CLINICAL PHARMACOLOGY REVIEW

BLA	208471/S004
Submission Dates	30th Sep and 25th Nov 2020
Brand Name	ADLYXIN
Generic Names	Lixisenatide/AVE0010
Reviewer(s)	Harisudhan Thanukrishnan, Ph.D. Hezheng Wang, Ph.D.
Team Leader(s)	Manoj Khurana, Ph.D. Justin Earp, Ph.D.
OCP Division(s)	Division of Cardiometabolic and Endocrine Pharmacology (DCEP) and Division of Pharmacometrics (DPM)
OND Division	Division of Diabetes, Lipid Disorders and Obesity (DDLO)
Sponsor	Sanofi-Aventis U.S. LLC
Formulation; Strength	3 mL solution in prefilled injector pen; 50 or 100 mcg/mL
Relevant IND	062724
Indication	To improve glycemic control in adults with type 2 diabetes mellitus together with diet and exercise

Purpose

This document summarizes clinical pharmacology assessment of the final study report for Study TDR14311 "*Randomized, double-blind, placebo-controlled, dose escalation study on safety, pharmacokinetics and pharmacodynamics of lixisenatide in pediatric patients with Type 2 diabetes mellitus not adequately controlled with metformin and/or basal insulin*", submitted in response to Post-marketing Requirement (PMR) under Section 506B.

Recommendations:

OCP/DCEP has reviewed the PMR study 3102-1 (TDR14311) and found it acceptable to support PMR fulfilment decision. This recommendation should be communicated to the sponsor as appropriate.

Background

Two Post-marketing required studies under Section 505B were issued at the time of approval of lixisenatide (see Approval Letter for ADLYXIN dated 27 July 2016):

3102-1 Conduct a repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

Study Completion: March 2018
Final Report Submission: September 2018

3102-2 Conduct a 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR 3102-1) have been submitted to and reviewed by the Agency.

Final Protocol Submission: March 2019
Study Completion: March 2024
Final Report Submission: September 2024

The sponsor was released from PMR study 3102-2 (see PMR/PMC released letter from FDA dated 01 Jul 2019).

In addition, one PMR study 3102-3 under Section 505(o) (Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes patients treated with lixisenatide to determine the incidence of neutralizing antibodies (NAb) and anti-lixisenatide antibodies that are cross-reactive with endogenous GLP-1 and glucagon peptides and are capable of neutralizing these endogenous peptides) was fulfilled by sponsor (see PMR fulfilled letter from FDA dated 28 Oct 2020).

The protocol for this study was submitted to IND 062724 on 27th Oct 2015, amendment 01 was only not applicable to US, amendment 02 was submitted on 15th Sep 2016 in Serial No. 0547 and amendment 03 was submitted on 19th Jul 2017 in Serial No. 0560. Final study report was submitted to BLA 208471 on 17th July 2020 in Serial No.0092.

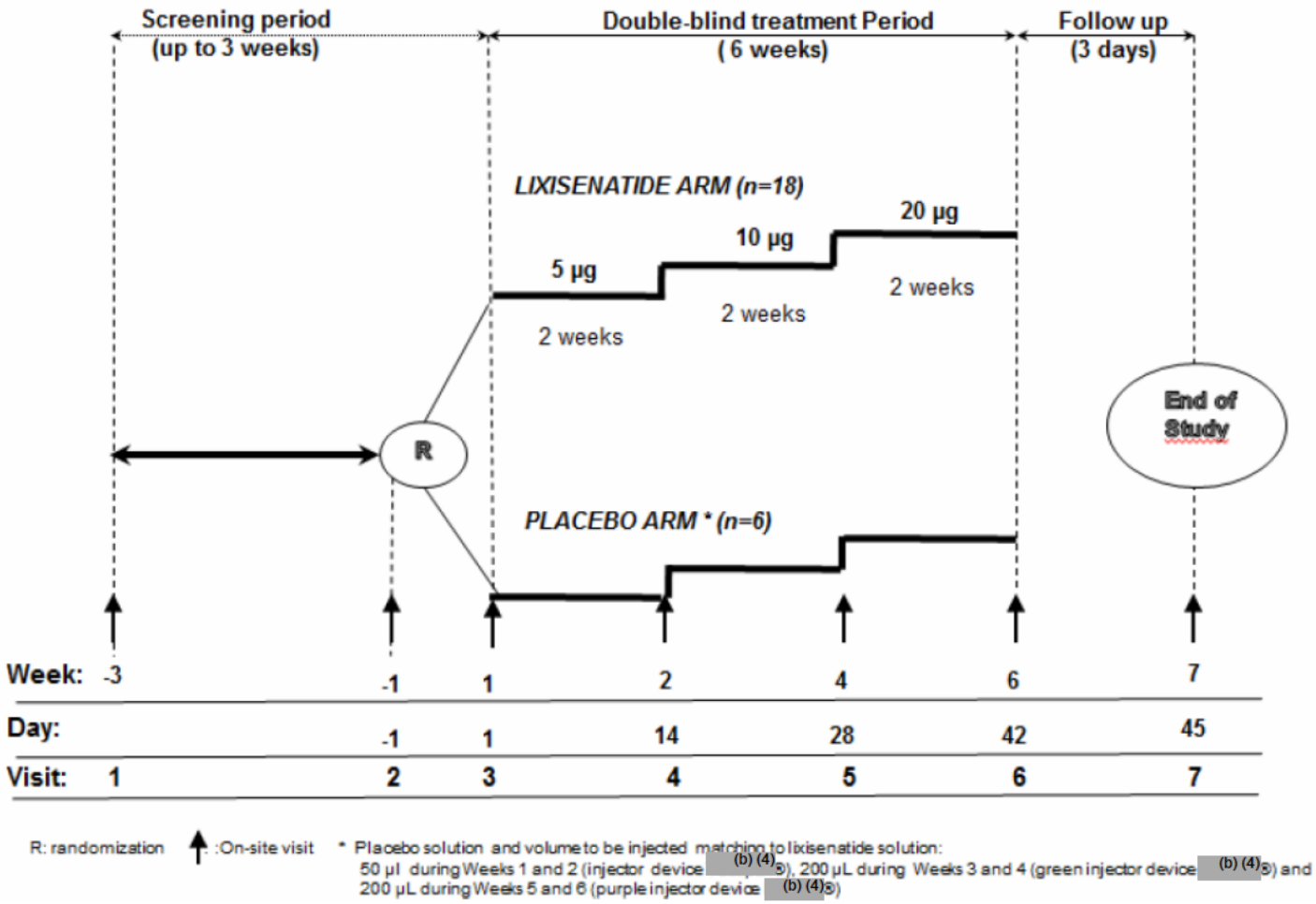
Findings of Current Submission

Design of Study TDR 14311

Study 14311 was a randomized, double-blind, placebo controlled, dose escalation study on safety, pharmacokinetics (PK) and pharmacodynamics (PD) of lixisenatide in pediatric patients with Type 2 diabetes mellitus (T2DM) not adequately controlled with metformin and/or basal insulin.

