CLINICAL PHARMACOLOGY REVIEW

NDA	022341 Supplement 31
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Submission Date(s)	December 17, 2018
Submission Type	505(b)(1)
Brand Name	VICTOZA®
Generic Name	Liraglutide
Dosage Form and Strength	Injection: 6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg
Route of Administration	Inject subcutaneously in the abdomen, thigh or upper arm
Proposed Indication	as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus
Applicant	Novo Nordisk
Clinical Pharmacology Review Team	Tao Liu, Ph.D., Lian Ma, Ph.D., Manoj Khurana, Ph.D.

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1 Executive Summary

The applicant has submitted the supplement to NDA 022341 (VICTOZA) on December 17th, 2018 (SEQ 0414) seeking approval for liraglutide as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus under 505(b)(1) pathway. The original NDA was approved in 2010 for liragutlide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The proposed dosing regimen for T2DM in pediatrics is identical to adults: *Initiate at 0.6 mg per day for one week then increase to 1.2 mg. Dose can be increased to 1.8 mg for additional glycemic control*.

The submission is intended to satisfy the required pediatric assessment per Pediatric Research Equity Act (PREA) issued at the time of original NDA approval (PMR 1583-2). The clinical study was also part of the Pediatric Written Request and sponsor is seeking pediatric exclusivity determination with this submission.

In this supplemental NDA submission, the applicant submitted the following to support their claim for the pediatric indication:

- one pediatric Phase 3 clinical study titled:
  "Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes: A 26-week double-blind, randomised, parallel group, placebo controlled multi-centre trial followed by a 26-week open-label extension" [PMR 1583-2: Study ID: NN2211-3659 (*ellipse*™)].

- A modeling report titled:
  "*Population pharmacokinetics and exposure-response of liraglutide in paediatric subjects with type 2 diabetes"*

- In addition, the applicant included a Phase 1 clinical study in adolescents, which was previously submitted on April 25th, 2012 (SEQ 0192) and May 23rd, 2012 (SEQ 0196) to NDA 022341 titled:
  "A Randomised, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Paediatric (10–17 years old) Subjects with Type 2 Diabetes" (Study ID: NN22111-1800)

With these two clinical studies in pediatrics and the pharmacometrics analyses, the clinical pharmacology review focused on answering two key questions:

1) Does the pharmacokinetic (PK) data support PK comparability between pediatrics and adults?
2) Is the proposed dosing regimen appropriate for pediatrics 10 years and older with T2DM?

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information provided within NDA 022341 and finds that the clinical pharmacology data under this supplemental NDA is acceptable to support a decision towards fulfillment of the PREA requirements and proposed use of liraglutide in pediatric population 10 years and older.

2 Summary of Clinical Pharmacology Assessment

2.1 Highlights on Trial design

Study NN2211-3659

Study NN2211-3659 was a multinational, multi-center, randomized, parallel-group, placebo-controlled trial with a 26-week double-blind period followed by a 26-week open-label extension in subjects with T2D aged 10−17 years (**Error! Reference source not found.**).

