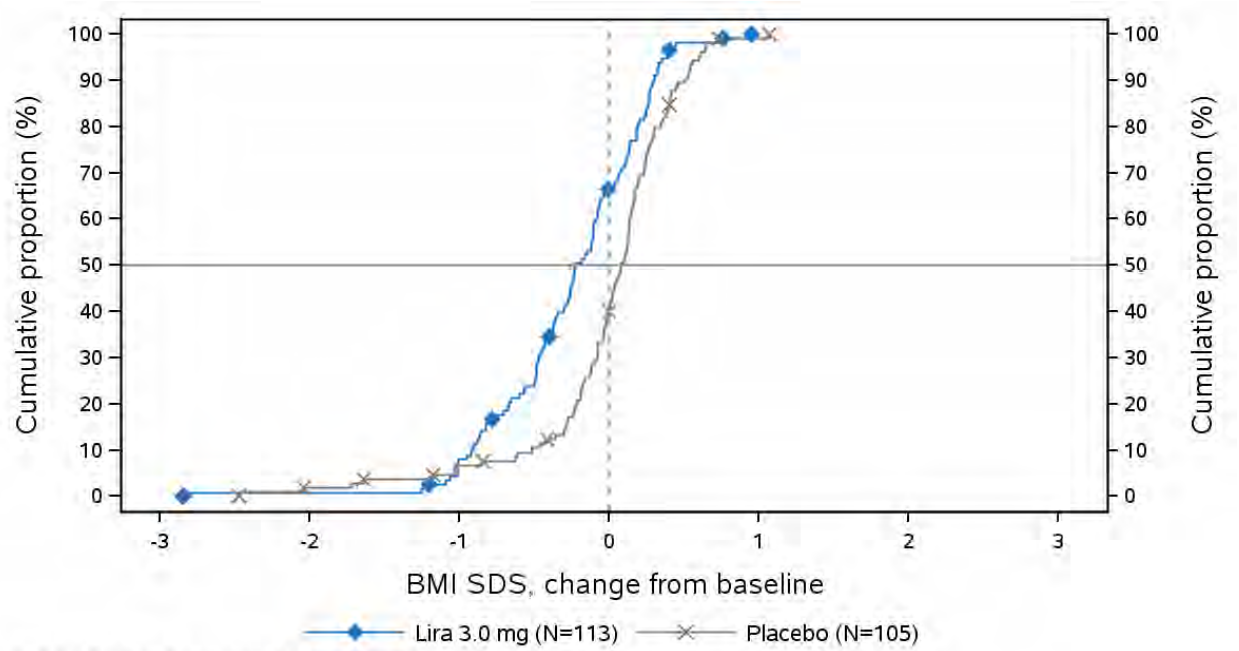
Figure 4: Change in BMI SDS from Baseline, Primary and Sensitivity Analyses



LOCF: last observation carried forward, BOCF: baseline observation carried forward, MMRM: mixed model for repeated measures
Source: Trial 4180 CSR, Figure 11-2

BMI SDS was also analyzed as proportion of patients achieving various changes from baseline. The following cumulative distribution figure illustrates that liraglutide is associated with greater proportions of BMI SDS across the categorical spectrum versus placebo.

Figure 5: Change in BMI SDS from Baseline at Week 56, Cumulative Distribution Plot



BMI SDS: Body Mass Index (kg/m^2) Standard Deviation Score.
Legend: Numbers of contributing subjects by treatment arm are shown in parentheses.
Baseline is defined as latest pre-dosing value.
Data available at the corresponding week 56 (Visit 25x) visit for subjects who discontinued trial product are considered as week 56 (Visit 25) data.

nn8022/nn8022-4180/ctr_20191025_er
04NOV2019:15:49:45 - fcdfeff/fvs-bmiz-cdf-fas.png

Source: Study 4180 CSR, Figure 14.2.5

Data Quality and Integrity

There was some concern regarding the accuracy of patient heights (a component of the primary endpoint) during this trial in adolescents.

Patient heights were to be measured in duplicate at each visit and then averaged at each visit. I compiled the number of times the duplicate height measures were recorded as exactly the same value at a single visit for each patient. This does not necessarily raise concerns if it happens occasionally, but in some sites, duplicate height measurements were *exactly the same* over 75% of the time: 102, 106, 108, 201, 202. This raises some concern that study staff were not measuring heights in duplicate as a routine practice, since one would expect some variation between measurements.

Furthermore, I evaluated the maximum number of times for any single patient that average heights were measured at *exactly the same* value over the course of the trial. Sites in which at least one patient had the same average measurement 5 times or more were identified (10/32 sites and 47/251 patients). In particular, at sites 201 and 202, 8 patients had exactly the same

height over 10 measurements in the course of the year-long study. Even if linear growth has stopped (which appears to be the case for many of these patients), I would still expect some variation from visit to visit.

The applicant was queried, and according to their response, 1 cm is thought to represent reasonable variability in height measurements. Heights were to be measured to the nearest 0.1 cm (or 0.1 inch). Unchanged heights (i.e., no variation) over the course of the trial could suggest that height was not measured at each visit and were instead replicated from a previous visit to the next visit.

From a practical standpoint, the height might not matter that much for this trial, since most patients have reached their full height, but it raises some concerns about general data reliability from these sites. From these evaluations, sites 201 and 202 appeared to be the most problematic, so an exploratory sensitivity analysis was conducted on the primary analysis removing sites 201 and 202.

Table 12: Change from Baseline in BMI SDS at Week 56, Excluding Sites 201 and 202

	Liraglutide	Placebo
FAS	N = 99	N = 106
Baseline mean	3.21	3.29
Change from baseline LS Means at week 56 (SE)	-0.24 (0.06)	-0.02 (0.06)
Treatment difference Lira - Placebo	-0.22 (0.09)	
95% CI P-value*	(-0.39, -0.05) 0.0109	
Multiple imputation: Jump-to-reference, *two-sided p-value Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment sex, region, baseline glycemic category, stratification factor for Tanner stage and interaction between baseline glycemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, age as covariates.		

Source: FDA Statistical Reviewer's Analysis

The results were highly similar to the overall results, providing confidence in the primary analysis. Furthermore, as discussed below, weight loss – which notably does not rely on measurement of height – was greater in the liraglutide group versus the placebo group in this trial to a clinically significant degree.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints were not adjusted for Type I error. Therefore, a selection of clinically relevant endpoints are included here in a descriptive fashion.

Change in BMI SDS at weeks 30 and 82

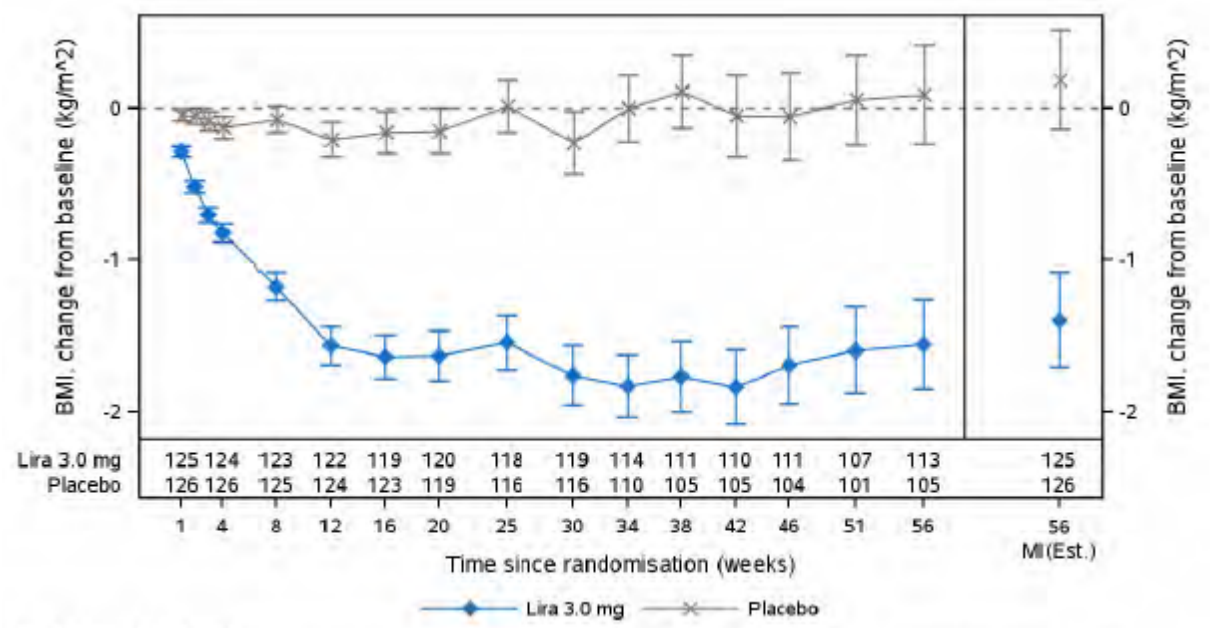
The estimated mean change in BMI SDS from baseline to week 30 was -0.25 in the liraglutide group and -0.04 in the placebo group. The estimated treatment difference (ETD) between liraglutide and placebo for the change in BMI SDS from baseline to week 30 was -0.21 (95% CI -0.30, -0.12).

The estimated mean change in BMI SDS from baseline to week 82 (26 weeks after treatment discontinuation) was -0.03 in the liraglutide group and +0.08 in the placebo group. The ETD between liraglutide and placebo for the change in BMI SDS from baseline to week 82 was -0.11 (95% CI -0.28, 0.06). Note that the 95% CI for the ETD includes zero, suggesting proportionally greater mean weight regain after drug discontinuation in the liraglutide group versus placebo, resulting in loss of treatment effect. This is not an unexpected finding.

Change in BMI at weeks 30, 56 and 82

At baseline, mean BMI in the liraglutide group was 35.3 kg/m^2 and in the placebo group was 35.8 kg/m^2. At week 30, the mean BMI was 33.9 kg/m^2 and the LS mean change in BMI was -1.7 kg/m^2 in the liraglutide group, and the mean BMI was 35.4 kg/m^2 and the LS mean change in BMI was -0.2 kg/m^2 (ETD -1.50 [95% CI -2.07, -0.93]). At week 56, the mean BMI was 34.2 kg/m^2 and the LS mean change in BMI was -1.4 kg/m^2 in the liraglutide group, and the mean BMI was 35.8 kg/m^2 and the LS mean change in BMI was -0.2 kg/m^2 (ETD -1.58 [95% CI -2.47, -0.69]). Figure 6 shows the trajectory in mean BMI by treatment over the randomized study period.

Figure 6: Change in BMI by Treatment Week



Source: Trial 4180 CSR, Figure 14.2.14

In the off-study-drug follow-up period (week 56 to week 82), the observed mean change in BMI was +1.5 kg/m^2 in the liraglutide group and +0.7 kg/m^2 in the placebo group.

Percent change in BMI at week 56

Mean percent change in BMI was not a pre-specified endpoint in the statistical analysis plan. However, because this endpoint is in favor for use in pediatric obesity trials, a *post hoc* analysis was requested of the sponsor for its inclusion in the label. At week 56, mean percent change in BMI from baseline was -4.29% in the liraglutide group and +0.35% in the placebo group for an ETD of -4.64%.

Categorical analyses of percent change from baseline in BMI were prespecified. At weeks 30 and 56, the estimated proportion of patients who achieved a reduction in BMI of ≥ 5% or ≥ 10% from baseline was greater in the liraglutide group than in the placebo group (Table 13).

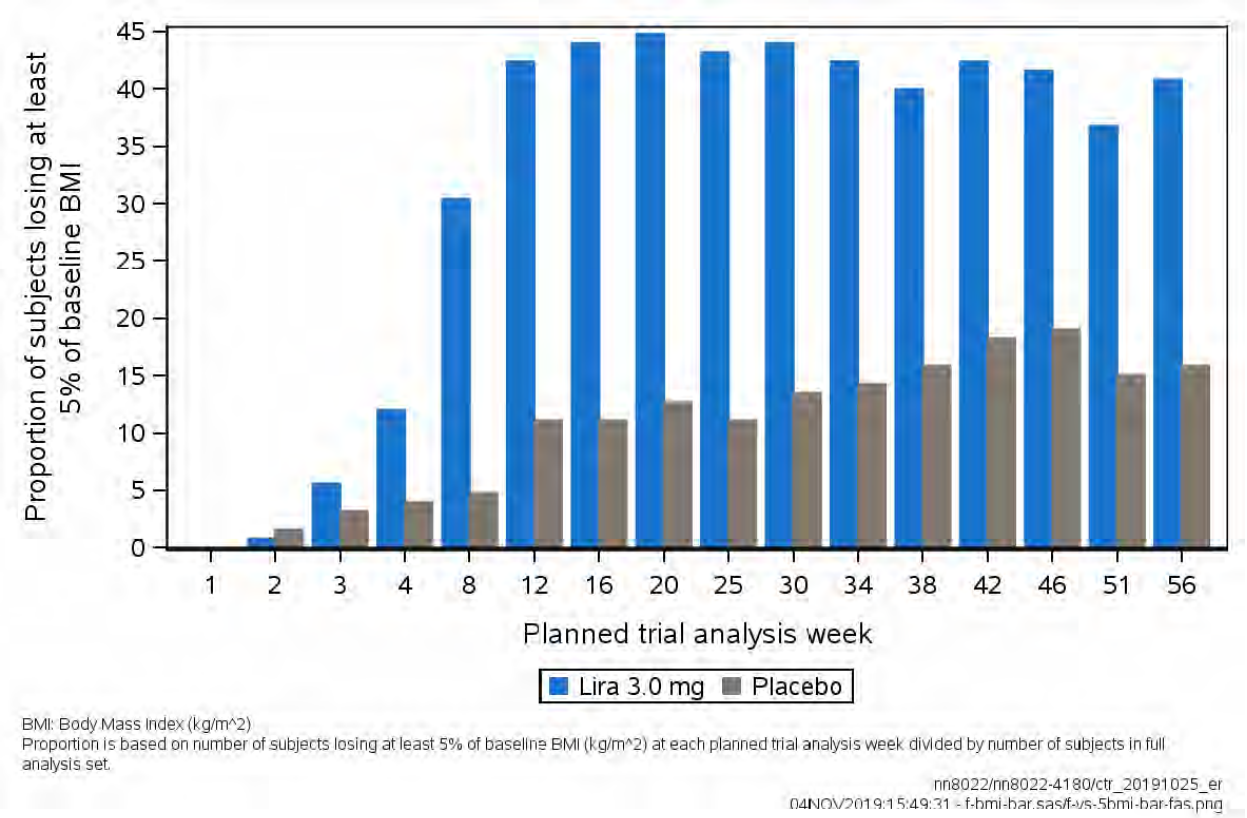
As noted above, after week 56 (during the off-drug follow-up period), patients on liraglutide regained some of the weight lost during the trial, which is reflected in the proportions with ≥ 5% and 10% BMI reduction at week 82 (Table 13). Note that at week 82, the 95% CI of the odds ratio includes 1 for both endpoints. Figure 7 and Figure 8 demonstrate the trajectory of at least 5% and 10% BMI decrease over the randomized treatment period (until week 56), respectively.

Table 13: Patients Losing at Least 5% or 10% of Baseline BMI after 30, 56, or 82 Weeks of Treatment

Endpoint	Liraglutide proportion	Placebo proportion	Odds ratio (95% CI)
≥ 5% reduction in BMI at week 30	44.51	13.68	5.06 (2.64, 9.71)
≥ 5% reduction in BMI at week 56	43.25	18.73	3.31 (1.78, 6.16)
≥ 5% reduction in BMI at week 82	27.46	18.79	1.64 (0.85, 3.13)
≥ 10% reduction in BMI at week 30	21.98	4.41	6.11 (2.38, 15.72)
≥ 10% reduction in BMI at week 56	26.08	8.11	4.00 (1.81, 8.83)
≥ 10% reduction in BMI at week 82	15.84	9.72	1.75 (0.78, 3.92)

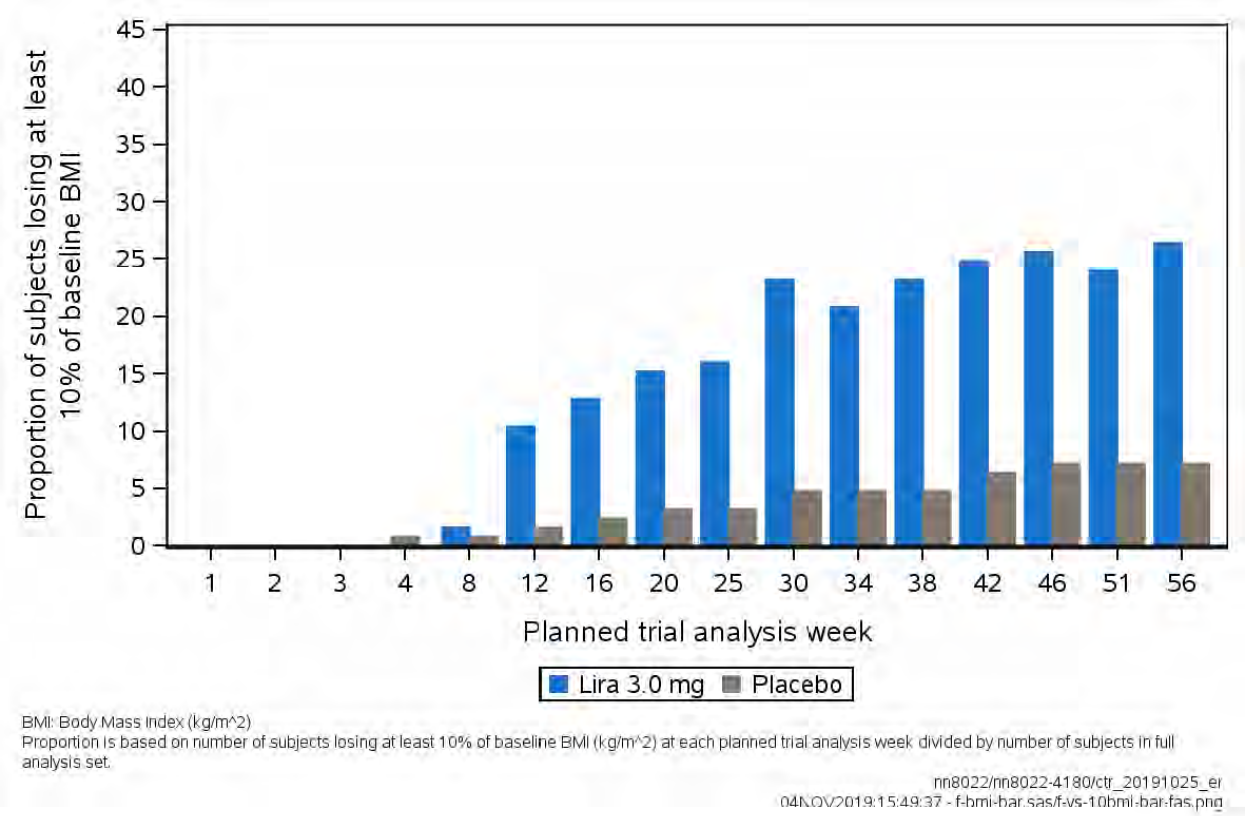
Source: Study 4180 CSR, Table 11-2

Figure 7: Proportion of Patients Losing at Least 5% Baseline BMI by Treatment Week



Source: Study 4180 CSR, Figure 14.2.19

Figure 8: Proportion of Patients Losing at Least 10% Baseline BMI by Treatment Week



Source: Study 4180 CSR, Figure 14.2.20

Change in Weight and Waist Circumference

The estimated mean change in body weight from baseline to weeks 30 and 56 for liraglutide versus placebo was:

Table 14: Change in Body Weight (kg and %), Weeks 30 and 56

	Liraglutide N=125	Placebo N=126	ETD (95% CI)
Body weight (kg)			
Week 30	-3.69 kg	+0.42 kg	-4.11 kg (-5.79, -2.44)
Week 56	-2.26 kg	+2.25 kg	-4.50 kg (-7.17, -1.84)
Body weight (%)			
Week 30	-4.03%	+0.42%	-4.45% (-6.09, -2.81)
Week 56	-2.65%	+2.37%	-5.01% (-7.63, -2.39)

Source: Study 4180 CSR, Table 11-7

In the off-study-drug follow-up period (week 56 to week 82), the observed mean change in body weight was +4.7 kg (5.3%) in the liraglutide group and +2.4 kg (2.3%) in the placebo group.

