Office of Clinical Pharmacology Review

NDA Number	206321
Link to EDR	\\Cdsesub1\evsprod\NDA206321\206321.enx
Submission Date	06 FEB 2020
Submission Type	505(b)(1)
Brand Name	SAXENDA
Generic Name	Liraglutide
Dosage Form and Strength	• Injection, pre-filled, (b) (4) pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg (6 mg/mL, 3 mL)
Route of Administration	Subcutaneous injection
Proposed Indication	Indicated as an adjunct to (b) (4) and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with : • body weight above 60 kg and • obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points)
Applicant	Novo Nordisk
Associated IND	IND-073206
OCP Review Team	Suryanarayana Sista, PhD; Justin Earp, PhD; Jayabharathi Vaidyanathan, PhD

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1. EXECUTIVE SUMMARY

This is a supplement to the original NDA submitted by Novo Nordisk on 06 Feb 2020, to fulfil a pediatric post-marketing requirement study PMR-2802-3 titled "*NN8022-4180: Effect of Liraglutide for Weight Management in Pubertal Adolescent Subjects with Obesity - A 56-week, double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug*". The Sponsor is seeking the following pediatric indication in this NDA supplement:

as an adjunct to [redacted] (b) (4) and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with :

- body weight above 60 kg and
- obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points)

SAXENDA is a clear, colorless solution. Each 1 mL of SAXENDA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains a 3 mL solution of SAXENDA equivalent to 18 mg liraglutide (free-base, anhydrous).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted to NDA 206321 and found it acceptable to support approval of SAXENDA as an adjunct to [redacted] (b) (4) and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with (a) body weight above 60 kg and (b) obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points).

Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness for the addition of proposed dosing regimen in pediatric patients 12 – to less than 18 years of age was obtained from data from one (1) efficacy trial in in Pubertal Adolescent Subjects with Obesity. The primary measure of evidence of efficacy in this trial was mean change in body mass index standard deviation score (BMI SDS) from baseline to week 56. With an estimated treatment difference (ETD) of -0.22, liraglutide 3.0 mg was superior to placebo with respect to weight reduction, evaluated as change in BMI SDS at week 56. This estimated reduction in BMI SDS of 0.23 in adolescent population is considered to be clinically relevant and has been compared to a weight loss of approximately 5%.
General dosing instructions	• Recommended dose of SAXENDA is 3 mg daily. Administer at any time of day, without regard to the timing of meals (2). • Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached (2). • Inject subcutaneously in the abdomen, thigh or upper arm (2). • The injection site and timing can be changed without dose adjustment

Dosing in patient subgroups	• SAXENDA should not be used in pediatric patients under 12 years of age or in pediatric patients 12 years and older with a body weight below or equal to 60 kg.
Bridge between the "to-be-marketed" and clinical trial formulations	The marketed formulation was used in the Clinical trial.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor analog with 97% amino acid sequence homology to human endogenous GLP-1. Liraglutide is approved to treat type 2 diabetes (T2DM) at doses up to 1.8 mg once a day (VICTOZA, NDA 22-341), and 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) at a dose of 3 mg once a day (SAXENDA, NDA 206321). This current supplemental NDA application is proposing to add adolescent patients (12 to less than 18 years of age) for the use of liraglutide for weight management at doses of 3.0 mg once daily based on the findings of a pediatric post-marketing requirement study PMR-2802-3 titled "*NN8022-4180: Effect of Liraglutide for Weight Management in Pubertal Adolescent Subjects with Obesity - A 56-week, double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug*".

Refer to details of general clinical pharmacology information of liraglutide in clinical pharmacology review under NDA 22-341. A population PK meta-analysis was conducted with the data from trial NN8022-4180 by also including data from three historical phase 1 trials; NN8022-4181 in children aged 7–11 years, NN8022-3967 in adolescents aged 12-17 years and NN8022-3630 in adults aged 18 years or above, all conducted in subjects with obesity. This review will focus on the population PK meta-analysis and relevant clinical pharmacology information for the proposed indication.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dose of SAXENDA as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management is as follows:

- 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)
- in pediatric patients aged 12 years and older with :
  - body weight above 60 kg and
  - obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points).

Recommended dose of SAXENDA is 3 mg daily. SAXENDA can be administered at any time of day, without regard to the timing of meals.

- Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached.
- Inject subcutaneously in the abdomen, thigh or upper arm
- The injection site and timing can be changed without dose adjustment

2.2.2 Therapeutic individualization

Based on population PK analysis, other than body weight, no other intrinsic factors affected the PK of liraglutide after SAXENDA administration. Liraglutide exposure was similar in adolescents and adults.

There is limited experience with SAXENDA in patients with mild, moderate, and severe renal impairment, including end stage renal disease. However, there have been post-marketing reports of acute renal failure and worsening of chronic renal failure with liraglutide, which may sometimes require hemodialysis. SAXENDA should be used with caution in patients with renal impairment.

There is limited experience in patients with mild, moderate, or severe hepatic impairment. SAXENDA should be used with caution in patients with hepatic impairment.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following preliminary labeling concepts be included in the final package insert:

Label Section	Acceptable to OCP?			Recommendation
	A	AWE	U	
2 DOSAGE AND ADMINISTRATION 2.3 Pediatric Dosage	☑	☐	☐	• The recommended dosage of SAXENDA is 3 mg daily. To allow for the maximum tolerated dose, initiate SAXENDA with a dose of 0.6 mg daily for one week. The dose escalation schedule in Table 1 should be used to reduce the likelihood of gastrointestinal symptoms. • If patients do not tolerate an increased dose during dose escalation, consider delaying dose escalation for approximately one additional week or lower the dose to the previous level for one week. Dose escalation could take up to 8 weeks.
8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use	☑	☐	☐	• The safety and effectiveness of SAXENDA as an adjunct to (b) (4) and increased physical activity for chronic weight management have been established in pediatric patients aged 12 to less than 18 years. Use of SAXENDA for this indication is supported by a 56-week double-blind, placebo-controlled clinical trial in 251 pediatric patients 12 to less than 18 years of age with obesity, an adolescent pharmacokinetic study, and studies in adults with obesity [*see Clinical Pharmacology (12.3) and Clinical Studies (14.1,14.2)*]. • The safety and effectiveness of SAXENDA have not been established in patients less than 12 years of age. • SAXENDA should not be used in pediatric patients under 12 years of age or in pediatric patients 12 years and older with a body weight below or equal to 60 kg.
12.3 Pharmacokinetics	☐	☑	☐	• Pediatric - A population pharmacokinetic analysis was conducted for SAXENDA using data from 134 adolescent subjects (12 to 17 years of age) with obesity. The liraglutide exposure in the adolescent subjects was (b) (4) similar to that in adults

A = Acceptable; AWE=Acceptable with minor edits; U=Unacceptable/substantive disagreement (must provide comment);

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Study NN8022-4180 was a multi-national study conducted as part of the pediatric development program of liraglutide 3.0 mg for weight management to assess the safety and efficacy of liraglutide in pubertal adolescents aged 12 to less than 18 years with obesity and to fulfill the regulatory requirements for pediatric trials from the FDA and other international regulatory bodies (EMA and PDCO).

The regulatory history relevant to the current application is summarized below:

Dates	Communication/Meeting Type	Key Communication Points
23 Dec 2014	NDA Approval Letter	• Notification that the deferred pediatric studies required by section 505B(a) of the FDCA are required post-marketing (PMR) studies. PMR study 2802-3 is a 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).

3.2 General Pharmacological and Pharmacokinetic Characteristics

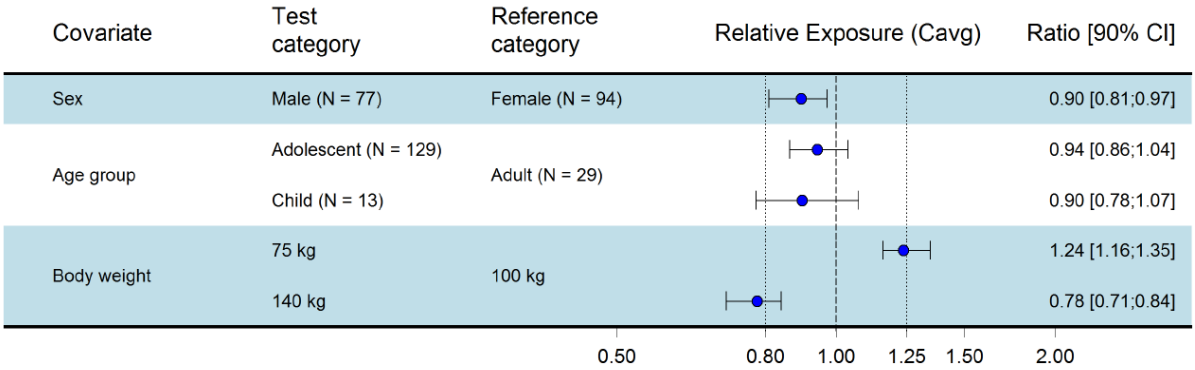
Refer to details of general clinical pharmacology information of liraglutide in clinical pharmacology review under NDA 22-341.

3.3 Clinical Pharmacology Review Questions

3.3.1 Is the impact of selected covariates, body weight, age group (children, adolescent and adult subjects) and sex on liraglutide exposure in adolescent subjects in accordance with previous results?

Yes, the impact of selected covariates, body weight, age group (children, adolescent and adult subjects) and sex on liraglutide exposure in adolescent subjects were in accordance with previous results observed in adults (Figure 1). The range of body weights were 74.2 kg – 131.6 kg for adults, 62.1 kg – 178.2 kg for adolescents and 53.9 kg – 86.8 kg for children. The range of ages were 20 – 72 years for adults, 12-17 years for adolescents and 8-11 years for children. As seen previously, body weight was the only covariate with an impact on the liraglutide exposure (*see reviews by Drs. Jain and Singh in DARRTS, Reference ID 3828218 and 4302250, respectively*).

Figure 1 Forest Plot of Covariate Analysis for Liraglutide Exposure in Subjects with Obesity

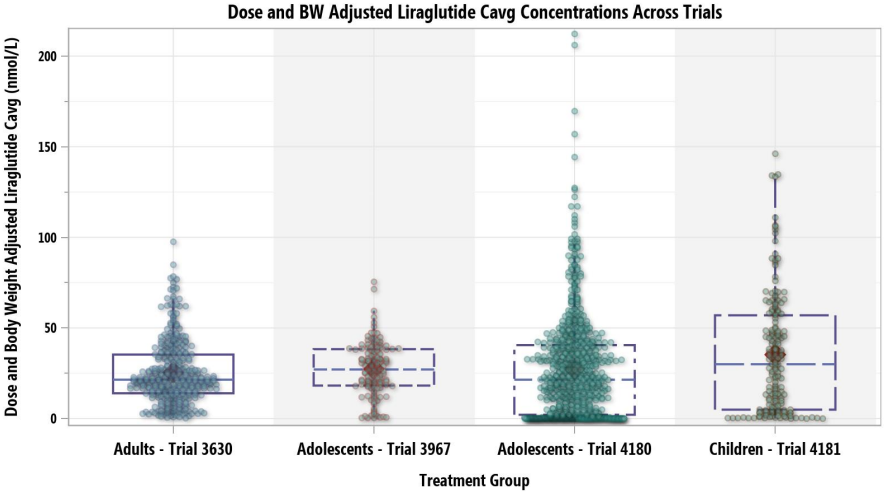


Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-2, page 23

3.3.2 Are the estimated exposure levels for adolescent subjects in trial 4180 as expected, compared to previous findings of exposures across age groups?

Yes, the estimated liraglutide exposure levels for adolescent subjects in trial 4180 were as expected, compared to previous findings of exposures across age groups (Figure 2). Trial 3630 was a randomized, placebo-controlled, double-blind, incomplete crossover design trial to evaluate the effects of liraglutide on gastric emptying, energy expenditure and appetite, and to evaluate liraglutide pharmacokinetics in non-diabetic obese subjects. Trial 3967 was a randomized, double-blind, placebo-controlled trial to assess safety, tolerability and pharmacokinetics of liraglutide in obese adolescent subjects aged 12 to 17 years. Trial 4181 was a randomized, double-blind, placebo-controlled trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in obese children aged 7 to 11 years.