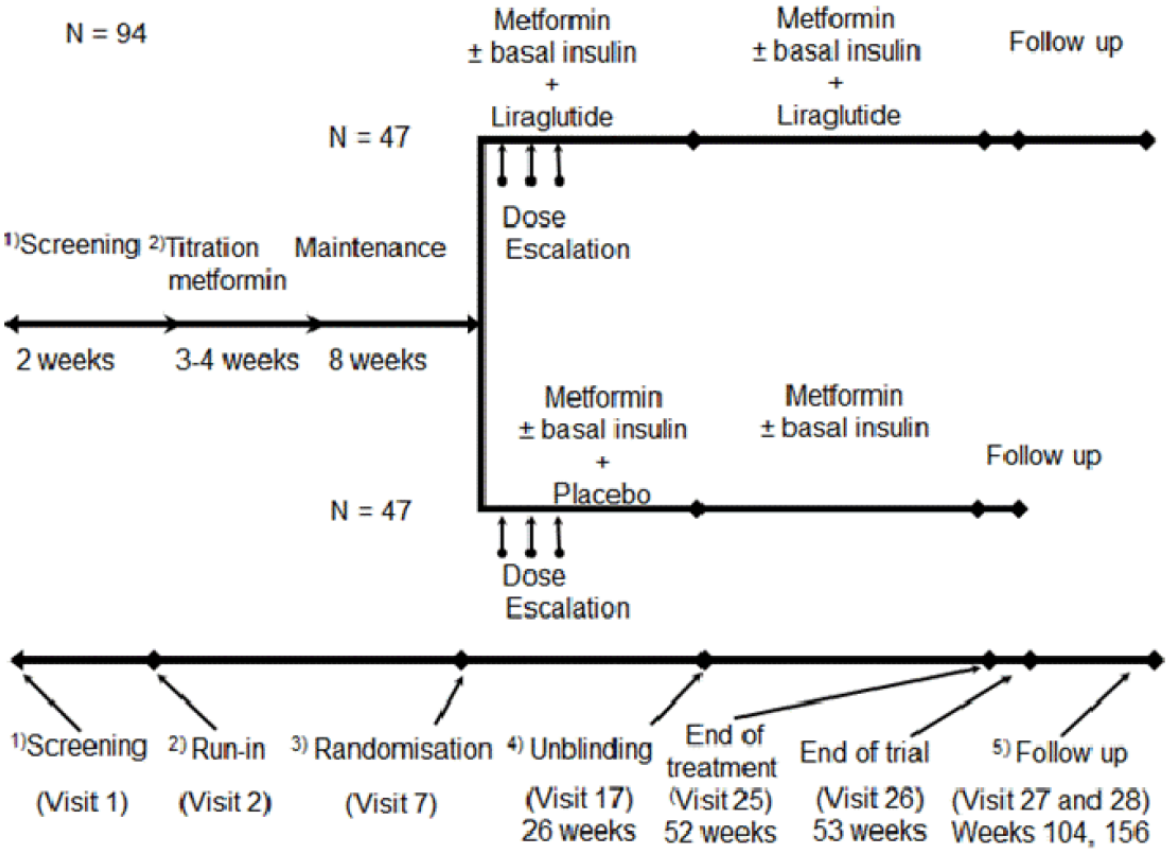


Figure 1 Study Design NN2211-3659

1) Screening prior to metformin titration
2) Run-in: metformin titration to 2000 mg daily, if possible, or a MTD ≥1000 mg and ≤2000 mg after verification of eligibility according to the inclusion and exclusion criteria. Subjects already treated with a stable dose ≥ 2000 mg of metformin or more for at least 56 days at the

time of screening could skip the run-in period and advance directly to randomization. Subjects who were treated with basal insulin should in addition to the stable dose of metformin have had a stable dose of basal insulin for at least 56 days to advance directly to visit 7.
3) Randomized treatment: Escalation of liraglutide in weekly 0.6 mg increments over 2-3 weeks to 1.8 mg, if possible, or a MTD. Subjects on basal insulin had their insulin dose decreased by 20% at randomization.
4) All subjects were unblinded at visit 17. Subjects treated with liraglutide continued with unchanged doses of metformin ± basal insulin and their treatment with liraglutide. Subjects treated with placebo discontinued placebo and continued on metformin ± basal insulin.
5) All subjects were to complete visit 26. Subjects treated with liraglutide for more than 3 months were to also complete visits 27 and 28.
Abbreviations: MTD = maximal tolerated dose; N = number of subjects
(source: Figure 9-1 in Clinical Trial Report NN2211-3659 Version 1.0 Date 02 November 2018)

Dose escalation strategy in study NN2211-3659 was similar to the FPG limited dose escalation in study NN2211-1800. The dose escalation strategy is depicted in Figure 2.

