CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22341
Priority or Standard	Priority
Submit Date(s)	17 December 2018
Received Date(s)	17 December 2018
PDUFA Goal Date	17 June 2019
Division/Office	DMEP/ONDII
Reviewer Name(s)	Tania A. Condarco M.D.
Review Completion Date	17 June 2019
Established/Proper Name	Liraglutide injection
(Proposed) Trade Name	Victoza
Applicant	Novo Nordisk
Dosage Form(s)	Solution in a pre-filled, multi-dose pen
Applicant Proposed Dosing Regimen(s)	Inject once daily at any time of day, independent of meals
Applicant Proposed Indication(s)/Population(s)	as an adjunct to diet and exercise to improve glycemic control in patients **10 years and older** with type 2 diabetes mellitus
Recommendation on Regulatory Action	**Approval**
Recommended Indication(s)/Population(s) (if applicable)	as an adjunct to diet and exercise to improve glycemic control in patients **10 years and older** with type 2 diabetes mellitus

Material Reviewed/Consulted	**Author**	**Date**
Clinical Efficacy and Safety Review	Dr. Tania Condarco	17 June 2019
Statistical Review (DBII)	Dr. Yoonhee Kim	17 May 2019
Clinical Pharmacology	Dr. Tao Liu	31 May 2019
Nonclinical reviews	Dr. Anthony Parola Dr. Calvin L Elmore (supervisory memo)	22 May 2019 22 May 2019
DPMH Consult	Dr. Amy Taylor	31 May 2019
Office of Biotechnology Products (OBP)	Dr. Susan Kirshner	3 June 2019

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Liraglutide is a glucagon like peptide 1 receptor 1 agonist (GLP-1 RA) (trade name Victoza) that was approved for marketing in the United States on January 25, 2010. Victoza is indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes and is also indicated 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 maximum recommended dosage for liraglutide for the above indications (marketed as Victoza) is 1.8 mg. Liraglutide is also marketed for weight management under the trade name Saxenda at a maximum dosage of 3.0 mg. In this document, "liraglutide" will refer to Victoza, unless otherwise stated.

Liraglutide is marketed as a 6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg and 1.8 mg and is injected subcutaneously once daily at any time of day independent of meals.

Liraglutide is initiated at 0.6 mg daily for one week to reduce gastrointestinal symptoms; this dose is not considered effective for glycemic control. The dose is subsequently increased to 1.2 mg; if "the 1.2 mg dose does not result in acceptable glycemic control the dose can be increased to 1.8 mg."

The current submission intends to expand the indication to "as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus."

1.2. Conclusions on the Substantial Evidence of Effectiveness

I recommend approval for supplement #31 submitted to NDA 22341. My recommendation is consistent with the recommendations of all review disciplines.

The efficacy of liraglutide in pediatric patients ages 10 and older is supported by the glycemic lowering results from trial NN2211-3659 (otherwise known as the *ellipse*^{TM} trial). This trial evaluated the efficacy of liraglutide as compared to placebo in pediatric patients aged 10-17 years of age, with type 2 diabetes mellitus, that were inadequately controlled on metformin with or without basal insulin. After 26-weeks, the treatment difference for liraglutide-placebo was -1.05% with a 95% confidence interval of (-1.65; -0.46); these results support the conclusion that liraglutide is superior to placebo.

In addition, the *ellipse*^{TM} trial fulfills the Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) 1583-2.[1]

The Pediatric Exclusivity Board agreed that *ellipse*^{TM} fulfilled the written request, issued on September 19, 2012 (and amended on January 15, 2015 and on March 20, 2017), in accordance to the Best Pharmaceuticals for Children Act (BPCA). Pediatric Exclusivity was granted for studies conducted with liraglutide effective May 1, 2019.

1.3. Benefit-Risk Assessment

[1] PMR 1583-2: A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months

Benefit-Risk Integrated Assessment

The prevalence of type 2 diabetes mellitus in youth is increasing in the United States.[2] Despite this growing number of patients, clinical trial development for therapeutic options has been challenging due to mostly recruiting difficulties in this population. *ellipse*™ is the first completed study of an antidiabetic therapy (i.e. since metformin and insulin) submitted for a pediatric indication in this population.

On December 17, 2018, Novo Nordisk submitted a supplemental new drug application for liraglutide (NDA 22341, supplement 31) for the *ellipse*™ study under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act. Novo Nordisk also requested Priority Review Designation and pediatric exclusivity, as *ellipse*™ was conducted for fulfillment of a written request, per the Best Pharmaceuticals for Children Act. Per the Pediatric Exclusivity Board, *ellipse*™ fulfills the September 19, 2012 issued written request (and amended on January 15, 2015 and on March 20, 2017). Per my review of the trial, *ellipse*™ also fulfills the Pediatric Research Equity Act (PREA) PMR #1583-2 and supports a proposed new indication in pediatric patients 10 years old and above with type 2 diabetes mellitus.

ellipse™ was a randomized, placebo controlled glycemic lowering trial with a blinded 26-week main trial period followed by a 26-week open labeled extension (and a 2 year safety follow up, which is not included in the submission) in 135[3] 10-17-year-old patients with type 2 diabetes mellitus randomized equally to liraglutide and placebo at maximally tolerated doses (0.6 mg, 1.2 mg or 1.8 mg), as add-on to metformin with or without basal insulin. Unlike adult trials where liraglutide's efficacy was determined at doses of 1.2mg and 1.8 mg, via parallel arm studies, *ellipse*™ did not randomize patients to a specific treatment dose, but rather titrated treatment over a period of 3 weeks, based on an average fasting plasma glucose above 110 mg/dL without intolerance symptoms up to the maximum dose of 1.8 mg daily. Therefore, the efficacy findings in this trial include the range of liraglutide doses (i.e. 0.6mg, 1.2 mg, and 1.8 mg).

The benefit seen in *ellipse*™ stems from the glycemic lowering observed at 26 weeks. The adjusted mean change from baseline HbA1c at 26 weeks was -0.64 for liraglutide and +0.42 for placebo, with an adjusted mean difference (liraglutide-placebo) of -1.06 with a 95% confidence interval of -1.65 to -0.46; $p < 0.001$. These findings support the conclusion of statistical superiority of liraglutide as compared to placebo on a background of metformin with or without insulin, and with a clinically meaningful treatment effect. Subgroup analyses and pre-specified hierarchical testing sequence for change in fasting plasma glucose, and responders with an HbA1c<7%, supported the primary efficacy

[2] Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014;311:1778–1786.
[3] Note that 134 patients were exposed and are counted as part of the efficacy analyses

endpoint. These efficacy findings were in light of a higher insulin use in the placebo arm. Although statistical analyses of each dose vs. placebo were not pre-specified, due to the titration design of the trial, clinical pharmacology data suggests glycemic lowering throughout the dosing range of liraglutide, including the 0.6 mg dose.

These efficacy findings were observed in a population of obese (mean BMI SDS 2.9), mostly female patients (>60% of the population) with mean chronological age of 14.6 years and an average HbA1c of 7.8%. Notably, the baseline HbA1c in this trial contrasts with the HbA1c in adult trials, where baseline HbA1c mostly ranges from 8.0%-8.5%. However, the effect size of approximately 1% is in line with adult monotherapy trials.

The risks associated with use of liraglutide generally mirrored the risks seen in adult trials, with the exception of hypoglycemia. The risk of hypoglycemia (incidence and event rate) in *ellipse*^{TM} was higher for liraglutide as compared to placebo patients despite protocol-specified measures to decrease this risk, (i.e. recommendation for a 20% decrease in basal insulin at randomization and use of a glycemic based titration regimen for liraglutide) and across the age groups (10-14 years and 14-17 years). The risk of hypoglycemia was higher for patients randomized to liraglutide with a baseline HbA1c~7% who had some decrease in HbA1c, or whose HbA1c remained stable, and in patients who had an HbA1c>8% with a larger decrease in HbA1c (~2%). The risk for hypoglycemia was also higher at the beginning of the trial. The hypoglycemia findings also seemed to be independent of insulin use, which contrasts with the liraglutide label, that warns of an increased risk of hypoglycemia when liraglutide is used with an insulin secretagogue or insulin. Of note, *ellipse*^{TM} excluded patients with recurrent severe hypoglycemia or hypoglycemic unawareness and enrolled patients with an HbA1c>6.5%. Therefore, it is unknown if the risk for hypoglycemia would be similar in patients with an established history of hypoglycemia. Furthermore, it is unclear if patients at the lower end of the HbA1c spectrum (HbA1c <7%) would be treated with liraglutide in clinical practice. However, given the limited therapeutic options in this population, it is possible.

There was no identified drug effect on puberty or linear growth, although most patients reached their final height at trial start.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The prevalence of type 2 diabetes in youth is expected to increase over time • Type 2 diabetes in youth is associated with: ○ Higher numbers of girls as compared to boys ○ Higher numbers of racial minority groups • Type 2 diabetes is characterized by insulin resistance without an autoimmune component. • Rapid decline in beta cell function • Rapid onset of aggressive diabetes related comorbidities	Type 2 diabetes in the youth is increasing and affects a disproportionate number of minority groups. Type 2 diabetes in youth is different than disease in adults due to its rapid decline in beta cell function and rapid onset of diabetes related comorbidities.
Current Treatment Options	• Metformin and insulin are the two labeled therapeutic options for youth with type 2 diabetes	There are limited treatment options for pediatric patients with type 2 diabetes mellitus

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• At 26 weeks treatment difference for liraglutide-placebo at a maximum tolerated dose (0.6 mg, 1.2 mg, and 1.8mg) added on to metformin with or without basal insulin therapy was -1.06 with a confidence interval of -1.65 to -0.46. • The following pre-specified hierarchical tested endpoints were also confirmed for superiority as compared to placebo at week 26: change in fasting plasma glucose and proportion of patients with HbA1c<7%. • Responder and subgroup analyses (including patients aged 10-14) were overall consistent with the primary endpoint findings (i.e., favoring liraglutide over placebo). • The use of insulin (including for rescue) and insulin dose were lower for liraglutide than placebo at week 26 and week 52. • At the end of the titration period, over 70% of patients were using at least 1.2 mg of liraglutide and 90% of patients were using at least 1.2 mg of placebo; this proportion remained relatively stable throughout the trial. ○ In the titration period, approximately 30% of patients reported a lack of dose increase due to having fasting plasma glucose values ≤ 110 mg/dL. ○ Intolerance was not a common reason given for lack of dose increase.	Liraglutide (at doses 0.6, 1.2, or 1.8 mg) added on to metformin with or without basal insulin showed superior glycemic lowering at 26 weeks as compared to placebo. Similar glycemic findings were observed in hierarchical endpoints of fasting plasma glucose and responders with HbA1c<7% and among subgroups. The lower use of insulin in the liraglutide arm suggests that the glycemic findings of liraglutide were not confounded by insulin use. Most patients reached doses of liraglutide 1.2 mg or above with about 30% of patients not titrating to a higher dose due to having an average fasting plasma glucose of 110 mg/dL. 0.6 mg seemed to be effective for a minority of patients.
Risk and Risk Management	• There were no deaths. • Serious adverse events varied across system organ classes and included infections, hyperglycemia and gastrointestinal-related adverse events. These are not inconsistent with AEs reported in adults. • Similar adverse events in pediatric and adult patients included: higher risk for gastrointestinal-related adverse events, increases in pulse, and	There was a higher event and incidence rate of hypoglycemia for liraglutide as compared to placebo across definitions of hypoglycemia (with the exception of severe hypoglycemia, which only had one event). It is unclear if this risk would be generalizable to the postmarketing setting (where patients with a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	increases in mean lipase. • The risk of hypoglycemia was higher for liraglutide in pediatrics despite measures to decrease this risk, including the recommended 20% decrease in basal insulin at randomization and the use of a glycemic-based titration regimen for liraglutide. ○ The risk of hypoglycemia was higher for patients with a baseline HbA1c ~7% (with stable HbA1c or with some decline in HbA1c) or patients with HbA1c>8% with a decrease of HbA1c of ~2%, i.e. a relatively larger decrease in HbA1c ○ The risk of hypoglycemia was higher for liraglutide independent of insulin use ○ It is uncertain if the risk of hypoglycemia is generalizable to the postmarketing setting • Most patients were in Tanner stage IV and V at baseline; there were no detected differences in pubertal progression between treatment arms	higher baseline HbA1c may be treated). However, the information should be included in labeling. Trends in adverse events were overall similar between the labeled safety of liraglutide in adult trials and *ellipse*™ with the exception of hypoglycemia. Hypoglycemia, independent of insulin use was higher for liraglutide as compared to placebo. Most patients had advanced pubertal status and reached final height at trial start.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The prevalence of type 2 diabetes is expected to increase over time; with the SEARCH study estimating a 4-fold increase in prevalence from 2010 to 2050.[2] From 2011 to 2012, approximately 5,300 new cases of type 2 diabetes in youth were diagnosed in the United

States.[4] Data suggest a higher proportion in girls over boys[5] and a disproportionately higher number in racial minority groups.

Similar to adults, youth with type 2 diabetes have insulin resistance without autoimmune mediated impaired insulin production. However, unlike adults, type 2 diabetes in youth is characterized by a more rapid decline in beta cell function, a rapid onset and aggressive diabetes-related comorbidities,[6] and rapid loss of glycemic control (shown by the TODAY study[7]).

2.2. Analysis of Current Treatment Options

Treatment options are limited in pediatric patients with type 2 diabetes. Metformin hydrochloride (immediate release[8]) is the only non-insulin approved therapeutic option indicated for pediatric patients with type 2 diabetes mellitus. The safety profile of metformin is similar in adults and children; common adverse reactions include: diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache. Metformin has a Warning and Precautions for the following: lactic acidosis (which is also a Boxed Warning), vitamin B12 deficiency, hypoglycemia with concomitant use with insulin and insulin secretagogues.

The metformin immediate release product information is the only product label to include any efficacy data in the pediatric type 2 population. The efficacy data comes from a double blind, placebo-controlled trial in pediatric patients 10-16 years old with type 2 diabetes. The trial results show a change in fasting plasma glucose at 16 weeks of -42.9 mg/dL for metformin as compared to +21.4 for placebo.

In addition to metformin immediate release, the following insulin analogs have an indication that includes pediatric patients with type 2 diabetes, i.e. "indicated to improve glycemic control in adults and children with diabetes mellitus":

- Novolog (insulin aspart injection)
- Levemir (insulin detemir injection)

[4] National Diabetes Statistics Report, 2017 Estimates of Diabetes and Its Burden in the United States, https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
[5] Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF, SEARCH for Diabetes in Youth Study. JAMA. 2014 May 7; 311(17):1778-86.
[6] Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. *Diabetes Care*. 2016;39(9):1635-42.
[7] TODAY Study Group, Zeitler P, Hirst K, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366(24):2247-56.
[8] Note that metformin hydrochloride extended-release is labeled only for adult use

- Apidra (insulin glulisine injection)
- Humalog (insulin lispro injection)
- Tresiba (insulin degludec) and Ryzodeg 70/30 (insulin degludec and insulin aspart) *have a slightly different indication* [9]

Most of these insulin analogs note that they have not been studied in pediatric patients with type 2 diabetes (approval based on studies in pediatric type 1 diabetes). And therefore, there is no clinical efficacy trial data labeled for pediatric type 2 patients in any insulin label.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Liraglutide is marketed in the United States under two trade names (Victoza and Saxenda), each with different indications and different dosages.

Victoza was approved on January 25, 2010 in the United States with a recommended dose of 1.2 mg and 1.8 mg daily. Victoza is indicated as "adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." On August 24, 2017 Victoza's indication was expanded to "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."

Saxenda was approved on December 23, 2014 in the United States with a recommended dose of 3 mg daily. Saxenda is indicated 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 (BMI) of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Liraglutide is also marketed as part of a combination drug product with insulin degludec as Xultophy 100/3.6 with the same indication as Victoza. Xultophy was approved for marketing in the U.S. on November 21, 2016.

All long-acting glucagon receptor agonists, including the liraglutide-containing products, listed above, have a boxed warning for a risk of thyroid C-cell tumors seen in rats and mice.

3.2. Summary of Presubmission/Submission Regulatory Activity

[9] is "indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus"

Table 1 shows the history of the modifications to the Written Request, PREA communications and global amendments to the study protocol.[10] A copy of the most recently approved Written Request (issued on March 20, 2017) is included in section 13.3.

Table 1- History of Written Request, PREA and protocol amendments

Date	Event/Description	Rationale for amendment
20 Jan 2012	Protocol Amendment 3	Changes based on EMA and FDA interactions
25-Jan-2010	Approval of Victoza and establishment of PMR 1583-2: PMR: A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months	
08-Feb-2012	Submission to NDA 22-341: PPSR	
24-May-2012	Inadequate PPSR issued	Rationale for inadequate letter was that submission was premature, awaiting PK/PD results from clinical pharmacology study NN2211-1800
26 July 2012	Protocol Amendment 4	Changes based on PERC's request to include yearly bone age assessment
31-Jul-2012	Revised PPSR and response to inadequate study request submitted	PPSR modified by Applicant to include additional safety monitoring as requested by FDA
10-Sept-2012	Revised PPSR submitted	PPSR modified in response to FDA request for bone age assessment
19-Sept-2012	Formal written request issued by the FDA	
12 Oct 2012	Protocol Amendment 7	
13-Nov-2012	First patient visit	
26-Nov-2012	PMR 1583-1: A phase 1 pharmacokinetic pediatric study to determine doses for the subsequent phase 3b study that will be conducted under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months is fulfilled	FDA sent letter on 26 Nov-2012 for fulfillment of this PMR
4 June 2013	Protocol Amendment 10	Changes in protocol due to delays in patient recruitment
15-May-2014	Pediatric Deferral Extension granted (due to difficulties recruiting)- see Amendment #1 for changes	
15-Jan-2015	Written Request Amendment #1 granted with the following changes:	-Bone age was removed at request of the Division, due to many foreign sites considering bone age unnecessary

[10] Local amendments are excluded from the table to facilitate reader's ease.

	- Removal of ~~bone age~~ assessment as a safety endpoint - Decrease in the number of randomized patients to ~~86~~ **75** in each arm (therefore total decrease ~~172~~ **150**) o This sample size will provide 80% power to detect a 0.~~6~~**7**% difference between the two treatment arms in HbA1c change from baseline, assuming a standard deviation of 1.~~3~~**2**% and a two-tailed alpha of 0.05. - Date of report submission changed: ~~March 30, 2016~~ **May 31, 2021**	because of hormonal measurements being performed and associated with unnecessary radiation exposure -Decrease in sample size was agreed upon due to difficulty in recruitment
12 Feb 2015	Protocol Amendment 13	Changes in protocol due to delays in patient recruitment
25-Mar-2015	Study report NN212291 -juvenile rat toxicity study submitted	Report was required as part of the Written Request, refer to section 4.4 for discussion.
20-Mar-2017	Written Request Amendment #2 granted with the following changes - Decrease in total patients studied: ~~172~~ to **94** with ~~75~~ **47** in each of the two treatment arms. - 80% statistical power to detect a 0.7% difference **(after adjusting for a 22% withdrawal rate for the liraglutide group)** - Statistical analyses for the 1ry endpoint are below: **For** the primary statistical analysis model, **all available data will be used, including data collected after treatment discontinuation and rescue initiation. A pattern mixture model using a multiple imputation procedure will be used that will impute missing week 26 measurements based on the completers from the placebo arm. Missing week 26 HbA1c measurements for patients who are on liraglutide will be imputed using only baseline information. Missing week 26 HbA1c measurements for patients who are on placebo will be imputed using the patients available HbA1c data available throughout the trial. The imputation procedure will be iterated 10,000 times, thus generating 10,000 complete data sets including observed and imputed values. For each of the imputed data sets, the change in HbA1c from baseline to week 26 will be analyzed using an ANCOVA with treatment and stratification groups (gender*age group) as categorical fixed effects and baseline HbA1c as a covariate. The results obtained from analyzing the datasets will be combined using Rubin's rule to draw inference.**	-Decrease in sample size was agreed upon due to difficulty in recruitment, the withdrawal rate was also added based on difficulty recruiting -The changes in the statistical analysis for the primary endpoint are consistent with FDA advice

	~~should be a repeated measures analysis with HbA1c change from baseline as the dependent variable. Treatment arm and stratification variables should be factors in the model, and baseline level ofHbA1c should be a covariate.~~ The model will be used to compare liraglutide and liraglutide-placebo at week 26.	
28-Mar-2017	Last patient, first visit	
23 May 2018	Trial completed	
KEY Protocol Amendment PREA changes Other changes Written request amendments		

3.3. Foreign Regulatory Actions and Marketing History

Liraglutide has marketing authorization from the European Union, Australia, Brazil, Canada, China, Japan, and Mexico for T2DM and weight management in adults. Victoza has been approved in over 100 countries for the treatment of adults with type 2 diabetes mellitus.

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

4.1. Office of Scientific Investigations (OSI)

There were no efficacy/safety or scientific misconduct concerns identified during the review that resulted in a request for an OSI review.

4.2. Product Quality

There is no new data with regards to chemistry, manufacturing and controls (CMC), sterility, or biopharmaceutics in the submission.

4.3. Clinical Microbiology

There is no new data with regards to microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

Dr. Anthony Parola was the non-clinical reviewer for the submission; Dr. Parola recommends

approval of the supplement.

There is no new data with regards to nonclinical pharmacology or toxicology in the submission. Below, I briefly discuss pertinent nonclinical findings (from a prior submission) since these are relevant to the Written Request.

In 2012, toxicity studies conducted in cynomolgus monkeys with multiple long acting GLP-1 receptor agonists (including liraglutide) revealed increase in weight of male reproductive tissue and accelerated sexual maturation in male monkeys. Because of these observations, and the concern of use of GLP-1 receptor agonists in prepubertal children, additional animal data was requested. An advice letter was sent to Applicants developing GLP-1 receptor agonists (including Victoza NDA 22431) planning clinical studies that included prepubertal children, requiring them to conduct a juvenile animal study. For Victoza, the required juvenile study was part of the written request (issued on September 2012), but was not a PMR. The written request specified the evaluation of the toxicity of liraglutide in juvenile rats treated from pre-puberty through reproductive maturity. Assessments in the rats, to support the phase 3 clinical study of liraglutide in pediatric patients with T2DM, included: cognition, behavior, age of onset of puberty, rate of sexual maturation, rate of overall growth, and reproductive organ maturation.

On March 25, 2015, Novo Nordisk submitted the juvenile toxicity study[11]. Dr. Parola reviewed[12] these data; his review did not identify any issues that would preclude the use of liraglutide in pediatric trials (age≥10 years old) with type 2 diabetes or in obese pediatric patients >7 years.

The study included the assessments specified in the written request. At systemic exposures in juvenile rats at least 4- and 11-times higher than human exposures at the maximum recommended dose of 1.8 mg/day liraglutide for the treatment of T2DM in pediatric patients, the length of ulna was slightly shorter and sexual maturation was delayed in males and females, motor activity was transiently increased, and weight of ovaries was decreased in females. At 11-times human systemic exposure, liraglutide reversibly increased the length of the estrous cycle, and although prior treatment of rats with liraglutide after weaning to young adulthood did not affect fertility, in mated females previously treated with liraglutide, the number of implantations and litter size were decreased, and the ratio of male offspring was increased. Decreased body weight gain may have contributed to effects of liraglutide on development in male juvenile rats, but not in females.

[11] Study number NN212291

[12] Review dated May 20, 2015 evaluated the definitive toxicity study of liraglutide in juvenile rats reviewed in this document was submitted to fulfill the requirements of the 19 June 2012 General Advice Letter (Appendix 1), the Written Request for Pediatric Studies for Victoza NDA 22341, and Saxenda NDA 206321 PMR 2802-1. The report for study 212291 was received 24 December 2014, prior to the 31 December 2014 goal date for Saxenda NDA 206321 PMR 2802-1.

Per Dr. Parola's review, "Study report 212291 for the definitive toxicity study of liraglutide in juvenile rats satisfied the requirements for a juvenile animal toxicity study specified in the 19 June 2012 Advice letter to Victoza NDA 22431, the Written Request for Pediatric Studies for Victoza NDA 22341 issued in September 2012, and Saxenda NDA 206321 PMR 2802-1."

A subsequent 2016 internal memo[13] addressed the non-clinical findings for long acting GLP-1 receptor agonists and the question of acceleration of and/or progression through puberty. This memo concluded that there was no evidence of precocious sexual maturation in juvenile toxicity studies of liraglutide, Bydureon, dulaglutide and lixisenatide. These findings therefore did not support the notion that long acting GLP-1 RAs resulted in pubertal acceleration in humans.

For the current supplement, there is non-concurrence among the Pharm Tox team with regards to the recommendation of labeling of the juvenile rat non-clinical data. Dr. Parola recommends "including results from the toxicity study of liraglutide in juvenile rats based on effects during development in rat based on effects during development in rats that were not likely to be adequately evaluated in clinical studies in pediatric patients." Dr. Elmore's nonclinical supervisory memo notes that it is difficult to reconcile the rat findings of developmental delay with the original purpose for conducting the study (which was due to accelerated sexual development in monkeys). Dr. Elmore does not recommend the labeling of non-clinical data because there was a modest degree of an effect seen in juvenile studies and "the absence of compelling clinical significance of a slight acceleration/delay in onset or progression through puberty." In addition, there was no noted safety signal that would warrant the labeling of non-clinical data. I agree with Dr. Elmore's recommendation to not label the non-clinical data. In addition, a slight delay in puberty (as seen in the rat study) may not be clinically important in the population of pediatric patients with type 2 diabetes who may be already in puberty at the time of diagnosis with type 2 diabetes and treatment with liraglutide.

4.5. Clinical Pharmacology

This section will briefly summarize the findings from previously reviewed clinical pharmacology trial NN2211-1800 and provide a summary of the population pharmacokinetic report in the current submission. The population pharmacokinetic analysis report included in this submission was reviewed by Dr. Tao Liu and Dr. Lian Ma in an integrated clinical pharmacology review. The Office of Clinical Pharmacology recommends approval of the supplement.

Trial NN2211-1800
On April 6, 2012 the Applicant submitted the final report for pediatric clinical pharmacology

[13] NDA 22341- internal memo in DARRTs dated 1/12/2016 authored by Dr. Wange.

trial (NN2211-1800; referred to as Trial 1800) for fulfillment of PMR 1583-1 (note this trial was not part of the written request). This was a five-week trial evaluating the tolerability profile and PK of liraglutide in 21 pediatric type 2 diabetic patients (ages 10-17 years). On November 26, 2012, a PMR fulfillment letter was sent to the Applicant by the FDA.

Per Dr. Khurana's review,[14] the results from this study supported the selection of liraglutide doses (ranging from 0.6 mg to 1.8mg) to be used in the long-term pediatric trial NN2211-3659 (i.e., *ellipse™*). Key findings from this review included that liraglutide exposure increased in a dose-proportional manner over 0.3 mg to 1.8 mg. There was a slightly higher apparent clearance and volume distribution of liraglutide in children (as compared to adults), and there was a slightly lower steady state exposure in children, as compared to adults.

Modeling Report for population PK (PopPK) and exposure-response of liraglutide in ellipse™ [15]

The Office of Clinical Pharmacology review concluded that the PK characteristics between pediatric and adults are comparable, based on the FDA's analysis of the PopPK data of pediatrics and adults separately (see Table 2) and based on the PopPK model comparing the simulated liraglutide concentration over time for adults and children (see Figure 1) .

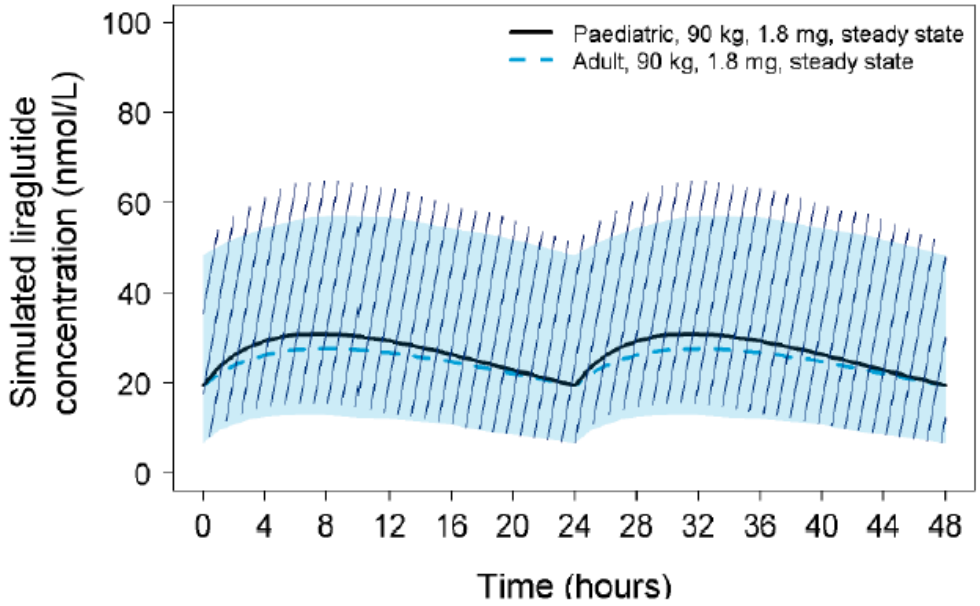
Table 2 – Pharmacokinetic Parameter comparisons between pediatrics and adults

Description	Parameters	Adults	Pediatrics
Absorption rate constant	**Ka (1/h)**	0.0608 (6%)	0.0689 (4%)
Apparent Clearance	**CL (L/h)**	1.11 (11%)	1.08 (5%)
Apparent Volume of Distribution	**V (L)**	15.7 (12%)	12.3 (19%)
Covariate affecting clearance	**BW effect on CL**	0.703 (30%)	0.995 (16%)
Covariate affecting clearance	**Male effect on CL**	1.32 (13%)	1.38 (12%)
Covariate affecting volume of distribution	**BW effect on V**	1.24 (26%)	1.13 (44%)
Covariate affecting volume of distribution	**Male effect on V**	1.4 (18%)	1.52 (41%)

[14] Review dated November 20, 2012
[15] The modeling analyses compared the PK characteristics in pediatric studies (NN2211-1800 and NN2211-3659) and previously conducted adult trials (NN2211-3534 and NN2211-3673).

Source: OCP review, table 4.

Figure 1- Simulated steady-state concentration-time profiles following liraglutide 1.8 mg once daily in pediatric (trial 3659) and adult patients (trial 1573)



Note: Lines are model-derived mean population profiles versus time, covering two dosing intervals (0-24 h and 24-48 h) for a reference subject profile (female subject, body weight 90 kg, stippled blue line: adult subject, solid black line: pediatric subject). The simulated 95% concentration range predicted from the between-subject variability in the full population PK model is illustrated for the pediatric (grey tilted stripes) and adult (light blue shading) population (N=1000 replications in each group).

Source: Clinical pharmacology review, Figure 5

Because pediatric patients in the *ellipse*^{TM} trial were not randomized to a specific final liraglutide dose, but rather had up-titration of the investigational drug based on tolerability and a target fasting plasma glucose (refer to page 31 for details on dosing), the baseline and pharmacokinetic characteristics varied between patients taking placebo, 0.6, 1.2 and 1.8 mg of liraglutide in *ellipse*^{TM}; see Table 3. This table shows that patients ultimately taking lower doses of liraglutide (i.e. 0.6 mg or 1.2 mg) as compared to a higher dose of liraglutide (i.e.,1.8 mg), had the following characteristics: lower baseline HbA1c, lower average fasting plasma glucose, lower proportion using basal insulin, lower BMI and lower body weight. Plasma clearance was also lower for the lower doses of liraglutide as compared to the higher doses, while steady state AUC remained similar between the 1.2 mg and 1.8 mg dose and was lower for 0.6mg.

The OCP review notes that the titration of liraglutide in *ellipse*^{TM} may have confounded the exposure response analysis and therefore it is challenging to draw conclusions on dose-response from this trial. However, factors such as the similarity in body weight and BMI between adults and pediatric patients, the known exposure-response of liraglutide in adults,

the similarity in PK between pediatric and adult patients, and the evident glycemic lowering at the 0.6 mg dose, support the dosing of liraglutide throughout the dosing range (i.e. include 0.6 mg in addition to 1.2mg and 1.8mg) in pediatric patients.

I agree with OCP, liraglutide use in pediatric patients ages 10 years and above, should include the entire dosing range (i.e. 0.6 mg, 1.2 mg, and 1.8 mg). There is long term efficacy and safety data (i.e. up to 52 weeks duration of *ellipse*^{TM}) to support the use of liraglutide in this population, which, as discussed above, has an unmet need for therapeutic options.

Table 3- Patient characteristics in each treatment group in *ellipse*^{TM}

Parameter		Placebo N = 68	Maximum Dose Level		
			0.6 mg N = 17	1.2 mg N = 12	1.8 mg N = 38
HbA1c(%)		7.62±1.36	6.96±1.24	7.88±0.95	8.31±1.30
FPG (mg/dL)		147±39	117±18	142±28	180±55
Basal Insulin [N (%)]		11 (16%)	3 (18%)	2 (17%)	10 (26%)
BMI		33.3±7.48	30.1±8.06	33.8±9.89	36.8±11.6
Weight (kg)		89.9±22.4	78.4±22.2	91.9±36.3	100.3±30.2
Plasma Clearance (L/h)		NA	0.94±0.27	1.00±0.52	1.37±0.58
AUCss (nmol.h/L)		NA	187±63.1	404±192	422±203
Chang from baseline in HbA1c(%)	Total	0.457	-0.176	-1.44	-0.495
	with basal insulin	1.64 (n=11)	-0.267 (n=3)	-2.5 (n=2)	-0.65 (n=10)
	without basal insulin	0.230 (n=57)	-0.157 (n=14)	-1.23 (n=10)	-0.439 (n=28)

Source: OCP review table 5

4.6. Devices and Companion Diagnostic Issues

There is no new pen device data in the submission. *ellipse*^{TM} used the marketed pen device that was anonymized (blinded) for both liraglutide and placebo.

4.7. Consumer Study Reviews

This section is not applicable to this submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary efficacy and safety data for this review were derived from the single trial *ellipse™*, described below:

Trial 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. (Clinical Trial Number: NCT01541215).

5.2. Review Strategy

My review strategy focused on the safety and efficacy findings from the *ellipse™* study, since this is the single study submitted to substantiate labeling claims. I reviewed the *ellipse™* protocol, protocol amendments, written request (and amendments), the statistical analysis plan, and study report. In addition, I also reviewed the safety data using the submitted datasets. Where pertinent, I evaluated the efficacy and safety in the total pediatric population as well as in age groups of interest (>14 years and 10-14 years of age).

Additional analyses were requested from the Applicant in information requests to evaluate additional points of interest.

Dr. Yoonhee Kim was the FDA primary statistical reviewer and independently confirmed the efficacy findings of the trial.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NN2211-3659

6.1.1. Study Design

Overview and Objective
Trial NN2211-3659 is referred to as "Trial 3659" and also referred to as "*ellipse™*."

Trial Sites: 84 sites in 25 countries

Primary objective: To confirm the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg) versus placebo when added to metformin with or without basal insulin treatment in controlling glycemia in children and adolescents (ages 10–17 years) with type 2 diabetes.

Secondary objective:
To assess and compare the effect of liraglutide versus placebo in combination with metformin with or without basal insulin treatment on:

- parameters of glycemic control
- parameters of beta-cell function
- parameters of body composition
- vital signs
- growth velocity (if patient is still growing)
- safety and tolerability
- growth and pubertal development at 1- and 2-year follow-up after trial drug cessation at week 52 (only applicable for patients treated with liraglutide for more than 3 months). Results for this objective will be reported in a future submission

Trial Design

Trial 3659 was a multinational, randomized, parallel-group, placebo-controlled trial with a 26-week double blinded period followed by a 26-week open labeled extension in patients with type 2 diabetes (ages 10-17 years). Figure 2 shows the trial design.

The trial had a 2-week screening period[16] followed by a 11-12-week run-in period. The run-in period was designed to ensure that all patients were on metformin. Patients not previously on metformin or on a dose of metformin <2000 mg without reaching the maximum tolerated dose (MTD), entered the run-in period. This period was made up of a 3-4-week metformin titration period and an 8-week maintenance period.[17] Patients who were already on stable doses (for 56 days) of ≥2000 mg of metformin, or on an MTD[18] of metformin ≥1000 mg and ≤2000 mg per day, and patients who completed the run-in phase were randomized 1:1 to liraglutide or placebo (week 0). Patients on basal insulin were required to be treated with stable doses for at least 56 days at screening.