Figure 2 **Dose and Body Weight Adjusted Liraglutide Average Steady-State Concentrations Across Clinical Trials**

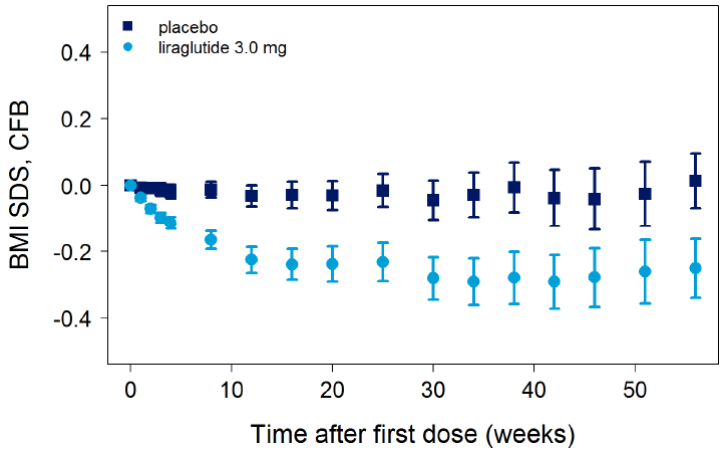


(Source: Reviewer generate plot)

3.3.3 Do the population PK, dose-response and exposure-response relationship of liraglutide in adolescent subjects for change from baseline in BMI SDS support the proposed dose?

The time course of BMI SDS in adolescents on placebo and on liraglutide 3.0 treatment indicate a substantial reduction in body weight over time in subjects on active treatment and an almost constant BMI SDS in subjects on placebo and (Figure 3). Similar to previous findings in adults, the response appeared to be close to maximal at 20 weeks of treatment.

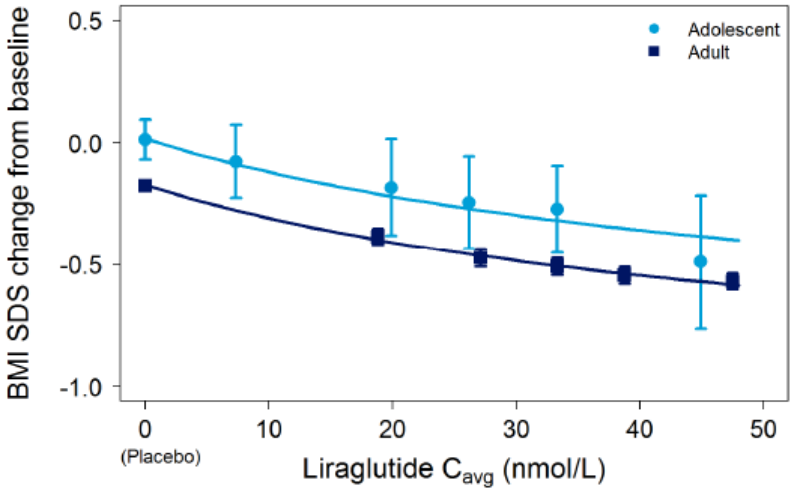
Figure 3 **Time-Course of Observed BMI SDS Change from Baseline in Adolescents**



Data are means and 95% CIs in trial 4180
Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-7, page 28

Apart from a lower placebo-response observed in adolescents compared to adults, the exposure-response analysis showed a similar exposure-response relationship for BMI SDS in adolescents and adults (Figure 4).

Figure 4 BMI SDS Change from Baseline Versus Liraglutide Exposure for Adolescents Compared to Adults

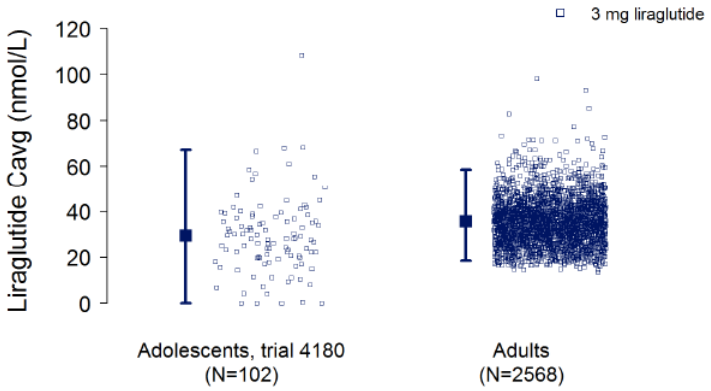


Data points with error bars are means with 95% CIs for each of 5 quantiles of Cavg for liraglutide and one quantile for placebo (at C_{avg} of 0 nmol/L). Lines are covariate-adjusted, model derived relations. Data from trial 1807 after 20 weeks of treatment, trials 4180 and 1839 after 56 weeks of treatment and trial 1922 after 50 weeks of treatment
Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-8, page 29

Liraglutide exposure was similar in adolescents and adults as shown by population PK analysis. Similar to earlier population PK analysis conducted in adults, Body weight was identified as the most important intrinsic factor for exposure. Exposure-response for BMI SDS change from baseline showed larger response with increasing liraglutide exposure.

The recommended liraglutide dose of 3.0 mg was shown to provide similar exposures in adolescents and adults, even without adjusting for baseline body weights (Figure 5), thus providing support to the proposed treatment dose in adolescent subjects.

Figure 5 Liraglutide Exposure Across Trials in Subjects Treated With 3.0 mg Liraglutide



Data are individual (open symbols) and geometric mean C_{avg} estimates with 95% CI (closed symbols with error bars) from the final PK model for each trial. Data from trials 4180, 1807, 1839 and 1922. In trial 4180, BLQ data was included and data cleaning was less strict compared to trials 1807, 1839 and 1922
Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-6, page 27

The primary measure of evidence of efficacy in trial 4180 was mean change in body mass index standard deviation score (BMI SDS) from baseline to week 56. With an estimated treatment difference (ETD) of -0.22, liraglutide 3.0 mg was superior to placebo with respect to weight reduction, evaluated as change in BMI SDS at week 56. This estimated reduction in BMI SDS of 0.23 in adolescent population is considered to be clinically relevant and has been compared to a weight loss of approximately 5%.

The primary endpoint was supported by results of weight-related secondary endpoints (BMI SDS [%], BMI [kg/m2], body weight [kg and %] and waist circumference [cm]). The secondary endpoints were statistically significant in favor of liraglutide 3.0 mg at week 56 compared to placebo treatment. The estimated proportion of subjects for whom there was a BMI (kg/m^2) decrease from baseline of ≥5% (43% vs. 19%) and ≥10% (26% vs. 8%) at week 56 was statistically significantly higher in the liraglutide 3.0 mg group compared to the placebo group (p=0.0002 and p=0.0006, respectively).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How is SAXENDA identified and what are the analytical methods used to measure them in plasma?

Bioanalysis of liraglutide in plasma samples in trial 4180 was performed using a liraglutide specific validated enzyme linked immunosorbent assay (ELISA) method. The method measured both protein-bound and unbound liraglutide. The method used was the same as for previously approved studies, was adequately validated for recovery, accuracy, precision, sensitivity and specificity and is acceptable. The lower level of quantification was 30 pmol/L.

4.2 Pharmacometrics Assessment

4.2.1 Executive Summary

4.2.1.1 Recommendations

Liraglutide is approvable from a pharmacometrics perspective.

4.2.2 Applicant's Population PK and PK/PD Analysis

Text with gray shadow indicates that the content was copied from the applicant's study report. Table numbers reported in the applicant's study report have been rearranged in this text to be consistent with the numbering of the full report.

4.2.2.1 Population PK analysis

In addition to trial 4180, data from three historical clinical pharmacology trials of liraglutide in children, adolescents and adults with obesity were included in the PK assessment; trials 4181, 3967 and 3630. The designs of all contributing trials with actual numbers of subjects included are summarized in Table 1.

Table 1 Tabular Listing of Studies Included in The Population PK Analysis

Group	Trial 4180[3]	Trial 4181[3]	Trial 3967[3]	Trial 3630[3]
Clinical stage	Phase 3	Phase 1	Phase 1	Phase 1
N	121	13	13	29[8]
No of adults with obesity	-	-	-	29
No of adolescents (11-17 years) with obesity	121	-	13	-
No of children (7-11 years) with obesity	-	13	-	-
Weekly dose escalation steps (mg/day)	0.6, 1.2, 1.8, 2.4, 3.0[4]	0.3, 0.6, 0.9, 1.2, 1.8, 2.4, 3.0[5]	0.6, 1.2, 1.8, 2.4, 3.0[7]	0.6, 1.2, 1.8, 2.4, 3.0
Actual maintenance doses (mg/day)[1]	0.6 (n=1) 1.2 (n=1) 1.8 (n=2) 2.4 (n=10) 3.0 (n=107)	2.4 (n=1) 3.0 (n=12)	2.4 (n=1) 3.0 (n=12)	3.0
Treatment duration (weeks)[2]	56 weeks	7 weeks	5–6 weeks	35 days
Sparse PK sampling weeks	8, 12, 16, 30, 42, 56	NA	NA	NA
Number of pre-dose (trough) PK samples during dose escalation	NA	7[6]	4	NA
Number of PK samples after last dose	NA	5	6	12
Nominal timing of PK sampling after the last dose	NA	Pre-dose, 1h, 2h, 3h, 24h, 72h	Varying according to assigned sequence	Pre-dose, 2h, 4h, 1h, 13h, 15h, 18h, 20h, 24h, 36h, 48h, 60h

[4]Numbers refer to the final data files following data cleaning. [1]Dose levels for the longest durations in trial 4180. [2]Including dose-escalation. [3]Actual numbers in the PK population, i.e. subjects on active treatment. [4]Dose escalation was flexible (5–8 weeks). [5]Dose escalation was flexible (7–13 weeks). [6]Including one trough sample before last dose. [7]Dose escalation over 5 weeks with flexibility. [8]Subjects exposed to 3.0 mg liraglutide.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 4-1, page 12

A total of 22 PK observations corresponding to 3.3% of the data were excluded. The final dataset comprised 646 PK observations from 121 subjects. A total of 94 observations were below the LLOQ, corresponding to 14.6% of the final dataset.

Demographic characteristics of subjects included in the PK dataset from all four trials are summarized in Table 2. A total of 176 subjects were included in the analysis; 13 children from trial 4181, 121 adolescents from trials 4180, 13 adolescents from trial 3967 and 29 adults from trial 3630. The majority of subjects (82.4%) were Whites and non-Hispanics or Latino (80.1%).

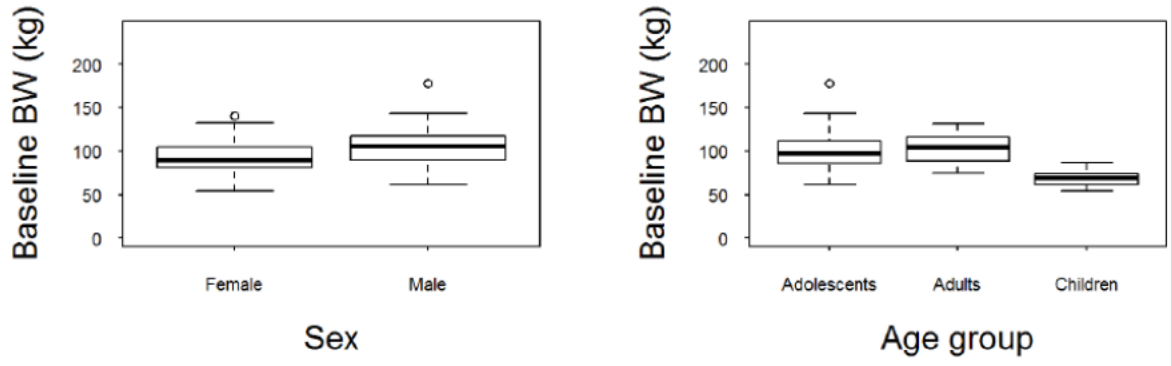
Table 2 Summary of Demographics Across Trials for the PK population

Category	Group	Trial 4180	Trial 3967	Trial 3630	Trial 4181	Total
All	N	121 (68.8%)	13 (7.4%)	29 (16.5%)	13 (7.4%)	176 (100%)
Sex	Female	67 (55.4%)	10 (76.9%)	11 (37.9%)	7 (53.8%)	95 (54%)
	Male	54 (44.6%)	3 (23.1%)	18 (62.1%)	6 (46.2%)	81 (46%)
Race	White	102 (84.3%)	12 (92.3%)	25 (86.2%)	6 (46.2%)	145 (82.4%)
	Black or African American	13 (10.7%)	-	-	7 (53.8%)	20 (11.4%)
	Asian	2 (1.7%)	-	-	-	2 (1.1%)
	Other	4 (3.3%)	1 (7.7%)	4 (13.8%)	-	9 (5.1%)
Ethnicity	Not Hispanic or Latino	92 (76%)	13 (100%)	26 (89.7%)	10 (76.9%)	141 (80.1%)
	Hispanic or Latino	29 (24%)	-	3 (10.3%)	3 (23.1%)	35 (19.9%)
Age (years)	Mean (SD)	14.6 (1.6)	15.1 (1)	47.8 (13.8)	9.8 (0.9)	19.7 (13.8)
	Range	[12-17]	[13-16]	[20-72]	[8-11]	[8-72]
Body weight (kg)	Mean (SD)	99.4 (19.7)	102.1 (12.2)	102.3 (15.6)	69.1 (10.8)	97.8 (19.7)
	Range	[62.1-178.2]	[79.9-119.2]	[74.2-131.6]	[53.9-86.8]	[53.9-178.2]

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 5-1, page 19

The distribution of individual body weights indicated large overlaps between males and females and between adolescents and adults, whereas body weights were lower in children, as expected (Figure 6).