The screening visit occurred within 21 days of the start of randomization. On Day-1 of Treatment Period, subjects were randomized in a 3:1 ratio to receive lixisenatide or matching placebo once daily. The treatment period was divided into 3 dose escalation steps of 2 weeks each, starting with 5 µg, then 10 µg and 20 µg lixisenatide or matching placebo. Subjects were followed up until 3 days after the last dose of the 6-week study, as shown in Figure 1:

Figure 1. Design and assessment schedule of Study TDR14311.



Source: Figure 1 in Clinical Study Report for Study No. TDR14311

The primary endpoint was assessment of the safety of 14-day repeated lixisenatide doses of 5 µg, 10 µg and 20 µg as compared to placebo in pediatric patients with T2DM.

Pharmacokinetic Assessment:

The secondary pharmacokinetic objectives for this study were to evaluate the plasma concentrations of lixisenatide after repeated doses of 5 µg, 10 µg and 20 µg and pharmacokinetic parameters of repeated lixisenatide doses of 20 µg in pediatric patients with T2DM. Blood samples for PK analysis were collected prior to the administration of lixisenatide/placebo and standardized breakfast and at post-dose time points on Days 14, 28 and 42, following repeated dosing of 5, 10 or 20 µg of lixisenatide, respectively. As indicated in Table 1, four blood samples were taken in the period of 0 (P00/pre-dose) to 2.5 h after each 5 and 10 µg dose and eight blood samples were taken after each 20 µg dose in the period of 0 to 4.5 h after dose.

Table 1. Blood sampling for lixisenatide plasma concentrations in Study No. TDR14311

Time (hour/min)	0 H	0H30	1 H	1H30	2 H	2H30	3H30	4H30
T (h)	T0[a]	T0.5[b]	T1	T1.5	T2	T2.5	T3.5	T4.5
Visit/Day:								
V4/D14	P00	P01		P02		P03		
V5/D28	P00	P01		P02		P03		
V6/D42	P00	P01	P02	P03	P04	P05	P06	P07

a Prior to IMP administration

b Just prior to the standardized breakfast ingestion

Source: Table 1 in Synopsis of clinical Study Report for Study No. TDR14311

Pharmacodynamic Assessments:

The secondary pharmacodynamic endpoints were to evaluate the change from baseline in fasting (FPG) and post-prandial (PPG) plasma glucose concentrations during a standardized meal test after repeated doses of lixisenatide 5 µg, 10 µg and 20 µg in comparison to placebo. Plasma glucose was measured using blood samples taken on Day-1 (Baseline), Day 14, Day 28, and Day 42, as indicated in Table 2. The first blood sampling (T0) for plasma glucose was drawn after 8-hour overnight fasting, 30 min prior to the standardized breakfast and prior to dosing of investigational medical product on Days 14, 28 and 42.

- Change from baseline in fasting and postprandial plasma glucose excursion i.e., difference T1.5-T0 and T2.5-T0, on Days 14, 28 and 42, following repeated dosing of 5, 10 or 20 µg of lixisenatide, respectively.
- Change from baseline in plasma glucose $AUC_{0\text{-}4.5h}$, on Day 42 following repeated dosing at 20 µg

Table 2. Blood sampling for plasma glucose in Study No. TDR14311

Time (hour/min)	0 H	1H	1H30	2H	2H30	3H30	4H30
T (h)	T0[a]	T1	T1.5	T2	T2.5	T3.5	T4.5
Visit/Day:							
V2/Day-1	X	X	X	X	X	X	X
V4/D14	X		X		X		
V5/D28	X		X		X		
V6/D42	X	X	X	X	X	X	X

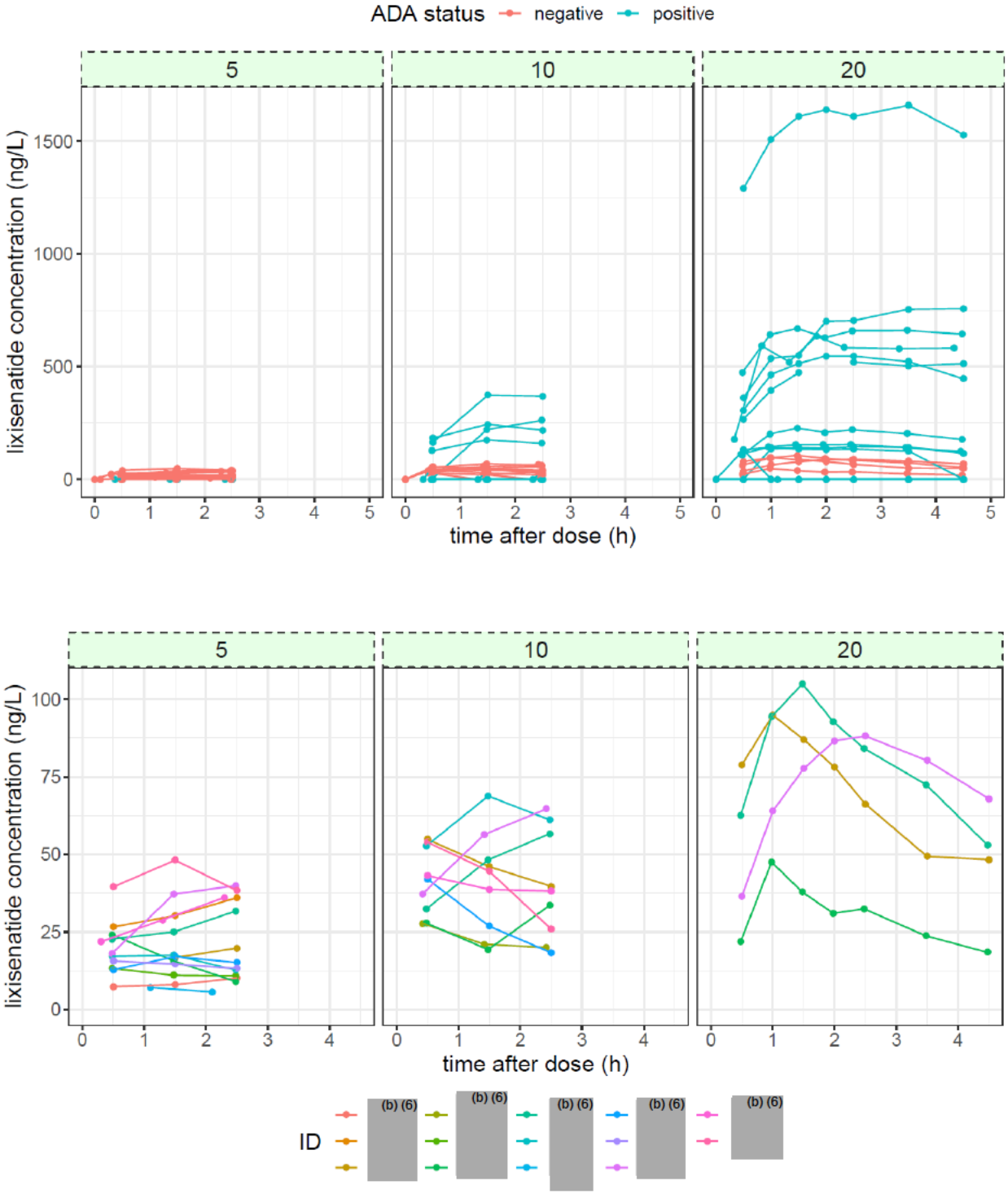
a 30 min before to the standardized breakfast ingestion and prior to IMP administration at V4/D14, V5/D28 and V6/D42