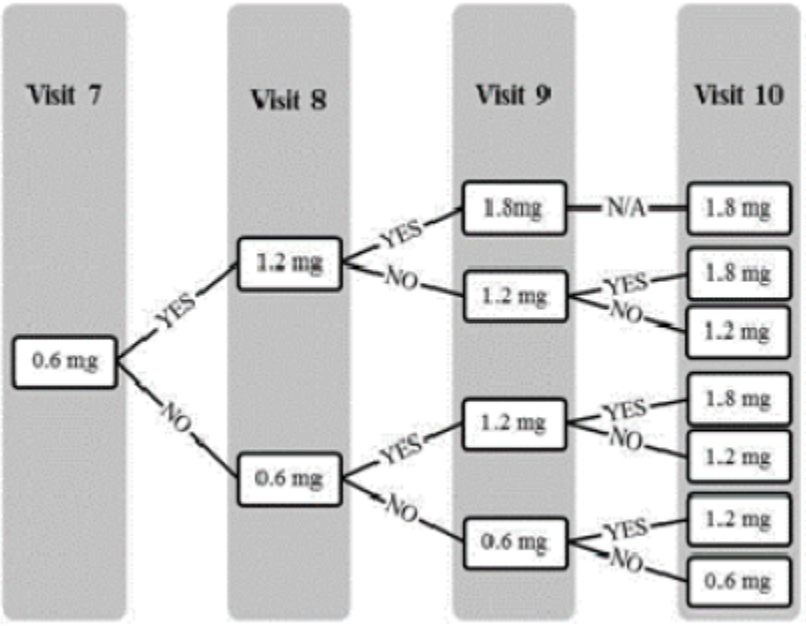


Figure 2 Dose escalation strategy of liraglutide

Note: During the blinded period, escalation at each YES/NO decision point was based on tolerability and on whether the subject's average FPG was >6.1 mmol/L (110 mg/dL).
(Source: Figure 9-2 in Clinical Trial Report NN2211-3659 Version 1.0 Date 02 November 2018)

Study NN2211-1800

Study NN2211-1800 was a randomized, double-blind, placebo-controlled trial in which pediatric subjects with type 2 diabetes were randomized 2:1 either to liraglutide or placebo treatment (administered subcutaneously once daily) for five weeks. Subjects randomized to liraglutide treatment received 0.3 mg liraglutide daily (starting on Day 1) during the first week, followed by 0.6 mg daily (starting on Day 8) during the second week, 0.9 mg daily (starting on Day 15)

during the third week, 1.2 mg daily (starting on Day 22) during the fourth week, and 1.8 mg daily (starting on Day 29) during the fifth and final treatment week. Subjects randomized to placebo were given matched placebo treatments during each of the corresponding five weeks in order to maintain blinding.

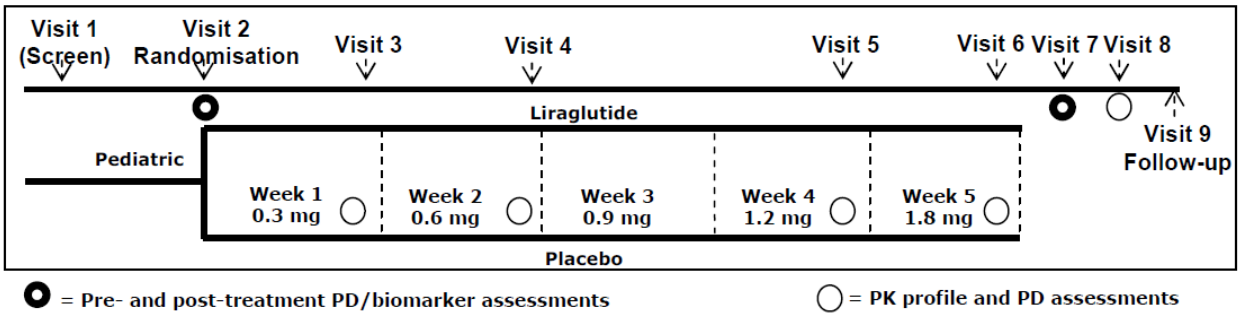


Figure 3. Study Design NN2211-1800

(Source: Figure 9-1 in NN2211-1800 Clinical Trial Report Version 1.0 Date 19 March 2012)

Dose escalation in study NN2211-1800 was based on safety and tolerability (as an average of 3 measurements of FPG >110 mg/dL [6.1 mmol/L]) at each dose level, which was similar to study NN2211-3659. If dose escalation was not applicable, subjects continued on the highest reached dose for the remainder of the trial.