Table 15: Change in Waist Circumference (cm), Weeks 30 and 56

	Liraglutide N=125	Placebo N=126	ETD (95% CI)
Waist circumference (cm)			
Week 30	-4.46 cm	-1.98 cm	-2.48 cm (-4.10, -0.86)
Week 56	-5.12 cm	-1.51 cm	-2.93 cm (-5.24, -0.63)

Source: Study 4180 CSR, Table 11-8

In the off-study-drug follow-up period (week 56 to week 82), the observed mean change in waist circumference was +3.58 cm in the liraglutide group and +1.24 cm in the placebo group.

Change in Lipids

As seen in Table 16, mean lipid parameters changed little in the trial, and were not appreciably different between groups (in exploratory statistical analysis, the 95% CI for the treatment ratio [liraglutide/placebo] crossed 1 for all parameters).

Table 16: Mean Fasting Lipids at Baseline, Week 30, and Week 56

Endpoint (mg/dL)	Liraglutide			Placebo		
	Week 0	Week 30	Week 56	Week 0	Week 30	Week 56
Total cholesterol	156.6	155.8	154.7	155.1	151.6	152.4
LDL cholesterol	88.6	88.6	86.6	86.6	85.9	85.9
HDL cholesterol	43.7	45.2	45.2	44.1	43.7	44.5
Non-HDL cholesterol	112.9	110.6	109.4	111.4	107.9	107.9
Triglycerides	120.5	109.8	112.5	124.0	113.4	110.7

Source: Study 4180 CSR, Table 11-9; reviewer converted mmol/L to mg/dL using https://www.omnicalculator.com/health/cholesterol-units

Change in Blood Pressure

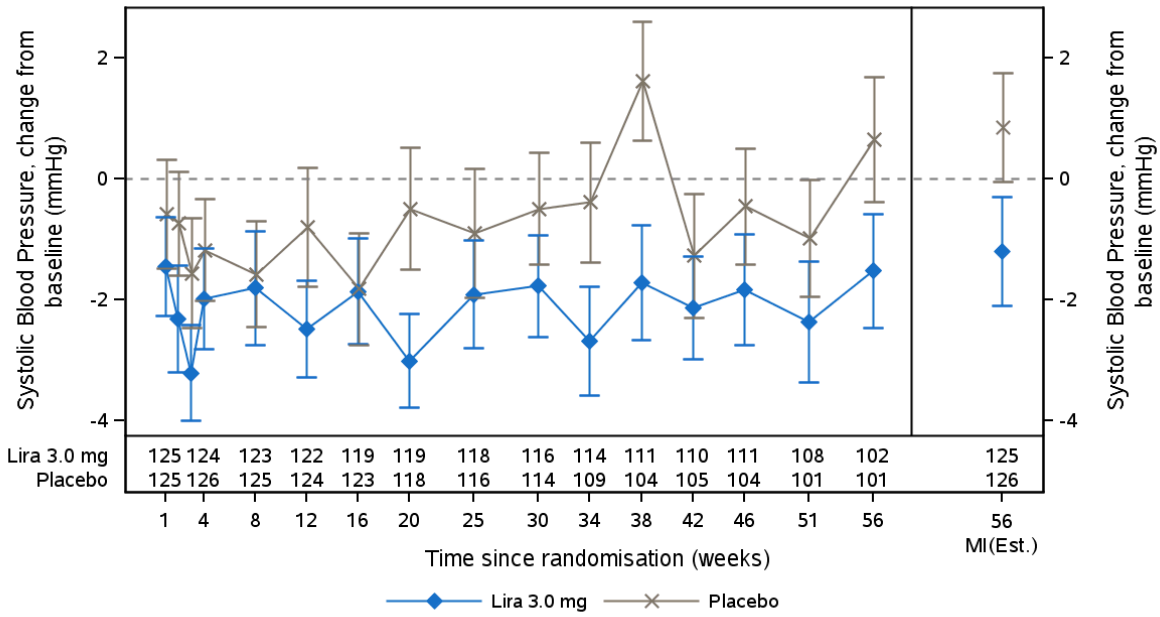
At baseline, systolic blood pressure (SBP) was 116 mmHg and 117 mmHg in the liraglutide and placebo groups, respectively, and diastolic blood pressure (DBP) was 72 mmHg and 73 mmHg, respectively.

At week 30, the estimated mean change in SBP from baseline was -2.03 mmHg in the liraglutide group and -0.19 mmHg in the placebo group, and the estimated treatment difference was -1.84 mmHg (-4.08, 0.41).

At week 56, the estimated mean change in SBP from baseline was -1.21 mmHg in the liraglutide group and 0.84 mmHg in the placebo group, and the estimated treatment difference was -2.05 mmHg (-4.53, 0.43).

Figure 9 illustrates the mean SBP over the study period by treatment.

Figure 9: Change in Systolic Blood Pressure (mmHg) by Treatment Week



Baseline is defined as latest pre-dosing value.
Mean values based on all in-trial observations. MI(Est.): Estimated treatment difference from ANCOVA model (Lira 3.0 mg - Placebo).
Bottom panel: Numbers of contributing subjects by treatment arm.
Error bar is: +/- standard error of mean.
Data from subjects who discontinued trial product before week 30 (Visit 19) or subjects who discontinued after week 30 (Visit 19) and before week 56 (Visit 25) their week 30 (Visit 19x) and week 56 (Visit 25x) respectively are included as week 30 (Visit 19) and week 56 (Visit 25).

nn8022/nn8022-4180/ctr_20191025_er
04NOV2019:15:50:52 - f-mean-eff.sas/f-vs-sbp-mean-wk56-fas.png

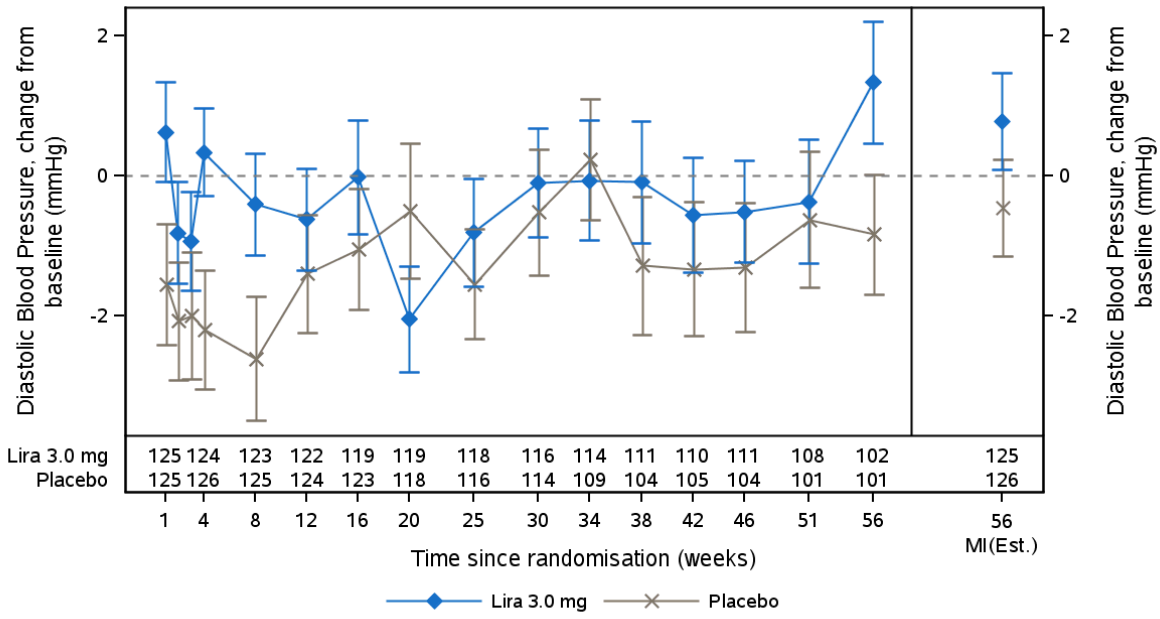
Source: Study 4180 CSR, Figure 11-7

At week 30, the estimated mean change in DBP from baseline was -0.51 mmHg in the liraglutide group and -0.50 mmHg in the placebo group, and the estimated treatment difference was -0.02 mmHg (-1.95, 1.92).

At week 56, the estimated mean change in DBP from baseline was 0.77 mmHg in the liraglutide group and -0.46 mmHg in the placebo group, and the estimated treatment difference was 1.24 mmHg (-0.66, 3.14). The mean DBP in the liraglutide group at week 56 was an outlier. The value was more than a full point higher than mean DBP in the liraglutide group at any timepoint after week 4, and the only mean DBP after week 4 above baseline in the liraglutide arm. The clinical significance of the increase relative to placebo is unclear.

Figure 10 illustrates the mean diastolic blood pressure over the study period by treatment.

Figure 10: Change in Diastolic Blood Pressure (mmHg) by Treatment Week



Baseline is defined as latest pre-dosing value.
Mean values based on all in-trial observations. MI(Est.): Estimated treatment difference from ANCOVA model (Lira 3.0 mg - Placebo).
Bottom panel: Numbers of contributing subjects by treatment arm.
Error bar is: +/- standard error of mean.
Data from subjects who discontinued trial product before week 30 (Visit 19) or subjects who discontinued after week 30 (Visit 19) and before week 56 (Visit 25) their week 30 (Visit 19x) and week 56 (Visit 25x) respectively are included as week 30 (Visit 19) and week 56 (Visit 25).

nn8022/nn8022-4180/ctr_20191025_er
04NOV2019:15:50:54 - f-mean-eff.sas/f-vs-dbp-mean-wk56-fas.png

Source: Study 4180 CSR, Figure 11-8

Changes in Glucose Metabolism

At baseline, mean HbA1c was 5.3% and mean fasting plasma glucose (FPG) was 93.6 mg/dL in both groups.

At week 30, the estimated treatment difference (liraglutide – placebo) for HbA1c was -0.10% (-0.17, -0.04) and the change in FPG was -3.6 mg/dL (-5.4, -1.8). At week 56, the estimated treatment difference for HbA1c was -0.06% (-0.14, +0.01) and the change in FPG was -1.8 mg/dL (-4.1, +0.54).

Although during the course of the trial fewer patients in the liraglutide arm had prediabetes-range glycemia, liraglutide was *not* associated with fewer patients developing type 2 diabetes (Table 17).

Table 17: Glycemic Category at Baseline, Week 30, and Week 56

	Liraglutide N=125	Placebo N=126
Baseline		
N	125	126
Normoglycemia	93 (74.4)	93 (73.8)
Prediabetes	31 (24.8)	32 (25.4)
Type 2 diabetes	1 (0.8)	1 (0.8)
Week 30		
N	116	116
Normoglycemia	95 (81.9)	86 (74.1)
Prediabetes	19 (16.4)	29 (25.0)
Type 2 diabetes	2 (1.7)	1 (0.9)
Week 56		
N	105	101
Normoglycemia	86 (81.9)	75 (74.3)
Prediabetes	17 (16.2)	24 (23.8)
Type 2 diabetes	2 (1.9)	2 (2.0)

Source: Study 4180 CSR, Table 11-16

The proportions of patients who were normoglycemic at baseline and developed prediabetes (category based on HbA1c and FPG) was 5.6% in the liraglutide group vs. 10.3% in the placebo group at week 30, and 8.0% vs. 7.1%, respectively, at week 56.

Conversely, the proportions of patients who were prediabetic at baseline and became normoglycemic was 13.6% liraglutide vs. 10.3% placebo at week 30, 12.8% vs. 7.1%, respectively, at week 56.

The proportion of patients who had prediabetes at baseline and progressed to a type 2 diabetes state was 0.8% liraglutide vs. 0 placebo at week 30, and 0.8% in both groups at week 56.

An exploratory analysis was conducted to evaluate the impact of liraglutide on the treatment difference for HbA1c and fasting plasma glucose (FPG) by baseline glycemic subgroups (normoglycemia and prediabetes/diabetes). Although all 95% CIs include zero, liraglutide appears to numerically reduce FPG versus placebo in the prediabetes/diabetes subgroup, but does not have much effect on HbA1c in either subgroup. This is consistent with very few patients having a type 2 diabetes diagnosis in the trial.

Table 18: Treatment Differences in HbA1c and Fasting Plasma Glucose (FPG) by Baseline Glycemia Subgroup

	Liraglutide	Placebo
HbA1c		
Normoglycemia		
n	93	93
Treatment Difference 95% CI	-0.07 -0.14, 0.01	
Prediabetes/diabetes		
n	32	33
Treatment Difference 95% CI	-0.03 -0.22, 0.16	
FPG		
Normoglycemia		
n	93	93
Treatment Difference 95% CI	-0.04 -0.17, 0.09	
Prediabetes/diabetes		
n	32	33
Treatment Difference 95% CI	-0.21 -0.53, 0.11	
n: number of observations Multiple imputation: Jump-to-reference Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment sex, region, baseline glycemic category, stratification factor for Tanner stage and interaction between baseline glycemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, age as covariates.		

Source: FDA Statistical Reviewer's Analysis

Change in IWQOL-Kids

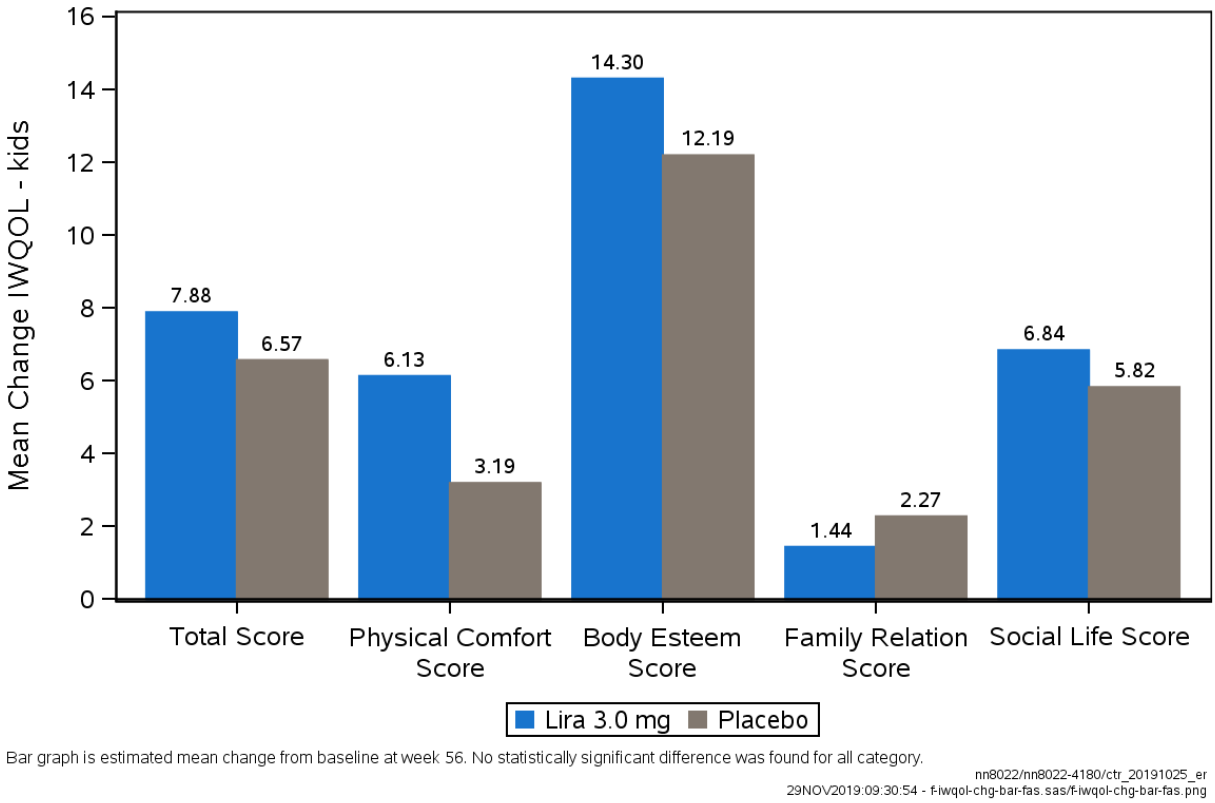
The IWQOL-Kids questionnaire was administered; the following four domain scores and a total score were calculated:

- Physical comfort
- Body esteem
- Social life
- Family life

The scale scores range from 0–100, with higher scores representing better health-related quality of life. Baseline mean total scores were 84.49 for the liraglutide group and 82.44 for the placebo group. Baseline mean domain scores were similar among groups, with the exception of the mean body esteem score, which was slightly higher for the liraglutide (72.74) versus placebo (67.99).