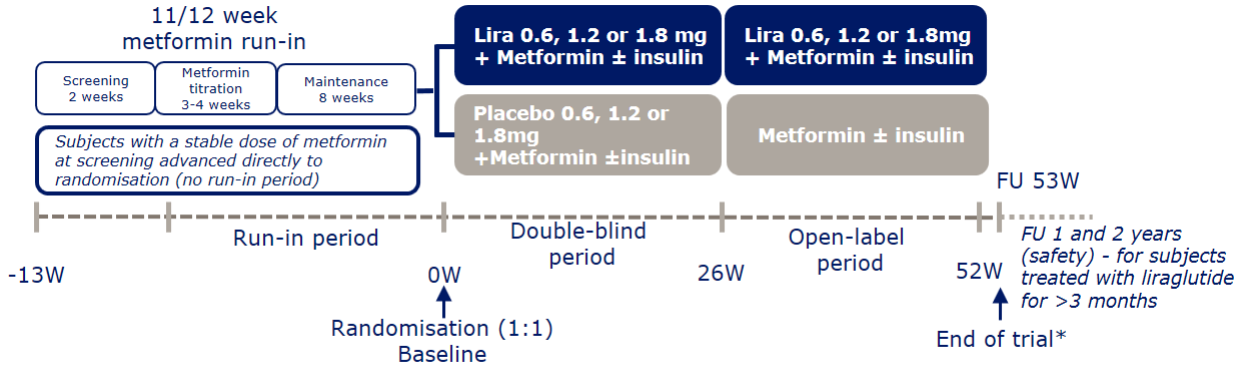
At randomization, patients were stratified by sex and according to age at the end of treatment.[19] Visits included telephone visits and site visits.[20]

At the conclusion of the 26-week double blinded period, the treatment allocation was unblinded to patients and site staff (treatment allocation remained blinded to Novo Nordisk staff assessing outcome). Patients randomized to liraglutide continued with therapy during the

[16] Informed consent/assent was obtained at least one day prior to screening visit. Inclusion/exclusion criteria, fasting blood work and physical exam were performed at screening
[17] In addition to ensuring metformin maintenance dose, the maintenance period allowed patients on stable doses of basal insulin for at least 30 days but less than 56 days at screening to achieve the required 56 total maintenance period prior to randomization.
[18] Defined as a dose when prior attempts to escalate the dose were not tolerated
[19] Stratification by ≤ 14 years or > 14 years, where ≤ 14 years of age is defined as not reaching 14 years and 11 months at the end of treatment (52 weeks).
[20] Visits were weekly for the first 6 weeks and then were every 3 weeks afterwards (to week 52). The trial had additional visits at week 4,5,7, and 8 for evaluation/treatment modifications for patients on basal insulin

open-labeled period; patients randomized to placebo discontinued placebo and continued therapy with metformin ± basal insulin. All patients were to attend a follow-up visit (visit 26, week 53) one week after the end of treatment (visit 25, week 52). The maximum duration of the trial was 67 weeks. Patients treated with liraglutide for >3 months were asked to return for follow-up visits one and two years after the end of the open labeled period at week 104 (1 year after trial end) and week 156 (2 years after trial end) for reporting of AEs and SAEs[21]. The safety data from the week 104 and week 156 is not part of the current submission (of note the 1 and 2 year follow up is not specified in the Written Request).

Figure 2- *ellipse*^{TM} trial design



*Patients were stratified according to sex and age at end of treatment (≤14;>14)
Source: Novo Nordisk slides, December 20, 2018 teleconference

Reviewer's comment: The study design is consistent with the written request. Multiple trial elements allow for adequate assessments of efficacy and safety in this trial. The 26-week blinded period is an adequate time frame to assess the glycemic efficacy for liraglutide. In addition, the double blinded design allows for the minimization of bias. The run-in period allows for standard of care therapy with metformin for all patients and allows for a period of glycemic stability prior to randomization. The open-labeled extension allows for an assessment of glycemic effect over a longer period of time. The week 104 and 156 follow up allow for evaluation of long-term effects on growth, puberty and safety.

Key inclusion /Exclusion and randomization criteria

Inclusion

- Informed consent /child assent must be obtained
- Children and adolescents between ages 10-16 years of age[22]
- Diagnosed with type 2 diabetes for at least 30 days and treated with diet and exercise ± metformin ± stable basal insulin (basal insulin dose adjustments up to 15% of insulin dose were considered stable)

[21] Since no diaries were available at these visits, the information was based on memory from care taker and patient.
[22] Patients cannot turn 17 years and 11 months before the end of treatment (52 weeks)

- HbA1c ≥7% and ≤11% if on diet and exercise or ≥6.5% and ≤11% if on medical therapy (i.e. metformin/basal insulin)
- BMI>85% percentile of the general age and gender matched population

Exclusion

- Hypersensitivity to trial products or contraindications to use of metformin
- Previous participation in the trial or use of investigational product 30 days prior to visit 1
- Female who is pregnant/breast-feeding or intends to become pregnant
- Other forms of diabetes: Type 1 diabetes, or Positive antibodies: IA-2 or anti-GAD, fasting C-peptide <0.6 ng/mL, maturity onset diabetes of the young
- Use of any antidiabetic agent other than metformin and or basal insulin 90 days prior to visit 1
- Previous treatment with liraglutide or use of any drug which could interfere with blood glucose level
- History of pancreatitis
- Screening calcitonin value ≥50 ng/L
- Personal/family history of MTC or MEN 2
- History of Impaired liver function (ALAT≥2.5 x the upper normal range), impaired renal function (serum creatinine> upper normal range), history of heart disease (within 6 months of visit 1), proliferative retinopathy or maculopathy requiring acute treatment, Hepatitis B or Hepatitis C positive, HIV positive, Uncontrolled HTN (>99% for age and gender), history of cancer in the last 5 years (except basal/squamous skin cancer), any clinically significant disorder, except for conditions associated with T2DM
- Recurrent severe hypoglycemia or hypoglycemic unawareness (per investigator)
- known or suspected alcohol/drug abuse or mental incapacity

Randomization criteria

1. Fasting plasma glucose (FPG) prior to randomization visit must be ≥126 mg/dL and ≤220 mg/dL[23]
2. Stable dose of at least 56 days of metformin ≥1000 mg and ≤2000 mg per day [24]
3. If on basal insulin must be on a stable dose for at least 56 days

Reviewer's comments: Overall, the inclusion/exclusion and randomization criteria are acceptable. The age of enrollment (10-17 years of age) is acceptable, given the rarity of T2DM below 10 years of age, and is consistent with the majority if not all pediatric type 2 diabetes programs. In addition, the inclusion of patients on basal insulin in the trial (as part of global amendment 10) was in agreement with prior communications with the FDA.

As discussed later in this review, the HbA1c criterion excluding patients with an HbA1c<6.5% resulted in the largest number of screen failures. For comparison, the TODAY study did not

[23] These measurements are based on an average of fasting SMPG taken on 3 consecutive days leading up to the randomization visit

[24] Patients on >2000 mg could be randomized continuing with that dose

have a minimum HbA1c inclusion criterion. However, since pediatric patients with an HbA1c below 6.5% could be managed with lifestyle interventions with or without metformin alone, it is reasonable to include patients above this cut-off.

The following criteria which were also stipulated in the written request and were instituted in the protocol:

- at least 30% of randomized subjects were to be 10-14 years
- at least 30% of randomized subjects were to be females

Study treatments and dose selection:

Non-investigational therapies

After randomization, the metformin dose was to remain unchanged through the trial (unless the patient needed rescue).

Basal insulin[25] was to be decreased by 20% at randomization. After the MTD of investigation medicinal product (IMP) was reached, the dose of basal insulin could be up-titrated to no higher than the screening dose level using the titration algorithm shown below.[26]

For patients with severe intolerance or recurrent hypoglycemia[29] the IMP dose was to be lowered to the next lower dose and documented. However, if the patient was also on insulin, the dose of insulin was to be decreased first, prior to the decrease in IMP.

Table 4 – Algorithm for up- and down-titration of basal insulin

Up titration	
Mean of 3 pre-breakfast (fasting) SMPG values (mg/dL)	**Increase in basal insulin dose**
>180	+6
141-180	+4
121-140	+2
100-120	+1
Down titration	
One or more SMPG values (mg/dL)	**Decrease in basal insulin dose**
<56	-4 units if dose is >50 units, a dose reduction of 10% is recommended
>1 value of 56-70	-2 units if dose is >50 units, a dose reduction of 5% is recommended
Source: table 9-1 and 9-2 CSR	

[25] Included intermediate acting human insulin, intermediate acting insulin analogue or long acting insulin analogue
[26] Up-titration was based on average of 3 pre-visit fasting SMPG before week 4 and 8- after week 8 there was additional titration of insulin allowed (except for rescue).

Reviewer's comment: the lowering of the basal insulin dose when starting IMP is appropriate since it may decrease the risk for hypoglycemia associated with use of basal insulin with liraglutide. The limiting of the basal insulin dose to no higher than the screening dose, also decreases the risk that insulin could drive the efficacy findings and is likely to be consistent with what would occur in clinical practice. The insulin up and down titration guidelines in the protocol is adequate.

Investigational medicinal products (IMPs)
Liraglutide and placebo (IMPs) were administered via the approved 3 mL pre-filled pen presentation. The IMPs were administered once daily (at any time of day and irrespective of meals) by subcutaneous injection in the abdomen, thigh or upper arm. The injection site did not have to be consistent throughout the trial, but it was recommended to keep the time of injection consistent.

The IMPs were started at a 0.6 mg/day on week 1 and escalated in weekly increments of 0.6 mg over 2-3 weeks. Dose escalation was based on tolerability (interpreted by the investigator) and home measures of FPG. If on 3 consecutive days preceding the dose escalation visit, patients had an average of 3 FPGs <110 mg/dL, no dose escalation was done. After the 3-week dose escalation period, no further dose escalation was done.

Reviewer's comment: the dosing approach in this trial differs from the labeled dosing of liraglutide, see excerpt from section 2.2 of the Prescribing Information below (underline was added for emphasis):

> **"The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration and <u>is not effective for glycemic control</u>. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg."**

In *ellipse*™, a dose of 0.6 mg was considered an "effective dose" based on the fact that patients did not have to titrate to higher doses.

In addition, the trial design differs from the original NDA design (in adults) because the liraglutide dose titration is not forced (as was the case in the adult trials).

<u>Rescue criteria:</u>
Rescue criteria were established to rescue patients with unacceptable levels of hyperglycemia. Patients requiring rescue were to <u>remain in the trial</u>. Patients meeting the below criteria were to have the value confirmed with a central FPG measure:

- First 14 weeks post randomization: If SMPG values on 3 consecutive days or any of the FPG samples >220 mg/dL or
- After 14 weeks post randomization: If SMPG >185 mg/dL

Patients meeting the above criteria could be rescued by adding (or increasing the dose of basal insulin) basal inulin with dosing at the discretion of the investigator. If there was persistent hyperglycemia, a rapid acting insulin could also be added.

Reviewer's comment: prior to amendment #3, rescue therapies included the addition of another antidiabetic agent or metformin dose escalation. Amendment #10 changed the rescue therapy to basal and short acting insulin. Also, after protocol amendment #3 and prior to protocol amendment #10, the randomization code for a subject could be broken in relation to the initiation of rescue treatment; however, in amendment 10 the blind was no longer broken since insulin could be used for rescue in both arms.

Withdrawal criteria:[27]

1. Patient may withdraw at any time
2. May be withdrawn due to safety concerns or if patient is non-compliant
3. Must be withdrawn if randomized in error
4. Pregnant or intending to become pregnant
5. If experiences persistent hyperglycemia[28] despite rescue treatments meets the following criteria:
    a. During the first 14 weeks after randomization (after the liraglutide dose escalation the patient has reached 1.8 mg or the maximum tolerated dose [MTD]): FPG>220 mg/dL
    b. After week 14: FPG>185 mg/dL
6. Patients who need to have their dose of metformin reduced due to tolerability (after reaching their MTD must be withdrawn
7. Patients treated with 0.6 mg of liraglutide who experience severe intolerance or recurrent hypoglycemia (per investigator)[29] For discussion of hypoglycemia, refer to section 8.4.4.
8. calcitonin≥50 ng/L[30]
9. If suspected acute pancreatitis, all drugs suspected to this event must be discontinued until confirmatory tests and treatment initiated. [31]
10. Use of any systemic treatment other than antidiabetic treatment with products which per investigator, could interfere with glucose metabolism

[27] The end of trial procedures for patients withdrawing prior to the end of the blinded period, had to undertake procedures for visit 17 as soon as possible; for patients withdrawing after visit 17 and before the end of the open-labeled period, undertook the procedures for visit 25 (end of treatment visit) as soon as possible. For patients using liraglutide>3 months, they were also return to the 1 and 2 year follow up visits.
[28] SMPG values taken on 3 consecutive days or any FPG (central lab) meets glycemic criteria, the patient must be called for an unscheduled visit and a confirmatory FPG must be obtained and analyzed by a central laboratory.
[29] Such as ≥3 unexplained minor hypoglycemic events or 1 unexplained severe hypoglycemic event in a week
[30] Referral to a thyroid disease specialist is recommended
[31] Acute pancreatitis is diagnosed by at least 2 of the following: abdominal pain, amylase and/or lipase>3 X UNR or characteristic findings on ultrasound, CT or MRI

Study Endpoints and Statistical Methods

For the efficacy analyses, the Applicant had the following fixed effects in the models: age group[32], concomitant diabetes treatment at baseline[33] and region.[34] For the primary and secondary endpoints, all the available data, including data collected after treatment discontinuation and imitation of rescue medication were used in the analyses (although additional analyses excluding this data was also performed for sensitivity analyses). Across analyses, baseline was defined as assessments made at randomization; if this value was missing and the screening value was available, then the screening value was used as the baseline value. The Applicant addressed missing efficacy data via imputation.

In addition, data points that were to be excluded[35] from efficacy analyses were specified prior to database lock.

Primary objective: To confirm the superiority of liraglutide at the maximum tolerated/needed dose (0.6 mg, 1.2 mg or 1.8 mg) versus placebo when added to metformin with or without basal insulin in controlling glycemia in children and adolescent (ages 10–17 years) with type 2 diabetes.

Reviewer's comment: The Written Request specified that the primary objective of this study as listed above, except that "basal insulin" was not included as part of the primary objective. Although the exact phrasing of the primary objective is slightly different from the Written Request's, the inclusion of patients previously on basal insulin were included in protocol amendment 10 (see Table 5); the addition of these patients was considered acceptable upon review of this protocol. In addition, in Type C meeting responses issued on 2/18/2014 the FDA agreed with the Applicant's proposal to change the inclusion/exclusion criteria to allow participants treated with basal insulin.

Primary efficacy endpoint: Change in HbA1c from baseline[36] to week 26

The primary endpoint was analyzed using a pattern mixture model using multiple imputations.[37] Superiority of liraglutide over placebo was concluded if the 95% confidence

[32] 10-14 and >14 years at end of trial (where age is calculated as age at baseline +1 year)
[33] This is defined as Y= patients on insulin and N= patients not on insulin at baseline
[34] Region is defined as Asia, Europe, North America, South America and Rest of world.
[35] The excluded data points included: assessments performed outside the scheduled visit windows, or if a patient was non-fasting when a fasting sample was to be taken, or if a measure was not the first value for that visit
[36] Refer to section on missing data for a definition of the definition of "baseline"
[37] For subjects in the liraglutide arm with missing week 26 HbA1c measurements, measurements were imputed using the subjects' baseline HbA1c in a regression model based on the data from completers from the placebo arm

interval for the treatment difference for change from baseline in HbA1c after 26 weeks was below 0%.

Reviewer's comments: As a result of correspondence with the Applicant, multiple imputations were the agreed upon method to handle missing data (refer to Table 5). The details regarding the imputation model specified in the Written Request are consistent with the imputation model used by the Applicant (see footnote 37; and Written Request Amendment 2, Table 1).

Sensitivity analyses: six sensitivity analyses were performed to evaluate the primary endpoint. These analyses included: 1) an analysis of covariance (ANCOVA) with last observation carried forward (LOCF) which treated data collected after treatment discontinuation/or initiation of rescue as missing data; 2) an ANCOVA model included data after treatment discontinuation or initiation of rescue treatment and LOCF imputation for missing data; 3) multiple imputation of missing values in both treatment groups based on parameters estimated from placebo group; 4) a repeated measurement analysis (MMRM) which excluded data collected after treatment discontinuation or initiation of rescue medications; 5) an MMRM model which included age of patient, concomitant diabetes treatment, and region nested within visit; 6) multiple imputation of missing value, in both treatment groups based on parameters estimated from placebo group.

Reviewer's comment: Potential sources of missing data include the lack of retrieved dropouts (in accordance with the protocol). In an information request,[38] the Applicant clarified that patients who withdrew prematurely from the trial were asked to attend a visit as soon as

(i.e., subjects in the placebo arm with HbA1c measurements at week 26). Multiple imputation of missing week 26 HbA1c data in the placebo arm was performed by utilizing the relationship between HbA1c measured at weeks 0 (baseline), 10 and 14 with that measured at week 26 in subjects in the placebo arm. The following four regression models will be built from the liraglutide placebo completers group for this purpose:

- Model 1: Only baseline covariates (baseline HbA1c, stratification group (gender*age group), concomitant diabetes treatment at baseline)
- Model 2: Baseline covariates and week 10 HbA1c as covariates
- Model 3: Baseline covariates and week 14 HbA1c as covariates
- Model 4: Baseline covariates, week 10 HbA1c, and week 14 HbA1c as covariates

Missing week 26 data will be imputed by selecting a random observation from a normal distribution centered at the value predicted by the regression model and with variance analogous to predicting a new observation in regression analysis. For subjects on the placebo arm, the model used will be dependent on the subjects' available HbA1c data throughout the trial. For example, if a subject had HbA1c measurements only at baseline and week 14, then model 3 would be used. For subjects on the liraglutide arm, the measurements will be imputed using only the subjects' baseline HbA1c (model 1).
The imputation procedure will be iterated 10,000 times, thus generating 10,000 complete data sets including observed and imputed values. For each of the imputed data sets the change in HbA1c from baseline to week 26 will be analyzed using an ANCOVA with treatment and stratification groups (gender*age group) as categorical fixed effects and baseline HbA1c as covariate. The results obtained from analyzing the datasets will be combined using Rubin's rule

[38] February 20, 2019 IR: \\CDSESUB1\evsprod\NDA022341\0423\m1\us

possible after withdrawal (to undergo an end-of trial visit- if patient withdrew prior to week 26, then the procedures of week 26 were to be followed, if a patient withdrew after week 26, then the 52-week procedures were to be followed). The Applicant states that there were no withdrawn patients who had an HbA1c data from an end of trial visit conducted within 5 days of what should have been the week 26 or week 52 visit; therefore, none of the data for the withdrawn patients was used in the primary efficacy analysis for HbA1c.

Secondary endpoints:
The following were considered "supportive" secondary endpoints:

- Change from baseline in fasting plasma glucose (FPG) to week 26
- HbA1c< 7% (yes/no) after 26 weeks of treatment
- Change from baseline in BMI standard deviation score (SDS) to week 26

A pattern mixture model using multiple imputation was used for each analysis of the secondary endpoints. The model was the same as the model used for the primary endpoint except that the baseline value for the analyzed endpoint was to be included. A logistic regression model was used for dichotomous endpoints. In addition, the MMRM sensitivity analysis #4 (listed above), which excluded data collected after treatment discontinuation or initiation of rescue medication was used as a second analysis.

Type 1 error prevention: The following hierarchical sequence of testing was pre-specified to maintain the type I error of 5%:

1. Primary efficacy endpoint
2. Change from baseline in FPG after 26 weeks of treatment
3. HbA1c<7% after 26 weeks of treatment (yes/no)
4. Change from baseline in BMI SDS after 26 weeks of treatment

To conclude significance for an endpoint in the above list, the test for that an endpoint and for the preceding endpoints must be considered "significant."

Supportive secondary endpoints:

Supportive secondary efficacy endpoints (assessed at 26 and 52 weeks of treatment) included the following:

- HbA1c: <7% (yes/no) (at 52 weeks only); ≤6.5% (yes/no); <7% without severe or minor hypoglycemic episodes(yes/no), HbA1c<7.5% (yes/no)
- 7-point self-measured plasma glucose
- Basal insulin dose
- Change from baseline at 26 and 52 weeks of treatment:
    - For the following glycemic parameters: HbA1c (52 weeks), FPG (52 weeks), mean 7-point SMPG, post-prandial increments
    - For the following anthropometric measures: body weight, waist circumference

Body mass index (BMI), BMI SDS (52 weeks), BMI percentile
    - Systolic and diastolic blood pressure
- Ratio to baseline at 26 and 52 weeks of treatment:
    - Fasting insulin, fasting pro-insulin to insulin ratio, fasting glucagon, fasting C-peptide and homeostasis model assessment (HOMA-B and HOMA IR)
    - Fasting lipid profile (cholesterol, LDL, VLDL, HDL, triglycerides and free fatty acids)

The supportive secondary endpoints were to be analyzed using the models for the confirmatory secondary analyses.

Safety:

Refer to section 8.3.2 for definitions of adverse events in this trial.

The following were safety endpoints assessed for change from baseline at 26 and 52 weeks of treatment:

- Clinical evaluations[39], electrocardiogram[40], pulse, clinical laboratory tests (see Table 20), height SDS, bone age assessment, pubertal assessment (Tanner staging)

The following assessments were conducted at week 26 and week 52:

- Assessment of compliance (questioning of patients and patient's legal representative), assessment of growth (i.e., height velocity if still growing[41]) and height velocity SDS, hypoglycemic episodes, adverse events (AEs) and serious adverse events (SAEs).

The following safety follow up measures (which are not reported in the submission since they are still being collected) were collected at 1 and 2 years after trial drug cessation at week 52, for patients randomized to liraglutide for>3 months:

- AEs and SAEs, growth (height) velocity and change in height SDS, pubertal assessment/progression, and bone age assessment

Reviewer's comment: the assessment of pubertal progression and growth, partially resulted from initial non-clinical observations in long acting glucagon-like peptide (GLP)-1 agonists having an acceleration of male sexual development in monkeys. Because the relevance and

[39] Physical exams including fundoscopy. Fundoscopy was performed at screening, end of blinded treatment period (visit 17) and end of treatment (visit 25) by the investigator or a local ophthalmologist according to local practice. If fundoscopy was performed 12 weeks prior to screening, the procedure did not need to be repeated at screening. Fundoscopy performed 2 weeks before visit 17 and 25 was accepted as data obtained at visit 17 and 25, respectively

[40] 12-lead ECG was performed at screening, end of the blinded treatment period (visit 17) and end of treatment (visit 25) and interpreted locally by the investigator in relation to the trial. An ECG performed for any reason unrelated to this trial within 12 weeks prior to visit 1 was acceptable. An ECG performed 2 weeks before visits 17 and 25 was accepted as data obtained at visits 17 and 25, respectively.

[41] A growth velocity<1 cm/year is defined as no longer growing

risk to the human pediatric population was unknown, the Written Request required adequate pubertal and growth (height) assessments in this trial; please refer to section 4.4 for further non-clinical details.

Refer to section 8.3.3 for routine clinical tests conducted in this trial.

Safety monitoring:
The trial had the following committees established to ensure safety in the trial:

- Novo Nordisk Safety Committee- was an internal safety committee that blindly evaluated safety data
- Data monitoring Committee- independently reviewed unblinded safety data on an ongoing basis and provided recommendations to Novo Nordisk on whether to continue, modify, or terminate the trial. The DMC was also to decide if there was evidence of hormonal disruption in the trial, which would indicate a need for a further juvenile animal study. Based on the review of the 26 week and 52-week data the DMC saw no evidence of hormonal disruption; the DMC did not recommend further animal testing. The DMC open and closed minutes were reviewed, and the safety signals discussed are consistent with the safety concerns discussed in section 8.

Please refer to section 8.4.4 for definitions and discussion regarding hypoglycemia.

Statistical Analysis Plan

Defined populations:
The following datasets were defined in the protocol:

- *Full analysis set (FAS)*- all randomized patients receiving at least one dose of liraglutide/placebo. The statistical evaluation of the FAS follows the intention to treat principle (ITT) and subjects contribute to the evaluation as randomized.
- *Safety analysis set (SAS)*- all subjects receiving at least one dose of the investigational drug. Patients will contribute to the evaluation as treated.

Randomized patients who were lost to follow up and where information about exposure to the IMP was unavailable after randomization, were to be handled as patients unexposed to randomized treatment.

All analyses of efficacy endpoints were based on the FAS; analyses of safety endpoints were based on the SAS.

Reviewer's comment: the definition of the FAS and SAS, and the use of the FAS to analyze the primary efficacy endpoint is consistent with what was stipulated in the written request.

Sample size calculation: The sample size for the primary endpoint (to confirm the efficacy of

liraglutide in patients on metformin ± basal insulin) was evaluated using a two-sided test and a significance level of 5%. The assumptions used to calculate the sample size were founded upon previously conducted studies with liraglutide. One assumption was that the change in HbA1c from baseline to week 26 would have a mean difference of 0.9% with a standard deviation of 1.2% for liraglutide vs. placebo. The second assumption was that the withdrawal rate in the 26-week period would be 22%. Based on these assumptions, the samples size of 47 patients per treatment arm was calculated to yield a power of 80%.

Reviewer's comment: Refer to Table 5, (amendments 10 and 13) and Table 1 (Written Request Amendment 1 and 2) that describe the decrease in sample size due to difficulties recruiting patients. These recruitment difficulties have been echoed across other development programs in this population. Despite amending the protocol and Written Request to a smaller sample size (i.e. 94 total enrollees), the trial ultimately enrolled a higher number of patients than planned (see Study Results).

Dr. Kim notes that the assumed standard deviation of 1.2% for the sample size calculation was underestimated. Using the mean difference and patient level residual standard deviation from her evaluation of the primary efficacy results, the estimated power was 88%.

Protocol Amendments

In total, there were 13 amendments to the protocol. Of these amendments, 5 amendments were global amendments, with the remaining 8 being local amendments; Table 5 shows the global protocol amendments. The amendments mainly reduced the trial's sample size due to difficulty recruiting, updated the efficacy analysis for the primary endpoint, enhanced safety monitoring, increased follow-up time, and adjusted entry criteria to increase enrollment.

There were no changes to the planned statistical analyses in the SAP nor protocol after unblinding.

Table 5- Protocol amendments

Date	Event/Description	Rationale for amendment
10 Jan 2012	Protocol Amendment 3	changes based on EMA and FDA interactions. <u>Based on EMA recommendations:</u> -Extended the titration period to 3-4 weeks - Lowered the MTD for metformin to ≥1000 mg (based on the TODAY study) -Extended maintenance period from 3 to 8 weeks -Patients on >2000 mg of metformin were to remain on this dose -liraglutide dose escalation period increased from 2 weeks to 3 weeks -liraglutide Ab assessment to be done at week 53 (a week after discontinuation of liraglutide) to avoid Ab interference <u>Based on FDA recommendations</u> -extension of the double blinded period from 14 to 26 weeks (to assess the durability of effect of liraglutide)

		-extension of the metformin maintenance period from 3 weeks to 8 weeks prior to randomization period -the trial stratification was changed to add sex and age (≤14 years and >14 years). The age stratification ensured that sufficient patients in early puberty. -rescue options changed to include liraglutide as an option for placebo patients and an option to increase the liraglutide dose to 1.8 mg for patients on 1.2 mg or 0.6 mg of liraglutide -Assessment of puberty added (i.e. testicular volume) -FDA requested that the age range by which patients should complete the 52-week portion of the study be 17 years and 11 months -FDA requested that 30% of randomized patients must be between 10-14 years of age -Exclusion of patients previously treated with liraglutide added -changes to the analysis of the 1ry analysis using an imputation method. Also, 2ndary endpoints should be controlled for type 1 error -FPG and weight were added as secondary endpoints
26 July 2012	Protocol Amendment 4	Changes based on PeRC's request to include yearly bone age assessment. Bone assessments have been included for all subjects as an x-ray of left hand and wrist at randomization and after 52 weeks of treatment for all subjects. In addition, subjects treated with liraglutide for more than three months will have a bone age assessment at 1 and 2 year follow up visits. -Patients on the blinded trial period requiring rescue, were to be unblinded but remain in the trial; however, if a patient has persistent hyperglycemia, despite rescue, the subject must be withdrawn
12 Oct 2012	Protocol Amendment 7	-addition of fasting blood sample to be drawn between 26 and 52 weeks -new timelines for MESI reporting
4 June 2013	Protocol Amendment 10	Changes in protocol due to delays in patient recruitment • The required duration of diabetes after diagnosis is changed from 90 to 30 days. • Inclusion of children and adolescents currently treated with basal insulin • Change in method to evaluate randomization criterion no. 1-is changed from the average of 3 FPG values measured at the randomization visit to an average of 3 fasting self-measured plasma glucose (SMPG) values measured on three consecutive days before randomization • Use of basal insulin as rescue therapy in both placebo and liraglutide treatment arms. In addition, for subjects who continue to experience confirmed hyperglycemia rapid acting insulin may be added and titrated at the discretion of the investigator • Eliminated requirement that randomization treatment be unblinded prior to rescue treatment initiation since patients in both treatment arms were to receive basal insulin for initial rescue treatment • Change in trial completion timelines • Change in sample size to 80% (from 85%) power and reduction of sample size from 172 to 150
12 Feb 2015	Protocol Amendment 13	Changes in protocol due to delays in patient recruitment • Changes in sample size calculation • Trial population enrollment decreased to 94 (from 150)

		• Changes to the analysis of the primary endpoint to use multiple imputations

Source: reviewer created

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant affirms that the studies were conducted in accordance with good clinical practice (GCP) and in accordance with the Declaration of Helsinki.

Financial Disclosure

Novo Nordisk adequately disclosed financial interests of investigators. Six of the 333 investigators received significant payment of other sorts. In total, 5 (3.7%) patients were randomized in sites of investigators with financial interests or arrangements. At most, 2 patients were randomized to a site with an investigator with financial interests/arrangements.

Overall, the investigator financial disclosures do not raise questions about the data integrity because the study was double blinded, and the primary endpoint was an objective laboratory measurement (HbA1c).

Patient Disposition

This section evaluates the patient's disposition by considering the impact it may have on the efficacy evaluation; discontinuation due to adverse events is discussed in section 8.4.3.

Of 307 screened patients, half were screening failures. The reasons for failing screening are listed below:

- Half of the screen failures did not fulfill the allowed HbA1c criteria for the trial;
  - In an information request,[42] the Applicant clarified that of the 76 patients that failed the HbA1c criteria, 61 had an HbA1c below 6.5%, with the remaining 15 patients, having an HbA1c>11%.
- 26% of screen failures did not meet the criteria for ALAT values
  - Of the 40 patients who were excluded due to ALAT criteria, >90% were excluded due to having an ALT ≥2.5 times upper normal range.
- 14% had a presence of IA-2, or anti-GAD antibodies, and
- 9% of screen failures were not randomized for other reasons.

Reviewer's comments: Across pediatric Type 2 diabetes programs there has been difficulty in recruiting and retaining pediatric patients. The Applicant's clarification regarding the screen

[42] January 22, 2019 IR, question 1.3, \\CDSESUB1\evsprod\NDA022341\0415\m1\us

failures suggests that most of the pediatric patients have lower HbA1c values (i.e.<6.5%). While some patients have transaminitis with likely fatty liver disease. Given that in the real world setting, patients with mild transaminitis are not precluding from using Victoza, it would be reasonable to not exclude these patients in future trials.

Of the patients withdrawn before randomization, the majority of patients were withdrawn due to not meeting randomization criteria.

A total of 135 patients were randomized, of these patients, 134 were exposed to either liraglutide of placebo. A third of patients in the trial were from the United States. As shown in Table 6, a larger proportion of patients randomized to liraglutide vs. placebo completed the 26-week (90.9% vs. 84.1%) and 52-week (84.8% vs. 76.8%) study periods. A smaller proportion of patients who completed the trial required rescue treatment in the liraglutide arm vs. placebo at 26 weeks (4.5% vs. 17.3%). The most common reason for lack of trial completion was meeting a withdrawal criterion, followed by non-compliance. Of note, one patient was noted as withdrawing due to non-compliance, however is counted as withdrawing due to an adverse event (PT: hyperglycemic events), in the table below (see section 8.4.3 for a discussion on withdrawal due to AEs).

Reviewer's comment: the proportion of patients who did not complete the 26-week (12.6%) period was lower than the predicted withdrawal rate of 22% used to derive the sample size calculation. It is unclear why the withdrawal rate was lower than predicted (i.e. trial elements that resulted in higher retention or perhaps an over estimation of the withdrawal rate).

Of note, the number of patients randomized is different than the number of patients counted in the FAS due to one patient in the placebo group who was randomized but did not receive investigational drug, therefore, this patient is not counted as part of the FAS.

Table 6 - Patient disposition

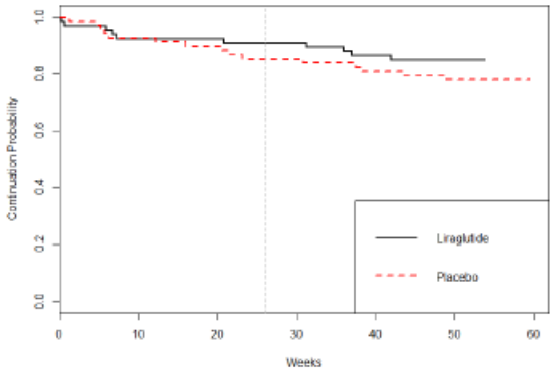
	Liraglutide N (%)	Placebo N (%)	All N (%)
Screened patients			307
Screen failures			152
Withdrew before randomization			20
Randomized	**66 (100)**	**69 (100)**	**135 (100)**
Randomized between age 10-14	21 (31.8)	20 (29.0)	40 (29.6)
Randomized>14 years of age	45 (68.1)	49 (71.0)	94 (69.6)
Randomized in the United States	17 (25.8)	28 (40.6)	45 (33.3)
Exposed	66 (100)	68 (98.6)	134 (99.3)
Completed treatment week 26	60 (90.9)	58 (84.1)	118 (87.4)
HbA1c missing values at week 26	7**(10.6)	10 (14.5)	17 (12.6)
Completed treatment week 26 and initiated rescue prior to week 26	3 (4.5)	12 (17.3)	15 (11.1)
Completed treatment week 52 (Completed trial)	56 (84.8)	53 (76.8)	109(80.7)
Completed treatment week 52 without rescue medication	47 (71.2)	35 (50.7)	82 (60.7)
Did not complete week 26	6 (9.1)	11 (15.9)	17 (12.6)
Did not complete trial	**10 (15.2)**	**16 (23.2)**	**26 (19.3)**
Adverse events	1 (1.5)*	2 (3.0)~	3 (2.2)
Non-compliance	3 (4.5)*	3 (4.3)~	6 (4.4)
Other^	0	3 (4.3)	3 (2.2)
Withdrawal criteria	6 (9.1)	8 (11.6)	14 (10.4)
W1	4 (6.1)	3 (4.3)	7 (5.2)
W2	1 (1.5)	1 (1.5)	2 (1.5)
W3	1 (1.5)	4 (5.8)	5 (3.7)
FAS	**66 (100)**	**68 (98.6)**	**134 (99.3)**

*a patient randomized to liraglutide who was discontinued for "non-compliance" was noted as having multiple hyperglycemic events- these events are considered adverse events, and therefore, the patient is **not** counted under "noncompliance" in this table, but rather is counted under AEs
** The applicant stated that one patient (subject ID (b) (6)) completed the trial for week 26 but could not use HbA1c measurement due to non-compliance prior to week 26.
~A patient randomized to placebo who was discontinued for "non-compliance" was noted by the investigator as being discontinued due to hyperglycemia, therefore this patient is **not** counted under "non-compliance" in this table, but rather is counted under AEs
^ includes the following reasons: rescue treatment within protocol was not enough to reach safe and healthy blood sugar levels (1 patient), lost to follow up (1 patient), and lack of efficacy (1 patient)
W1: patient may withdraw at any time; W2: May be withdrawn due to safety concerns of if patient is non-compliant
W3 must be withdrawn if randomized in error

Source: reviewer generated from ADSL dataset, CSR table 14.1.1, and Table 3 from Dr. Kim's review

With regard to missing data, there were 7 (10.6%) patients randomized to liraglutide and 10 (14.5%) patients randomized to placebo with a missing week 26 HbA1c measurement. Dr. Kim notes that there was no concern for early treatment discontinuation during the 26-week efficacy period, based on the time to treatment discontinuation analysis shown below. This Kaplan-Meier plot (Figure 3) shows that separation between treatment arms begins at approximately 15 weeks, with a higher discontinuation occurring in the placebo arm.

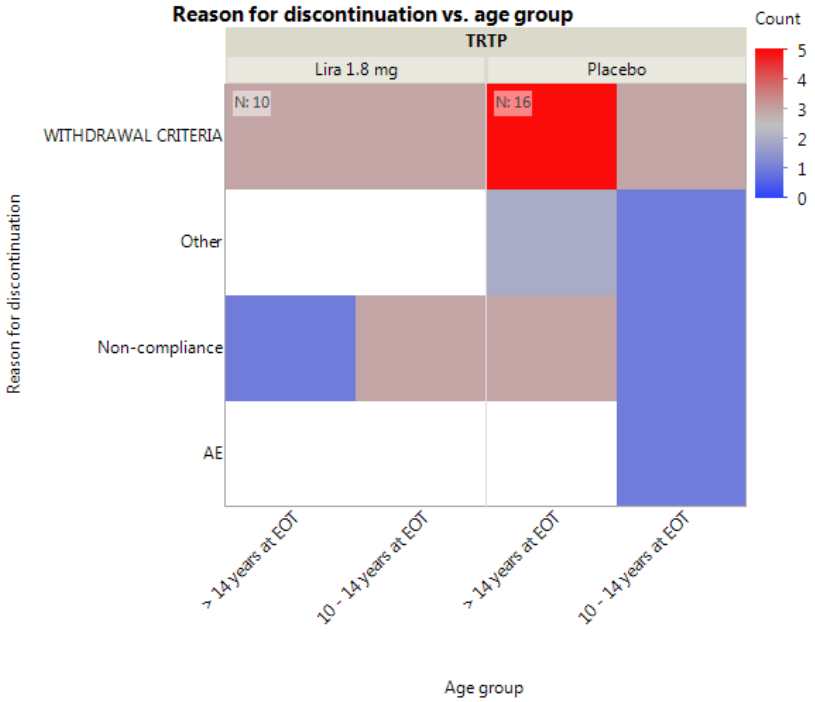
Figure 3 –Time to treatment discontinuation for all patients (FAS)



Source: Dr. Kim's review, Figure 2

Of the patients randomized, approximately 30% were between the ages of 10-14 years old, as was stipulated in Written Request. The proportion of patients aged 10-14 were similar between treatment arms; see Table 6. Of the patients aged 10-14, 6 patients for liraglutide and 6 patients for placebo withdrew from the trial; of the patients aged>14 years, 4 patients randomized to liraglutide and 10 patients randomized to placebo withdrew from the trial; Figure 4 shows the reasons for trial discontinuations by age groups.

