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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	NDA 206321
Supplement #:	12
Drug Name:	Saxenda (liraglutide) injection 3 mg
Indications:	Weight management
Applicant:	Novo Nordisk
Dates:	Stamp date: 2/6/2020 Primary review Due date: 10/28/2020 PDUFA date: 12/6/2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kiya Hamilton, Ph.D.
Concurring Reviewers:	Feng Li, Ph.D., Acting Team Leader Mark Rothmann, Ph.D., DBII Director
Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity Product
Clinical Team:	Julie Golden, M.D., Reviewer John Sharretts, M.D., Team Leader
Project Manager:	Martin White

Keywords: overweight or obesity, pediatrics

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Liraglutide is a GLP-1 receptor agonist. It is approved as Victoza (1.2 mg and 1.8 mg liraglutide) for the treatment of Type 2 Diabetes Mellitus (T2DM). It is also approved as Saxenda (3.0 mg liraglutide) as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index of

- 30 kg/m^2 or greater or
- 27 kg/m^2 or greater in the presence of at least one weight related comorbidity.

Novo Nordisk Inc. is seeking a new pediatric indication as follows:

SAXENDA 3.0 mg is indicated as an adjunct to (b) (4) and 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 (b) (4) 30 kg/m^2 for adults (obese) by international cut-offs.

One phase 3 study was submitted to support this new indication, study NN8022-4180, hereafter referred to as study 4180. The primary objective of study 4180 was to compare the efficacy of liraglutide versus placebo on weight loss in adolescent subjects with obesity after 56 weeks of treatment. The primary endpoint was change in body mass index (BMI) standard deviation score (SDS) from baseline to week 56.

Study 4180 demonstrated superiority of liraglutide 3.0 mg over placebo for the primary endpoint. The difference (liraglutide-placebo) for the primary endpoint, change in BMI SDS from baseline to week 56, was -0.21, with 95% confidence interval (-0.35, -0.07). No major statistical issues were identified in this submission. Endpoints related to BMI SDS, BMI, body weight, and waist circumference were consistently in favor of liraglutide compared to placebo. However, there was no pre-specified multiplicity control strategy for these secondary endpoints. There was a numerically larger decrease from baseline in HbA1c in liraglutide group than the placebo group at week 56.

There were no severe hypoglycemic events seen in this study. Significant differences in documented symptomatic hypoglycemia with or without symptoms was seen between the two treatment groups. More events occurred in the liraglutide group.

Overall, the study supports the proposed indication for chronic weight management in pediatric patients aged 12 years and older.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Liraglutide is a once-daily GLP-1 analogue with 97% homology to human GLP-1. Novo Nordisk Inc. is seeking a new pediatric indication for chronic weight management in pediatric patients aged 12 years and older.

2.1.2 History of Drug Development

There were some interactions between Novo Nordisk and the Agency regarding study 4180 under IND 073206 and NDA 206321. The discussion all focused on the proposed labeling.

2.1.3 Studies Reviewed

This review will focus on the results from study 4180.

2.2 Data Sources

The submission of NDA 206321 was received on February 6, 2020. The study reports, protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path \\CDSESUB1\evsprod\NDA206321\0243. Information necessary for this review was contained in Module 1, Module 2, and Module 5.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted data are acceptable in terms of quality. I was able to reproduce the primary and secondary endpoint analyses for the clinical study submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 4180 was a phase 3, randomized, double-blind, parallel-group, placebo-controlled, multinational study in pubertal adolescent subjects aged 12 years to less than 18 years with obesity. Subjects were randomized 1:1 to receive either liraglutide or placebo once daily subcutaneous (s.c.) injection.

A total of 251 subjects were randomized into the study, 125 in the liraglutide arm and 126 in the placebo arm. Randomization was stratified by pubertal development (Tanner staging) and glycemic status. Tanner staging was categorized by Tanner 2 or 3 and Tanner 4 or 5. The

glycemic status is classified as normoglycemia versus dysglycemia (pre-diabetes and T2DM), defined Table 1 below.

Table 1. Glycaemic category

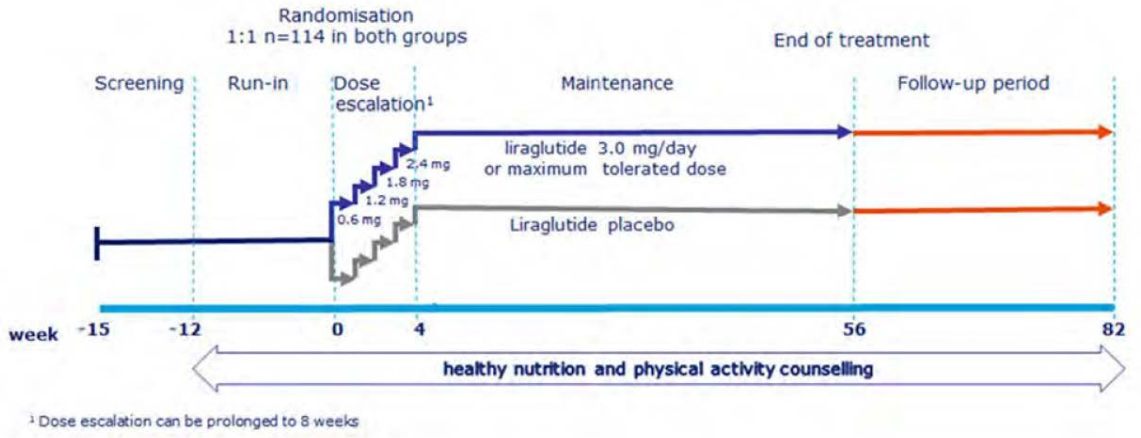
Normoglycemia	FPG <5.6 mmol/L (<100 mg/dL) and/or HbA1c <5.7%
Pre-diabetes	FPG 5.6−6.9 mmol/L (both inclusive), FPG 100–125 mg/dL (both inclusive) or HbA1c 5.7−6.4% (both inclusive)
Type 2 diabetes (T2DM)	FPG ≥7.0 mmol/L (≥126 mg/dL) and/or HbA1c ≥6.5%