Figure 11 illustrates the mean changes in domain and total scores from baseline to week 56.

Figure 11: Change in IWQOL-Kids Score from Baseline at Week 56



Source: Study 4180 CSR, Figure 14.2.45

None of the 95% CIs for the estimated treatment differences crossed zero.

Dose/Dose Response

An evaluation of dose response was not conducted in this trial, as patients were all randomized to the same regimen.

The starting dose of liraglutide or placebo was 0.6 mg daily during the first week after randomization, and then was escalated in weekly increments of 0.6 mg to maximally tolerated dose (MTD) or 3 mg daily dose per schedule. The dose was escalated based on the patients' individual response to treatment (tolerability and safety as judged by the investigator). Dose escalation of the trial product was not allowed if the patient had a self-monitored plasma glucose <56 mg/dL, or <70 mg/dL in the presence of symptoms of hypoglycemia. If a patient experienced tolerability issues at the MTD during the trial, as judged by the investigator, the trial product dose could be lowered to the next lower dose level as needed. Following the 4- to

8-week dose escalation period, the dose levels of liraglutide and placebo remained relatively constant in most patients throughout the treatment period.

Table 19: Maximum Tolerated Dose Exposure

	Liraglutide N=125		Placebo N=126	
	n (%)	Median percentage of time on each dose	n (%)	Median percentage of time on each dose
0.6 mg	3 (2.4)	62.5	0	
1.2 mg	4 (3.2)	68.6	1 (0.8)	29.4
1.8 mg	4 (3.2)	86.0	1 (0.8)	14.3
2.4 mg	11 (8.8)	87.2	0	
3.0 mg	103 (82.4)	92.8	124 (98.4)	92.8

Source: Study 4180 CSR, Table 14.1.12

Durability of Response

See Figure 2, which illustrates the mean change in BMI SDS over the 56-week duration of the trial. The effect was durable over the treatment period.

Persistence of Effect

See the discussion of BMI SDS change and related parameters after study drug discontinuation, from weeks 56 to 82. In both groups, but to a greater extent in the liraglutide group, patients experienced mean increases in BMI SDS, BMI, and body weight, suggesting that drug effect does not persist after discontinuation.

Additional Analyses Conducted on the Individual Trial

None.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable; there was only one safety and efficacy 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 Saxenda in this population will likely be similar to the adult population, but will depend, at least in part, on drug availability, patient willingness to take a daily injectable medication on a chronic basis, adherence to lifestyle changes, and labeling (e.g., the stopping rule). Furthermore, although not observed in this trial, cardiometabolic improvements that are expected with Saxenda in adult patients with obesity could potentially occur in the adolescent population to the extent there is significant metabolic derangement. It is possible that adolescent patients have not had the degree of metabolic decompensation due to their obesity that adults have. The treatment paradigm in adolescents is generally one of prevention (i.e., treat adolescent obesity in order to prevent future adverse health effects).

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

Despite some concerns about the BMI SDS primary endpoint, given its ceiling effect, in a severely obese adolescent population, mean changes across a variety of supportive endpoints, such as BMI, weight, and waist circumference, support the efficacy of liraglutide in this population for the duration studied. Furthermore, missing data were reasonably low (particularly in the liraglutide group) and the primary analysis was supported by a number of sensitivity analyses, supporting the robustness of the estimated treatment effect.

There are some limitations to the efficacy evaluation. Cardiometabolic parameters that are expected to improve with weight loss (e.g., lipids, glycemic parameters, and blood pressure) were essentially unchanged. It should be noted that a lack of improvement in these parameters was also observed in the orlistat pediatric trial,[8] and might reflect the lack of metabolic decompensation in the adolescent population despite significant obesity.

[8] Kehoe T, clinical review of NDA 20766 S-018, 12 Dec 2003

Furthermore, metabolic changes in the liraglutide group were not worse, nor did they trend towards being worse, than metabolic changes in the placebo group.

Unsurprisingly, once liraglutide was discontinued, patients regained body weight. This phenomenon has been described in adults with this drug and others,[9] supporting the chronic nature of obesity treatment.

[9] See original clinical reviews for Saxenda (liraglutide, NDA 206321), Belviq (lorcaserin NDA 22529), and Xenical (orlistat NDA 20766)

8. Review of Safety

8.1. Safety Review Approach

There was only one trial submitted with this supplement. The safety review was informed by the well-characterized safety profile of liraglutide and other GLP1 RAs in the adult population (obesity and diabetes) and pediatric population (diabetes).

The applicant summarized AEs by three different periods, defined as follows:

- 'Run-in' period: Events with onset date between visit 2 (included) and the first day of trial product administration (not included). This review does not focus on AEs in the run-in period.

- 'In-trial' period: Events with onset date between the first day of trial product administration and the last study visit.

- 'On-treatment' period: Events with onset date between the first day of trial product administration and any of the following date, whichever came first:
    - 14 days after the last day on trial product, or
    - follow-up visit (visit 26) for patients with trial product discontinued, or
    - last study visit (patients withdrawn without follow-up visit)

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 'on-trial period'.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 251 patients, 125 in the liraglutide group and 126 in the placebo group, were exposed to study drug in this trial. Total patient-years of exposure were 125.6 and 124.9, respectively.

The mean duration of exposure was 52.4 weeks in the liraglutide group and 51.7 weeks in the placebo group during the 'on-treatment' period. The majority of patients in the liraglutide group (103 out of 125 patients, 82.4%) were escalated to the 3.0 mg dose and remained on this dose for 92.8% median time during the 56-week double-blind treatment period (see Table 19 under Section 6.1.2, Dose/Dose Response, above).

Table 20: Duration of Exposure

	Number of patients exposed to the study drug:		
	>= 1 dose	>=30 weeks	>=56 weeks
Liraglutide	N=125	N=111	N=101
Placebo	N=126	N=110	N=100

Source: Study 4180 CSR, Table 14.1.5

8.2.2. Relevant characteristics of the safety population:

Refer to Section 6.1.2 for discussion of demographic and baseline characteristics.

8.2.3. Adequacy of the safety database:

The number of adolescents and extent of exposure to liraglutide in this trial meets the expectations of the Division. The trial was not powered for any particular 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

No issues were identified.

8.3.2. Categorization of Adverse Events

MedDRA version 22.0 was used to code adverse events. I assessed the categorization of events by comparing the verbatim terms used by investigators to the preferred terms, focusing on events that led to discontinuation, temporary withdrawal of treatment, and dose reduction.

Reviewer comment: Based on this evaluation, I believe that AEs were generally categorized appropriately.

8.3.3. Routine Clinical Tests

Safety assessments and their timing can be found in the study flowchart (Appendix 13.3).

8.4. Safety Results

8.4.1. Deaths

There was one fatal adverse event in this trial, in the liraglutide group (1/125, 0.8%). Subject (b) (6) had an SAE of 'Completed suicide' after ~339 days (48.4 weeks) of trial product exposure, during the on-treatment period. The narrative for and full discussion of this event is

included in Section 8.4.4, which is a dedicated safety subsection that describes psychiatric adverse events including suicidality and related psychiatric questionnaires from this trial.

8.4.2. Serious Adverse Events

A total of 4 patients (3.2%) in the liraglutide arm and 9 patients (7.1%) in the placebo arm reported a serious adverse event (SAE) during the trial (Table 21). Of the SAEs listed in the table below (all SAEs 'in-trial'), 9 occurred during the 'on-treatment' period: 3 occurred in 3 patients in the liraglutide group (myositis, post-procedural hemorrhage, and completed suicide) and 6 occurred in 5 patients in the placebo group (appendicitis, pneumonia, cholecystitis acute, cholelithiasis, hemorrhagic ovarian cyst, and thrombophlebitis). The narrative for the completed suicide is included in Section 8.4.4, in the dedicated safety subsection on psychiatric events including suicidality. Narratives for the SAEs of myositis and post-procedural hemorrhage follow below.

Table 21: Serious Adverse Events, In-Trial

	Liraglutide		Placebo	
	N (%)	E (R)	N (%)	E (R)
Number of patients	125		126	
Patient-years of observation		188.9		186.5
Total SAEs	4 (3.2)	4 (21.2)	9 (7.1)	11 (59.0)
Psychiatric disorders	2 (1.6)	2 (10.6)	1 (0.8)	1 (5.4)
Suicide attempt	1 (0.8)	1 (5.3)	1 (0.8)	1 (5.4)
Completed suicide*	1 (0.8)	1 (5.3)	0	0
Injury, poisoning and procedural complications	1 (0.8)	1 (5.3)	2 (1.6)	2 (10.7)
Post procedural hemorrhage*	1 (0.8)	1 (5.3)	0	0
Ankle fracture	0	0	1 (0.8)	1 (5.4)
Intentional overdose	0	0	1 (0.8)	1 (5.4)
Infections and infestations	0	0	3 (2.4)	3 (16.1)
Appendicitis*	0	0	2 (1.6)	2 (10.7)
Pneumonia*	0	0	1 (0.8)	1 (5.4)
Musculoskeletal and connective tissue disorders	1 (0.8)	1 (5.3)	0	0
Myositis*	1 (0.8)	1 (5.3)	0	0
Hepatobiliary disorders	0	0	1 (0.8)	2 (10.7)
Cholecystitis acute*	0	0	1 (0.8)	1 (5.4)
Cholelithiasis*	0	0	1 (0.8)	1 (5.4)
Metabolism and nutrition disorders	0	0	1 (0.8)	1 (5.4)
Obesity	0	0	1 (0.8)	1 (5.4)

Reproductive system and breast disorders	0	0	1 (0.8)	1 (5.4)
Hemorrhagic ovarian cyst*	0	0	1 (0.8)	1 (5.4)
Vascular disorders	0	0	1 (0.8)	1 (5.4)
Thrombophlebitis*	0	0	1 (0.8)	1 (5.4)
* Occurred during the 'on-treatment' period				

Source: Study 4180 CSR, Table 14.3.1.24

- Myositis SAE (verbatim term: "Left arm and hand swollen and blue. Patient had a muscle inflammation that led to the immobilization and swelling of the arm."): Subject (b) (6) was a 15-year-old female from Sweden with a baseline BMI of 38.8 kg/m^2. Medical history included obesity, recurrent gastritis, hypothyroidism, crisis reaction and anxiety that started when parents separated, unspecific depressive episode, liver steatosis, and hypercholesterolemia. After 3 weeks on study drug, the patient sought medical attention at the ER because of sudden swelling and blueness of left arm and hand. On examination the arm was described as red and discretely swollen but within 30 minutes the symptoms resolved. The patient also experienced numbness of left arm and hand and difficulties moving the hand. The patient also complained of pain on palpation of the AC joint. Initially there was a suspicion of venous thrombosis and the patient was admitted to a pediatric ward for observation and further investigations. D-dimer and ultrasound of the venous system was performed, and the diagnosis of venous thrombosis was dismissed. The patient was also investigated with x-ray of lungs, left shoulder and clavicle which all were normal. Furthermore, laboratory testing with myoglobin, CK, electrolytes, creatinine, glucose, hemoglobin, leucocytes, neutrophils, lactate, INR, and activated partial thromboplastin time were all normal. C-reactive protein was 5 (no units and reference range provided) and red blood cell sedimentation rate was 25 (no units and reference range provided). The patient received two doses of dalteparin. Final diagnosis was muscle inflammation that led to the immobilization and swelling of the arm.

Reviewer comment: The report is somewhat unclear on the etiology of this event. There was not a description of the injection site in relation to the "muscle inflammation"; it seems unlikely but cannot be completely dismissed without additional information.

- Post procedural hemorrhage SAE (verbatim term: "Posttonsillectomy bleeding"): Subject (b) (6) was a 16-year-old male patient from the United States with a baseline BMI of 34.7 kg/m^2. Medical history included obesity. Approximately 2 months prior to starting treatment in the trial, the patient presented with adenoid and tonsillar hypertrophy. Approximately 6 weeks into the trial the patient had an adenotonsillectomy; 5 days later he presented to the ER with posttonsillectomy bleeding. The patient was admitted to the hospital and was taken into surgery where the active bleeding site was cauterized. He recovered and was discharged the following day.

Reviewer comment: This SAE – a common complication of tonsillectomy – appears unlikely related to liraglutide treatment.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Approximately 10% of patients treated with liraglutide and no patients randomized to placebo discontinued study drug due to an adverse event (Table 22). Most AEs leading to discontinuation were due to gastrointestinal disorders (nausea, vomiting, and abdominal pain). Discontinuations due to 'Pancreatitis' and 'Pancreatic enzymes increased' are discussed separately in Section 8.4.4, in the dedicated safety subsection on pancreatitis. Discontinuations due to 'Completed suicide' and 'Depression' are also discussed separately in the dedicated subsection on psychiatric disorders including suicidality.

The other AE leading to discontinuation was 'Injection site pain':

- Injection site pain AE leading to discontinuation: Subject (b) (6) was a 14-year-old female with a medical history of postural dizziness and vitamin D deficiency. The AE (mild severity) was reported on trial day 234, liraglutide was discontinued on day 379, and the AE was reported as recovered/resolved on day 407.

Table 22: Adverse Events Leading to Premature Discontinuation, On-Treatment

	Liraglutide		Placebo	
	N (%)	E (R)	N (%)	E (R)
Number of patients	125		126	
Patient-years of observation		125.6		124.9
Total AEs leading to drug discontinuation	13 (10.4)	19 (151.3)	0	0
Gastrointestinal disorders	10 (8.0)	15 (119.5)		
Vomiting	6 (4.8)	6 (47.8)		
Nausea	4 (3.2)	4 (31.9)		
Abdominal pain upper	2 (1.6)	2 (15.9)		
Abdominal discomfort	1 (0.8)	1 (8.0)		
Pancreatitis	1 (0.8)	1 (8.0)		
Retching	1 (0.8)	1 (8.0)		
Psychiatric disorders	2 (1.6)	2 (15.9)		
Completed suicide	1 (0.8)	1 (8.0)		
Depression	1 (0.8)	1 (8.0)		
General disorders and administration site conditions	1 (0.8)	1 (8.0)		
Injection site pain	1 (0.8)	1 (8.0)		

Investigations	1 (0.8)	1 (8.0)		
Pancreatic enzymes increased	1 (0.8)	1 (8.0)		

Source: Study 4180 CSR, Table 12-6

8.4.4. Significant Adverse Events

This section includes adverse events with additional data collection conducted by the applicant, in addition to adverse events and issues of medical interest compiled by the reviewer.

Acute Gallstone Disease

No patients randomized to liraglutide reported AEs of acute gallstone disease, in either the 'in-treatment' or 'in-trial' periods.

There were 5 AEs reported in 3 patients in the placebo group during the 'in-trial' period: 1 SAE of 'cholecystitis acute' and 1 SAE of 'cholelithiasis' in 1 patient (b) (6), 1 AE of 'cholelithiasis' in 1 patient (b) (6) and 2 AEs of 'Blood bilirubin increased' in 1 patient (b) (6)

Pancreatitis and Elevated Pancreatic Enzymes

Pancreatitis and suspicion of pancreatitis were to be reported as AEs by the investigator. In the case of acute, severe, persistent abdominal pain leading to a suspicion of acute pancreatitis, the trial product was to be interrupted until pancreatitis could be excluded. If acute pancreatitis was ruled out, the patient could resume dosing at the discretion of the investigator.

If an event of pancreatitis was observed during the trial, the following information was to be reported, if available, on the pancreatitis form:

- Signs and symptoms of pancreatitis
- Specific laboratory tests supporting a diagnosis of pancreatitis
- Imaging
- Treatment given
- Relevant risk factors

The clinical diagnosis of acute pancreatitis was considered 'confirmed' on the presence of at least 2 of the following diagnostic criteria:

- Severe acute abdominal pain
- Blood amylase and/or lipase >3x upper limit of normal (ULN)
- Characteristic findings on relevant imaging (e.g., computerized axial tomography/magnetic resonance imaging/ultrasound)

A MedDRA search to identify potential events of pancreatitis or suspected pancreatitis was performed based on prespecified narrow terms. Based on the MedDRA search, there were 2

AEs with the preferred term of 'Pancreatitis': 1 AE of 'clinically confirmed pancreatitis' was reported in 1 patient in the liraglutide group (and led to drug discontinuation) and 1 AE of 'suspicion of pancreatitis' reported by the physician that was not confirmed by laboratory results in 1 patient in the placebo group.