Figure 4- Reason for trial discontinuation by age groups



Source: ADSL dataset- note that the data is slightly different than the patient disposition table above because the 2 patients (a patient randomized to liraglutide and placebo) who were discontinued for

"non-compliance" are not counted as having discontinued due to an AE. The data used to generate this figure is from the Applicant submitted datasets.

Protocol Violations/Deviations

The Applicant provided listings of protocol deviations by site and by subject level. Deviations listed included deviations with informed consent,[43] inclusion/exclusion/randomization criteria[44], withdrawal/discontinuation criteria,[45] trial product handling,[46] treatment compliance,[47] assessment deviations[48] and other deviations[49]. Review of these deviations did not reveal any differences between treatment arms that would potentially invalidate the trial results.

In total the randomization code was broken for 11 patients (4 for liraglutide and 7 for placebo):

- 3 patients had the code broken because of SAEs (2 for liraglutide, 1 for placebo)[50]
- 8 patients[51] had the code broken because rescue medication was initiated; 2 for liraglutide and 6 for placebo (as specified in protocol versions prior to protocol version 10)[52]

In addition, the Applicant reports instances where during the open label period of the trial, some data points that could reveal individual treatment allocation were unintentionally made available to various groups, including the statistician (these were made available from 17 Oct 2013 to 04 Jul 2016, possibly affecting 29 liraglutide/27 placebo patients who had a visit 18

[43] Affected 23 liraglutide and 27 placebo patients
[44] Affected 5 liraglutide and 9 placebo patients
[45] Affected 12 liraglutide and 23 placebo patients – although there is an imbalance in the numbers listed here the majority of the PDs were due to confirmatory FPG assessments to evaluate for hyperglycemia were not done- since more patients in the placebo required this procedure(based on the rescue results), it is not unexpected to see a difference between treatment arms
[46] Affected 26 liraglutide and 15 placebo patients – half of the PDs were related to dispensing/administration of IMP stored incorrectly, with some sites not having the IMP at site-patients were instructed to return to the site when new IMP arrived.
[47] Affected 56 liraglutide and 51 placebo patients
[48] Affected 92 liraglutide and 89 placebo patients
[49] Affected 32 liraglutide and 20 placebo patients
[50] Subject ID (b) (6) (liraglutide) experienced vertigo 3.5 months after randomization and was hospitalized with resolution of symptoms; subject ID (b) (6) (liraglutide) experienced abdominal pain and was admitted to the hospital and released on the same day; subject ID (b) (6) (placebo) ECG taken on a tonsillectomy pre-operation visit showed potential cardiomegaly, which was not confirmed on repeat ECG and evaluation by cardiologist.
[51] subject IDs (b) (6).
[52] Protocol version 10 no longer required unblinding prior to starting rescue therapy

during this period).[53] The Applicant asserts that the statistician and programmer responsible for data processing did not review any of the data during the period it was made available.[54] However, there was no tracking system that documented that the statistician and programmer did not review any data in the period. The Applicant asserted that the validity of the results was not compromised since all the blinding was maintained, according to the protocol for all patients and for all data points in the double-blinded period of the trial. The Applicant also states that the SAP version 1 was finalized before any information that could reveal treatment allocation became available and that the changes in version 2 were made as a result of the FDA's input regarding the primary analysis.

Reviewer's comment: Based on the Applicant's response, it appears that the unblinding episode was limited to the open-labeled period of the trial.

In regard to protocol deviations which might impact the study result, the following were observed:

- 5 patients were randomized in error (due to not meeting inclusion/exclusion or randomization criteria).
- There were no patients who met withdrawal criteria but were not withdrawn
- There was one patient randomized to placebo who was erroneously dispensed liraglutide (visit 7) and took it for 6 days.

Reviewer's comment: the totality of the protocol deviations/unblinding events do not raise concerns regarding the overall data quality or integrity of the trial.

Patient Demographics

Table 7 shows the demographics and baseline characteristics for patients in the full analysis set. Overall, the demographic characteristics were balanced between the two groups. The mean chronological age was 14.6 years with an advanced mean bone age of 16.5 years. At baseline, the proportion of patients>14 years (70%) was larger than the patients aged 10-14 years. Over 60% of the enrollees were female. The mean duration of diabetes was 1.9 years. Approximately 65%, 12%, 29% were White, Black or African American or Hispanic, respectively.

[53] Treatment allocation became available to statisticians when the IV/WRS system which revealed treatment allocation at week 26 to allow investigators to continue treatment with liraglutide in the open-labeled period. However, only some of the data points could potentially disclose treatment allocation.

[54] In an information request dated 2/11/19, the applicant clarified that "all blinding was maintained according to protocol for all subjects and data points in the double-blinded period of the trial… In addition, every effort was made to maintain the blinding for the programmer and statistician regarding the data that was collected during the open-label period of the trial. . ." The applicant asserted that that preventative and corrective actions were initiated when they discovered this and data access for the programmer and statistician was revoked until corrective action had been implemented.

The mean BMI was 34 kg/m^2 and the mean BMI SDS was 2.9.

Reviewer's comment: Some notable points in the demographic characteristics are the mean BMI SD and the racial and ethnic make-up of the population. The mean BMI SDS indicates that the population as a whole had a BMI 2.9 standard deviations above the average BMI value across age groups, indicating that on average patients were obese. Interestingly, the BMI SDS in *ellipse*^{TM} was above the baseline BMI SDS for the TODAY study.[55]

Although the mean weight, systolic, diastolic measures were similar between treatment arms, the interpretation of these measures is difficult across the age ranges in the study; it would have been more helpful to collect SDS (or Z scores) to better assess the clinical significance of these measures.

Another interesting observation is the racial makeup of the trial. The larger proportion of White participants in the trial is not reflective of the racial make-up in the US. For context, the Centers of Disease Control estimates that the incidence of type 2 diabetes among US children in 2011-2012 was higher in ethnic minorities.[56]

A total of 15 (22.7%) patients randomized to liraglutide and 10 (14.5%) patients randomized to placebo were using insulin at baseline. Among these patients, the average dose of insulin was 29.6 units.

Reviewer's comment: there was slightly more patients in the liraglutide on insulin at baseline as compared to placebo. The use of insulin during the trial is further explored as part of the efficacy endpoint discussion.

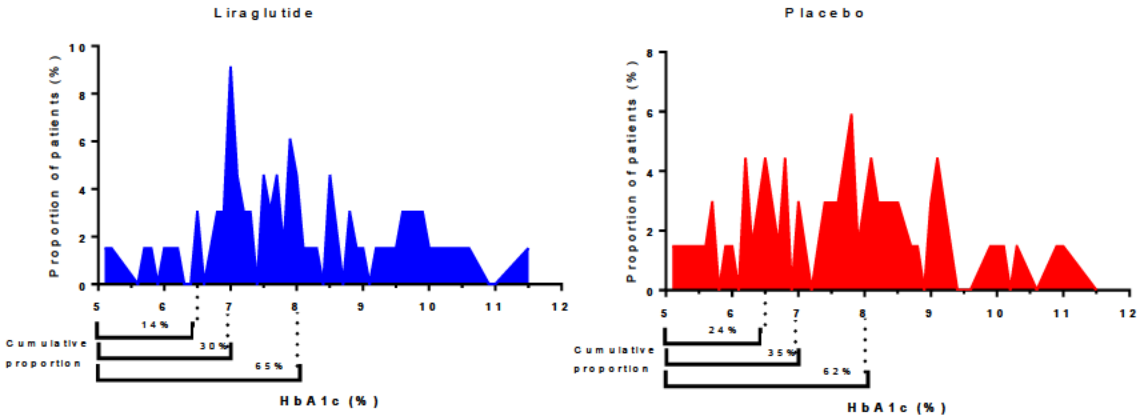
Another notable characteristic of the enrolled population is the mean baseline HbA1c, which was 7.78%. As noted earlier, a large proportion of patients were screen failures due to having an HbA1c below 6.5. For comparison, the Victoza PI shows that for most of the adult trials, the average baseline HbA1c ranged between 8.0% and 8.5%.

Figure 5 shows the distribution of HbA1c in both treatment arms. This figure shows that approximately 14% and 24% of liraglutide and placebo patients had an HbA1c of 6.5% or below and that 30% and 35% of patients had an HbA1c of 7% or below. Dr. Kim's review notes that there were twenty patients (7 patients in the liraglutide arm and 14 patients in the placebo arm) with an HbA1c < 6.5% as a result of treatment with metformin during the run-in period.

[55] Mean BMI SDS score was 2.15 in the TODAY study Kenneth C. Copeland, Philip Zeitler, Mitchell Geffner, Cindy Guandalini, Janine Higgins, Kathryn Hirst, Francine R. Kaufman, Barbara Linder, Santica Marcovina, Paul McGuigan, Laura Pyle, William Tamborlane, Steven Willi; Characteristics of Adolescents and Youth with Recent-Onset Type 2 Diabetes: The TODAY Cohort at Baseline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 96, Issue 1, 1 January 2011, Pages 159–167, https://doi.org/10.1210/jc.2010-1642

[56] https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017-508.pdf

Figure 5- Baseline HbA1c for liraglutide and Placebo



Source: reviewer generated form baseline HbA1c

Reviewer's comment: The HbA1c distribution in the pediatric population shows that a considerable number of patients have lower HbA1c values as compared to adult T2DM trials. The lower HbA1c in these patients may diminish some of the effect of liraglutide in the trial (since HbA1c does not have as much room to decrease) and may predispose patients to a higher risk of hypoglycemia; see section 8.4.4. Also, the decline in HbA1c after metformin therapy is consistent with an expected glycemic response in metformin-responsive patients.

Table 7- Demographic characteristics-FAS

		Liraglutide	Placebo	All
		N=66	N=68	N=134
Age (years)	Mean (Std Dev)	14.6 (1.7)	14.6 (1.7)	14.6 (1.7)
	Min; max	10.0; 16.9	10.4; 16.9	10.0; 16.9
	Age group 10-14 years (%)	21 (31.8)	19 (27.9)	40 (29.9)
Sex, N (%)	Male	25 (37.9)	26 (38.2)	51 (38.1)
	Female	41 (62.1)	42 (61.8)	83 (61.9)
Bone age, years	Mean (St Dev)	16.6 (2.0)	16.4 (1.8)	16.5 (1.9)
	Min, max	10; 19	11. 19	10; 19
Race, N (%)	American Indian or Alaska native	2 (3)	1 (1.5)	3 (2.2)
	Asian	10 (15.2)	8 (11.8)	18 (13.4)
	Black or African American	9 (13.6)	7 (10.3)	16 (11.9)
	Other	3 (4.5)	7 (10.3)	10 (7.5)
	White	42 (63.6)	45 (66.2)	87 (64.9)
Ethnic, N (%)	Hispanic or Latino	16 (24.2)	23 (33.8)	39 (29.1)
	Not Hispanic or Latino	50 (75.8)	45 (66.2)	95 (70.9)
Diabetes duration (yrs.)	Mean (Std Dev)	1.85 (1.68)	1.93 (1.32)	1.89 (1.51)
	Min; Max	0.3;10.1	0.2;6.2	0.2; 10.1
Height (m)	Mean (Std Dev)	1.64 (0.12)	1.64 (0.09)	1.64 (0.10)
	Min; Max	1.34; 1.92	1.45; 1.83	1.34; 1.92
Height SDS	Mean (Std Dev)	0.27 (1.33)	0.35 (1.30)	0.31 (1.31)
	Min; Max	-2.84; 3.49	-2.69; 3.14	-2.84; 3.49

Body Weight (kg)	Mean (Std Dev)	93.23 (30.98)	89.83 (22.13)	91.50 (26.81)
	Min; Max	41.8; 201.7	48; 141.7	41.8;201.7
Mean BMI, kg/m2	Mean (Std Dev)	34.55 (10.87)	33.27 (7.36)	33.90 (9.25)
	Min; Max	20.9; 81.16	21.91; 57.05	20.90; 81.16
BMI, SDS	Mean (Std Dev)	3.03 (1.47)	2.86 (1.11)	2.94 (1.30)
	Min; Max	1.00; 9.29	1.07;6.32	1.00;9.29
Waist circumference (cm)	Mean (Std Dev)	106.11 (20.69)	104.29 (14.98)	105.19 (17.97)
	Min; Max	69.17; 181.67	79.67; 141.17	69.17; 181.67
Systolic blood pressure (mmHg)	Mean (Std Dev)	118.39 (11.4)	115.28 (12.2)	116.81 (11.78)
	Min; Max	94; 147	85; 146	85; 147
Diastolic blood pressure (mmHg)	Mean (Std Dev)	73.15 (8.51)	71.22 (7.62)	72.17 (8.10)
	Min; Max	52; 97	53;86	52; 97
Heart rate (beats/min)	Mean (Std Dev)	82.08 (10.58)	78.88 (9.75)	80.46 (10.25)
	Min; Max	62; 110	56; 102	56; 110
HbA1c (%)	Mean (Std Dev)	7.87 (1.35)	7.69 (1.34)	7.78 (1.34)
	Min; Max	5.1; 11.5	5.1;11.0	5.1; 11.5
Insulin use, N (%)	No	51 (77.3)	59 (85.5)	110 (81.5)
	Yes	15 (22.7)	10 (14.5)	25 (18.5)
Dose of basal insulin use (units)	Mean (Std Dev)	29.6 (19.46)	29.6 (17.7)	29.6 (18.39)
	Min; Max	5;76	6;62	5;76

Source: Reviewer generated table from CSR table 10-2 to table 106, in addition to the ADSL dataset.

Analyses using the ADSL dataset, were used to evaluate the demographic characteristics of patients ≥14 years and 10-14 years between treatment arms. Overall, the demographic characteristics were similar between treatment arms for these subgroups. Some expected differences between the >14 years of age subgroup and the 10-14 years of age subgroup were a higher mean duration of diabetes, bone age, BMI, and body weight in the >14 years subgroup as compared to the 10-14 years subgroup. In the liraglutide arm a similar proportion of patients regardless of age subgroup were on basal insulin at baseline (i.e. ~22%), while for placebo a slightly higher proportion of patients >14 years were on basal insulin (16.3%) as compared to the 10-14-year-old subgroup (10.5%).

Table 8 – Demographic and baseline characteristics by age subgroups

	Liraglutide			**Placebo**		
	Age range			**Age range**		
	> 14 years at EOT	**10 - 14 years at EOT**	**All**	**> 14 years at EOT**	**10 - 14 years at EOT**	**All**
N	**45**	**21**	**66**	**49**	**19**	**68**
RACE						
White, N (%)	29 (64.4)	13 (61.9)	42 (63.6)	32 (65.3)	13 (68.4)	45 (66.2)
Asian, N (%)	8 (17.8)	2 (9.5)	10 (15.2)	8 (16.3)	0 (0)	8 (11.8)
Black or African American, N (%)	5 (11.1)	4 (19)	9 (13.6)	3 (6.1)	4 (21.1)	7 (10.3)
OTHER, N (%)	2 (4.4)	1 (4.8)	3 (4.5)	5 (10.2)	2 (10.5)	7 (10.3)

American Indian or Alaska native, N (%)		1 (2.2)	1 (4.8)	2 (3)	1 (2)	0 (0)	1 (1.5)
SEX							
Female, N (%)		25 (55.6)	16 (76.2)	41 (62.1)	27 (55.1)	15 (78.9)	42 (61.8)
Male, N (%)		20 (44.4)	5 (23.8)	25 (37.9)	22 (44.9)	4 (21.1)	26 (38.2)
ETHNIC							
Not Hispanic or Latino, N (%)		35 (77.8)	15 (71.4)	50 (75.8)	35 (71.4)	10 (52.6)	45 (66.2)
Hispanic or Latino, N (%)		10 (22.2)	6 (28.6)	16 (24.2)	14 (28.6)	9 (47.4)	23 (33.8)
Basal insulin use							
Yes No		10 (22.2) 35 (77.8)	5 (23.8) 16 (76.2)	15 (22.7) 51 (77.2)	8 (16.3) 41 (83.7)	2 (10.5) 17 (89.5)	10 (14.7) 58 (85.3)
Dose of basal insulin (units)	Mean	34.8	19.2	29.6	28.4	34.5	29.6
Diabetes duration (yrs.)	Mean	1.88	1.77	1.85	1.95	1.88	1.93
Bone age (yrs.)	Mean	18	14	17	17	15	16
Baseline BMI (kg/m^2)	Mean	36.19	31.03	34.55	33.75	32.05	33.27
Body weight (kg)	Mean	100.3	78.02	93.23	92.91	81.87	89.83
HBA (%)	Mean	8	7.59	7.87	7.62	7.86	7.69

Source: reviewer derived table using ADSL dataset

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

Table 9 shows commonly reported medical history[57] (by preferred terms with an incidence of at least ≥5%) at baseline.[58] The most common conditions in the trial were obesity (38.1%), acanthosis nigricans (19.4%), and hypertension (13.4%). When comparing between treatment groups, there were slight imbalances in the proportion of patients reported with "obesity" (47% for liraglutide and 29.4% for placebo), "hypertension" (19.7% for liraglutide and 7.4% for placebo). Few patients reported a history of diabetes complications: diabetic nephropathy (3 patients)[59], diabetic neuropathy (2 patients)[60] and diabetic retinopathy (1 patient).[61]

Reviewer's comment: the differences in the reported medical history may be in part affected by the lack of systematic collection of specific medical conditions (since the forms that

[57] Clarified in January 22 IR: \\CDSESUB1\evsprod\NDA022341\0415\m1\us -Medical history data were collected by asking the question ""Has the subject had any relevant conditions/illnesses in the past or currently has any conditions/illnesses not listed in the Complications form?" If the answer was 'yes', information on the diagnosis, date of onset and whether the condition was continuing (yes/no) was to be provided (if continuing was answered 'no', the stop date was also to be provided). Thus, this form did not include dedicated fields for conditions of interest.

[58] Refer to table 14.1.10 in the CSR for a listing of all the medical history reported at baseline

[59] 2 patients in the liraglutide arm and 1 patient in placebo

[60] One patient each for liraglutide and placebo

[61] In the liraglutide group

collected this information did not have dedicated fields for conditions of interest; and may be affected by reporter bias). Even at this young age, the presence of any complications from diabetes points to the severity of diabetes in this population.

Table 9- Most common medical history at baseline (with an incidence of at least ≥5%) -FAS

System Organ Class Preferred Term	Liraglutide N=66	Placebo N=68	All N=134
Metabolism and nutrition disorders	39 (59.1)	27 (39.7)	66 (49.3)
Obesity	31 (47.0)	20 (29.4)	51 (38.1)
Vitamin D deficiency	6 (9.1)	4 (5.9)	10 (7.5)
Dyslipidemia	4 (6.1)	3 (4.4)	7 (5.2)
Hyperlipidemia	5 (7.6)	1 (1.5)	6 (4.5)
Skin and subcutaneous tissue disorder	20 (30.3)	14 (20.6)	34 (25.4)
Acanthosis nigricans	15 (22.7)	11 (16.2)	26 (19.4)
Respiratory, thoracic and mediastinal disorders	13 (19.7)	11 (16.2)	24 (17.9)
Asthma	4 (6.1)	5 (7.4)	9 (6.7)
Sleep Apnea	4 (6.1)	2 (2.9)	6 (4.5)
Vascular disorders	14 (21.2)	5 (7.4)	19 (14.2)
Hypertension	13 (19.7)	5 (7.4)	18 (13.4)
Psychiatric disorders	9 (13.6)	9 (13.2)	18 (13.4)
Attention deficit/hyperactivity disorder	4 (6.1)	8 (11.8)	12 (9.0)
Immune system disorders	6 (9.1)	8 (11.8)	14 (10.4)
Seasonal allergy	4 (6.1)	4 (5.9)	8 (6.0)
Reproductive system and breast disorders	11 (16.7)	3 (4.4)	14 (10.4)
Dysmenorrhea	5 (7.6)	1 (1.5)	6 (4.5)
Eye disorders	8 (12.1)	5 (7.4)	13 (9.7)
Myopia	6 (9.1)	2 (2.9)	8 (6.0)
Gastrointestinal disorders	7 (10.6)	6 (8.8)	13 (9.7)
Gastroesophageal reflux disease	3 (4.5)	4 (5.9)	7 (5.2)
Hepatobiliary disorders	6 (9.1)	5 (7.4)	11 (8.2)
Hepatic steatosis	6 (9.1)	3 (4.4)	9 (6.7)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance

The Written Request stipulated that compliance should be assessed in this study.

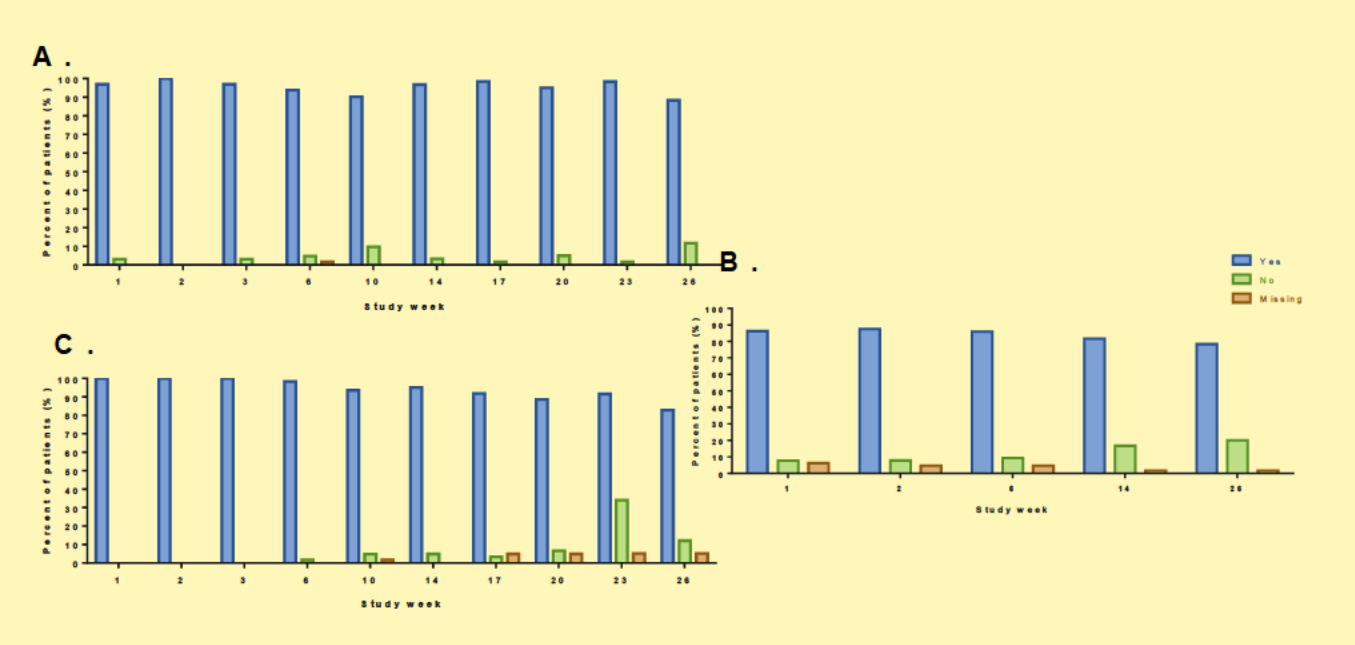
Treatment compliance was assessed and recorded in a dedicated Compliance form at each visit

(visits 3-25 for the period preceding each visit)[62] based on the following parameter: adherence to visit schedule, completion of the patient's diary, metformin treatment and use of investigational drug (each measure was categorized as compliant yes or no). Oral confirmation of compliance from the patient/legal representative was assessed at each visit. Also, the investigators monitored the drug accountability by assessing the amount of the IMP and metformin against the dispensed amount; in case of discrepancy the patient was questioned. Compliance for metformin was defined as taking 80%-120% of the prescribed dose; there was no compliance range defined for liraglutide or placebo; therefore, it was at the investigator's discretion to determine if the patient's degree of compliance was adequate.

Figure 6 shows compliance based on patient self-reports for liraglutide (A) and placebo (B) as well as by compliance in the liraglutide arm based on measured PK assessments (C).

Self-reported compliance for liraglutide and placebo was over 90% in the 26-week treatment period; however, when assessing compliance by PK assessments, compliance for liraglutide was closer to 80% throughout the trial.

Figure 6- Compliance assessed by patient reports for liraglutide (A) and placebo (B); compliance as assed by presence of detectable liraglutide in plasma (C)



Source: reviewer graphed Applicant provided data Table 1 and Table 2: Yes, refers to compliant, No refers to not compliant, and missing refers to a missing value for the visit
\\CDSESUB1\evsprod\NDA022341\0417\m1\us (IR dated 2/1/19)

[62] From visit 18-25 only liraglutide compliance was assessed, as patients on placebo stopped taking IMP injections during the open-labeled period

Reviewer's comment: treatment compliance tended to be overestimated by self-reports, as compared to an evaluation of compliance by the presence of liraglutide in plasma. Nonetheless, the Applicant's assessment of treatment compliance was adequate for the purposes of the Written Request.

Rescue therapy

Table 10 shows the rescue therapies used in this trial at 26 and 52 weeks. Throughout the trial insulin (mostly long acting or intermediate acting) was the main therapy used for rescue. Only one patient (randomized to placebo) received a sulfonylurea for rescue.

Table 10 – Rescue therapy used by patients during the 26 and 52-week periods- FAS

	Week 26		Week 52	
Rescue therapy used	Liraglutide N (%)	Placebo N (%)	Liraglutide N (%)	Placebo N (%)
Number of patients	**66**	**68**	**66**	**68**
Number of patients on rescue medication	3 (4.5%)	13 (19.1%)	9 (13.6)	21 (30.9)
Insulin	3 (4.5)	13 (19.1)	9 (13.6)	21 (30.9)
Long acting/intermediate Acting (basal insulin)	2 (3.0)	12 (17.6)	8 (12.1)	19 (27.9)
Short acting	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)
Both long/intermediate and short acting insulin	0	0	0	0
GLP1- receptor agonist	0	0	0	0
SGLT2 inhibitor	0	0	0	0
Sulfonylureas	0	0	0	1 (1.5)

Source: information request2/1/19, table 3 \\CDSESUB1\evsprod\NDA022341\0417\m1\us

Reviewer's comment: the higher use of rescue therapy in the placebo group could potentially reduce the observed effect size of liraglutide (particularly with the use of insulin, a titratable drug); however, the efficacy findings show that despite the higher use of rescue in the placebo arm, the treatment difference still favored the liraglutide arm at both 26 and 52 weeks (see discussion pertaining to the primary endpoint below).

To better understand the types of patients required rescue, I show the baseline characteristics of these patients in Table 11. Patients who required rescue and were randomized to liraglutide were older, had a longer diabetes duration, and had a higher baseline HbA1c as compared to placebo patients requiring rescue.

Table 11- Baseline characteristics of patients who required rescue

		Liraglutide N=9	Placebo N=21	All N=30

Sex	Female	6 (66.7)	10 (47.6)	16 (53.3)
	Male	3 (33.3)	11 (52.4)	14 (46.7)
Race	American Indian or Alaska native	1 (11.1)	1 (4.8)	2 (6.7)
	Asian	1 (11.1)	5 (23.8)	6 (20)
	Black or African American	1 (11.1)	2 (9.5)	3 (10)
	Other	1 (11.1)	4 (19)	5 (16.7)
	White	5 (55.6)	9 (42.9)	14 (46.7)
Ethnicity	Hispanic or Latino	1 (11.1)	7 (33.3)	8 (26.7)
	Not Hispanic or Latino	8 (88.9)	14 (66.7)	22 (73.3)
Age (mean yrs.)		15	13	14
Age group	> 14 years at EOT	8 (88.9)	12 (57.1)	20 (66.7)
	10 - 14 years at EOT	1 (11.1)	9 (42.9)	10 (33.3)
Diabetes duration (mean yrs.)		2.09	1.41	1.61
HbA1c% baseline (mean)		9.31	8.2	8.53
Source: reviewer derived from ADSL dataset				

Efficacy Results – Primary Endpoint

Dr. Yoonhee Kim reviewed the efficacy data in detail; Dr. Kim did not identify any major statistical issues during the review and recommends approval of the supplement.

The primary efficacy endpoint in this trial (as consistent with the Written Request) was the change in HbA1c from baseline to week 26 (the end of the double blinded period).

The primary analysis included all randomized and treated patients regardless of initiation of rescue therapy; note that retrieved drop outs, or data from patients who discontinued treatment prior to week 26 were not collected. As noted earlier, week 26 missing HbA1c data was 10.6% and 14.5% for liraglutide and placebo, respectively. To address the missing data, Dr. Kim performed a "wash-out" analysis using placebo completers; this method is consistent with the applicant's pre-specified analysis.

Because the FAS population was defined as all randomized patients who took at least one dose of study drug, one patient in the placebo group who was randomized but did not take study drug was excluded from this analysis.

For the 134 patients in the FAS population, the baseline HbA1c was numerically higher for liraglutide (7.87%) as compared to placebo (7.69%). The adjusted mean change from baseline in HbA1c (%) using a pattern mixture model (PMM) with multiple imputations, at 26 weeks was -0.64 for liraglutide and 0.42 for placebo, with an adjusted mean difference (Lira-placebo) of -1.06 and a 95% confidence interval of (-1.65; -0.46) p-value<0.001; see Table 12. These findings show that the change in HbA1c for liraglutide was statistically significant superior to placebo, since the treatment difference for change from baseline in HbA1c at week 26 was entirely below 0%.

Table 12 – Primary analysis result- change 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

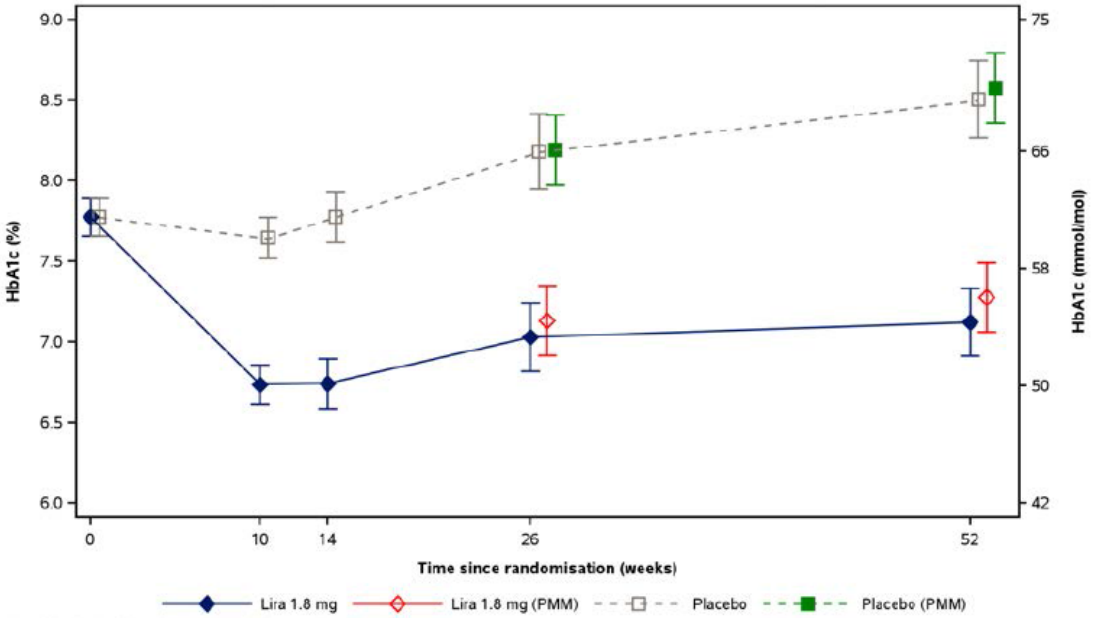
*Mean: least squared mean using Rubin's rule to combine results from the multiple imputation data sets; PMM: the sponsor's analysis using pattern mixture model multiple imputation (n=10,000); FAS: full analysis set
** The reviewer's analysis using washout model multiple imputation (n=1,000)
***Estimates from ANCOVA model with treatment and stratification groups (sex*age group) as categorical fixed effects and baseline HbA1c as a covariate.

Source: Dr. Kim's review, Table 5

Dr. Kim notes that all sensitivity analyses by the applicant showed the statistical superiority of liraglutide over placebo. In addition, Dr. Kim's washout model multiple imputations analysis was also consistent with primary endpoint's treatment effect of -1.05 with a 95% CI of -1.72 to -0.38.

Evaluation of HbA1c by treatment week is shown in Figure 7. This figure shows that HbA1c declined sharply for liraglutide at week 10 while the HbA1c remained somewhat stable for placebo. After week 14 until week 52, HbA1c increased for both treatment arms, although the HbA1c increased above baseline only for placebo.

Figure 7 - HbA1c by treatment week- mean plot including primary analysis results- FAS

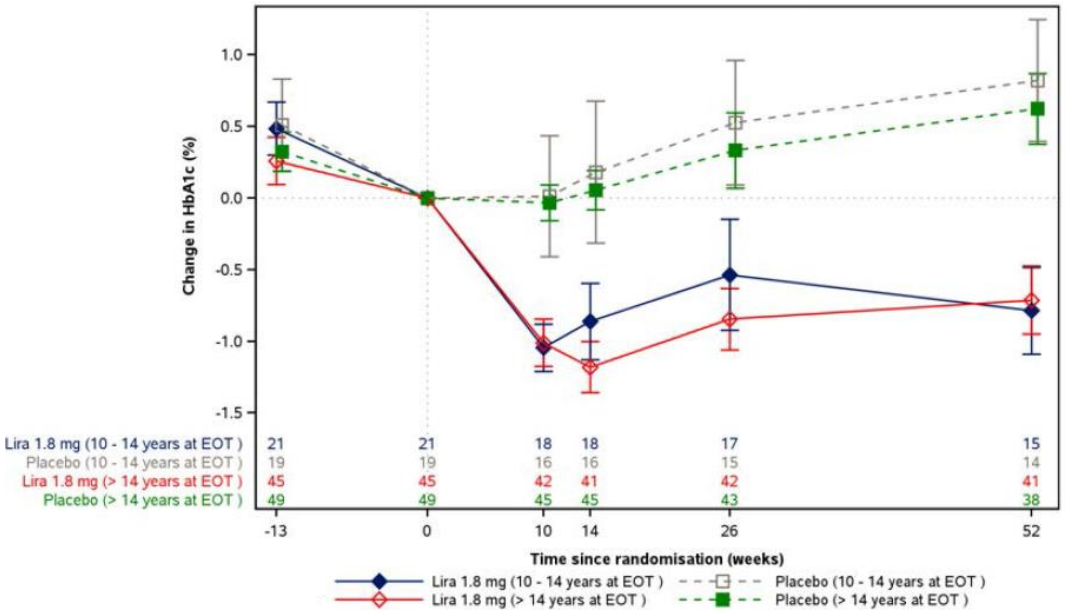


Lira: Liraglutide, Error bars: +-standard error (mean)
Means are estimated from a mixed model of repeated measurements (MMRM) containing treatment, (sex*age) group as fixed effects and baseline value as covariate, all nested within visit. Results from a pattern mixture model (PMM) are shown at weeks 26 and 52.
For MMRM results data collected after treatment discontinuation or initiation of rescue medication were handled as missing data.

Source: CSR Figure 11-1

Figure 8 shows the observed trends in change of HbA1c for the age groups of 10-14 years and >14 years. Overall, the trends in change HbA1c were similar between age groups. Regardless of age, patients randomized to liraglutide had a greater decrease in HbA1c as compared to patients randomized to placebo.

Figure 8- HbA1c by treatment week-meal plot of observed change form baseline by age group 10-14 vs>14 years-FAS



Source: CSR Figure 14.2.21

Insulin used during the trial

Refer to Table 10 for a listing of other medications used for rescue. Since insulin was the main rescue medicine used in the trial, I focus my discussion on insulin. The purpose of this evaluation is to better understand potential variables which could affect the efficacy findings. As previously discussed (see Table 7) 15 and 10 patients were using insulin at baseline for liraglutide and placebo, respectively. Over the course of the trial the proportion of patients using insulin increased. As shown in Table 13, a total of 16 and 25 patients randomized to liraglutide and placebo, respectively, required insulin at any point during the 26-week period. The numbers increased to 20 and 30 patients for liraglutide and placebo by 52 weeks.