Serial sampling for the 13-hours liraglutide PK profile was performed for each subject at the end (Day 7) of Weeks 1 (0.3 mg), 2 (0.6 mg), 4 (1.2 mg) and 5 (1.8 mg). Additional single samples for the final dose, 72-hours liraglutide PK profile were obtained for each subject at Week 6 Day 1 (24 hours), Week 6 Day 2 (48 hours) and Week 6 Day 3 (72 hours).

2.2 Highlights on Clinical Pharmacology Information

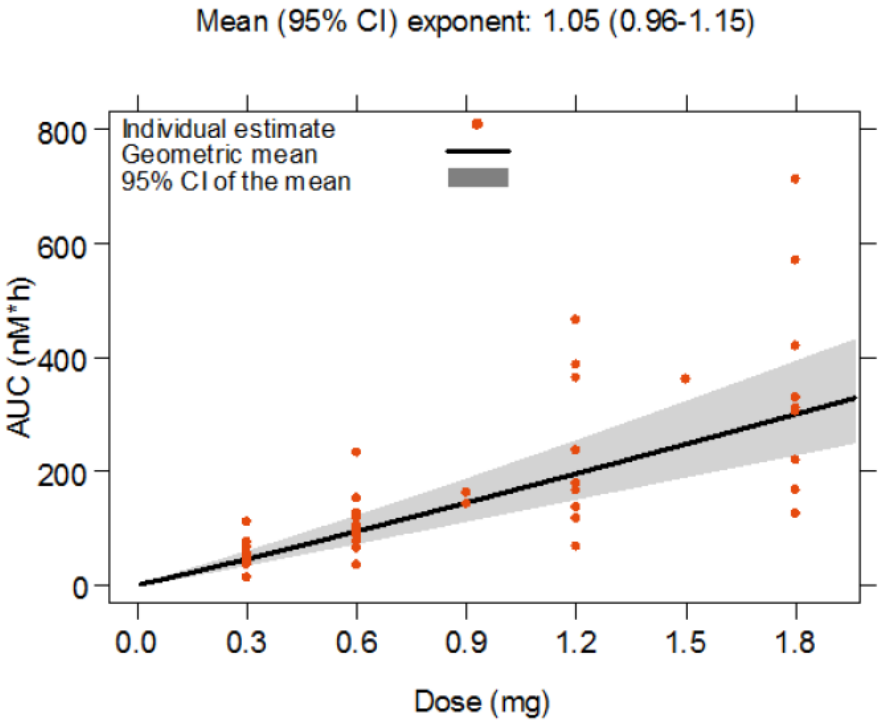
2.2.1 Pharmacokinetics Characteristics in Pediatric Patients with T2DM

Based on the rich sampling PK samples collected from patients in study NN2211-1800, the applicant characterized the PK profiles and demonstrated dose proportionality from 0.3 mg to 1.8 mg for liraglutide. The PK parameters are given in Table 1, and the dose proportionality (power model) is depicted in Figure 4. The estimated $AUC_{SS,0-24}$ following 0.3 - 1.8 mg indicates dose proportionality (slope: 1.05 (95% CI 0.96 - 1.15) in the investigated pediatric population with type 2 diabetes.

Table 1 Pharmacokinetic endpoints at steady state by dose based on 13-hour profiles

Pharmacokinetic endpoint	Liraglutide dose level			
	0.3 mg (N=9[a])	0.6 mg (N=10[a])	1.2 mg (N=6[a])	1.8 mg (N=9[a])
AUC_{0-13h} (h*pmol/L)	27,212 (51.3)	54,637 (47.9)	87,444 (75.6)	146,868 (62.0)
C_{max} (pmol/L)	2,647 (46.2)	5,446 (41.2)	9,881 (56.4)	16,288 (65.2)
t_{max} (h)	8.2	10.0	8.1	8.0
C_{trough} (pmol/L)	1,219 (56.5)	2,777 (69.2)	3,519 (88.0)	4,994 (78.1)

