Office of Clinical Pharmacology Review

BLA Number	125469; SDN 1677; Supplement 51
Link to EDR	\\CDSESUB1\evsprod\BLA125469\1421\
Submission Date	05/17/2022
Submission Type	Priority
Brand Name	Trulicity
Generic Name	Dulaglutide
Dosage Form and Strength	• Injection: 0.75 mg/0.5 mL solution in a single-dose pen • Injection: 1.5 mg/0.5 mL solution in a single-dose pen
Route of Administration	Subcutaneous injection
Proposed Indication	as an adjunct to diet and exercise to improve glycemic control in patients 10 years of age and older with type 2 diabetes mellitus
Applicant	Eli Lilly and Company
Associated IND	070930
OCP Review Team	Mohamad Kronfol, PhD, Hezhen Wang, PhD, Justin Earp, PhD Edwin C. Y. Chow, PhD
OCP Final Signatory	Edwin C. Y. Chow, PhD

Table of Contents

1. EXECUTIVE SUMMARY

Trulicity (dulaglutide) is a glucagon-like peptide-1 (GLP 1) receptor agonist indicated:

1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
2. To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.

Upon approval of Trulicity (BLA125469) in 2014, Eli Lilly and Company (the Applicant) was required to conduct a pediatric study for patients with type 2 diabetes mellitus (T2DM) 10 years of age and older under PMR 2781-1. The Applicant conducted study H9X-MC-GBGC (GBGC) to fulfill PMR 2781-1. Study GBGC is a phase 3, randomized, double-blind, placebo controlled, parallel-arm, multicenter superiority trial with an open-label extension to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics in pediatric patients, 10 to less than 18 years old, with T2DM receiving dulaglutide 0.75 mg or 1.5 mg compared to placebo, who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin. The Applicant has submitted this pediatric efficacy supplement on 05/17/2022 with results from GBGC and is seeking approval of a pediatric indication as follows "as an adjunct to diet and exercise to improve glycemic control in patients 10 years of age and older with type 2 diabetes mellitus".

Study GBGC was conducted evaluating the safety and efficacy of the dulaglutide 0.75 mg and 1.5 mg doses in 2 separate arms, which were the only doses approved at the time the study initiated. In this supplement (S-51), the Applicant submitted a pediatric (10 years of age and older) population pharmacokinetic/pharmacodynamic (PK/PD) model from observed data from study GBGC to support labeling changes to the Clinical Pharmacology subsections 12.3 and 12.6 of the US Prescribing Information (USPI). The clinical pharmacology team reviewed the pediatric (10 years of age and older) population PK/PD model results to support proposed labeling on pediatric dosages, pediatric PK, and pediatric immunogenicity.

The results from the study in this submission are updated to the currently approved USPI.

PREA PMR 2781-1 is considered fulfilled from a clinical pharmacology perspective.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology and Division of Pharmacometrics has reviewed the information submitted in sBLA125469 Supplement 51. The sBLA contains sufficient data to support approval from a clinical

pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The Applicant completed study GBGC to provide pivotal evidence of effectiveness of dulaglutide 0.75 mg and 1.5 mg in patients 10 years of age and older with type 2 diabetes mellitus. At 26 weeks, once weekly dulaglutide resulted in a 1.2% and 1.5% decrease from baseline in mean HbA1c for the 0.75 mg and the 1.5 mg doses compared to placebo, respectively.
General dosing instructions	The proposed dosages in pediatric patients aged 10 and older are acceptable (see section 2.2.1).
Dosing in patient subgroups (intrinsic and extrinsic factors)	NA
Labeling	See section 2.4 for labeling recommendation.
Bridge between the to-be-marketed and clinical trial formulations	NA. The applicant used the approved 0.75mg/0.5mL and 1.5 mg/0.5mL single-dose pen in the pediatric study GBGC.
Immunogenicity	See section 3.2.2 for immunogenicity assessment and 2.4 for labeling recommendation on immunogenicity.