Source: Table 2 in Synopsis of clinical Study Report for Study No. TDR14311

Summary of Results from the study CSR:

- Twenty-three patients were randomized and treated in the study: 5 received placebo and 18 received lixisenatide. One patient in the lixisenatide group did not complete the study treatment period due to poor compliance to the protocol. All patients received their assigned treatment of placebo or lixisenatide for at least 42 days. Cartridges were used for lixisenatide and placebo (for the 5 µg dose) or pens were used (for the 10 µg and 20 µg doses).
- Patients were 13 through 17 years of age at baseline, with the median age being 16 years in both groups. Overall, 16 patients were female (69.6%) and 16 patients (69.6%) were white. The mean body weight and BMI were slightly higher in the placebo group (98.0 kg, 37.4 kg/m^2) than in the lixisenatide group (91.3 kg, 33.2 kg/m^2). The baseline mean HbA1c values were similar between the placebo group (8.14%) and the lixisenatide group (8.16 %).
- Repeated doses of lixisenatide 5 µg, 10 µg and 20 µg were safe and well tolerated in pediatric patients with T2DM of age ≥10 and <18 years old, on top of metformin and/or basal insulin. The overall safety results from this study were consistent with the known safety profile of lixisenatide in adults.
- All PK samples were analyzed within the documented stability period (24 months at -20 °C) using validated assay methods DOH1569 and DOH1570, both of which employ the double-antibody sandwich immunoassay technique. DOH1569 has an acid dissociation step (assay range is 100-5000 pg/mL), whereas DOH1570 has no acid dissociation step (but has a different assay range of 5.5-220 pg/mL). All samples (N=359) were first analyzed using DOH1569 but only those falling below the LLOQ and with a negative ADA (N=200) were selected for re-assay with DOH1570. The performance of calibration and quality control standards as well as the incurred sample reproducibility were found to be within the acceptance limits for both methods and the plasma concentration results from the bioanalytical runs are considered acceptable.
- Anti-lixisenatide antibodies were analyzed using a validated assay based on surface plasmon resonance (SPR) employing Biacore technology. Samples were first analyzed in a screening assay followed by a confirmatory assay. To be classified antibody-positive, a subject had to be above the cut-point for both binding and enhancement steps.
- Patients with anti-drug antibodies (ADA) were summarized by dose level. Mean concentrations and inter-subject variability were generally higher for patients with positive ADA status however, mean lixisenatide concentrations generally increased with each increase in dose irrespective of ADA status, as shown in Figure 2. The PK parameters at 20 µg dose level were summarized by antibody status, as in Table 3. At 20 µg lixisenatide, the mean C_{max} and $AUC_{0\text{-}4.5h}$ were approximately 6- to 9-fold higher for ADA-positive patients compared to ADA-negative patients.
- Exploratory analysis results for PD parameters are presented in Figure 3 and Table 4. The estimated treatment difference (lixisenatide versus placebo) was -4.20 mmol/L for the change from baseline to Day 42 in FPG and -31.18 mmol/L for the change from baseline to Day 42 in glucose $AUC_{0\text{-}4\ 5h}$. A dose-dependent decrease in mean 1H-PPG and 2H-PPG was observed in the lixisenatide group, with the maximum decrease observed at the 20 µg lixisenatide dose. The estimated treatment difference (lixisenatide versus placebo) for the change from baseline to Day 42 was -3.71 mmol/L for 1H-PPG and -3.85 mmol/L for 2H-PPG.

Figure 2. Lixisenatide concentrations versus time after dose by anti-lixisenatide antibody status, facetted by dose (upper panel) and lixisenatide concentrations versus time after dose in patients of study TDR14311 with negative anti-lixisenatide antibody status, facetted by dose and colored by ID (lower panel)



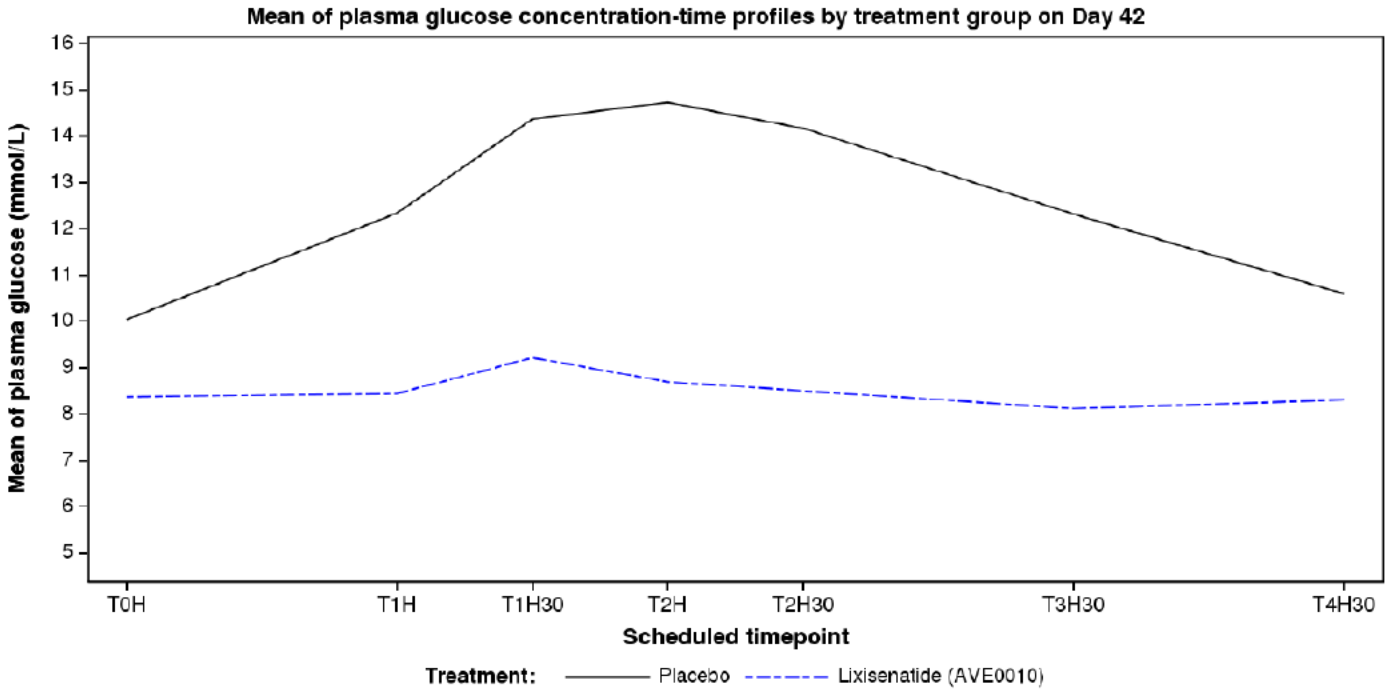
Source: Figure 9 in Amended final Population PK study report POH0636