Abbreviations: FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin
Source: Clinical Trial Report Trial ID: NN8022-4180 Table 9-1, page 35

The primary objective was to compare the efficacy of liraglutide versus placebo on weight loss in adolescent subjects with obesity after 56 weeks of treatment. The secondary objectives were to compare the efficacy of liraglutide versus placebo on glycaemic control, cardiovascular risk factors and Impact of Weight on Quality of Life-Kids (IWQOL-Kids) in adolescent subjects with obesity after 30 and 56 weeks of treatment.

The study enrolled patients from a total of 32 sites in 5 countries, where 12 sites were in the United States. The total study duration was 82 weeks. There was a 12-week run-in period where subjects received counseling on healthy nutrition and physical activity, which continued throughout the 56-week double-blind treatment period, and a 26-week off study drug follow-up period. Each subject went through dose escalation during the first 4 weeks after randomization with weekly increments of 0.6 mg (or equivalent volume of placebo). Dose escalation could be prolonged to 8 weeks. The goal was to reach a dose of 3.0 mg or the maximum tolerated dose (MTD). Figure 1 below shows the scheme of the study design for study 4180.

Figure 1: Study Design for Study 4180



Source: Clinical Trial Report Trial ID: NN8022-4180 Figure 9-1, page 34

The primary endpoint was change in BMI SDS from baseline to week 56. The sponsor noted in their Analysis Data Reviewer's Guide that BMI SDS score will be calculated using external reference data on BMI from the World Health Organization (WHO). These reference data were downloaded from https://www.who.int/growthref/en/ . The derivation below is from

http://www.who.int/growthref/computation.pdf?ua=1 (sd3, sd23, sd3neg, sd23neg are all defined in the link).

SDS score was derived as follow:

z=(((bmi_val/m)**l)-1)/(s*l); (where bmi_val is BMI value.)

if -3<=z<=3 then aval=z;

else if z>3 then aval=3+((bmi_val-sd3)/sd23);

else if z<-3 then aval=-3+((bmi_val-sd3neg)/sd23neg);

where sd23neg=sd2neg-sd3neg.

The applicant defined primary objective was met if superiority of liraglutide 3.0 mg vs. placebo was demonstrated for the primary endpoint. The secondary supportive endpoints were as follows:

- **Percent of subjects achieving ≥5% reduction in baseline BMI at weeks 30, 56 and 82**
- **Percent of subjects 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], and percent [%])**
  - **Waist circumference**
  - **Waist-to-hip circumference ratio**
  - Cardiovascular risk factors: hsCRP and fasting lipids: total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol, VLDL-cholesterol, triglycerides (TG) and free fatty acids (FFA)
  - Systolic and diastolic blood pressure
  - **Glucose metabolism: glycosylated hemoglobin (HbA1c),** fasting plasma glucose (FPG), fasting insulin, fasting C-peptide, glycaemic category and homeostasis model assessment of beta-cell function and insulin resistance parameters (HOMA-B and HOMA-IR)
  - Patient reported outcome (PRO) assessed by Impact of Weight on Quality of Life-Kids (IWQOL-Kids)[a]

[a]Not assessed at week 82 and does not have associated endpoints.

In addition to all the supportive secondary efficacy analysis, the following added endpoints were analyzed:

- Change from baseline to 30 and 56 weeks:
  - BMI SDS (%)
  - Glycaemic category will be summarized by frequency count for each treatment group
  - Nutritional compliance will be summarized using descriptive statistics for each treatment group.

The bolded supportive secondary endpoints appear in the applicant's proposed label. Thus, only those endpoints evaluated at 56 weeks will be included in this review.

There were no key secondary efficacy endpoints proposed in this study. The applicant did not propose any pre-specified multiplicity adjustments for testing the supportive secondary endpoints. The supportive secondary endpoints discussed in this review are shown for descriptive purpose only.

3.2.2 Statistical Methodologies

All analyses were performed using the full analysis set (FAS) which was defined as all randomized subjects who had received at least one dose of trial product and had any post-randomization data. The applicant defined two observation periods, in-trial and on-treatment. In-trial was defined as events with onset date between the first day of trial product administration and the last study visit. On-treatment was defined as events with onset date between the first day of trial product administration and whatever comes first: a) 14 days after the last day on trial product, b) follow-up visit (V26 for subjects with trial product discontinued), or c) last study visit (subjects withdrawn without follow-up visit). All analyses in this review were conducted on the in-trial period. No primary estimand was stated by the applicant.