1.2 Post-Marketing Requirements and Commitments

PREA PMR 2781-1 is considered fulfilled from a clinical pharmacology perspective. There is no new PMR or PMC based on this submission at this time.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Dulaglutide is glucagon-like peptide-1 (GLP 1) receptor agonist. In study GBGC, a population PK/PD approach was conducted to evaluate pediatric exposure (10 years of age and older) following administration of dulaglutide 0.75 mg and 1.5 mg. The population PK/PD analysis was conducted for dulaglutide 0.75 mg and 1.5 mg using data from 128 pediatric patients with T2DM 10 years of age and older. The exposure in pediatric patients 10 years of age and older was approximately 37 % lower than that in the adults. In addition, male pediatric patients had approximately 36% numerically lower exposure compared to female pediatric patients. However, these differences were not determined to be clinically meaningful. Refer to Clinical and Statistics team reviews for final conclusions on efficacy and safety from Study GBGC.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Pediatric Dosage 10 years of age and older

- The recommended initiating dose of dulaglutide is 0.75 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dose to the maximum dose of 1.5 mg once weekly after at least 4 weeks on the 0.75 mg dose.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling comments.

Label Section	Recommendation
12.3 Pharmacokinetics	Agree with the Applicant to include the subheading on pediatric PK information but with proposed edits to statement on the PK of dulaglutide in pediatric patients 10 years of age and older. See final language in the updated USPI.
12.6 Immunogenicity	Agree with the Applicant but with proposed edits on incidence of antibodies against dulaglutide and GLP1-R in pediatrics and their effect on PK. See final language in the updated USPI.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Dulaglutide injection for subcutaneous use is marketed in the US as Trulicity (BLA 125469) by the Applicant. The Applicant submitted supplement 51 under this BLA 125469 application on May 17, 2022, for approval to market its dulaglutide 0.75 mg/0.5 mL and 1.5 mg/0.5 mL solution for injection as a single-dose pen in patients 10 years of age and older with T2DM based on results from Study GBGC. The Applicant is providing findings of safety and effectiveness for dulaglutide to support this supplement BLA.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action

Dulaglutide is a human GLP-1 receptor agonist with 90% amino acid sequence homology to endogenous human GLP-1 (7-37). Dulaglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase in pancreatic beta cells. Dulaglutide increases intracellular cyclic AMP (cAMP) in beta cells leading to glucose-dependent insulin release. Dulaglutide also decreases glucagon secretion and slows gastric emptying.

Pharmacodynamics

Dulaglutide lowers fasting glucose and reduces postprandial glucose (PPG) concentrations in patients with type 2 diabetes mellitus. The reduction in fasting and postprandial glucose can be observed after a single dose.

Fasting and Postprandial Glucose

In a clinical pharmacology study in patients with type 2 diabetes mellitus, treatment with once weekly dulaglutide resulted in a reduction of fasting and 2-hour PPG concentrations, and postprandial serum glucose incremental AUC, when compared to placebo (-25.6 mg/dL, -59.5 mg/dL, and -197 mg*h/dL, respectively); these effects were sustained after 6 weeks of dosing with the 1.5 mg dose.

First- and Second-Phase Insulin Secretion

Both first- and second-phase insulin secretion were increased in patients with type 2 diabetes treated with dulaglutide compared with placebo.

Insulin and Glucagon Secretion

Dulaglutide stimulates glucose-dependent insulin secretion and reduces glucagon secretion. Treatment with dulaglutide 0.75 mg and 1.5 mg once weekly increased fasting insulin from baseline at Week 26 by 35.38 and 17.50 pmol/L, respectively, and C-peptide concentration by 0.09 and 0.07 nmol/L, respectively, in a monotherapy study. In the same study, fasting glucagon concentration was reduced by 1.71 and 2.05 pmol/L from baseline with dulaglutide 0.75 mg and 1.5 mg, respectively.

Gastric Motility

Dulaglutide causes a delay of gastric emptying. The delay in gastric emptying is dose-dependent but is attenuated with adequate dose escalation to higher doses of dulaglutide. The delay is largest after the first dose and diminishes with subsequent doses.

