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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22341
Supplement #:	31
IND #:	IND 61040
Drug Name:	Victoza ® (liraglutide) injection
Indication(s):	An adjunct to diet and exercise to improve glycemic control in patients 10 year and older with T2DM
Applicant:	Novo Nordisk
Date(s):	Stamp date: December 21, 2018 Primary review due date: May 24, 2019 PDUFA goal date: June 17, 2019
Review Priority:	Priority Review Designation
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Keywords: pediatric, pattern mixture model, wash-out model, Bayesian hierarchical modelling

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1 EXECUTIVE SUMMARY

The applicant, Novo Nordisk, submitted a supplemental new drug application (sNDA) for liraglutide (Victoza) to fulfill the FDA post-marketing requirement (PMR1583-2). This sNDA contained results of a pediatric study, ellipse™ (Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycemic control in children and adolescents with type 2 diabetes (T2DM)). The applicant seeks to update the liraglutide label with pediatric study results in INDICATIONS AND USAGE and CLINICAL STUDIES sections in the label.

1.1 Brief overview of Clinical Study

Ellipse™ was a 26-week double-blind, randomized, placebo-controlled and multi-center clinical study followed by a 26-week open-label extension (NCT01541215; N=135) to compare the impact of liraglutide up to 1.8 mg vs. placebo add-on to metformin with or without basal insulin on glycemic control (primary endpoint: changes in HbA1c at Week 26) in pediatric patients (ages 10-17 years) with T2DM (see details in Section 2.1.3).

1.2 Statistical Issues

No major statistical issues have been identified. Overall, for evaluation of efficacy, the applicant handled missing data adequately in the pre-specified primary analysis based on treatment-policy estimand with pattern mixture model. All randomized and treated patients regardless of initiation of rescue therapy were included in the primary analysis. The retrieved dropouts were not collected and there were ~12% missing Week 26 efficacy data.

The following issues are explored and do not change conclusion of treatment efficacy: design of clinical trial, an assessment of optimal dose and effectiveness, handling missing data, similarity to adult data results, subgroup analysis (see details in Section 3.2), safety including growth/development (see details in Section 3.3), and benefit-risk assessment (see details in Section 3.4).

1.3 Collective Evidence

- **Robust effectiveness of liraglutide:** The primary analysis results showed statistically significant superiority of liraglutide compared to placebo add-on to metformin (treatment difference in mean changes in HbA1c (95% CI): -1.06 (-1.65, -0.46), Table 1). Sensitivity analyses including "washout" model did not alter conclusion. Also, glycemic control results were similar to adult study results with similar trial design and across age subgroups: 10< age ≤14 vs. age >14 (see details in Section 3.2.4).
- **Numerically Higher hypoglycemia numbers in liraglutide:** More hypoglycemic episodes were observed with liraglutide compared to placebo. However, there were no clinically relevant differences between treatment arms in any other safety signals including growth and development (see details in Section 3.3).
- **Favorable Benefit- Risk assessment:** Illustrations of benefit (changes of HbA1c at week 26) and risk (the number of hypoglycemia) with baseline HbA1c confirmed the benefit outweigh the risk of liraglutide compared to placebo add-on to metformin (see details in Section 3.4).

Table 1. Primary analysis results for changes in HbA1c at Week 26 using Full Analysis Set

Mean change in HbA1c (%) from baseline to Week 26 add-on to metformin	*Liraglutide 1.8 mg LSM(SE) N=66*	*Placebo LSM(SE) N=68*	*Difference (Liraglutide - placebo) LSM Estimate (SE)*	*[95% CI]*
Pre-specified PMM	-0.64 (0.22)	0.42 (0.22)	**-1.06 (0.30)**	**[-1.65, -0.46]**
Washout analysis	-0.64 (0.26)	0.40 (0.22)	**-1.05 (0.34)**	**[-1.72, -0.38]**

**PMM: the sponsor's pre-specified analysis using pattern mixture model based on washout multiple imputation; FAS: full analysis set ** The reviewer's analysis using washout model multiple imputation (section 3.2.2 for methodology details)*

1.4 Conclusion and Recommendations

Statistical findings in ellipse™ demonstrated robust superiority of liraglutide up to 1.8 mg compared to placebo as an add-on to metformin in pediatric patients (10-17 years) with T2DM. There is reliable statistical evidence to support updating information in INDICATIONS AND USAGE by indicating the target population as patients 10 year and older with T2DM for liraglutide treatment as well as CLINICAL STUDIES sections by adding ellipse™ results in the label (see Section 5.4).

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue. The current indications of liraglutide (Victoza®) are for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. The approved doses for liraglutide are 0.6 mg, 1.2 mg, or 1.8 mg once daily subcutaneous injection.

In this submission, the applicant proposed to update indication for use of liraglutide as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus.

2.1.2 History of Drug Development

Liraglutide was originally approved by the FDA on January 2010 and has been approved in many countries for the treatment of adults with T2DM under the trade name Victoza®. For pediatric subjects (ages 10-17 years) with T2DM, phase 2 trial with a small group of subjects (N=21) was conducted for assessing its safety, tolerability, pharmacokinetics and pharmacodynamics (NN2211-1800). Daily doses of up to 1.8 mg liraglutide were well-tolerated in the pediatric population. In the present trial, ellipse™ (NN2211-3659), larger number of pediatric subjects with T2DM were used to assess the efficacy and safety of liraglutide for fulfilling the PMR requested by the agency.

Main communications regarding statistical consideration between the agency and the applicant for PMR of liraglutide were done through IND 061040. The applicant had revised the original PMR protocol based on communications with the agency until June 2017. Main changes included reduction of sample size, updating efficacy analysis set to all randomized subjects receiving at least one dose of study drug, and revising efficacy analysis method to pattern mixture model based on "wash-out" analysis instead of the mixed-effect model repeated measurement (MMRM). Final statistical analysis plan (SAP) was dated June 25, 2018. The data cut-off date was June 27, 2018 and sNDA including ellipse™ results was submitted on December 2018.

2.1.3 Studies Reviewed

This submission consists of a single efficacy and safety study NN2211-3659, *Efficacy and Safety of liraglutide in combination with metformin versus metformin monotherapy on glycemic control in children and adolescents with type 2 diabetes (Ellipse™).* Table 2 is an overview of key factors of Ellipse™.

Table 2. Trial NN2211-3659 (Ellipse™) summary in statistical review

	***Ellipse* ™**
Phase and Design	• Phase 3a, double-blind, 1:1 randomized, parallel group, placebo controlled multi-center trial • In combination with metformin with or without basal insulin treatment, on a background of diet and exercise • Stratification factor for randomization by sex and according to their age at end of treatment (52 weeks) o Female ≤ 14 years o Male ≤ 14 years o Female > 14 years o Male >14 years
# of Subjects randomized per Arm	Liraglutide: 66 Placebo: 69 (68 treated)
Trial Period	November 2012- May 2018 (cutoff date: June 2018)
Study Population	Children and adolescents (pediatric) patients (ages of 10 – 17 years) with T2DM
Analysis Population	FAS consisted of all patients randomized and treated
Primary Objective	To compare the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg, 1.8 mg) in combination with metformin in controlling glycemia versus placebo add-on to metformin in children and adolescent (ages 10-17 years) with T2DM
Primary Endpoint	Change from baseline in HbA1c after 26 weeks of treatment
Primary Hypothesis	H_0: difference = liraglutide - placebo = 0 H_1: difference ≠ 0 concluding by upper limit of the 95% CI for the treatment difference lies entirely below 0 (Superiority with the two-sided p-value < 0.05)

*Note: T2DM type 2 diabetes mellitus; FAS full analysis set;

2.2 Data Sources

The applicant submitted materials for this review electronically in the electronic common technical document (eCTD) form which were archived under the network path location: \\CDSESUB1\evsprod\NDA022341\022341.enx. The sponsor did not submit all ADAM datasets in the first submission in the eCTD sequence number #414 (\\CDSESUB1\evsprod\NDA022341\0414). Upon agency's request, the applicant re-submitted all data sets for ellipse in ADAM and STDM formats in the eCTD sequence number #417 (\\CDSESUB1\evsprod\NDA022341\0417\m5\datasets) with additional ad-hoc subgroup analysis results and codes.