The narrative of the pancreatitis AE in the liraglutide group follows:

- Pancreatitis AE leading to discontinuation: Subject (b) (6) was a 14-year-old female from Belgium with a baseline BMI of 36.9 kg/m^2. Medical history included headache and nasopharyngitis. The patient was not on concomitant medications at the time of onset of the AE. On trial day 86, the patient experienced an AE of pancreatitis. The case report form noted the patient had abdominal pain. This event was reported as a non-serious event of moderate severity. The ultrasound imaging did not confirm a diagnosis of pancreatitis. At the time of the event this patient was noted to have increased lipase [lipase 91 U/L (normal range 4–29 U/L)]. Treatment with the trial product was discontinued as a result of the AE of pancreatitis. The event had an outcome of recovered on day 121 and was judged to be probably related to the trial product (liraglutide) by the investigator. This patient did not receive any treatment for the AE of pancreatitis. The patient was lost to follow-up and was later withdrawn from the trial.

Reviewer comment: Liraglutide and other GLP-1 RAs are associated with elevations in pancreatic enzymes of unclear clinical significance in the absence of other signs and symptoms of pancreatitis. In this case, 'confirmed' pancreatitis is based on modest lipase elevation and abdominal pain. I believe the event would be classified as 'mild' by the Atlanta criteria[10] (absence of organ failure or systemic complications), and it is possible that the ultrasound was negative because it is not a very sensitive diagnostic test for mild pancreatitis. It is noted that the patient recovered without treatment.

Although not reported as 'Pancreatitis', another patient randomized to liraglutide discontinued treatment due to AEs of 'Pancreatic enzymes increased', 'Retching', and 'Vomiting'.

- Pancreatitis enzymes increased AE leading to discontinuation: Subject (b) (6) was a 12-year-old female from Mexico with a baseline BMI of 28.8 kg/m^2. Medical history included hypertriglyceridemia and pancreatic enzymes increased (screening lipase 3 months prior to starting treatment 105 U/L, baseline 168 U/L). Concomitant medications taken at the time of onset of the AE included bezafibrate. On trial day 22, the patient experienced an AE of 'Pancreatic enzyme increased' of mild severity (lipase 483 U/L). On trial day 24, the patient

[10] Banks PA, et al. Classification of acute pancreatitis – 2012 revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62(1): 102.

experienced AEs of 'Retching' and 'Vomiting' of mild severity. No therapeutic measures were administered, and the investigator considered the AEs probably related to treatment. Treatment was discontinued on trial day 26 as a result of these AEs. Retching and vomiting were reported as recovered/resolved on trial day 27 and pancreatic enzymes increased was reported as recovered/resolved on trial day 351 (last recorded lipase 173 U/L).

Reviewer comment: Liraglutide can cause increases in pancreatic enzymes as well as vomiting, so the relationship to drug to this combination of events cannot be dismissed. It is noted, however, the patient has a history of increased pancreatic enzymes, and hypertriglyceridemia and use of bezafibrate are confounding factors. Imaging does not appear to have been done, so no conclusion can be drawn on whether this patient had a case of pancreatitis.

Pancreatic enzymes were measured at randomization and every 12-18 weeks during the trial. At baseline, mean amylase (51 U/L and 50 U/L) and lipase activity (27 U/L and 25 U/L) were similar in the liraglutide and placebo groups, respectively.

Small elevations in mean amylase and lipase, compared to baseline and to placebo, were observed during treatment with liraglutide. The following shift table demonstrates that more patients with liraglutide than placebo experienced amylase and particularly lipase >ULN during Weeks 30, 56, and 82. In some patients, elevations in lipase >ULN persisted even at the end of the off-drug follow-up period (Week 82).

Table 23: Amylase and Lipase, Shift from Baseline to Highest Value

	Low or Normal at Week 0			High at Week 0		
	>ULN	>2xULN	>3xULN	>ULN	>2xULN	>3xULN
Amylase						
Week 30						
Lira N=125	4/122 (3.3)	0	0	1/3 (33.3)	0	0
Placebo N=126	3/123 (2.4)	0	0	2/3 (66.7)	0	0
Week 56						
Lira N=125	3/122 (2.5)	0	0	0	0	0
Placebo N=126	0	0	0	1/3 (33.3)	0	0
Week 82						
Lira N=125	1/122 (0.8)	0	0	0	0	0
Placebo N=126	1/123 (0.8)	0	0	2/3 (66.7)	0	0
Lipase						
Week 30						
Lira N=125	25/103 (24.3)	0	0	11/22 (50.0)	3/22 (13.6)	1/22 (4.5)
Placebo N=126	10/101 (9.9)	0	1/101 (1.0)	11/25 (44.0)	1/25 (4.0)	0
Week 56						
Lira N=125	10/103 (9.7)	0	0	11/22 (50.0)	1/22 (4.5)	0
Placebo N=126	4/101 (4.0)	0	0	7/25 (28.0)	1/25 (4.0)	0

Week 82						
Lira N=125	10/103 (9.7)	0	0	11/22 (50.0)	0	0
Placebo N=126	2/101 (2.0)	0	0	7/25 (28.0)	0	0

Source: Study 4180 CSR, Table 14.3.5.4 (numerators); Table 14.3.5.6 (denominators)

No patients had amylase >3×ULN in this trial. Four patients (2 patients in the liraglutide group and 2 patients in the placebo group) had lipase >3×ULN. (Note: not all incidences were captured in the above table, which shows only selected visits.) The liraglutide patients with lipase >3xULN were (b) (6) (AE: 'Pancreatitis') and (b) (6) (AE: 'Pancreatic enzymes increased') and are described in the narratives above. The 2 patients on placebo with lipase >3xULN did not have associated AEs reported. One occurrence was at screening (105 U/L) and one was at Week 30 (210 U/L).

As noted below in Section 8.4.5 with the discussion of common AEs (Table 31), the preferred term 'Lipase increased' was reported more frequently in liraglutide-treated patients (3.2%) as compared to placebo-treated patients (0.8%). None of the liraglutide-treated patients with this AE reported had lipase values >3xULN.

Neoplasms

A predefined MedDRA search for neoplasms was performed based on the SMQs to identify and summarize all *potential* neoplasm events. Based on the MedDRA search, there were 6 AEs reported in 4 patients in the liraglutide group and 3 AEs reported in 3 patients in the placebo group during the in-trial period.

Neoplasm AEs in the liraglutide group were: 'Benign pituitary tumor' (1 patient), 'Skin papilloma' (2 events in 1 patient), 'Cyst' (1 patient), 'Ovarian cyst' (1 patient), and 'Acanthosis nigricans' (1 patient). Neoplasm AEs in the placebo group were: 'Benign pituitary tumor' (1 patient), 'Cyst' (1 patient), and 'Hemorrhagic ovarian cyst' (1 patient).

The only neoplasm SAE reported was the hemorrhagic ovarian cyst in the placebo group (Table 21).

The AEs of pituitary tumor ('Pituitary adenoma' and 'Pituitary microadenoma' in the liraglutide and placebo groups, respectively), were the only AEs from the system organ class 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)'. The pituitary adenoma in the liraglutide patient is described as follows:

- Pituitary adenoma AE: Subject (b) (6) was a 14-year-old male patient with a history of obesity and hypercholesterolemia. On trial day 123, an AE of 'pituitary tumor benign' was reported, which was of mild severity. No action was taken with the trial product as a result of the event. No therapeutic measures were administered to treat the AE. The investigator

considered the AE to be unlikely related to the trial product. The outcome of the event was reported as recovered/resolved on day 516. The patient completed the trial on day 589.

Reviewer comment: There was no information regarding the circumstances regarding the diagnosis of this adenoma (i.e., whether it was found incidentally or due to symptoms). No information was provided that would allow for a determination of causality.

Psychiatric Adverse Events, Including Suicidality

Psychiatric events were not collected in this trial as adverse events of special interest; however, suicidality and depression are safety issues of concern for all the centrally acting obesity drugs.[11,12,13,14] Suicidal behavior and ideation are labeled in the Warnings and Precautions section of the Saxenda label due to an imbalance in the phase 3 trials of 9 Saxenda patients (0.3%) to 2 placebo patients (0.1%).[15]

The adolescent population (of any BMI) might be especially vulnerable to this risk.[16] Notably, children and adolescents have been shown to be at increased risk of suicidality when treated with antidepressant medications.[17]

Mental health was prospectively monitored in this adolescent trial using questionnaires recommended by FDA for suicidality (Columbia-Suicide Severity Rating Scale, C-SSRS[18,19]) and mood (Patient Health Questionnaire-9, PHQ-9[20]).

Table 24 presents all AEs on-treatment in the 'Psychiatric disorders' MedDRA system organ class (SOC) and by preferred term (PT). There was no imbalance of events overall. Narratives of events of special interest in the liraglutide group, specifically deaths, SAEs, discontinuations, and events of suicidality, are presented.

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[11] Egan A. FDA Clinical Review of NDA 21888 (rimonabant), EMDAC 13 Jun 2007.
[12] Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 Sep 2010 and 10 May 2012.
[13] Roberts M. FDA Clinical Review of NDA 22580 (phentermine/topiramate), EMDAC 15 July 2010 and 22 Dec 2012.
[14] Craig E. FDA Clinical review of NDA 200063 (naltrexone/bupropion), EMDAC 7 Dec 2010.
[15] Saxenda (liraglutide) package insert.
[16] Cash SK and Bridge JA. Epidemiology of youth suicide and suicidal behavior. Curr Opin Pediatr. 2009; 21(5): 613-9.
[17] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications
[18] https://cssrs.columbia.edu/
[19] FDA *Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*, August 2012.
[20] Kroenke K, et al. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9): 606-13.

Table 24: Psychiatric Adverse Events, On-Treatment

	Liraglutide N=125		Placebo N=126	
	n (%)	Events (Rate/1000 PY)	n (%)	Events (Rate/1000 PY)
Psychiatric disorders SOC	13 (10.4)	16 (127.4)	18 (14.3)	21 (168.1)
Depression	5 (4.0)	5 (39.8)	3 (2.4)	3 (24.0)
Depressed mood	2 (1.6)	3 (23.9)	2 (1.6)	2 (16.0)
Insomnia	1 (0.8)	1 (8.0)	4 (3.2)	4 (32.0)
Sleep disorder	1 (0.8)	1 (8.0)	1 (0.8)	1 (8.0)
Suicidal ideation	1 (0.8)	1 (8.0)	1 (0.8)	1 (8.0)
Bulimia nervosa	1 (0.8)	1 (8.0)	0	0
Completed suicide	1 (0.8)	1 (8.0)	0	0
Eating disorder	1 (0.8)	1 (8.0)	0	0
Panic attack	1 (0.8)	1 (8.0)	0	0
Social anxiety disorder	1 (0.8)	1 (8.0)	0	0
Anxiety	0	0	3 (2.4)	3 (24.0)
Nightmare	0	0	1 (0.8)	2 (16.0)
Attention deficit / hyperactivity disorder	0	0	1 (0.8)	1 (8.0)
Fear of injection	0	0	1 (0.8)	1 (8.0)
Negative thoughts	0	0	1 (0.8)	1 (8.0)
Stress	0	0	1 (0.8)	1 (8.0)
Tic	0	0	1 (0.8)	1 (8.0)

Source: Study 4180 CSR, Table 14.3.1.7

- Completed suicide fatal SAE: Subject (b) (6) was a 17-year-old Black male patient with medical history of obesity (baseline weight 93.3 kg, baseline BMI 35.8 kg/m^2, and baseline BMI SDS 3.1) and attention deficit hyperactivity disorder (ADHD). The patient had no history of psychiatric disease, had never been diagnosed with depression, other mood disorders, anxiety, or sleep disorder. The patient had never demonstrated any suicidal behavior.

  Concomitant medications included atomoxetine hydrochloride, paracetamol, and ibuprofen. Atomoxetine was stopped approximately 3 months into the trial after the patient graduated from high school. He elected to not continue with any other ADHD medications at that time.

  After approximately 11 months in the trial, the patient completed suicide by drowning. It was unknown if an autopsy was performed or planned.

  Despite the ADHD diagnosis, there was no report of impulsivity or any acute stress that site was made aware of or reported by the patient.

There was no relevant co-reported event in relation to the suicide.

It was reported unknown if there were any (social or environmental) circumstances that may have led/contributed to the event (e.g., death in the family, divorce/break-up, unemployment/financial problems, illicit drug use, chronic physical illness or stress).

According to the Investigator, the site worked with the patient very closely during his visits and "there were no indications concerning his ADHD". The patient was a shift leader at his job and doing very well, and he was also planning trips with his friends. There were reportedly no behavioral concerns noted by the site. Furthermore, the C-SSRS and PHQ-9 did not indicate any suicidality or depression prior to the event.

Multiple queries regarding circumstances which may have led/contributed to the event, if an autopsy was performed or not, and why the drowning was considered a suicide were made to the family, but no responses were received.

Per Investigator, the site had no further information to provide and was not expecting to receive any.

Reviewer comment: Not enough information was provided regarding the circumstances of the fatal event to make a clinical judgment about this case. There was a temporal relationship to liraglutide, so a causal relationship cannot be completely dismissed.

- Depression AE leading to discontinuation: Subject (b) (6) was a 12-year-old female with a medical history of arthralgia and taking no concomitant medications. On trial day 258, the patient experienced an AE of 'Depression' considered of moderate severity. No therapeutic measures were administered to treat the AE. Treatment with liraglutide was discontinued on trial day 276 as a result of the AE and the patient discontinued the trial. The investigator considered the AE of depression unlikely related to the trial product. The outcome of the AE was reported as recovering/resolving.

Reviewer comment: There was a temporal relationship to liraglutide, so a causal relationship cannot be completely dismissed.

- Suicidal ideation AE: Subject (b) (6) was a 14-year-old female with a history of obesity. Vitamin D deficiency, and suicidal ideation and suicide thoughts or attempts with positive response on the screening C-SSRS questionnaire indicating wish to be dead. On trial day 1, the patient experienced an AE of 'Suicidal ideation' of mild severity. The AE was further described in the verbatim term as: "affirmative responses for C-SSRS question 1 - 'wish to be dead' and question 2- 'non-specific suicidal thought' with no resultant complication." No

action was taken with the trial product as a result of this AE. No therapeutic measures were administered to treat the AE. The investigator considered the AE to be unlikely related to the trial product. The outcome of the event was reported as recovered/resolved on trial day 8. The patient completed the trial on trial day 931.

Reviewer comment: As this event occurred on trial day 1 (apparently part of baseline questionnaires), this event would seem to be unrelated to liraglutide, although it is unclear why it is considered 'on-treatment'. Importantly, the patient recovered from the event after 1 week and she continued in and completed the trial.

As described in Table 21 (SAEs), 2 events of suicide attempt, 1 in a liraglutide-treated patient, and 1 in a placebo-treated patient were reported in the trial; both occurred 'off-treatment', 'in-trial'. The following is the narrative for the liraglutide-treated patient:

- Suicide attempt SAE (on-trial but non-treatment-emergent): Subject (b) (6) was a 14-year-old male with a history of depression on sertraline. Two months after discontinuing liraglutide, the patient attempted suicide (PT: 'Suicide attempt'). By report, the patient went to bed on the night of the event after taking extra doses of his sertraline with the intent to not wake up in the morning. Once the patient woke up the next morning, he informed his mother what he did with the intention of not waking up the next day and was admitted into the hospital for one week. Sertraline was discontinued. Prior to the attempt, the patient was seeing a counselor frequently. The C-SSRS assessment had not indicated any suicidal ideation/behavior in this patient prior to the occurrence of the SAE. The PHQ-9 total score was below 10 for this patient at all the visits prior to the occurrence of the SAE. According to investigator depression was a baseline condition and the patient had no history of suicide attempts before the event. One month after the event, the patient and his guardian attended the site for Visit 28. As part of the C-SSRS evaluation, he denied any suicidal thoughts, ideations, or attempts. Following the site visit, the patient's psychiatrist placed him on clonidine and escitalopram for worsening depression.

Reviewer comment: This case is highly confounded by history of depression and sertraline use (SSRIs have been associated with suicidality in children and adolescents). Furthermore, the patient had not been on liraglutide for 2 months. Therefore, it seems unlikely related to the investigational drug, although the relationship of the event to his participation in this weight loss trial cannot be excluded.

PHQ-9

The PHQ-9 is a 9-item depression subscale of the self-administered patient health questionnaire (mental disorder instrument for use in primary care).[20] The patient rates the frequency of the following 9 items on the scale from 0 (not at all) to 3 (nearly every day) in the last 2 weeks:

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed, or the opposite – being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or hurting yourself in some way

The total score ranges from 0 to 27. Total scores of 0–4 represent no to minimal depression, total scores of 5–9 represent mild depression, total scores of 10–14 represent moderate depression, total scores of 15–19 represent moderately severe depression, and total scores of 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," counts if present at all, regardless of duration.

Before making a final diagnosis, the clinician is expected to rule out physical causes of depression, normal bereavement, and history of a manic episode.[20]

At baseline, the mean PHQ-9 total scores for depression were similar between liraglutide (4) and placebo (4). During the treatment period, the mean PHQ-9 total scores decreased slightly (improvement) in both treatment groups. The maximum PHQ-9 total score recorded was 27 (liraglutide). A summary of results is presented in Table 25 and Table 26.