Cardiac Electrophysiology (QTc)

The effect of dulaglutide on cardiac repolarization was tested in a thorough QTc study. Dulaglutide did not produce QTc prolongation at doses of 4 and 7 mg. The maximum recommended dose is 4.5 mg once weekly.

Pharmacokinetics

The pharmacokinetics of dulaglutide is similar between healthy subjects and patients with type 2 diabetes mellitus. Following subcutaneous administration, the time to maximum plasma concentration of dulaglutide at steady state ranges from 24 to 72 hours, with a median of 48 hours. After reaching steady state, the accumulation ratio was approximately 1.56. Steady-state plasma dulaglutide concentrations were achieved between 2 and 4 weeks following once weekly administration. Site of subcutaneous administration (abdomen, upper arm, and thigh) had no statistically significant effect on the exposure to dulaglutide.

Absorption

The mean absolute bioavailability of dulaglutide following subcutaneous administration of single 0.75 mg and 1.5 mg doses was 65% and 47%, respectively. Absolute subcutaneous bioavailability for 3 mg and 4.5 mg doses were estimated to be similar to 1.5 mg although this has not been specifically studied. Dulaglutide concentrations increased approximately proportional to dose from 0.75 mg to 4.5 mg.

Distribution

Apparent population mean central volume of distribution was 3.09 L and the apparent population mean peripheral volume of distribution was 5.98 L.

Metabolism

Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways.

Elimination

The apparent population mean clearance of dulaglutide was 0.142 L/h. The elimination half-life of dulaglutide was approximately 5 days.

Specific Populations

The intrinsic factors of age, gender, race, ethnicity, body weight, or renal or hepatic impairment do not have a clinically relevant effect on the PK of dulaglutide.

Renal Impairment

Dulaglutide systemic exposure was increased by 20, 28, 14 and 12% for mild, moderate, severe, and ESRD renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in C_{max} were 13, 23, 20 and 11%, respectively. Additionally, in a 52 week clinical study in patients with type 2 diabetes mellitus and moderate to severe renal impairment, the PK behavior of dulaglutide 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies.

Hepatic Impairment

Dulaglutide systemic exposure decreased by 23, 33 and 21% for mild, moderate and severe hepatic impairment groups, respectively, compared to subjects with normal hepatic function, and C_{max} was decreased by a similar magnitude.

Drug Interactions

The potential effect of co-administered medications on the PK of dulaglutide 1.5 mg and vice versa was studied in several single- and multiple-dose studies in healthy subjects, patients with type 2 diabetes mellitus, and patients with hypertension.

Potential for Dulaglutide to Influence the Pharmacokinetics of Other Drugs

Dulaglutide slows gastric emptying and, as a result, may reduce the extent and rate of absorption of orally co-administered medications. In clinical pharmacology studies, dulaglutide at a dose of 1.5 mg did not affect the absorption of the tested orally administered medications to any clinically relevant degree. The delay in gastric emptying is dose-dependent but is attenuated with the recommended dose escalation to higher doses of dulaglutide. The delay is largest after the first dose and diminishes with subsequent doses.

Potential for Co-administered Drugs to Influence the Pharmacokinetics of Dulaglutide

In a clinical pharmacology study, the co-administration of a single dose of 1.5 mg dulaglutide with steady-state dose of 100 mg sitagliptin caused an increase in dulaglutide AUC and C_{max} of approximately 38% and 27%, which is not considered clinically relevant.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The submitted Clinical Pharmacology information provide supportive evidence of effectiveness and includes characterization of pharmacokinetics, pharmacodynamics, exposure-response (E-R) analyses, and immunogenicity of dulaglutide in pediatric T2DM population 10 years of age and older (see sections 3.3.2 and 4.2).

3.3.2 Is the proposed dosing regimen appropriate for the general pediatric patient population 10 to less than 18 years of age for which the indication is being sought?

Yes, the proposed dosages for pediatric patients 10 years of age and older are acceptable. Exposure-response (E-R) analyses were performed to understand the relationships between PK and efficacy, and safety parameters. These analyses support the proposed dosing regimen of 0.75 mg and 1.5 mg once every week (QW) and demonstrated that no dose modifications are needed based on age, body weight, and sex.