In addition to the sponsor's analyses, this reviewer performed independent analyses to obtain the descriptive statistics, plots and analyses results using SAS (modified from the sponsor's code) and R language.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

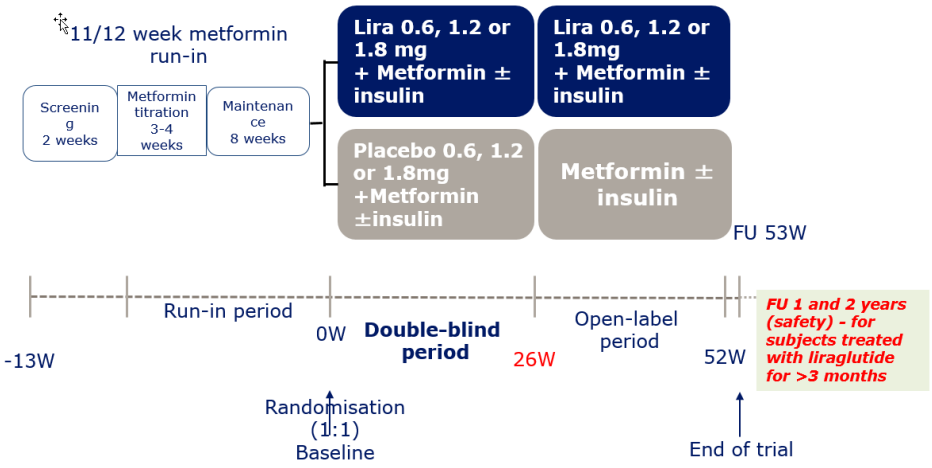
Despite the applicant not wholly submitting all ADAM datasets, the applicant later re-submitted all datasets with programs of high quality and made it possible for the statistical reviewer to reproduce their results of pre-specified primary analysis as well as sensitivity analyses. For data integrity, this reviewer checked derived variables from STDM to ADAM datasets and basic summary statistics including patient dispositions. There was no issue on data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Ellipse™ was a double-blind, 1:1 randomized, parallel group, placebo controlled and multi-center trial (Figure 1). During Run-in period, subjects received metformin daily with stable dose after appropriate titration and verification of eligibility according to the inclusion and exclusion criteria. After randomization, first 26 weeks were double-blind period for liraglutide and placebo in combination with metformin with/without basal insulin, followed by 26-week open-label period. The liraglutide dosing was started at 0.6 mg/day during the first week and escalated in weekly increments of 0.6 mg over the following 2-3 weeks up to 1.8 mg or maximal tolerated dose (MTD). After randomization, basal insulin could be also adjusted per investigator's determination.

Figure 1. Ellipse™ trial design



Source: Replotted from original figure in clinical trial report page 41

Subjects who were treated with liraglutide over 3 months would be followed up for 1 and 2 years for safety purpose. This follow-up is ongoing, and the current clinical trial report does not contain the results of this safety follow-up.

Because the objective of the study is to evaluate the efficacy of liraglutide add-on to metformin with/without basal insulin, the run-in period was inevitable for stable metformin medication before randomization prior to double-blind period.

Reviewer's Note: there were twenty patients (7 patients in the liraglutide arm and 14 patients in the placebo arm) who had HbA1c < 6.5% at the baseline due to Run-in period with metformin treatment.

Sample size

The sample size was originally planned for 150 subjects but was modified in the final revised protocol of trial NN2211-3659 (dated February 12, 2015) to a total of 94 subjects (47 to each arm) with assumption of 22% withdrawal rate and 0.9% difference of treatment effect with 1.2% standard deviation to produce 80% power with a two-sided α=0.05. In reality, total of 135 were randomized: 66 subjects in liraglutide arm and 69 subjects in the placebo arm. It appeared that ellipse™ had adequate power to detect the superiority of treatment effect of liraglutide (see details in Section 3.2.4.1).

Primary and key secondary endpoints for efficacy evaluation

The primary endpoint and key secondary endpoints were analyzed in a hierarchical manner in the following order:

Primary endpoint

- Change in HbA1c from baseline to week 26

Key secondary endpoints

- Change from baseline in FPG (Fasting plasma glucose)
- Proportions of HbA1c < 7% at week 26
- Change from baseline in standardized BMI (BMI SDS, Z score): calculated using LMS[1] method adjusted by age and sex for children/adolescents

The hierarchically testing is used to maintain a one-sided family-wise type I error of 2.5%.

3.2.2 Statistical Methodologies

3.2.2.1 Estimand

The applicant defined the primary estimand as "treatment policy" with the following attributes:

[1] *Population:* FAS including all subjects who were randomized and treated;
[2] *Variable (endpoint)*: changes in HbA1c from baseline to Week 26;
[3] *Intercurrent events*: regardless of initiation of rescue medication or discontinuation of study/treatment;
[4] *Population-level summary parameter*: difference in variable means between liraglutide arm and placebo arm for evaluating of superiority of liraglutide.

The applicant retained the subjects who initiated rescue medication prior to Week 26 for HbA1c values at Week 26. However, the applicant did not follow up subjects who discontinued treatment prior Week 26 assessment.

3.2.2.2 Statistical analysis

The applicant's primary analyses

The study protocol specified that the change in HbA1c from baseline to week 26 would be analyzed using a pattern mixture model (PMM) with multiple imputations. The null hypothesis was that there is no difference in the changes from baseline in HbA1c (%) after 26 weeks of randomized treatment with liraglutide add-on to metformin vs. placebo add-on to metformin, each with or without basal insulin (H_0: difference= liraglutide -placebo=0). Superiority of liraglutide over placebo was to be concluded if the 95% confidence interval for the treatment difference for change from baseline in HbA1c (%) at Week 26 was entirely below 0%.

To handle missing Week 26 HbA1c data in the liraglutide arm, multiple imputations were performed based on the subjects' baseline HbA1c in a regression model using the data from completers from the placebo arm (i.e., subjects in the placebo arm with HbA1c measurements at Week 26).

[1] Where L, M and S are median (M), skewness(L) and variation coefficient (S) of children BMI provided for each sex and age: reference: https://www.who.int/childgrowth/mgrs/en/

For missing Week 26 HbA1c data in the placebo arm, multiple imputations were performed based on baseline HbA1c and pattern of HbA1c observed at intermediate weeks (Week 10 and Week 14). The following four regression models were created based on the data from completers in the placebo arm:

- Model 1: only baseline covariates (baseline HbA1c, stratification group (sex* age group), concomitant diabetes treatment (basal insulin) at baseline (Yes/No))
- Model 2: baseline covariates and week 10 HbA1c as a covariate
- Model 3: baseline covariates and week 14 HbA1c as a covariate
- Model 4: baseline covariates, week 10 HbA1c and week 14 HbA1c as a covariate

Missing data were imputed by selecting random observations from a normal distribution centered at the value predicted by the regression model and with variance analogous to predicting a new observation. The imputation procedure was iterated 10,000 times to generate 10,000 complete datasets including observed and imputed values.

ANCOVA model was performed for each complete data set with treatment and stratification groups (sex*age group) as categorical fixed effects and baseline HbA1c as a covariate. Rubin's rule was used for combining results to draw inference.

Key secondary endpoints were also analyzed using the PMM model for imputing the missing data like primary analysis for primary endpoint. For responder analysis to test for proportions of patients achieved HbA1c (%) < 7%, multiple imputed values for continuous HbA1c were used to determine dichotomous endpoint (responder/non-responder). A logistic regression analysis was used to calculate the odds ratio and statistical significance.

The applicant did not use an option "obsmargins" in the PROC MIXED in their SAS code, so this reviewer reproduced the results with this option.

The applicant performed several sensitivity analyses including an ANCOVA model with LOCF imputation, an ANCOVA model based on "While on treatment strategy" by not including data observed after initiation of rescue medication and mixed model for repeated measures (MMRM) model.

Statistical reviewer's primary analyses

The preferred method for addressing missing data under "treatment policy" estimand would be to model patients with missing data after retrieved drop-outs by assumption of missing data would have been like retrieved drop-outs if they were assessed. However, in ellipse™, the applicant did not follow up patients who discontinued treatments to measure Week 26 endpoints. Because there were no available retrieved dropouts and ellipse™ was a placebo-controlled trial, this reviewer performed "wash-out" analysis instead of retrieved drop-out analysis.

The missing HbA1c Week 26 data were imputed by wash-out the effect of treatment using placebo completers. This method is in line with the pre-specified analysis by the applicant but technically used only one model for missing data in the placebo arm. Specifically, measurements

for patients on the placebo arm without observed Week 26 data were imputed using a monotone regression model based on observed HbA1c data of completers on the placebo arm with intermediate measurements, baseline HbA1c and stratification group. For patients on the liraglutide arm who had missing Week 26 data, the imputation model with only baseline HbA1c and stratification group was used.