Table 3. Mean ± SD (geometric mean) [CV%] of lixisenatide pharmacokinetic parameters following repeat subcutaneous administration of 20 µg lixisenatide

PK parameters	ADA negative	ADA positive
N	4	14
C_{max} (pg/mL)	83.9 ± 25.2 (80.4) [30]	508 ± 453 [b] (362) [89]
t_{max} [a] (h)	1.2 (0.9,2.5)	2.0 [b] (0.5,4.5)
$AUC_{0-4.5}$ (pg.h/mL)	267 ± 96.1 (250) [36]	2300 ± 1940 [c] (1710) [84]

a Median (Min, Max)
b n = 11; all results were <LLOQ for Subjects [redacted] (b) (6), and [redacted] (b) (6).
c n = 9; not calculable for Subjects [redacted] (b) (6) and [redacted] (b) (6) where t_{last} was 3.5 h or where there were <3 quantifiable samples, respectively.
Source: Table 22 in clinical Study Report for Study No. TDR14311

Figure 3. Mean of plasma glucose concentration-time profiles by treatment group on Day 42



Source: Figure 16.2.6.5.5.1 in supportive information for clinical Study Report for Study No. TDR14311

Table 4. Exploratory analysis and point estimates of treatment differences (with 95% confidence intervals) on changes from baseline in FPG, in Glucose AUC0-4.5, 1H-PPG and 2H-PPG excursion

Comparison	Visit	Parameter	Point estimate	95% CI
Lixisenatide (AVE0010) 5 ug vs. Placebo	D14	Fasting Plasma Glucose (mmol/L)	-2.8314	(-4.5238 to -1.1391)
	D14	1 Hour Postprandial Plasma Glucose (mmol/L)	-1.6870	(-4.1511 to 0.7770)
	D14	2 Hours Postprandial Plasma Glucose (mmol/L)	0.3122	(-1.6938 to 2.3182)
Lixisenatide (AVE0010) 10 ug vs. Placebo	D28	Fasting Plasma Glucose (mmol/L)	-3.1367	(-5.7946 to -0.4787)
	D28	1 Hour Postprandial Plasma Glucose (mmol/L)	-2.2826	(-4.7024 to 0.1371)
	D28	2 Hours Postprandial Plasma Glucose (mmol/L)	-2.1223	(-4.3229 to 0.0782)
Lixisenatide (AVE0010) 20 ug vs. Placebo	D42	Fasting Plasma Glucose (mmol/L)	-4.1971	(-6.7949 to -1.5994)
	D42	1 Hour Postprandial Plasma Glucose (mmol/L)	-3.7132	(-6.7572 to -0.6691)
	D42	2 Hours Postprandial Plasma Glucose (mmol/L)	-3.8537	(-6.7604 to -0.9470)
	D42	Glucose AUC (mmol.h/L)	-31.1846	(-46.2485 to -16.1207)

Source: Table 16.2.6.5.2 in supportive information for clinical Study Report for Study No. TDR14311

Reviewer's comments:

The review team acknowledges the completion of this PMR study. The results are summarized and found acceptable. The sponsor is not proposing a change to the indication or seeking approval for pediatric use based on the study results.

1. Population PK analysis

1.1 Review Summary

The applicant's population pharmacokinetics (PopPK) analysis for lixisenatide is acceptable, to support the submission as outlined in Table 1. The applicant applied a Bayesian approach based on a previously developed PopPK model in NDA208471 (healthy adult subjects and patients) to study TDR14311 (pediatrics) and PDY6797 (adult patients), with its parameter estimates as prior estimates for the assessment of individual parameters and concentration predictions for exposure-response analysis.

The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The visual predictive check (VPC) plots showed a good agreement between the observed and the simulated concentrations. In addition, under quality assessment, there is no clear bias between predicted and observed concentration.

Table 1. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Intrinsic and extrinsic factors	Intrinsic factor	Based on a model optimization on a previous population pharmacokinetic base model, AUC were predicted for pediatric and adult patients, which is used in exposure-response analysis.	Based on evaluation of the final model on likelihood of the data, goodness-of-fit plots, η-shrinkage, VPC, quality assessment and measures for bias and precision, the final model is acceptable.
	Extrinsic factor		
Derive exposure metrics for Exposure-response analyses	AUC		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 7).
Predict exposures at alternative dosing regimen	NA		NA

1.2 Introduction

The primary objectives of applicant's analysis were to:

- characterize the pharmacokinetics of lixisenatide in the anti-drug antibody (ADA) negative pediatric patients with type 2 diabetes mellitus (T2DM) from 10 to less than 18 years of age and provide individual

estimates of exposure metrics, i.e. area under the concentration-time curve (*AUC)* using a Bayesian approach based on a previously developed PopPK model for exposure-response analysis.

- evaluate allometric principles appropriateness for clearance and volume of distribution of lixisenatide.

1.3 Model development

Data

The data to be analyzed were comprised of ADA negative lixisenatide pharmacokinetic (PK) samples and by the demographic characteristics collected in studies TDR14311 and PDY6797, which were assessed by a maximum a posteriori probability (MAP) Bayesian approach. Study TDR14311 was a randomized, placebo-controlled, 6-week, double-blind, multicenter, multi-national, dose escalation trial (subcutaneous once-daily doses of 5, 10, and 20 µg lixisenatide) on safety, PK and pharmacodynamics (PD) of lixisenatide in pediatric patients (≥10 to <18 years) with T2DM not adequately controlled with metformin and/or basal insulin. Study PDY6797 was a randomized, placebo-controlled, 5 to 6-week, double-blind, multicenter, multinational, dose escalation (either once or twice daily following dose escalation from 5 to 30 µg) trial of lixisenatide in Japanese and Caucasian adult patients with T2DM not adequately controlled with sulfonylurea or sulfonylurea and metformin.[1]

For comparison with adults, the Caucasian subset of patients included in study PDY6797 was considered to balance the amount of data between pediatric and adult patients as well as to avoid ethnicity/race to act as a confounder.

Lixisenatide concentrations in the presence of ADAs and concentrations below the lower limit of quantification (LLOQ) were excluded from the analysis by using the missing data variable in non-linear mixed effect modeling (NONMEM) software. In total the dataset contained 1827 lixisenatide plasma concentrations from 52 patients (n = 14 pediatric patients). For the analysis 43.8% of the samples were excluded due to either positive ADA status or concentrations <LLOQ, i.e. 1026 samples remained for analysis, shown in Table 2 and 3.

Table 2: Overview of included and excluded PK samples (observations)

	Level	N	%
SAMPLES	excluded	801	43.8
	included	1026	56.2

Table 3: Overview of subjects and observations with anti-lixisenatide antibody negative status

Study	N, subjects	N, >LLOQ	N, <LLOQ	% LLOQ
TDR14311	18	92	36	28.1
PDY6797	38	934	461	33.0

Source: study-poh0636 on Page 25 (link).