Table 25: PHQ-9 – Total Scores in the Treatment Period

	Liraglutide N=125	Placebo N=126
Baseline		
N	124	126
Mean (SD)	4 (3)	4 (3)
Median	3	3
Min, Max	0, 13	0, 14
Week 30		
N	114	115
Mean (SD)	3 (4)	3 (4)
Median	1	2
Min, Max	0, 27	0, 20
Week 56		
N	102	100
Mean (SD)	2 (3)	3 (3)
Median	1	2
Min, Max	0, 14	0, 17

Source: Study 4180, CSR Table 12-17

Table 26: PHQ-9 Category Summary, Post-Baseline

	Liraglutide N=125		Placebo N=126	
	n (%)	E	n (%)	E
Moderate ≥ 10 to < 15	13 (10.4)	43	25 (19.8)	60
Moderately Severe ≥ 15 to < 20	4 (3.2)	13	8 (6.3)	14
Severe ≥ 20	7 (5.6)	7	2 (1.6)	3

Source: Response to Clinical Information Request #7, Table 1-6

As per the protocol, patients who had a PHQ-9 score ≥ 15 on any questionnaire were referred to a mental health professional (MHP). However, 9 patients with PHQ-9 score ≥ 15 were not referred to an MHP, and an important protocol deviation was documented.

The majority of patients (> 90%) answered Question 9 ("thoughts that you would be better off dead or hurting yourself in some way") as "not at all" at baseline and at all visits during the trial, in both groups. At Week 56, 2 patients (1.6%) in the liraglutide group and 5 patients (4.0%) in the placebo group reported an increase in this question ("not at all" to "several days" in the last 2 weeks).

C-SSRS

The C-SSRS is a standardized assessment to quantify the severity of suicidal ideation and behavior,[21] and was utilized at all visits. The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of the ideation, and 6 questions addressing suicidal behavior. The following categories are used in order to classify the events:

- Suicidal ideation:
  1. Wish to be dead (type 1)
  2. Non-specific active suicidal thoughts (type 2)
  3. Active suicidal ideation with any methods (not plan) without intent to act (type 3)
  4. Active suicidal ideation with some intent to act, without specific plan (type 4)
  5. Active suicidal ideation with specific plan and intent (type 5)

- Suicidal behavior:
  1. Completed suicide
  2. Actual suicide attempt
  3. Interrupted suicidal attempt
  4. Aborted suicide attempt
  5. Preparatory acts or behavior towards making a suicidal attempt

- Non-suicidal self-injurious behavior

Patients reporting active suicidal ideation on the C-SSRS at screening and randomization were excluded from the trial. The lifetime C-SSRS assessment performed at screening identified a total of 10 (8.0%) patients with lifetime suicidal behavior and/or ideation with liraglutide and 4 patients (3.2%) with placebo. There were 2 patients (1.6%) in the liraglutide group and 3 patients (2.4%) in the placebo group who had reported suicidal ideation or suicidal behavior at baseline (week 0).

There were no type 4 or 5 positive responses recorded on the C-SSRS for suicidal ideation or behavior in this trial. A similar proportion of patients in each group had any positive response on the C-SSRS:

[21] Posner K, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Amer J Psych. 2011; 168: 1266-77.

Table 27: C-SSRS, Any Positive Response

	Liraglutide N=125	Placebo N=126
Patients with any positive responses to suicidal behavior and/or ideation in the C-SSRS	13 (10.4)	14 (11.1)
Suicidal ideation	11 (8.8)	12 (9.5)
Suicidal behavior	4 (3.2)	4 (3.2)

Source: Response to FDA Clinical Information Request 27 July 2020, Table 8

Hypoglycemia

At randomization, patients were provided with a blood glucose (BG) meter and instructions for use for self-monitored plasma glucose (SMPG). At each visit, the patient demonstrated how to use the BG meter device by measuring the SMPG. The SMPG measurement was required before instructing the patient in dose escalation; see Section 6.1.1 for details of glucose requirements for dose escalation.[22]

Patients were instructed in symptoms of hypoglycemia and were to conduct SMPG anytime (including between visits) in the event a hypoglycemic episode was suspected. All plasma glucose values occurring in conjunction with hypoglycemic symptoms were reported. Upon onset of a hypoglycemic episode, the patient was to measure plasma glucose every 15 minutes until the SMPG value was > 70 mg/dL and/or the symptoms were resolved. Patients were to contact the investigator in case of low SMPGs.

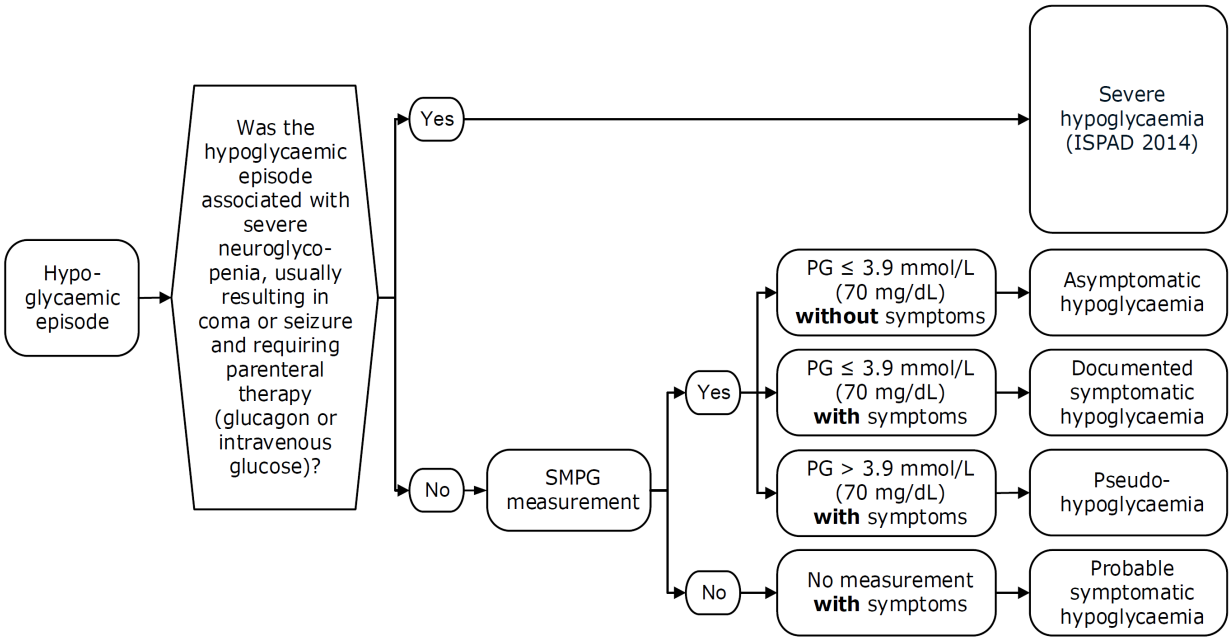
A hypoglycemic episode during the trial was to be recorded as an AE according to standard AE reporting.[23] If the hypoglycemic episode fulfilled the criteria for an SAE, then an AE form and a safety information form was to be filled in.

If the question, "Was the hypoglycemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?" was answered "yes", the hypoglycemic episode was classified as "severe".

Classifications according to American Diabetes Association/International Society for Pediatric and Adolescent Diabetes (ADA/ISPAD) and Novo Nordisk (NN) are presented in the figures below.

[22] Note that this glucose monitoring protocol prior to dose escalation is in contrast to the weight management trials in adults without diabetes, in which BG meters were not provided and no systematic measurement of BG was done.
[23] Hypoglycemia was recorded in a separate database (ADHYPO) in this NDA; not the AE database (ADAE).

Figure 12: ADA/ISPAD Classification of Hypoglycemia in Pediatrics

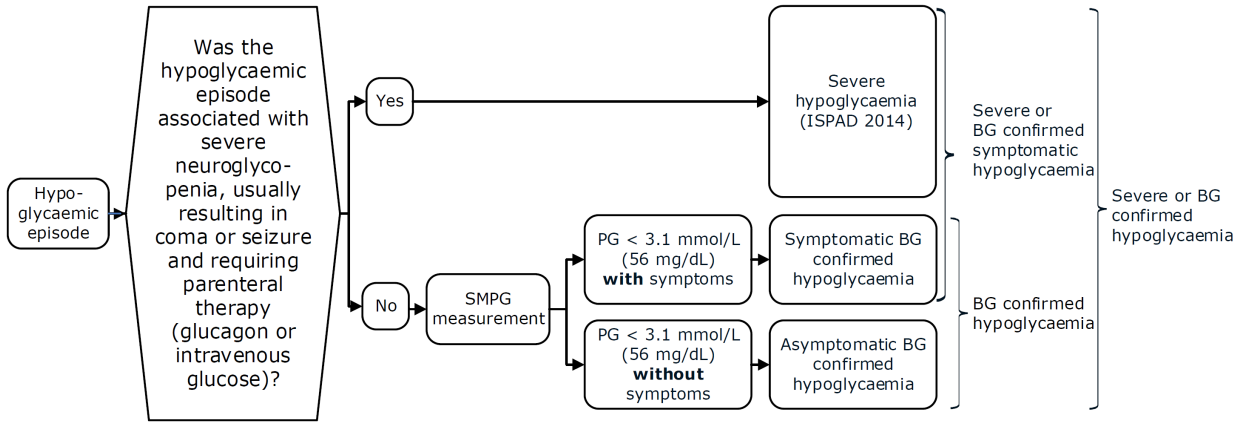


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

PG: plasma glucose SMPG: Self-measured plasma glucose

Source: Study 4180 Protocol, Figure 17-2

Figure 13: NN Classification of Hypoglycemia in Pediatric Patients



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

Source: Study 4180 Protocol, Figure 17-1

No severe hypoglycemic events were reported in the liraglutide- or placebo-treated patients during the trial. No hypoglycemia SAEs were reported. No hypoglycemia events led to treatment discontinuation.

Table 28 enumerates hypoglycemic episodes overall and by classification category. In the liraglutide group, 26 patients (20.8%) reported 78 hypoglycemic events (621.2 episodes per 1000 on-treatment PYE) and in the placebo group, 18 patients (14.3%) reported 28 events (224.1 episodes per 1000 on-treatment PYE).

Table 28: Hypoglycemic Episodes by Classification, On-Treatment

	Liraglutide N=125 125.6 PYE		Placebo N=126 124.9 PYE	
	n (%)	Events (/1000PY)	n (%)	Events (/1000PY)
Hypoglycemic episodes	26 (20.8)	78 (621.2)	18 (14.3)	28 (224.1)
ADA/ISPAD classification				
Severe hypoglycemia	0		0	
Asymptomatic hypoglycemia	8 (6.4)	12 (95.6)	14 (11.1)	17 (136.1)
Documented symptomatic hypoglycemia	19 (15.2)	31 (246.9)	5 (4.0)	6 (48.0)
Probable symptomatic hypoglycemia	1 (0.8)	1 (8.0)	2 (1.6)	2 (16.0)
Pseudo-hypoglycemia	7 (5.6)	30 (238.9)	3 (2.4)	3 (24.0)
Unclassifiable	3 (2.4)	4 (31.9)	0	
NN classification				
Severe hypoglycemia	0		0	
Asymptomatic BG < 56 mg/dL	1 (0.8)	1 (8.0)	1 (0.8)	1 (8.0)
Symptomatic BG < 56 mg/dL	3 (2.4)	4 (31.9)	0	
Unclassifiable	25 (20.0)	73 (581.3)	17 (13.5)	27 (216.1)
BG < 54 with or without symptoms	2 (1.6)	4 (31.9)	1 (0.8)	1 (8.0)

Source: Study 4180 CSR, Table 14.3.1.61, Response to FDA Clinical Information Request 27 July 2020, Table 1-1

Further information about patients with any hypoglycemia episodes is as follows:

Table 29: Selected Characteristics of Patients with Hypoglycemia Episodes

	Liraglutide n=26	Placebo n=18
Mean age (SD), y	14.54 (1.33)	14.56 (1.54)
Female, n (%)	20 (76.9)	11 (61.1)
Mean BMI (SD), kg/m^2	35.05 (3.94)	36.59 (6.77)
Baseline diabetes status, n (%)		
Normoglycemia	17 (65.4)	10 (55.6)
Pre-diabetes	9 (34.6)	8 (44.4)
Diabetes	0	0
Blood glucose (mg/dL) at time of event[a]		
Mean (SD)	64.5 (10.3)	65.8 (5.2)
Median	66.0	66.3
Min, Max	43.2, 93.7	52.3, 74.0
a If there were multiple events for a single patient, the lowest glucose value was used		

Source: Reviewer created from ADHYPO dataset

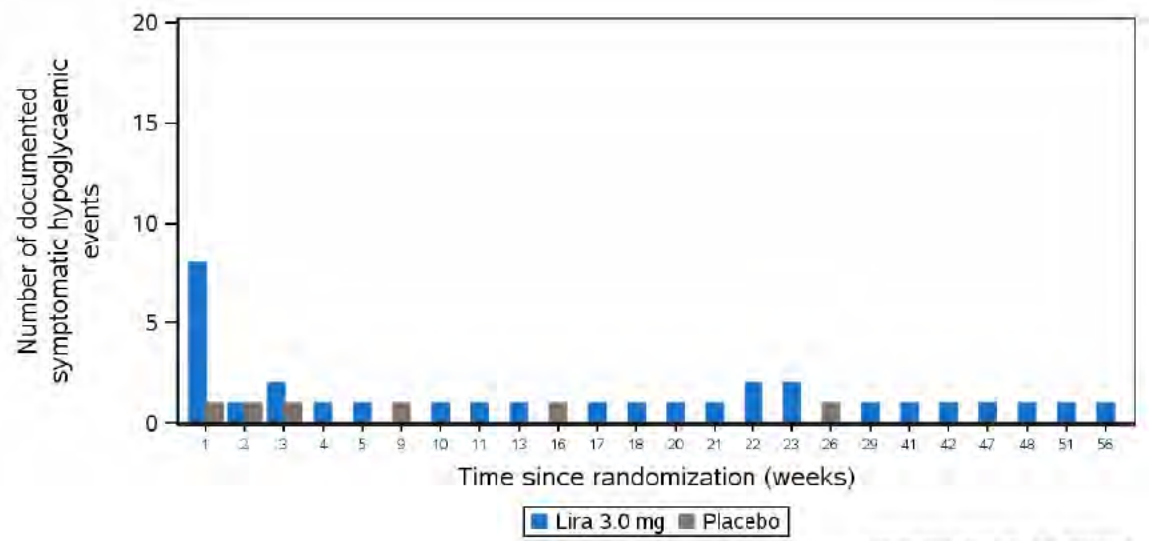
Table 30 provides a statistical analysis of documented symptomatic events by ADA/ISPAD classification, where the imbalance was observed, and Figure 14 below illustrates that while there was a slightly higher frequency of events the first week, documented symptomatic hypoglycemia was reported by patients in the liraglutide group throughout the trial.

Table 30: Documented Symptomatic Hypoglycemia, In-Trial, Statistical Analysis

	Liraglutide	Placebo
Safety Population	N = 125 n (%)	N = 126 n (%)
Yes DSH	19 (15.2%)	5 (4.0%)
Difference in % (95% CI)	11.23 (4.07, 18.39)	
Nominal P-value	0.0025	
Number of Events	31	6
Rate ratio (95% CI)	5.93 (2.08, 16.95)	
Nominal P-value	0.0010	
Abbreviations: DSH: Documented Symptomatic Hypoglycemia, Lira: liraglutide, Yes DSH: number of patients with at least one event Rate Ratio with 95% CL and p-values were obtained from a GLM, which included treatment, sex, region, baseline glycemic category, stratification factor for Tanner stage and interaction between baseline glycemic category and stratification factor for Tanner stage as fixed effects, age as factors and an offset term for log of study duration. The event rates were modeled as a negative binomial process.		

Source: FDA Statistical Reviewer's Analysis; adhypo.xpt

Figure 14: Documented Symptomatic Hypoglycemia Events by Study Week



Source: Response to FDA Clinical Information Request #8, Dated Nov 5, 2020, Figure 4

According to information provided in the concomitant medication dataset (in a reviewer's search of concomitant glucose-lowering therapies), two patients, one on liraglutide (1/26, 3.8%) and one on placebo (1/18, 5.6%), were taking concomitant metformin at the time of a hypoglycemia episode. (Another liraglutide patient appears to have been started on metformin during the trial, but not at the time of the hypoglycemia event.) Antidiabetic therapies other than metformin were prohibited in this trial.

Finally, it should be noted that according to the Victoza (liraglutide for type 2 diabetes) label, the risk of hypoglycemia was higher in pediatric patients 10 years of age and older than adults, regardless of concomitant antidiabetic therapies.

Thyroid Neoplasms and Calcitonin

Given the boxed warning of thyroid c-cell neoplasms for GLP1 RAs, thyroid neoplasms, particularly medullary thyroid cancer, and increases in calcitonin continue to be events of interest for liraglutide.

There were no thyroid neoplasms in this trial. The only AE of 'calcitonin increased' was in a patient randomized to placebo.

If any calcitonin value post randomization was ≥ ULN, a repeat calcitonin measure had to be taken within 4 weeks. All cases ≥ 20 ng/L were to be reviewed by an external expert who would provide recommendations to the investigator whether further evaluation was indicated. None of the patients in either treatment groups had calcitonin levels ≥ 20 ng/L in this trial.

There was only 1 liraglutide-treated patient with a treatment-emergent (week 42) calcitonin that was equal to the ULN (5 ng/L); this patient also had a value of 5.1 ng/L at baseline. The other calcitonin values for this patient ranged from 2.4 to 3.9 ng/L during the treatment period.

Other patients had calcitonin values ≥ ULN, including 1 patient with calcitonin ≥ 1.5xULN during the follow-up period, but they were all randomized to placebo.

Liver Events and Related Laboratory Values

The only PTs related to liver in the 'Hepatobiliary disorders' SOC were of 'Hepatic steatosis': 2 patients on liraglutide and 1 patient on placebo had treatment-emergent (non-serious) AEs of hepatic steatosis.

No patient fulfilled biochemical Hy's law (ALT or AST ≥3xULN + total bilirubin >2xULN). According to a reviewer's analysis of ALT, similar proportions of patients in each group had any values of ≥ 3xULN while in the maintenance period (1 (0.8%) liraglutide versus 4 (3.2%) placebo). Liver-related laboratory abnormalities reported as AEs were evenly distributed between both treatment groups and there was no imbalance observed.