One thousand data sets were generated and an ANCOVA with the protocol specified factors and covariates was run on each data set and point estimates and standard errors were computed and the results were combined to yield a multiple imputation point estimate and standard error.

All HbA1c (%) measurements at Week 26 were used in the reviewer's primary analysis even though some of them were observed outside of pre-specified assessment window for Week 26. This reviewer also performed a sensitivity analysis after treating those measurements out of visit window as missing.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 135 patients were randomized but 1 patient was not treated with study drug, so a total of 134 patients were used as full analysis set (FAS) for the efficacy analyses (Table 3). Of those within the randomized set, 26 (19.3%) patients prematurely discontinued study drug prior to end of trial at Week 52. The most frequent reason of drug discontinuation was withdrawal by subjects (Table 3). The sponsor did not follow up patients who have discontinued study drug but remained in the study to assess HbA1c endpoint (i.e. retrieved dropouts). HbA1c measurements at Week 26 were missing for 7 (10.6%) subjects in the liraglutide arm and 10 (14.5%) subject in the placebo arm.

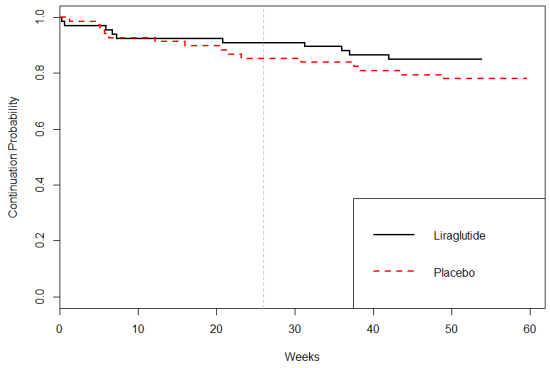
Table 3. Patient disposition in ellipse™ and reasons for treatment discontinuation

	Liraglutide ***n (%)*** ***N=66***	***Placebo*** ***n (%)*** ***N=69***	***Total*** ***n (%)*** ***N=135***
Randomized	66 (100%)	69 (100%)	135(100%)
Randomized & Treated Study drug (FAS*)	**66 (100%)**	**68 (98.6%)**	**134 (99.3%)**
Completed trial/treatment week 26	60 (90.9%)	58 (84.1%)	118 (87.4%)
Initiated rescue medication prior to week 26	3 (4.5%)	12 (17.3%)	15 (11.1%)
HbA1c values missing for week 26	7** (10.6%)	10 (14.5%)	17 (12.6%)
Completed trial/treatment week 52	56 (84.8%)	53 (76.8%)	109 (80.7%)
Discontinued trial prior to week 52	10 (15.2%)	16 (23.2%)	26 (19.3%)
Withdrawal criteria	6 (9.1 %)	8 (11.6 %)	14 (10.4%)
Non-compliance	3 (4.5 %)	4 (5.8%)	8 (5.9%)
Adverse events	1 (1.5%)	1 (1.4%)	1 (0.7%)
Other (reasons: lack of efficacy, lost to follow up)	0	3 (4.3%)	3 (2.2%)

* FAS full analysis set; **The applicant stated that one subject (NN2211-3659/ (b) (6)) completed trial for Week 26 but cannot use HbA1c measurement due to non-compliance prior to Week 26.
Source: reviewer's analysis (data from adsl dataset)

Kaplan- Meier plot for treatment discontinuation (Figure 2) showed separation between liraglutide and placebo arms began at 15 weeks and a wider separation in later weeks in the trial. There was no notable concern for early treatment discontinuation during double-blind period up to Week 26 in the lirgalutide arm. Note that in the ellipse™ trial, study drug were given in addition to metformin with/without basal insulin and initiation of rescue medication was allowed during trial.

Figure 2. Illustration of Treatment Discontinuation for all patients (FAS)



**Grey vertical line: Week 26*
Source: reviewer's analysis (data from adsl dataset)

Major baseline characteristics by treatment arm are summarized in Table 4. They were well-balanced between arms. As stated in the written response for PMR, 30% of population was of age ≤ 14 years at the end of treatment in this trial. More girls (61.9%) were enrolled in this trial than boys (38.1%), and the boy to girl ratio was similar between treatment arms. Most of population (81%) did not take basal insulin at baseline.

Table 4. Demographics and Baseline Characteristics- FAS

		Liraglutide N=66	***Placebo N=68***	***Total N=134***
Age				
	Mean (SD)	14.6 (1.7)	14.6 (1.7)	14.6 (1.7)
	Median (Min, Max)	15.0 (10, 16.9)	14.8 (10.4, 16.9)	14.9 (10,16.9)
	≤ 14 years at EOT (%)	21 (31.8)	19 (27.9)	40 (29.9)
	>14 years at EOT (%)	45 (68.2)	49 (72.1)	94 (70.1)
Sex				
	Female (%)	41 (62.1)	42 (61.8)	83 (61.9)
	Male (%)	25 (37.9)	26 (38.2)	51 (38.1)
Ethnicity				
	Hispanic or Latino	16 (24.2)	23 (33.8)	39 (29.1)
	No Hispanic or Latino	50 (75.8)	45 (66.2)	95 (70.9)
Race				
	White	42 (63.6)	45 (66.2)	87 (64.9)
	Black	9 (13.6)	7 (10.3)	16 (11.9)
	Asian	10 (15.2)	8 (11.8)	18 (13.4)
	Others	5 (7.5)	8 (11.8)	13 (9.7)

Region			
North America	19 (28.8)	28 (41.2)	47 (35.1)
South America	9 (13.6)	7 (10.3)	16 (11.9)
Europe	24 (36.4)	21 (41.2)	45 (33.6)
Rest of the world	14 (21.2)	12 (17.6)	26 (19.4)
Basal insulin at baseline			
Yes (%)	15 (22.7)	10 (14.7)	25 (18.7)
No (%)	51 (77.3)	58 (85.3)	109 (81.3)
Duration of diabetes (years)			
Mean (SD)	1.85 (1.68)	1.93 (1.32)	1.89 (1.51)
Median (Min, Max)	1.26 (0.3, 10.1)	1.5 (0.2, 6.2)	1.41 (0.2, 10.1)
HbA1c (%)			
Mean (SD)	7.87 (1.35)	7.69 (1.34)	7.78 (1.34)
Median (Min, Max)	7.7 (5.1, 11.5)	7.7 (5.1, 11)	7.7 (5.1, 11.5)
Body mass index (BMI) (kg/m^2)			
Mean (SD)	34.6 (10.9)	33.3 (7.4)	33.9 (9.3)
Median (Min, Max)	31.8 (20.9, 81.2)	32.9 (21.9,57.1)	32.5(20.9,81.2)
BMI Standard Deviation Score (SDS)			
Mean (SD)	3.03(1.5)	2.86 (1.1)	2.94 (1.30)
Median (Min, Max)	2.7 (1.0, 9.3)	2.7 (1.1, 6.3)	2.8 (1.0, 9.3)

Source: extracted from clinical trial report Table 10-2, 10-3, 10-4, 10-5 and 10-6 (pages 104-108)

3.2.4 Results

3.2.4.1 Primary Endpoint: Changes in HbA1c (%) from baseline to Week 26

Mean HbA1c (%) decreased from baseline to Week 26 in the liraglutide arm; while increased in the placebo arm (Table 5).

Table 5. Primary Analysis Results for Changes in HbA1c at Week 26 – FAS

HbA1c (%)	***Add-on to metformin***		***Difference (Liraglutide - placebo)***	
	Liraglutide 1.8 mg N=66	***Placebo N=68***	***Estimate (SE)***	***[95% CI]***
Mean at baseline (SE)	7.87 (0.17)	7.69 (0.16)		
Mean at Week 26 (SE)	7.13 (0.22)	8.19 (0.22)		
Mean change from baseline to week 26 (SE) using PMM*	-0.64 (0.22)	0.42 (0.22)	**-1.06 (0.30)**	**[-1.65, -0.46] p-value <0.001**
Washout model analysis**	-0.64 (0.26)	0.40 (0.22)	-1.05 (0.34)	[-1.72, -0.38] p-value=0.002

*Mean: least squared mean using Rubin's rule to combine results from the multiple imputation data sets; PMM: the sponsor's analysis using pattern mixture model multiple imputation (n=10,000); FAS: full analysis set

** The reviewer's analysis using washout model multiple imputation (n=1,000)

***Estimates from ANCOVA model with treatment and stratification groups (sex*age group) as categorical fixed effects and baseline HbA1c as a covariate.

source: the applicant's analysis and reviewer's analysis at CSR Page 126 (data from adlb, adsl datasets)

Treatment difference between liraglutide and placebo in mean change of HbA1c from baseline to Week 26 was estimated as -1.06 with 95% CI as (-1.65, -0.46) by the applicant's pre-specified PMM multiple imputation analysis with obsmargins option. Because the upper limit of 95% CI of treatment difference is entirely below 0, superiority of liraglutide is established. All sensitivity analyses by the applicant (clinical trial report page 127) showed similar results and did not alter the conclusion of superiority of liraglutide. Of note, treatment difference between liraglutide and placebo for patients without rescue medication using PMM multiple imputation method was -0.85 (95% CI: -1.49, -0.22).