The applicant's pre-specified analysis of the first primary endpoint, change in BMI SDS from baseline to week 56, was performed using the analysis of covariance (ANCOVA) model. The model included treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, and age as covariates.

The null and alternative hypotheses for the test for superiority of liraglutide 3.0 mg vs. placebo were as follows:

$$H_O: \mu_{liraglutide} = \mu_{placebo} \text{ against the alternative } H_A: \mu_{liraglutide} \neq \mu_{placebo}.$$

Where $\mu_{liraglutide}$ and $\mu_{placebo}$ denote the true mean change in BMI SDS for liraglutide 3.0 mg and placebo group, respectively. The null hypothesis was rejected if the two-sided 95% confidence interval (CI) excluded 0, and superiority would be claimed if the upper limit of the CI of the treatment difference (liraglutide - placebo) was below 0.

The second primary endpoints, change in

- BMI from baseline to week 56
- Body weight from baseline to week 56
- Waist circumference ratio from baseline to week 56
- Waist-to-hip circumference ratio from baseline to week 56
- HbA1c (%) from baseline to week 56

were analyzed similarly to the primary endpoint using an ANCOVA model except with the corresponding baseline for each endpoint as a covariate instead of the baseline for BMI SDS.

The endpoints, proportion of subject losing at least 5% of baseline body weight at week 56 and proportion of subjects losing at least 10% of baseline body weight at week 56, were both analyzed using a logistic regression model. The model included treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI, and age as covariates.

Missing data for the primary endpoint at week 56 was about 13%. The applicant used jump to reference multiple imputation to impute missing data at week 56. Where missing data were imputed by sampling among all available assessments at week 56 in the placebo arm. Jump to reference assumes that subjects who discontinue treatment early will no longer have any benefit of the drug's effect and thus have outcomes similar to subjects in the placebo group. No other visits were used in the imputation. An additional analysis using return to baseline imputation approach was conducted by the Agency. This missing data imputation produced similar results to the jump to reference. There were not enough retrieved dropouts to conduct a retrieved dropout imputation, 12 in the liraglutide group and 5 in the placebo group. The results using the jump to reference analysis will be shown.

Safety endpoints include documented symptomatic hypoglycemia and blood glucose less than 54 mg/dL hypoglycemia with or without symptoms, will be covered in the safety section of this review. A documented symptomatic hypoglycemic episode was defined as an episode during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration $\leq$ 3.9 mmol/L (70 mg/dL).

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The summary of the subject disposition in study 4180 is given below in Table 2. There were 125 subjects randomized to the liraglutide and 126 subjects in the placebo group. Approximately 14% of the subjects withdrew from the study and about 20% of subjects prematurely discontinued randomized treatment. The main reason for discontinuation from the study drug was "other" followed by adverse events.

Table 2. Subject Disposition

	Lira 3.0mg N = 125 n (%)	Placebo N = 126 n (%)	Total N = 251 n (%)
FAS	125 (100)	126 (100)	251 (100)
Exposed	125 (100)	126 (100)	251 (100)
Completed treatment period	101 (80.8)	100 (79.4)	201 (80.1)
Discontinuation from treatment	24 (19.2)	26 (20.6)	50 (19.9)
Premature discontinuation of study drug			
Not withdrawing from study	13 (10.4)	4 (3.2)	17 (6.8)
Adverse event	7 (5.6)	0	7 (2.8)
Other	6 (4.8)	4 (3.2)	10 (4.0)
Withdrawing from the study	11 (8.8)	22 (17.5)	33 (13.1)
Adverse event	6 (4.8)	0	6 (2.4)
Protocol violation	1 (0.8)	0	1 (0.4)
Other	4 (3.2)	22 (17.5)	26 (10.4)
Completed study product and withdrawn from the study	2 (1.6)	1 (0.8)	3 (1.2)
Withdrawn from study	13 (10.4)	23 (18.3)	36 (14.3)
Lost to follow-up	3 (2.4)	6 (4.8)	9 (3.6)
Withdrawal by subject	5 (4.0)	15 (11.9)	20 (8.0)
Withdrawal by parent/guardian	2 (1.6)	1 (0.8)	3 (1.2)
Other	3 (2.4)	1 (0.8)	4 (1.6)

Abbreviations: Lira: liraglutide
Source: Clinical Study Report- Trial ID: NN8022-4180 Table 10-1, page 87; adsl.xpt, advs.xpt

Baseline demographics for the FAS population are shown in Table 3. The subjects' mean age was approximately 14.5 years old. The majority of the subjects were white (approximately 88%) and female (59%). About 24% of the subjects were from the United States.