Figure 6 Box-Plots of Distribution of Body Weights Across Categories of Sex and Age Groups



Boxes represent the 25th, 50th and 75th percentiles. Whiskers represent the 5th and the 95th percentiles. Circles are outliers. Data from trials 4180, 3967, 3630 and 4181.

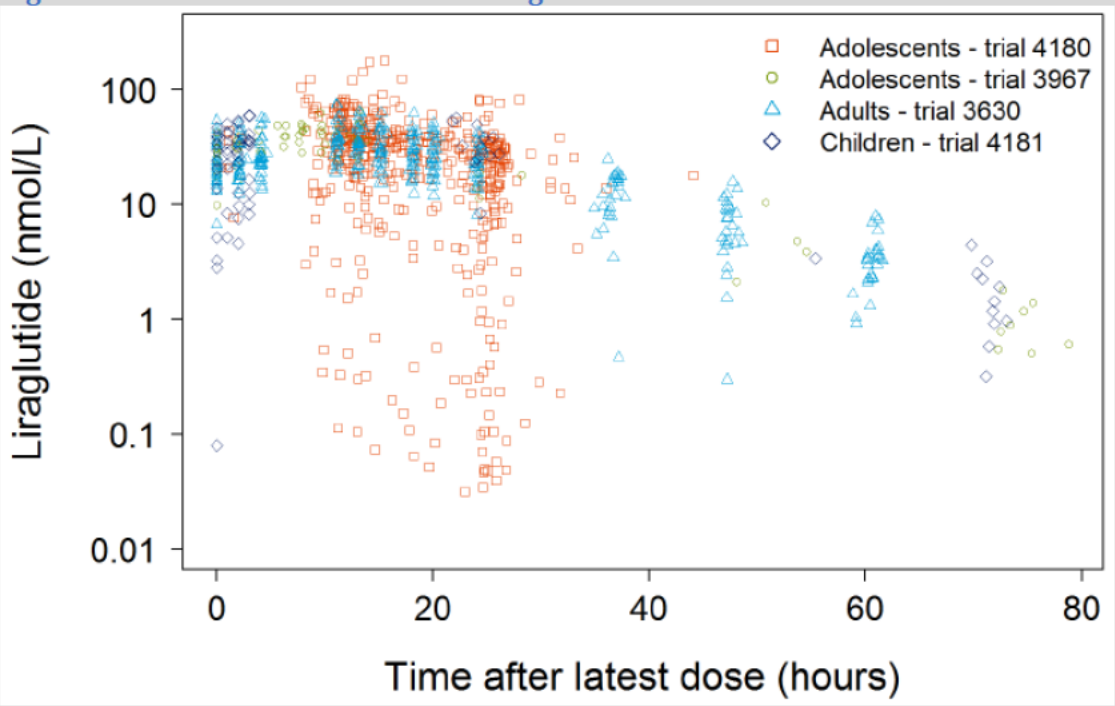
Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-2, page 38

4.2.2.1.1 Graphical analysis of observed PK data

Individual observed liraglutide concentrations versus time since the latest dose revealed a number of lower than expected values in trial 4180 (Figure 7). These observations could indicate compliance issues with some of the subjects in trial 4180, which were also indicated previously in children in trial 4181.

The possible lack of compliance by some subjects is also reflected in the summary concentrations over time as shown in Figure 8 for trial 4180. Instead of the expected constant exposure during steady-state maintenance dosing, exposures appeared to decrease, thus indicating a possible lack of compliance over time.

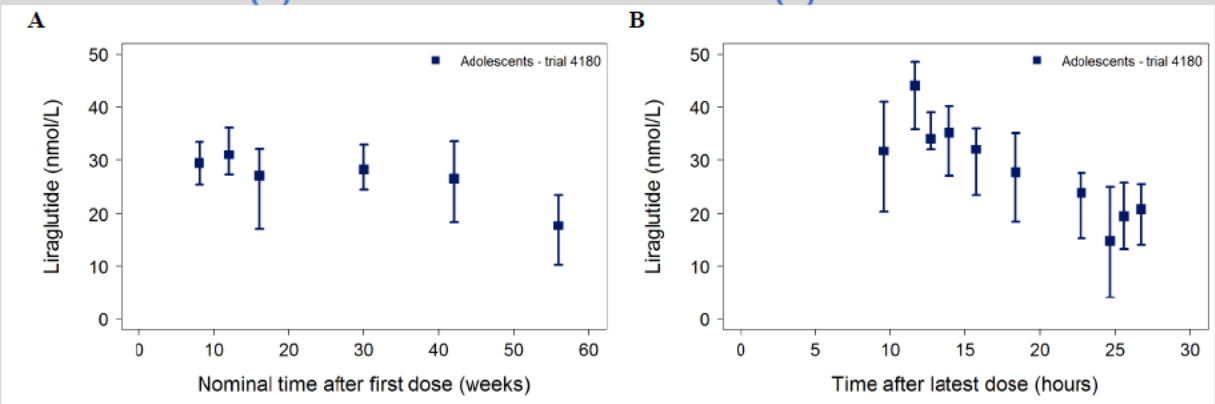
Figure 7 Individual Observed Liraglutide Concentrations Across Trials



Data from trials 4180, 3967, 3630 and 4181.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-1, page 38

Figure 8 Observed Liraglutide Concentrations in Trial 4180 Versus Time Since First Dose (A) And Versus Time Since Latest Dose (B)



Data are median observed concentrations with 95% CIs for each time point for 3.0 mg dose. Data from trial 4180.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-1, page 20

4.2.2.1.2 Structural PK model

A standard one-compartment model with first-order absorption and elimination was the starting point for the description of liraglutide PK. The structural model was parameterized in terms of the following parameters:

- ka (absorption rate constant)
- CL/F (apparent clearance)
- V/F (apparent volume of distribution)

4.2.2.1.3 Variability models

Between-subject variability was included for CL/F and V/F, assuming log-normal distributions without correlation between parameters. Furthermore, CL/F and V/F were estimated with a full variance-covariance matrix. No between-subject variability was included for ka. Within-subject variability (residual) was described by a proportional error model.

4.2.2.1.4 Models of covariate effects

An analysis of the influence of covariates on exposure was carried out with the full model including all tested covariates in one step. This was performed using a confirmatory approach, estimated in one run, disregarding any interactions between age group and sex.

Covariate effects in terms of body weight, sex and age group (children, adolescents, adults) was investigated for clearance (CL/F) and in terms of body weight for volume of distribution (V/F). The CL/F and V/F was parameterized as follows for the i'th subject (shown for CL/F only):

$$CL/F_i = TVCL \cdot E_{body\ weight,CL} \cdot E_{sex} \cdot E_{age\ group} \cdot \exp(\eta_{CL,i}) \quad \text{(Eq. 1)}$$

$$E_{body\ weight,CL} = \left(\frac{body\ weight_i}{100\ kg}\right)^{\theta_{body\ weight,CL}} \quad \text{(Eq. 2)}$$

$$E_{sex} = (\theta_{male})^{male} \quad \text{(Eq. 3)}$$

$$E_{age\ group} = (\theta_{child})^{child} \cdot (\theta_{adolescent})^{adolescent} \quad \text{(Eq. 4)}$$

$$V/F_i = TVV \cdot E_{weight} \cdot \exp(\eta_{V,i}) \quad \text{(Eq. 5)}$$

Here, TVCL and TVV are typical values of apparent clearance and volume of distribution, respectively, for a reference subject (adult female with a body weight of 100 kg) and the θ values are the estimated covariate effect parameters. Exponents are indicator variables taking the value 1 for the actual category and otherwise 0.

Subject specific steady-state exposures were based on the full model, including all covariates. This was derived from the subject-specific post-hoc apparent clearance estimates (CL/F), the maintenance dose and the dose interval (24 h):

$$C_{avg} = \frac{Dose}{\left(\frac{CL}{F}\right)*24h} \quad \text{(Eq. 6)}$$

The confidence intervals for full model parameters were estimated using bootstrapping.

4.2.2.1.5 Estimation of population PK models

Building on previous population PK analysis of liraglutide, a one compartment model with first-order absorption and elimination was applied with values of ka and V/F fixed to previously estimated values, to allow for estimation of CL/F in trial 4180 with sparse PK sampling. A confirmatory approach was used regarding covariates with estimation of a base model without covariates, a full model with all investigated covariates and a final model including only significant covariates. In the current analysis, all covariates included in the full model were statistically significant except for age group. As age group was the covariate under investigation for this analysis, the full model was also used as the final model and a reduced model with exclusion of non-significant covariates was not estimated.

Parameter estimates from the base and final models are provided in Table 3 and Table 4.

Table 3 Parameter Estimates from Base PK Model

Parameter	Parameter name [unit]	Estimate	95% CI Lower bound	95% CI Upper bound	RSE (%)	IIV (%CV)	Shrinkage (%)
Absorption rate constant	KA [1/h]	0.0804	Fixed	Fixed	Fixed	NA	NA
Apparent Clearance	CL/F [L/h]	1.07	1.01	1.12	2.7	38.3	6.5
Apparent Volume of Distribution	V/F [L]	13.1	Fixed	Fixed	Fixed	38	13.9
NA	Prop. Error	43.2	NA	NA	NA	NA	6.9

CI: confidence interval. RSE: relative standard error. CV: coefficient of variation

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 8-2, page 51

Table 4 Parameter Estimates from Final PK Model

Parameter	Parameter name [unit]	Estimate	95% CI Lower bound	95% CI Upper bound	RSE (%)	IIV (%CV)	Shrinkage (%)
Absorption rate constant	KA [1/h]	0.0813	Fixed	Fixed	Fixed	NA	NA
Apparent Clearance	CL/F [L/h]	1.01	0.922	1.09	4.25	31.2	10.2
Apparent Volume of Distribution	V/F [L]	13.8	Fixed	Fixed	Fixed	31.7	19.2
Body weight exponent on CL/F	CL-BW	0.762	0.565	0.958	13.2	NA	NA
Sex contrast (MALE/FEMALE) on CL/F	CL-Male	1.12	0.993	1.24	5.64	NA	NA
Age contrast (CHILD/ADULT) on CL/F	CL-Child	1.11	0.89	1.34	10.2	NA	NA
Age contrast (ADOLE/ADULT) on CL/F	CL-Adole	1.06	0.931	1.19	6.24	NA	NA
Body weight exponent on V/F	V-BW	0.587	0.475	0.7	9.75	NA	NA
NA	Prop. Error	43.3	NA	NA	NA	NA	6.4

CI: confidence interval. RSE: relative standard error. CV: coefficient of variation

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 8-3, page 52

4.2.2.1.6 PK model qualification

The PK models were qualified in accordance with guidelines from EMA, FDA and PMDA:

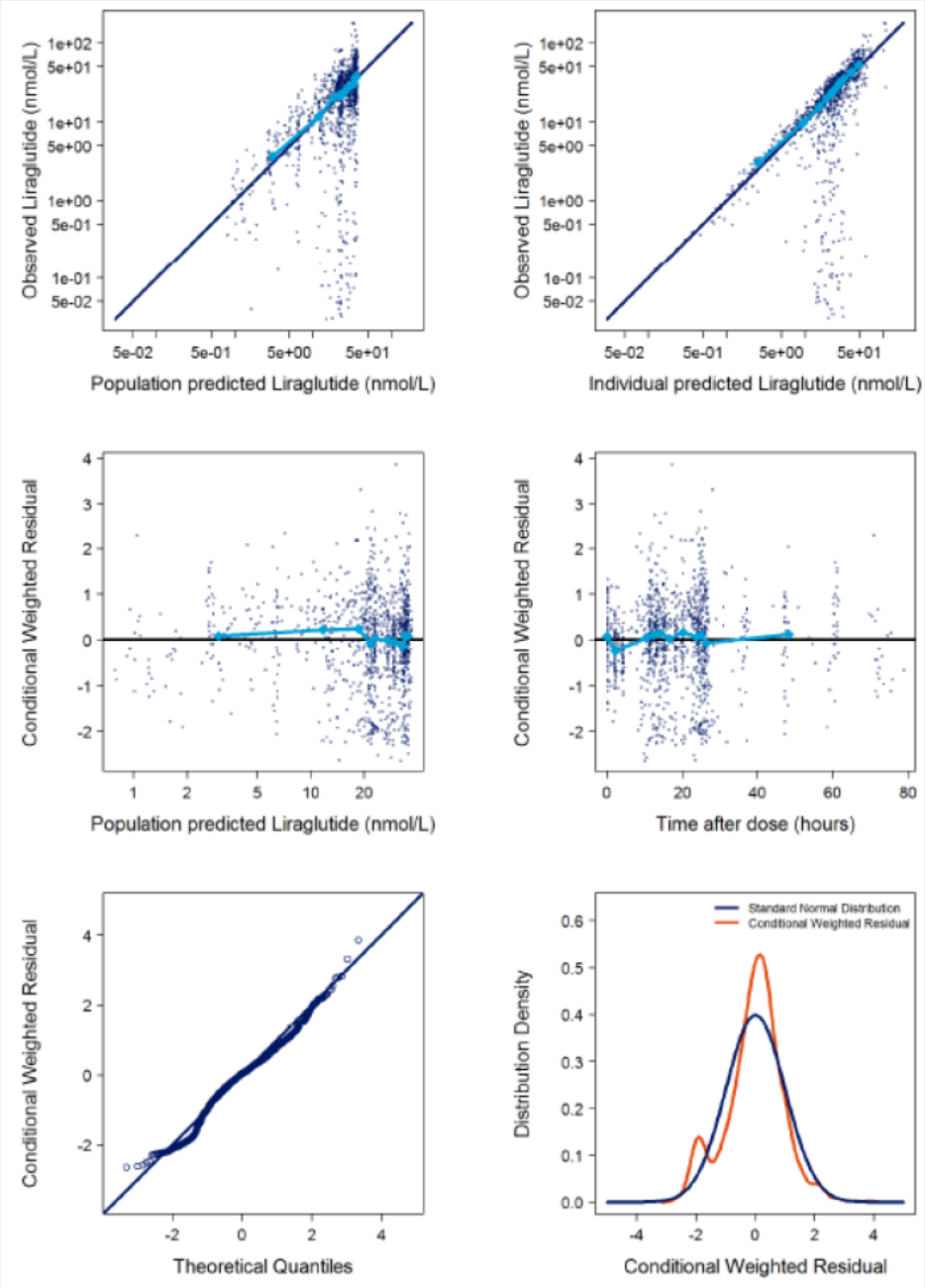
1. *Check for co-linearity of covariate data (*Table 3*)*

Baseline body weights were higher in males compared to females but with a large overlap and were similar in adolescents and adults. As expected, body weights were lower in children (aged 7–11 years) compared to the two other age groups.

2. *Standard goodness-of-fit plots* (Figure 9 and Figure 10)

The model fits for the base and final models were acceptable and there were no critical trends in the conditional weighted residuals vs. neither liraglutide concentration nor time. The individual clearance estimates appeared to approximate log-normal distributions.

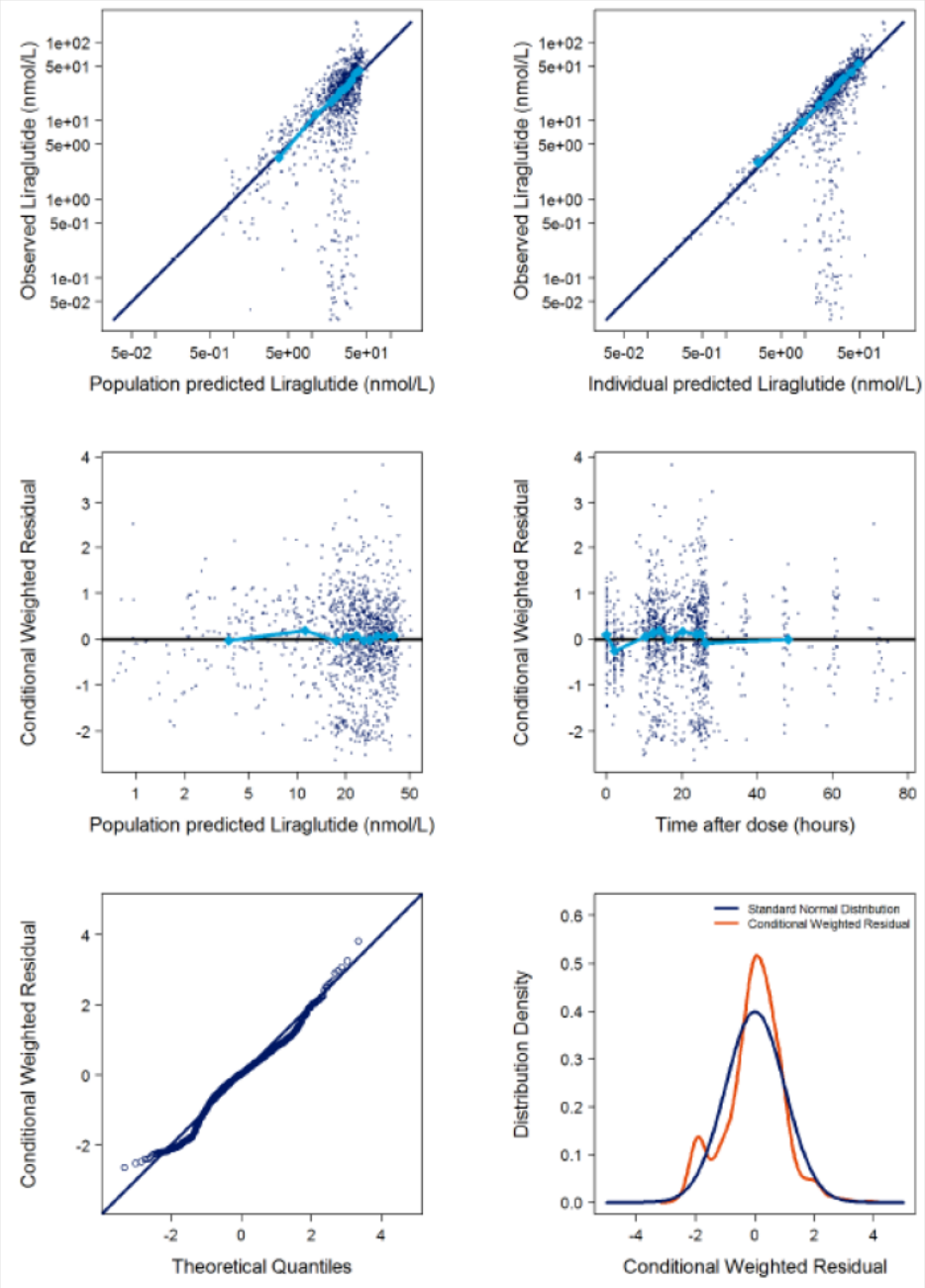
Figure 9 Standard GOF Plots for Base PK Model



Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Data from trials 41,80, 4181, 3967 and 3630.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-3, page 40

Figure 10 Standard GOF Plots for Final PK Model



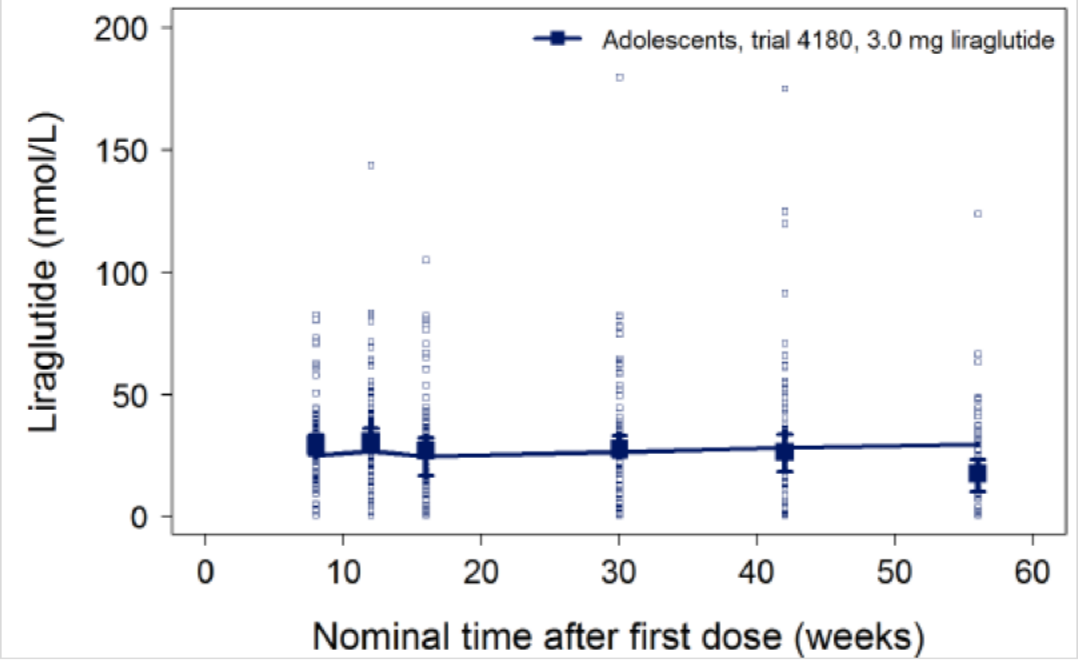
Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Data from trials 4180, 3967, 3630 and 4181.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-5, page 42

3. *Overall and individual model fits to data (Figure 11)*

The fits of the final model to the overall and individual concentration data versus time since the first dose were adequate and no systematic prediction errors could be identified. Some subjects in trial 4180 had lower concentrations than expected immediately after dosing, possibly due to compliance deviations.

Figure 11 Observed and Model-Derived Concentrations Versus Time for Adolescents



Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-7, page 44

4. *Evaluation of the fixed effects parameter estimates and their uncertainties (Table 4)*

The estimate of clearance (1.07 L/h for an adolescent female) from the final model in the current analysis was comparable to the estimate previously obtained by population PK modelling in trial 3630 (1.15 L/h) and trial 3967 (0.96 L/h).

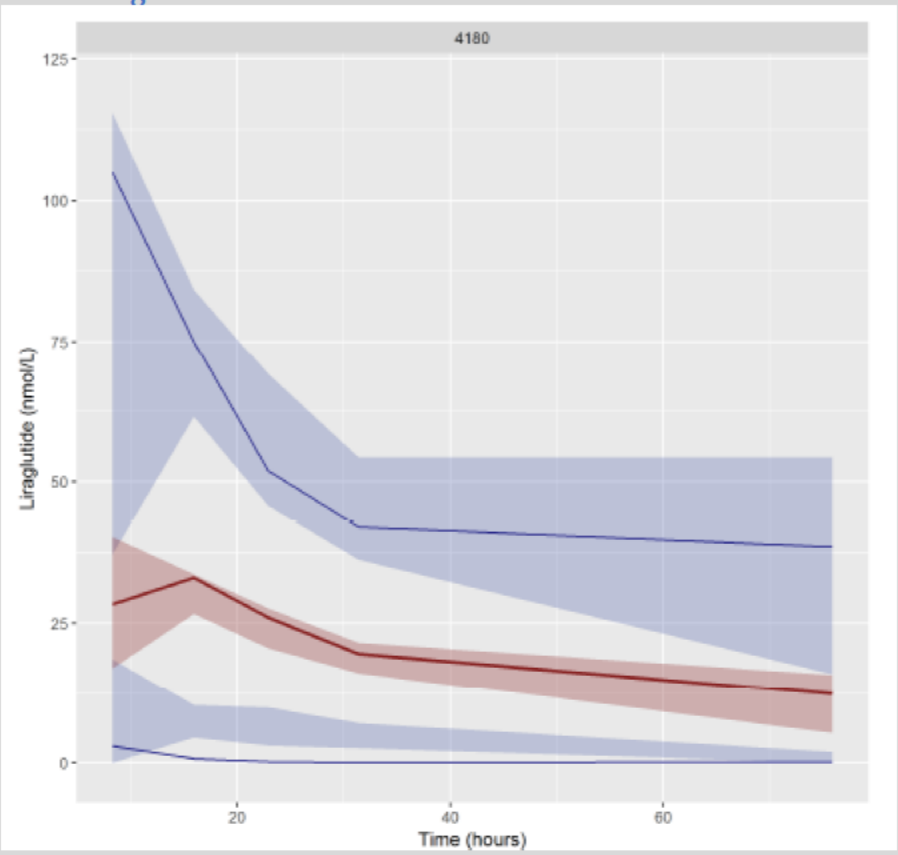
5. *Assessment of shrinkage for the random effects (Table 4)*

In the full population PK model, shrinkage was 10.2% for CL/F and 19.2% for V/F. These were within the upper recommended limit of 20-30% for empirical Bayes estimates. The shrinkage for the residual error was 6.4%.