Values are geometric means (coefficient of variation percentage), except for t_{max}, for which the median is presented.
N: number of subjects. N reflects the number of subjects who followed the dosing regimen as planned.
[a] N for C_{trough} was, respectively, for the 4 dose levels (left to right): 13, 12, 8 and 8.
(Source: Table 3-4 in 2.7.2 Summary of Clinical Pharmacology Studies Date 14 November 2018)



Estimates for CL/F for each individual and the corresponding dose level were used to estimate AUC^{SS}_{0-24}. The individual estimates are shown as red dots. The solid black line is AUC^{SS}_{0-24} as estimated by the log-log linear mixed effects model used for the dose proportionality test, back-transformed to normal scale as geometric mean and plotted versus dose.

Figure 4 Dose proportionality test based on model-estimated $AUC_{SS,0-24}$.
(Source: Figure 11–3 in NN2211-1800 clinical trial report version 1.0 Final date 19 March 2012)

Reviewer's assessment:
The applicant's NCA for PK parameters and dose proportionality analysis are reasonable and consistent with previous experience in adults.

2.2.2 Does the pharmacokinetic (PK) data support PK comparability between pediatrics and adults?

Yes, the PK comparability between pediatrics and adults is overall supported by the submitted PK data.

The applicant conducted a population pharmacokinetic (PopPK) analysis to compare the PK characteristics between pediatrics (study NN2211-1800 and NN2211-3659) and adults (study NN2211-3534 and NN2211-3673). In the applicant's analysis, PK data from pediatrics and adults were pooled together to develop a one compartment PK model. Same covariate effect was assumed in pediatrics and adults, and then difference between pediatrics and adults were tested in part of the PK parameters. Totally, 557 PK samples in 72 pediatric patients from study NN2211-1800 and NN2211-3659 and 560 PK samples in 44 adult patients from study NN2211-3534 and NN2211-3673 were included in the PopPK analysis. A summary of baseline demographics in the PopPK dataset is given in Table 3.

Liraglutide followed one compartment PK model, with body weight and sex identified as statistically significant covariates on clearance and volume of distribution. This finding is consistent with the original NDA submission (see Dr. Manoj Khurana's clinical pharmacology review at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000clinpharmr.pdf.). The patient population (pediatric vs adults) was not identified as significant covariate on PK, indicating no statistical or clinically meaningful difference in pediatric PK compared to those in adults. The final parameter estimates are given in Table 2.

In addition, the applicant simulated a typical patient's PK profile at steady state based on their final PopPK model to demonstrate the PK comparability between pediatrics and adults (Note: Lines are model-derived mean population profiles versus time, covering two dosing intervals (0-24 h and 24-48 h) for a reference subject profile (female subject, body weight 90 kg, stippled blue line: adult subject, solid black line: pediatric subject). The simulated 95% concentration range predicted from the between-subject variability in the full population PK model is illustrated for the pediatric (grey tilted stripes) and adult (light blue shading) population (N=1000 replications in each group).
Figure 5).

Table 2 Parameter estimates for the full PK model

Parameter	Estimate	CI95 lower limit	CI95 upper limit	RSE (%)	IIV (%CV)	Shrinkage (%)
KA	0.0693	0.0644	0.0742	3.62	NA	NA
CL/F	1.14	0.935	1.34	9.09	42.7	4.10
V/F	18.4	14.1	22.8	12.1	65.1	44.5
CL/F - Body weight	0.877	0.62	1.13	14.9	NA	NA
CL/F - Sex	1.38	1.12	1.65	9.64	NA	NA
CL/F - Paediatric	0.918	0.737	1.10	10.0	NA	NA
V/F - Body weight	1.11	0.607	1.61	23.0	NA	NA
V/F - Sex	1.44	0.907	1.98	19.0	NA	NA
V/F - Paediatric	0.649	0.337	0.961	24.5	NA	NA
Prop. Error	31.4	NA	NA	NA	NA	5.30