Table 3. Demographics and Baseline Characteristics – FAS

	Lira 3.0mg N = 125	Placebo N = 126	Total N = 251
Age (years)			
Mean (SD)	14.6 (1.6)	14.5 (1.6)	14.5 (1.6)
Sex, n (%)			
Female	71 (56.8)	78 (61.9)	149 (59.4)
Male	54 (43.2)	48 (38.1)	102 (40.6)
Region, n (%)			
Belgium	15 (12.0)	18 (14.3)	33 (13.1)
Mexico	26 (20.8)	20 (15.9)	46 (18.3)
Russian Federation	30 (24.0)	38 (30.2)	68 (27.1)
Sweden	19 (15.2)	25 (19.8)	44 (17.5)
United States	35 (28.0)	25 (19.8)	60 (23.9)
Ethnicity, n (%)			
Hispanic or Latino	32 (25.6)	24 (19.0)	56 (22.3)
Not Hispanic or Latino	93 (74.4)	102 (81.0)	195 (77.7)
Race, n (%)			
America Indian or Alaska Native	0	1 (0.8)	1 (0.4)
Asian	2 (1.6)	0	2 (0.8)
Black or African American	14 (11.2)	6 (4.8)	20 (8.0)
Native Hawaiian or Other Pacific Islander	0	0	0
White	105 (84.0)	115 (91.3)	220 (87.6)
Other	4 (3.2)	4 (3.2)	8 (3.2)
BMI (kg/m^2)			
Mean (SD)	35.3 (5.1)	35.8 (5.7)	35.6 (5.4)
HbA_{1c} (%)			
Mean (SD)	5.3 (0.4)	5.3 (0.4)	5.3 (0.4)
Body Weight (kg)			
Mean (SD)	99.3 (19.7)	102.2 (21.6)	100.8 (20.7)
Overall Tanner Stage, n (%)			
Stage 2	6 (4.8)	8 (6.3)	14 (5.6)
Stage 3	16 (12.8)	13 (10.3)	29 (11.6)
Stage 4	38 (30.4)	40 (31.7)	78 (31.1)
Stage 5	65 (52.0)	65 (51.6)	130 (51.8)

Abbreviations: Lira: liraglutide
N: Number of subjects; SD: standard deviation
Source: Clinical Study Report- Trial ID: NN8022-4180 Table10-3, page 90 and Table 10-4, pages 92-93; adsl.xpt

3.2.4 Results and Conclusions

The primary analysis results for the primary endpoint, change in BMI SDS from baseline at week 56 is shown in Table 4. These results include imputed data for missing BMI SDS values using jump-to-reference imputation. The mean baseline BMI SDS was 3.14 in the liraglutide group and 3.20 in the placebo group. There was a greater decrease in BMI SDS in the liraglutide group compared to placebo. The liraglutide group achieved a statistically significant difference in mean change in BMI SDS from baseline compare to placebo. The magnitude of the difference was -0.21.

Table 4. Change from Baseline in BMI SDS at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
Baseline mean	3.14	3.20
Change from baseline LS Means at week 56 (SE)	-0.23 (0.05)	-0.01 (0.05)
Treatment difference Lira – Placebo	-0.21 (0.07)	
95% CI	(-0.35, -0.07)	
P-value*	0.0029	

Lira: liraglutide; SE: standard error
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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, age as covariates.
Source: Statistical Reviewer's Analysis; advs.xpt

The supportive secondary endpoints were not included in a multiplicity adjustment; thus, the statistical significance is difficult to interpret. However, these endpoints are all correlated with weight change.

The results for the supportive secondary endpoints, proportion of subjects losing at least 5% of baseline BMI at week 56 and proportion of subjects losing at least 10% of baseline BMI at week 56 are shown in Table 5. The results include imputed data for missing BMI values using jump-to-reference imputation. There were more subjects in the liraglutide group that achieved at least 5% reduction in BMI from baseline than in the placebo group. Similarly, there were more subjects in the liraglutide group that achieved at least 10% reduction in BMI from baseline than in the placebo group. The odds ratio was 3.24 and 3.97, respectively.

Table 5. Proportion of Patients Losing at least 5% or 10% of Baseline BMI at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
≥ 5%		
Responder %	43.78	20.78
Treatment Odds Ratio Lira/Placebo	3.24	
95% CI	(1.71, 6.15)	
Nominal P-value*	0.0003	
≥10%		
Responder %	27.78	9.40
Treatment Odds Ratio Lira/Placebo	3.97	
95% CI	(1.78, 8.85)	
Nominal P-value*	0.0007	

Lira: liraglutide
Multiple imputation: Jump-to-reference, *two-sided p-value
Note: Post-Baseline mean estimates and p-values were obtained from logistic model with treatment sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI, age as covariates.
Source: Statistical Reviewer's Analysis; advs.xpt

The results for the supportive secondary endpoint, change in BMI from baseline at week 56 is shown in Table 6. The results include imputed data for missing BMI values using jump-to-reference imputation. The mean baseline BMI was 35.3 kg/m^2 in the liraglutide group and 35.8 kg/m^2 in the placebo group. There was greater decrease in BMI in the liraglutide group compared to placebo. The mean change in BMI from baseline was trending in favor of liraglutide compared to placebo. The magnitude of the difference was -1.52 kg/m^2.

Table 6. Change from Baseline in BMI (kg/m^2) at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
Baseline mean (kg/m^2)	35.3	35.8
Change from baseline LS Means at week 56 (SE)	-1.41 (0.31)	0.11 (0.32)
Treatment difference Lira – Placebo	-1.52 (0.45)	
95% CI	(-2.40, -0.64)	
Nominal P-value*	0.0007	

Lira: liraglutide; SE: standard error
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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI, age as covariates.
Source: Statistical Reviewer's Analysis; advs.xpt

The change in body weight (kg and %) from baseline at week 56 are shown in Table 7. These results include imputed data for missing body weight values using jump-to-reference imputation. The mean baseline body weight (kg) was 99.3 kg in the liraglutide group and 102.2 kg in the placebo group. There was greater percentage of body weight loss in the liraglutide group compared to placebo. There was a greater decrease in body weight in kg in the liraglutide group compared to placebo. The placebo group had an increase in percent body weight. The magnitude of the difference in body weight was -4.36 kg and -4.90% in percent change.