Table 13- Insulin use during the trial- FAS

	Liraglutide	Placebo
Total N of patients requiring any insulin	20	30
Patients on **long** acting or **intermediate** insulin at any point in the trial	20	30
• During the 26 week period	16	25
• During the 52 week period	20	30
Patients on short acting insulin*	5	9
• During the 26 week period	3	4
• During the 52 week period	5	9
Patients on short acting and long/intermediate acting insulin	1	2
• During the 26 week period	1	1
• During the 52 week period	1	2

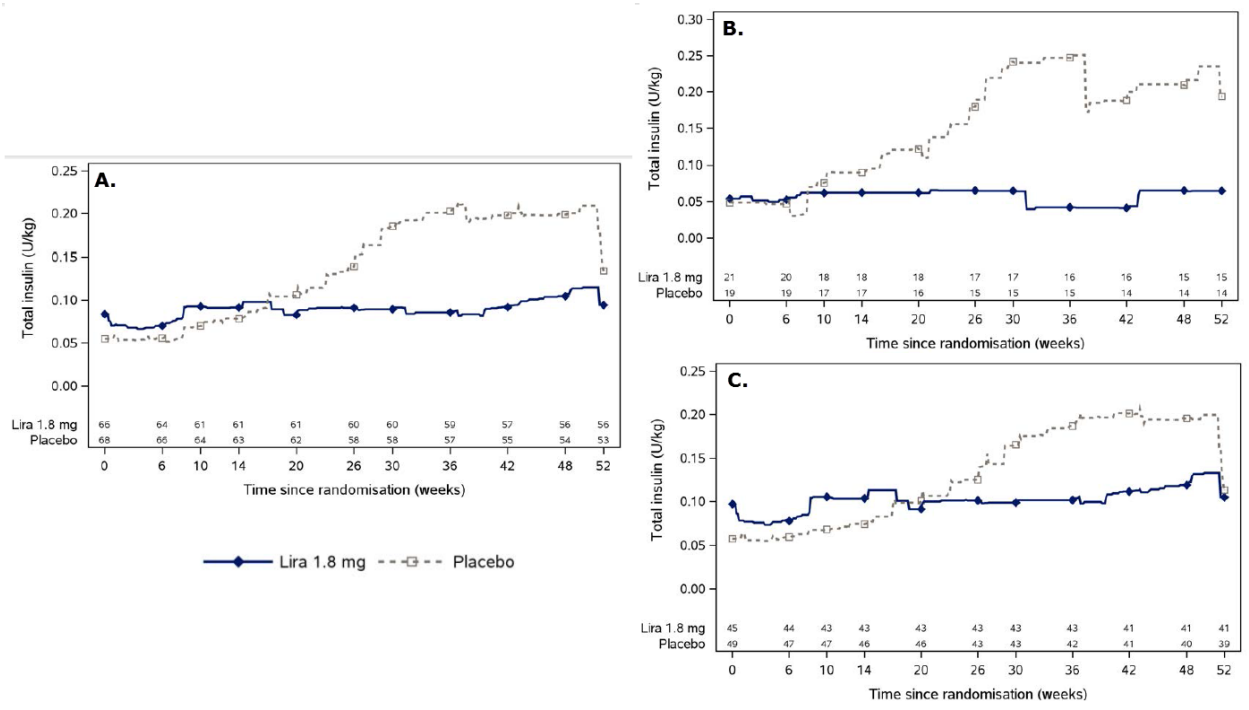
N: Number of subjects. *No subject took only short acting insulin.

ATC codes: Long/intermediate acting: A10AC and A10AE; Short acting: A10AB; Short and long acting: A10AD.

Source, Table 1, IR1/22/19: \\CDSESUB1\evsprod\NDA022341\0415\m1\us

Figure 9 shows total insulin dose over time for patients throughout the trial (A), and by age subgroups (B and C). Insulin doses, for all patients and by age subgroups, remained relatively stable for the liraglutide arm, as compared to the placebo arm, where insulin doses increased.

Figure 9- Total insulin dose (units/kg) by treatment week for the total population using insulin (A); for the age group 10-14 years (B); and for the age group>14 years (C)

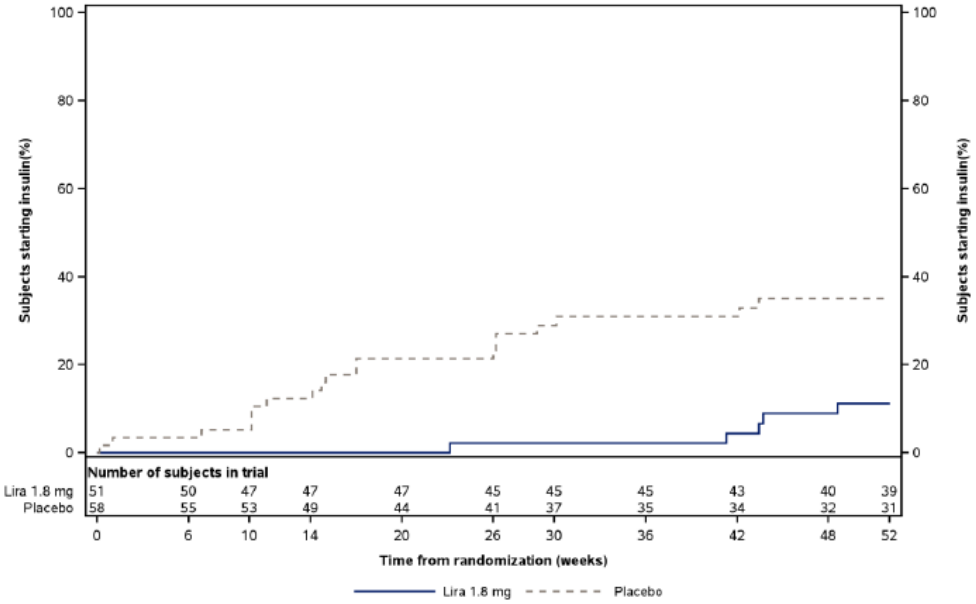


Source, Table 1.9, IR 2/1/19: \\CDSESUB1\evsprod\NDA022341\0417\m1\us

Reviewer's comments: The insulin dose trends may be interpreted in light of the trial design which allowed patients to increase the insulin dose to screening basal insulin dose (after an initial 20% dose reduction) until week 8 (see footnote 26). The graphs show that the insulin dose increase beyond week 8 was seen for placebo, and not liraglutide, reflecting rescue therapy.

To understand the time-trends in starting insulin for in this trial, the Applicant was asked to perform a time to starting insulin event analysis (which essentially evaluates a time to rescue initiation); this analysis is shown in Figure 10.

Figure 10- Time from randomization to starting insulin (weeks)- patients who were not on insulin prior to starting the trial-FAS



Source: Figure 1, IR1/22/19: \\CDSESUB1\evsprod\NDA022341\0415\m1\us;

Reviewer's comments: Across analyses, proportion of patients using insulin, insulin dosage trends, and time to insulin initiation, it does not appear that excess use of insulin in the liraglutide arm contributed to the liraglutide arm's treatment effect. In fact, the higher insulin use in the placebo arm may have lowered the treatment difference (liraglutide-placebo) in this trial.

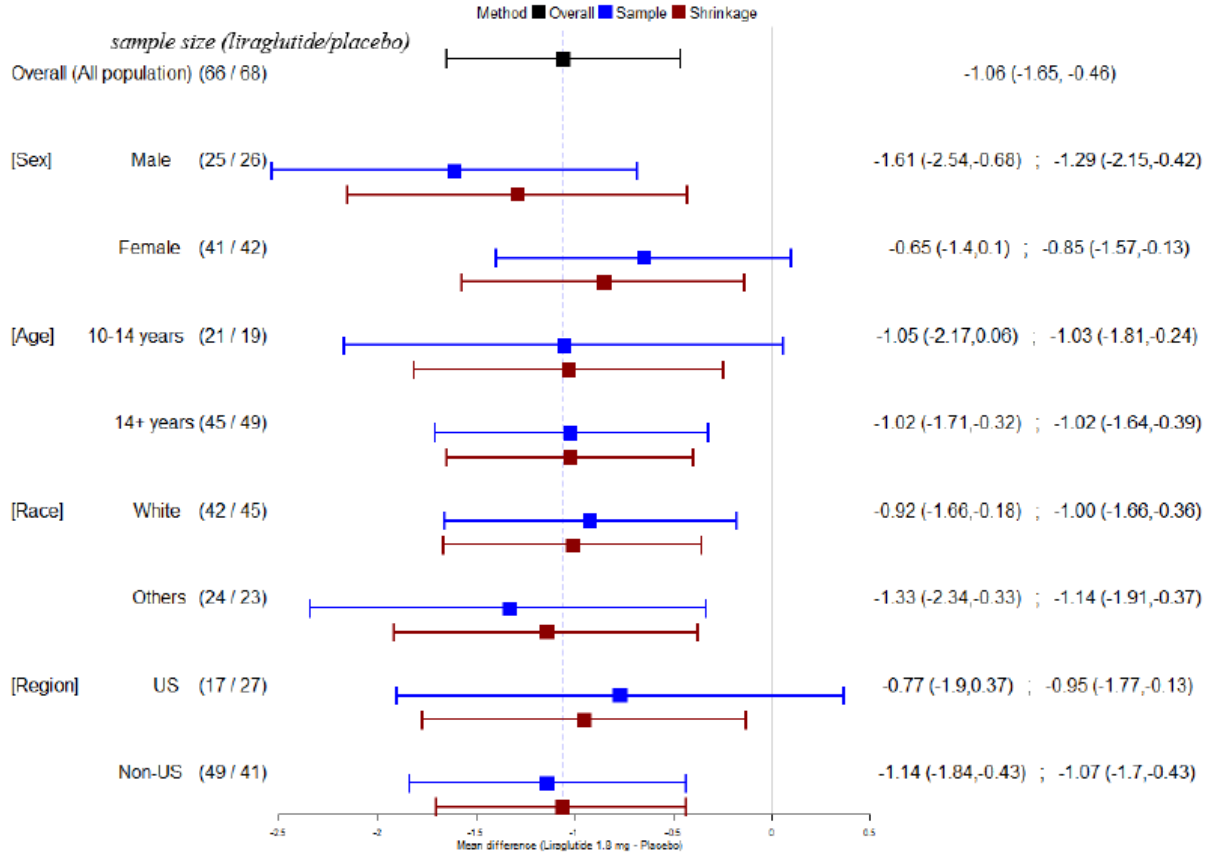
Subgroup analyses

Dr. Kim performed subgroup analyses for the primary endpoint using the PMM multiple imputations model. Dr. Kim also performed a shrinkage analysis due to the random lows and random highs seen due to the small sample size and large variability in some subgroups; refer

to the statistical review for details regarding the statistical methods/assumptions to conduct this analysis.

The results of the subgroup analysis are shown in Figure 11. See Dr. Kim's review for the details of the model. None of the interaction terms between subgroup and treatment group were significant. Dr. Kim concludes that the "subgroup treatment effects are consistent across subgroups and with the overall treatment effect."

Figure 11– Forest plot of subgroup analysis using Bayesian Shrinkage methods



Source: Dr. Kim's review, figure 11

Data Quality and Integrity

There were no potential issues concerning the submitted data quality or integrity identified during the review of the efficacy results.

Efficacy Results – Secondary and other relevant endpoints

Table 14 shows Dr. Kim's analysis of the pre-specified secondary endpoints which were tested in a hierarchical sequence. Each analysis used a pattern mixture multiple imputation analysis

which was the same type of analysis which was use for the primary efficacy analysis. There was a statistically significant difference for the treatment difference of liraglutide versus placebo for the change in fasting plasma glucose from baseline to week 26 and a statistically significant difference in the odds ratio of responders who had an HbA1c<7% at week 26. The treatment difference between liraglutide-placebo in BMI SDS did not show statistical significance.

Table 14 – Analysis of secondary endpoints in hierarchical sequence

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)*

Source: Dr. Kim's review, table 7

The results of the secondary confirmatory endpoints are discussed in detail below.

Change in fasting plasma glucose at week 26

The baseline FPG was numerically higher for liraglutide (156.8 mg/dL) as compared to placebo (146.8 mg/dL). The adjusted mean change from baseline in FPG at 26 weeks was –19.39 for liraglutide and 14.439 for placebo, with an adjusted mean difference (lira-placebo) of -33.83 and a 95% confidence interval of (-55.74; -11.92), p-value 0.002; see Table 15. These findings support the conclusion of superiority of liraglutide vs. placebo for glycemic control because the upper bound of the 95% confidence interval for the treatment difference is below 0%.

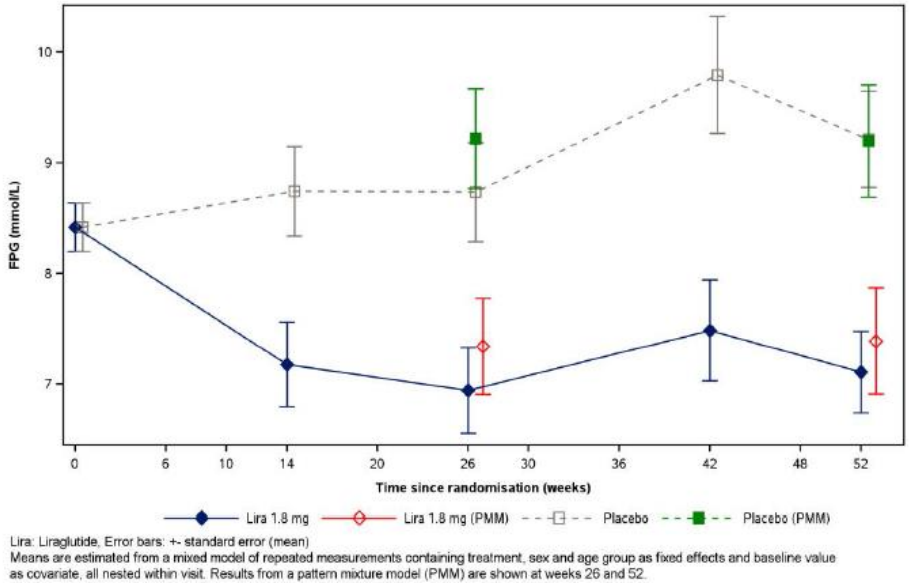
Table 15 - Change from baseline FPG at week 26-FPG-PMM-FAS

FPG (mg/dL)	FAS	N	Estimate	SE	95% CI	P-Value
Mean baseline						
Liraglutide	66	66	156.77	6.428		
Placebo	68	68	146.78	4.646		
Mean at week 26						
Liraglutide	66	66	132.31	7.863		
Placebo	68	68	166.14	8.098		
Mean change from baseline at week 26						
Liraglutide	66	66	-19.39	7.863		
Placebo	68	68	14.439	8.098		

Treatment difference at week 26: liraglutide-placebo			-33.83	11.179	[-55.74; -11.92]	0.002
Analysis using a pattern mixture model of observed data with missing observations imputed from the placebo arm based on multiple (x10.000) imputations. The data for week 26 were then analyzed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate. The estimated treatment differences and confidence intervals were combined using Rubin's formula. Source: CSR Table 11-3						

Evaluation of FPG by treatment week is shown in Figure 12. This figure shows that FPG declined gradually for liraglutide from randomization to week 26 with a possible increase at week 42 followed by decline at week 52. In comparison, the placebo arm had either stable FPG measures or increases in FPG throughout the trial.

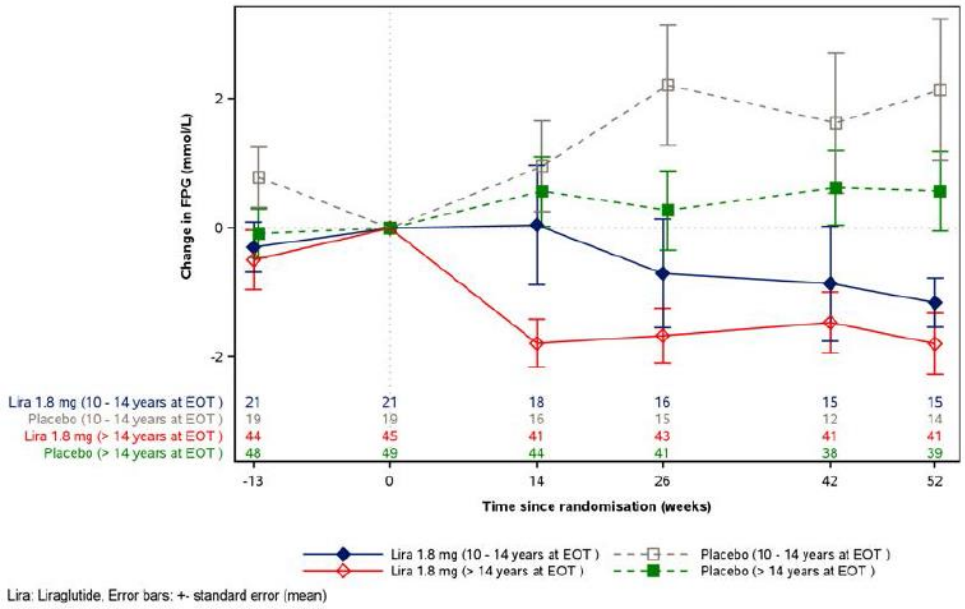
Figure 12 - FPG by treatment week- mean plot including primary analysis results- FAS



Source: CSR figure 11-3

Figure 13 shows the observed trends in FPG for the age groups of 10-14 years and >14 years. Although patients randomized to liraglutide in both age groups had a decline in FPG, there was a larger decline in FPG in patients >14 years of age.

Figure 13- FPG by treatment week-meal plot of observed change form baseline by age group 10-14 vs>14 years-FAS



Source: CSR figure 14.2.49

HbA1c<7% at week 26

The proportion of patients at baseline with HbA1c<7% was lower for liraglutide (21.2%) as compared to placebo (32.4%). At week 26, there were 63.7% and 36.5% of patients with an HbA1c<7% for liraglutide and placebo, respectively. The treatment odds ratio of liraglutide/placebo was 5.353 with a 95% confidence interval of (2.105; 13.615) p-value <0.001; see Table 16. These findings support the conclusion of superiority of liraglutide vs. placebo for glycemic control.

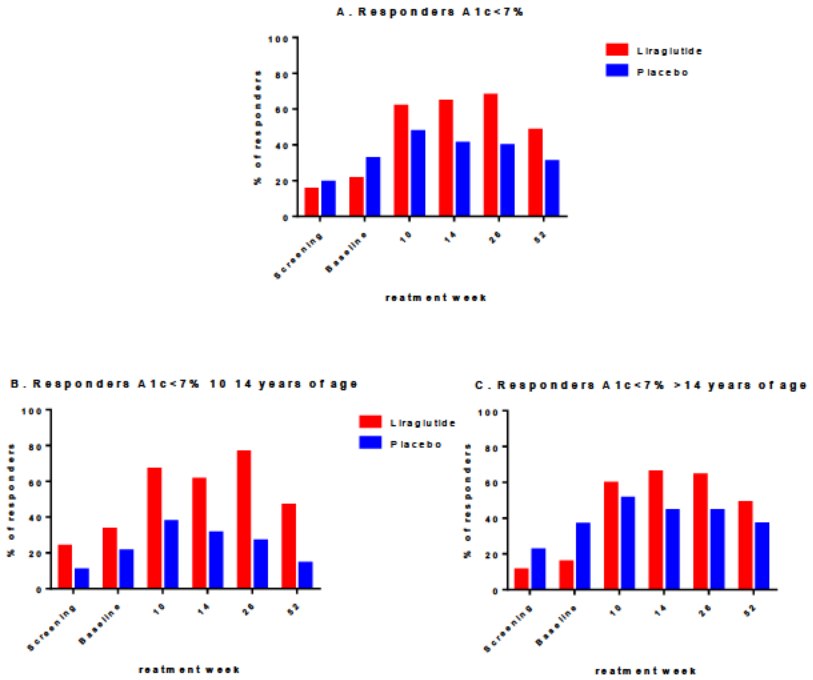
Table 16 – HbA1c<7% at week 26--PMM-logistic regression-FAS

			Responder				
Baseline HbA1c<7%	FAS	N	n	%	Estimate	95% CI	P-Value
Liraglutide	66	66	14	21.2			
Placebo	68	68	22	32.4			
LS mean Frequency (%) at week 26							
Liraglutide	66	66	42.0	63.7	2.251		
Placebo	68	68	24.8	36.5	0.421		
Treatment odds ratio Liraglutide/Placebo					5.353	2.105; 13.615	<0.001
The response status is derived from the corresponding continuous endpoints. Missing data is imputed from the analysis of the primary endpoint (pattern mixture model). For each imputed data set the binary response was analyzed in a logistic regression model using a logit link with treatment and stratification group (gender*age group) as fixed factors and baseline HbA1c as covariate. The estimated treatment effects and							

confidence intervals were combined using Rubin´s formula. Data after treatment discontinuation or start of rescue medication is included.

Figure 14 shows the responder analysis (HbA1c<7%) for the entire population and by subgroup of ages. Regardless of age group, the liraglutide arm had a larger proportion of patients with HbA1c<7% than placebo (after baseline). There were larger percentages of patients randomized to liraglutide in the 10-14 age group who achieved HbA1c<7% than in placebo.

Figure 14- Responder analysis HbA1c<7% by treatment week (A) and by subgroup ages (B and C)-FAS



Source: data from table 14.2.27 and 14.2.28 graphed by reviewer values are observed values

Reviewer's comments: the responder analyses suggest that specifically in the younger age group, use of liraglutide resulted in a larger proportion of patients achieving HbA1c<7%.

Change in BMI SDS at week 26

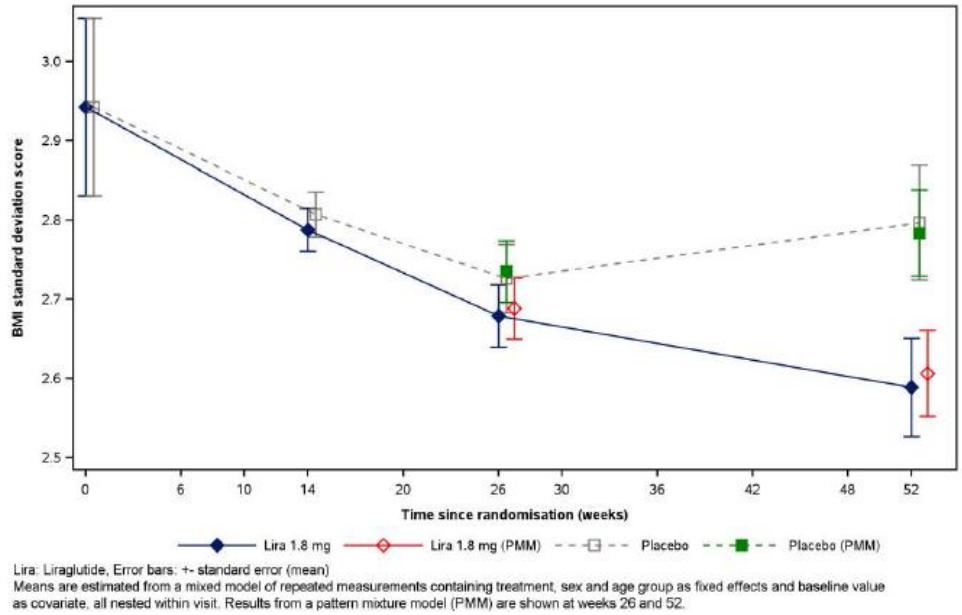
The baseline BMI SDS was numerically higher for liraglutide (3.03) as compared to placebo (2.86). The adjusted mean change from baseline in BMI SDS at 26 weeks was –0.254 for liraglutide and -0.208 for placebo, with an adjusted mean difference (lira-placebo) of -0.047 and a 95% confidence interval of (-0.153; 0.060) p-value 0.392; see Table 17. (b) (4)

Table 17 - Change from baseline at week 26-BMI SDS -PMM-FAS

BMI SDS	FAS	N	Estimate	SE	95% CI	P-Value
Mean baseline						
Liraglutide	66	66	3.03	0.181		
Placebo	68	68	2.86	0.135		
Mean at week 26						
Liraglutide	66	66	2.688	0.039		
Placebo	68	68	2.735	0.039		
Mean change from baseline at week 26						
Liraglutide	66	66	-0.254	0.039		
Placebo	68	68	-0.208	0.039		
Treatment difference at week 26: liraglutide-placebo			-0.047	0.055	-0.153; 0.060	0.392
Analysis using a pattern mixture model of observed data with missing observations imputed from the placebo arm based on multiple (x10.000) imputations. The data for week 26 were then analyzed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate. The estimated treatment differences and confidence intervals were combined using Rubin's formula. Source: CSR Table 11-5						

Figure 15 shows that BMI SDS declined over the initial 26 weeks for both liraglutide and placebo. At week 52, BMI SDS increased for placebo and continued to decline slightly for liraglutide.

Figure 15 – BMI SDS by treatment week- mean plot- FAS

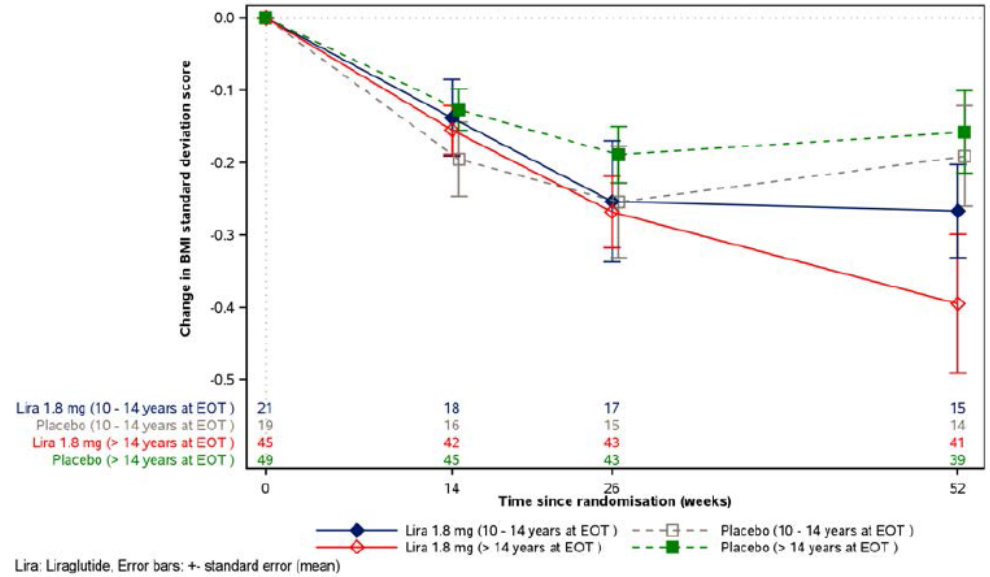


Source: CSR, figure 11-4

Figure 16 shows the observed trends in BMI SDS for the age groups of 10-14 years and >14 years. The change in BMI SDS over the first 26 weeks, regardless of age were similar for each

treatment arm; for both treatment arms there was a decline in BMI SDS. At week 52, patients randomized to liraglutide continued to experience a decrease in BMI SDS (for patients>14 years) or remained with a stable BMI SDS (for ages 10-14); whereas patients randomized to placebo (regardless of age) had increases in BMI SDS.

Figure 16- BMI SDS by treatment week- mean plot of observed change from baseline by age group 10-14 vs. >14 years- FAS



Source: CSR, figure 14.2.176

Reviewer's comment: The BMI SDS trends in the first 26 weeks suggests that regardless of medicinal intervention, trial participation may result in a decrease in BMI SDS across age groups. However continued improvements in BMI SDS beyond 26 weeks are seen in patients using liraglutide and no longer seen in patients using placebo.

Supportive secondary endpoints

Endpoints which were not in the testing hierarchy were considered "supportive" secondary endpoints by the Applicant, this terminology is also used in this section for consistency with the Applicant's documents.

Table 18 shows the treatment differences between liraglutide and placebo at 26 and 52 weeks for some of these endpoints. These analyses provide further insight into the effect of liraglutide in pediatric patients with type 2 diabetes; however, because the results were not controlled in a testing hierarchy, the findings have potential for a type I error; therefore, although p-values are shown in Table 18, these findings are not recommended for labeling.

Findings which favored liraglutide over placebo (and were significant) included change in HbA1c, FPG, BMI SDS, and body weight at week 52 and for change in mean 7-point SMPG for

week 26. No difference between treatment arms was noted for waist circumference, systolic blood pressure or diastolic blood pressure. There was no difference between treatment arms in analyses (not shown here) for change from baseline for total cholesterol, HDL cholesterol, and LDL cholesterol (at 26 nor 52 weeks).

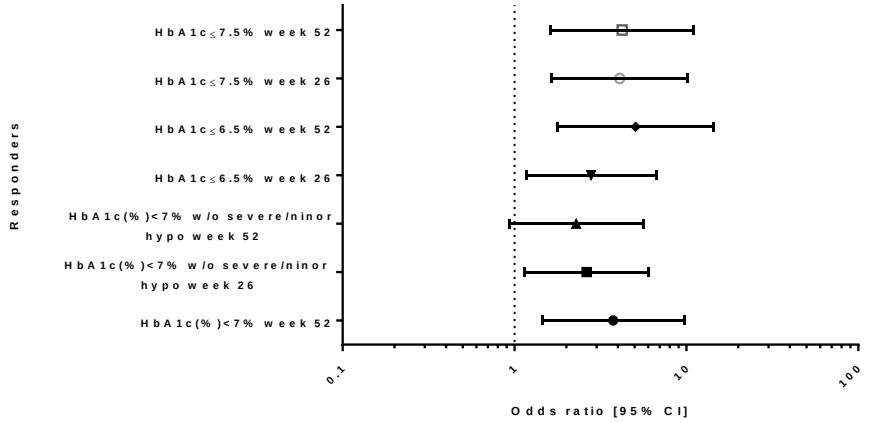
Table 18 – Supportive secondary endpoints- change from baseline at week 26 or 52 using a pattern mixture model with multiple imputation-FAS

	Estimate	SE	95% CI	P-Value
HbA1c%				
Treatment difference at week 52: liraglutide-placebo	-1.299	0.304	-1.895; -0.704	<0.001
FPG, mg/dL				
Treatment difference at week 52: liraglutide-placebo	-32.58	12.566	-57.21; -7.946	0.010
Mean 7-point SMPG, mg/dL				
Treatment difference at week 26: liraglutide-placebo	-29.66	8.593	-46.50; -12.82	<0.001
Treatment difference at week 52: liraglutide-placebo	-8.480	7.827	-23.82; 6.862	0.279
BMI SDS				
Treatment difference at week 52: liraglutide-placebo	-0.177	0.077	-0.327; -0.027	0.021
BMI, kg/m^2				
Treatment difference at week 26: liraglutide-placebo	-0.308	0.319	-0.932; 0.317	0.334
Treatment difference at week 52: liraglutide-placebo	-0.920	0.407	-1.718; -0.123	0.024
Body weight (kg)				
Treatment difference at week 26: liraglutide-placebo	-1.318	0.865	-3.013; 0.377	0.128
Treatment difference at week 52: liraglutide-placebo	-2.774	1.143	-5.014; -0.535	0.015
Waist circumference (cm)				
Treatment difference at week 26: liraglutide-placebo	-0.072	1.161	-2.347; 2.203	0.951
Treatment difference at week 52: liraglutide-placebo	-1.566	1.446	-4.399; 1.268	0.279
Systolic blood pressure (mmHg)				
Treatment difference at week 26: liraglutide-placebo	0.034	1.754	-3.404; 3.472	0.985
Treatment difference at week 52: liraglutide-placebo	-2.073	1.737	-5.477; 1.332	0.233
Diastolic blood pressure (mmHg)				
Treatment difference at week 26: liraglutide-placebo	-1.081	1.376	-3.778; 1.616	0.432
Treatment difference at week 52: liraglutide-placebo	-0.257	1.457	-3.112; 2.598	0.860

PMM - Analysis using a pattern mixture model of observed data with missing observations imputed from the placebo arm based on multiple (x10.000) imputations. The data for week 52 were then analyzed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate. The estimated treatment differences and confidence intervals were combined using Rubin's rule.
Source: CSR Table 14.2.60 (7point SMPG), 14.2.45 (FPG), Table 11-6 (HbA1c), Table 11-11 (BMI SDS), table 14.2.184 (BMI), 14.2.159 (body weight), 14.2.165 (waist circumference), 14.2.193 (systolic BP), and 14.2.199 (diastolic BP)

Additional responder analyses are shown in Figure 17. Responder analyses tended to favor liraglutide over placebo.

Figure 17- Responders-HbA1c treatment targets at week 26 and 52-logistic regression with imputation from PMM- FAS



Source: graph created by reviewer from Table 11-8

Reviewer's comments: the analyses for responders suggest that the treatment effect of liraglutide persisted into week 52.

Dose/Dose Response

The dose and exposure response relationship are discussed in section 4.5. The PK modelling analysis suggests that exposure between pediatric patients in *ellipse*™ and adults in previously conducted adult trials was similar. The evaluation of exposure-response suggests a concentration response relationship across the dosing range of 0.6 mg, 1.2 mg and 1.8 mg.

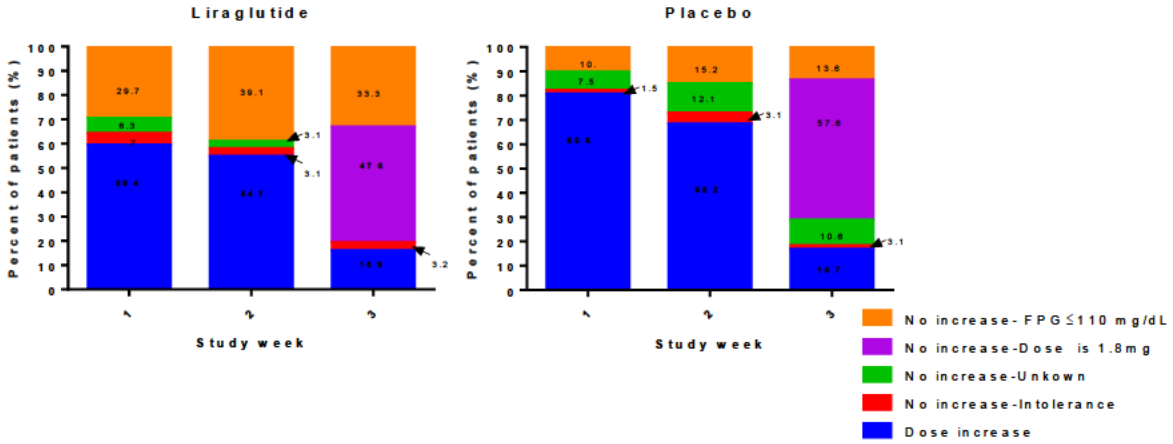
In this section I discuss the reasons for dose increases or lack of dose increases and the trends in investigational drug product doses by week.

ellipse™ was not designed to compare the response by dose level since patients were not randomized to the 3 dose levels in parallel, but rather were titrated to the dose level based on tolerability and glycemic criteria (see page 30). As previously discussed, the titration of IMP was limited to the first 3 weeks after randomization. To understand the rationale for not titrating the dose further, the Applicant was asked to provide the rationale for why the dose of IMP was not titrated; see Figure 18.

These stacked bar graphs show that in weeks 1 and 2, over 50% of patients for liraglutide and over 60% for placebo increased in dose. Approximately 30-40% of patients did not increase their dose in the liraglutide group due to having FPG values≤110 mg/dL; while 10-15% of patients in the placebo group had this rationale for not increasing their dose. In total there were 6 and 4 patients for liraglutide and placebo respectively who did not increase their dose

due to intolerance. Review of the reasons for intolerance were varied, although gastrointestinal symptoms were more commonly provided as reasons for liraglutide than placebo.[63] By week 3, only 16% and 17% of patients randomized to liraglutide and placebo, respectively had a dose increase, while 48% and 58% of patients randomized to liraglutide and placebo had reached a dose of 1.8 mg of IMP.

Figure 18 – Liraglutide and placebo dose escalation



Source: reviewer graphed data from table 12 from 2/1/19 information request\\CDSESUB1\evsprod\NDA022341\0417\m1\us

Reviewer's comment: Across the 3 weeks of titration of IMP, most of dose titration occurred in the first 2 weeks after randomization. Drug intolerance did not appear to be a significant factor that limited dose titration.

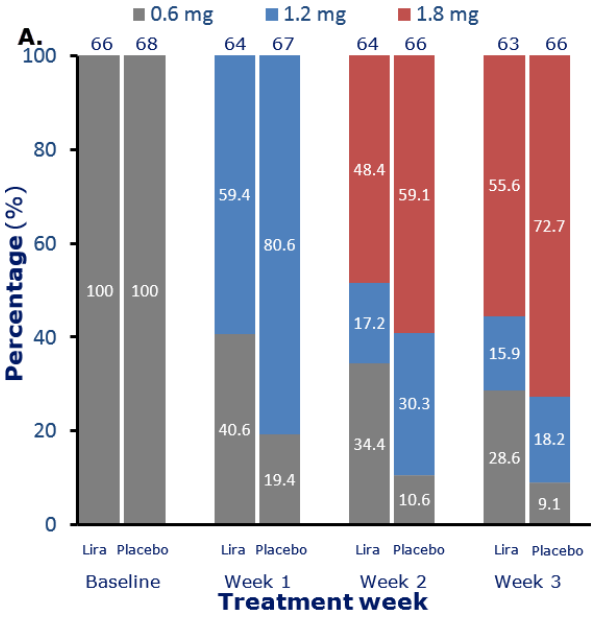
To provide some perspective on the primary efficacy results, I discuss the trends in investigational drug product doses below.