6. *Visual predictive check (VPC) of the final model (Figure 12)*

The VPC indicated that the final model was capable of reproducing the data used for estimation and thus can be used for performing PK simulations. The apparent overprediction of the 5th percentile reflected the lower than expected observed concentrations presumably due to compliance issues for some subjects in the adolescent population

Figure 12 Visual Predictive Check of The Final Population PK Model of Liraglutide in Overweight or Obese Adolescents



Data are observed (lines) and simulated (shaded area, n=2000) medians and 5th and 95th percentiles for concentrations after the first dose. Data from trial 4180.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-8, page 50

7. *Sensitivity analyses* (Table 5)

A total of 5 sensitivity analyses were conducted for check of robustness:

1. The fixed value of k_a was reduced by 25%: this had little influence except for the body weight exponent on volume, due to interrelationships between volume and k_a.
2. The fixed value of k_a was increased by 25%: this had little influence except for the body weight exponent on volume, due to interrelationships between volume and k_a.
3. BLQ values included as LLOQ/2: this had effects on clearance, body weight exponent on clearance and body weight effect on volume due to the relatively large numbers of BLQ values in the data.
4. Exclusion of all concentration values below 1 nmol/L to identify a population with improved compliance compared to the actual trial. This had little influence except for a larger body weight exponent on volume. Thus, the reported PK analysis provided results which were similar to the analysis for a compliant population.
5. Excluding data from children (from trial 4181) had little influence except for a larger body weight exponent on volume.

Table 5 Sensitivity Analyses of The Population PK Model

Parameter	Parameter name [unit]	Estimate	95% CI Lower bound	95% CI Upper bound	Low Ka[1]	High Ka[2]	Include BLQ[3]	Minimum exposure[4]	Children excluded[5]
Absorption rate constant	KA [1/h]	0.0813	Fixed	Fixed	0.061	0.102	0.0813	0.0813	0.0813
Apparent Clearance	CL/F [L/h]	1.01	0.922	1.09	1.19	0.906	0.836	1	0.994
Apparent Volume of Distribution	V/F [L]	13.8	Fixed	Fixed	13.8	13.8	13.8	13.8	13.8
Body weight exponent on CL/F	CL-BW	0.762	0.565	0.958	0.848	0.689	0.0254	0.746	0.782
Sex contrast (MALE/FEMALE) on CL/F	CL-Male	1.12	0.993	1.24	1.17	1.09	1.11	1.12	1.18
Age contrast (CHILD/ADULT) on CL/F	CL-Child	1.11	0.89	1.34	1.08	1.11	1.14	1.04	1
Age contrast (ADOLESCENT/ADULT) on CL/F	CL-Adole	1.06	0.931	1.19	0.932	1.12	1.59	0.952	1.05
Body weight exponent on V/F	V-BW	0.587	0.475	0.7	0.916	0.474	0.102	0.726	0.757
NA	Prop. Error	43.3	NA	NA	44.5	43	50.3	29.4	44.4

CI: confidence interval. BLQ: below limit of quantification

Key to sensitivity analysis:

[1]Fixed k_a value 25% lower than in final model

[2]Fixed k_a value 25% higher than in final model

[3]BLQ values included as LLOQ/2

[4]Subjects with cncentration data below 1 nmol/L excluded

[5]Data from children (trial 4181) excluded

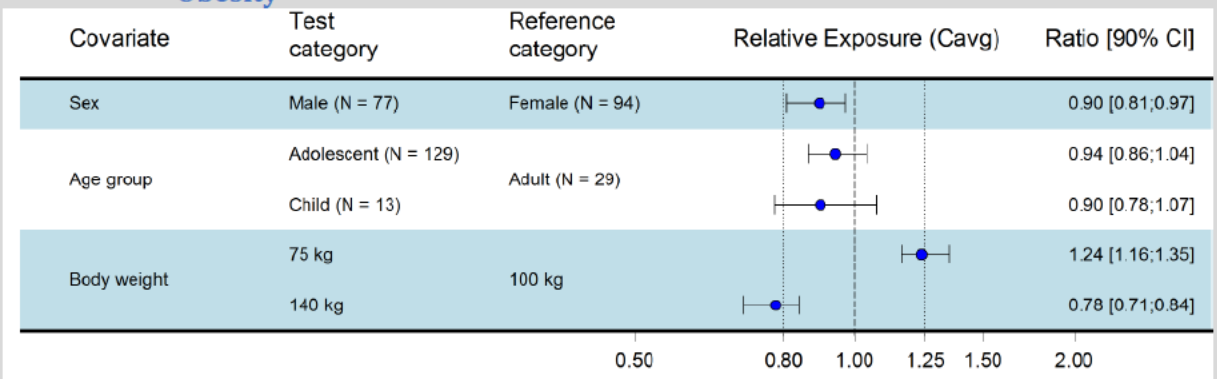
Source: the applicant's Population PK and Exposure-Response Modelling Report, Appendix J, page 53

In conclusion, the population PK model of liraglutide was qualified and found suitable for estimation of covariate effects and exposures in adolescents as well as in children and adults.

4.2.2.1.7 Evaluation of covariate effects on liraglutide exposure

Effects of intrinsic covariates on liraglutide exposure are shown in Figure 13. In accordance with previous findings in adults, body weight was the main intrinsic covariate for liraglutide exposure with lower exposure at higher body weights. Age group and sex were of no or little importance.

Figure 13 Forest Plot of Covariate Analysis for Liraglutide Exposure in Subjects with Obesity

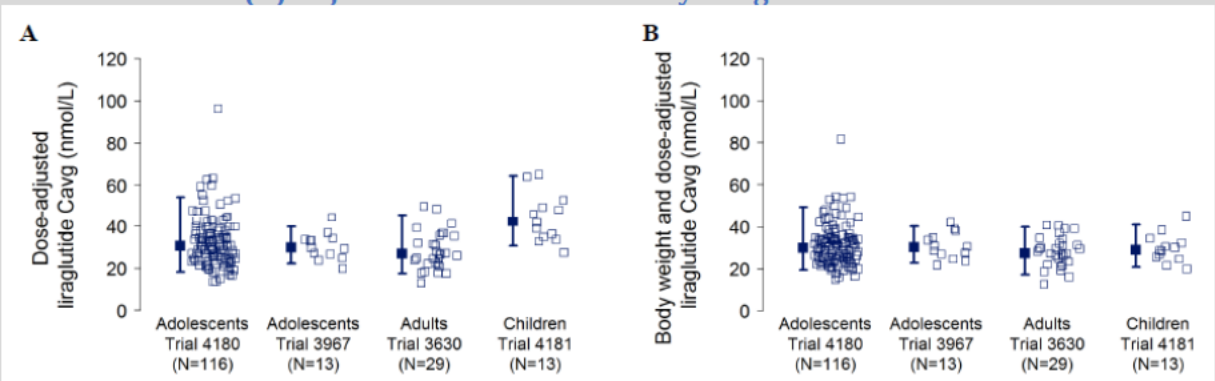


The reference category profile was a female adult subject with a body weight of 100 kg. The column to the right shows numerical means and 90% CI for the relative exposures. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80–1.25). Data from trials 4180, 3967, 3630 and 4181.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-2, page 23

In accordance with the outcome of the covariate analysis, individual and mean C_{avg} values appeared to be similar in adolescents and adults when adjusted to 3.0 mg dose whereas children had slightly higher concentrations (Figure 14A). When adjusting for body weight, exposures were similar across trials and age groups, including children (Figure 14B).

Figure 14 Liraglutide Exposure Across Trials in Subjects with Obesity, without (A) and with (B) Adjustment for Baseline Body Weight



Data are individual (open symbols) and geometric mean C_{avg} estimates adjusted to 3.0 mg dose with 95% CI (closed symbols with error bars) from the final PK model for each trial. Data from trials 4180, 3967, 3630 and 4181.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-4, page 24

A summary of model-derived clearance (CL/F) values and average exposures across trials is provided in Table 6.

Table 6 Summary of Clearance and Exposure Estimates Across Trials Included in the PK Analysis

Trial	Baseline body weight (kg)	Clearance (CL/F) (L/h)	Cavg (nmol/L)
4180 - adolescents	97.5 [94.1, 101.1]	1.09 [1.02, 1.16]	30.7 [28.8, 32.7]
3967 - adolescents	101.4 [94.1, 109.2]	1.11 [0.98, 1.26]	30.0 [26.4, 34.0]
3630 - adults	101.1 [95.3, 107.3]	1.23 [1.09, 1.40]	27.0 [23.9, 30.5]
4181 - children	68.3 [62.2, 75.0]	0.78 [0.67, 0.92]	42.6 [36.4, 49.9]

Data are geometric means of individual model-derived estimates with 95% CI.1Average concentrations estimated for 3.0 mg dose of liraglutide

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 5-2, page 24

Reviewer's comment:

The applicant's final population PK model was able to describe the liraglutide PK data collected from clinical studies. This model was developed with data from earlier clinical trials with liraglutide (reviewed by Drs. Jain and Singh in DARRTS, Reference ID 3828218 and 4302250, respectively). The current population PK model pooled data from earlier trials with the data from the current trial (#4180) in adolescents. The ETA shrinkage value of CL/F (10.2%) and V/F (19.2%) from the final population PK model were low. The shrinkage of residual error of 6.4% is acceptable. Thus, the applicant's final population PK model is acceptable to be used for PK labeling description and providing PK concentrations for the exposure-response analyses.

4.2.2.2 Exposure-response analysis

4.2.2.2.1 Data used for exposure-response analysis

The exposure-response analyses for weight management in adolescents were conducted as meta-analyses with inclusion of clinical data from phase 2 and phase 3 trials for weight management in adults (Table 7). The historical data from treatment of adults were included in the analysis to compare the exposure-response relationships for liraglutide in weight management between adults and adolescents.

The exposure-response dataset comprised placebo and treatment data from a total of 4619 subjects; 4372 adults from trials 1807, 1839 and 1922 and 247 adolescents from trial 4180 (Table 8). The exposure-response analysis related the model-derived Cavg exposures at steady-state to the change from baseline of the weight-related responses at end of trials. The historical data in adults were used as reported from the original analysis without further modification. Reference is made to the modelling report for adults for further detail.

Table 7 Summary of Trials Included in The Exposure-Response Analysis

Group	Trial 4180	Trial 1807	Trial 1839	Trial 1922
Clinical stage	Phase 3	Phase 2	Phase 3	Phase 3
Total no of subjects	247	415	3250	707
No of subjects on liraglutide treatment	121	331	2339	584
No of subjects on placebo treatment	126	84	911	123
No of adults with overweight or obesity	-	415	3250	707
No of adolescents with obesity 12-17 years	247	-	-	-
No of subjects with normoglycaemia	183	205	1250	0
No of subjects with pre-diabetes	62	210	2000	0
No of subjects with T2D	2	0	0	707
Weekly dose escalation steps (mg/day)	0.6, 1.2, 1.8, 2.4, 3.0	0.6, 1.2, 1.8, 2.4, 3.0	0.6, 1.2, 1.8, 2.4, 3.0	0.6, 1.2, 1.8, 2.4, 3.0
Actual maintenance doses (mg/day)	0,6, 1.2, 1.8, 2.4, 3.0[1]	1.2, 1.8, 2.4, 3.0	3.0	1.8, 3.0
Treatment duration[2]	56 weeks	20 weeks	56 weeks	50 weeks

[1]Maintenance dose for the majority of subjects in trial 4180 was 3.0 mg/day, a few subjects used lower doses (Table 4-1). [2]Including dose-escalation.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 4-2, page 15

Table 8 Summary of Demographic Characteristics Across Trials for the Exposure Response Data