[1] *Source: study-poh0636 on Page 3 (link).*

Reviewer comment: The pediatrics with available PK dataset in study TDR14311 is 14 rather than 18 because 4 subjects (unique subject ID: (b) (6)) were excluded due to either the presence of ADAs or concentrations below LLOQ.

Study TDR14311 included only adolescents (age range: 14 to 17 years) and no children (age range: 10 to 12 years), which shows that body weight at baseline largely overlaps between adult and pediatric patients, with a slight tendency to higher body weight (median 81 versus 92 kg) in pediatric patients, shown in Table 4.

Table 4: Summary statistics of baseline demographic covariates

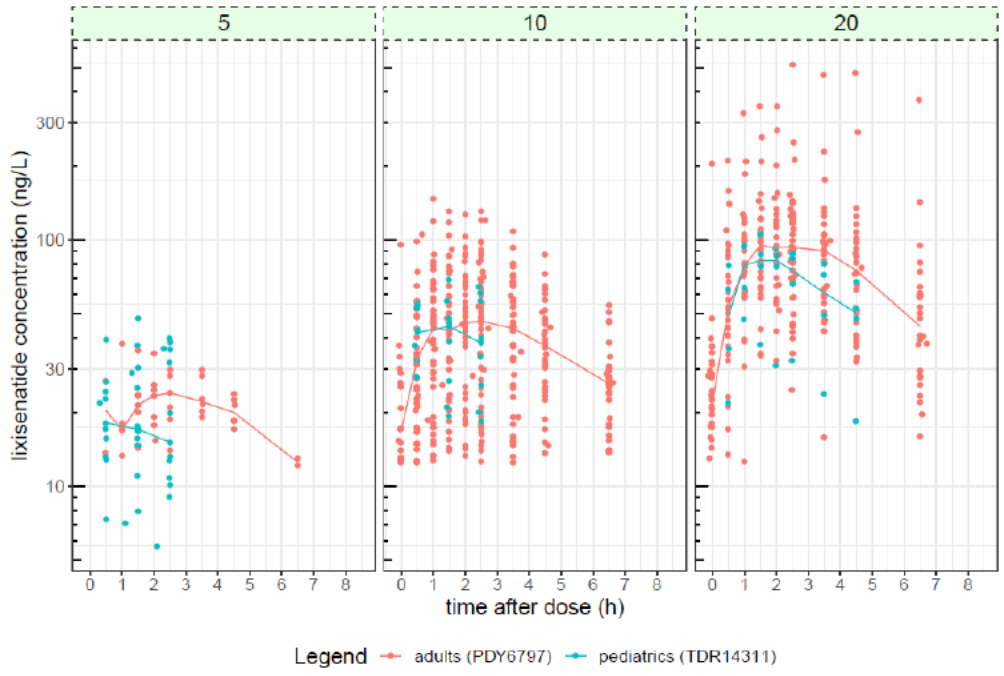
	Group	N	Mean	SD	Min	Median	Max
Age (y)	adults (PDY6797)	38	62.13	8.04	44.00	62.00	75.00
	pediatrics (TDR14311)	18	15.61	1.04	14.00	16.00	17.00
BMI (kg/m²)	adults (PDY6797)	38	28.60	3.27	23.00	27.80	34.60
	pediatrics (TDR14311)	18	33.15	4.83	24.48	32.44	42.26
WT (kg)	adults (PDY6797)	38	85.22	15.48	56.00	80.95	120.00
	pediatrics (TDR14311)	18	91.32	18.84	61.10	92.00	123.00
HT (cm)	adults (PDY6797)	38	172.05	9.03	154.00	172.00	188.00
	pediatrics (TDR14311)	18	165.48	12.23	139.60	164.30	194.70
LBW (kg)	adults (PDY6797)	38	60.51	9.99	44.18	61.41	79.29
	pediatrics (TDR14311)	18	54.92	12.44	37.29	51.64	84.22
PNWT (kg)	adults (PDY6797)	38	77.81	12.14	53.91	77.20	102.73
	pediatrics (TDR14311)	18	73.75	15.05	48.48	71.97	109.76
CLCR (mL/min)	adults (PDY6797)	38	103.69	30.88	43.66	93.60	176.77
	pediatrics (TDR14311)	18	218.91	46.25	130.65	226.93	303.17

Source: study-poh0636 on Page 56 (link).

Reviewer comment: The pediatric age range for lixisenatide should be from 14 to 17 rather than from 10 to 17 because study TDR14311 included only adolescents (age range: 14 to 17 years) and no children (age range: 10 to 12 years).

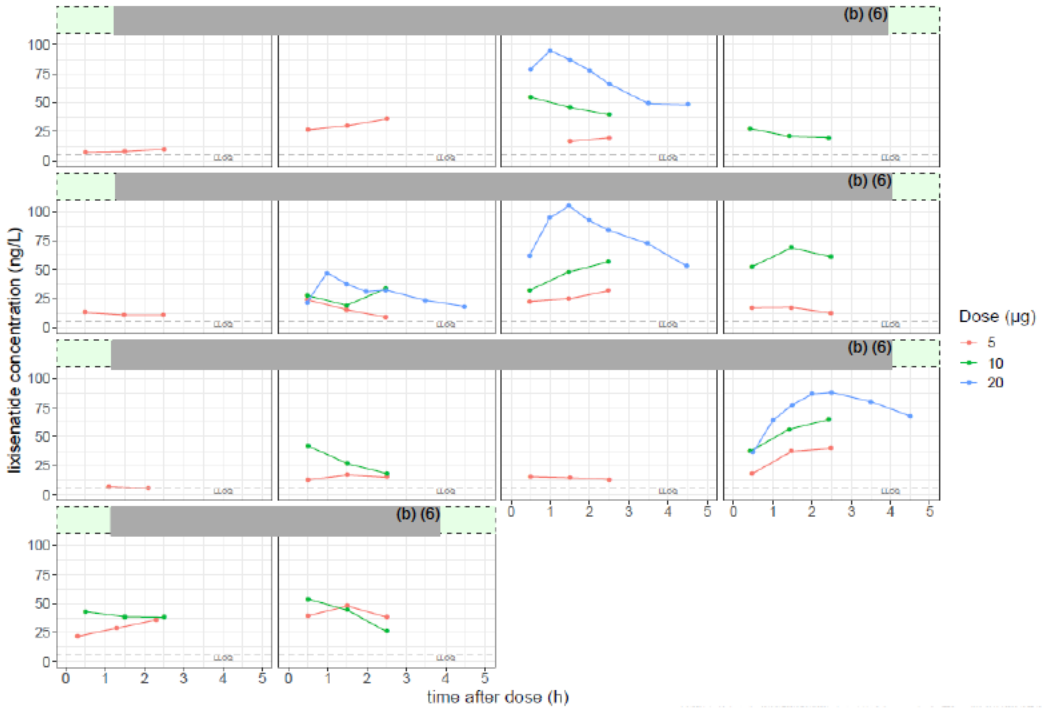
Pediatric PK profiles from ADA negative patients were consistent with a dose-proportional increase in exposure in Figure 1. Individual lixisenatide concentrations versus time profiles in pediatric patients with ADA negative status are presented in Figure 2.