Table 7. Change from Baseline in Body Weight (kg and %) at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
Baseline mean (kg)	99.3	102.2
Body weight (kg)		
Change from baseline LS Means at week 56 (SE)	-2.31 (0.92)	2.05 (0.97)
Treatment difference Lira – Placebo	-4.36 (1.34)	
95% CI	(-6.98, -1.73)	
Nominal P-value*	0.0011	
Body Weight (%)		
Change from baseline LS Means at week 56 (SE)	-2.71 (0.90)	2.19 (0.93)
Treatment difference Lira – Placebo	-4.90 (1.29)	
95% CI	(-7.43, -2.37)	
Nominal P-value*	0.0002	

Lira: liraglutide; SE: standard error
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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline body weight, age as covariates.
Source: Statistical Reviewer's Analysis; advs.xpt

The mean baseline waist circumference was 104.8 cm in the liraglutide group and 107.0 cm in the placebo group. Table 8 shows the results using a jump-to-reference analysis to account for missing data. A decrease in waist circumference at week 56 was seen in the liraglutide group compared to the placebo group. The magnitude of difference in change in waist circumference was -2.83 cm.

Table 8. Change from Baseline in Mean Waist Circumference (cm) at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
Baseline mean (cm)	104.8	107.0
Change from baseline LS Means at week 56 (SE)	-4.40 (0.84)	-1.57 (0.82)
Treatment difference Lira – Placebo	-2.83 (1.17)	
95% CI	(-5.13, -0.53)	
Nominal P-value*	0.0161	

Lira: liraglutide; SE: standard error
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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline waist circumference, age as covariates.
Source: Statistical Reviewer's Analysis; advs.xpt

The mean baseline waist-to-hip circumference ratio was 0.91 in both groups. Table 9 shows the results using a jump-to-reference analysis to account for missing data. The estimated mean change in waist-to-hip circumference ratio from baseline to week 56 was -0.02 in both groups. The estimated treatment difference for waist-to-hip circumference ratio from baseline to week 56 is -0.002.

Table 9. Change from Baseline in Mean Waist-to-Hip Circumference (Ratio) at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
Baseline mean (ratio)	0.91	0.91
Change from baseline LS Means at week 56 (SE)	-0.02 (0.005)	-0.02 (0.005)
Treatment difference Lira – Placebo	-0.002 (0.007)	
95% CI	(-0.02, 0.01)	
Nominal P-value*	0.7467	

Lira: liraglutide; SE: standard error
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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline waist-to-hip circumference, age as covariates.
Source: Statistical Reviewer's Analysis; advs.xpt

The last supportive secondary endpoint discussed in this review was, change from baseline to week 56 in HbA1c (%). The mean baseline HbA1c was 5.3% in both groups. Table 10 shows the results for change in HbA1c. Missing data was not imputed for this endpoint. A greater decrease

was seen in HbA1c at week 56 for the liraglutide group compared to placebo. The magnitude of difference in change in HbA1c was -0.06%.

Table 10. Change from Baseline in HbA1c (%) at Week 56 - FAS Population using In-Trial Observation Period

	Lira 3.0mg	Placebo
FAS	N = 125	N = 126
n	105	101
Baseline mean (%)	5.3	5.3
Change from baseline LS Means at week 56 (SE)	-0.11 (0.03)	-0.03 (0.03)
Treatment difference Lira - Placebo	-0.08 (0.04)	
95% CI	(-0.16, 0.001)	
P-value*	0.0535	

Lira: liraglutide; n: number of observed subjects; SE: standard error
*two-sided p-value
Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline HbA1c, age as covariates.
Source: Statistical Reviewer's Analysis; adlb.xpt

3.3 Evaluation of Safety

All safety analyses were conducted on the safety analysis set, which was defined as all randomized subjects that were treated with at least one dose of the study treatment.

Severe Hypoglycemia
Severe hypoglycemia was defined as the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)? No severe hypoglycemic episodes occurred in this study.

Documented Symptomatic Hypoglycemia
Documented symptomatic hypoglycemia was defined as an episode during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

Table 11 shows the results for documented symptomatic hypoglycemia (with or without symptoms). There were 19 subjects that had at least one event in the liraglutide group and 5 subjects in the placebo group. Numerically, more documented symptomatic hypoglycemic events occurred in the liraglutide group. A statistically significant difference was seen between the liraglutide and placebo groups, trending in favor of placebo. Note the 95% CI are wide for both the difference in percent and the rate ratio.