Study GBGC was a 26-week randomized, double-blind, placebo-controlled, parallel-arm, multicenter superiority trial with an open-label extension for an additional 26 weeks. In this study pediatric patients with type 2 diabetes mellitus aged 10 years and older were randomized to

dulaglutide once weekly or placebo once weekly in combination with or without metformin and/or basal insulin treatment.

Overall, demographic and baseline clinical characteristics were comparable across the treatment groups. At baseline, 71.4% of patients were female, and patients had a mean age of 14.5 years. At 26 weeks, once weekly dulaglutide resulted in a 1.2% and 1.5% decrease from baseline in mean HbA1c for the 0.75 mg and the 1.5 mg doses compared to placebo, respectively, as measured by baseline to Week 26 change in HbA1c, in children and adolescents with type 2 diabetes mellitus who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin (See Clinical team review in DARRTS for final efficacy and safety conclusion).

Based on the PK/PD exposure-response model for fasting glucose (FG) and HbA1c, a dose related improvement in glycemic control was apparent in pediatric T2DM patients treated with dulaglutide 0.75 mg and 1.5 mg once weekly (QW) (see pharmacometrics reviewer analysis in section 4.2). Baseline body weight and patient sex were identified as statistically significant covariates on clearance (CL) and age was also identified as a statistically significant covariate on absorption rate constant (KA) in the final population PK model (see section 4.2). However, similar to adult T2DM patients, dose adjustment for dulaglutide based on age, weight, and sex is not warranted for pediatric T2DM patients.

The immunogenicity of dulaglutide was assessed in Study GBGC. This review includes assessment of the Applicant's conclusion on the effect of immunogenicity on dulaglutide PK from study GBGC in pediatric patients 10 years of age and older. The Applicant concludes that there is no clinically relevant impact on PK in the pediatric population 10 years of age and older based on the population PK model results. However, because of the limited number of pediatric patients who are anti-drug antibody (ADA) positive and have neutralizing antibody (NAb), the effect of these antibodies on the PK of dulaglutide products has not been fully characterized (see pharmacometrics reviewer analysis section 4.2). For the final immunogenicity conclusion on safety and efficacy in pediatric population, refer to the Clinical review in DARRTS. The immunogenicity profile of dulaglutide has been characterized in the adults in the original application (refer to the original BLA 125469 Clinical review Reference ID: 3609106).

Study GBGC used validated ADA and NAb assays that were determined to be adequate for this supplement by the OBP reviewer (refer to OBP review of this supplement). Overall, a 4.0 % (4 of 101 evaluable patients) incidence of treatment-emergent ADA (TE-ADA) was observed over 26 weeks in dulaglutide-treated patients. A 5.8 % (6 of 103 evaluable patients) incidence of TE-ADA was observed through the safety follow-up. One pediatric patient (1.0 %) developed NAbs against dulaglutide, four patients (3.9%) were native GLP-1 (nGLP-1) cross reactive. None of the pediatric patients had NAbs against nGLP-1 through the safety follow-up (**Table 1**). Maximum TE ADA titers ranged from 1:4 to 1: 32 through safety follow-up.

Table 1 : Study GBGC Summary of Immunogenicity (Source Table 4.1. page 7 of Applicant response 8/22/2022)

Dose regimen	Observation period	Evaluable Patients n	Treatment emergent n (%)	Treatment boosted n (%)	Treatment induced n (%)	Persistent[a] n (%)	Transient[b] n (%)	Potential persistent[c] n (%)	NAb Positive (against Dulaglutide): n (%)	NAb Positive (against nGLP-1): n (%)
Dulaglutide 0.75 mg or 1.5 mg	Week 0 to safety follow-up	103	6 (5.8%)[d]	0	6 (5.8%)	0	5 (4.9%)	1 (1.0%)	1 (1.0%)	0
Placebo/Dulaglutide 0.75 mg	Weeks 0 to 26	48	1 (2.1%)[e]	0	1 (2.1%)	0	0	1 (2.1%)	1 (2.1%)	0
	Week 27 to safety follow-up	46	3 (6.5%)	1 (2.2%)	2 (4.3%)	0	1 (2.2%)	2 (4.3%)	0	0