Figure 19 shows the doses of liraglutide and placebo used during the trial. The Applicant's analysis showed that by week 3, approximately 28.6%, 15.9%, and 55.6%, of patients were on 0.6, 1.2 and 1.8 mg of liraglutide and 9.1%, 18.2%, and 72.7% patients were on 0.6, 1.2 and 1.8 mg of placebo, respectively. Dr. Kim's analysis showed that at week 26 there was a larger proportion of patients who were on 1.2 mg or below in the liraglutide versus placebo arm (44% for liraglutide and 19.1% for placebo) while there were 47% of liraglutide and 64.7% of placebo patients using 1.8 mg of investigational drug by week 26.

[63] Reported in 3 liraglutide patients and 1 placebo patient.

An analysis by age subgroups is shown in Figure 37 (in the appendix). These data suggest that doses of IMP were increased according to the protocol for both age groups.

Figure 19 – Doses of liraglutide and placebo during the trial-A. Applicant's analysis for the first 3 weeks, B. Dr. Kim's analysis for week 26



B.

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: Figure A -Applicant power point slide from teleconference on December 20, 2018. Figure B-Dr. Kim's review table 6

Reviewer's comment: The spread of the 26-week doses suggests that although half of the patients used 1.8 mg at week 26 (47%), a considerable proportion of patients used doses of 1.2 mg (18.2%) and 0.6 mg (25.8%). Furthermore, age did not seem to limit the titration of liraglutide with large proportion of patients aged 10-14 and over 14 years achieving a dose ≥1.2 mg.

Of note, in a teleconference with the Applicant on December 20, 2018, the FDA asked the Applicant if they had performed an analysis of HbA1c reductions by dose. On a January 7, 2019 response[64], the Applicant replied that they had not performed a statistical analysis by liraglutide level, since patients reached dose levels based on tolerability and glycemic criteria (rather than being randomized to 0.6mg 1.2 mg or 1.8 mg) and therefore comparisons between dose levels were considered possibly biased.

Durability of Response

As discussed above, the glycemic lowering effects of liraglutide persisted to week 52.

[64] This IR is in DARRTs as an information request dated January 16, 2019

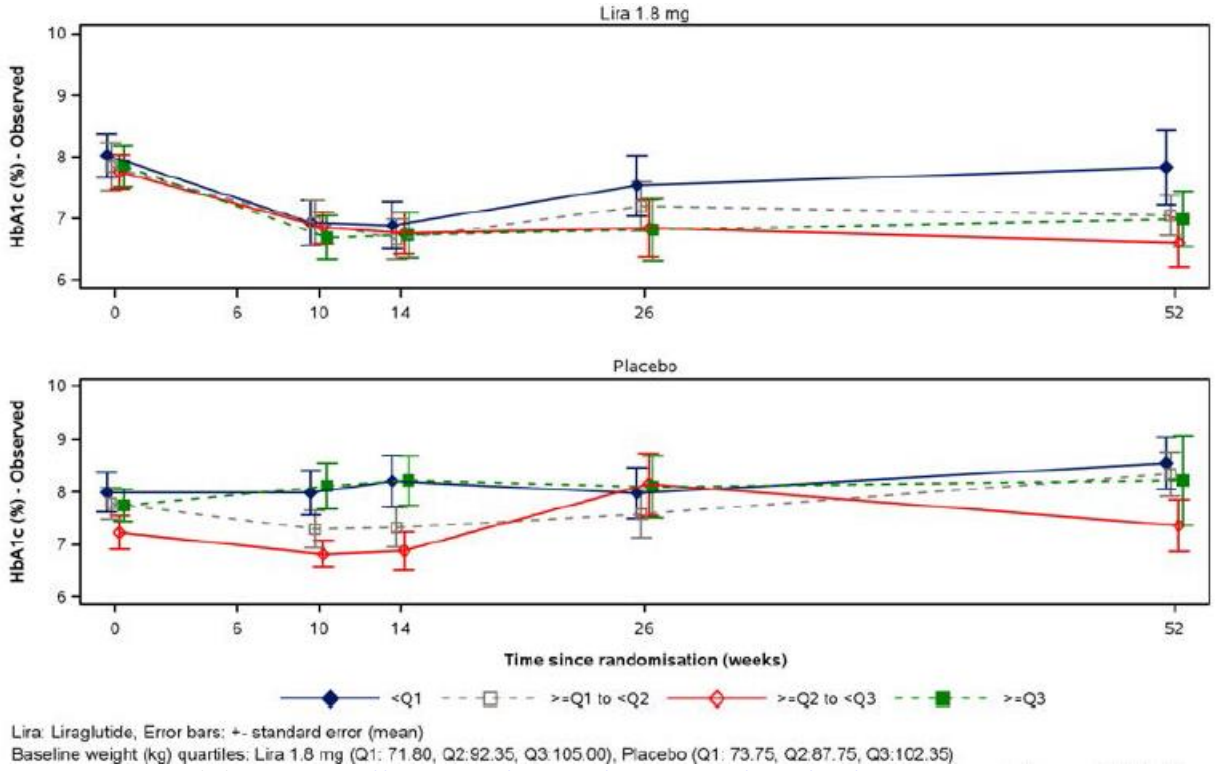
Persistence of Effect

The effect of liraglutide over time after treatment discontinuation was not assessed in this trial. Treatment discontinuation occurred at week 52, there was a safety follow up a week later, at week 53, however there was no scheduled assessment for HbA1c at week 53. There was no scheduled efficacy assessment for patients following up at 1 and 2 years after study end.

Additional Analyses Conducted on the Individual Trial

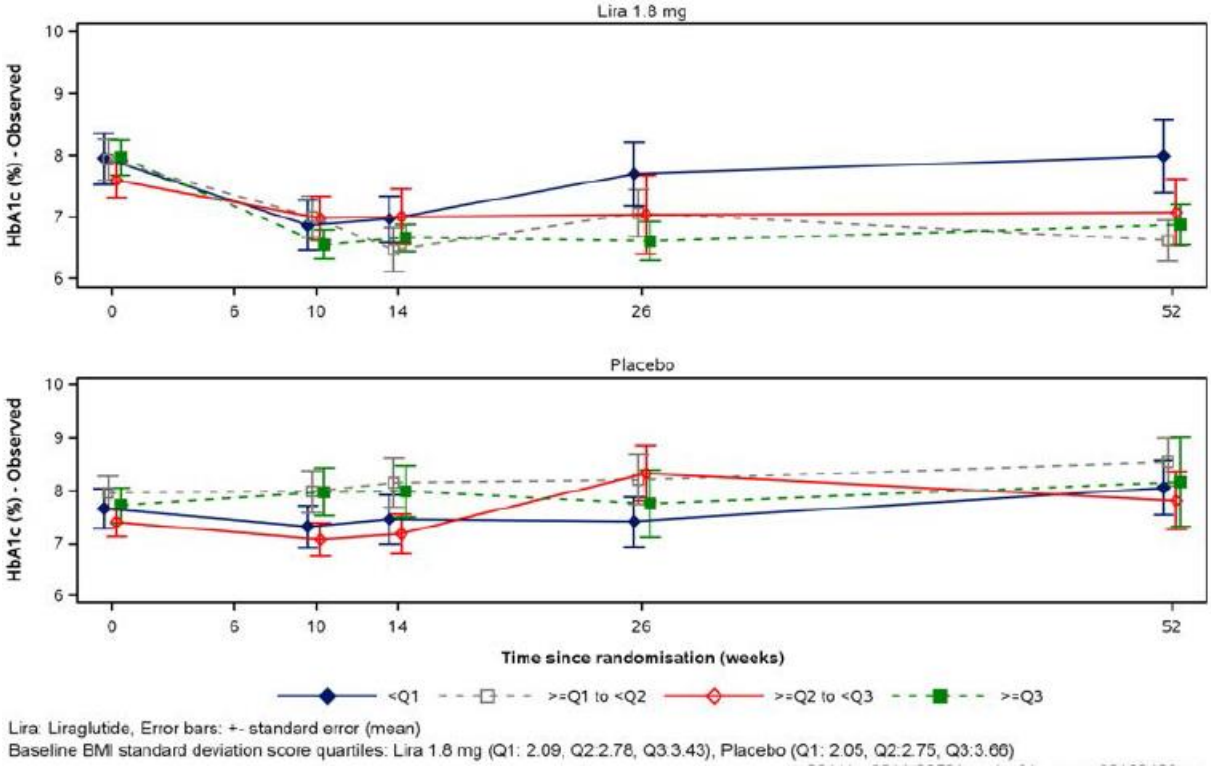
To better understand factors that may have affected the HbA1c findings, the Applicant was asked to perform exploratory analyses evaluating HbA1c as related to weight, BMI SDS and sex. These analyses are presented in the following graphs. Trends in the liraglutide arm, for both weight and BMI SDS suggest that the effect for all quartiles was similar from baseline to week 14. After week 14, it appears that the glycemic lowering benefit is maintained in the patient with higher body mass index (i.e. patients above the second quartile for weight or BMI SDS).

Figure 20 – HbA1c by treatment week- mean plot by weight quartiles at baseline-FAS



Lira: Liraglutide, Error bars: +- standard error (mean)
Baseline weight (kg) quartiles: Lira 1.8 mg (Q1: 71.80, Q2:92.35, Q3:105.00), Placebo (Q1: 73.75, Q2:87.75, Q3:102.35)
Source: IR dated 2/1/19 Figure 13, \\CDSESUB1\evsprod\NDA022341\0417\m1\us

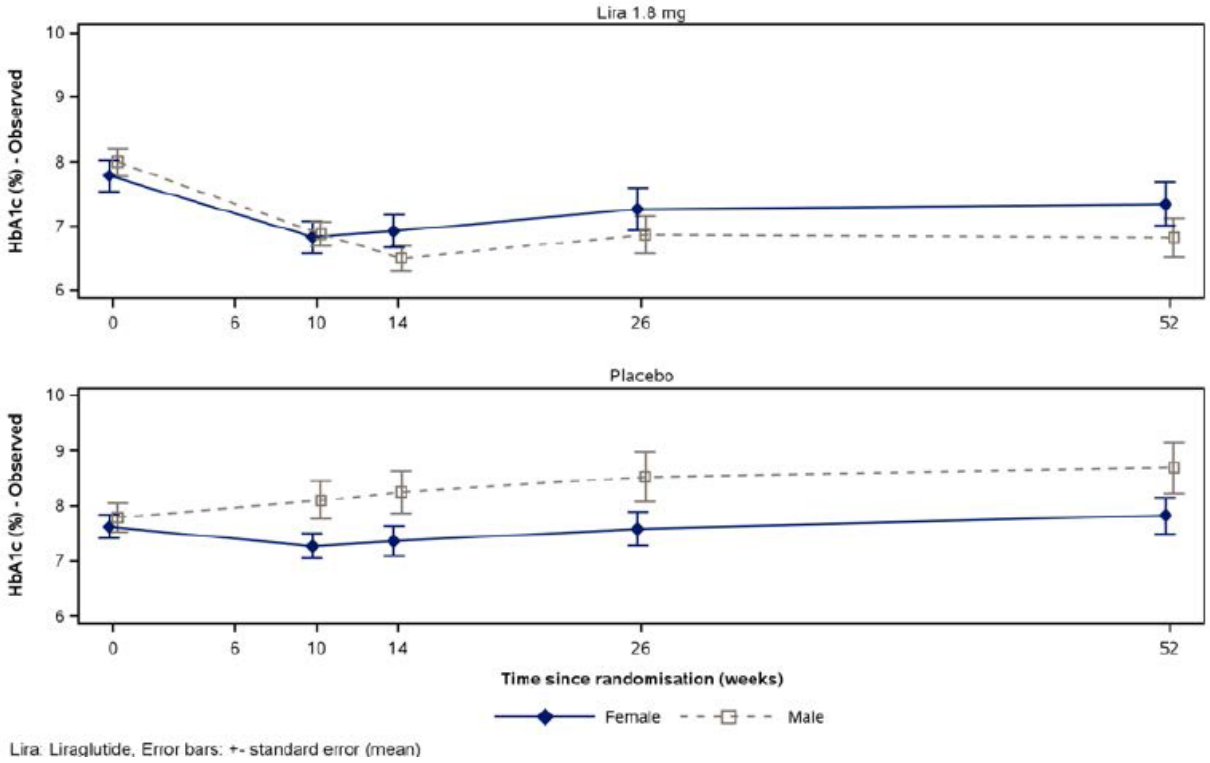
Figure 21 – HbA1c by treatment week- mean plot by BMI SDS quartiles at baseline-FAS



Source: IR dated 2/1/19 Figure 14, \\CDSESUB1\evsprod\NDA022341\0417\m1\us

An additional analysis evaluating HbA1c by sex (see Figure 22), suggests that the effect of liraglutide is similar for both males and females up to week 10. After week 10, however, the glycemic effect tends to favor males over females for the remaining of the trial.

Figure 22 – HbA1c by treatment week- mean plot by sex-FAS



Lira: Liraglutide, Error bars: +- standard error (mean)

Source: IR dated 2/1/19 Figure 15, \\CDSESUB1\evsprod\NDA022341\0417\m1\us

Reviewer's comments: although these trends suggest that there was improved glycemic lowering for higher BMI SDS patients and male patients, the subgroup evaluations (discussed previously) did not reveal that weight or sex had significant interactions in analysis of the change of HbA1c to week 26.

7. Integrated Review of Effectiveness

Since there was only one trial submitted for review, subsections not applicable to this submission have been deleted. [65]

7.3 Integrated assessment of effectiveness

ellipse^{TM} (trial NN2211-3659) was a randomized placebo-controlled trial, with a 26- week double blinded period, followed by a 26 week open labeled extension period, in pediatric (ages 10-17 years) patients with type 2 diabetes. Liraglutide or placebo at a maximum tolerated dose (0.6 mg, 1.2 mg, and 1.8mg) was titrated over the course of 3 weeks and was added on to

[65] Deleted sections include: 7.1 Assessment of efficacy across trials, 7.1.1 primary endpoints, 7.1.2 secondary endpoints, 7.1.3. subpopulations, 7.1.4 dose and dose-response, 7.1.5 Onset, duration and durability of efficacy effects, 7.2 additional efficacy considerations, 7.2.1 considerations on benefit in post market setting, and 7.2.2 other relevant benefits.

metformin with or without basal insulin therapy. Titration was dependent on average fasting plasma glucose values being above 110 mg/dL and drug tolerability. During the open-labeled period, investigators and patients were unblinded; patients randomized to liraglutide continued use of liraglutide with metformin with or without basal insulin therapy, while patients randomized to placebo discontinued placebo and continued on metformin with or without basal insulin therapy.

Of the 307 patients that were screened, 56% were screen failures. Reasons for screen failures included not fulfilling the HbA1c criteria (with most patients having an HbA1c<6.5%), and elevation of alanine aminotransferase values above 2.5 times the upper normal range. A total of 135 patients were randomized and 134 patients were exposed to investigational drug product.

Of the randomized patients, a larger proportion of patients randomized to liraglutide, as compared to placebo, completed the 26- and 52-week treatment period. Approximately a third of patients came from the United states; the mean chronological age was 14.6 years, and the mean HbA1c was 7.78%.

At 26 weeks, at least a quarter of patients were using 0.6mg of liraglutide as compared to 9% of placebo patients; while the largest proportion of patients was using 1.8mg (i.e. 47% and 65% of liraglutide and placebo patients respectively). In the liraglutide arm, approximately 30% of patients reported a lack of dose increase due to having fasting plasma glucose values ≤ 110 mg/dL; intolerance was not a common reason given for lack of dose increase.

The use of insulin (including for rescue) was lower for liraglutide than placebo. Also, insulin doses for the liraglutide arm remained relatively stable during the trial as compared to placebo, whereas the insulin doses for placebo tended to increase throughout the trial.

The primary efficacy analysis showed that at 26 weeks, the HbA1c change from baseline was -0.64 for liraglutide and 0.42 for placebo. The treatment difference between liraglutide and placebo met the pre-specified superiority margin of 0%, with a treatment difference for liraglutide-placebo of -1.06 and a confidence interval of -1.65 to -0.46. Responder and subgroup analyses (including patients aged 10-14) were overall consistent with the primary endpoint findings (i.e., favoring liraglutide over placebo).

In the statistical hierarchical testing scheme, in addition to the primary endpoint, the following endpoints were also confirmed for superiority as compared to placebo at week 26: change in fasting plasma glucose and proportion of patients with HbA1c<7%.

8. Review of Safety

8.1. Safety Review Approach

The review of safety focuses on the entire 52-week trial period of the *ellipse*^{TM} trial. The focus is on patients in the safety analysis set (SAS) experiencing treatment emergent adverse events (TEAEs) as defined below. For evaluation of subject level data and summary data, the Applicant's adverse event dataset (adae.xpt) was interrogated and results were compared to the Clinical Trial Report. When appropriate, information requests were sent to the Applicant for clarifications or additional analyses.

Dr. Kim, from the office of Biostatistics performed additional safety analysis for hypoglycemia and height SDS.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Exposure to liraglutide in the *ellipse*^{TM} trial is shown in Table 19 and Figure 23 (for a discussion on dose exposure refer to page 67). At 26 weeks, approximately 91% and 85% of patients randomized to liraglutide and placebo, were still participating in the trial. The proportion of patients in the trial declined over time, at 52 weeks, there were approximately 61% and 54% of patients randomized to liraglutide and placebo, respectively. As discussed earlier, patients randomized to placebo, discontinued placebo therapy after week 26 and continued with metformin ± basal insulin.

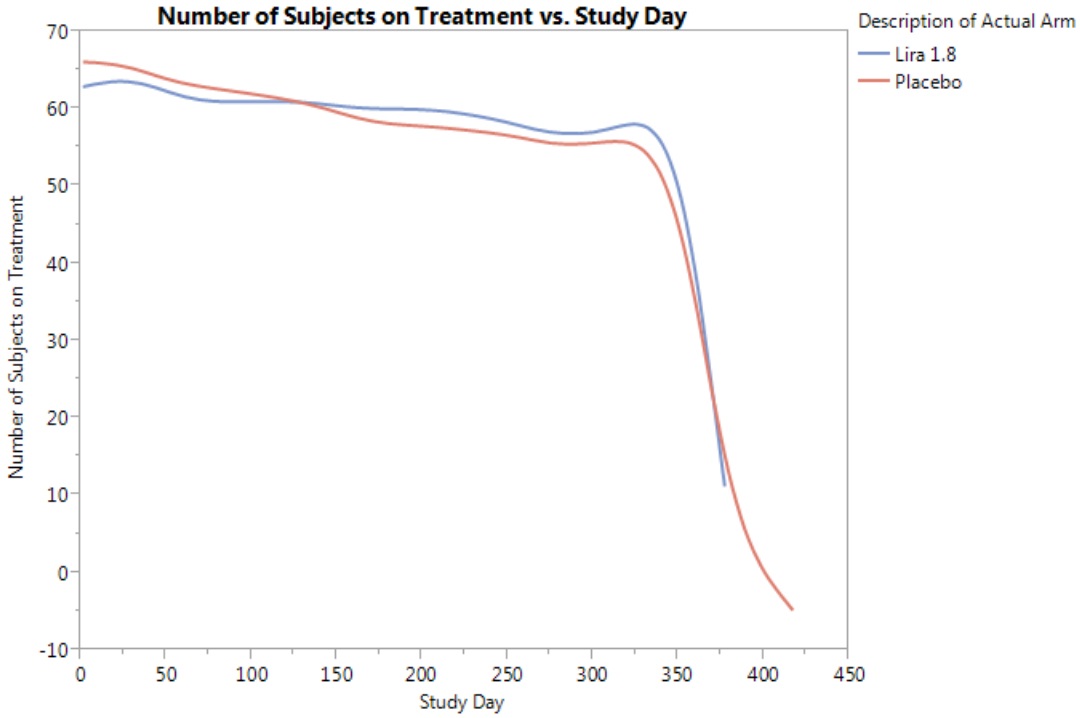
Table 19 – Summary of exposure by weeks and treatment-FAS

	liraglutide	Placebo
Number of subjects with duration of study treatment by category [n(%)]	N (%)	N (%)
Missing duration	0	0
>= 1 Weeks	64 (97)	68 (100)
>= 6 Weeks	63 (95.5)	64 (94.1)
>= 14 Weeks	61 (92.4)	62 (91.2)
>= 20 Weeks	61 (92.4)	61 (89.7)
>= 26 Weeks	60 (90.9)	58 (85.3)
>= 36 Weeks	59 (89.4)	57 (83.8)
>= 42 Weeks	57 (86.4)	55 (80.9)
>= 48 Weeks	56 (84.8)	54 (79.4)
>= 52 Weeks	40 (60.6)	37 (54.4)

Source: 2/1/19 IR, table 14: \\CDSESUB1\evsprod\NDA022341\0417\m1\us

Figure 23 shows that throughout the trial, the number of patients participating in the trial was slightly higher for placebo until approximately 4 months, after which, the trend reversed; patients in the liraglutide arm was slightly higher than the placebo arm.

Figure 23- Exposure over time- SAS



Source: reviewer generated figure from Applicant sdtm datasets

Reviewer's comment: Overall, the exposure to liraglutide is adequate to make assessments regarding common safety signals in this program. The reports for the 2- and 3-year safety follow up are not included in this submission; these reports may be more helpful in elucidating more rare safety signals and effects on growth or maturation.

8.2.2. Relevant characteristics of the safety population:

As noted earlier, the racial make-up of the population in *ellipse*^{TM} differs from the racial make-up in the US population that has a higher prevalence of T2DM in racial minority groups. Nonetheless, the development program has sufficient safety data in a broad enough population to allow generalizability of the safety findings to the US pediatric T2DM population. As previously discussed (and shown in Table 7), characteristics that allow for representation of the US population include: the inclusion of at least 30% of patients aged 10-14 years, the large proportion of female patients (>60%), and an adequate representation of Hispanics (~30%).

8.2.3. Adequacy of the safety database:

The size and assessments provided in the safety database is adequate. The trial size and safety assessments were previously reviewed by the Division and agreed upon in a written request.

Further safety assessments (not part of the written request) at 1 and 2 years after trial completion, for patients exposed to liraglutide>3 months, is expected to be submitted when these assessments are completed.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

I did not identify any important issues regarding data quality that affected the safety review. An assessment of random samples of subject level data of adverse events did not identify any issues when comparing case report forms, dataset information, and narratives. The submission was well organized, and information was easy to find.

8.3.2. Categorization of Adverse Events

All AEs were coded using MedDRA version 21.0.

AEs were defined as any untoward medical occurrence in the patient administered a product that does not necessarily have a causal relationship to treatment and includes a clinical worsening of a concomitant illness, and a laboratory abnormality. The severity (mild/moderate/severe)[66] of AEs was assessed in addition to the outcome of the event (recovered/resolved, recovering/resolving, recovered/resolving with sequelae, nor recovered/not resolved, fatal or unknown).[67]

An SAE was an event that resulted in death, a life-threatening experience, in-patient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability

[66] Mild - no or transient symptoms, no interference with the subject's daily activities. Moderate - marked symptoms, moderate interference with the subject's daily activities. Severe - considerable interference with the subject's daily activities; unacceptable.

[67] Definitions of final outcome of an AE: Recovered/resolved - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent. Recovering/resolving - The condition is improving, and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE. Recovered/resolved with sequelae - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE. Not recovered/not resolved - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known. Fatal - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE. Unknown - This term is only applicable if the subject is lost to follow up.

or incapacity, a congenital anomaly/birth defect or an important medical event based on medical judgment.

MESIs focused on *a priori* concerns, and included the following: medication errors concerning trial products, suspected transmission of an infectious agent via a trial product, altered renal function, acute pancreatitis/suspicion of acute pancreatitis, elevated lipase>3 x UNR, any calcitonin≥20 ng/L, neoplasms excluding thyroid neoplasms, thyroid disease including thyroid neoplasm, severe hypoglycemia, immunogenicity (immune complex disease, and allergic reactions), and AEs leading to withdrawal.

Treatment emergent adverse events were defined as events that had an onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment, with the exception of hypoglycemia events, for which the TEAE was defined as events on or after the first day of exposure to randomized treatment and no later than one day after the last day on randomized treatment.

Overall the definitions used to categorize adverse events were adequate; review of the investigators' verbatim terms and correlation to preferred terms was also adequate.

8.3.3. Routine Clinical Tests

Table 20 shows the routine clinical laboratory tests that were performed throughout the duration of the study. The laboratory tests were performed at a central laboratory or a special laboratory (for PK and antibody samples). The central laboratory results were to be sent to the investigator on an ongoing basis. If a result was outside the normal range, the investigator was to judge and document if the abnormality was considered clinically significant or not.

Laboratories performed on visits 1, 7, 13, and 25 were collected with subjects in a fasting state.

A laboratory abnormality that was considered clinically significant, such as suggesting a disease or organ toxicity was considered an adverse event (as defined above).

The written request specified that the HbA1c should be centrally analyzed using a NGSP certified hemoglobin A1c assay[68].

The reference range for the laboratories were age dependent.

[68] Per an information request received on 3/28/19 the applicant clarified that the HBA1c were centrally analyzed by (b) (4) which is a certified NGSP level 1 laboratory for the assessment of HbA1c. The NGSP certification is renewed every year.

Table 20- Clinical laboratory tests

Glucose related laboratories HbA1c, fasting plasma glucose, fasting insulin, pro-insulin, glucagon, C-peptide	**Fasting lipids** Total cholesterol, LDL cholesterol, HDL cholesterol, VLDL, triglycerides, free fatty acids
Hematology Hemoglobin, hematocrit, thrombocytes, erythrocytes, leucocytes, differential cell count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)	**Pregnancy test in females of child bearing potential** Beta-human chorionic gonadotropin Urine pregnancy tests
Biochemistry Creatinine, creatinine phosphokinase (CK), albumin, bilirubin (total), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Urea, sodium, potassium, calcium, lipase and amylase	**Hormones** Calcitonin, prolactin, FSH, Estradiol (females only), LH, testosterone (males only), DHEAS, CEA, IGF-1, IGFBP-3, TSH
Antibodies Anti-liraglutide antibodies Anti-insulin antibodies: insulinoma associated protein 2 (IA1), anti-glutamic acid decarboxylase (anti-GAD)	**Urinalyses** Microalbumin, creatinine, protein, glucose, ketones, pH, albumin-to creatinine ratio
Other laboratory tests HIV, Hepatitis B, hepatitis C, alcohol and drug screen **Bone metabolism markers** Bone-specific alkaline phosphatase, Serum type 1 procollagen (P1NP), N-telopeptide (NTX) and C-telopeptide (CTX)	

Source: CSR, table 9-5

Reviewer's comment: Overall, the safety assessment methods and time points seem reasonable and are adequate for the population enrolled in this trial.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in the trial.

8.4.2. Serious Adverse Events

There were 15 serious adverse events in the trial. Nine patients randomized to liraglutide had 10 events, while 4 patients randomized to placebo had 5 events; see Table 21. SAEs varied across SOC. The two events in the Gastrointestinal disorders SOC were seen only in the liraglutide arm. SAEs related to loss of glycemic control (included the following PTs: "hyperglycemia," "Glycosylated hemoglobin increased," and "Diabetes mellitus inadequate control") occurred in 2 (3%) patients randomized to liraglutide and 3 (4.5%) patients randomized to placebo.

Review of the narratives for the SAEs in the liraglutide arm revealed causality to liraglutide use for the PT term "Diarrhea"[69] in a patient who developed symptoms after re-starting full dose liraglutide and metformin without titration.

Table 21 – Serious adverse events-SAS

		Description of Actual Arm					
		Liraglutide			Placebo		
Body System or Organ Class	**Dictionary-Derived Term**	**N (%)**	**Event**	**R**	**N (%)**	**Event**	**R**
TOTAL		9 (13.6)	10	168	4 (5.9)	5	85
Infections and infestations	Abscess neck	1 (1.5)	1	17	0	0	0
	Appendicitis perforated	0	0	0	1 (1.5)	1	17
	Pneumonia	0	0	0	1 (1.5) ^	1	17
	Viral infection	1 (1.5)	1	17	0	0	0
Metabolism and nutrition disorders	Hyperglycemia	1 (1.5)	1	17	1 (1.5) ^	1	17
	Diabetes mellitus inadequate control	0	0	0	1 (1.5)	1	17
Gastrointestinal disorders	Abdominal pain	1 (1.5)	1	17	0	0	0
	Diarrhea	1 (1.5)*	1	17	0	0	0
Investigations	Glycosylated hemoglobin increased	1 (1.5)	1	17	1 (1.5)^	1	17
Ear and labyrinth disorders	Vertigo	1 (1.5)	1	17	0	0	0
Musculoskeletal and connective tissue disorders	Scoliosis	1 (1.5)	1	17	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Fibroadenoma of breast	1 (1.5)	1	17	0	0	0
Nervous system disorders	Nervous system disorder	1 (1.5)	1	17	0	0	0

*Patient had a dose reduction as a result of this SAE
^Patients either had the drug withdrawn or drug interrupted as a result of the SAE
Source: Reviewer generated using AE dataset.

Reviewer's comment: the PT's across serious adverse events are either consistent with the AEs expected in this population (i.e. "scoliosis"), due to worsening of glycemic control, or related to use of liraglutide (i.e. gastrointestinal adverse events).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The case report forms were manually reviewed for each of the 25 patients who did not complete the trial to identify patients who may have withdrawn due to adverse events. There were no additional patients identified other than those identified in Table 6. There were 3 patients[70] (1 for liraglutide and 2 for placebo) who did not complete the trial due to adverse

[69] Patient ID (b) (6) (randomized to liraglutide): was a 16-year-old female treated with liraglutide. Patient discontinued use of liraglutide and metformin for an undetermined number of days and was restarted on 1.8 mg of liraglutide and 2000 mg of metformin without titration. After re-starting drugs, she developed vomiting and diarrhea. Patient was admitted due to symptoms for monitoring and IV hydration.
[70] Subject ID (b) (6) (liraglutide), subject ID (b) (6) (placebo), subject ID (b) (6) (placebo)

events (2 patients were noted to have discontinued for "non-compliance," but had hyperglycemic events in the investigator explanation for withdrawal, and hence are counted as having withdrawn due to adverse events), the third patient, randomized to placebo withdrew due to an increase in HbA1c.

Although there was no difference in discontinuations due to gastrointestinal–related adverse events, numerically, more gastrointestinal adverse events resulted in dose reduction, or interruption for liraglutide as compared to placebo, see Table 28 (in appendix).

Reviewer's comment: there were few discontinuations due to adverse events in *ellipse*™. Unlike the adult studies, where withdrawals due to gastrointestinal adverse reactions were higher for liraglutide than placebo (labeled under section 6.1 of the Victoza PI), there were no withdrawals due to gastrointestinal adverse events in *ellipse*™. Hyperglycemia was the only adverse event reported as resulting in discontinuation for both liraglutide and placebo.

8.4.4. Significant Adverse Events

This section discusses hypoglycemia; refer to section 8.4.5 for a discussion of adverse events by severity.

Hypoglycemia Adverse Events
Hypoglycemia is considered a significant adverse event for antidiabetic treatment therapies. This section will summarize the methods of capture, definitions, and hypoglycemia findings.

All hypoglycemic episodes were captured in the hypoglycemic report forms, only SAEs of hypoglycemia were listed as AEs.

Plasma glucose was to be measured when a hypoglycemic episode was suspected; all plasma glucose values≤ 70 mg/ or blood glucose values >70mg/dL with symptoms of hypoglycemia were to be recorded.[71]

The hypoglycemia definitions are shown in Table 22**.** The definitions include the American Diabetes Association definitions for hypoglycemia and the Novo Nordisk hypoglycemia, (a hybrid between documented symptomatic and asymptomatic hypoglycemia). In addition, hypoglycemia with a glucose concentration <54 mg/dL with or without symptoms, is also discussed because this hypoglycemia (i.e. "level 2" hypoglycemia) has been recently defined as a clinically important hypoglycemia definition; see the 2016 American Diabetes Association

[71] The record was to contain the plasma glucose before treating the episode, date/time, symptoms, ability of self-treatment, antidiabetic treatment prior to episode and last meal and relationship to exercise

Position Statement[72] and the 2018 ISPAD Clinical Guidelines.[73] Note that hypoglycemia with a glucose concentration <54 mg/dL was not predefined in the study protocol.

Table 22 – Classification of hypoglycemia

	Symptoms? (Yes/No)	Glucose value	Patient able to self-treat (Yes/ No*)
ADA classification: **Severe hypoglycemia**	Yes	not necessary	No
ADA classification: **Asymptomatic hypoglycemia**	No	≤70 mg/dL	Yes
ADA classification: **Documented symptomatic hypoglycemia**	Yes	≤70 mg/dL	Yes
ADA classification: **Relative hypoglycemia**	Yes	>70 mg/dL	Yes
ADA classification: **Probable hypoglycemia**	Yes	No measurement	Yes
Novo Nordisk hypoglycemia Minor hypoglycemia	Yes or No	<56 mg/dL	Yes
*No if food, glucagon, IV glucose was administered by another person due to severe central nervous system dysfunction associated with hypoglycemia			

The review of hypoglycemia addressed a broad assessment of hypoglycemia as an assessment across categories, and a narrower assessment which includes a focus on severe hypoglycemia and hypoglycemia events< 54 mg/dL.

Table 23 shows the hypoglycemia findings across hypoglycemia categories.

Table 23- Hypoglycemic episodes -TEAEs-SAS

	Liraglutide				Placebo				Total			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	66				68				134			
PYE	59.63				59.63				118.80			
Hypoglycemia <54 mg/dL with or without symptoms	14	21.2	20	335	6	8.8	10	169	20	14.9	30	253
Minor hypoglycemia	16	24.2	23	386	7	10.3	13	220	23	17.2	36	303

[72] https://doi.org/10.2337/dc16-2215
[73] Abraham, MB, Jones, TW, Naranjo, D, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2018; 19(Suppl. 27): 178– 192. https://doi.org/10.1111/pedi.12698

ADA classification	30	45.5	160	2683	17	25	63	1065	47	35.1	223	1877
severe	0	0	0	0	1	1.5	1	17	1	0.7	1	8
Asymptomatic	21	31.8	75	1258	12	17.6	23	389	33	24.6	98	825
Documented symptomatic	19	28.8	55	922	6	8.8	26	439	25	18.7	81	682
Relative	1	1.5	21	352	0	0	0	0	1	0.7	21	177
Probable symptomatic	3	4.5	3	50	3	4.4	3	51	6	4.5	6	51
Unclassifiable	3	4.5	6	101	4	5.9	10	169	7	5.2	16	135

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of events, R: Rate (number of events divided by patient years of exposure multiplied by 1000), PYE: Patient years of exposure (1 PYE = 365.25 days).
The entire treatment period is from randomization to week 52 visit, including both days.
Source: CSR- Table 12-18 and IR dated 2/13/19

Across hypoglycemia categories (except for severe hypoglycemia), there was a higher number of patients and hypoglycemia events for the liraglutide arm as compared to the placebo arm.

The one event of severe hypoglycemia in the trial occurred in a patient randomized to placebo;[74] and was likely a result of use of basal insulin and exercise.

To better understand the differences in hypoglycemia between liraglutide and placebo, the following evaluations were performed (and are discussed in detail below):

- Evaluation across hypoglycemia definitions for exploratory statistical treatment arm differences
- Evaluation of hypoglycemia by insulin use
- Evaluation of the relationship of baseline HbA1c and change in HbA1c at week 26
- Evaluation of hypoglycemia trends over time

Evaluation across hypoglycemia definitions for exploratory statistical treatment arm differences

To better understand the treatment differences in hypoglycemia, Dr. Kim performed exploratory analyses comparing the incidence of hypoglycemia across hypoglycemia definitions; see Table 24. The nominal p-values from Fisher's exact tests and risk ratio with a 95% CI using a negative binomial regression model were presented for descriptive purposes. The findings suggest that the proportion of patients and event rates of hypoglycemia were higher for liraglutide as compared to placebo across definitions, with the exception of severe hypoglycemia, which as noted above, had only one case in the placebo arm. Dr. Kim notes that

[74] ID (b) (6) (Placebo)15-year-old male developed severe hypoglycemia on day 67. The episode occurred in relation to exercise and was not self-treated. The patient received oral administration of oral carbohydrates by another person. Blood glucose was 46 mg/dL at the time of the event. Patient was being treated with metformin 2000 mg and 35 units of insulin glargine. No change was made to the dose of placebo as a result of the episode; the patient completed the trial.

of the 30 patients in the liraglutide arm with a hypoglycemia event (i.e. ADA classification), 12 patients or 40% of the liraglutide patients with an event had a baseline HbA1c less than 7%. These same 12 patients had 75 hypoglycemia events which made up approximately 47% of the total 160 hypoglycemia episodes.