The reviewer's washout model multiple imputation analysis with obsmargins option in the SAS programming showed similar treatment effect: -1.05 with 95% CI as (-1.72, -0.38).

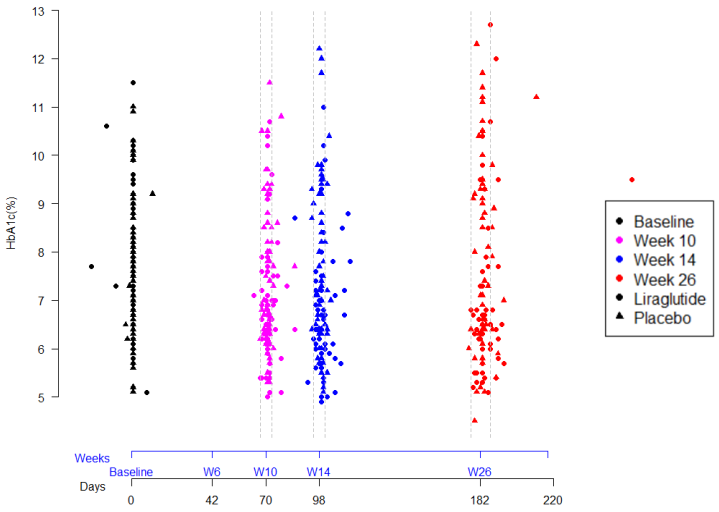
Patient level residual standard deviation

Using standard deviation for difference in mean change (SE: 0.30 and 0.34 from PMM and washout model respectively from Table 5), the patient level residual standard deviations (σ) were calculated as 1.7% and 2.0% for PMM and washout model respectively. Although the assumed standard deviation of 1.2% for sample size calculation was underestimated, ellipse™ was adequately powered (power of 88%) as recalculated with the mean difference and patient level residual standard deviation(σ) from reviewer's primary analysis results.

HbA1c (%) measurements out of visit window

HbA1c (%) were measured at Baseline, Week 10, Week 14, and Week 26. For data integrity check, Figure 3 illustrated the HbA1c (%) measurements (Y-axis) by analysis day (X-axis). There were some data out of window for Week 26. Sensitivity analyses after removing out of window data resulted in similar treatment effect estimate (95% CI): -1.15 (-1.73, -0.57).

Figure 3. HbA1c (%) measurements by visit window



Source: reviewer's analysis (data from adlb dataset)

Final dose at Week 26

Currently liraglutide is approved for doses of 0.6 mg, 1.2 mg or 1.8 mg. The ellipse™ was designed to study effectiveness of liraglutide at 1.8mg, if possible, or maximal tolerated dose after escalation of liraglutide in weekly 0.6mg increments over 2-3 weeks in pediatric population. Thus, the final dose at Week 26 was among 0.6 mg, 1.2 mg or 1.8 mg as a maximal tolerated dose (Table 6). More patients were at lower doses (0.6 mg and 1.2 mg) in the liraglutide arm compared to the placebo arm (25.8% vs 8.8% at 0.6 mg and 18.2% vs 10.3% at 1.8 mg for liraglutide and placebo respectively) due to tolerability. At 1.8 mg dose, there were 31 patients (47%) in the liraglutide and 44 patients (65%) in the placebo arm.

Table 6. Number of Patients at Final Doses at Week 26

Final dose at Week 26	***Liraglutide arm N= 66***	***Placebo N=68***
0.6 mg	17 (25.8%)	6 (8.8%)
1.2 mg	12 (18.2%)	7 (10.3%)
1.8 mg	31 (47.0%)	44 (64.7%)
Missing data	6 (9.0%)	11 (1 patient for 0 mg) (16.2%)

Source: reviewer's analysis (data from adec dataset)

3.2.4.2 Secondary Endpoints

Because primary endpoint showed the superiority of liraglutide, further hypothesis testing was performed for secondary endpoints. Results for key secondary endpoints (i.e., changes in FPG, proportion of patients achieving HbA1c < 7 %, and BMI SDS from baseline at Week 26) by multiple imputation PMM analysis using FAS (same as primary analysis) are shown in Table 7.

Table 7. Analysis Results for Key Secondary Endpoints

PMM-FAS at week 26	**Liraglutide 1.8 mg N=66**	**Placebo N=68**	**Difference (Liraglutide - placebo) Estimate (SE)**	**[95% CI]**
Fasting Plasma Glucose (mg/dL)				
Change from baseline (LSM (SE))	-19.38 (7.87)	14.61 (8.07)	-33.99 (11.21)	[-55.96, -12.01] p-value=0.002
Proportion of Patients achieving HbA1c < 7.0% (%)				
Number of patients (%) with HbA1c < 7%	42 (63.6%)	24.8 (36.5%)	5.32 (odds ratio)	[2.10, 13.49] p-value < 0.001
BMI SDS				
Change from baseline (LSM (SE))	-0.26 (0.04)	-0.21 (0.04)	-0.05 (0.05)	[-0.15, 0.06] p-value =0.386

**Source: reviewer's analysis using pattern mixture multiple imputation (n=10000 with obsmargins option used in proc mixed for stratification factor) (data from adlb, adsl, advsen datasets)*

FPG decreased at Week 26 with liraglutide meanwhile increased with placebo, and there is a significant difference in change in FPG between liraglutide and placebo (-33.99 with 95% CI (-

55.96, -12.01)). There was also significant difference in proportions of patients who achieved HbA1c < 7% at Week 26 between liraglutide and placebo arms (odds ratio of 5.32 with 95% CI (2.1, 13.5)). The difference between changes from baseline to Week 26 in BMI SDS did not show statistical significance (-0.05 with 95% CI (-0.15, 0.06)). No further hypothesis testing was performed due to failure to show superiority of liraglutide in BMI SDS.

Similarity of efficacy to adult study of liraglutide Add-on to Metformin

Liraglutide add-on to metformin was approved for adult population (mean age of patients: 57 years) with T2DM. The key efficacy results for adults (extracted results for liraglutide 1.8 mg and 1.2mg from the current labeling) and pediatric studies were listed side-by-side in Table 8 for exploratory purpose.

Table 8. Comparison to Adult Study Results for Efficacy of liraglutide add-on to Metformin

Liraglutide vs. placebo add-on to metformin	**Adult study results from current label for liraglutide**		**Pediatric study (10 - 17 years)**
Dose	**1.8 mg**	**1.2 mg**	**1.8 mg**
ITT population (N)	242 vs 121 (placebo)	240 vs 121 (placebo)	66 vs 68 (placebo)
Difference in changes of HbA1c (%) at week 26 liraglutide vs. placebo (95% CI)	-1.1 (-1.3, -0.9)**	-1.1 (-1.3,-0.9)**	-1.06 (-1.65, -0.46)**
HbA1c < 7.0% at week 26	42% vs 11%	35% vs 11%	64% vs 37% **
Change from baseline in FPG (mg/dL) at week 26	-38 (-48, -27)**	-37 (-47,-26)**	-34 (-56, -12) **
Change from baseline in Body Weight (kg)/ BMI SDS at week 26	-1.3 (-2.2, -0.4)*	-1.1 (-2.0,-0.2)*	BMI SDS for children -0.05 (-0.15, 0.06)

**p-value <0.05; **p-value <0.001*
**Source: extracted from CLINICAL STUDIES (Section 14) Add-on to Metformin in the current label of liraglutide*

Not only statistical significance but also effect sizes of changes in HbA1c and FPG at Week 26 were similar in both adult and pediatric studies. Proportions of subjects achieving HbA1c < 7 % were also significantly greater in the liraglutide add-on to metformin arm in both studies. In adult population, change from baseline in body weight (kg) to Week 26 showed statistically significant superiority of liraglutide but BMI SDS changes in pediatric population did not establish superiority. In Ellipse™, there were no other significant results at Week 26 for body weight related endpoints such as body weight (-1.32 kg with 95% CI [-3.01,0.38]), and BMI (-0.31 kg/m^2 with 95% CI [-0.93, 0.32].