Abbreviations: ADA = anti-drug antibody; n = number of patients in the specified category; NAb = neutralizing antibodies; nGLP-1 = native glucagon-like peptide-1; TE ADA = treatment-emergent ADA.

a Persistent ADA was defined as TE ADA detected at 2 or more sampling time points, with the first and last TE ADA+ samples separated by ≥16-weeks.

b Transient ADA was defined as TE ADA detected with the first and last TE ADA+ samples separated by a period of <16 weeks and with TE ADA not detected at the last sampling time point.

c Potential persistent ADA was defined as TE ADA detected with the first and last TE ADA+ samples separated by a period of <16 weeks and with TE ADA detected at the last sampling time point

d TE ADA incidence in dulaglutide-treated patients during the double-blinded treatment period (through 26 weeks) was 4 out of 101 evaluable patients (4.0%).

e Patient ID H9X-MC-GBGC-(b) (6) discontinued the study at Visit 7 (Week 18). Therefore, this patient is not included in the 46 evaluable patients in the Placebo/Dulaglutide 0.75-mg treatment group who were monitored through safety follow-up nor in the computation of the patients with TE ADA of that same group.

In the group that received placebo over 26 weeks and dulaglutide 0.75 mg after 26 weeks through safety follow up, one (2.1%) placebo-treated patient was TE-ADA positive through week 26 and was classified as having NAbs against dulaglutide and being nGLP-1 cross reactive. Three (6.5%) placebo-treated patients who received at least 1 dose of dulaglutide through safety follow-up were TE-ADA positive and were each classified as being nGLP-1 cross-reactive and no patients developed NAbs against nGLP-1 or against dulaglutide through safety follow up in this group.

Based on the exposure-response relationships and population PK analysis, ADA status did not appear to be a significant covariate on PK model (see pharmacometrics reviewer analysis section 4.2). However, due to the low number of patients with NAbs with evaluable PK (1 in placebo and 1 in dulaglutide arm), a final conclusion on effect of NAbs on PK, safety and efficacy cannot be made.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Plasma samples collected in study H9X-MC-GBGC were analyzed for dulaglutide concentrations using a validated radioimmunoassay (RIA) method ICD 373 by (b) (4) This method was described and reviewed in the original NDA submission.

4.2 Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

The applicant's population pharmacokinetics (PopPK) and pharmacodynamic (PD) analysis for dulaglutide, used to justify pediatric dosage (aged between 10 and less than 18 years with type 2 diabetes mellitus (T2D or T2DM) and inadequate glycemic control despite diet and exercise, with or without metformin and/or basal insulin), is acceptable to support the current submission as outlined in **Table 1**. The applicant's final PopPK and PD model adequately described the observed dulaglutide plasma concentrations. The final PopPK parameter estimates were estimated with acceptable precision as indicated by the relative standard errors (RSE) for total clearance (CL, 6% RSE), volume of distribution in central compartment (V2, 21% RSE), volume of distribution in peripheral compartment (V3, 14% RSE), and covariates (baseline body weight and patient sex on CL, age was on KA). 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 plots showed a good agreement between the observed and the simulated concentrations. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

Per the current approved labeling, the dosage (0.75 mg and 1.5 mg) is recommended for pediatric T2DM patients. The applicant's analysis of dulaglutide Cmax and daily AUC estimated by the pediatric PopPK model did show notable change from the estimates from previous adult T2DM model. Despite this difference in exposure, dosing recommendations have not changed in part because of the clinical efficacy information.

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**	subcutaneous weekly doses of 0.75 and 1.5 mg of dulaglutide in children and adolescents aged between 10 and less than 18 years with T2DM	The applicant recommended dosage for pediatric is acceptable based on the efficacy study.
	Extrinsic factor	NA	NA
Derive exposure metrics for Exposure-response analyses	Cmax, AUC		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (**Table 4**).