Table 24- Fisher's exact test comparing the incidence of hypoglycemia across definitions (FDA analysis)

	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)

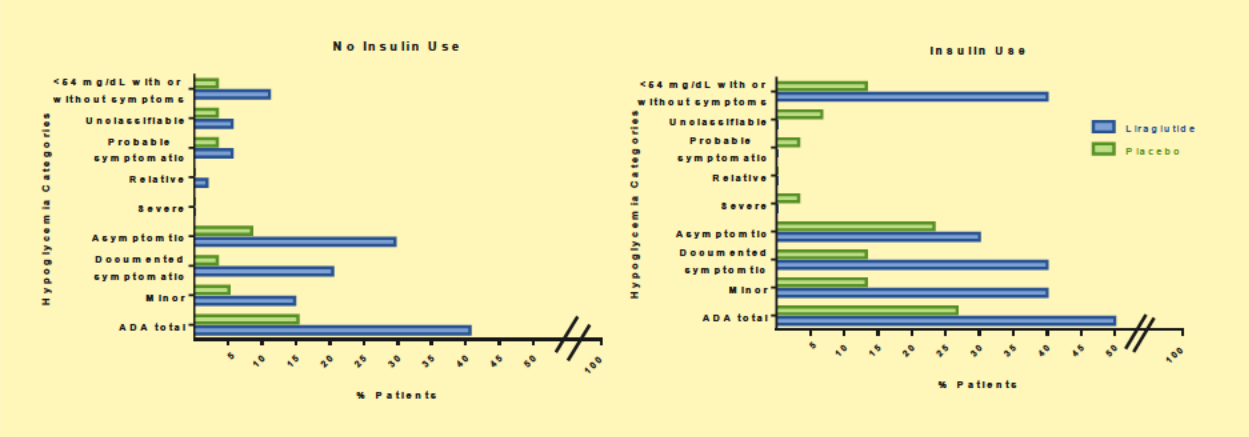
**Minor: the applicant's definition of blood glucose < 3.1 mmol/L (56 mg/dL) with or without symptoms*
***NB negative binomial regression model for count data with stratification factor and offset of log transformed treatment duration*

Source: Dr. Kim's review, table 9

Evaluation of differences in hypoglycemia by insulin use

Figure 24 shows the proportion of patients experiencing hypoglycemia by basal insulin. Across hypoglycemia definitions, there was a higher proportion of patients in the liraglutide arm with hypoglycemia as compared to placebo, regardless of basal insulin use.

Figure 24 – Hypoglycemic episodes with/without insulin treatment during the entire treatment period- treatment emergent-summary- SAS

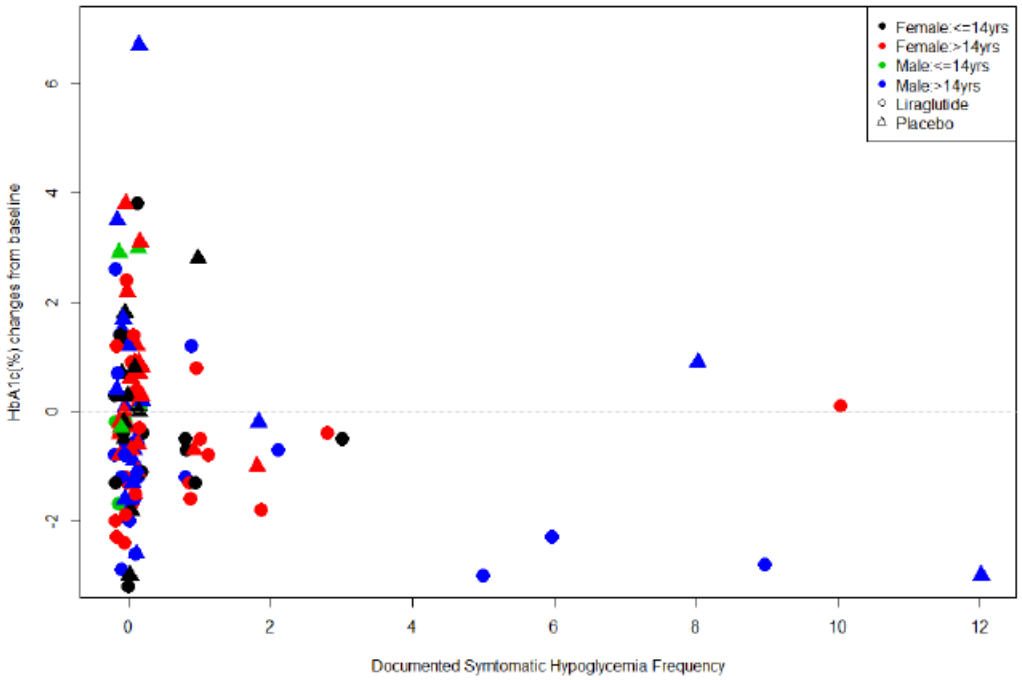


Source: CSR reviewer graphed results from Table 14.3.1.37 and IR dated 3/1/19: \\CDSESUB1\evsprod\NDA022341\0424\m1\us (table 3); the total number of patients with hypoglycemia associated with use of insulin for liraglutide was 20, and 30 for placebo; the total number of patients with hypoglycemia not associated with use of insulin was 54 and 59 for liraglutide and placebo respectively.

Evaluation of the relationship of baseline HbA1c and change in HbA1c at week 26

Dr. Kim performed analyses evaluating the benefit of HbA1c reduction at week 26 to the risk of hypoglycemia during the entire treatment period. As shown in Figure 25, a larger proportion of patients experienced hypoglycemia with a larger reduction in HbA1c at week 26 with liraglutide as compared to placebo.

Figure 25 - Change in HbA1c and number of documented symptomatic hypoglycemia- FAS population



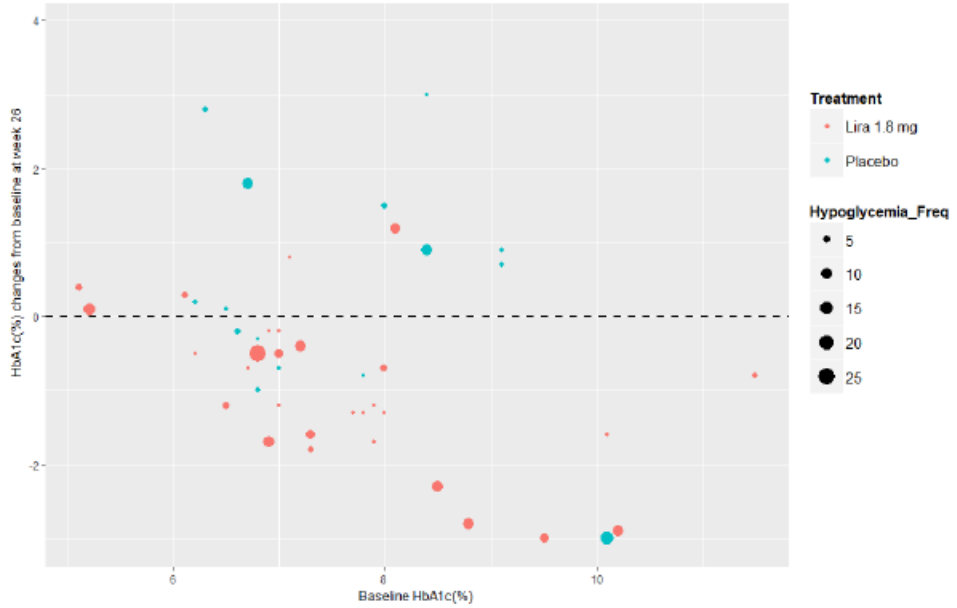
Source: Dr. Kim's review, figure 6

Dr. Kim also performed analyses evaluating the change in HbA1c, baseline HbA1c and frequency of hypoglycemic episodes for all hypoglycemia episodes (i.e. ADA classification) during the entire treatment period; see Figure 26. My interpretation of this figure is that the risk of hypoglycemia for patients randomized to liraglutide was higher for patients with a baseline HbA1c of ~7% or below, whose HbA1c decrease some, or whose HbA1c remained stable at week 26. A second liraglutide-treated group with a higher risk of hypoglycemia was patients with a higher baseline HbA1c, (i.e., HbA1c>8%) who experienced a larger HbA1c decrease at week 26 (i.e. decrease of HbA1c of ~2%). The hypoglycemia pattern for liraglutide-treated patients contrasts with the hypoglycemia findings for the placebo arm, where hypoglycemia events were not as clearly related to HbA1c decline (hypoglycemia events are notable with an increase and decrease in HbA1c at week 26).

In the discussion of Figure 26, Dr. Kim's review notes that the risk of hypoglycemia may outweigh the benefit of glycemic lowering (i.e. HbA1c) for patients with lower baseline HbA1c; however, these are episodes of non-severe hypoglycemia for which clinical significance is not established. In addition, these findings are exploratory. Labeling restrictions for use in 'higher' baseline HbA1c are therefore, not warranted.

A more specific assessment, using documented symptomatic hypoglycemia events is shown in the appendix (see Figure 38), the findings are overall consistent to what is discussed here.

Figure 26- Hypoglycemia events by baseline HbA1c and change in HbA1c at week 26



Source: reviewer's analysis (data from adhypo, adlb datasets)
Source: Dr. Kim's review Figure 10

Evaluation of hypoglycemia trends over time
An analysis by number of events over time is shown in Figure 27 for all hypoglycemia events and for confirmed hypoglycemia events. These two categories were chosen for analysis since they provide a broad and narrow perspective of hypoglycemia trends. From this figure it appears that although the risk of hypoglycemia spans the duration of the trial, for liraglutide, there is a higher risk for hypoglycemia early in the trial (i.e. first month).

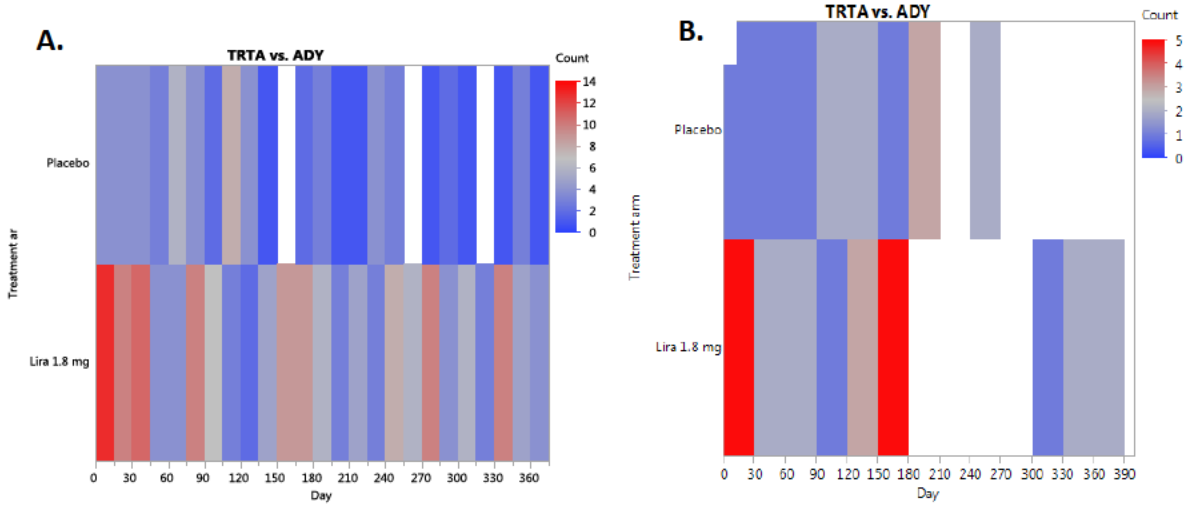
For Figure 27A, of the 23 hypoglycemia events (in 10 patients) identified in the first 30 days, 4 patients had multiple events of hypoglycemia (accounting for 17 of the 23 events in this period).[75] Only 3 patients (none of which had multiple events) were also on basal insulin.

For Figure 27B, the 5 events identified in the first month were seen in 5 different patients, 2 of which were on basal insulin. The 5 events identified on days 150-180 were again seen 5 different individuals, 4 of which were on basal insulin. Similar findings were seen for patients with hypoglycemia <54 mg/dL with or without symptoms (see appendix, Figure 39).

Reviewer's comments: This exploratory analysis of hypoglycemia suggests that hypoglycemia was more common earlier in the trial (for liraglutide).

[75] ID (b) (6) 6 events, (b) (6) -4 events, (b) (6) -4 events and (b) (6) -3 events

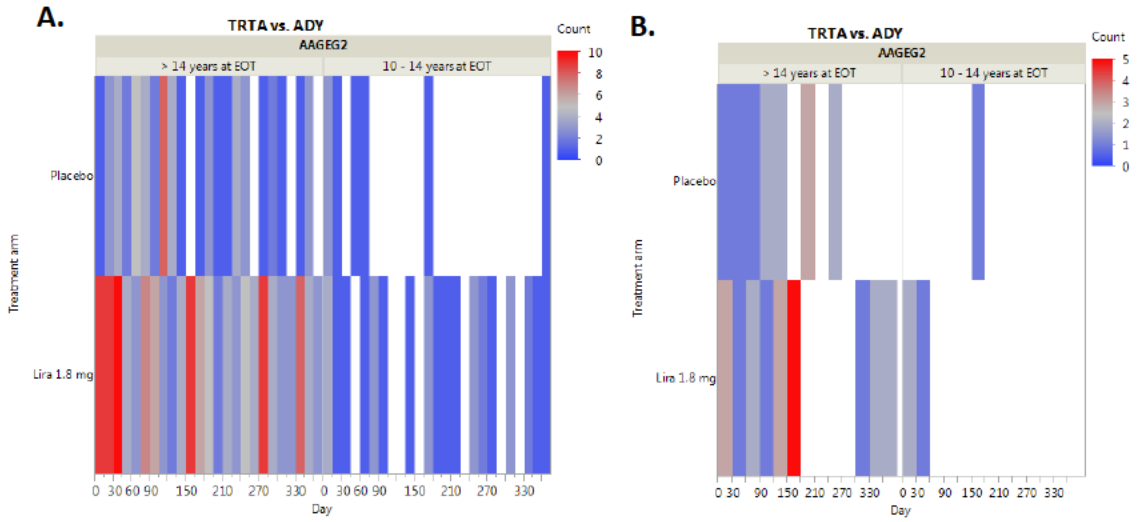
Figure 27- A- All hypoglycemia events B- Confirmed hypoglycemia events over time-treatment emergent events-SAS



Source: reviewer derived analysis from ADHYPO dataset

An analysis by age is shown in Figure 28. Although the risk of hypoglycemia seems to be concentrated in patients over the age of 14 years, it is important to remember that this population made up 70% of the enrollees, therefore it is not unexpected to see trends. However, it is important to note that younger patients did not drive the hypoglycemia findings.

Figure 28- A- All hypoglycemia events B- Confirmed hypoglycemia events over time by age groups 10-14 and >14 years of age-treatment emergent events-SAS



Source: Reviewer derived analysis using the ADHYPO dataset

General comments regarding hypoglycemia:

Victoza has a Warnings and Precautions for Serious hypoglycemia when "Victoza is used with insulin secretagogue (e.g. sulfonylurea) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia." The hypoglycemia findings in *ellipse*™ contrast with what is currently labeled in that, there was a higher event and incidence rate across hypoglycemia definitions (that were beyond numerical imbalances) for liraglutide as compared to placebo regardless of concomitant drug therapies (i.e. insulin) used.

The risk of hypoglycemia for liraglutide was higher when initiating liraglutide, despite the recommended 20% decrease in basal insulin dose (for patients on insulin) at randomization, and despite the use of a glycemic-based titration for liraglutide (i.e. no dose increases if FPG <110 mg/dL). Both of these factors were likely implemented to reduce the risk of hypoglycemia and likely mitigated the overall hypoglycemia findings in this trial.

Exploratory subgroups of patients at higher risk for hypoglycemia included patients randomized to liraglutide with a "lower" baseline HbA1c (i.e.~7%) whose HbA1c remained stable or slightly declined, or patients with higher baseline HbA1c (i.e. HbA1c above 8%) with a larger decline in HbA1c at week 26 (~2% decline).

From a postmarketing perspective, it is unclear if pediatric patients with type 2 diabetes will be treated with liraglutide at such low HbA1c values, as was done in this trial. Since the risk of hypoglycemia seems to be at least somewhat related to the lower baseline HbA1c values in these patients, it is unknown if the same risk would be generalizable to the postmarketing setting. In addition, the risk of hypoglycemia for patients with a history of hypoglycemia is also unknown, since patients with recurrent severe hypoglycemia or hypoglycemic unawareness were excluded from *ellipse*™.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In total there were 366 AEs reported in the trial (192 and 174 events reported in liraglutide and placebo). Approximately 98% of adverse events were mild or moderate in severity. Although similar proportion of patients experienced adverse events, the differences in event rate were primarily driven by a higher number of gastrointestinal adverse events in the liraglutide arm as compared to the placebo arm (across levels of severity).

There was a total of 11 patients (5 for liraglutide and 6 for placebo) who experienced severe events. A listing of the events is shown in Table 30 (in appendix). The greatest imbalance between treatment arms was in the SOC of Gastrointestinal disorders (5 patients for liraglutide vs 2 patients for placebo).

Table 25 shows the proportion of patients with treatment emergent adverse events by SOCs.

The greatest imbalances, not favoring liraglutide, were seen for gastrointestinal disorders, eye disorders and musculoskeletal and connective tissue disorders.

Table 25- Patients with TEAEs by SOC-SAS

	Description of Actual Arm				
	Liraglutide		Placebo		
Body System or Organ Class	**Count**	**%**	**Count**	**%**	**Total**
Infections and infestations	32	48.5%	39	57.4%	71
Gastrointestinal disorders	37	56.1%	25	36.8%	62
Nervous system disorders	18	27.3%	16	23.5%	34
Investigations	11	16.7%	15	22.1%	26
General disorders and administration site conditions	14	21.2%	11	16.2%	25
Metabolism and nutrition disorders	12	18.2%	13	19.1%	25
Respiratory, thoracic and mediastinal disorders	10	15.2%	14	20.6%	24
Injury, poisoning and procedural complications	10	15.2%	9	13.2%	19
Musculoskeletal and connective tissue disorders	12	18.2%	6	8.8%	18
Skin and subcutaneous tissue disorders	10	15.2%	4	5.9%	14
Reproductive system and breast disorders	5	7.6%	8	11.8%	13
Eye disorders	7	10.6%	1	1.5%	8
Renal and urinary disorders	5	7.6%	3	4.4%	8
Blood and lymphatic system disorders	3	4.5%	1	1.5%	4
Ear and labyrinth disorders	3	4.5%	1	1.5%	4
Immune system disorders	.	.	3	4.4%	3
Psychiatric disorders	1	1.5%	2	2.9%	3
Vascular disorders	.	.	2	2.9%	2
Endocrine disorders	1	1.5%	.	.	1
Hepatobiliary disorders	.	.	1	1.5%	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1.5%	.	.	1

Reviewer generated from submitted datasets

Table 26 examines the PT terms in the SOCs with the greatest imbalances. The findings in the Gastrointestinal disorders SOC were primarily driven by the following PT terms: nausea (28.8% vs 13.2% for liraglutide vs. placebo), diarrhea (22.7% vs. 16.2% for liraglutide vs. placebo), vomiting (25.8% vs. 8.8% for liraglutide vs. placebo), abdominal pain (18.2% vs. 7.4%), dyspepsia (7.6% vs. 1.5%) and constipation (6.1% vs. 1.5%). There was no clear PT(s) term driving the findings for the SOCs under musculoskeletal and connective tissue disorders and eye disorders; there was no obvious clustering of terms to suggest an underlying pathology in these SOCs.

Table 26- Patients with TEAEs by Gastrointestinal disorders, musculoskeletal and connective tissue disorders and eye disorders SOCs-SAS

		Description of Actual Arm				
		Liraglutide		Placebo		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
Gastrointestinal disorders	Nausea	19	28.8%	9	13.2%	28
	Diarrhoea	15	22.7%	11	16.2%	26
	Vomiting	17	25.8%	6	8.8%	23
	Abdominal pain	12	18.2%	5	7.4%	17
	Abdominal pain upper	2	3.0%	8	11.8%	10
	Dyspepsia	5	7.6%	1	1.5%	6
	Constipation	4	6.1%	1	1.5%	5
	Toothache	3	4.5%	1	1.5%	4
	Abdominal discomfort	2	3.0%	1	1.5%	3
	Abdominal distension	.	.	1	1.5%	1
	Epigastric discomfort	1	1.5%	.	.	1
	Flatulence	1	1.5%	.	.	1
	Food poisoning	1	1.5%	.	.	1
	Frequent bowel movements	1	1.5%	.	.	1
	Gastrooesophageal reflux disease	1	1.5%	.	.	1
	Mouth ulceration	1	1.5%	.	.	1
	Regurgitation	1	1.5%	.	.	1
Musculoskeletal and connective tissue disorders	Epiphyses premature fusion	3	4.5%	2	2.9%	5
	Musculoskeletal chest pain	3	4.5%	.	.	3
	Arthralgia	1	1.5%	1	1.5%	2
	Back pain	2	3.0%	.	.	2
	Groin pain	1	1.5%	1	1.5%	2
	Scoliosis	2	3.0%	.	.	2
	Ankle deformity	.	.	1	1.5%	1
	Intervertebral disc degeneration	1	1.5%	.	.	1
	Intervertebral disc protrusion	1	1.5%	.	.	1
	Joint swelling	.	.	1	1.5%	1
	Pain in extremity	1	1.5%	.	.	1
Eye disorders	Visual acuity reduced	2	3.0%	.	.	2
	Astigmatism	1	1.5%	.	.	1
	Conjunctival irritation	1	1.5%	.	.	1
	Conjunctivitis allergic	1	1.5%	.	.	1
	Eye pruritus	.	.	1	1.5%	1
	Hypermetropia	1	1.5%	.	.	1
	Vision blurred	1	1.5%	.	.	1

Source: Reviewer generated from submitted datasets

Table 29, in section 13.2, shows TEAEs with at least 2 events per PT. In this table, it was also noted that there were imbalances not favoring liraglutide for the PT dizziness (12.1% vs. 2.9%). None of the reviewed events with imbalances were SAEs, therefore there are no narratives to

help further elucidate the differences between treatment arms.

Reviewer's comment: The common adverse reactions in *ellipse*™ are similar to the overall common adverse reactions seen in adult trials. Specifically, the Victoza PI adequately addresses the risk for gastrointestinal-related adverse events. I do not recommend any changes to section 6 of the Common Adverse Reactions section of the PI.

8.4.6. Laboratory Findings

Table 20 shows the centrally and non-centrally measured laboratories measured in *ellipse*™. Refer to section 8.5 for laboratories related to specific safety findings. Most patients had normal laboratory values throughout the trial. Evaluation of hematology, biochemistry and urinalysis central tendencies were similar between treatment arms when comparing by mean change from baseline and mean trends per visit. Overall, the central tendency evaluations remained generally stable for the 52-week treatment period, without clear clinically relevant differences between liraglutide and placebo.

In addition to central tendency analyses, I also evaluated outlier analyses by reviewing shift tables and reviewing categorical changes in laboratory values over time (i.e. proportions of patients who had normal, high or low values by visit). Overall, outlier results were similar between liraglutide and placebo.

Notable differences in this analysis included the following:

- Baseline proportion of patients with elevated ALAT were similar between treatment groups at baseline (30.3% vs 33.8% for liraglutide vs. placebo, respectively); however, there was a decrease in the proportion of patients favoring liraglutide at 26 weeks (21.7% [liraglutide] vs. 39.7% [placebo]) and at 52 weeks (7.1% [liraglutide] vs. 17% [placebo]). Evaluation of peak liver function tests over the entire trial also favored liraglutide over placebo or were similar.[76]
- Review of the laboratory datasets did not identify any cases meeting Hy's law[77].

8.4.7. Vital Signs

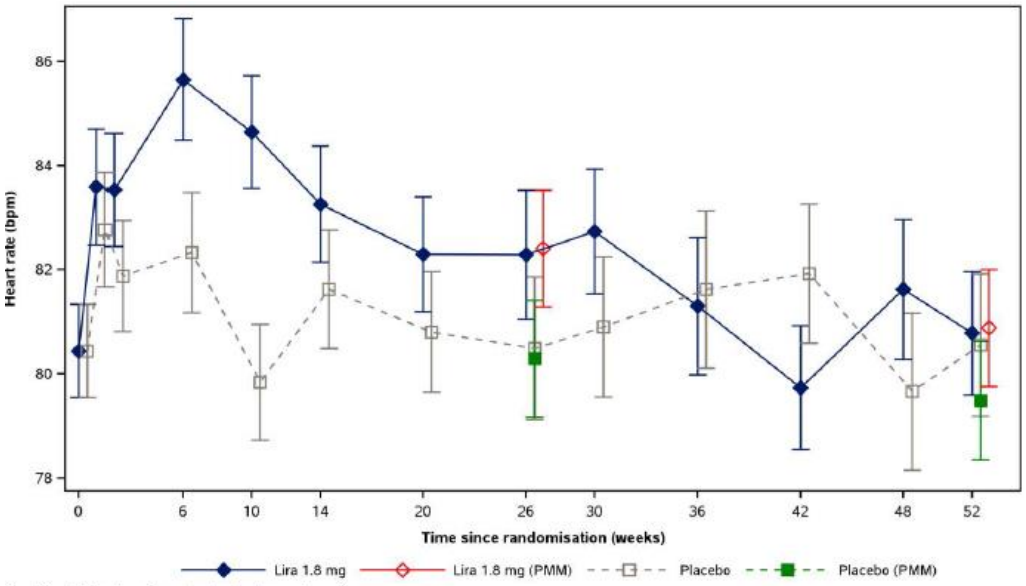
Pulse was measured in a sitting position after 5 minutes of rest.

[76] 8 (liraglutide) and 18 (placebo) patients had ALT elevation between 2-5x ULN; 2 (liraglutide) and 3 (placebo) patients had AST elevations between 2-5x ULN.
[77] Hy's law was defined as: (increase in ALAT and/or ASAT >3×ULN and an increase in total bilirubin >2×ULN and without elevated ALP.

Victoza is labeled for mean increases from baseline in heart rate of 2 to 3 beats per minute as compared to placebo.

The Applicant conducted a statistical analysis of pulse over time; see Figure 29 (Figure 42, in the appendix shows the observed values). Figure 29 shows that for liraglutide, pulse was the highest at week 6 with a gradual decline over time; for placebo, pulse remained relatively stable with some variation during the trial. For most of the trial, pulse for liraglutide was higher than pulse for placebo.

Figure 29- Mean pulse estimated over time using a mixed model of repeated measurements-SAS



Source: CSR, figure 12-4

Reviewer's comment: the pulse trends for liraglutide in pediatric patients are consistent with the labeled findings in adults.

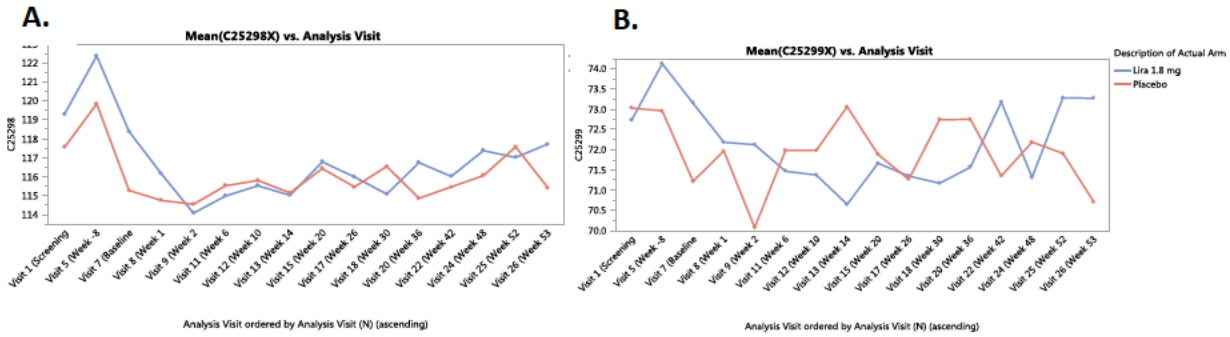
The protocol specified standard measurement techniques for the capture of systolic and diastolic blood pressures.[78] Systolic and diastolic blood pressure at 26 and 52 weeks were

[78]The patients were to avoid caffeine, smoking and exercise at least 30 minutes prior to the blood pressure measurement. The measurement was to be taken with the patient in a sitting position, with legs uncrossed, the back and arm supported. The patient was to remain seated for at least 5 minutes before the first measurement was taken. The patient was to avoid talking during the measurement. The site was to measure blood pressure using their usual method; however, the same method and device were to be used throughout the trial. For blood pressure at the screening visit (visit 1), three measurements were to be performed and all three values entered into the eCRF.

evaluated as part of the efficacy analysis; there were no statistical differences between liraglutide and placebo (see Table 18).

Figure 30 shows the observed trends of systolic and diastolic blood pressure over time.

Figure 30- Observed values for A. mean systolic blood pressure (mmHg) and B. mean diastolic blood pressure (mmHg)



Source: reviewer generated graphs from datasets

Review of systolic blood pressure by age groups (10-14) and >14 years of age (see Figure 43 in appendix) revealed that systolic blood pressure and diastolic blood pressure for patients >14 tended to be higher than for patients 10-14. There were no treatment differences by age group noted.

Reviewer's comment: Overall, there were no obvious clinically evident differences in systolic or diastolic blood pressure between treatment arms.

8.4.8. Electrocardiograms (ECGs)

ECGs were performed at screening, week 26 and week 52. ECG findings were categorized by the investigator as either: normal; abnormal, not clinically significant; or as abnormal, clinically significant. There were no abnormal clinically significant ECG findings reported for the liraglutide arm and one report for placebo.[79] Shift tables of ECG findings did not reveal any clear treatment differences.

8.4.9. QT

Thorough QT studies were conducted at the time of the original NDA review. There were no QT studies performed as part of the evaluation in pediatric T2DM population.

[79] Subject ID (b) (6) finding reported at week 26; corresponding AE report of "electrocardiogram abnormal."

8.4.10. Immunogenicity

Hypersensitivity reactions are labeled in the Warnings and Precautions section of the Victoza PI.

This section addresses immunogenicity as the presence of anti-liraglutide antibodies and addresses immunogenicity by specific adverse events, as predefined by the Applicant.[80]

Anti-liraglutide antibodies
Dr. Kirshner from the Office of Biotechnology Products (OBP) notes that all assays (screening, titering, neutralizing ADA assay, and ADA cross-reactivity assay to endogenous human GLP-1) were previously reviewed and found to be acceptable.[81]

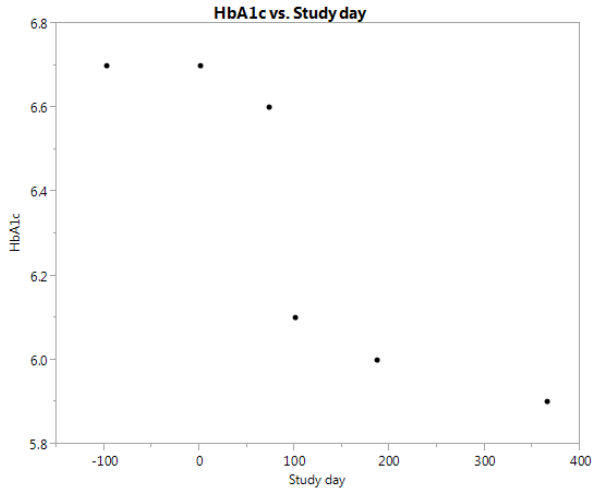
Patients underwent antibody testing for anti-liraglutide antibodies at baseline (week 0), week 26, and week 53 (a week after end of treatment). Samples that were positive for anti-liraglutide antibodies were also analyzed for cross-reactivity to native GLP-1. Positive anti-liraglutide antibody samples at week 53, also were analyzed *in vitro* for neutralizing effects on liraglutide.

There were no patients with positive anti-liraglutide antibodies at baseline. At 26 and 53 weeks there were 1 (1.5%)[82] and 5 (8.5%)[83] patients, respectively, with positive anti-liraglutide antibodies in liraglutide treated patients. There were no patients who had cross-reactivity to native GLP-1 or who had evident neutralizing effects. Quantification of antibody was low for all patients (%B/T[84] <5.3).

To further characterize association of anti-liraglutide antibodies and adverse events and HbA1c, I reviewed the adverse events and efficacy trends for the single patient who had positive antibodies at 26 and 53 weeks. The patient had 4 AEs during the treatment period, however it was difficult to ascertain if the AEs were affected by the immunogenicity status[85] since there was no narrative to accompany the AE reports. The HbA1c trends over time for this patient are shown below. Based on the observed decline in HbA1c from baseline, for this patient, it does not appear that a positive anti-liraglutide Ab status decreased the drug's efficacy.

[80] Event identification for these events occurred by both investigator-reported MESI for immune complex disease and allergic reaction (including injection sites) and by predefined MedDRA search for allergic reactions, injection site reactions and immune complex disease. The applicant used specific definitions to identify immediate hypersensitivity reactions, delayed hypersensitivity reactions and de novo development or exacerbation of pre-existing immune complex disease.
[81] For details refer to Dr. Hallett's review August 2017, supplement 27.
[82] Subject ID (b) (6)
[83] Subject IDs (b) (6)
[84] Refers to the amount of radioactivity as a percentage of the total amount of added radioactivity, the higher the %B/T, the more anti-liraglutide antibodies are present in the sample
[85] Subject ID (b) (6) had the following AEs: cough (2 events), conjunctivitis, conjunctival irritation

Figure 31- HbA1c trends for subject ID (b) (6)



Source: reviewer derived graph from ADHBA1C dataset

Reviewer's comment: The interpretation of the antibody findings is limited because there were few patients with positive antibodies. There is insufficient data to ascertain whether the presence anti-liraglutide antibodies affects efficacy of safety.

Adverse events related to immunogenicity

Investigators were to report events related to immune complex disease and allergic reactions, including allergic reactions at injection sites as MESIs. There were 2 patients with 3 events (all in the liraglutide arm) reported as having "immunogenicity" MESIs. The events were reported as allergic conjunctivitis[86] and rash (2 events).[87] Review of the narratives for both events did not reveal a clear association with liraglutide use.

The Applicant's predefined MedDRA search for immunogenicity reactions revealed 10 patients with 12 events for liraglutide and 4 patients with 5 events for placebo; see Table 27. None of the events was serious.

Table 27 – Allergic reaction events by SOC and PT-SAS

	Liraglutide N=66		Placebo N=68	
	N (%)	Events	N (%)	Events
Events	10 (15.2)	12	4 (5.9)	5
Skin and subcutaneous tissue disorders	7 (10.6)	9	1 (1.5)	2

[86] Subject ID (b) (6) -the episode of allergic conjunctivitis was associated with the flowering season of lime trees
[87] Subject ID (b) (6) - 15-year-old female was diagnosed with tonsillitis 2 days after starting treatment with liraglutide. She also developed a rash (in right cheek) while she had tonsillitis. Rash continued while patient was being treated with penicillin for tonsillitis and while liraglutide was being held (due to tolerability issues) for one day. Upon restarting liraglutide rash was gone but returned a month later in upper chest.

Rash	4 (6.1)	5	1 (1.5)	1
Rash generalized	1 (1.5)	1	1 (1.5)	1
Dermatitis acneiform	1 (1.5)	1	0	0
Eczema	1 (1.5)	1	0	0
Urticaria	1 (1.5)	1	0	0
Immune system disorders	0	0	2 (2.9)	2
Drug hypersensitivity	0	0	1 (1.5)	1
Hypersensitivity	0	0	1 (1.5)	1
Respiratory, thoracic and mediastinal disorders	1 (1.5)	1	1 (1.5)	1
Rhinitis allergic	1 (1.5)	1	1 (1.5)	1 (1.5)
Blood and lymphatic system disorders	1 (1.5)	1	0	0
Immune thrombocytopenic purpura*	1 (1.5)	1	0	0
Eye disorder	1 (1.5)	1	0	0
Conjunctivitis allergic	1 (1.5)	1	0	0
*there are no additional details regarding this event (i.e. no narrative provided) to assess causality. Source: information request dated 3/1/19 \\CDSESUB1\evsprod\NDA022341\0424\m1\us				

Evaluation of injection site reactions revealed a total of 3 patients with 3 events (2 patients with 2 events for liraglutide and 1 patient with one event for placebo). Patients randomized to liraglutide experienced 1 case of injection site pain and one case of injection site atrophy; the patient randomized to placebo experienced one case of injection site atrophy.

Reviewer's comments: the immunogenicity findings in antibody trends and immunogenicity-related adverse events are overall consistent with the liraglutide PI. Although there were numerically larger number of patients and events identified in immunogenicity evaluation (i.e., via MedDRA searches) there is insufficient information from these events (i.e. due to lack of narratives) to ascertain causality.

I recommend the labeling of the liraglutide antibody findings, as proposed by the Applicant.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Pancreatitis

Liraglutide is labeled with a Warnings and Precautions for pancreatitis due to postmarketing reports of fatal and non-fatal hemorrhagic or necrotizing pancreatitis. *ellipse*^{TM} evaluated this risk through collection of two MESIs: "acute pancreatitis or suspicion of pancreatitis" [88]and "elevated amylase and lipase>3x upper limit of normal."[89] There was one adverse event detected on scheduled blood work that was reported as "pancreatic enzymes increase" in the

[88] Two of the following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: a) Severe acute upper abdominal pain, b) Elevated blood levels of one of pancreatic enzymes (lipase, amylase) ≥ 3x UNR, c) Characteristic imaging finding (ultrasound, computerized axial tomography (CT), magnetic resonance imaging (MRI))
[89] Both MESIs were identified by investigator reports of these MESIs and thru pre-defined MedDRA searches

liraglutide group which was associated with AEs: overdose and blood creatinine increased.[90] Based on the narrative, the elevation of pancreatic enzymes remained at less than 2 times the upper limit of normal, and the patient was not reported as having any symptoms associated with the event. Therefore, in my opinion, it is unlikely that this event represented a pancreatitis event.