3.2.5 Conclusion

Statistical findings in ellipse™ showed a beneficial treatment effect of liraglutide add-on to metformin compared to placebo add-on to metformin in reduction of HbA1c (%) and FPG after 26-week treatment. There is robust and reliable statistical evidence in efficacy of liraglutide.

3.3 Evaluation of Safety

3.3.1 Safety Analysis Population and Endpoints

Of 135 randomized patients, 134 patients were treated with study drugs. Patients were treated with randomized treatment as planned, safety analysis population (SAS) was the same as full analysis population (66 in the liraglutide and 68 in the placebo arm).

For pediatric populations, growth and development are not supposed to be disturbed by the drug. Thus, growth and development parameters should be considered in evaluating the long-term safety of a treatment in addition to adverse events, clinical laboratory values, and vital signs. In ellipse™, as growth and development parameters, the applicant assessed height, weight, and tanner staging at screening, baseline, Week 14 and Week 26 and Week 52. Note that ellipse™ was a 1-year study and is still on-going to collect the long-term (2 year) safety.

A full evaluation of safety of ellipse™ is included in the FDA clinical review by Dr. Tania Condarco of the DMEP. In this statistical review, one of the adverse events, hypoglycemic incidence and number of episodes and one of growth and development parameters, height SDS, during the entire treatment period from randomization to Week 52 visit were considered in safety evaluation.

3.3.2 Statistical Methods

Even though hypothesis testing for safety endpoints is not pre-specified in the protocol of ellipse ™, exploratory analyses were performed to assess treatment differences in incidence of hypoglycemia. The number of patients who had at least one hypoglycemia episode between treatment arms was analyzed by Fisher's exact test. Over-dispersed episode counts of hypoglycemia were tested between liraglutide and placebo arms using negative binomial model with stratification factor and offset of treatment duration.

As mentioned in previous section, 1-year and 2-year safety trial for growth and development is ongoing. In this review, height SDS was descriptively analyzed to compare the liraglutide arm to placebo arm at baseline, Week 14, Week 26 and Week 52 by correlation plots and boxplot of group mean by the treatment arm.

3.3.3 Results

Hypoglycemia

Hypoglycemic episodes were classified according to the applicant's classification (minor hypoglycemia) and the ADA classification including but not limited to severe hypoglycemia and documented symptomatic hypoglycemia. Upon request by DMEP, results for hypoglycemia <54 mg/dL with or without symptoms was also included.

For descriptive purpose, nominal p-value from Fisher's exact test for proportions of patients and risk ratio with 95% CI from negative binomial regression model for count of episodes are presented in the Table 9.

Table 9. Hypoglycemic Episodes During the Entire Treatment Period – Safety Population

	Liraglutide 1.8 mg N=66		***Placebo N=68***		***Fisher's exact test nominal p-value for proportions of patients***	***Risk Ratio (95% CI) from NB**model for counts of episodes***
	n (%)	***Events***	***n (%)***	***Events***		
Minor hypoglycemia*	16 (24.2 %)	23	7 (10.3%)	13	0.039	2.11 (1.46, 3.05)
ADA classification	30 (45.5%)	160	17 (25%)	63	0.018	3.45 (2.52, 4.73)
Severe hypoglycemia	0 (0%)	0	1 (1.5%)	1	1	NA
Documented symptomatic hypoglycemia (<56 mg/dL)	19 (28.8%)	55	6 (8.8%)	26	0.004	3.49 (2.25, 5.41)
Hypoglycemia (<54 mg/dL) with/without symptoms	14 (21.2%)	20	6 (8.8%)	10	0.054	2.37 (1.60, 3.50)

**Minor: the applicant's definition of blood glucose < 3.1 mmol/L (56 mg/dL) with or without symptoms*

***NB negative binomial regression model for count data with stratification factor and offset of log transformed treatment duration*

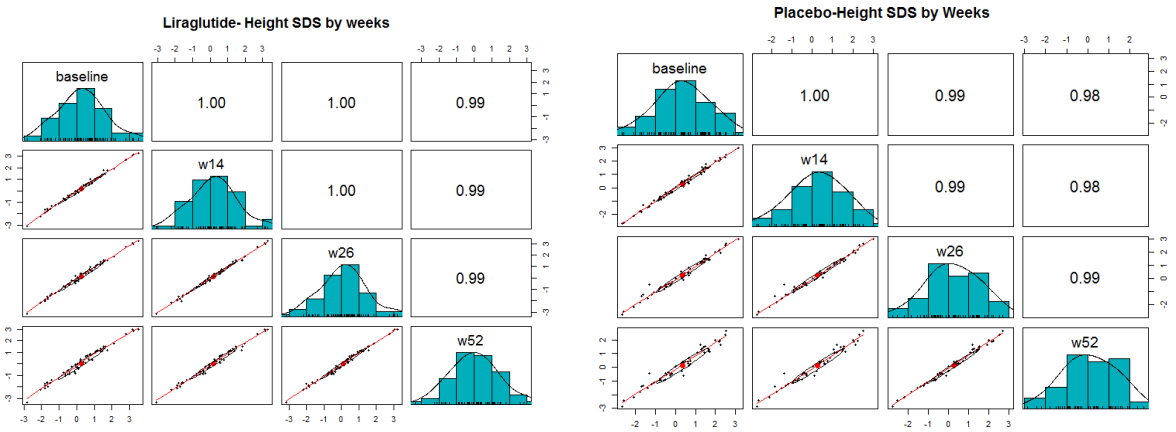
Source: reviewer's analysis (data from adhypo, adsl datasets)

During the entire treatment period, the proportion of patients experiencing hypoglycemia (i.e., incidence) as well as the episode rate were higher in the liraglutide arm than in the placebo arm except severe hypoglycemia (no patients with liraglutide). Of note, in ADA classification, there were 30 patients experienced hypoglycemia and 160 episodes in the liraglutide arm compared to 17 patients and 63 episodes in the placebo arm. Out of 30 patients with liraglutide, 12 (40%) patients who had 75 (47%) hypoglycemic episodes had baseline HbA1c (%) less than 7%.

Growth and development

The applicant calculated height SDS using LMS method adjusted by age and sex for children/adolescents. Height at each assessed time point (Baseline, Week 14, Week 26 and Week 52) were compared in a pairwise fashion to evaluate the treatment impact on growth and development. Correlation coefficients of individual height SDS throughout the entire treatment period were also calculated between time points (Figure 4). High pairwise correlations (Pearson's correlation coefficient ≥ 0.98) were observed in both treatment arms and there was no notable difference in height SDS between treatment arms.

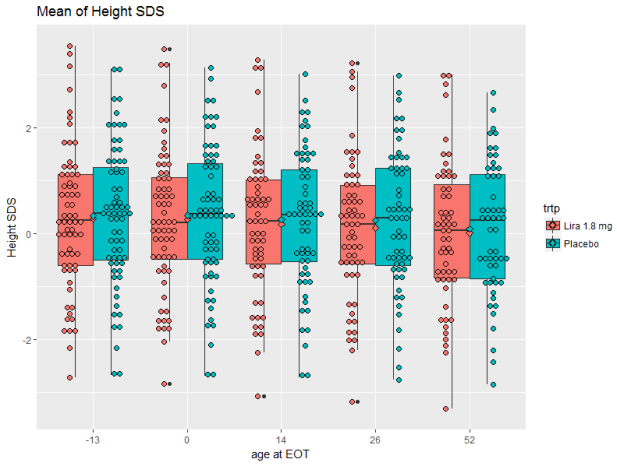
Figure 4. Pairwise correlation of Height SDS of baseline, Week 14, Week 26 and Week 52



**Upper panels- correlation coefficients (Pearson's method)*
Source: reviewer's analysis (data from advsen, adsl datasets)

Figure 5 illustrates boxplots of height SDS to compare the height distribution by treatment group at each time point. Mean of each group (diamond shape in the figure) shows no to little changes across time points.