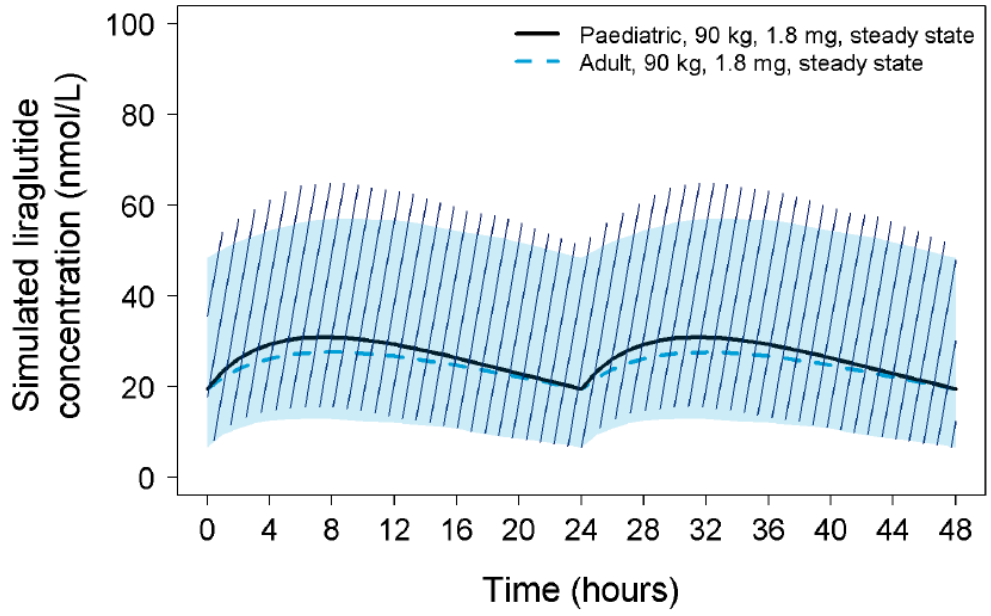
(Source: Table 2 in Appendix H in applicant's modeling report Version 1.0 Date 13 November 2018)

Table 3 Summary of baseline demographics across trials

Category	Group	3659	3534	3673	1800	Total
All	N (% of total)	59 (50.9%)	12 (10.3%)	32 (27.6%)	13 (11.2%)	116 (100%)
Population	Paediatric subjects (10 to <18y) with T2D	59 (100%)	-	-	13 (100%)	72 (62.1%)
	Adults with T2D	-	12 (100%)	32 (100%)	-	44 (37.9%)
Race	White	36 (61%)	12 (100%)	25 (78.1%)	9 (69.2%)	82 (70.7%)
	Black or African American	8 (13.6%)	-	6 (18.8%)	4 (30.8%)	18 (15.5%)
	Asian	10 (16.9%)	-	1 (3.1%)	-	11 (9.5%)
	American Indian or Alaska native	2 (3.4%)	-	-	-	2 (1.7%)
	Other	3 (5.1%)	-	-	-	3 (2.6%)
Ethnicity	Not Hispanic or Latino	46 (78%)	12 (100%)	16 (50%)	10 (76.9%)	84 (72.4%)
	Hispanic or Latino	13 (22%)	-	16 (50%)	2 (15.4%)	31 (26.7%)
	Not known	-	-	-	1 (7.7%)	1 (0.9%)
Sex	Female	36 (61%)	6 (50%)	9 (28.1%)	8 (61.5%)	59 (50.9%)
	Male	23 (39%)	6 (50%)	23 (71.9%)	5 (38.5%)	57 (49.1%)
Body weight (kg)	Mean (SD)	94.7 (31.7)	82.4 (9.8)	96.1 (21.8)	114.7 (38.1)	96 (29.3)
	Range	[41.8-201.7]	[71.6-104.1]	[57.7-140.1]	[57.3-214.4]	[41.8-214.4]
Age (years)	Mean (SD)	13.9 (1.6)	64.3 (6.2)	49.9 (8.5)	14.6 (2.2)	29.2 (20.4)
	Range	[10-16]	[54-73]	[33-68]	[10-17]	[10-73]
BMI (kg/m^2)	Mean (SD)	34.9 (11.2)	29.4 (4)	33 (6.5)	40.3 (10.7)	34.4 (9.8)
	Range	[21.2-81.2]	[24.4-37.3]	[23-44.4]	[29.2-71.6]	[21.2-81.2]

Abbreviations: y: years; BW: body weight; BMI: body mass index; N: number of subjects; SD: standard deviation; T2D: type 2 diabetes.