Table 11. Documented Symptomatic Hypoglycemic Episodes- Safety Population – In-Trial Observation Period

	Lira 3.0mg	Placebo
Safety Population	N = 125	N = 126
Yes DSH, n (%)	19 (15.2)	5 (4.0)
Difference in %	11.23	
95% CI	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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic 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: Statistical Reviewer's Analysis; adhypo.xpt

Novo Nordisk Hypoglycaemic Episodes with a Blood Glucose Value <54 mg/dL (3.0 mmol/L) Regardless of Symptoms

The analysis results of blood glucose less than 54 mg/dL for hypoglycaemic episodes with or without symptoms is shown in Table 12. There were 2 subjects that had at least one event in the liraglutide group and 1 subject in the placebo group. Numerically, more blood glucose less than 54 mg/dL hypoglycemic events occurred in the liraglutide group. No statistically significant difference was seen between the liraglutide and placebo groups, however, there is a trend in favor of placebo. Note the 95% CI are wide for both the difference in percent and the rate ratio.

Table 12. Blood Glucose < 54 mg/dL with or without Symptoms Hypoglycemic Episodes-Safety Population – In-Trial Observation Period

	Lira 3.0mg	Placebo
Safety Population	N = 125	N = 126
Yes BGH, n (%)	2 (1.6)	1 (0.8)
Difference in %	0.81	
95% CI	-1.88, 3.50	
Nominal P-value	0.5575	
Number of Events	4	1
Rate ratio (95% CI)	21.44 (0.10, 4595.27)	
Nominal P-value	0.2617	

Abbreviations: BGH: Blood Glucose<54 Hypoglycemia, Lira: liraglutide, Yes BGH: 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 glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic 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.

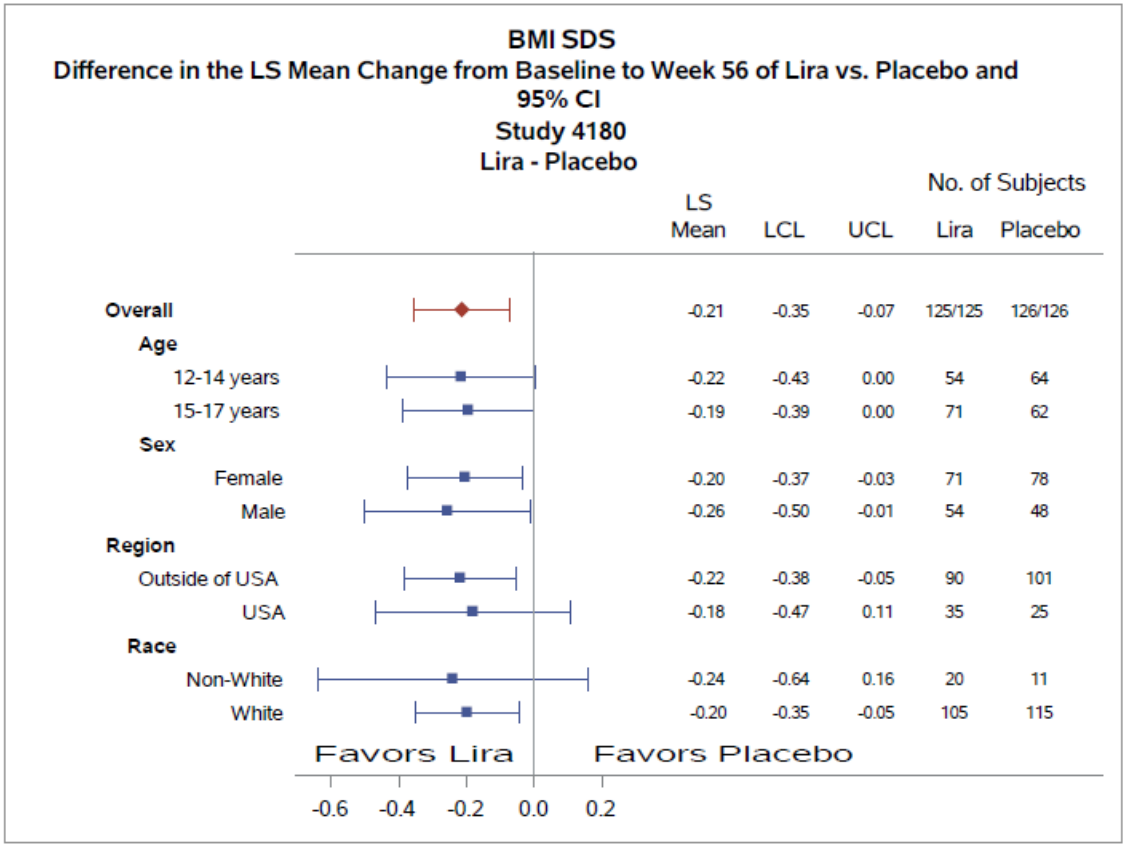
Source: Statistical Reviewer's Analysis; adhypo.xpt

For more details regarding the safety findings for liraglutide refer to the review from the Medical Reviewer, Julie Golden, M.D.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