Figure 5. Boxplots of Height SDS at screening, baseline, Week 14, Week 26, and Week 52 the liraglutide arm (red) and the placebo arm (green)



**source: reviewer's analysis (data from advsen, adsl datasets)*

3.3.4 Safety Conclusion

More hypoglycemic incidence and episodes were observed with liraglutide compared to placebo during the entire treatment period of the trial. However, there was no severe hypoglycemia occurred with the liraglutide and overall hypoglycemic adverse reaction in pediatric population was comparable to that observed in the adult population in the currently approved label. Also, there were no clinically relevant differences between treatment arms in height SDS as an evaluation of growth and development.

3.4 Benefit-Risk Assessment

Benefit-Risk was assessed visually for additional information. For each patient, benefit was defined as treatment effect on changes in HbA1c (%) at Week 26 and risk was defined as hypoglycemic episodes during the trial. Classifications of hypoglycemia used for benefit-risk assessment are documented symptomatic hypoglycemia by ADA classification and hypoglycemia <54 mg/dL with or without symptoms. Table 10 is the frequency table for these two classifications of hypoglycemia. The highest frequency of documented symptomatic hypoglycemia was 12 episodes from one patient in the placebo arm. For hypoglycemia (<54 mg/dL) with or without symptoms, most of patients had none or one-time episode (94% vs. 95.6% in the liraglutide and the placebo arm respectively).

Table 10. Frequency Tables of Documented Symptomatic Hypoglycemic Episodes and Hypoglycemic (<54 mg/dL) Episodes – Safety Population

Frequency	***Documented Symptomatic Hypoglycemia***		***Hypoglycemia (<54 mg/dL) with/without symptoms***	
	Liraglutide 1.8 mg N=66	*Placebo N=68*	*Liraglutide 1.8 mg N=66*	*Placebo N=68*
0	47 (71.2%)	62 (91.2%)	52 (78.8%)	62 (91.2%)
1	10 (15.2%)	2 (2.9%)	10 (15.2%)	3 (4.4%)
2	2 (3%)	2 (2.9%)	2 (3%)	2 (2.9%)
3	2 (3%)	0	2 (3%)	1 (1.4%)
5	2 (3%)	0		
6	1 (1.5%)	0		
8	0	1 (1.4%)		
9	1 (1.5%)	0		
10	1 (1.5%)	0		
12	0	1 (1.4%)		

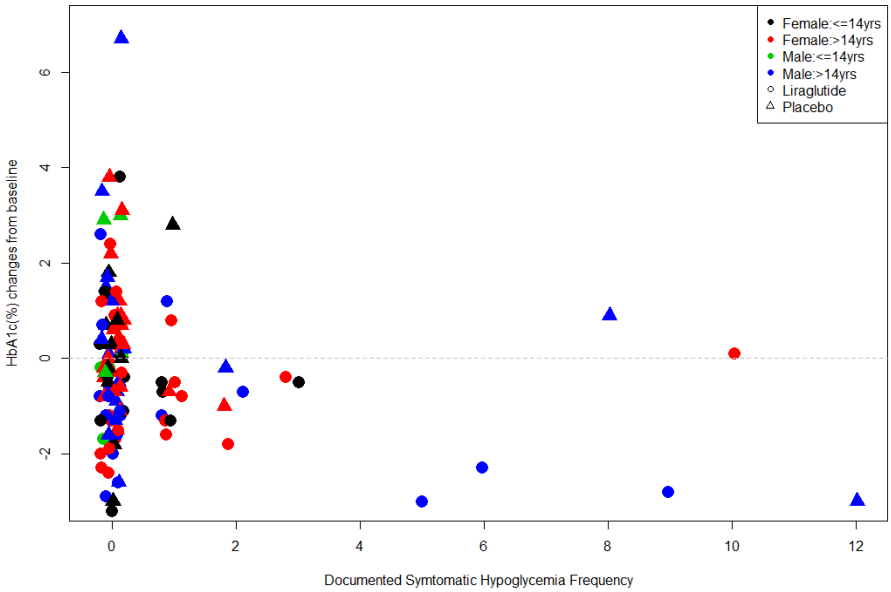
**Source: reviewer's analysis (data from adhypo dataset)*

Changes in HbA1c (%) and frequency of hypoglycemic episodes

In Figures 6 and 7, benefit (Y-axis: changes in HbA1c (%) at Week 26) and risk (X-axis: the number of hypoglycemic episodes during the entire treatment period) are visualized for documented symptomatic hypoglycemia and hypoglycemia <54 mg/dL respectively. Shapes of points indicate treatment group (i.e., circle: liraglutide, triangle: placebo) and colors indicate the stratification factors (i.e., black: female ≤ 14 years, red: female > 14 years, green: male ≤ 14 years, blue: male > 14 years). To avoid overlapped points, points were plotted with jitters.

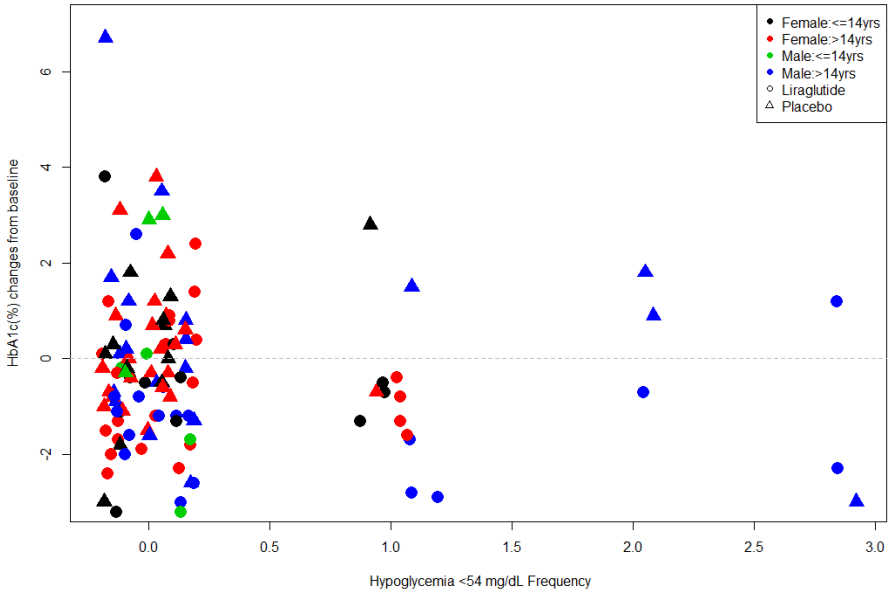
Most subjects who experienced more hypoglycemia had more reduction in HbA1c (%) at Week 26 with liraglutide treatment. In Figure 6, one patient in the liraglutide arm (NN2211-3659/(b) (6)) showed no changes in HbA1c (%) but had 10 times documented symptomatic hypoglycemia. This subject did not initiate rescue medication. In Figure 7, one patient in the liraglutide arm (NN2211-3659/(b) (6)) showed increase of HbA1c (%) at Week 26 and 3 times had hypoglycemia (<54 mg/dL). This subject initiated the rescue medication during the trial and accidentally overdosed (clinical trial report page 191).

Figure 6. Changes in HbA1c (%) and Number of Documented Symptomatic Hypoglycemia – FAS population



Source: reviewer's analysis(data from adhypo, adlb datasets)

Figure 7. Changes in HbA1c (%) and Number of Hypoglycemia < 54 mg/dL with/without symptoms– FAS population



Source: reviewer's analysis(data from adhypo, adlb datasets)

Changes in HbA1c (%) and frequency of hypoglycemic episodes with baseline HbA1c (%)

In Figures 8 and 9, baseline HbA1c (%) was added into above scatter plots as a 3rd factor for illustrating documented symptomatic hypoglycemia and hypoglycemia < 54 mg/dL respectively. One point in the plot indicates one patient with changes in HbA1c (%) at Week 26 on Y-axis and