Renal Events and Related Laboratory Values

PTs reported in the 'Renal and urinary disorders' SOC were of ureter and bladder lithiasis in 2 patients on liraglutide: 1 patient had an AE of 'Ureterolithiasis' on study day 118 and 1 patient had an AE of 'Calculus bladder' on study day 240. Descriptions of the types of stones were not provided.

Reviewer comment: In children, urinary stones can form due to metabolic or dietary causes (e.g., hypovolemia, fat malabsorption [oxalate stones], metabolic acidosis [hypocitraturia], hyperuricosuria, increased bone resorption [increased calcium excretion])[24] in addition to genetic factors. There are a number of possible mechanisms whereby liraglutide could contribute to urinary stone formation in children and therefore a causal relationship in these cases cannot be dismissed.

There were no AEs related to abnormal renal laboratory tests and changes in serum creatinine were similar among groups. There was a small decrease in observed mean (SD) urea in the liraglutide versus placebo groups throughout the treatment period (e.g., at week 56: -0.26 (1.01) vs. -0.05 (1.19), respectively).

[24] https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-nephrolithiasis-in-children Accessed 20 Oct 2020

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Gastrointestinal (GI) disorders are well-described AEs associated with liraglutide and were the most frequently reported SOC in this trial, with 65% of liraglutide-treated patients versus 37% of placebo-treated patients reporting at least one GI AE (Table 31).

Additional on-treatment preferred terms with incidence of greater than 3% and of higher incidence than placebo of note included dizziness, lipase increased, and rash. Other imbalances represented small numerical differences (Table 31).

Table 31: Common AEs, Incidence Greater than 3%, Greater than Placebo, On-Treatment

	Liraglutide N=125		Placebo N=126	
	n	%	n	%
Gastrointestinal disorders	81	64.8	46	36.5
Nausea	53	42.4	18	14.3
Vomiting	43	34.4	5	4.0
Diarrhea	28	22.4	18	14.3
Abdominal pain upper	17	13.6	17	13.5
Abdominal discomfort	6	4.8	1	0.8
Constipation	6	4.8	3	2.4
Dyspepsia	5	4.0	3	2.4
Flatulence	4	3.2	0	0.0
Infections and infestations	72	57.6	86	68.3
Gastroenteritis	16	12.8	6	4.8
Upper respiratory tract infection	11	8.8	11	8.7
Nervous system disorders	42	33.6	40	31.7
Dizziness	13	10.4	4	3.2
General disorders and administration site conditions	28	22.4	26	20.6
Pyrexia	10	8.0	9	7.1
Fatigue	6	4.8	4	3.2
Musculoskeletal and connective tissue disorders	21	16.8	21	16.7
Pain in extremity	5	4.0	3	2.4
Investigations	19	15.2	15	11.9
Blood creatine kinase increased	4	3.2	3	2.4
Lipase increased	4	3.2	1	0.8
Injury, poisoning and procedural complications	19	15.2	16	12.7
Respiratory, thoracic and mediastinal disorders	15	12.0	27	21.4
Cough	5	4.0	4	3.2
Metabolism and nutrition disorders	13	10.4	11	8.7
Dyslipidemia	6	4.8	4	3.2
Decreased appetite	4	3.2	2	1.6

Skin and subcutaneous tissue disorders	13	10.4	11	8.7
Rash	4	3.2	0	0
Psychiatric disorders	13	10.4	18	14.3
Depression	5	4.0	3	2.4
Reproductive system and breast disorders	8	6.4	10	7.9
Ear and labyrinth disorders	5	4.0	1	0.8
Blood and lymphatic system disorders	4	3.2	5	4.0
Renal and urinary disorders	2	1.6	0	0.0
Cardiac disorders	2	1.6	1	0.8
Neoplasms benign, malignant and unspecified	2	1.6	1	0.8
Hepatobiliary disorders	2	1.6	2	1.6
Eye disorders	1	0.8	3	2.4
Vascular disorders	1	0.8	3	2.4
Immune system disorders	1	0.8	4	3.2
Endocrine disorders	1	0.8	6	4.8
Surgical and medical procedures	0	0.0	1	0.8

Source: Study 4180 CSR, Table 14.3.1.7

8.4.6. Laboratory Findings

Amylase, lipase, calcitonin, liver, and renal-related laboratory values are discussed in the respective subsections in Section 8.4.4. In addition, markers of bone metabolism and sex hormones are discussed in Sections 8.5.1 and 8.5.2, respectively. Hypoglycemia is discussed separately in Section 8.4.4.

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

An exploratory search of in-trial anemia AEs (PT: anaem*) resulted in 4 liraglutide and 2 placebo patients with AEs of iron-deficiency anemia and anemia. One of the patients on liraglutide was not on treatment at the time of the AE and one of the patients on placebo reported an event on day 1 of the study. An exploratory evaluation of hemoglobin demonstrated similar central tendency results between groups.

Laboratory-related adverse events from the 'Investigations' SOC were infrequent with an imbalance seen not favoring liraglutide in the 'Lipase increased' PT (4 vs. 1) and 'Glucose increased' PT (2 vs. 1).

8.4.7. Vital Signs

Liraglutide is associated with decreased blood pressure and increased heart rate in adult patient populations.

Blood pressure was assessed as an efficacy endpoint and is discussed in Section 6.1.2.

Three treatment-emergent AEs related to increased BP were reported: 1 patient on liraglutide ('Blood pressure systolic increased') and 2 patients on placebo ('Blood pressure increased' and 'Blood pressure systolic increased'). All patients recovered and completed the trial.

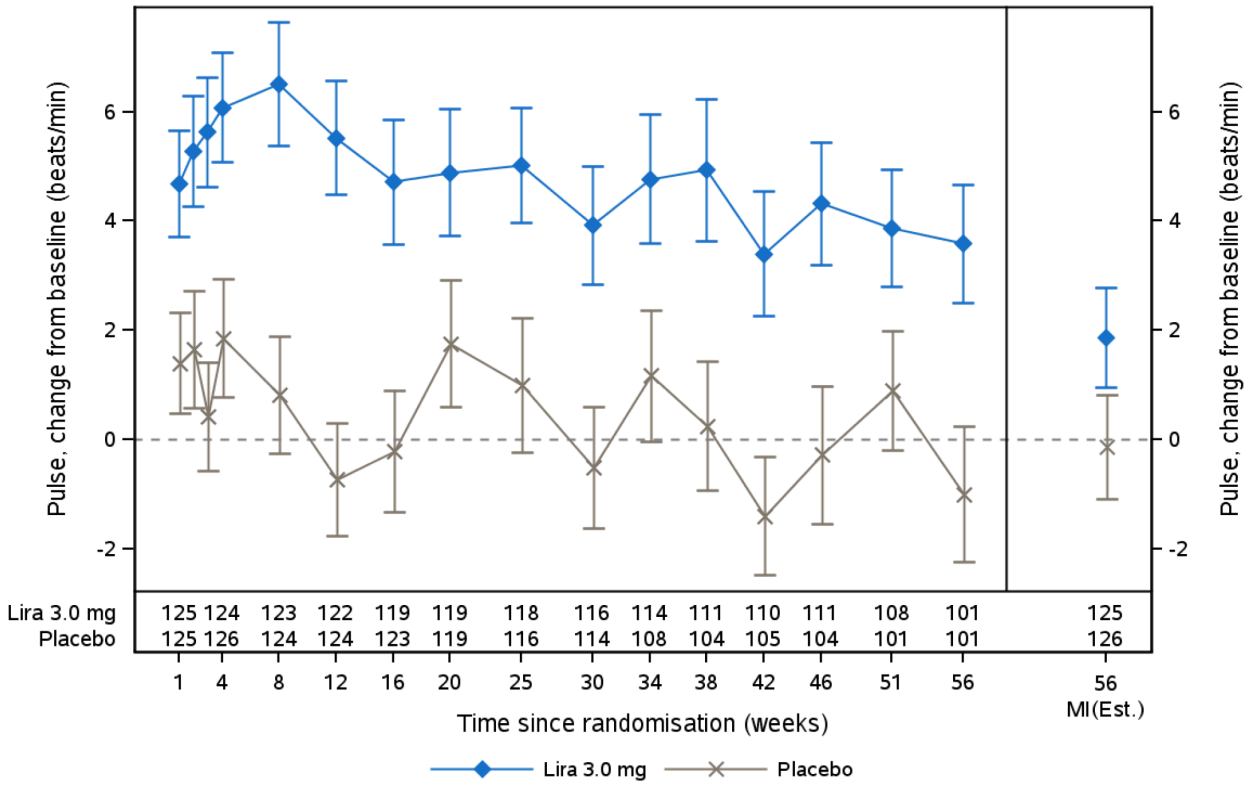
At baseline, mean heart rate was 75 beats/min in the liraglutide group and 78 beats/min in the placebo group.

At week 30, the estimated mean change in heart rate from baseline was 2.92 beats/min in the liraglutide group and 0.42 beats/min in the placebo group, and the estimated treatment difference was 2.50 beats/min (0.15, 4.84).

At week 56, the estimated mean change in heart rate from baseline was 1.87 beats/min in the liraglutide group and -0.14 beats/min in the placebo group, and the estimated treatment difference was 2.01 beats/min (-0.50, 4.52).

Figure 15 presents change in mean heart rate by week. Mean resting heart rate peaked in the liraglutide group at week 8 (increased from baseline by +7 beats/min vs. +1 beat/per min in the placebo group) and then the mean increase in the liraglutide group ranged from +3 to +5 beats/min from week 16 until week 56. Mean heart rate in the placebo group was essentially unchanged (mean: -1 to +1 beats/min) throughout the trial.

Figure 15: Change in Mean Heart Rate by Week



Source: Study 4180 CSR, Figure 12-4

Table 32 presents heart rate increases by categorical cut-offs. More patients in the liraglutide group had increases of greater than 10 and 20 beats/min, although the proportions with greater than 20 beats/min at 2 consecutive visits was essentially similar among groups. The proportions with at least 1 episode of heart rate of 100 beats/min or greater was similar among groups. There were fewer patients overall with heart rate of 100 beats/min or greater at 2 consecutive visits, although this was seen more frequently in liraglutide versus placebo patients (8.0% vs. 4.8%, respectively). No increased heart rate AEs in the 'Investigations' SOC were reported. See Section 8.4.8 on electrocardiograms for discussion of other cardiac AEs.

Table 32: Categorical Changes in Heart Rate

	Liraglutide N=125	Placebo N=126
> 10 bpm at 1 visit	80 (64.0)	75 (59.5)
> 10 bpm at 2 consecutive visits	60 (48.0)	39 (31.0)
> 20 bpm at 1 visit	49 (39.2)	39 (31.0)
> 20 bpm at 2 consecutive visits	18 (14.4)	16 (12.7)
≥ 100 bpm at 1 visit	33 (26.4)	34 (27.0)
≥ 100 bpm at 2 consecutive visits	10 (8.0)	6 (4.8)

Source: Response to FDA Clinical Information Request #7, Tables 1-4 and 1-5

8.4.8. Electrocardiograms (ECGs)

ECG assessments were performed at screening, week 30, and week 56/EOT. The findings were categorized as 'normal', 'abnormal, not clinically significant (NCS)', or 'abnormal, clinically significant (CS)' by the investigator. Most patients had normal ECGs and ECGs considered 'abnormal, NCS' were well-balanced among groups throughout. No patients had clinically significant ECGs.

Table 33: ECG Results by Treatment Week

	Liraglutide N=125	Placebo N=126
Screening		
N	125	126
Normal	102 (81.6)	100 (79.4)
Abnormal, NCS	23 (18.4)	26 (20.6)
Abnormal, CS	0	0
Week 30		
N	117	116
Normal	97 (82.9)	95 (81.9)
Abnormal, NCS	20 (17.1)	21 (18.1)
Abnormal, CS	0	0
Week 56		
N	104	103
Normal	83 (79.8)	80 (77.7)
Abnormal, NCS	21 (20.2)	23 (22.3)
Abnormal, CS	0	0

Source: Study 4180 CSR, Table 14.3.6.1

There were no AEs related to abnormal ECG ('Investigations' SOC) in the trial.

There were 3 cardiac AEs in the trial: 2 events in 2 patients on liraglutide ('Ventricular

extrasystoles' and 'Palpitations') and 1 event in 1 patient on placebo ('Tachycardia'). The event of ventricular extrasystoles in the liraglutide patient was described in the verbatim term as "sinus rhythm with bigeminal PVCs" on study day 393 and was reported as not recovered. No action was taken due to the AE and the patient completed the trial.

8.4.9. QT

QT has been evaluated in the adult populations and does not require additional assessment. There is no QT signal described with liraglutide.

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

8.4.10. Immunogenicity

Samples from patients treated with liraglutide were analyzed for anti-liraglutide antibody formation including cross-reactivity to endogenous GLP-1 at week 0 (baseline), week 30, week 56 (end of the double-blind treatment period), week 58, week 70 and week 82. Samples found to be positive to anti-liraglutide antibodies at weeks 58, 70, and 82 were analyzed for *in vitro* neutralizing effect. Samples that were cross-reacting with native GLP-1 at weeks 58, 70 and 82 were analyzed for *in vitro* neutralizing effect to native GLP-1.

None of the patients had anti-liraglutide antibodies at baseline. Thirteen liraglutide-treated patients (10.4%) had at least 1 post-baseline positive sample; most were transient. Five patients (4.0%) had persistent antibodies as defined by more than 2 antibody visits at least 16 weeks apart. Two patients (1.6%) remained positive throughout the follow-up period.

Changes in clinical endpoints as shown in Table 34 suggest some attenuation of response in association with anti-liraglutide antibodies; however, the number of patients who developed antibodies is too small to draw any firm conclusions.

Table 34: Change in Body Weight, HbA1c, and BMI SDS by Anti-Liraglutide Antibodies (Abs)

	Anti-liraglutide Ab		Persistent Ab		Abs cross-reacting to native GLP-1	
	positive	negative	yes	no	positive	negative
Number of patients*	14	111	5	9	3	11
Body weight, change from baseline (kg)						
Week 30						
N	14	105	5	9	3	11
Mean (SD)	-3.3 (5.5)	-4.0 (6.3)	-1.5 (3.8)	-4.3 (6.1)	-2.1 (5.1)	-3.7 (5.7)
Week 56						
N	14	99	5	9	3	11
Mean (SD)	-0.4 (8.3)	-3.0 (9.2)	0.1 (9.7)	-0.6 (8.1)	1.5 (10.4)	-0.9 (8.2)
Week 82						

N	14	98	5	9	3	11
Mean (SD)	3.2 (8.9)	1.4 (10.3)	3.9 (11.9)	2.9 (7.6)	6.8 (11.6)	2.3 (8.5)
HbA1c, change from baseline (%)						
Week 30						
N	14	101	5	9	3	11
Mean (SD)	-0.2 (0.2)	-0.1 (0.3)	-0.1 (0.2)	-0.2 (0.3)	-0.2 (0.2)	-0.2 (0.2)
Week 56						
N	13	92	5	8	3	10
Mean (SD)	-0.1 (0.2)	-0.1 (0.4)	-0.2 (0.1)	-0.1 (0.2)	-0.2 (0.1)	-0.1 (0.2)
Week 82						
N	13	87	5	8	3	10
Mean (SD)	0.0 (0.3)	0.0 (0.3)	-0.0 (0.2)	0.0 (0.3)	-0.1 (0.1)	0.0 (0.3)
BMI SDS, change from baseline						
Week 30						
N	14	105	5	9	3	11
Mean (SD)	-0.25	-0.26	-0.17	-0.29	-0.23	-0.25
Week 56						
N	14	99	5	9	3	11
Mean (SD)	-0.13	-0.27	-0.10	-0.15	-0.07	-0.15
Week 82						
N	14	98	5	9	3	11
Mean (SD)	0.02	-0.07	0.07	-0.00	0.14	-0.01
* Assessment of antibodies in liraglutide patients at any post-baseline visit Persistent abs were defined as treatment induced anti-liraglutide abs detected at 2 or more sampling timepoints at least 16 weeks apart						

Source: FDA Clinical IR #7, response dated 04 Aug 2020, Table 1-3

8.5. Analysis of Submission-Specific Safety Issues

The safety of weight loss in pediatric patients on linear growth, bone density, and sexual development is an area of interest, given the complexities of body adiposity, nutritional status, and weight loss affecting growth and development, particularly over the pubertal period.

Obese children are often taller than[25] and have more advanced bone age[26] relative to their normal weight peers (in this trial, baseline mean bone age was advanced relative to mean chronological age). Obesity is also associated with earlier ages of pubertal changes.[25]

8.5.1. Bone Age, Bone Metabolism, and Linear Growth

Bone safety was assessed a number of different ways in this trial.

[25] He Q and Karlberg J. BMI in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res. 2001; 49(2): 244–51.
[26] De Groot CJ, et al. Determinants of advanced bone age in childhood obesity. Horm Res Paediatr. 2017; 87(4): 254-63.

An x-ray of the left hand and wrist was performed at randomization and week 56 for evaluation of bone age. An X-ray was not performed at week 56 for patients for whom the bone age evaluation at randomization indicated that the epiphyses were fused.

Mean bone age was similar in the treatment groups throughout the trial.