1.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the structural pharmacokinetic (PK) model and quantify the population variability in the PK parameters of dulaglutide.
- Describe the effects of intrinsic and/or extrinsic factors on dulaglutide exposure.
- Generate individual clearance estimates for patients in Phase 3 studies that can be used for subsequent exposure-response analyses
- Compare the key efficacy and safety PD outcomes for dulaglutide 0.75 and 1.5 mg following once-weekly dosing.

1.3 PopPK Model development

Data

PopPK models were developed based on Study H9X-MC-GBGC (GBGC), a phase 3 multicenter, randomized double-blind parallel arm placebo-controlled superiority trial with an open-label extension (**Figure 1**), to characterize the PK and PD of dulaglutide following subcutaneous weekly doses of 0.75 and 1.5 mg doses in children and adolescents with type 2 diabetes mellitus (T2DM or T2D) and compare with adult T2DM patients. The popPK data included 444 plasma dulaglutide concentrations from 128 patients and 1019 FG and 1006 HbA1c measurements from 154 patients, in which there are 44 male and 110 female children and adolescents (aged between 10 and less than 18 years), with T2DM and inadequate glycemic control with diet and exercise alone or with diet and exercise plus metformin and/or basal insulin. The clinical study included in the PopPK analysis was summarized in **Table 2** and demographic covariates for analysis were summarized in **Table 3**. Meanwhile, there are 215 concentration values were below the quantitation limit

of the assay (BQL), representing 32.5% of the total concentration samples, which were excluded from the analysis.

Table 2: Summary of Clinical Study Designs

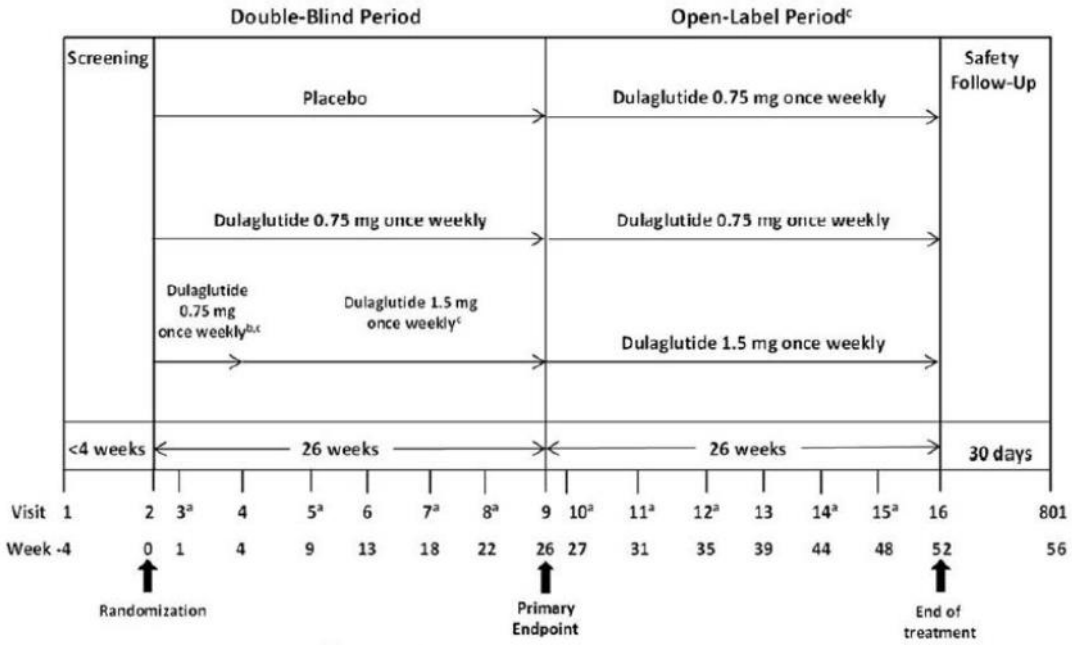
Study Alias and Treatment Duration	Participant Type (N)	Treatment Regimen/ Formulation	Objective
GBGC (52 weeks)	T2DM patients aged 10 to less than 18 years (154)	Dulaglutide 0.75 mg and 1.5 mg[a] given subcutaneously QW versus placebo up to Week 26 whereby placebo were assigned to dulaglutide 0.75 mg QW from Week 26 onwards.	**Primary:** • Evaluate dulaglutide 0.75 mg and 1.5 mg (pooled) is superior to placebo in the treatment of T2DM, as measured by baseline to Week 26 change in HbA1c. **Secondary:** • Assess the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled), relative to placebo, for ○ safety ○ efficacy ○ PK, and ○ PD (FG, BMI), at Week 26 and Week 52.