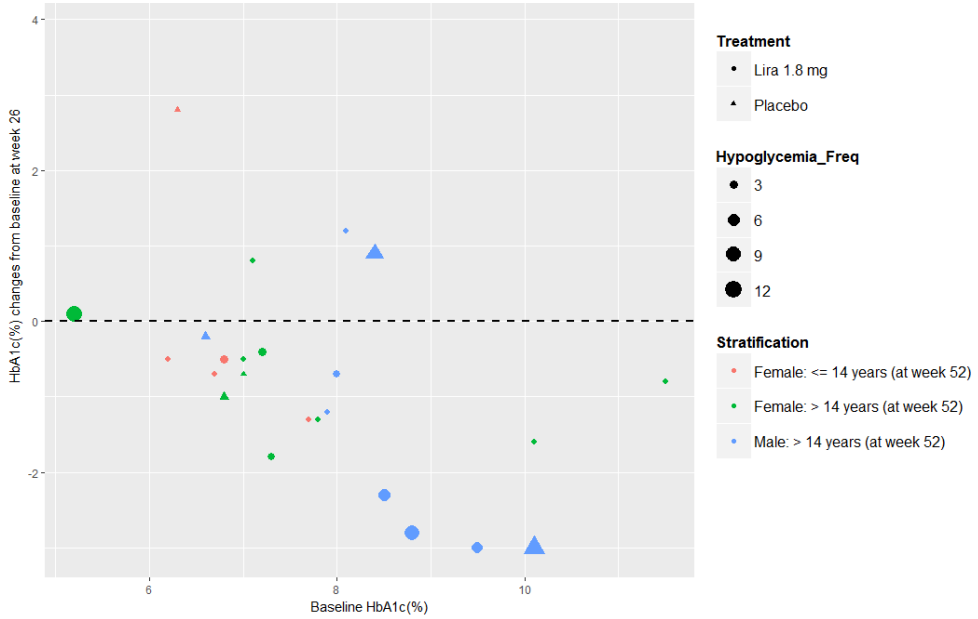
baseline HbA1c (%) on X-axis. Note that the area of symbols is based on the number of hypoglycemic episodes during the entire treatment period. The larger points correspond to the greater number of episodes. Patients who did not have episodes are not shown in the plot because area of symbols are zero. Solid circle indicates a patient in the liraglutide and solid triangle indicates a patient in the placebo arm. Color of points in the figure represent the stratum of a patient. There were no hypoglycemic episodes in the patients who are male and ≤ 14 years in Figures 8 and 9. Thus the legend of strata does not include the Male:<=14 years (at week 52).

In Figures 8 and 9, overall, patients in the liraglutide arm had the greater reduction in HbA1c (%) from baseline to week 26 (i.e., below zero dashed line in the plot) while having higher number of episodes (i.e., larger point size) across various baseline HbA1c (%). In addition, patients whose baseline HbA1c (%) ≥ 7% showed greater reduction in HbA1c than patients whose baseline HbA1c (%) < 7%. It is not surprising that older patients (> 14 years) were dominant in the plot because older patients (blue and green) were of 70% of the population in both Figures 8 and 9.

In Figure 8, of note, the green and big circle on the left side close to zero HbA1c (%) change indicates a patient in the liraglutide arm (NN2211-3659/ (b) (6)) who experienced a risk overweighing benefit. The baseline HbA1c (%) of this patient was at 5.1%.

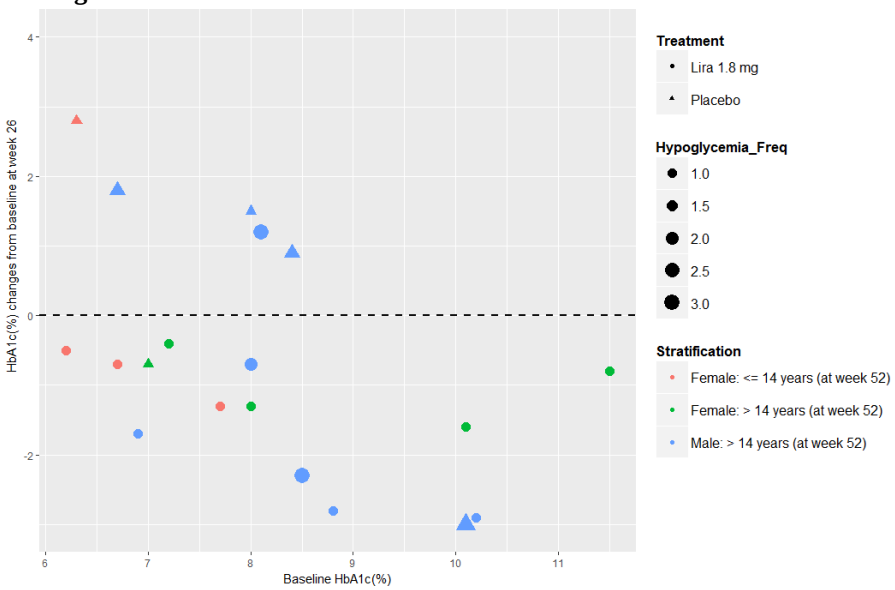
Similarly, in Figure 9, the blue and big circle above zero line of HbA1c (%) change indicates a patient in the liraglutide arm (NN2211-3659/ (b) (6)) who experienced no benefit and higher risk. As abovementioned in Figure 7, this subject initiated the rescue medication during the trial and accidentally overdosed (clinical trial report page 191).

Figure 8. Changes in HbA1c (%) and baseline HbA1c (%) with Sizing of Points based on Number of Documented Symptomatic Hypoglycemia



**Note: There was no hypoglycemia episodes in the stratification of male <=14 years(at week 52). Thus the legend of stratification do not show the Male:<=14 years (at week 52).*
Source: reviewer's analysis (data from adhypo, adlb datasets)

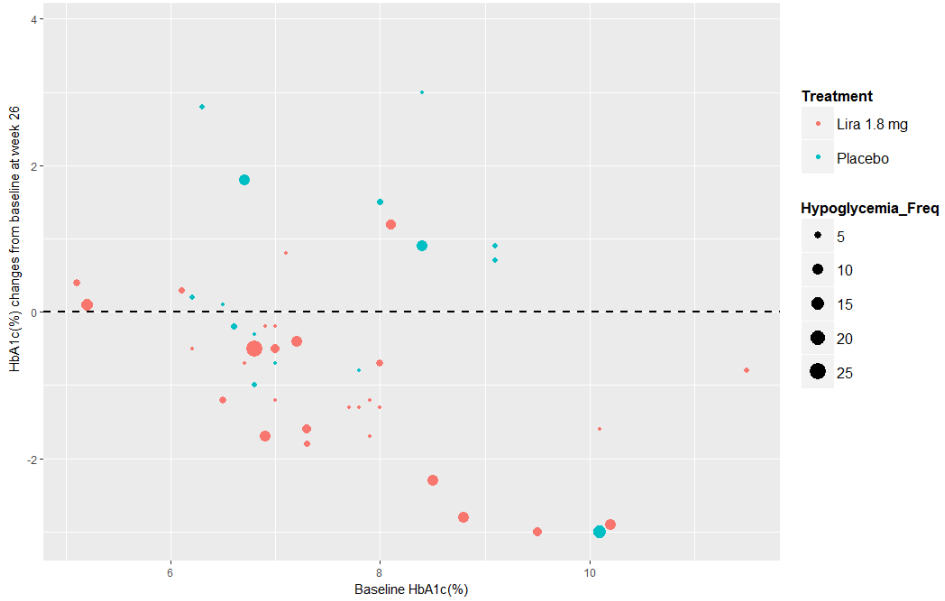
Figure 9. Changes in HbA1c (%) and baseline HbA1c (%) with Sizing of Points based on Number of Hypoglycemia < 54 mg/dL



**Note: There was no hypoglycemia episodes in the stratification of male <=14 years(at week 52). Thus the legend of stratification do not show the Male:<=14 years (at week 52).*
Source: reviewer's analysis (data from adhypo, adlb datasets)

In addition to selected hypoglycemia categories, all ADA classification hypoglycemia events are plotted without stratification factor to show simplified pattern of relationship for benefit-risk across baseline HbA1c (%) (Figure 10). In Figure 10, color coding was based on the treatment group, red solid circles representing patients in the liraglutide and green solid circles for patients in the placebo arm.

Figure 10. Changes in HbA1c (%) and baseline HbA1c (%) with Sizing of Points based on Number of all ADA classification



Source: reviewer's analysis (data from adhypo, adlb datasets)

Overall, whoever had more episodes in the liraglutide arm showed more reduction in HbA1c (%) and most patients who had higher risk relative to benefit were with lower baseline HbA1c (%).