Table 35: Bone Age Assessments by Treatment Week

	Liraglutide N=125	Placebo N=126
Week 0		
N	125	126
Mean (SD)	16.55 (1.63)	16.44 (1.69)
Median	17.00	17.00
Min, Max	12.00, 19.00	13.00, 19.00
Week 56		
N	53	59
Mean (SD)	16.89 (1.65)	16.81 (1.62)
Median	17.00	17.00
Min, Max	13.00, 19.00	14.00, 19.00

Source: Study 4180 CSR, Table 12-15

Table 36: Change from Baseline in Bone Age

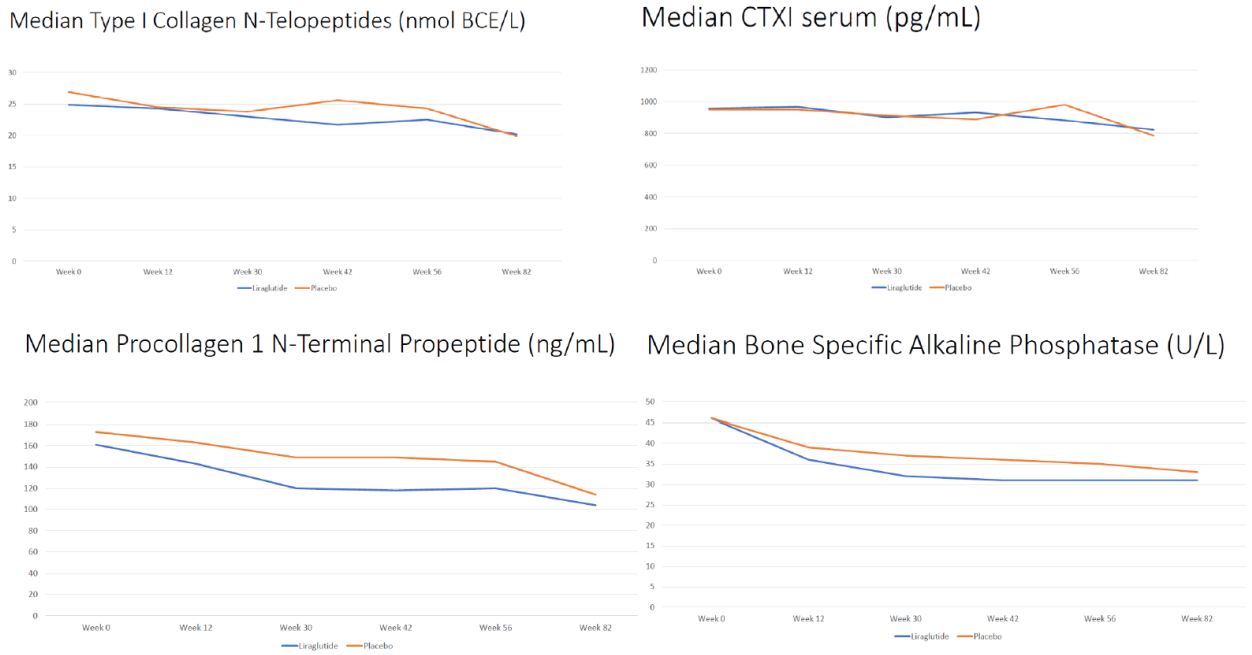
	Liraglutide N=125	Placebo N=126
N	53	59
Mean (SD)	1.40 (1.18)	1.37 (0.96)
Median	2.00	1.00
Min, Max	-2.00, 4.00	0.00, 3.00

Source: Study 4180 CSR, Table 12-16

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 randomization and at weeks 12, 30, 42, 56/end-of-treatment, and at week 82 (end-of-follow-up).

NTX1 and CTX1 are markers of bone resorption, while P1NP and BSAP are markers of bone formation. In general, markers over time and changes in markers were similar among groups. By visual inspection, median NTX1 and CTX1 were generally similar over time, whereas median P1NP and BSAP seemed to trend slightly lower in the liraglutide arm versus the placebo arm.

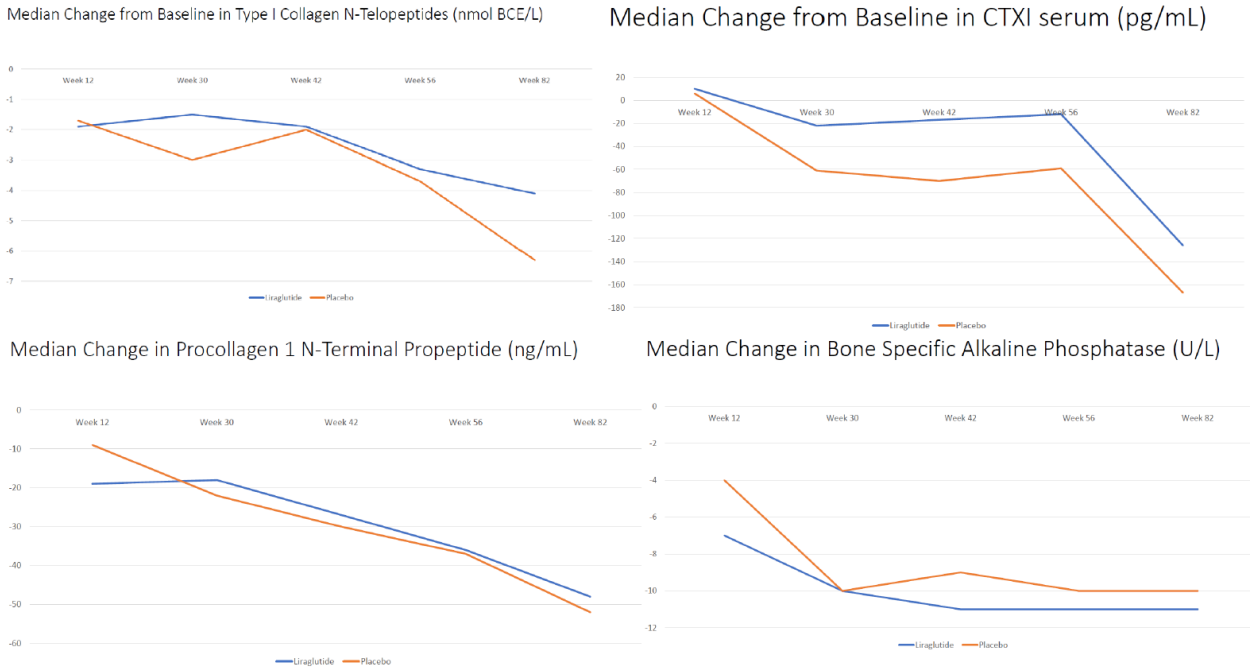
Figure 16: Bone Metabolism Markers by Treatment Week



Source: Reviewer created from Study 4180 CSR, Table 14.3.5.17

Median decreases from baseline were seen in all bone marker parameters, which appears consistent with the trends described in typical adolescence.[27] Upon visual inspection, there is a suggestion of a greater median decrease in NTX1 and CTX1 in the placebo arm, whereas a slightly greater median decrease in BSAP is suggested in the liraglutide arm.

[27] Jurimae J. Interpretation and application of bone turnover markers in children and adolescents. Curr Opin Pediatr. 2010 Aug; 22(4): 494-500.



Source: Reviewer created from Study 4180 CSR, Table 14.3.5.18

The number of patients with AEs of abnormal bone markers was similar among groups:

Table 37: Bone Marker AEs, In-Trial

	Liraglutide N=125	Placebo N=126
Bone marker AEs	3 (2.4)	5 (4.0)
C-telopeptide increased	1 (0.8)	0
N-telopeptide urine increased	1 (0.8)	3 (2.4)
Serum procollagen type I N-terminal propeptide decreased	1 (0.8)	2 (1.6)

Source: Reviewer created from ADAE dataset

Height was measured at visit 2 (screening), visit 8, baseline (week 0, visit 9), week 12, week 30, week 30 follow-up, week 42, week 56, week 56 follow-up, week 82, and week 82 follow-up.

At baseline, the liraglutide group had a slightly lower mean height SDS than the placebo group. Mean change in height SDS was similar in the liraglutide and placebo treatment groups during the trial. See Section 6.1.2, Study Results, for height measurements as a component of the BMI composite efficacy outcome (and a discussion of data collection concerns at some sites).

Figure 17: Height SDS by Treatment Week

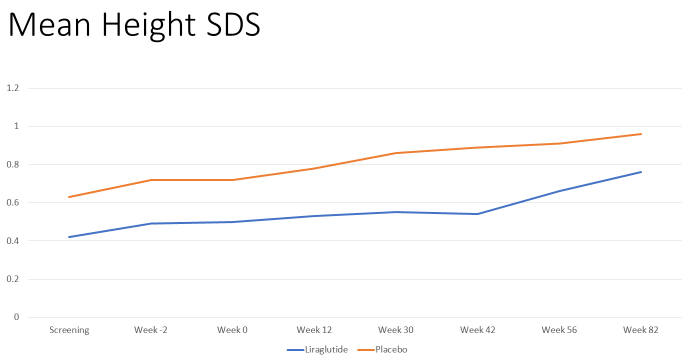
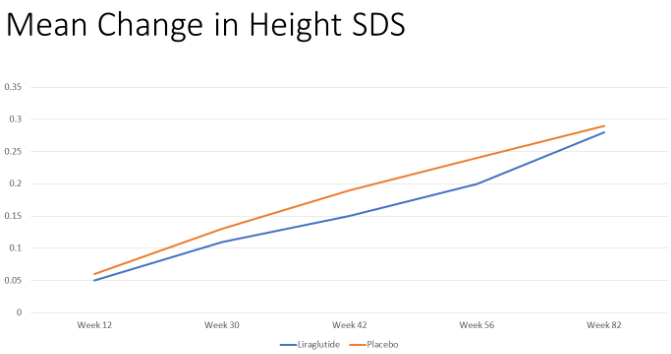


Figure 18: Mean Change in Height SDS by Treatment Week



Source: Reviewer created from Study 4180 CSR, Table 14.3.6.9

8.5.2. Sexual Development

Pubertal assessment by Tanner staging was conducted during the trial at screening, baseline and weeks 30, 56/end-of-treatment, and 82. Once a patient reached Tanner V, as judged by the investigator, Tanner assessments were no longer conducted; at baseline, 51.8% of patients had reached full sexual maturity. The following tables present Tanner staging at baseline and week 56 for girls and boys. Missing data make the results difficult to interpret, but the general pattern appears similar in both treatment groups; although there is some suggestion of additional progression in genital development in boys randomized to placebo versus liraglutide, the clinical significance of this observation (or whether is it a chance finding) is unclear. Tanner staging shift tables were reviewed and are generally consistent with these summary findings; see Appendix 13.4.

Table 38: Tanner Staging, Females

	Tanner Stage	Lira 3.0 mg (N=71)	Placebo (N=78)
Breast Development			
Visit 9 (week 0)	II	2 (2.82)	1 (1.28)
	III	6 (8.45)	8 (10.26)
	IV	23 (32.39)	30 (38.46)
	V	40 (56.34)	39 (50.00)
Visit 25 (week 56)	II	0	0
	III	2 (2.82)	2 (2.56)
	IV	14 (19.72)	20 (25.64)
	V	41 (57.75)	41 (52.56)

Source: Study 4180 CSR, Table 12-13

Table 39: Tanner Staging, Males

	Tanner Stage	Lira 3.0 mg (N=54)	Placebo (N=48)
Genital Development			
Visit 9 (week 0)	II	4 (7.41)	7 (14.58)
	III	11 (20.37)	8 (16.67)
	IV	16 (29.63)	14 (29.17)
	V	23 (42.59)	19 (39.58)
Visit 25 (week 56)	II	1 (1.85)	0
	III	6 (11.11)	6 (12.50)
	IV	15 (27.78)	6 (12.50)
	V	26 (48.15)	29 (60.42)

Source: Study 4180 CSR, Table 12-14

No notable differences between groups were observed in testicular volume.

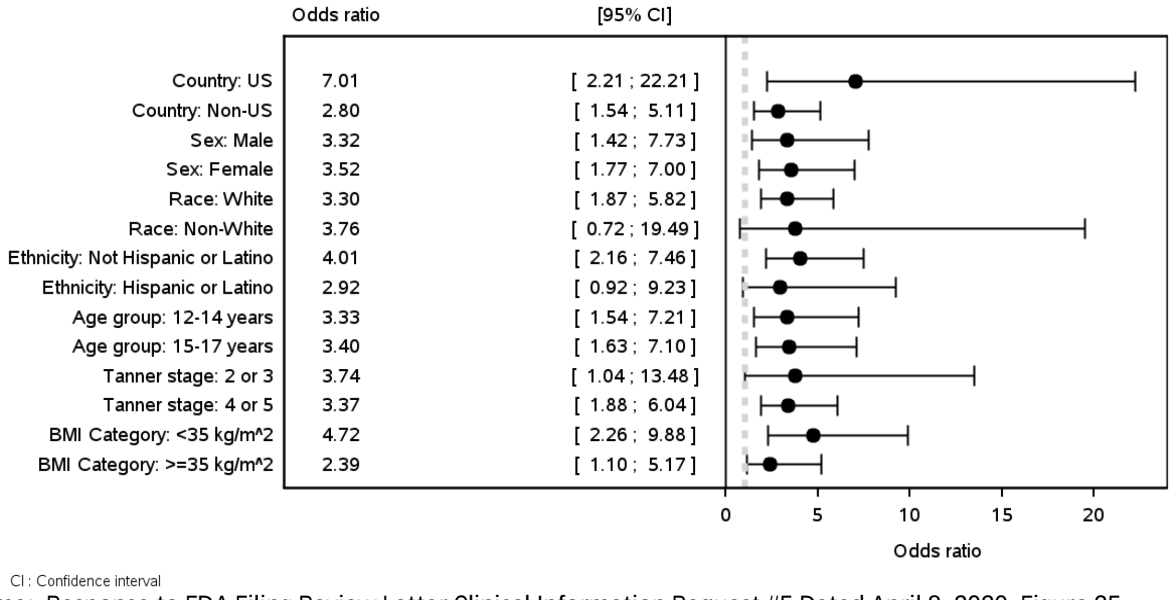
No notable differences between groups were observed in sex hormones: LH, FSH, estradiol (females), or testosterone (males).

On patient had an AE of serum testosterone decreased (verbatim term: “decrease of total testosterone”): a 16-year-old male on liraglutide on study day 295. By report, the AE was mild and he recovered.

8.6. Safety Analyses by Demographic Subgroups

Gastrointestinal AEs were evaluated for demographic subgroup differences. No significant interaction p-values were observed.

Figure 19: Gastrointestinal Adverse Events, Subgroups



Source: Response to FDA Filing Review Letter Clinical Information Request #5 Dated April 8, 2020, Figure 25

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 in Section 8.4.4, Significant Adverse Events.

8.8.2. Human Reproduction and Pregnancy

There were no pregnancies in this trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

See Section 8.5, Analysis of Submission-Specific Safety Issues.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable; liraglutide is not a drug of abuse. See Section 6.1.2 for a discussion of the effects of liraglutide on the primary endpoint when the drug is withdrawn.

8.9. Safety in the Postmarket Setting

Liraglutide has a well-characterized safety profile in adults in type 2 diabetes and obesity, and this trial did not identify new safety concerns. Therefore, it is expected that postmarket safety in this adolescent population will be consistent with the known safety profile. Mitigation of safety concerns can be addressed with labeling.

8.10. Integrated Assessment of Safety

There was one fatal adverse event in this trial, in the liraglutide group (1/125, 0.8%).

A total of 4 patients (3.2%) in the liraglutide arm and 9 patients (7.1%) in the placebo arm reported an SAE during the trial; during the 'on-treatment' period, 3 occurred in 3 patients in the liraglutide group (myositis, post-procedural hemorrhage, and completed suicide) and 6 occurred in 5 patients in the placebo group (appendicitis, pneumonia, cholecystitis acute, cholelithiasis, hemorrhagic ovarian cyst, and thrombophlebitis).

Approximately 10% of patients treated with liraglutide and no patients randomized to placebo discontinued study drug due to an adverse event. Most AEs leading to discontinuation were due to gastrointestinal disorders (nausea, vomiting, and abdominal pain).

Although adverse events associated with liraglutide in this trial of obese adolescents was generally consistent with its known safety profile, there are a number of findings that are worth highlighting and should be considered in labeling and future pediatric trials. Of note, there were no thyroid neoplasms (including no medullary thyroid carcinoma, c-cell hyperplasia, or significant calcitonin increases).

- Suicidality and depression

There was one completed suicide in the liraglutide group. There was not enough information to make a causality determination about the completed suicide, but other events of suicidality were observed in both groups. One patient in each group (liraglutide and placebo) experienced an AE of suicidal ideation on-treatment (the liraglutide patient had a negative rechallenge to

liraglutide), and one patient in each group (liraglutide and placebo) reported a suicide attempt, in-trial but off-treatment (the liraglutide patient had multiple confounders). There was no imbalance of psychiatric events overall in this trial, although one event of depression led to discontinuation in a liraglutide patient. This population may be at high risk for suicidality and depression.

- Hypoglycemia

Self-monitored plasma glucose was measured throughout the trial and was required prior to dose escalation and anytime patients had symptoms of suspected hypoglycemia. No severe hypoglycemic events were reported in the liraglutide- or placebo-treated patients during the trial. No hypoglycemia SAEs were reported. No hypoglycemia events led to treatment discontinuation. Documented symptomatic hypoglycemia was reported more frequently in liraglutide patients (19 patients (15%), 31 events) versus placebo patients (5 patients (4%), 6 events). Events were reported throughout the trial. Two (2) liraglutide patients reported 4 events of blood glucose less than 54 mg/dL with or without symptoms versus 1 placebo patient who reported 1 event.

- Pancreatitis

There were 2 AEs with the preferred term of 'Pancreatitis': 1 AE of 'Clinically confirmed pancreatitis' was reported in 1 patient in the liraglutide group (and led to drug discontinuation) and 1 AE of 'Suspicion of pancreatitis' reported by the physician that was not confirmed by laboratory results in 1 patient in the placebo group. Another patient randomized to liraglutide discontinued treatment due to AEs of 'Pancreatic enzymes increased', 'Retching', and 'Vomiting'. Small elevations in mean amylase and lipase, compared to baseline and to placebo, were observed during treatment with liraglutide. More patients with liraglutide than placebo experienced amylase and particularly lipase greater than the upper limit of normal during the trial.