Figure 1: Lixisenatide concentrations versus time after dose facetted by dose in pediatric and adult patients with T2DM negative for ADAs. The solid lines represent the median



Source: study-poh0636 on Page 26 (link).

Figure 2: Lixisenatide concentrations versus time after dose in anti-lixisenatide antibody negative patients of study TDR14311



Source: study-poh0636 on Page 65 (link).

Table 5. Summary of Clinical Study Designs

Study Number	Phase	Study Title	Treatment	Study Population	Sampling Times
TDR14311	1	Randomized, placebo controlled, 6-week, double-blind, multicenter, multinational, dose escalation trial	Subcutaneous injections 0 to 60 minutes before breakfast; dose escalation every 14 days (5 µg, 10 µg and 20 µg or matching placebo)	n=23 randomized patients with T2DM aged ≥10 to <18 years receiving lixisenatide, not adequately controlled with metformin and/or basal insulin	• After repeated dosing at 5 µg (Day 14) and 10 µg (Day 28): 0 (predose), 0.5, 1.5, and 2.5 hours after dose • After repeated dosing at 20 µg (Day 42): 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3.5, and 4.5 hours after dose
PDY6797	2	Randomized, placebocontrolled, 5 to 6-week, double-blind, multicenter, multinational, dose-escalation trial	Subcutaneous injections,30 minutes before morning and/or evening meals administered for 5 or 6 weeks, either once or twice daily, following dose escalation from 5 to 30 µg in Japanese and Caucasian patients with T2DM	n=38 randomized Caucasians with T2DM aged 20 to 75 years receiving lixisenatide, not adequately controlled with sulfonylurea or sulfonylurea and metformin	Single-dose phase: at 0.0 (preinjection),0.5, 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 6.5, 10, 12.5, and 24 hours after injection • Repeated-dose phase: at 0.0 (pre morning-injection), 0.5, 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 6.5, and 10.0 h post-morning injection and 2.5 h post-evening injection

Source: study-poh0636 on Page 19 (link).

Base model

The population pharmacokinetic (PopPK) base model POH0347, which is a basic model developed for lixisenatide in healthy adult subjects and patients with T2DM from phase 1 (BDR6864, POP6053), phase 2 (PDY6797, DRI6012) and phase 3 (EFC6018, EFC10887, EFC6015) clinical studies in NDA208471[2] was applied to the current dataset (study TDR14311 and PDY6797), with its parameter estimates as prior estimates for the assessment of individual parameters and concentration predictions.

The base model POH0347 was a one-compartment model with first-order absorption. *CL*/*F* was 39.3 L/h, *V*/*F* was 37.1 L, and absorption rate constant (*ka*) was about 0.29 h^{-1}, corresponding to an absorption half-life of approximately 2.4 hours. The typical elimination rate constant (k_e) was 0.94 h^{-1} (i.e., an elimination half-life of about 0.7 hours). Thus, the PK of lixisenatide is absorption rate limited, and the influence of absorption and elimination are inverted. IIV and IOV were identified on *CL*/*F*, *V*/*F*, and mean absorption time (*MAT*) (~1/*ka*).

[2] *Source: study-poh0636 on Page 21 (link).*
Source NDA208471 study-poh0347 page 35 (link).

The inter-occasion variability (IOV) of *CL/F* was higher than its inter-individual variability (IIV), whereas IIV of *V/F* was higher than its IOV, shown in Table 6.

Table 6: Model parameters of the base model of study POH0347

Structural model:			
$CL/F = \theta_{CL/F} \cdot e^{\eta_{CL_{IIV}} + \eta_{CL_{IOV}}}$ $V/F = \theta_{V/F} \cdot e^{\eta_{V_{IIV}} + \eta_{V_{IOV}}}$ $MAT = \theta_{MAT} \cdot e^{\eta_{MAT_{IIV}} + \eta_{MAT_{IOV}}}$			
Residual random effect model:			
$log(y(t)) = log(f(t) + m) + \frac{f(t)}{f(t)+m} \cdot e_1(t) + \frac{m}{f(t)+m} \cdot e_2(t)$			
Parameter[a]	Estimate	95% CI	Description
CL/F (L/h)	39.3	37.3-41.4	Apparent clearance
V/F (L)	37.1	33.5-41.1	Apparent volume of distribution
MAT (h)	3.46	3.23-3.70	Mean absorption time
IIV in CL/F (%CV)	35.6	27.0-42.5	Inter-individual variability in CL/F
IIV in V/F (%CV)	61.4	52.4-69.2	Inter-individual variability in V/F
IIV in MAT (%CV)	33.2	23.7-40.5	Inter-individual variability in MAT
IOV in CL/F (%CV)	51.3	44.9-57.0	Inter-occasion variability in CL/F
IOV in V/F (%CV)	38.9	32.8-44.2	Inter-occasion variability in V/F
IOV in MAT (%CV)	21.0	13.5-26.4	Inter-occasion variability in MAT
Proportional residual variability (%CV)	15.3	13.3-17.3	
Additive residual variability (SD ng/L)	1.79	1.48-2.09	
$cor(\eta_{CL_{IIV}}, \eta_{V_{IIV}})$	0.24		Correlation between IIV for CL/F and V/F
$cor(\eta_{CL_{IOV}}, \eta_{V_{IOV}})$	0.20		Correlation between IOV for CL/F and V/F

[a] IIV and IOV estimates (%CV) are in log domain.

Source: study-poh0636 on Page 55 (link).

Reviewer comment: In the above model NONMEM codes, SC=V while SC=V/1000 in the base model in NDA208471 due to the AMT unit differences in two NONMEM datasets.

The estimation step was omitted using the option MAXEVAL = 0 to compute the individual estimates based on the population estimates of θ, ω and σ obtained in the base model POH0347.

Final model

A hypothesis test was performed in NONMEM to evaluate whether inclusion of allometric relationships into the base model of POH0347 resulted in an improvement of the model fit. Apparent clearance (*CL/F*) was a function of body weight centered on the typical (median) value in the original population (82.1 kg) with an exponent of 0.75 (θ_{CL} [WT/82.1]$^{0.75}$). Apparent volume of distribution (*V/F*) was a function of body weight centered on the same typical value with an exponent of 1 (θ_V [WT/82.1]).

The inclusion of allometric relationships into the model resulted in an insignificant decrease in OFV (ΔOFV = -3.37, P > 0.05), but an improvement in shrinkage of clearance (η_{CL})[3]. Therefore, the sponsor used the model with allometry as the final model.

The AUC was calculated for every study visit using the typical predicted or the individual estimated value of clearance (as appropriate) and the administered dose by $AUC = dose \cdot F/CL$, where dose was the actual amount

[3] *Source: study-poh0636 on Page 26 (link).*

of drug administered and CL was the individual predicted clearance obtained from the pharmacokinetic model with bioavailability (*F*) assumed as 1.