Abbreviations: BMI = body mass index; FG = fasting glucose; HbA1c = glycated hemoglobin; ITT = intent-to-treat; N = number of participants randomized (ITT population); PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; T2DM = type 2 diabetes mellitus.

[a] Dulaglutide 1.5 mg QW was initiated using 0.75 mg QW for 4 weeks before escalating to 1.5 mg QW.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 18 (link).

Figure 1: Study design of H9X-MC-GBGC



a Phone visits.

b Patients who tolerate the 0.75 mg/week dose in the opinion of the investigator will be changed to dulaglutide 1.5 mg/week at Week 4.

c If patients do not tolerate the higher dose, they will be allowed to go back to the previous dose.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 16 (link).

Table 3: Summary of Baseline Demographic Covariates for Analysis

	Placebo / 0.75 mg QW	0.75 mg QW	1.5mg QW	All
N	51	51	52	154
		Mean (SD, Range)		
Age (years)	14.2 (2.08, 10 - 17)	14.7 (2.21, 10 - 17)	14.7 (1.81, 10 - 17)	14.5 (2.04, 10 - 17)
Body Weight (kg)	88.9 (29.4, 50.8 - 165)	90 (28.3, 50.5 – 175)	92.6 (21.5, 56.1 - 149)	90.5 (26.5, 50.5 – 175)
Female	89.9 (29.1, 51.6 - 165)	86.9 (28.8, 52.3 - 175)	90.6 (19.8, 63.4 - 134)	89.2 (26.3, 51.6 - 175)
Male	84.7 (31.7, 50.8 - 143)	96.9 (26.7, 50.5 - 147)	96.2 (24.7, 56.1 - 149)	93.8 (26.9, 50.5 - 149)
HbA1c (%)	8.14 (1.12, 6.5 - 10.7)	7.92 (1.27, 5.4 - 11.4)	8.16 (1.39, 6.3 - 12.5)	8.08 (1.26, 5.4 - 12.5)
Fasting Glucose (mmol/L)	8.85 (3.3, 4.22 - 20.1) [a]	8.29 (3.35, 4.22 - 20)	9.06 (3.41, 4.17 - 18.7)	8.74 (3.35, 4.17 - 20.1) [b]
BMI (kg/m^2)	34.3 (10.2, 22 - 66)	33.6 (9.04, 22.5 - 61.7)	34.3 (6.98, 21 - 52)	34.1 (8.79, 21 - 66)
CKD-EPI eGFR ($mL/min/1.73m^2$)	111 (18.4, 69.7 – 159)	112 (15.9, 83.4 - 148)	109 (17.7, 77.7 - 171)	111 (17.3, 69.7 - 171)
CGCL (mL/min)	254 (90, 124 – 653)	257 (80.7, 132 - 478)	253 (72.3, 141 – 484)	254 (80.7, 124 - 653)
Duration of Diabetes (years)	2.02 (1.83, 0 - 9)	1.82 (1.77, 0 - 7)	2.13 (1.6, 0 - 6)	1.99 (1.73, 0 - 9)
		n/N (percentage)		
Sex				
Female	41/51 (80.4%)	35/51 (68.6%)	34/52 (65.4%)	110/154 (71.4%)
Male	10/51 (19.6%)	16/51 (31.4%)	18/52 (34.6%)	44/154 (28.6%)
CKD-EPI eGFR Categories [c]				
Stage 1	45/51 (88.2%)	47/51 (92.2%)	44/52 (84.6%)	136/154 (88.3%)
Stage 2	6/51 (11.8%)	4/51 (7.84%)	8/52 (15.4%)	18/154 (11.7%)
Ethnicity				
Hispanic	26/51 (51%)	31/51 (60.8%)	28/52 (53.8%)	85/154 (55.2%)
Non-Hispanic	25/51 (49%)	18/51 (35.3%)	22/52 (42.3%)	65/154 (42.2%)
Missing	-	2/51 (3.92%)	2/52 (3.85%)	4/154 (2.6%)
Origin				
White	25/51 (49%)	29/51 (56.9%)	30/52 (57.7%)	84/154 (54.5%)
Black or African American	5/51 (9.8%)	9/51 (17.6%)	9/52 (17.3%)	23/154 (14.9%)
Asian	11/51 (21.6%)	4/51 (7.84%)	4/52 (7.69%)	19/154 (12.3%)
American Indian or Alaskan Native	6/51 (11.8%)	6/51 (11.8%)	4/52 (7.69%)	16/154 (10.4%)
Mixed Race	3/51 (5.88%)	1/51 (1.96%)	3/52 (5.77%)	7/154 (4.55%)
Native Hawaiian or other Pacific Islander	1/51 (1.96%)	-	-	1/154 (0.649%)
Missing	-	2/51 (3.92%)	2/52 (3.85%)	4/154 (2.6%)