- Immunogenicity

Thirteen (13) liraglutide-treated patients (10.4%) had at least 1 post-baseline positive anti-liraglutide antibody sample; most were transient. Five patients (4.0%) had persistent antibodies as defined by more than 2 antibody-positive visits at least 16 weeks apart. Two (2) patients (1.6%) remained positive throughout the follow-up period.

- Bone metabolism

Median decreases from baseline were seen in all bone marker parameters, consistent with typical adolescence. There is a suggestion of a greater median decrease in NTX1 and CTX1

(markers of bone resorption) in the placebo arm, whereas a slightly greater median decrease in BSAP (marker of bone formation) is suggested in the liraglutide arm. Mean changes in height and bone age were similar among groups.

- Urinary lithiasis

There were two events of urinary lithiasis in patients treated with liraglutide. Adequate hydration while on liraglutide should be reinforced in the adolescent population.

- Increased heart rate

Mean increase in heart rate in the liraglutide group ranged from +3 to +7 bpm during the trial. More patients in the liraglutide group had increases of greater than 10 and 20 beats/min and heart rate of 100 beats/min or greater at 2 consecutive visits.

- Common AEs

Gastrointestinal (GI) AEs were more frequently reported with liraglutide (65% reported at least one GI AE) than placebo (37%). Other common AEs of noted imbalance not in favor of liraglutide included dizziness, lipase increased, and rash. Other AEs of incidence greater than 3% with numerical imbalances (e.g., depression, fatigue) should be included in labeling.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

- Section 1
  - Add indication in pediatric patients aged 12 years and older with body weight above 60 kg (b) (4) and an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs
  - Include a limitation of use that the safety and effectiveness of liraglutide in pediatric patients with type 2 diabetes have not been established
- Section 2
  - Add BMI chart for diagnosing obesity in pediatric patients
  - Expand pediatric dose titration to 8 weeks if necessary
  - Allow for reduction of dose to 2.4 mg, with discontinuation if dose cannot be tolerated
  - Include a pediatric stopping rule
- Section 5
  - Include pediatric study-specific information for pancreatitis, hypoglycemia, heart rate increase, and suicidal behavior and ideation
- Section 6
  - Include a pediatric AE table
  - Include pediatric data for hypoglycemia, gastrointestinal adverse reactions, and immunogenicity
- Section 8
  - Add pediatric use section
- Section 12
  - Add pediatric pharmacokinetic data
- Section 14
  - Add pediatric safety and efficacy trial data:
    - Describe run-in, dose escalation criteria, patient population, and discontinuations
    - Describe results of primary endpoint in text
    - Update figure to present BMI SDS in completers over time through end of randomized period (56 weeks)
    - Include table of % weight change, % BMI change, and proportions losing 5% and 10% BMI from baseline
    - Include table of waist circumference, blood pressure, glucose parameters, heart rate, and lipids to parallel adult data

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended for this supplement.

12. Postmarketing Requirements and Commitments

This supplement fulfills PMR 2802-3: A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).

No new PMRs or PMCs are recommended. A trial to evaluate liraglutide in obese children 6-11 is being conducted as a PMR. In the study in younger children, patients' mental health and blood sugar concentrations should be monitored carefully, and patients should be reminded to stay well-hydrated.

13. Appendices

13.1. References

Literature references are presented as footnotes within the document.

13.2. Financial Disclosure

Covered Clinical Study: NN8022-4180

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 156		
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)): Not applicable 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 ☐ Not applicable	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ Not applicable	No ☐ (Request explanation from Applicant)

13.3. Additional Study Information

Supportive secondary endpoints were as follows:

- Supportive secondary:
  - Percent of patients achieving ≥5% reduction in baseline BMI at weeks 30, 56* and 82
  - Percent of patients achieving ≥10% reduction in baseline BMI at weeks 30, 56* and 82
  - Change in BMI SDS from baseline to 30 and 82 weeks and change from 56 weeks to 82 weeks
  - Change from baseline to 30 and 56 weeks and change from 56 weeks to 82 weeks in:
    - BMI*
    - Body weight (kilogram [kg], pounds [lb] and percent [%])*
    - Waist circumference
    - Waist-to-hip circumference ratio
    - Cardiovascular risk factors: hsCRP and fasting lipids: TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, TG, and FFA
    - Systolic and diastolic blood pressure*
    - Glucose metabolism: HbA1c*, FPG*, fasting insulin, fasting C-peptide, HOMA-B, and HOMA-IR
    - IWQOL-Kids

- Supportive secondary safety:
  - Number of treatment emergent adverse events*
  - Number of treatment emergent hypoglycemic episodes:
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification
  - Occurrence of anti-liraglutide antibodies
  - Change from baseline to 56 weeks in bone age assessment
  - Change from baseline to 30 and 56 weeks and change from 56 weeks to 82 weeks in:
    - Pulse
    - ECG[a]
    - Laboratory parameters:
      - Hematology: hemoglobin, hematocrit, thrombocytes, erythrocytes, leukocytes, differential count
      - Biochemistry: creatinine, creatine kinase, BUN, albumin, total bilirubin, ALT, sodium, potassium, total calcium, albumin-corrected calcium, amylase, lipase, CEA
      - Hormones: calcitonin, IGF-1, TSH, free T4, DHEAS, LH, FSH, estradiol (females), testosterone (males), prolactin, ACTH, cortisol
      - Bone metabolism markers: NTX1, CTX1, P1NP, bone alkaline

phosphatase

- Pubertal status
- Physical examination
- Height SDS
- C-SSRS and PHQ-9

[a]Not assessed at week 82

* According to applicant: "Key supportive secondary endpoint prospectively selected for disclosure"

Trial Flowchart

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance											End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	± 2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
SUBJECT RELATED INFO/ASSESSMENTS																																	
Informed consent and assent 18.2	X																																
In/exclusion criteria 6.2 6.3		X	X																														
Randomisation criteria 6.4									X																								
Criteria for premature discontinuation of trial product 6.5										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Demography 8.2.1		X																															
Concomitant illness and medical history 8.2.2		X[3]																															
History of psychiatric disorders 8.2.2.1		X																															
Concomitant medication 8.2.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tobacco use 8.2.5		X																	X						X					X			
Childbearing potential 8.2.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
EFFICACY																																	
Body weight 8.3.1.1		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hip and waist circumference 8.3.1.2									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Systolic and diastolic blood pressure 8.3.2		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Lipids 8.5.3		X							X						X				X			X			X					X			

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance											End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	± 2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
hsCRP 8.5.3		X							X						X				X			X			X					X			
Glucose metabolism 8.5.3		X						X							X				X			X			X					X			
IWQOL-Kids 8.3.3									X						X				X			X			X								
SAFETY																																	
Height 8.4.1		X						X	X						X				X			X			X					X	X	X	X
Adverse events 8.4.10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints 12.4										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Additional safety assessments, if applicable 8.4.10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes 8.4.13 and SMPG 8.4.2										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Pulse 8.4.3		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECG 8.4.4		X																	X						X									
Pregnancy test[3] 8.2.4.1 and 8.2.4.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
First day of menstrual period[4] 8.4.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Physical examination 8.4.6		X							X						X				X			X			X					X			
Biochemistry 8.5.4		X							X						X				X			X			X					X			
Haematology 8.5.4		X							X						X				X			X			X					X			
Hormones[5] 8.5.4									X						X				X			X			X					X			
Calcitonin 8.4.12, 8.5.4 and Appendix C		X							X						X				X			X			X					X			
Biomarkers (bone age) 8.5.4									X						X				X			X			X					X			

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance											End of Treatment	Follow-up (FU)						TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	± 2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
Anti-liraglutide antibodies 8.5.5									X										X						X	X		X		X			
Tanner staging 8.4.7		X							X										X						X					X			
Bone age (x-ray) 8.4.8									X																X[6]									
PHQ-9 and C-SSRS 8.4.9		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
OTHER ASSESSMENTS																																	
Liraglutide plasma concentration 8.6.1														X	X	X			X			X			X	X		X		X			
Counselling in healthy nutrition and physical activity 8.6.2			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X[7]	X	X[7]	X	X	X	X
Healthy nutrition compliance 8.6.2.1				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
TRIAL MATERIAL																																	
Dispensing visit 9									X				X	X	X	X	X	X	X	X	X	X	X	X									
Hand-out direction for use for trial product 8.1.7, 9.2									X				X	X	X	X	X	X	X	X	X	X	X	X									
Drug accountability 9.4									X				X	X	X	X	X	X	X	X	X	X	X	X	X								
IWRS session 10	X								X				X	X	X	X	X	X	X	X	X	X	X	X	X								
New dose of trial product 8.1.8										X	X	X	X																				
REMINDERS																																	
Training in trial product and pen handling (including injection technique)[8] 8.1.7									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									

Trial Period	Information	Screening	Run-in						Randomisation	Dose Escalation				Maintenance										End of Treatment	Follow-up (FU)					TPD FU 30 weeks	TPD FU 56 weeks	TPD FU 82 weeks
Visit number	1	2	3	4[1]	5	6[1]	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	19 x	25 x	30 x
Timing of visit (weeks)	-15	-14	-12	-10	-8	-6	-4	-2	0	1	2	3	4	8	12	16	20	25	30	34	38	42	46	51	56	58	64	70	76	82	30	56	82
Visit window (days)		-6	±2	±2	±2	±2	±2	±2		±2	±2	±2	±2	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±5	-5	±5	±5	±5
Hand-out BG meter 8.4.2									X																								
BG meter finger prick test 8.4.2									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Hand-out diary, females 8.6.3		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Collect diary, females 8.6.3									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hand-out diary, males 8.6.3									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Collect diary, males 8.6.3										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Attend visit fasting 8.1.2		X						X	X						X				X			X			X	X[9]		X[9]		X			
End of trial (EoT)																														X			

Footnotes:
[1] Can be performed as phone visit.
[2] At V2, all pre-existing conditions should be reported as medical history or concomitant illness.
[3] At V2 and V25 performed as serum pregnancy test and from V3-V24 and V26-V30 performed as urine-stick pregnancy test, if applicable (see Section 8.2.4.1 and 8.2.4.2).
[4] At screening the first date of last menstrual period should be collected. For other visits, first date of all menstrual periods since the last visit should be collected.
[5] Estradiol for female subjects only and testosterone for male subjects only
[6] An x-ray will not be performed at V25 for subjects for whom the bone age evaluation at randomisation indicates that the epiphyses are fused.
[7] Can be performed by phone
[8] At V3-V24, training in trial product and pen handling (including injection technique) is at the investigator's discretion.
[9] Only 2 hour fasting before blood sampling.

Source: Study 4180 Protocol, Section 2

13.4. Pubertal Status Shift Tables

	Status at Visit 9 (week 0)			
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)
Female				
Breast Development				
Visit 19 (week 30)				
Lira 3.0 mg 125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	1 (0.8)	3 (2.4)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	3 (2.4)	19 (15.2)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	4 (3.2)	35 (28.0)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	0 (0.0)	6 (4.8)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	2 (1.6)	23 (18.3)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	7 (5.6)	36 (28.6)
Visit 25 (week 56)				
Lira 3.0 mg 125				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	2 (1.6)	11 (8.8)	0 (0.0)
Stage 5	0 (0.0)	1 (0.8)	8 (6.4)	32 (25.6)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	5 (4.0)	15 (11.9)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	10 (7.9)	31 (24.6)

N: Number of subjects, %: Percentage of subjects.
Stage 2-5 refers to Tanner stage 2-5.
Percentages are based on all subjects with in safety analysis set.

Pubertal status by treatment week - shift table - safety analysis set

	Status at Visit 9 (week 0)			
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)
Female				
Breast Development				
Visit 30 (week 82)				
Lira 3.0 mg 125				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	1 (0.8)	5 (4.0)	0 (0.0)
Stage 5	0 (0.0)	3 (2.4)	14 (11.2)	29 (23.2)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	2 (1.6)	11 (8.7)	0 (0.0)
Stage 5	0 (0.0)	2 (1.6)	13 (10.3)	31 (24.6)
Pubic Hair Development				
Visit 19 (week 30)				
Lira 3.0 mg 125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	1 (0.8)	3 (2.4)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	3 (2.4)	17 (13.6)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	4 (3.2)	37 (29.6)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	1 (0.8)	3 (2.4)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	2 (1.6)	22 (17.5)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	4 (3.2)	41 (32.5)

N: Number of subjects, %: Percentage of subjects.
Stage 2-5 refers to Tanner stage 2-5.
Percentages are based on all subjects with in safety analysis set.

Pubertal status by treatment week - shift table - safety analysis set

	Status at Visit 9 (week 0) Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)
Female				
Pubic Hair Development				
Visit 25 (week 56)				
Lira 3.0 mg 125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	2 (1.6)	11 (8.8)	0 (0.0)
Stage 5	0 (0.0)	1 (0.8)	7 (5.6)	33 (26.4)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Stage 4	2 (1.6)	3 (2.4)	16 (12.7)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	6 (4.8)	34 (27.0)
Visit 30 (week 82)				
Lira 3.0 mg 125				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	1 (0.8)	6 (4.8)	0 (0.0)
Stage 5	0 (0.0)	3 (2.4)	12 (9.6)	30 (24.0)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	1 (0.8)	12 (9.5)	0 (0.0)
Stage 5	0 (0.0)	2 (1.6)	9 (7.1)	34 (27.0)

N: Number of subjects, %: Percentage of subjects.
Stage 2-5 refers to Tanner stage 2-5.
Percentages are based on all subjects with in safety analysis set.

Pubertal status by treatment week - shift table - safety analysis set

	Status at Visit 9 (week 0)			
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)
Male				
Pubic Hair Development				
Visit 19 (week 30)				
Lira 3.0 mg 125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	4 (3.2)	6 (4.8)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	1 (0.8)	13 (10.4)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	4 (3.2)	20 (16.0)
Placebo 126				
Stage 2	3 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	6 (4.8)	1 (0.8)	0 (0.0)	0 (0.0)
Stage 4	0 (0.0)	3 (2.4)	6 (4.8)	0 (0.0)
Stage 5	0 (0.0)	1 (0.8)	5 (4.0)	20 (15.9)
Visit 25 (week 56)				
Lira 3.0 mg 125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	3 (2.4)	4 (3.2)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	3 (2.4)	11 (8.8)	0 (0.0)
Stage 5	1 (0.8)	0 (0.0)	5 (4.0)	18 (14.4)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	6 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	2 (1.6)	3 (2.4)	1 (0.8)
Stage 5	1 (0.8)	2 (1.6)	6 (4.8)	19 (15.1)

N: Number of subjects, %: Percentage of subjects.
Stage 2-5 refers to Tanner stage 2-5.
Percentages are based on all subjects with in safety analysis set.

Pubertal status by treatment week - shift table - safety analysis set

	Status at Visit 9 (week 0)			
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)
Male				
Pubic Hair Development				
Visit 30 (week 82)				
Lira 3.0 mg 125				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	2 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)
Stage 4	2 (1.6)	3 (2.4)	5 (4.0)	0 (0.0)
Stage 5	1 (0.8)	1 (0.8)	10 (8.0)	18 (14.4)
Placebo 126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 4	5 (4.0)	1 (0.8)	1 (0.8)	1 (0.8)
Stage 5	1 (0.8)	3 (2.4)	7 (5.6)	17 (13.5)
Penis Development				
Visit 19 (week 30)				
Lira 3.0 mg 125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	2 (1.6)	9 (7.2)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	1 (0.8)	12 (9.6)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	3 (2.4)	22 (17.6)
Placebo 126				
Stage 2	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3	4 (3.2)	3 (2.4)	0 (0.0)	0 (0.0)
Stage 4	1 (0.8)	5 (4.0)	5 (4.0)	0 (0.0)
Stage 5	0 (0.0)	0 (0.0)	7 (5.6)	18 (14.3)

N: Number of subjects, %: Percentage of subjects.
Stage 2-5 refers to Tanner stage 2-5.
Percentages are based on all subjects with in safety analysis set.

Pubertal status by treatment week - shift table - safety analysis set

		Status at Visit 9 (week 0)			
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)	
Male					
Penis Development					
Visit 25 (week 56)					
Lira 3.0 mg	125				
Stage 2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Stage 3	2 (1.6)	4 (3.2)	0 (0.0)	0 (0.0)	
Stage 4	1 (0.8)	5 (4.0)	9 (7.2)	0 (0.0)	
Stage 5	0 (0.0)	1 (0.8)	5 (4.0)	20 (16.0)	
Placebo	126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Stage 3	5 (4.0)	1 (0.8)	0 (0.0)	0 (0.0)	
Stage 4	1 (0.8)	3 (2.4)	2 (1.6)	0 (0.0)	
Stage 5	0 (0.0)	3 (2.4)	8 (6.3)	18 (14.3)	
Visit 30 (week 82)					
Lira 3.0 mg	125				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Stage 3	2 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)	
Stage 4	1 (0.8)	4 (3.2)	6 (4.8)	0 (0.0)	
Stage 5	1 (0.8)	2 (1.6)	8 (6.4)	20 (16.0)	
Placebo	126				
Stage 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Stage 3	2 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)	
Stage 4	4 (3.2)	2 (1.6)	0 (0.0)	0 (0.0)	
Stage 5	0 (0.0)	4 (3.2)	9 (7.1)	16 (12.7)	

N: Number of subjects, %: Percentage of subjects.
Stage 2-5 refers to Tanner stage 2-5.
Percentages are based on all subjects with in safety analysis set.

Source: Study 4180 CSR, Table 14.3.6.28

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
12/03/2020 06:38:55 PM

JOHN M SHARRETTS
12/03/2020 10:12:04 PM
I concur with the conclusions of this review, which serves as the decisional memo for the supplemental application.