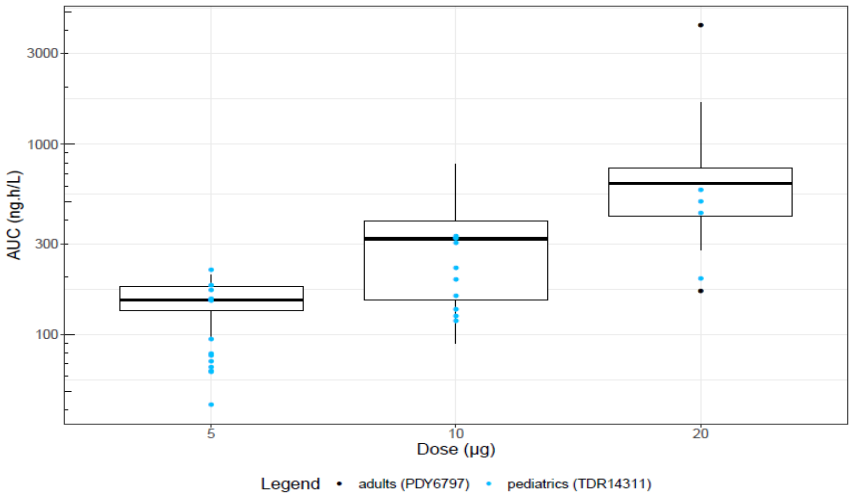
Summary statistics of AUC of pediatric patients in study TDR14311 for 5, 10, and 20 µg were derived from the Bayesian estimates of *CL*/*F*, shown in Table 7. Dose-proportionality was illustrated in Figure 3, in which exposures are comparable between adolescents and adults. Based on current available data, there is no clear influence of age on AUC in pediatric patients of study TDR14311 shown in Figure 4.

Table 7: Summary statistics for lixisenatide AUC in study TDR14311

	DOSE	N	Mean	SD	Min	Q1	Median	Q3	Max
AUC (ng.h/L)	5	17	114.17	50.57	42.41	72.17	101.59	153.61	218.70
	10	18	221.15	69.73	117.79	160.45	229.83	283.82	327.59
	20	18	444.87	104.58	197.73	376.60	466.88	501.30	617.07

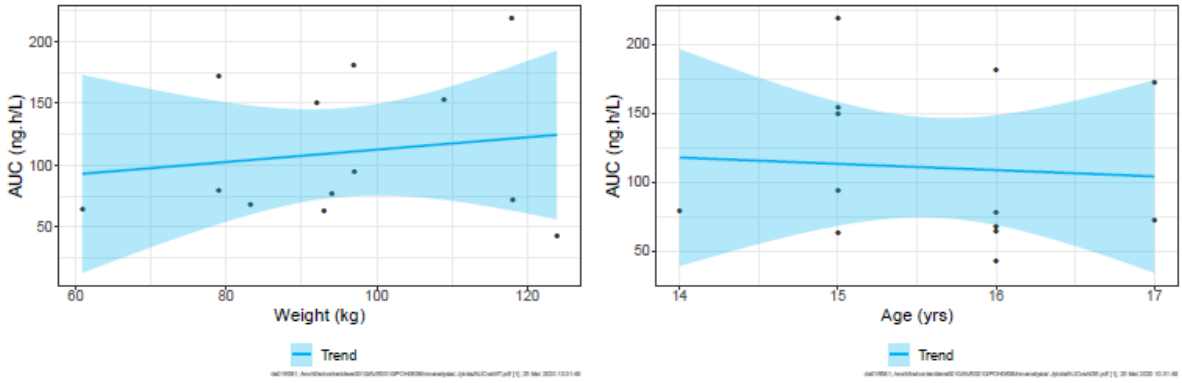
Source: study-poh0636 on Page 5 (link).

Figure 3: Comparison of AUC in pediatric and adult patients with T2DM and negative for ADAs. Box and whisker plots represent the adult and blue dots the pediatric population



Source: study-poh0636 on Page 5 (link).

Figure 4: Relationship between AUC and body weight and age in pediatric patients with T2DM and negative for ADAs of study TDR14311



(a) body weight (b) age

Source: study-poh0636 on Page 6 (link).

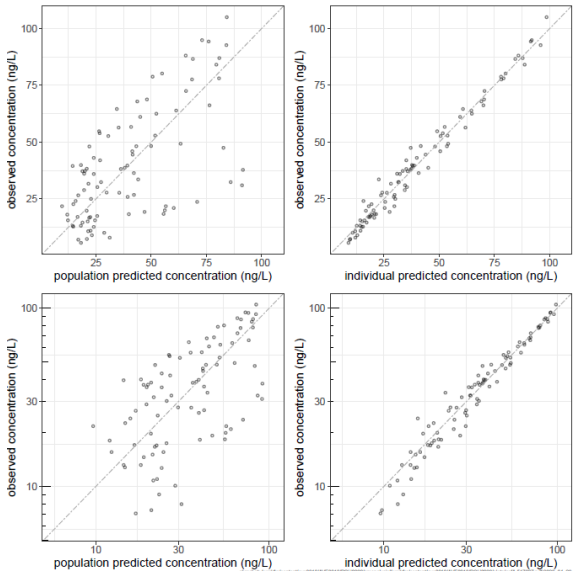
Model evaluation

The evaluation of the usability of the final model for Bayesian dataset was based on likelihood of the data (OFV), goodness-of-fit plots, η-shrinkage, VPC, quality assessment and measures for bias and precision.

Goodness of fit plots:

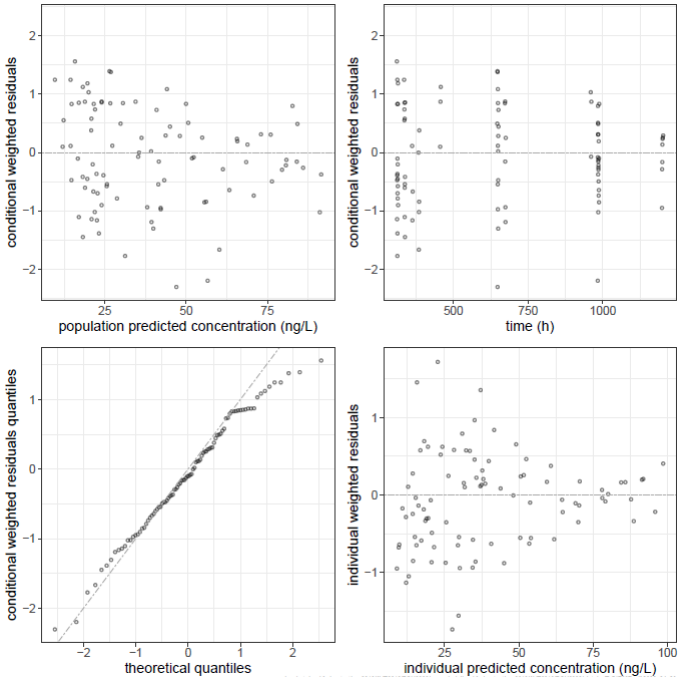
The observed lixisenatide concentrations versus predicted concentrations (PRED and IPRED) were investigated to determine if the model described the data accurately, shown in Figure 5. For each concentration, weighted residuals evaluated at individual conditional estimates (CWRES) and absolute individual weighted residuals (IWRES) were calculated. The plots of IWRES or CWRES versus IPRED and PRED were used to detect potential bias in individual and population predictions, respectively. The graph of CWRES versus time was plotted to assess a potential time dependency. No bias was concluded if data points were (more or less) scattered evenly around the horizontal zero-line and were between -5 and 5. Histograms and/or quantile-quantile probability plots [Q-Q plots]) were drawn to assess the normality of a given distribution shown in Figure 6.