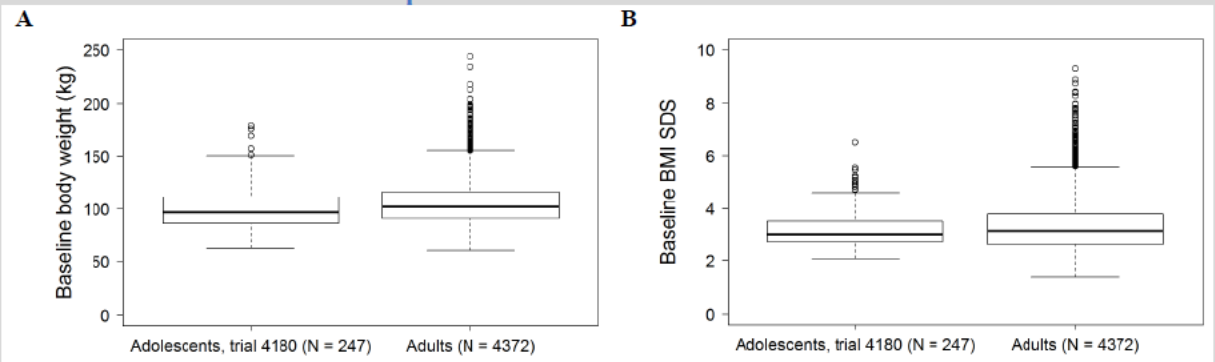
Category	Group	Trial 4180	Trial 1807	Trial 1839	Trial 1922	Total
All	N[1]	247 (5.3%)	415 (9%)	3250 (70.4%)	707 (15.3%)	4619 (100%)
Sex	Female	145 (58.7%)	313 (75.4%)	2535 (78%)	352 (49.8%)	3345 (72.4%)
	Male	102 (41.3%)	102 (24.6%)	715 (22%)	355 (50.2%)	1274 (27.6%)
Race	White	217 (87.9%)	413 (99.5%)	3072 (94.5%)	669 (94.6%)	4371 (94.6%)
	Asian	2 (0.8%)	-	118 (3.6%)	16 (2.3%)	136 (2.9%)
	Black or African American	19 (7.7%)	-	-	-	19 (0.4%)
	American Indian or Alaska Native	1 (0.4%)	-	7 (0.2%)	4 (0.6%)	12 (0.3%)
	Native Hawaiian or other Pacific Islander	-	-	2 (0.1%)	-	2 (0%)
	Other	8 (3.2%)	2 (0.5%)	51 (1.6%)	18 (2.5%)	79 (1.7%)
Ethnicity	Not Hispanic or Latino	194 (78.5%)	415 (100%)	2913 (89.6%)	638 (90.2%)	4160 (90.1%)
	Hispanic or Latino	53 (21.5%)	-	337 (10.4%)	69 (9.8%)	459 (9.9%)
Age (years)	Mean (SD)	14.5 (1.6)	46.4 (10.4)	45.3 (11.9)	54.8 (10.2)	45.2 (13.8)
	Range	[12-17]	[18-65]	[18-78]	[24-82]	[12-82]
Body weight (kg)	Mean (SD)	100.8 (20.7)	97.7 (12.9)	106.7 (21.4)	106.0 (21.2)	105.4 (20.8)
	Range	[62.1-178.2]	[69.2-141.2]	[63.0-244.0]	[60.1-193.3]	[60.1-244.0]

[1]Four subjects from the full analysis set from trial 4180 were excluded from the exposure-response dataset due to missing exposure observations.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 5-3, page 26

The data comprised an overall larger proportion of females compared to males and with several race and ethnicity categories represented for adolescents as well as for adults. The mean baseline body weights were similar across trials with slightly lower weights in the phase 2 trial in adults (trial 1807) compared to the other trials (Table 8). As shown in Figure 15, there were large overlaps in body weights and BMI SDS values between adolescents and adults. In summary, the demographic characteristics of adolescents and adults included in the exposure-response analyses are similar apart from the age distribution.

Figure 15 Box-Plot of Distribution of Body Weights (A) And BMI SDS Values (B) for Adolescents Compared to Adults

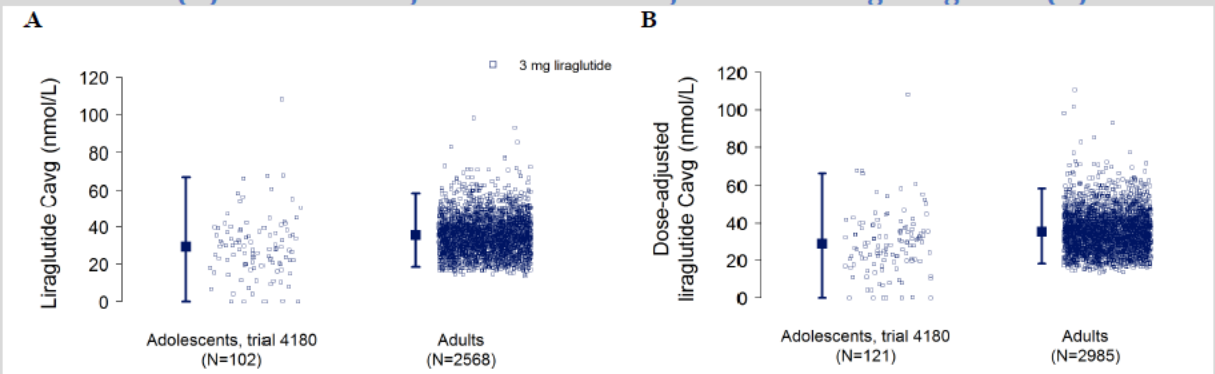


Boxes represent the 25th, 50th and 75th percentiles. Whiskers represent the 5th and the 95th percentiles. Circles are outliers. Data from trials 4180, 1807, 1839 and 1922.

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-544, page 27

In accordance with the similar demographic characteristics of adults and adolescents included in the exposure-response analyses, the exposures of liraglutide were similar in the two populations. This is shown in Figure 16 for subjects on 3.0 mg liraglutide (panel A) and for all subjects with exposures adjusted to 3.0 mg dose (panel B).

Figure 16 Liraglutide Exposure Across Trials in Subjects Treated With 3.0 mg Liraglutide (A) and in All Subjects with Doses Adjusted to 3.0 mg Liraglutide (B)



Data are individual (open symbols) and geometric mean C_{avg} estimates with 95% CI (closed symbols with error bars) from the final PK model for each trial. Data from trials 4180, 1807, 1839 and 1922. In trial 4180, BLQ data was included and data cleaning was less strict compared to trials 1807, 1839 and 1922.

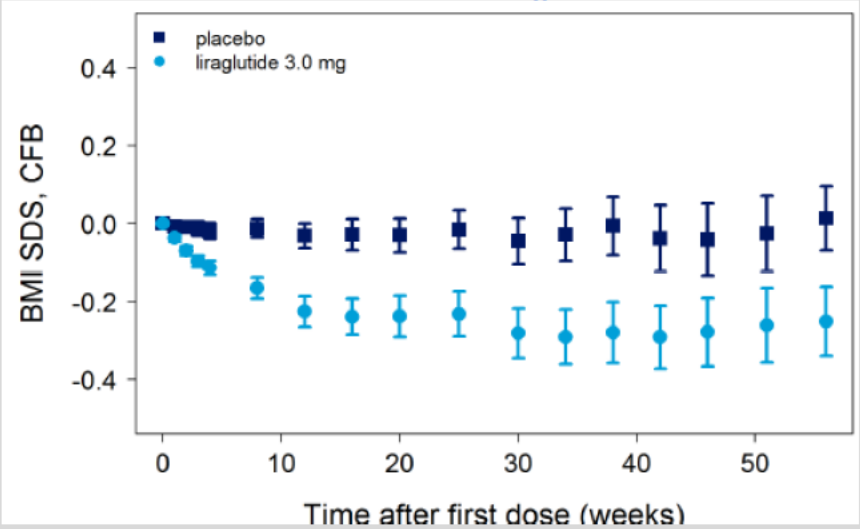
Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-6, page 27

4.2.2.2.2 Exposure-response analysis of BMI SDS change from baseline

The primary metric used for exposure-response of weight management was BMI SDS in which the weight change due to age progression and differences between male and female subjects are accounted for.

The time course of BMI SDS in adolescents on placebo and on liraglutide 3.0 treatment indicate an almost constant BMI SDS in subjects on placebo and a substantial reduction over time in subjects on active treatment (Figure 17). The response appeared to be close to maximal at 20 weeks of treatment, in accordance with previous findings in adults.

Figure 17 Time-Course of Observed BMI SDS Change from Baseline in Adolescents



Data are means and 95% CIs in trial 4180

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-7, page 28

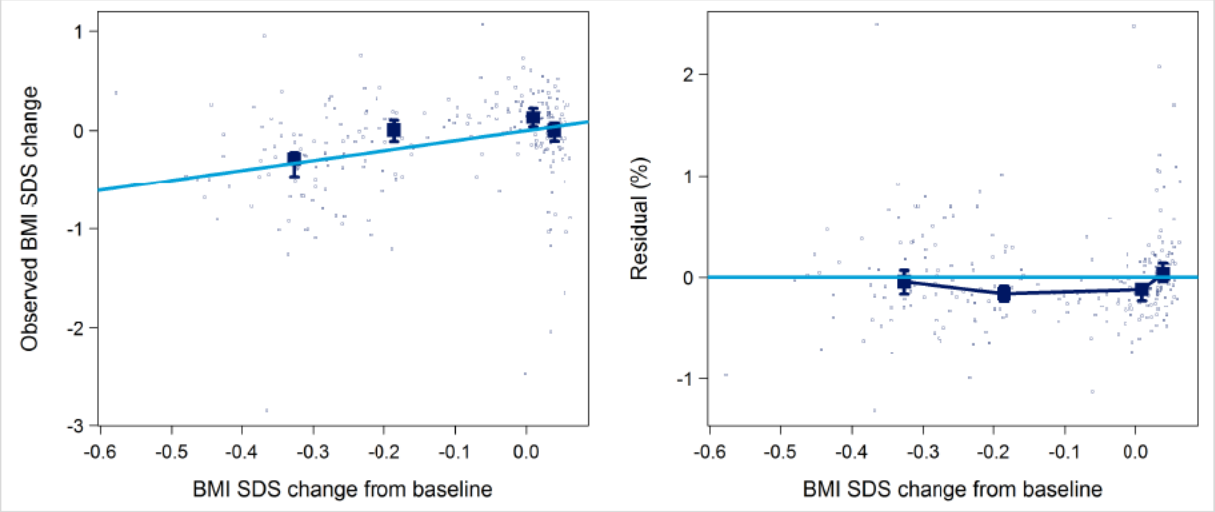
The exposure-response relationship at end of trial for BMI SDS was successfully described by an E_{max} model with baseline BMI SDS and age group as covariates on the placebo response. Reference is made to the run log for model development, diagnostic plots and parameter estimates of the final model (Table 9, Table 10, Figure 18 and Figure 19) and to the summary of covariates included across exposure-response models (Table 11).

Table 9 Run Log for Development of The Exposure-Response Model of BMI SDS, Change from Baseline

Run number	Description	Log likelihood	Convergence	Reference model	Significance
000	Base model	-2421.55	TRUE	NA	NA
001	Base + Emax cov (Sex) + E0 covs (Sex, Baseline BMI SDS, Age group)	-2371.79	TRUE	000	<0.00001
002	Reduce E0 covs: Sex removed	-2373.00	TRUE	001	0.12110
003	Add Emax covs: Age grops added	-2372.94	TRUE	002	0.75098
004	Reduced Emax covs: Sex removed	-2373.21	TRUE	003	0.47022
005	Reduced Emax covs: Age group removed	-2373.26	TRUE	004	0.75095
007	Testing Baseline BMI(%) as E0 cov, not significant	-2372.17	TRUE	005	0.14063
005	Final model: E0 covs: Baseline BMI SDS, Age group	-2373.26	TRUE	004	0.75095

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 8-4, page 54

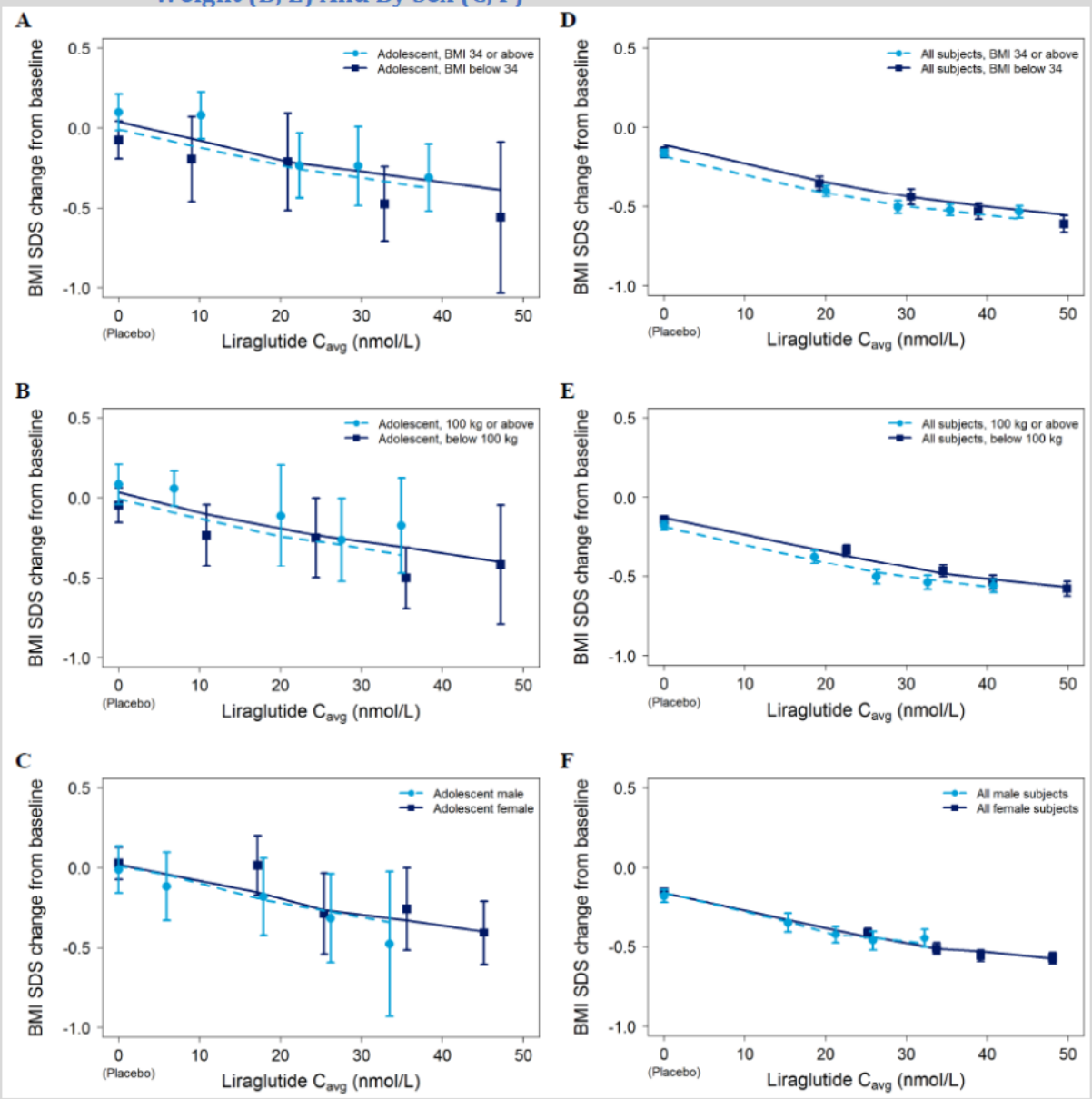
Figure 18 Diagnostic Plots for The Final Exposure-Response Model For BMI-SDS Change from Baseline