The Applicant reported that there were 2 patients, each reporting an adverse event related to elevated pancreatic enzymes.[91] One event was in a patient randomized to placebo; the patient was reported as having an amylase increase; the second event was in a patient randomized to liraglutide who had an elevation of lipase. Both events resolved on their own and the IMP was continued despite the finding. Neither event contained information to suggest a diagnosis of pancreatitis. In addition to these 2 patients, I identified 2 additional patients with PT terms suggestive of elevations of pancreatic enzymes.[92] These patients were not reported as MESIs since their elevation in pancreatic enzymes was less than 3X the upper limit of normal.

Reviewer's comments: evaluation of potential pancreatitis events, by reported adverse events, identified few events. These events were predominantly associated with mild pancreatic enzyme increases without reports of additional findings (i.e., imaging confirmation or presence of abdominal pain).

---

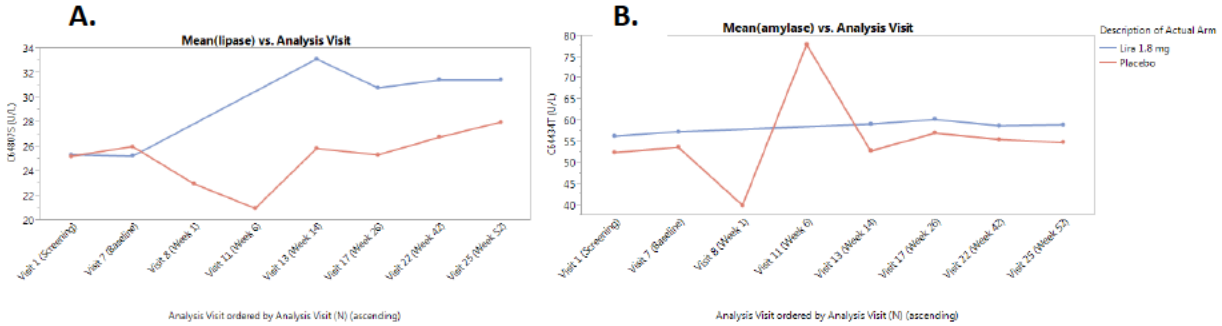
[90] Subject ID (b) (6) (liraglutide)- 13 year old girl who had blood work at visit 17 with the following parameters: serum creatinine was 3.12 mg/dL (reference range 0.57-0.87), amylase was 103 U/L (normal range 28-100 U/L), and lipase was 42 U/L (normal range 4-29 U/L), from these laboratory abnormalities, the following AEs were reported: suspicion of overdose, pancreatic enzymes elevated, and blood creatinine increased. 8 days after the findings the patient was seen in an unscheduled visit and examined. The laboratory findings normalized, and the event was reported as resolved. There were no changes made to the liraglutide or metformin dose because of these AEs. In an information request received 3/1/19, the applicant clarified that the patient was questioned and examined for signs and symptoms of adverse events related to the onset of kidney injury/pancreatitis (but did not report any of these) and was counseled regarding these symptoms.

[91] Subject ID (b) (6) (placebo)- 14-year-old male reported a s having a threefold elevated level of amylase. The patient was reported as having a previous ultrasound showing diffuse changes of pancreas without elevated amylase. Ten months after this US/laboratory findings, the patient was reported as having an amylase of 297 (normal range 28-100 U/L) without any symptoms. 5 days later, the patient had repeat blood work which showed a normal amylase and was treated with mebeverine and pancreatic enzymes, due to ultrasound findings suggesting chronic pancreatitis. Patient was seen by a gastroenterologist 3 months later and was diagnosed with nonalcoholic fatty liver disease, steatohepatitis. Pancreatitis was excluded, and the elevations of amylase were thought to be due to a "transitional reaction." The treatment drug was discontinued due to hyperglycemia. Subject ID (b) (6) (liraglutide)- 12-year-old male reported as having "elevated lipase >3 UNR" by investigator. Four months after starting liraglutide the patient was found to have a lipase level of 114 U/L (reference range 4-29); the patient was asymptomatic. 2 months later the value decreased to 57 U/L; liraglutide was continued without changes. There are no further details provided.

[92] Subject ID (b) (6) (liraglutide) 12-year-old female was reported as having a mild event of "elevated lipase levels in lab" by the investigator. Level was noted to increase from 30's to 78 U/L at week 14, with repeat value of 56 U/L. Subject ID (b) (6) (liraglutide) 12-year-old female was reported as having a mild event of "elevated lipase" by the investigator; review of lipase values revealed all values ranged from 30-42 U/L. Neither event was serious and there is no narrative available for these patients.

Review of the central tendency (mean values over time) for pancreatic enzymes suggested a trend for slightly higher lipase values in the liraglutide arm as compared to the placebo arm. The difference in lipase between treatment arms is difficult to detect when considering the difference in magnitude (a trend for values in the mid 20's U/L for placebo vs. values in the 30's U/L for liraglutide). When considering box plots trends over time (Figure 40; see appendix), this difference is almost imperceptible. When reviewing individual graphs for lipase trends (Figure 41; see appendix), only a few patients were noted to have values above the upper limit of normal. No treatment specific trends were evident for amylase over time.

Figure 32- A. mean lipase and B. mean amylase over time



Source: reviewer derived from laboratory datasets. Please note that the measurements at week 1 and week 6 in the graphs were not pre-specified for collection of pancreatic enzymes, and so, the measurements in these time periods reflect values for a small subset of patients and should be interpreted accordingly.

Reviewer's comments: In adult trials, patients using liraglutide tended to have higher amylase values as compared to baseline; these trends are not clearly visible in *ellipse*™. The slightly higher lipase values, seen in adult trials, is suggested in the lipase trends of *ellipse*™.

8.5.2. Cardiovascular events

Cardiovascular events were pre-specified as MESIs by the Applicant.[93] My review of cardiovascular events focused on a review of arrhythmias, since pediatric patients with type 2 diabetes are not likely to have atherogenic cardiovascular events (unlike the adult type 2 diabetes population). Of note, the LEADER trial was the cardiovascular outcomes trial for Victoza. This trial showed that liraglutide use resulted in a reduction in the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. This cardiovascular benefit was noted despite the mean increases from baseline in heart rate of 2-3 beats per minute with liraglutide use. The pulse trends in *ellipse*™ are discussed in section 8.4.7.

[93] Event identification for these events occurred by predefined MedDRA search for cardiovascular disorders and for cardiac arrhythmia AEs.

In total, the Applicant's search identified 2 patients with 2 cardiovascular AEs in the liraglutide arm[94] and 4 patients with 5 AEs in the placebo arm.[95] None of the events identified was serious. An independent review by broad and narrow SMQs for cardiac arrhythmias did not reveal any events for liraglutide and one event for placebo.

Reviewer's comment: As would be expected in a pediatric population, there were few cardiovascular events observed. The captured events had varied etiologies; there was no clustering of events to suggest a trend for cardiovascular events or arrhythmias.

8.5.3. Neoplasms

Neoplasms were pre-specified as MESIs by the Applicant.[99] Given the relative short duration of the trial (1 year) as compared to the time to develop these events (years), the exposure period was not considered sufficient to adequately address this risk. There was one MESI reported as a neoplasm in a patient who had a fibroadenoma of the breast in the liraglutide arm.[96] Two other neoplasm events were identified by MedDRA search and included acanthosis nigricans (liraglutide) and ovarian cyst (placebo).

Reviewer's comment: detected neoplasms in *ellipse*™ are consistent with common neoplasms in this population or associated with disease complications. There is no clear causality identified from the events in this trial.

8.5.4. Thyroid disease

All long acting GLP-1 receptor agonists (including liraglutide) have a boxed warning for the risk of medullary thyroid cancer. To evaluate this risk, the Applicant pre-specified the collection of MESIs defined as calcitonin ≥20 ng/dL and evaluated the risk of "thyroid disease."[97] There was one case of a goiter identified in the AE dataset.[99]

There were no calcitonin values meeting this threshold. Review of the AE dataset did not identify any reports of adverse events related to calcitonin. There was one case of "goiter"[98] identified during physical exam in a liraglutide treated patient.

---

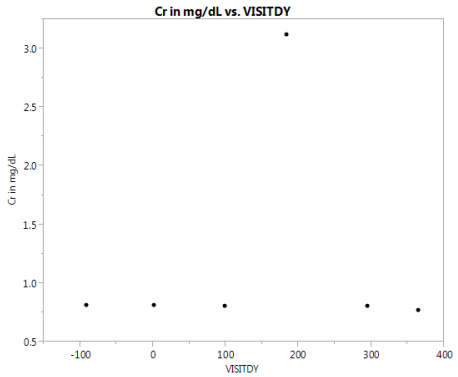
[94] Subject ID (b) (6) peripheral swelling, subject ID (b) (6) chest pain
[95] Subject ID (b) (6) vertebrobasilar insufficiency, subject ID (b) (6) Electrocardiogram abnormal, syncope, subject ID (b) (6) syncope, subject ID (b) (6) electrocardiogram QT prolongation
[96] Subject ID (b) (6) (liraglutide)- 15-year-old female found lump in left breast which underwent US with benign findings and biopsy which revealed fibroadenoma vs benign phyllodes tumor. The patient underwent for lumpectomy; pathology was consistent with fibroadenoma.
[97] This category covers all disorders of the thyroid gland, including thyroid neoplasms
[98]Subject ID (b) (6) (liraglutide)- 15 year-old-female reported as "slightly enlarged thyroid gland" by investigator

Reviewer's comments: there were few cases of thyroid-related abnormalities in *ellipse*^{TM} to make definitive conclusions regarding drug-related effects.

8.5.5. Altered renal function

Altered renal function was a predefined MESI event.[99] The Applicant's analysis identified 2 cases (one in the liraglutide and one in the placebo arm). I also performed an independent Broad SMQ search for acute renal failure, which identified 4 patients experiencing single events (3 patients randomized to liraglutide[100] and 1 patient randomized to placebo[101]). My analysis included the patients identified by the Applicant. None of the events was serious, but the patient randomized to placebo experienced a severe event of proteinuria. I manually reviewed the trends in creatinine for the patients identified in the SMQ and noted that all patients who were identified with creatinine elevations returned towards baseline. I show the creatinine trends for patient (b) (6) (see footnote 90 for narrative) below since this patient was the most affected by a change in creatinine. As can be seen in
Figure **33**, there was only a transient increase in creatinine before returning to baseline.

Figure 33 – Trends in creatinine for subject ID (b) (6) over time



Source: graph generated from LB dataset

Review of creatinine (biochemistry) and urinary protein were performed as part of the general laboratory review (see section 8.4.6).

Reviewer's comment: there were few events suggestive of acute renal failure, mostly characterized by transient effects on serum creatinine which normalized. There was no

[99] Event identification for these events occurred by both investigator-reported MESI and by predefined MedDRA search. The definition of altered renal function was acute renal failure insufficiently or clinically significant paraclinical abnormalities indicating a decrease in renal function.
[100] Subject ID (b) (6) blood creatinine increased (review of trends revealed creatinine increased from a nadir of 0.6 to 1 mg/dL and then declined again), subject ID (b) (6) protein urine present (trace), subject ID (b) (6) blood creatinine increased (see footnote 90 for narrative)
[101] Subject ID (b) (6) proteinuria (which increased to +3 on urinalysis and then decreased to +1)

evidence of permanent renal insufficiency, (i.e. dialysis, renal death) in this trial. Overall, there is no convincing evidence of renal insufficiency as a result of liraglutide use.

8.5.6. Acute gallstone disease

Liraglutide has a Warnings and Precautions for acute gallbladder disease. Acute gallstone disease was a predefined MESI event that was captured by the Applicant via pre-defined MedDRA search.

The Applicant conducted predefined MedDRA search did not reveal any acute gallstone disease adverse events in *ellipse*^{TM}; I confirmed the Applicant's findings through an independent MedDRA search and evaluation of PT terms.

8.5.1. Medication errors and overdose

Medication errors and overdose were pre-specified MESIs in *ellipse*^{TM}. In total, there were 3 patients (all in the liraglutide arm) each experiencing an event of medication error. None of the events were serious, and all events recovered. Two patients were identified overdosing upon the investigator reviewing the returned trial product;[102] neither patient had any reported signs/symptoms/laboratory abnormalities reported with the event. One patient was identified from an elevated creatinine value.[90] All events were reported during the blinded period of the trial.

Reviewer's comment: Only one event related to overdose was related to clinically significant changes. See section Altered renal function 8.5.5 for further comments regarding this event.

8.6. Safety Analyses by Demographic Subgroups

Throughout the safety review of subgroup analyses (by age) are presented, as pertinent. A general review of adverse events by sex and race did not identify a difference in incidence of adverse events (results not shown). Formal statistical assessments for interactions on safety signals have not been conducted given the overall small subgroup sizes.

8.7. Specific Safety Studies/Clinical Trials

There were no specific studies/clinical trial conducted to evaluate a specific safety concern in this submission.

[102] Subject ID (b) (6) (liraglutide)- 14-year-old male who was calculated as taking more than 1.8 mg of liraglutide per day. The narrative does not note any signs/symptoms consistent with overdose. Subject ID (b) (6) (liraglutide) 16-year-old male who was calculated as taking more than 1.8 mg of liraglutide per day. The narrative does not note any signs/symptoms consistent with overdose.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no information relevant to this section of the review in the submission.

8.8.2. Human Reproduction and Pregnancy

There is no information relevant to this section of the review in the submission.

8.8.3. Pediatrics and Assessment of Effects on Growth

Dr. Taylor of the Division of Pediatric and Maternal health was consulted to evaluate the pubertal and growth trends in this trial and to provide an assessment of whether the results provide sufficient assurance that liraglutide does not affect growth and development in children.

Pubertal and growth assessments were conducted as part of safety assessments in this population. Effects on growth were assessed by pubertal, bone age, height and sex hormone assessments[103] Overall, there were no clinically relevant differences in sex hormone or bone metabolism markers between treatment arms.

Pubertal assessments
Investigators were supplied with an orchidometer and a booklet on Tanner staging and were trained on Tanner staging. Pubertal assessments were performed at baseline (week 0), week 14, week 26 and week 52. Tanner staging was not required to be conducted once the patient reached Tanner stage V. Acceleration of pubertal development after visit 1, as judged by the investigator, was to be recorded as an AE.

Figure 34 shows the pubertal progression by breast (in girls), penis (in boys), and pubic hair (in both sexes) development over time for liraglutide and placebo.

At baseline, over 63% of liraglutide and 55% of placebo-treated patients were at Tanner V for breast development. There were only 7.3% of liraglutide treated patients and no patients in placebo who were Tanner stage I or II at baseline. Review of shift tables did not show a clear imbalance noted in the progression of breast development between treatment arms.

At baseline, there was a larger proportion of patients in Tanner stage IV or V for penis development for liraglutide as compared to placebo (80% vs 65%, respectively). There were 12% for either treatment arm at Tanner stage I or II at baseline. In general, there were

[103] The applicant assessed hormonal changes of LH, FSH and estradiol in female patients thru a clinical evaluation to determine the menstrual cycle phase and interpreted the laboratory results based on this assessment

numerically fewer liraglutide patients who advanced in puberty as compared to placebo patients.

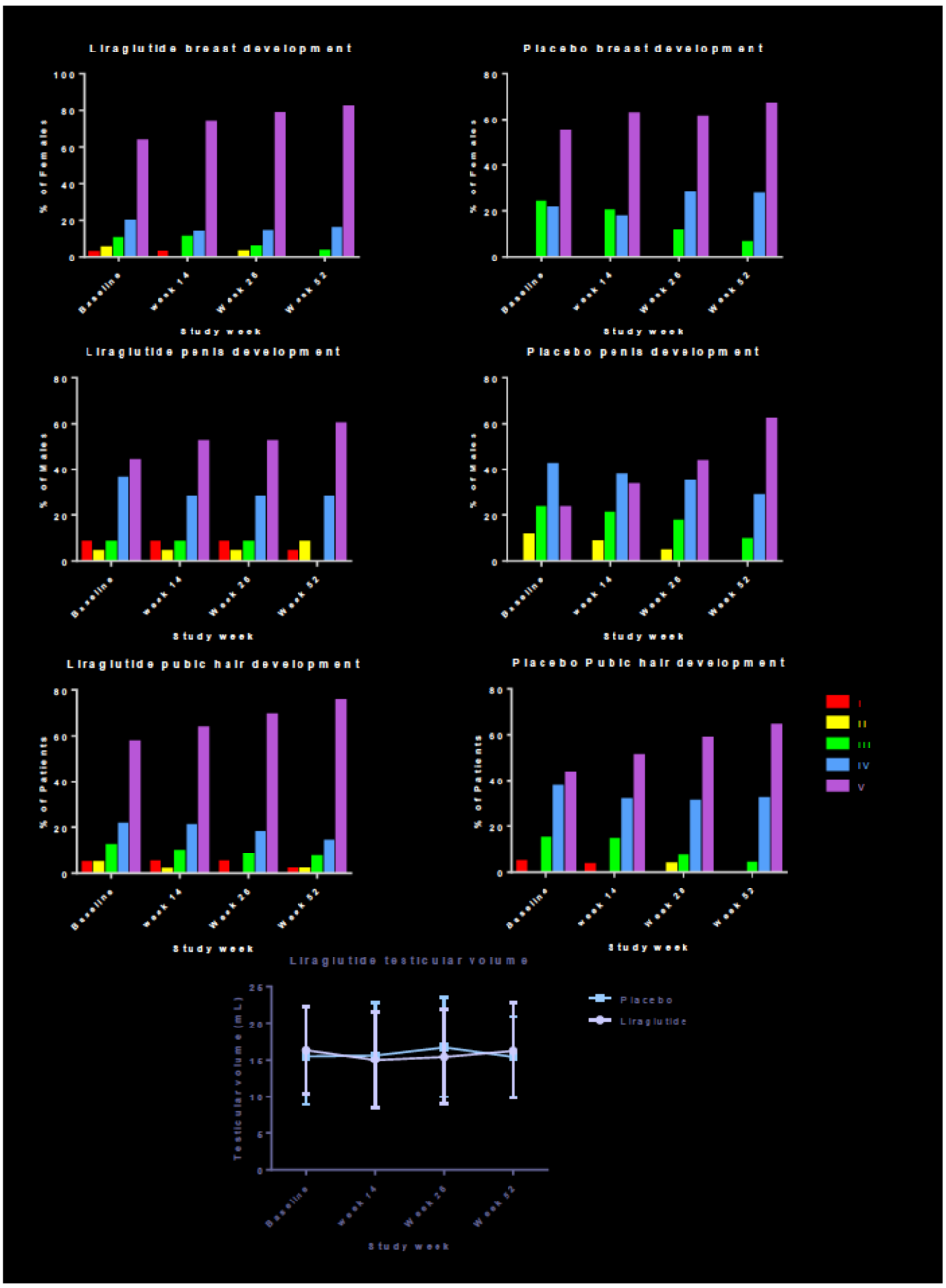
At baseline, there was a similar proportion of patients in Tanner stage IV or V for pubic hair for liraglutide and placebo (78.8% vs. 79.4%, respectively). There were 9% vs 4.5% of patients at Tanner stage I or II at baseline for liraglutide and placebo, respectively. Throughout the trial, there was a numerically lower proportion of patients who shifted up in pubertal for liraglutide as compared to placebo.

Assessment of testicular volume over time for males revealed overall similar trends for liraglutide and placebo; see Figure 34.

An assessment of puberty for the age group of 10-14 is shown in the appendix (see Figure 44). The trends in puberty are somewhat difficult to assess for this subgroup due to the small numbers in some of the categories (i.e. 9 patients for penis development); however, it appears that (for both groups) across assessments (breast, penis and pubic hair development) patients continued to advance in puberty throughout the trial, and that at baseline there were patients having reached mature (adult) traits.

Reviewer's comments: There were small numerical differences between treatment arms in the proportion of patients progressing through puberty; there was no clear treatment effect on puberty progression identified.

Figure 34 – Puberty progression by breast, penis and pubic hair development and testicular volume over time -SAS



Source: Reviewer graphed based on table 14.3.6.12 in CSR

Sex hormones

Hormonal assessments of puberty were performed at randomization, week 14, week 26 and week 52. In female patients, assessments of hormones (LH, FSH and estradiol) were assessed in relation to the individual patient's menstrual cycle. The Applicant notes that there was some

difficulty in interpreting these values in some patients since some patients had not started menarche and other patients were using oral contraceptives or had polycystic ovarian syndrome. Most patients in both treatment arms had normal hormone values throughout the trial. Evaluation of central tendency and outlier trends for hormone values did not reveal any clear treatment difference.

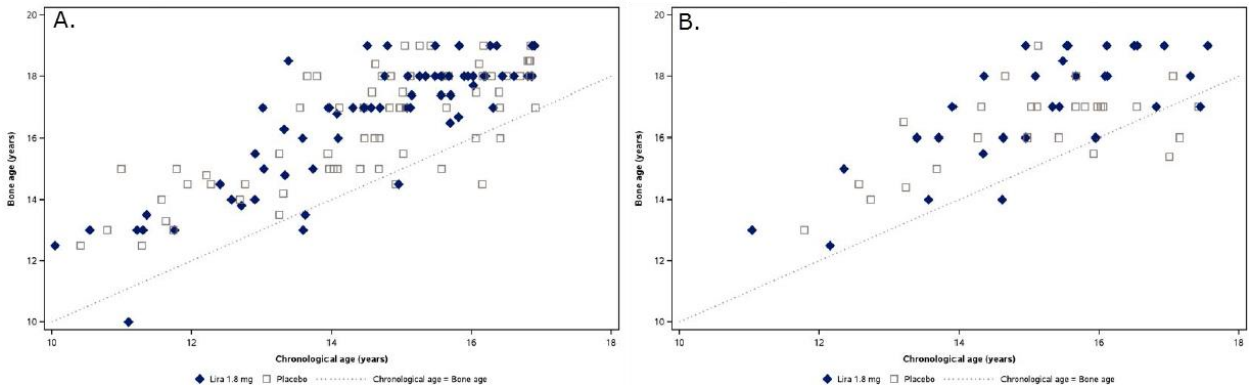
Figure 45 (in the appendix) shows the relationship of hormone levels by sex (male/female) and Tanner Stage[104]. As noted earlier, there were few patients at subsets of Tanner stages, therefore the assessment in these groups is somewhat limited, since the variations in laboratory values were driven by 1 or 2 patients. In addition, the trends in hormone values are more difficult to interpret for female patients due to expected normal hormonal variations throughout the menstrual cycle. Overall, for males across Tanner stages (excluding patients with Tanner Stage II, for which data is limited as just noted), levels of FSH, LH and testosterone remained mostly stable in the trial. For females, there was slight variation in FSH and LH trends throughout the trial and no clear trends in estradiol values.[105] .

The Data Monitoring Committee monitored hormone trends to evaluate for pubertal disruption related to drug use. Five days prior to the last patient visit, the DMC concluded that they did not see evidence of hormonal disruption in the trial that would necessitate another animal study; the DMC also felt that there was insufficient evidence to conclude that there was no hormonal disruption in pediatric trial patients.

Bone age assessments
An x-ray of the left hand and wrist was performed at randomization and at week 52. If epiphysis were fused, no subsequent X-rays were to be performed; note that three quarters of patients had fusion of epiphyses at baseline. X-rays were analyzed by a central reader for determination of bone age. Figure 35 shows the relationship of chronological age to bone age at baseline and at week 52. Overall, bone age was advanced over as compared to the chronological age at baseline and at week 52 without clear difference between treatment arms. The mean bone age at baseline was 16.6 years and 16.4 years for liraglutide and placebo, respectively; while the mean bone age at week 52 was 17.0 years and 16.3 years for liraglutide and placebo, respectively. Dr. Taylor, from DPMH notes that given the large proportion of patients with fused epiphyses, and the small number of patients with unfused epiphysis, it is difficult to assess for a potential drug effect on linear growth.

[104] For this figure an analysis by pubic hair was chosen to be consistent between males and females; trends when evaluating breast size Tanner Stage (for females) or penis Tanner Stage (for males) were similar to the findings by Pubic hair Tanner Stage (not shown in the review).
[105] Estradiol values increased throughout the trial for Tanner I stage patients. No trends were visible for Tanner stage II. Estradiol decreased slightly for liraglutide in Tanner stage III and initially decreased, followed by increased for placebo. Estradiol decreased for liraglutide Tanner Stage IV patients and increased for placebo patients. Estradiol remained stable (for liraglutide) or increased (for placebo) Tanner Stage V patients.

Figure 35- bone age (years) vs. chronological age (years) at baseline (A) and at week 52 (B)- FAS



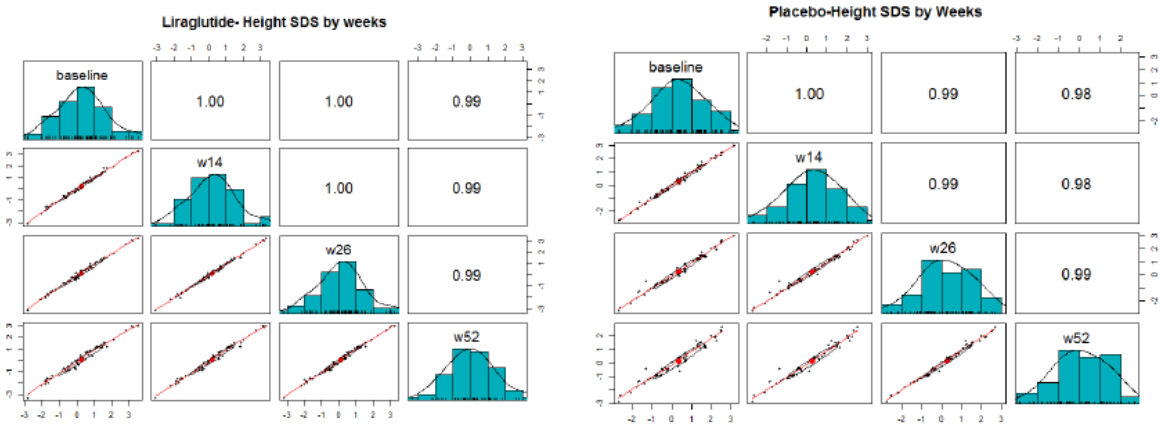
Source: CSR Figure 14.3.6.23 and 14.3.6.24

Reviewer's comments: there were no obvious treatment differences in bone age at baseline or at week 52. However, I agree with Dr. Taylor that it is difficult to assess for an effect on linear growth when the majority of the population has fused epiphyses.

Height

Height was measured at screening, baseline, week 14, week 26 and week 52. Two height measurements were to be performed by a single observer using an identical technique with a wall mounted stadiometer, with the patient repositioned between the measurements. Dr. Kim evaluated the pairwise correlation of height SDS throughout the study; see Figure 36. Dr. Kim's analysis revealed that there was a high pairwise correlation observed in both treatment arms and that there was no notable difference in height SDS between treatment arms. In addition, Dr. Kim observed similar height distribution between treatment arms with no notable change in height SDS across time points; refer to Dr. Kim's review for details.

Figure 36- 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)

Source: Dr. Kim's review, figure 4.

Dr. Taylor notes that the applicant's assessment of growth did not follow the 2007 FDA Guidance on Growth assessment[106] in the number of height measurements, the duration of the baseline period, and the lack of analyses of males and females separately. Because three quarters of the patients had fused epiphyses (by bone age assessment), it is likely that "the trial could not generate sufficient data regarding linear growth to support a conclusion that there was no effect on growth." I agree with Dr. Taylor's assessment; the trial did not generate sufficient information to determine a drug effect on growth. However, given that patients in the postmarketing setting will likely reflect the patients enrolled in this trial (pediatric patients with advanced pubertal status and completed growth) at the time of diagnosis and treatment of type 2 diabetes, a potential drug effect on growth may not be clinically significant and I do not see a need to conduct a development study in less mature patients.

Evaluation of central tendency and outlier trends for IGF-1, IGFBP-3, and bone metabolism markers (see Table 20) did not reveal any clear difference between the treatment arms and generally remained within normal limits (data not shown in review).

Reviewer's comments: Given that most patients completed growing at the time of trial start, a drug effect on growth cannot be determined.

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

This section was evaluated as part of the original NDA review. Section 8.5.1 addresses

[106] FDA Guidance for Industry, Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. March 2007. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm071968.pdf

medication errors and overdose.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

As part of the evaluation of the postmarketing setting, I reviewed the Applicant's PSUR/PBRER (dated 01 Jan 2018-30 Jun 20118) and focused on the information pertinent to Victoza (for adult T2DM). I agree with the PSUR/PBRER's assessment that over the total patient year exposure to date (9,171,136 PYE), there are no new safety concerns that were identified within the reporting period.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety of Victoza in the postmarketing setting is expected to be no worse than observed in the *ellipse*^{TM} trial, or from what is currently labeled.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

ellipse^{TM} had sufficient safety data in a broad enough population to allow generalizability of the safety findings to the United States' pediatric T2DM population.

There were no deaths in the trial. Serious adverse events varied across system organ classes and included events related to infections (seen similarly in both arms), gastrointestinal disorders (seen in the liraglutide arm) and hyperglycemia (seen in both arms). Discontinuations due to adverse events, for both treatment arms were related to hyperglycemia related adverse events.

There was a higher event and incidence rate across hypoglycemia definitions (beyond numerical imbalances) for liraglutide as compared to placebo. These findings tended to be independent of insulin use. The risk of hypoglycemia for liraglutide was higher when initiating liraglutide, despite the recommended 20% decrease in basal insulin dose (for patients on insulin) at randomization, and despite the use of a glycemic-based titration for liraglutide (i.e. no dose increases if FPG <110 mg/dL). A higher number of hypoglycemia events were seen for patients with a baseline HbA1c ~ 7% with some HbA1c decline at week 26, and for patients with a baseline HbA1c above 8% with ~2% HbA1c decline at week 26.

The following liraglutide related adverse events were similar in pediatric patients as adult patients: higher risk for gastrointestinal-related adverse events, increases in pulse, and increases in mean lipase.

Most patients were in Tanner stage IV and V at baseline and reached final height at baseline; therefore, an evaluation of pubertal progression and effects on height were difficult to assess.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this efficacy supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Section 2

- Recommend reorganizing section 2.1 and 2.2 to include an Important dosing and administration section and a separate adult dosage section
- Recommend including a new pediatric dosage section which includes pediatric dosing language based on glycemic control. Pediatric dosing information should reflect that 0.6 mg daily dose of liraglutide is the starting dose, which may be increased by 0.6 mg weekly depending on glycemic control, to a maximum dose of 1.8 mg. The Applicant's proposed language that (b) (4) is not acceptable, since this language would omit the 0.6 mg dosing of liraglutide.
- (b) (4)
-

Section 5

- Recommend including information that notes that the risk of hypoglycemia in pediatric patients 10 years of age and older was higher with liraglutide regardless of concomitant antidiabetic therapies.

Section 6

- The clinical trial experience section will be updated with data from *ellipse*^{TM} and clinically important hypoglycemia events (with blood glucose<54 mg/dL with or without symptoms and severe hypoglycemia) will be included.
- The pediatric immunogenicity findings will be included.

Section 7

- Recommend including a new section which recommends dose adjustments to other antidiabetic therapies concomitantly administered with liraglutide.

Section 8

- The Clinical Consideration section for Pregnancy will be updated with language used across the class of drugs.
- The Pediatric Use section of the label will be updated to include information regarding the data which supports the pediatric indication. The higher risk of hypoglycemia with use of liraglutide, regardless of concomitant antidiabetic therapies will also be highlighted in this section.

Section 12

- The pharmacokinetic profile of liraglutide in pediatric in type 2 diabetes patients 10 years of age and older will be included.

Section 14

- The clinical trial experience section will be updated with data from the *ellipse*^{TM} study.
- Proposed information regarding (b) (4) will be deleted as this information is not clinically relevant and not consistent with the labeling approach in this section.
- Information regarding basal insulin dose modifications at trial start, and titration of liraglutide will be included.
- Additional patient characteristics, including BMI SDS, duration of diabetes, proportion of patients using basal insulin at baseline, and baseline HbA1c will be included in the text.
- Information regarding responder analyses will be added to the efficacy results table since responder analyses were pre-specified in the testing hierarchy and met statistical significance.
- (b) (4)

10.2. Nonprescription Drug Labeling

This section is not applicable to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no REMS recommended.

12. Postmarketing Requirements and Commitments

No new postmarketing requirement or commitment is recommended.

The following is considered fulfilled:

PMR 1583-2 A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.

13. Appendices

13.1. References

References are included throughout the document.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NN2211-1800

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 81		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: **Not applicable**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **Not applicable**	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NN2211-3659

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 333		

Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 6 investigators. Of these investigators one received an Honorarium/fees of $302,240 in the span of 5+ years ((b) (6) randomized). (b) (6) had disclosable financial interests below $100,000. Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Last Written Request issued (Amendment #2)

REVISED WRITTEN REQUEST, AMENDMENT #2

The prevalence of type 2 diabetes among pediatric patients is increasing, concurrent with the obesity epidemic. However, metformin is the only non-insulin treatment approved for use in children 10 years of age and older with type 2 diabetes. Metformin is limited by gastrointestinal adverse reactions and the need for multiple daily dosing in most cases. In addition, diabetes is a progressive disease such that patients may need additional antidiabetic therapy added to metformin to achieve adequate glycemic control. Liraglutide would provide a useful additional

treatment option for pediatric patients with type 2 diabetes based on the low risk of hypoglycemia and the fact that it does not have adverse effects on body weight. The pharmacokinetics of liraglutide in the pediatric population has been established from results of the pediatric clinical pharmacology trial: A Phase 1 Randomized, Double-blind, Placebo-Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics and Pharmacodynamics of Liraglutide in Pediatric Subjects (10 – 16 years and 11 month old) with Type 2 Diabetes. Efficacy of liraglutide must be established in the pediatric population because it is unknown whether the effects of liraglutide are sufficiently similar between adults and the pediatric population.

To obtain needed pediatric information on liraglutide, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- Nonclinical study:

Repeat-dose studies of long-acting glucagon-like peptide (GLP)-l receptor agonists in monkeys suggest that these drugs may accelerate the onset of puberty or the rate of maturation of males. In 52-week and 87-week studies of liraglutide in monkeys, most males were sexually immature at study initiation. In these studies, testes weight trended higher in liraglutide-treated male monkeys at clinically relevant exposures over the study duration. Transient exposure of immature rodents to GLP-1 receptor agonists can cause behavioral and endocrine changes that persist into adulthood. To assess the potential for liraglutide to cause accelerated development, a juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity is required (e.g., postnatal day 21-90). Endpoints for development in the study of liraglutide toxicity in juvenile rats must include assessment of effects on cognition (memory and learning), behavior (aggression and anxiety), age of onset of puberty, rate of sexual maturation, rate of overall growth, and reproductive organ maturation. The timing of this study can be concurrent with the proposed pediatric clinical study.

- *Clinical study:*

Study 1: A randomized and controlled study to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years. The study must contain a 26-week, double-blind, controlled period up until the primary efficacy endpoint. The study must have a 26-week controlled period after the primary efficacy endpoint, which, together with the double-blind period, totals at least 52 weeks in duration.

- *Objective of each study:*

Study 1:

- To establish the superiority of liraglutide at the maximum tolerated dose (0.6mg,

1.2 mg, or 1.8 mg) in combination with metformin controlling glycemia versus metformin and liraglutide placebo in children and adolescents (ages 10 to 17 years) with type 2 diabetes to support an indication for the treatment of type 2 diabetes in the pediatric population.

- To evaluate the long-term safety of liraglutide in the pediatric population.

- *Patients to be studied:*

The study must randomize at least 94 male and female adolescents age 10 years to 17 years. At least 30% of randomized patients must be 10-14 years old so that the effects of liraglutide on early puberty can be assessed. At least 30% of the randomized patients must be female.

All patients who receive run-in treatment with metformin must have at least 8 weeks of stable metformin therapy prior to randomization.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study Endpoints:*

Efficacy Endpoints:
The primary efficacy endpoint must be the change in hemoglobin A1c from baseline to the end of the 26-week double-blind treatment period and must be assessed by a centrally analyzed, NGSP-certified hemoglobin A1c assay.

Important secondary endpoints must include fasting plasma glucose assessed by a centrally analyzed plasma glucose assay as well as body weight.

The protocol must describe how patient compliance will be assessed.

Safety Endpoints must include:

Nature, frequency, severity, and relationship to treatment of all adverse events Vital signs including heart rate
Laboratory parameters including hematology, biochemistry, sex hormones, serum calcitonin and anti-liraglutide antibodies
Pubertal development based on Tanner staging
Growth parameters based on height standard deviation score
Incidence of hypoglycemia

- The following adverse events must be actively monitored:

Pancreatitis by adverse event reporting, serum amylase and lipase

Gastrointestinal adverse events
Thyroid adverse events, including serum calcitonin
Hypoglycemia using the American Diabetes Association definitions
Renal impairment by serum creatinine monitoring
Immune/hypersensitivity reactions
Acceleration of puberty

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

All adverse events must be captured when spontaneously reported.

A Data Monitoring Committee (DMC) must be included because the study is being performed in children, a potentially fragile population.