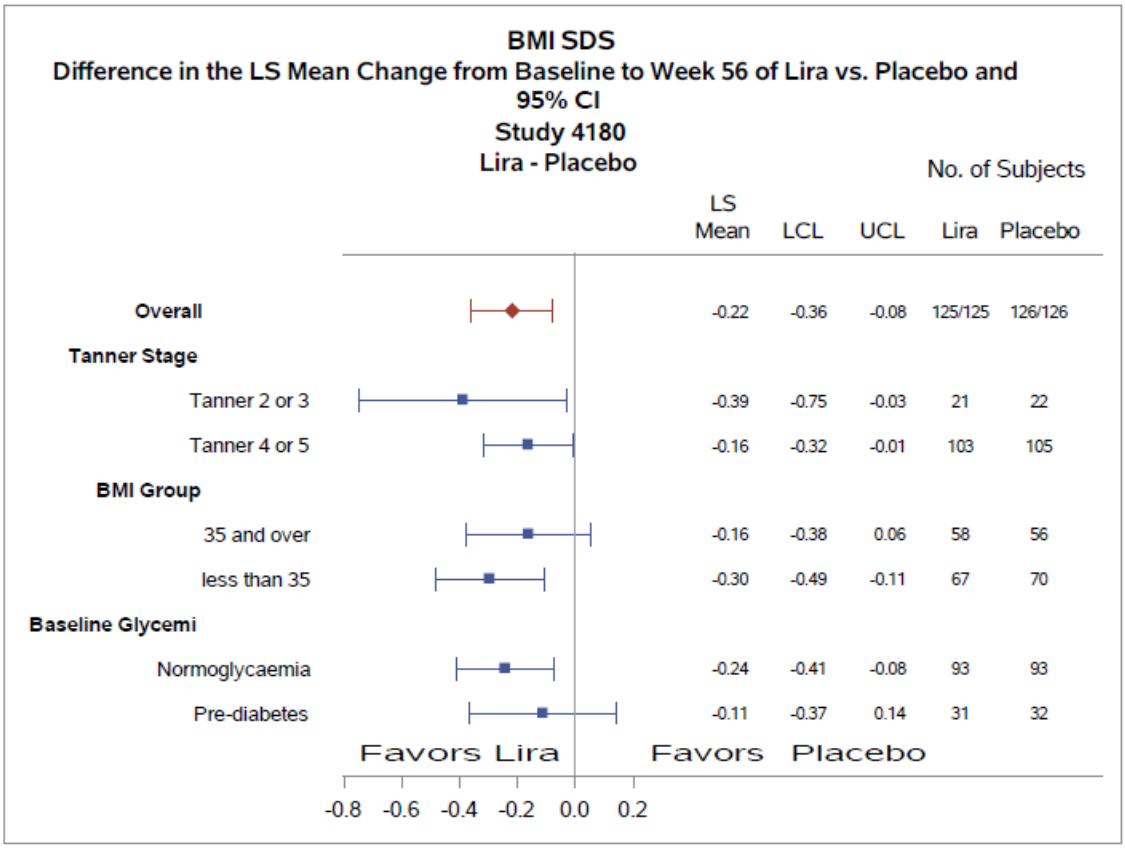
Subgroup analyses were performed on the primary endpoint, BMI SDS by age (12-14, 15-17), sex (Male, Female), region (Outside of USA, USA), and race (White vs. Non-White) (see Figure 2). As well as, Tanner stage (2 or 3, 4 or 5), BMI group (<35 kg/m^2, ≥35 kg/m^2), and baseline glycemic category (Normoglycemic, pre-diabetes, Type 2 diabetes) (see Figure 3). There were only 2 subjects with type 2 diabetes, one in each treatment group. Thus, they are not included in the subgroup analyses. The subgroup analyses were performed using the FAS population with missing data imputed using jump-to-reference. Overall, the treatment effects of the subgroups were consistent with that of the overall population. Note that the treatment effect for the USA subgroup is not significant but is trending in favor of liraglutide.

Figure 2. Subgroup Analysis: Change in BMI SDS from Baseline to Week 56



Abbreviations: Lira: liraglutide
Source: Statistical Reviewer's Analysis; advs.xpt

Figure 3. Subgroup Analysis: Change in BMI SDS from Baseline to Week 56, by Other Covariates



Abbreviations: Lira: liraglutide
Source: Statistical Reviewer's Analysis; advs.xpt

There were likely some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions for change in BMI SDS from baseline to week 56 are:

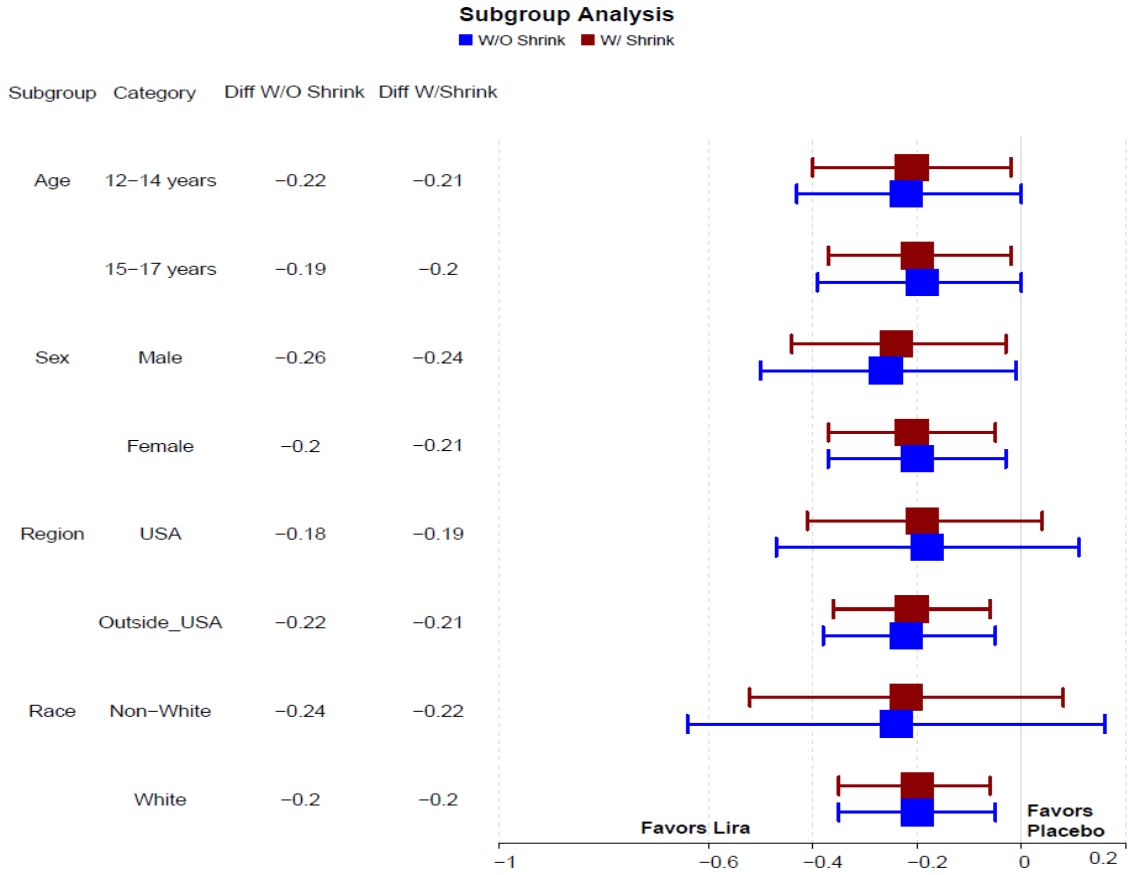
For $i = 1, 2\ldots$ Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$

- $\mu \sim N(0, 1)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

Figure 4 compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of change from baseline in BMI SDS at week 56. The overall treatment effect is -0.21 (95% CI: -0.35, -0.07). Subgroup analysis using Bayesian shrinkage estimate exhibits narrower confidence interval, and the shrinkage subgroup estimate is closer to the overall mean.

Figure 4. Subgroup Shrinkage Analysis: Change in BMI SDS from Baseline to Week 56



Abbreviations: Lira: liraglutide
Source: Statistical Reviewer's Analysis; advs.xpt

5 SUMMARY AND CONCLUSION

5.1 Statistical Issues

There were no major statistical issues identified during the course of this review. Both the statistical review team and the Division of Diabetes, Lipid Disorders, and Obesity Product sent an information request (IR) asking for subgroup analyses for age (12-14; 15-17), gender, race, Tanner stage, and BMI group for the primary and secondary supportive endpoints.

Missing data for the primary endpoint at week 56 was about 13%. There were not enough retrieved dropouts to conduct a retrieved dropout imputation. The applicant used jump to reference multiple imputation to impute missing data at week 56. Where missing data were imputed by sampling among all available assessments at week 56 in the placebo arm. Jump to reference assumes that subjects who discontinue treatment early will no longer have any benefit of the drug's effect and thus have outcomes similar to subjects in the placebo group. Additional analyses using return to baseline imputation produced similar results.

5.2 Collective Evidence

The primary endpoint was change in BMI SDS from baseline to week 56. Superiority of liraglutide over placebo was confirmed for the primary endpoint. Since there was 13% missing data, we conducted both the jump to reference imputation and the return to baseline imputation method. The results were similar. There was a greater reduction in favor of liraglutide in both the supportive secondary endpoints, proportion of subjects achieving at least 5% reduction in BMI from baseline and proportion of subjects achieving at least 10% reduction in BMI from baseline. A decrease in BMI from baseline was seen in the liraglutide group while an increase in BMI was seen in the placebo group. An increase in body weight was seen in the placebo group. There was a greater decrease seen in the liraglutide group for waist circumference. None of the supportive secondary endpoints were adjusted for multiplicity by the applicant.

Results from subgroup efficacy analyses were consistent with findings from the overall population.

5.3 Conclusions and Recommendations

Overall, the study has demonstrated efficacy of liraglutide in the proposed indication. It seems that liraglutide was associated with an increase in the rate of confirmed documented symptomatic hypoglycemia compared to placebo. However, there were no severe hypoglycemic events. Overall, there were no concerns on the benefit-risk profile to preclude approval.

5.4 Labeling and Recommendations

Labeling review is still ongoing while this review is finalized. Based on the review of the submitted data, the following are proposed edits to the label in section 14.

- No adjustments were made for multiplicity for any of the supportive secondary endpoints. We suggest that (b) (4) be removed from the statement below

  (b) (4)

- Results of some of the supportive secondary endpoints that are closely related to the primary endpoint could be included.
- Table 9 should not reference p-values in the footnotes for the supportive secondary endpoints.

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/

KIYA HAMILTON
10/29/2020 01:48:35 PM

FENG LI
10/29/2020 02:04:31 PM