(Source: Table 5-1 in applicant's modeling report Version 1.0 Date 13 November 2018)



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

Figure 5 Simulated steady-state concentration-time profiles following liraglutide 1.8 mg once daily in pediatric (Trial 3659) and adult subjects (Trial 1573)

(Source: Figure 5-6 in applicant's modeling report Version 1.0 Date 13 November 2018)

Reviewer's assessment:

The applicant's PopPK analysis submitted to this sNDA is replicable, reasonable and acceptable. The reviewer analyzed the PopPK data in pediatrics and adults separately using the final model from the sponsor's analysis, and the corresponding results (Table 4) also suggested a comparable PK characteristic between pediatrics and adults. Overall, the reviewer concluded that liraglutide PK is comparable between pediatrics and adults.

Table 4 Pharmacokinetic Parameter Comparison between Pediatrics and Adults

Description	Parameters	Adults	Pediatrics
Absorption rate constant	**Ka (1/h)**	0 0608 6%)	0 0689 4%)
Apparent Clearance	**CL (L/h)**	1 11 11%)	1 08 5%)
Apparent Volume of Distribution	**V (L)**	15 7 12%)	12 3 19%)
Covariate affecting clearance	**BW effect on CL**	0 703 30%)	0 995 16%)
	Male effect on CL	1 32 13%)	1 38 12%)
Covariate affecting volume of distribution	**BW effect on V**	1 24 26%)	1 13 44%)
	Male effect on V	1 4 18%)	1 52 41%)

2.2.3 Is the proposed dosing regimen appropriate for pediatrics 10 years and older with T2DM?

Yes, the proposed dosing regimen for pediatrics 10 years and older with T2DM is generally supported by the efficacy and safety results from study NN2211-3659, as well as similar PK between pediatric and adults. Since 0.6 mg dose without dose escalation was also associated with clinically meaningful reduction in HbA1c in 17 patients (Table 5), it should also be considered as initiation and maintenance dose in pediatrics.

The proposed dosing regimen including the FPG-based titration scheme was evaluated in the phase 3 study NN2211-3659. The primary efficacy analysis results showed statistically significant superiority of liraglutide compared to placebo add-on to metformin (treatment difference in mean changes in HbA1c (95% CI): -1.06 (-1.65, -0.46). Refer to the clinical/statistical review for details on benefit/risk assessment.

As additional support, the applicant conducted exposure-response (E-R) analysis for efficacy using PK and HbA1c data collected from study NN2211-3659. The E-R relationship was described by an E_{max} model, and the observed and model predicted ER relationship is depicted in Figure 6.