Data are observed BMI SDS values versus population predictions and residuals versus population predictions. Data from trial 4180

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-9, page 54

Figure 19 BMI SDS Change from Baseline Versus Liraglutide Exposure in Adolescents (A–C) And in All Subjects (D-F) Stratified By Baseline BMI (A, D), By Baseline Body Weight (B, E) And By Sex (C, F)



Data points with error bars are means with 95% CIs for each of 5 quantiles of Cavg for liraglutide and one quantile for placebo (at C_{avg} of 0 nmol/L). Lines are covariate-adjusted, model derived relations. Data in A–C from trial 4180. Data in D–F from trials 4180, 1807, 1839 and 1922

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 8-10, page 55

Table 10 Parameter Estimates from The Exposure-Response Model of BMI SDS Change from Baseline*

Parameter	Unit	Estimate	95% CI Lower bound	95% CI Upper bound	RSE (%)
Emax	-	-0.903	-1.371	-0.674	18.8
EC50	nmol/L	56.620	33.068	107.239	31.8
Placebo	-	-0.033	-0.078	0.013	70.5
Placebo cov.: Baseline BMI SDS	-	-0.042	-0.054	-0.030	14.7
Placebo cov.: Age group	-	0.183	0.131	0.236	14.6
Residual standard error	-	0.405	NA	NA	NA

*Based on data from trials 4180, 1807, 1839 and 1922. CI: confidence interval. RSE: relative standard error. CV:coefficient of variation

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 8-5, page 56

Table 11 Summary of Covariates Included in The Final Exposure-Response Models

Models	BMI SDS	Body weight % change from baseline	BMI % change from baseline	Proportion reaching ≥5% weight loss
Covariates on the placebo effect	• Baseline BMI SDS • Age group	• Age group	• Age group	• Age group
Covariates on E_{max}	-	• Sex • Age group	• Sex	• Sex

Source: the applicant's Population PK and Exposure-Response Modelling Report, Table 5-4, page 28

The exposure-response analysis showed a similar exposure-response relationship for BMI SDS in adolescents and adults apart from a lower placebo-response (at C_{avg} of 0 nmol/L) observed in adolescents compared to adults (Figure 20). The difference in placebo response between adults and adolescents could be due to a combination of factors including continued growth in the adolescent population, potentially lower adherence to treatment in adolescents, and potential differences in the diet and exercise programmes.

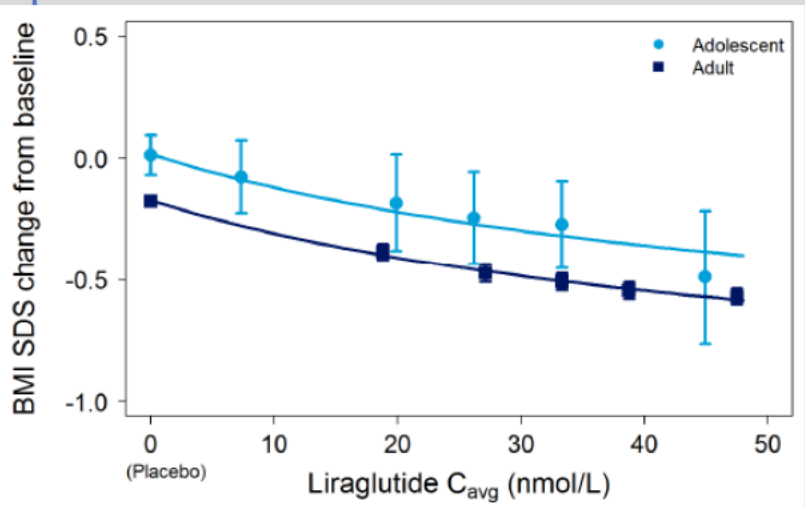
4.2.2.2.3 Exposure-response rationale for the proposed treatment dose in adolescent subjects

The proposed liraglutide dose for weight management of adolescents with obesity is 3.0 mg once daily similarly to the approved dose in adults.

As seen in Figure 14A, the recommended dose was shown to provide similar exposures in adolescents and adults, even without adjusting for baseline body weights.

Moreover, the modelling analyses provided evidence of relevant exposures and responses in adolescents treated with 3.0 mg liraglutide daily albeit with lower values compared to adults (Table 12). The added benefits of increasing exposures of liraglutide were similar in adolescent and adult subjects with overweight or obesity (Figure 20), thus further supporting the 3.0 mg treatment dose.

Figure 20 BMI SDS Change from Baseline Versus Liraglutide Exposure for Adolescents Compared to Adults



Data points with error bars are means with 95% CIs for each of 5 quantiles of Cavg for liraglutide and one quantile for placebo (at C_{avg} of 0 nmol/L). Lines are covariate-adjusted, model derived relations. Data from trial 1807 after 20 weeks of treatment, trials 4180 and 1839 after 56 weeks of treatment and trial 1922 after 50 weeks of treatment

Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-8, page 29

Table 12 Model-Derived Exposures and Responses in Adolescents and Adults*

Group	Number of subjects	Baseline body weight (kg)	Cavg (nmol/L)	BMI SDS change	BMI change (%)	Body weight loss (%)
Adolescent subjects	121	97.6	19.2	-0.27	-4.47	-3.49
Adult subjects	2985	103.6	33.8	-0.51	-8.28	-8.27

*Model-derived estimates based on data from trials 4180, 1807, 1839 and 1922. Concentration values are geometric means and response values are arithmetic means of individual estimates.

Reviewer's comment:

The applicant's exposure-response model is acceptable. It showed that larger response for increasing exposure was established for BMI SDS change from baseline, body weight % change from baseline, BMI % change from baseline and for the proportion of subjects with at least 5% weight loss. Increasing exposures of liraglutide were similar in adolescent and adult subjects with overweight or obesity.

4.2.3 Reviewer's analysis

4.2.3.1 Objectives:

The objectives of reviewer's analysis were to confirm the Sponsor's analysis to address the following key questions in the meta-analyses as follows:

Population PK analysis:

- Investigate body weight, age group (children, adolescent and adult subjects) and sex as covariates; is the impact of selected covariates on liraglutide exposure in adolescent subjects in accordance with previous results?
- Are the estimated exposure levels for adolescent subjects in trial 4180 as expected, compared to previous findings of exposures across age groups?

Exposure-response analyses:

- What is the exposure-response relationship of liraglutide in adolescent subjects for change from baseline in BMI SDS?
- Is the exposure-response relationship for change from baseline in BMI SDS similar in adults and adolescent subjects?

Dose recommendation:

- Do the population PK and exposure-response analyses support the proposed treatment dose in adolescent subjects?

4.2.3.2 Data

The dataset used in the reviewer's population PK and exposure-response analysis was the same dataset the applicant used.

4.2.3.3 Methods

NONMEM (Version 7.3) was used for all population PK analyses. The R software was used for data table generation and post-NONMEM graphing and reporting.

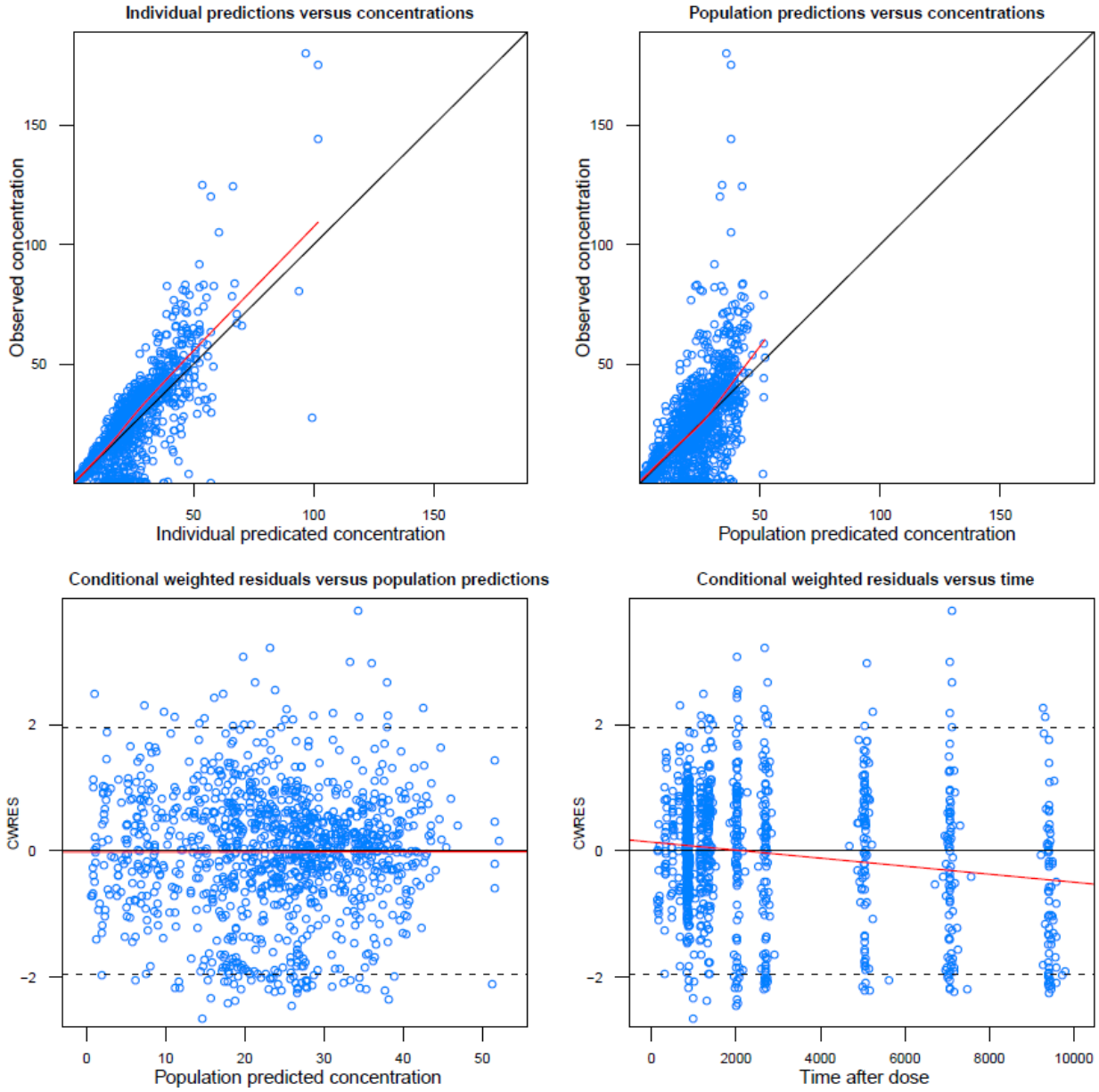
The applicant's final population PK/PD model was used as the starting point. PsN built-in parallel retries were used to optimize the initial value. Testing the fitting adequacy and evaluating the parameter estimates were conducted on the updated population PK/PD model.