Benefit-risk assessment conclusion

In ellipse™, patients who experienced risk outweighed benefit turned out to have either lower baseline HbA1c (%) or take rescue medication that might probably cause more hypoglycemic episodes. Overall, liraglutide showed favorable benefit-risk compared to placebo.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses using the primary efficacy analysis (i.e., PMM multiple imputation for change in HbA1c (%) from baseline to Week 26 in FAS population) were performed. Due to small sample size in race and region subgroups, race other than White and region other than US were collapsed into one group. Subgroups are defined by sex (Female vs. Male), race (White vs. Others), region (US vs. non-US) and age ($\geq$ 14 vs. < 14) in this review. Interaction between subgroup and treatment arm was tested. Because stratification factors were based on sex and age in the ANCOVA model for primary analysis, stratification factor was removed from the ANCOVA model for age and sex subgroups, instead either sex or age was modeled as covariate in the model if the other factor was tested for interaction.

Shrinkage methods- Bayesian hierarchical model

In the above-mentioned traditional subgroup analyses, there were 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 estimates 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. With a shrinkage method, sample estimate is "shrunk" towards the 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).

The Bayesian hierarchical model was used in this review as a shrinkage method with sample estimates from the traditional subgroup analysis with the same flat prior to derive shrinkage estimates for all subgroups and assumptions as followings:

Y_i: the observed sample estimate of treatment effect in a subgroup level i (i=1,2, … , total number of subgroups), assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$ with $\mu \sim N(0, (4*1.7)^2)$, $1/\tau^2 \sim$ Gamma (0.001, 0.001) (noted as "shrinkage", 1.7 from patient-level standard deviation (see details in Section 3.2.4.1)

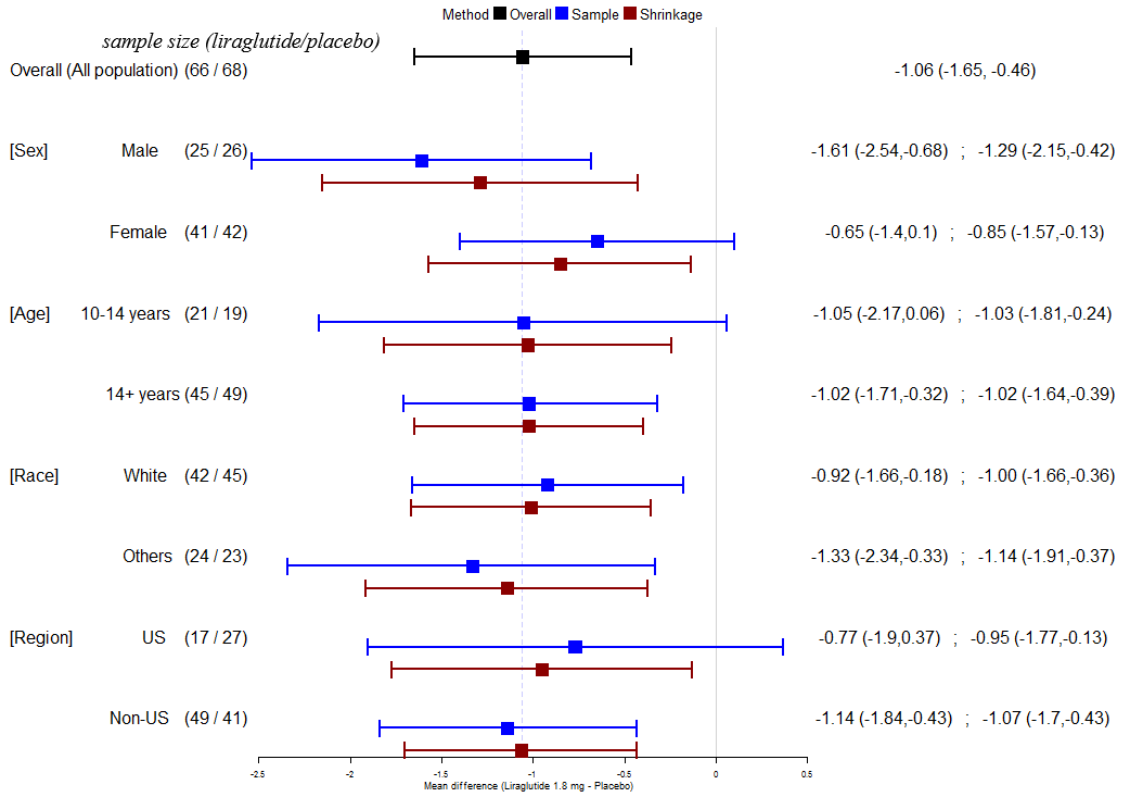
Shrunken estimates and 95% credible interval (equivalent to confidence interval of sample estimate) are calculated and depicted in the forest plot.

4.1 Gender, Age, Race, and Geographic Region

No interaction terms between subgroup and treatment group were significant. The sample and shrinkage estimate of treatment effect in subgroups, are presented in Figure 11. The vertical dotted line presented the overall treatment effect of -1.06 using all population.
The subgroup treatment effects are consistent across subgroups and with the overall treatment effect. Subgroup analysis using Bayesian shrinkage estimate exhibits narrower credible interval (equivalent to confidence interval of sample estimates), and the shrinkage subgroup estimate is closer to the overall mean.

Sample estimates for treatment difference were below zero across subgroups. However, upper limits of 95% CI of female, younger age (10-14 years old) and US region were above zero. The variability of the subgroups of female, younger age (10-14 years old), and US was corrected with shrinkage method using borrowed information from the rest of data and resulted in narrower 95% credible interval and upper limits below zero.

Figure 11. Forest plot of subgroup analysis using Bayesian shrinkage methods



**Source: reviewer's analysis (data from summary statistics in Figure 13)*

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed due to small sample sizes.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There is no major statistical issue for efficacy and safety evaluation in this submission.

5.2 Collective Evidence

Overall, the applicant handled missing data (10.6% in the liraglutide arm and 14.5% in the placebo arm; Table 3) appropriately in the pre-specified primary analysis. They derived treatment-policy estimand with pattern mixture model using all randomized and treated patients regardless of initiation of rescue therapy (Section 3.2.2.2). This pre-specified primary analysis was similar to the preferred method by the agency using wash-out model in the placebo-controlled trial.

The liraglutide add-on to metformin showed robust statistically significant treatment effect compared to placebo add-on to metformin (Table 5). Also, the treatment effect on HbA1c change of liraglutide compared to placebo was at least 1% difference in pediatric study. Sensitivity analyses including "washout" model did not alter conclusion.

Patients had statistically significant decrease in their FPG level and more patients achieved HbA1c < 7% at Week 26 in the liraglutide arm (Table 7). However, body weight related parameters such as body weight, BMI, BMI SDS and BMI percentile, did not achieve statistical significance for superiority of liraglutide despite reduction of body weight at Week 26 (Table 7). Glycemic control results in ellipse™ were consistent with adult study results with similar trial design (Table 8) and were consistent across subgroups (Figures 11).

Numerically more hypoglycemic episodes and higher proportions of patients experienced hypoglycemic event were observed with liraglutide compared to placebo (Table 9). However, illustrations of benefit (changes of HbA1c at week 26) and risk (the number of hypoglycemia) with baseline HbA1c (%) (Figures 8-10) explained that more hypoglycemic events were accompanied with greater reduction in HbA1c except when patients have lower baseline HbA1c or have initiated rescue medication. Therefore, lowering dose and/or restricting liraglutide to pediatric patients who had baseline HbA1c (%) greater than 7% could mitigate the risks in practice. In addition, there were no clinically relevant differences between treatment arms in height SDS (Figures 4 to 5), which suggests the lack of evidence that liraglutide disturbs growth and development in this pediatric population in the ellipse™. However, as the applicant stated the study is ongoing to collect safety parameters including growth and development for 2-3 year timepoints for patients who received liraglutide 3 months or longer. Further data and analysis are needed based on longer study duration to check the long-term impact of liraglutide on growth and development. In summary, this reviewer believes liraglutide shows benefits outweighing risks.

5.3 Conclusions and Recommendations

The statistical findings in ellipse™ demonstrated robust effectiveness and favorable benefit-risk for liraglutide compared to placebo as an add-on to metformin. These results do provide adequate statistical evidence to support the applicant's claims proposed in this NDA.

5.4 Labeling Recommendations

The applicant proposed the following sentence in Section 14 of the label "(b) (4) It is recommended to remove this sentence because it does not align with our preference of treatment policy. (b) (4)

In the proposed result table in Section 14, the applicant did not include the statistically significant results of the proportions of patients who achieved HbA1c < 7% at Week 26. It is acceptable to add HbA1c <7% results in the result table because it was statistically significant and consistent with other result tables in the current label.

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/

YOONHEE KIM
05/17/2019 02:23:55 PM

YUN WANG
05/17/2019 02:31:16 PM