- *Known drug safety concerns and monitoring*: Safety issues that must be assessed include gastrointestinal tolerability, pancreatitis, hypersensitivity, dehydration and renal impairment, anti-liraglutide antibodies (and their impact on efficacy and safety), severe hypoglycemia, calcitonin and thyroid cancers, and acceleration of sexual maturation.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request.
If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

Dosage form - Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL)
Route of administration- Subcutaneous injection

Regimen- Depending on the tolerance level and efficacious dose in the participating individual, a dose of 0.6 mg, 1.2 mg, or 1.8 mg will be administered. Liraglutide and liraglutide placebo will be administered once daily by subcutaneous injection in the abdomen, thigh, or upper arm. After randomization, liraglutide or liraglutide placebo will be escalated weekly, starting at 0.6 mg and increasing with 0.6 mg increments. The starting and maintenance doses were determined based on FDA review of the results of the pediatric clinical pharmacology trial titled *A Phase 1 Randomized, Double-blind, Placebo- Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics and Pharmacodynamics of Liraglutide in Pediatric Subjects (10 - 16 years and 11 month old) with Type 2 Diabetes.*

Use an age-appropriate formulation in the study described above. If an age appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if
1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(l) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- Statistical information, including power of study and statistical assessments:

Patients must be allocated to the treatment arms of the study by a valid randomization procedure, in a 1:1 allocation. The treatment assignments from the time of randomization to the week at which the primary endpoint is determined must be double-blind.

The primary statistical evaluation of the active product arm compared to the comparator arm must control for Type I error at a two-tailed α of 0.05. The superiority test must be a two-sided test of the null hypothesis of no difference in the primary endpoint between the liraglutide +

metformin arm and the liraglutide placebo + metformin arm. The alternative hypothesis is that there is a difference between the two treatment arms. Superiority of liraglutide over liraglutide placebo will be concluded if the 95% confidence interval for the mean treatment difference for the primary endpoint lies entirely below 0%, implying that the corresponding two-sided p-value is less than 5%. The sample size of 47 patients in each of the two treatment arms (a total of 94 patients) will provide at least 80% power to detect a 0.7% difference (after adjusting for a 22% withdrawal rate for the liraglutide group) between the two treatment arms in HbAlc change from baseline, assuming a standard deviation of 1.2% and a two- tailed α of 0.05.

For the primary statistical analysis model, all available data will be used, including data collected after treatment discontinuation and rescue initiation. A pattern mixture model using a multiple imputation procedure will be used that will impute missing week 26 measurements based on the completers from the placebo arm. Missing week 26 HbA1c measurements for patients who are on liraglutide will be imputed using only baseline information. Missing week 26 HbA1c measurements for patients who are on placebo will be imputed using the patients available HbA1c data available throughout the trial. The imputation procedure will be iterated 10,000 times, thus generating 10,000 complete data sets including observed and imputed values. For each of the imputed data sets, the change in HbA1c from baseline to week 26 will be analyzed using an ANCOVA with treatment and stratification groups (gender*age group) as categorical fixed effects and baseline HbA1c as a covariate. The results obtained from analyzing the datasets will be combined using Rubin's rule to draw inference. The model will be used to compare liraglutide and liraglutide placebo at week 26.

The primary analysis population to analyze the primary efficacy endpoint should be the Full Analysis Set. The Full Analysis Set consists of all randomized patients who took at least one dose of study drug.

The study protocol should provide a detailed description of the primary analysis model. The protocol should also describe the additional sensitivity analyses of the comparison between liraglutide and liraglutide placebo in the primary HbA1c endpoint.

The analysis should include a descriptive summary of the primary and secondary efficacy results by age group, categorized by (10 -14 years) and (> 14 years). As stated above, at least 30% of randomized patients must be 10-14 years old.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that liraglutide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more

frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latina or Not Hispanic/Latina. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CPR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications available at ttp://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf

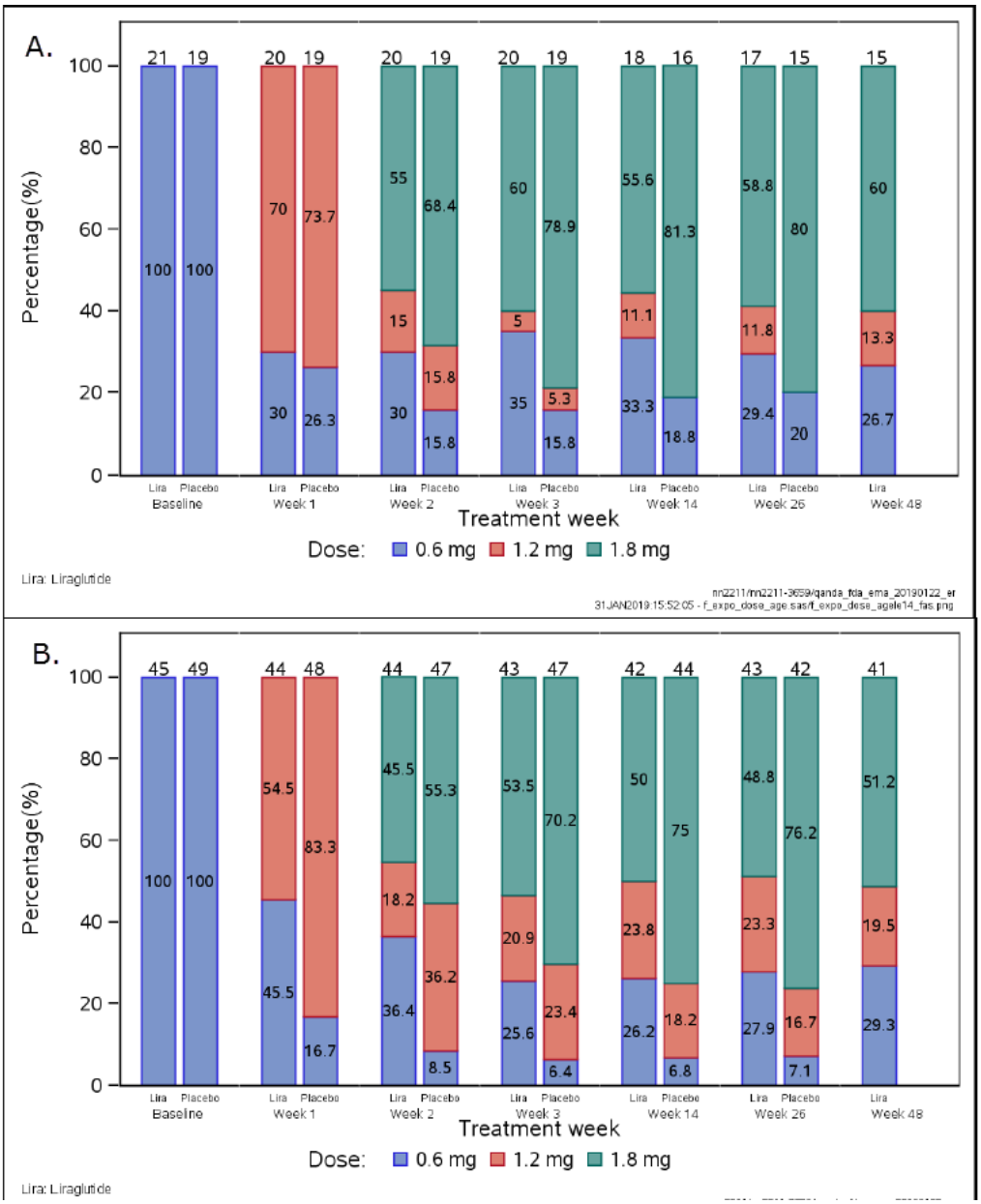
- *Timeframe for submitting reports of the study*: Reports of the above study must be submitted to the Agency on or before May 31, 2021. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

13.1. Additional Efficacy Analyses

Figure 37: A- prescribed liraglutide/placebo doses by treatment week for ages 10-14 years; B: prescribed liraglutide/placebo doses by treatment group for ages>14 years- FAS



Source: IR 20/1/19- figure 11 and 12\\CDSESUB1\evsprod\NDA022341\0417\m1\us

13.2. Additional Safety analyses

Table 28- AEs resulting in dose reduction, drug interruption, or drug withdrawal-TEAs- SAS

		Description of Actual Arm												
		Liraglutide				Placebo				All				
				Total				Total				Total		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Total**
Gastrointestinal disorders	Nausea	1	1.5%	1	1	1	1.5%	1	1	2	3.0%	2	2	2
	Abdominal discomfort	1	1.5%	1	1	.	.	0	0	1	1.5%	1	1	1
	Diarrhoea	1	1.5%	1	1	.	.	0	0	1	1.5%	1	1	1
Infections and infestations	Gastroenteritis	1	1.5%	1	1	.	.	0	0	1	1.5%	1	1	1
	Pneumonia	.	.	0	0	1	1.5%	1	1	1	1.5%	1	1	1
Metabolism and nutrition disorders	Hyperglycaemia	1	1.5%	1	1	1	1.5%	1	1	2	3.0%	2	2	2
Investigations	Glycosylated haemoglobin increased	.	.	0	0	1	1.5%	1	1	1	1.5%	1	1	1
Respiratory, thoracic and mediastinal disorders	Asthma	.	.	0	0	1	1.5%	1	1	1	1.5%	1	1	1
All	All	5	7.6%	5	5	5	7.4%	5	5	10	14.9%	10	10	10

Where (Action Taken with Study Treatment = DOSE REDUCED, DRUG INTERRUPTED, DRUG WITHDRAWN)
Source: reviewer generated table from Applicant datasets

Table 29- TEAEs occuring≥2 patients per PT term-SAS

		Description of Actual Arm				
		Liraglutide		Placebo		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
Gastrointestinal disorders	Nausea	19	28.8%	9	13.2%	28
	Diarrhoea	15	22.7%	11	16.2%	26
	Vomiting	17	25.8%	6	8.8%	23
	Abdominal pain	12	18.2%	5	7.4%	17
	Abdominal pain upper	2	3.0%	8	11.8%	10
	Dyspepsia	5	7.6%	1	1.5%	6
	Constipation	4	6.1%	1	1.5%	5
	Toothache	3	4.5%	1	1.5%	4
	Abdominal discomfort	2	3.0%	1	1.5%	3
Infections and infestations	Upper respiratory tract infection	6	9.1%	5	7.4%	11
	Influenza	4	6.1%	6	8.8%	10
	Gastroenteritis	7	10.6%	2	2.9%	9
	Pharyngitis	4	6.1%	4	5.9%	8
	Viral infection	2	3.0%	3	4.4%	5
	Bronchitis	2	3.0%	2	2.9%	4
	Tonsillitis	3	4.5%	1	1.5%	4
	Otitis media	1	1.5%	2	2.9%	3

		Description of Actual Arm				
		Liraglutide		Placebo		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
	Pneumonia	2	3.0%	1	1.5%	3
	Respiratory tract infection	2	3.0%	1	1.5%	3
	Urinary tract infection	1	1.5%	2	2.9%	3
	Conjunctivitis	1	1.5%	1	1.5%	2
	Gastroenteritis viral	1	1.5%	1	1.5%	2
	Localised infection	1	1.5%	1	1.5%	2
	Otitis externa	2	3.0%	.	.	2
	Sinusitis	1	1.5%	1	1.5%	2
	Vulvovaginal mycotic infection	.	.	2	2.9%	2
Nervous system disorders	Headache	14	21.2%	13	19.1%	27
	Dizziness	8	12.1%	2	2.9%	10
	Somnolence	.	.	3	4.4%	3
	Syncope	.	.	2	2.9%	2
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	4	6.1%	6	8.8%	10
	Cough	4	6.1%	4	5.9%	8
	Rhinorrhoea	1	1.5%	4	5.9%	5
	Epistaxis	1	1.5%	2	2.9%	3
	Rhinitis allergic	1	1.5%	1	1.5%	2
General disorders and administration site conditions	Pyrexia	4	6.1%	5	7.4%	9
	Fatigue	2	3.0%	3	4.4%	5
	Influenza like illness	3	4.5%	1	1.5%	4
	Asthenia	2	3.0%	1	1.5%	3
	Injection site atrophy	1	1.5%	1	1.5%	2
	Malaise	2	3.0%	.	.	2
	Pain	1	1.5%	1	1.5%	2
Investigations	Urine albumin/creatinine ratio increased	3	4.5%	3	4.4%	6
	Alanine aminotransferase increased	.	.	4	5.9%	4
	Lipase increased	3	4.5%	1	1.5%	4
	Blood creatinine increased	2	3.0%	.	.	2
	Blood follicle stimulating hormone increased	2	3.0%	.	.	2
	Glycosylated haemoglobin increased	1	1.5%	1	1.5%	2
	Hepatic enzyme increased	1	1.5%	1	1.5%	2
	Laboratory test abnormal	2	3.0%	.	.	2
Metabolism and nutrition disorders	Hyperglycaemia	5	7.6%	5	7.4%	10
	Decreased appetite	4	6.1%	3	4.4%	7
	Diabetes mellitus inadequate control	.	.	2	2.9%	2
	Dyslipidaemia	2	3.0%	.	.	2
	Vitamin B12 deficiency	1	1.5%	1	1.5%	2
Musculoskeletal and connective tissue disorders	Epiphyses premature fusion	3	4.5%	2	2.9%	5
	Musculoskeletal chest pain	3	4.5%	.	.	3
	Arthralgia	1	1.5%	1	1.5%	2

		Description of Actual Arm				
		Liraglutide		Placebo		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
	Back pain	2	3.0%	.	.	2
	Groin pain	1	1.5%	1	1.5%	2
	Scoliosis	2	3.0%	.	.	2
Injury, poisoning and procedural complications	Limb injury	3	4.5%	2	2.9%	5
	Ligament sprain	2	3.0%	2	2.9%	4
	Fall	1	1.5%	2	2.9%	3
	Accidental overdose	2	3.0%	.	.	2
Skin and subcutaneous tissue disorders	Rash	4	6.1%	1	1.5%	5
	Acne	2	3.0%	.	.	2
	Pruritus	1	1.5%	1	1.5%	2
	Rash generalised	1	1.5%	1	1.5%	2
Reproductive system and breast disorders	Dysmenorrhoea	3	4.5%	6	8.8%	9
Renal and urinary disorders	Dysuria	1	1.5%	1	1.5%	2
	Microalbuminuria	1	1.5%	1	1.5%	2
Ear and labyrinth disorders	Ear pain	1	1.5%	1	1.5%	2
Eye disorders	Visual acuity reduced	2	3.0%	.	.	2
Vascular disorders	Hypertension	.	.	2	2.9%	2

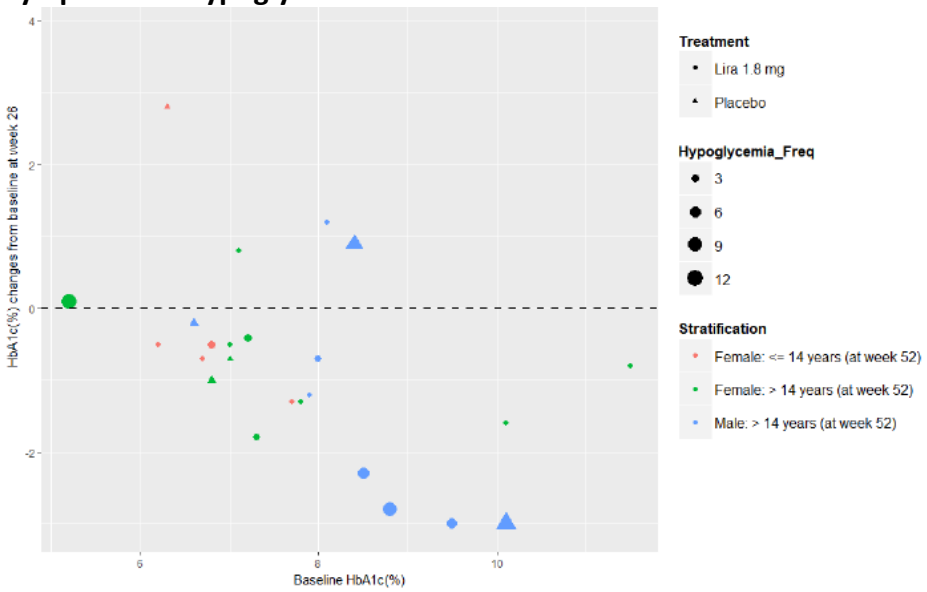
157 rows have been excluded.
Where(Total Count > 1.897 & Total Count < 30 | Is Missing(Total Count))
Source: Reviewer derived table derived from datasets.

Table 30- Severe events- SAS

		Description of Actual Arm						
		Liraglutide		Placebo		All		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Total**
Total patients		66		68		134		
Patients with severe events		*5*	*7.6%*	*6*	*8.8%*	*11*	*8.2%*	
Gastrointestinal disorders	Abdominal pain	2	3.0%	1	1.5%	3	4.5%	3
	Constipation	.	.	1	1.5%	1	1.5%	1
	Dyspepsia	1	1.5%	.	.	1	1.5%	1
	Nausea	1	1.5%	.	.	1	1.5%	1
	Vomiting	1	1.5%	.	.	1	1.5%	1
	All	5	7.6%	2	2.9%	7	10.5%	7
Infections and infestations	Appendicitis perforated	.	.	1	1.5%	1	1.5%	1
	Pneumonia	.	.	1	1.5%	1	1.5%	1
	All	.	.	2	2.9%	2	2.9%	2
Nervous system disorders	Headache	2	3.0%	.	.	2	3.0%	2
	All	2	3.0%	.	.	2	3.0%	2
Renal and urinary disorders	Dysuria	.	.	1	1.5%	1	1.5%	1
	Proteinuria	.	.	1	1.5%	1	1.5%	1
	All	.	.	2	2.9%	2	2.9%	2
Metabolism and nutrition disorders	Hyperglycemia	.	.	1	1.5%	1	1.5%	1
	All	.	.	1	1.5%	1	1.5%	1
Musculoskeletal and connective tissue disorders	Scoliosis	1	1.5%	.	.	1	1.5%	1
	All	1	1.5%	.	.	1	1.5%	1
Respiratory, thoracic and mediastinal disorders	Asthma	.	.	1	1.5%	1	1.5%	1
	All	.	.	1	1.5%	1	1.5%	1

Source: Reviewer generated from submitted datasets

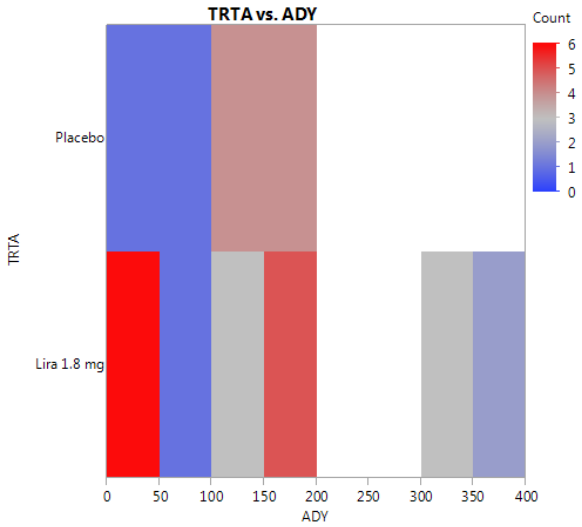
Figure 38- Chante in HbA1c and baseline HbA1c with sizing points based on number of documented symptomatic hypoglycemia



**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).*

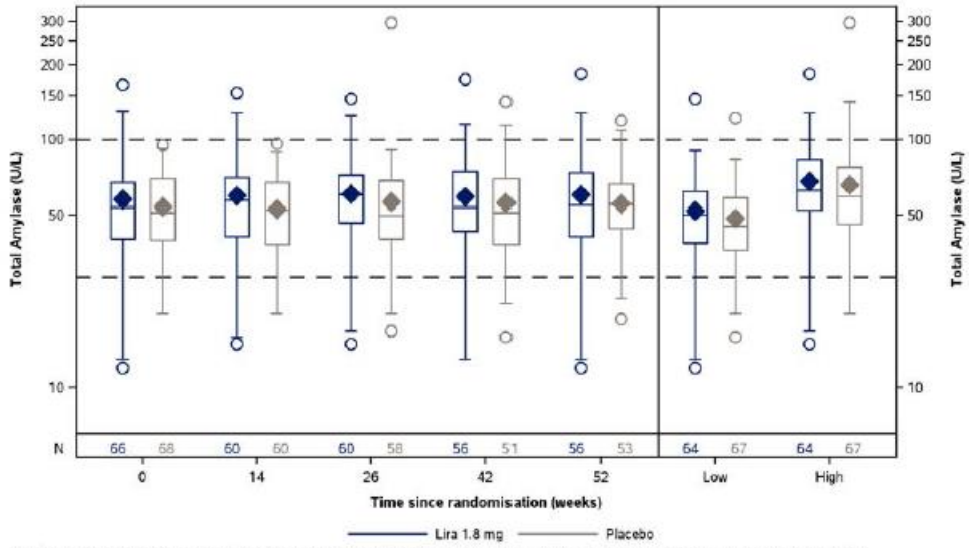
Source: Dr. Kim's review, Figure 8

Figure 39- Hypoglycemia<54 mg/dL events during the trial-TEAEs-SAS



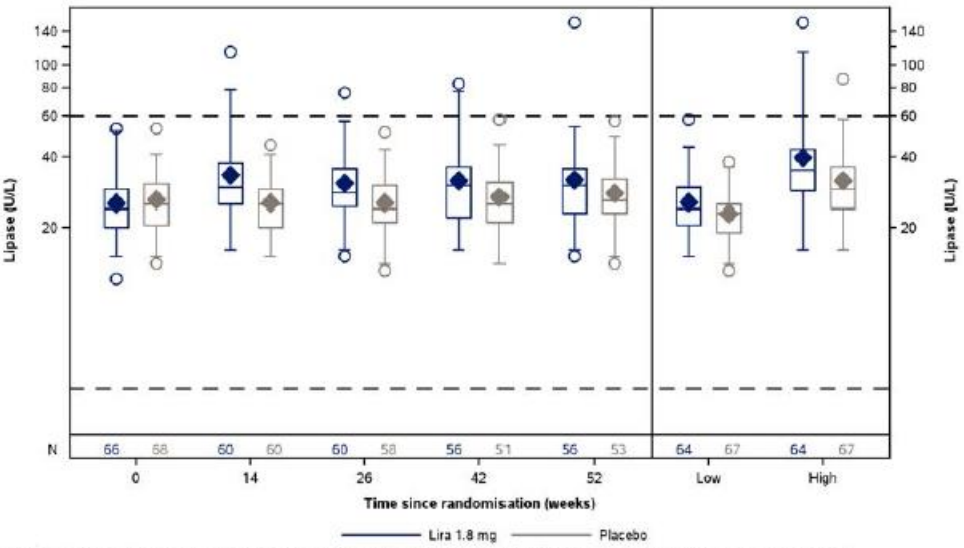
Source: reviewer derived graph from the new Applicant provided hypoglycemia datasets

Figure 40- Total amylase and lipase box-plot trends over time-SAS



Lira: Liraglutide. Dashed lines show the minimum of lower and maximum of upper normal ranges, if ranges differ by age or sex. Box legend: Mean (symbol), median (centre line), 25th and 75th percentiles (box), and extremes (circles). Whiskers are from 2.5% to 97.5%. Number of subjects contributing to the data points appears in the bottom panel. High/Low are subject-wise highest/lowest value across all post baseline values including values captured at unscheduled visits and retest. Due to skewed data the y-axis is set to log-scale.

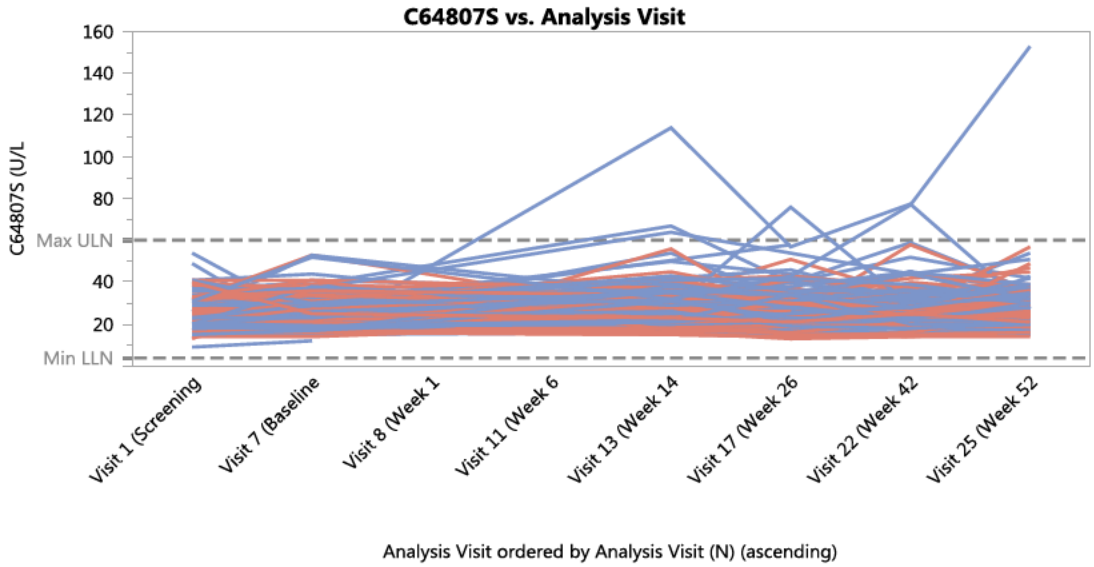
Source: CSR figure 14.3.5.31



Lira: Liraglutide. Dashed lines show the minimum of lower and maximum of upper normal ranges, if ranges differ by age or sex. Box legend: Mean (symbol), median (centre line), 25th and 75th percentiles (box), and extremes (circles). Whiskers are from 2.5% to 97.5%. Number of subjects contributing to the data points appears in the bottom panel. High/Low are subject-wise highest/lowest value across all post baseline values including values captured at unscheduled visits and retest. Due to skewed data the y-axis is set to log-scale.

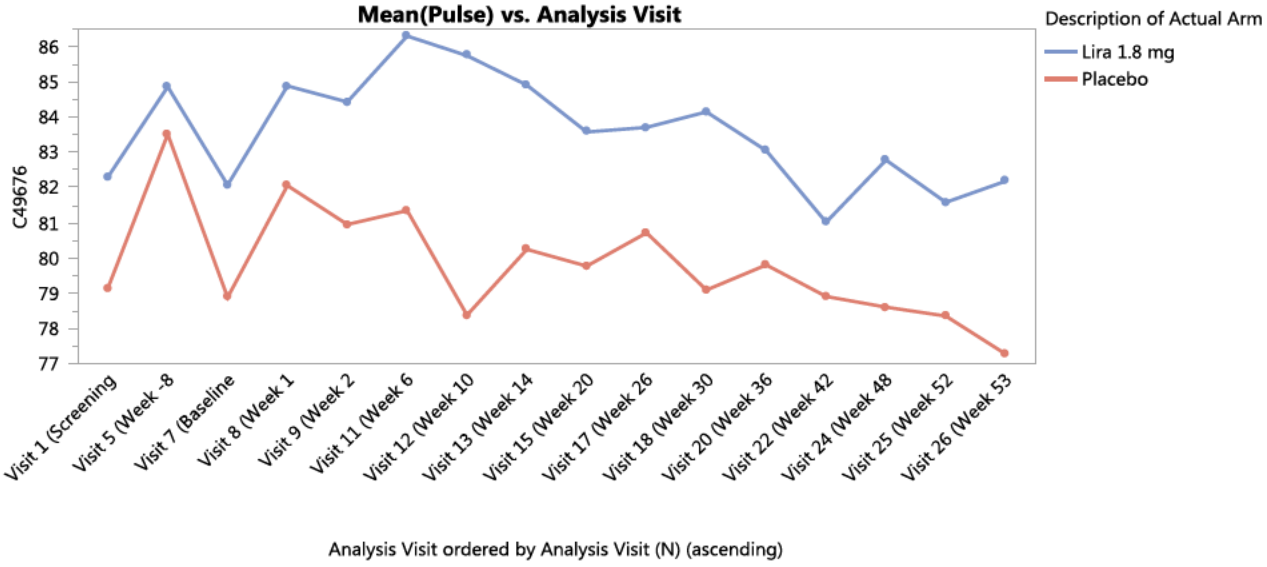
Source: CSR figure 14.3.5.32

Figure 41- Subject level time trends for Lipase (U/L)



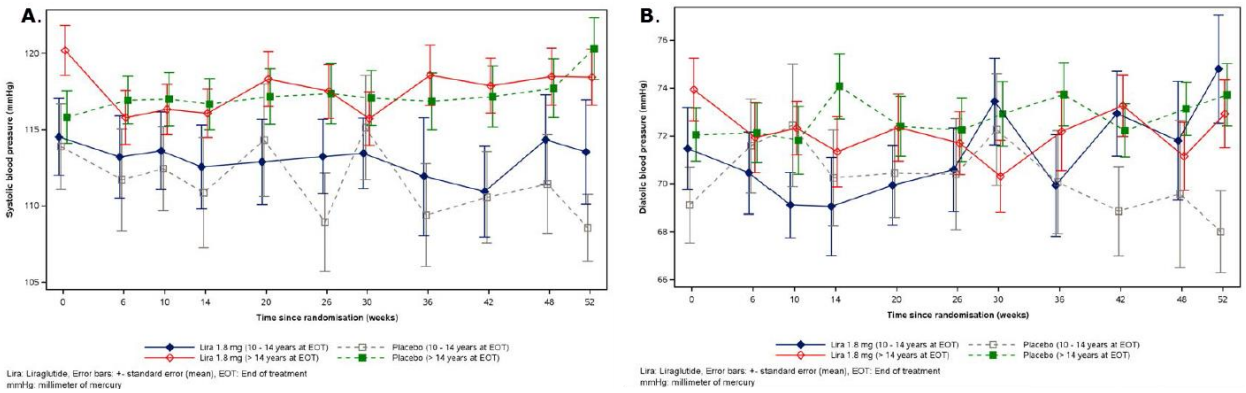
Source: Reviewer derived graph from Applicant's datasets

Figure 42- Observed values for mean pulse (beats/min) by visit



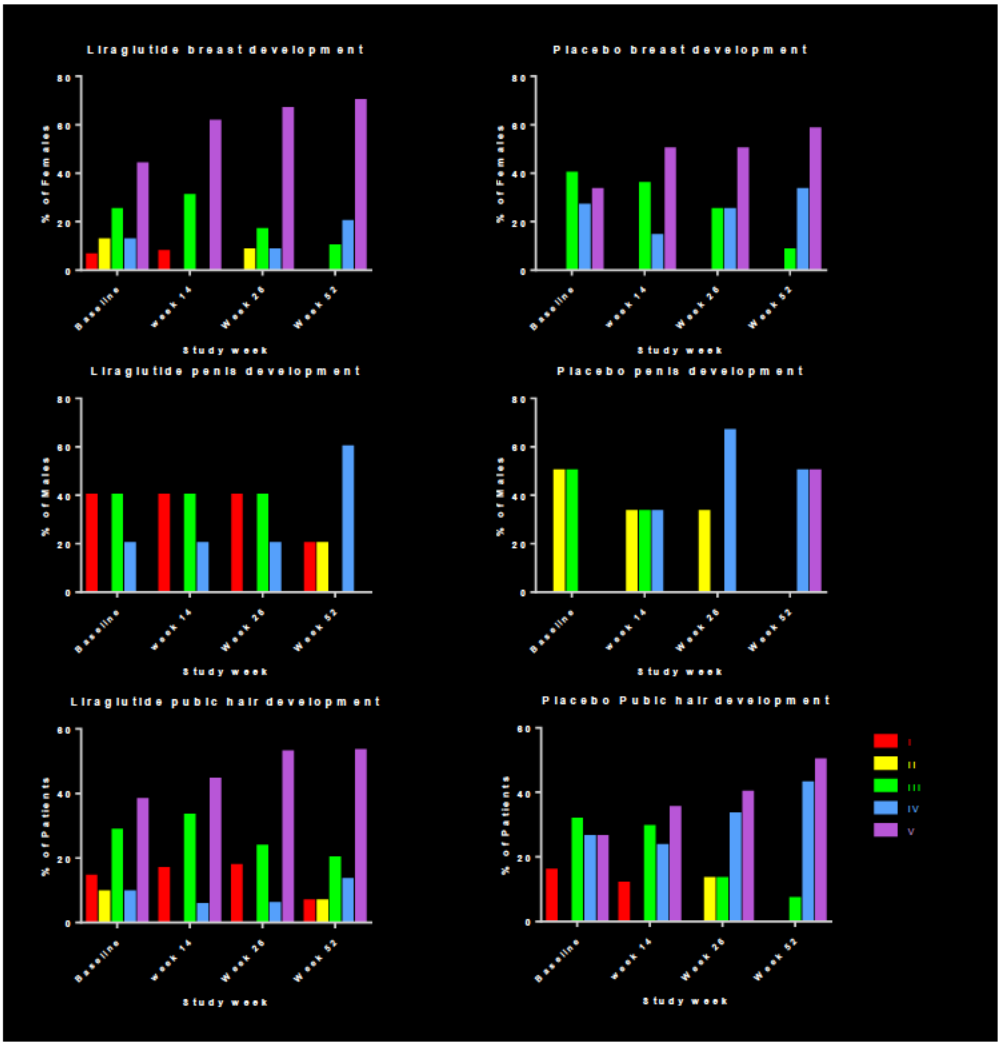
Source: Reviewer derived graph from Applicant's datasets

Figure 43- systolic (A.) and diastolic (B) blood pressure by treatment week-mean plot of observed values by age group 10-14 vs >14 years-FAS



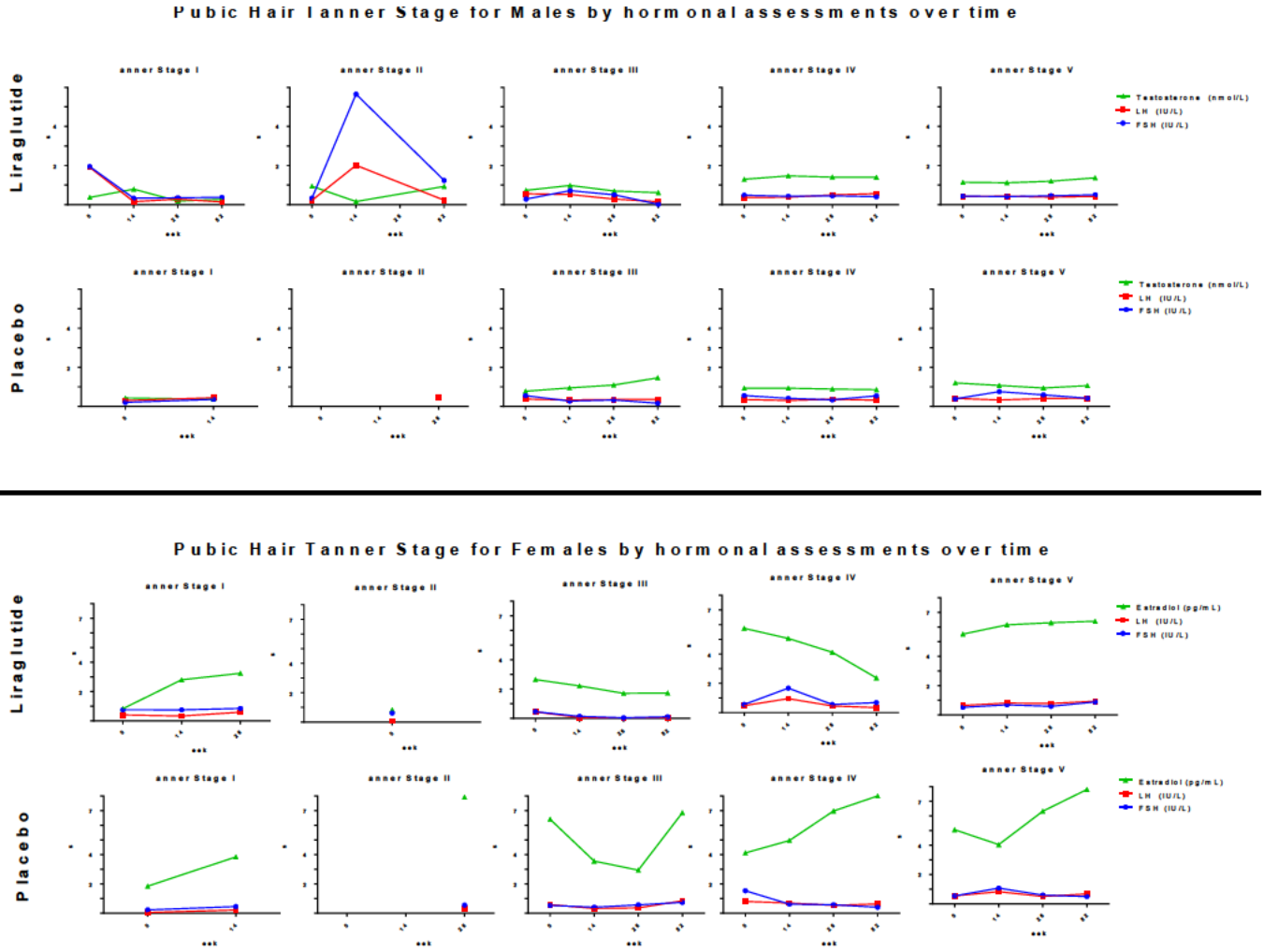
Source: IR dated 2/1/19 \\CDSESUB1\evsprod\NDA022341\0417\m1\us

Figure 44- Puberty progression by breast, penis and pubic hair development and testicular volume over time for ages 10-14- SAS



Source: IR received 3/1/19 \\CDSESUB1\evsprod\NDA022341\0424\m1\us

Figure 45 – Hormonal assessments by Tanner Stage for Males and Females



Source: data from information request \\CDSESUB1\evsprod\NDA022341\0430 was graphed by reviewer

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANIA A CONDARCO
06/17/2019 02:20:55 PM

LISA B YANOFF
06/17/2019 02:34:32 PM