4.2.3.4 Results

4.2.3.4.1 Population PK analysis

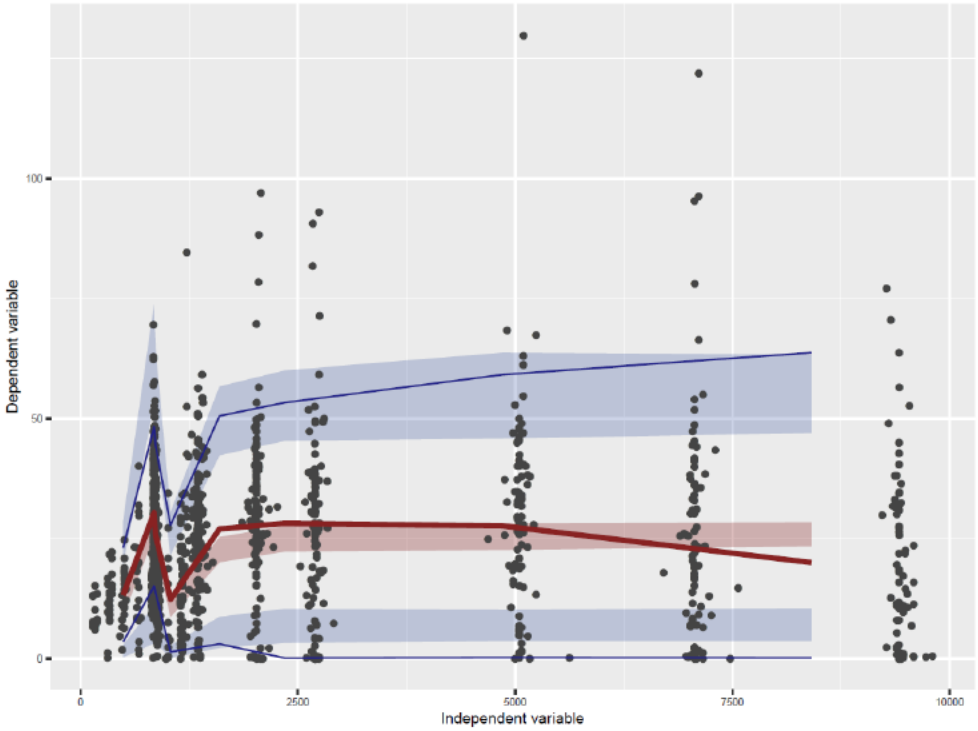
The reviewer verified the applicant's population PK model. The goodness-of-fit plots and visual predictive check plot are shown in Figure 21 and Figure 22, respectively. Based on these diagnostic plots and visual predictive check, there was a good agreement between observed and model-predicted liraglutide concentrations. Parameter estimates from the final model are listed in Table 13.

Figure 21 Goodness-Of-Fit for Final Population PK Model



Note: the red lines are smooth lines showing the trend.

Figure 22 Visual Predictive Check of Population PK Model of Liraglutide in Overweight or Obese Adolescents



Data are observed (lines) and simulated (shaded area, n=2000) medians and 5th and 95th percentiles for concentrations after the first dose. Data from trial 4180.
Source: Reviewer's independent analysis

Table 13 Parameter Estimates from Reviewer's Final Population PK/PD model

Parameter Description	Parameter Estimate	% RSE	95%CI
(KA [1/h])	0.0813	0%	0.081-0.081
(CL/F [L/h])	1.01	4.1%	0.929-1.091
(V/F [L])	13.8	0%	13.8-13.8
(F)	0.741	0%	0.741-0.741
(CL-BW)	0.812	21.4%	0.471-1.153
(CL-Male)	1.11	5.4%	0.992-1.228
(CL-Child)	1.08	10.1%	0.866-1.294
(CL-Adolescent)	1.05	5.5%	0.937-1.163
(V-BW)	0.671	23.4%	0.363-0.979

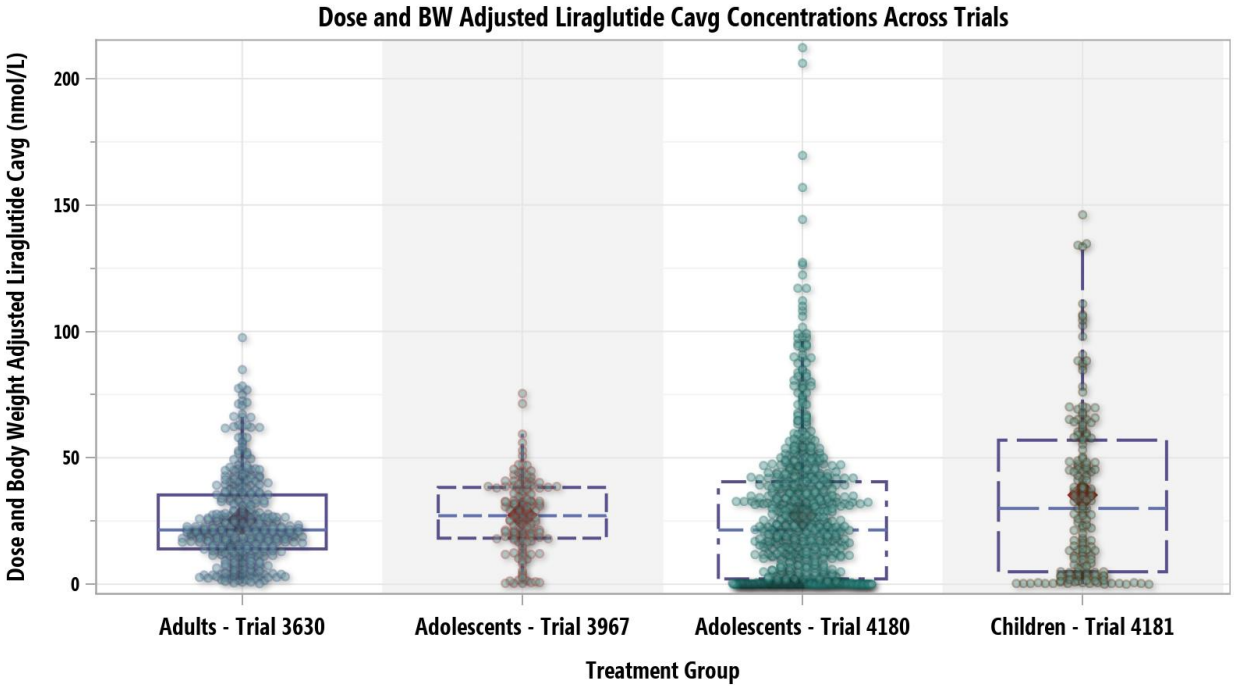
KA = Absorption rate constant; CL = Clearance; F = Bioavailability; V = Volume of distribution; BW = Body weight;

The impact of body weight, age group (children, adolescent and adult subjects) and sex as covariates investigated in this PopPK model showed that the effect of selected covariates on liraglutide exposure in adolescent subjects was in accordance with previous results.

Estimated exposure levels for adolescent subjects in trial 4180:

Dose and body weight adjusted average steady-state liraglutide concentrations shown in Figure 23 indicate that the estimated exposure levels for adolescent subjects in trial 4180 are as expected, compared to previous findings of exposures across age groups.

Figure 23 Dose and Body Weight Adjusted Average Steady-State Liraglutide Concentrations

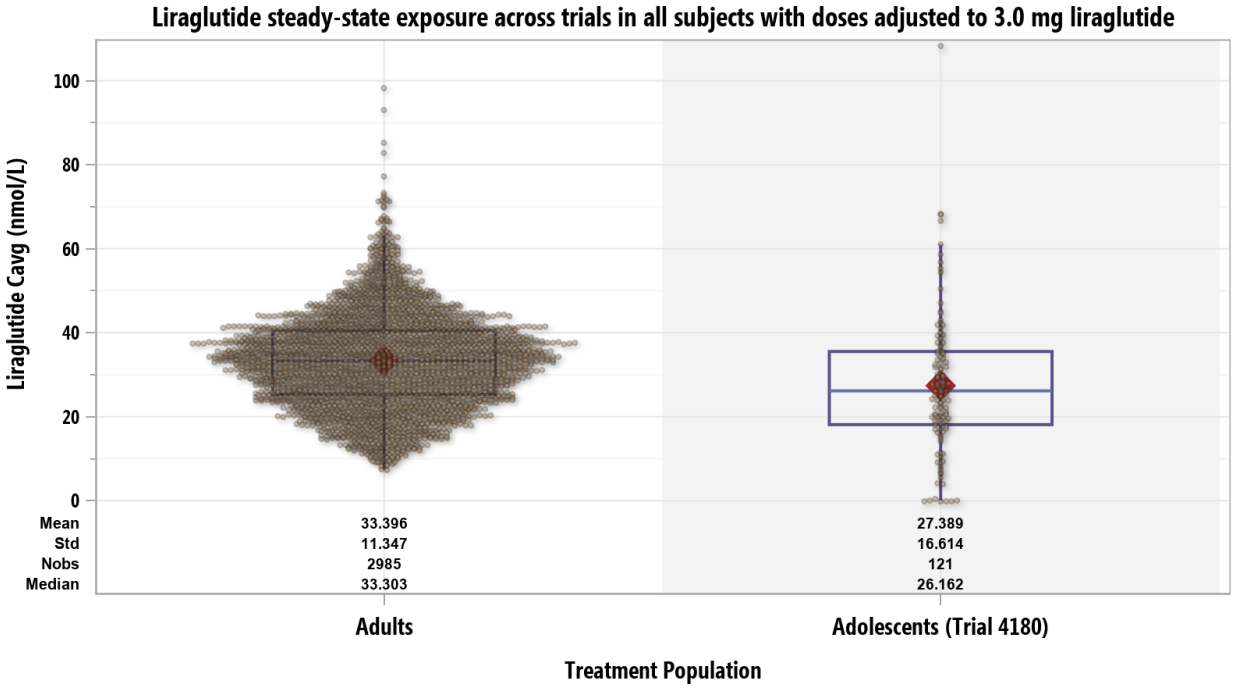


(Source: reviewer generated plot)

4.2.3.4.2 Exposure-response analyses

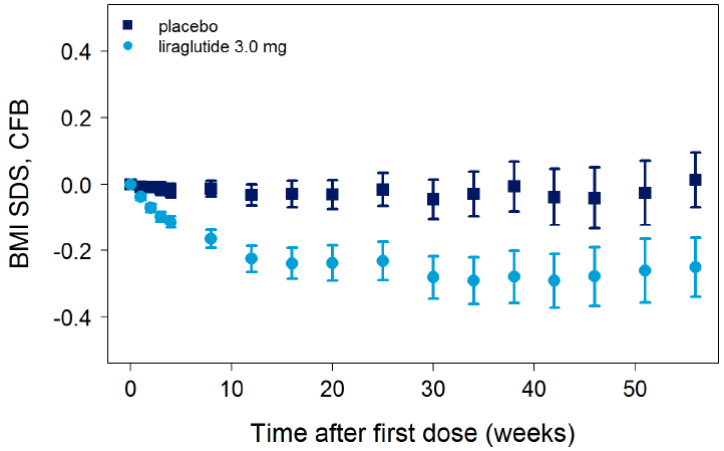
Mean liraglutide exposure at a dose of 3.0 mg was similar in adolescents from trial 4180 compared to the mean exposure in adults from trials 1807, 1839 and 1922 in the exposure-response population with a large overlap of individual exposures between the two age groups (Figure 24).

Figure 24 Liraglutide Steady-State Exposure Across Trials in Subjects with Doses Adjusted to 3.0 mg



Body mass index standard deviation score (BMI SDS) which accounts for the weight change due to age progression and differences between male and female subjects, was the primary metric used for exposure-response analysis. The time course of BMI SDS in adolescents on placebo and on liraglutide 3.0 treatment indicate a substantial reduction over time in subjects on active treatment compared to an almost constant BMI SDS in subjects on placebo (Figure 25). Similar to previous findings in adults, the response in adolescents appeared to be close to maximal at 20 weeks of treatment.

Figure 25 Time-Course of Observed BMI SDS Change from Baseline in Adolescents



Source: the applicant's Population PK and Exposure-Response Modelling Report, Figure 5-7, page 28

The exposure-response relationship at end of trial for BMI SDS was successfully described by the Applicant by an E_{max} model with baseline BMI SDS and age group as covariates on the placebo response. Apart from a lower placebo-response (at C_{avg} of 0 nmol/L) observed in adolescents compared to adults, the Applicant indicated that exposure-response analysis showed a similar exposure-response relationship for BMI SDS in adolescents and adults (Figure 20). Continued growth in the adolescent population, potentially lower adherence to treatment in adolescents (as noted by relatively high fraction of lower than expected liraglutide concentrations in this trial), and potential differences in the diet and exercise programs between and adults and adolescents are possible explanations for the lower placebo response in adolescents compared to adults.

4.2.3.4.3 Dose recommendation

Liraglutide exposure was similar in adolescents and adults as shown by population PK analysis. Similar to earlier population PK analysis conducted in adults, Body weight was identified as the most important intrinsic factor for exposure. Exposure-response with larger response for increasing exposure was established for BMI SDS change from baseline.

The recommended liraglutide dose of 3.0 mg was shown to provide similar exposures in adolescents and adults, even without adjusting for baseline body weights (Figure 14A), thus providing support to the proposed treatment dose in adolescent subjects.

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