Figure 5: Relationship between observed concentrations and population predicted or individual predicted concentrations in pediatric patients of study TDR14311 on linear and semi-logarithmic scale



Source: study-poh0636 on Page 68 (link).

Figure 6: Relationship between CWRES and population predicted concentrations or time (upper panel), and between IWRES and individual predicted concentrations or time (lower panel).



Source: study-poh0636 on Page 69 (link).

Eta shrinkage:

η-shrinkage was calculated according to

$$\eta - shinkage = 1 - \frac{SD(\eta_{EBE,P})}{\omega_P}$$

η: between individual variation,

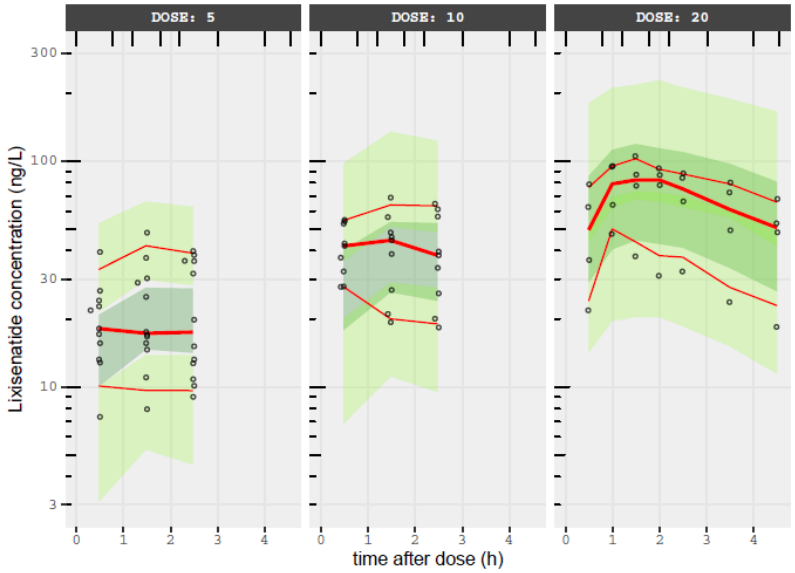
ω: population model estimate of the standard deviation in η,

with Empirical Bayes Estimates (EBE), given for a parameter *P*, which is used to assess the eta shrinkage between models. The eta shrinkages for the final model and model with allometry are 48% and 40% respectively. [4]

Visual predictive check (VPC)

A VPC was performed to evaluate the predictive ability of the Bayesian model. Five hundred simulation runs were performed in NONMEM. Each simulation run used the subjects in the pediatric dataset and considered allometric principles. The 5th, 50th, and 95th percentiles of the observations were compared with the 90% confidence interval (CI) around the 5th, 50th, and 95th percentiles of the simulations, shown in Figure 7.

Figure 7: Visual predictive check plot for pediatric patients of study TDR14311 stratified by dose. Dots represent observations. The solid red lines represent 5th, 50th (median) and 95th percentiles of observations. The green shaded areas represent the 90% confidence interval around the 5th, 50th (median) and 95th percentiles of the simulations (n = 500 subproblem simulations)



Source: study-poh0636 on Page 83 (link).

Quality criteria

The observed concentrations (DV or OBS) and the corresponding predicted concentrations (PRED and IPRED), computed given the individual dosing history, sampling times and given the base model and estimates from the Bayesian dataset, were compared. The predictive ability of the PopPK model was evaluated in terms mean prediction error (MPE, also named bias), root mean squared error (RMSE, also named precision) and absolute average fold error (AAFE) using the following set of formulas.

[4] *Source: study-poh0636 on Page 26 (link).*

$$MPE = \frac{1}{n}\sum_{i=1}^{i=n}[(I)PRED_i - DV_i]$$

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{i=n}[(I)PRED_i - DV_i]^2}$$

$$AAFE = 10^{\frac{\sum_{i=1}^{i=n}\left|log_{10}\frac{(I)PRED_i}{DV_i}\right|}{n}}$$

$$MPE\% = \frac{1}{n}\sum_{i=1}^{i=n}[(I)PRED_i - DV_i] \cdot \frac{100}{\overline{DV}}$$

$$RMSE\% = \sqrt{\frac{1}{n}\sum_{i=1}^{i=n}[(I)PRED_i - DV_i]^2} \cdot \frac{100}{\overline{DV}}$$

n is the sample size (PRED and DV having the same size)[5].

For an unbiased prediction, the MPE should not differ significantly from zero. A bias of ≥20% was considered unacceptable with regard to IPRED.
At the population (PRED) and individual level (IPRED) MPE (bias) does not exceed 20% of the observations. The AAFE is always smaller than MPE and RMSE and characterizes the predictions as reasonable, shown in Table 8 and 9.

Table 8: Quality criteria (MPE and AAFE) for Lixisenatide PK model

Parameter	n	MPE	95% CI (lower bound)	95% CI (upper bound)	MPE%	AAFE
PRED	92	0.12	-3.94	4.17	0.30	1.57
IPRED	92	0.12	-0.66	0.89	0.29	1.12

Source: study-poh0636 on Page 27 (link).

Table 9: Quality criteria (RMSE) for Lixisenatide PK model

Parameter	n	RMSE	95% CI (lower bound)	95% CI (upper bound)	RMSE%
PRED	92	19.74	16.00	22.88	49.71
IPRED	92	3.78	3.15	4.32	9.52

Source: study-poh0636 on Page 28 (link).

1.4 APPLICANT's CONCLUSIONS

- The introduction of allometric principles into the existing PK model of lixisenatide (prior model) does not lead to a contradictory description of the known kinetics of lixisenatide.
- The increase in exposure of lixisenatide was proportional to dose.
- There were no age-dependent changes in the exposure of lixisenatide from adolescents to adults.

1.5 Reviewer's Comments

The applicant's model appears to capture the central tendency of the data and variability. The submitted pediatric PK data is inclusive to the age range from 14 to 17 years and individual PK estimates are acceptable for descriptive purposes.

[5] *Source: study-poh0636 on Page 23 (link).*

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/

HARISUDHAN THANUKRISHNAN
06/14/2021 04:46:22 PM

HEZHEN WANG
06/14/2021 04:48:48 PM

JUSTIN C EARP
06/14/2021 04:51:37 PM

MANOJ KHURANA
06/14/2021 09:43:56 PM