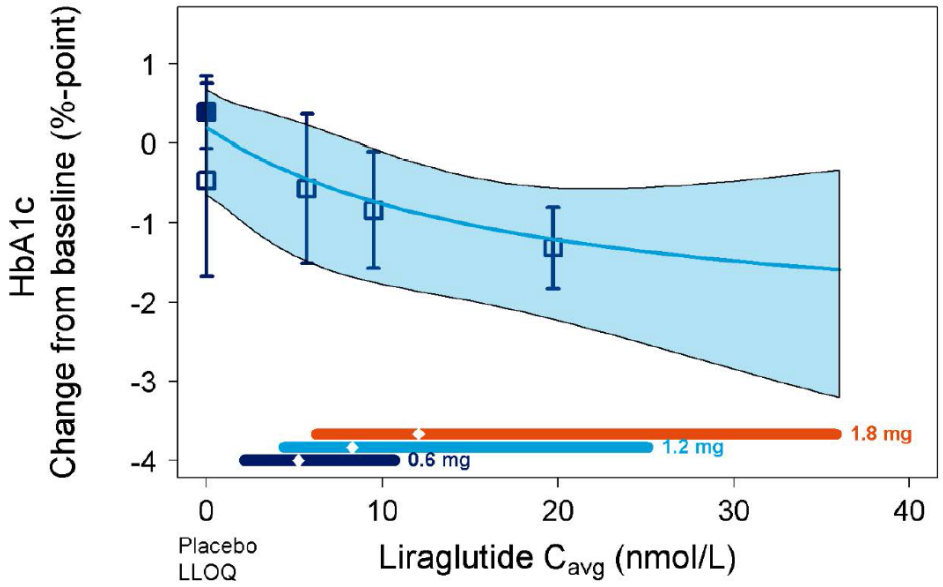


Figure 6 HbA1c change from baseline versus exposure of liraglutide in pediatric subjects

Note: Data are mean values of HbA1c change from baseline with 95% CIs obtained after 26 weeks of treatment versus exposure expressed as quantiles of Cavg. Open squares: Subjects randomized to liraglutide. Closed square: Subjects randomized to placebo. The line through the data represents the covariate-adjusted (baseline HbA1c, baseline body weight and sex) model-derived exposure-response relationship with 95% CI. Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges for subjects grouped by highest achieved dose (0.6 mg, 1.2 mg or 1.8 mg), subjects with concentration below LLOQ excluded. Estimates for Trial 3659, obtained from the full PK model including only data from week 26 for Trial 3659, N=109. Abbreviations: Cavg: steady-state average concentration; N: number of subjects; LLOQ: Lower limit of quantification.
(Source: Figure 1-3 in applicant's modeling report Version 1.0 Date 13 November 2018)

However, given the treat-to-target design of the study, drawing any conclusions on dose-response or E-R would be challenging. Patients in study NN2211-3659 was randomized to either placebo or liraglutide, but patients who received liraglutide was not randomized to either of the three dose levels (0.6 mg QD, 1.2 mg QD, and 1.8 mg QD). Because of the FPG-based dose titration strategy, the baseline demographic and disease characteristics in patients taking the maximum dose level of 0.6 mg, 1.2 mg, and 1.8 mg were different as depicted in Table 5. Patients who were titrated to a higher dose of liraglutide generally had a higher baseline HbA1c%, FPG, BMI and body weight. Also, the plasma clearance of liraglutide was higher in those patients required 1.8 mg QD

compared to those patients responded at only 0.6 mg QD and 1.2 mg QD, which resulted in similar steady state AUC at 1.8 mg QD compared to 1.2 mg QD.

Patients on basal insulin accounted for 16% and 26% in placebo group and liraglutide group, respectively. The small number of patients on basal insulin was considered as an important driver of efficacy. As such, the comparison between the patients with or without basal insulin was also generated by the reviewer and is given in Table 5. In summary, the results suggested that in the FPG based titration design, both disease characteristics and pharmacokinetics could have an impact on the dose titration. Therefore, the homogeneity assumption between different dosing regimens cannot be held anymore and the E-R analysis conducted by the applicant was confounded by the FPG based titration design.

Nevertheless, the demonstration of comparability in systemic exposure of liraglutide between pediatric and adult population, given that pediatric population in this trial has body weight/BMI distribution similar to adult T2DM population, and known exposure-response of liraglutide in adults (from parallel arm forced titration design trials) is re-assuring. Therefore, there are no concerns for the proposed pediatric doses from clinical pharmacology perspective.

Table 5 Patient Characteristics Across Dose Groups

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

2.2.4 Labeling Recommendations

Two changes in section 12.3 Pharmacokinetics were proposed in the label by the applicant.

1. *Pediatric* - A population pharmacokinetic analysis was conducted for VICTOZA using data from 72 (b) (4)-pediatric subjects (10 to 17 years of age) with type 2 diabetes. The

pharmacokinetic profile of VICTOZA in the pediatric subjects was consistent with that in adults.

Reviewer's Comments: The proposed labeling information is acceptable, see section 2.2.2 above for detailed information. However, the number of pediatric patients contributed to the population pharmacokinetic analysis should be 72 not (b) (4)

(b) (4)

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