Abbreviations: BMI = body mass index; CGCL = Cockcroft-Gault creatinine clearance; CKD-EPI = glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration method; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; n = number of patients satisfying the criteria; N = total number of patients in the treatment group; QW = once weekly; SD = standard deviation.

[a] N = 49

[b] N = 152

[c] CKD-EPI Severity Categories:

Stage 1 (Baseline CKD-EPI ≥90 $mL/min/1.73m^2$);

Stage 2 (60 mL/min ≤ Baseline CKD-EPI eGFR <90 $mL/min/1.73m^2$)

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 23-24 (link).

Base model

The base model, similar to the final adult T2D PopPK model in the submission report (Phase 3 GBGL Population PK/PD Report; 2019, link), was developed by a first order conditional estimation with interaction by NONMEM. It is a two-compartment PK model with first-order absorption and elimination from the central compartment.

Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. The inter-individual variability was considered for subcutaneous (SC) absorption rate constant (KA), total body clearance of drug (CL), volume of distribution for central compartment (V2).

Intra-individual variability was tested as proportional on the dependent variable.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0) by bootstrap, successful model convergence, and diagnostic visual predictive check (VPC).

Covariate analysis

Covariate parameters include body weight, body mass index, age, sex, dose, ethnic origin, race, Creatinine clearance (CGCL), baseline chronic kidney disease epidemiology collaboration equation for estimated glomerular filtration rate (CKD-EPI eGFR), screening anti-dulaglutide antibody status, anti-dulaglutide antibody titer, treatment-emergent antidrug antibody (TE-ADA) and neutralizing antibody status. In the final population PK model, baseline body weight and patient sex met prespecified criteria for covariate effect retention and were included as covariates on CL. Age was also retained as a covariate on KA in the final population PK model. TE-ADA was not identified as a statistically significant time-varying covariate.

Covariates (power model, piece-wise linear model, power + linear combination model and multiplicative model) were assessed for covariates with forward selection criteria of the significant level of 0.01 based on $\chi 2$ test ($p < 0.01$, a decrease in OBJ > 6.64 for one degree of freedom) and backward deletion criteria with the significance level of 0.001 based on $\chi 2$ test ($p < 0.001$, an increase in OBJ > 10.83 for one degree of freedom)

SC bioavailability (**F1**) was not specifically investigated and could not be reliably estimated. In addition, in phase 3 GBGL population PK/PD report (page 44 of report), the F1 for dose of 0.75, 1.5, 3 and 4.5 mg is about 0.47. Furthermore, in population pharmacokinetic and

pharmacodynamic analyses of studies: GBCF, GBDA, and GBDC (page 41 of report), the F1 for dose 0.75 and 1.5 mg is about 0.47. Therefore, F1 was fixed to 0.47 based on absolute SC bioavailability of 0.75-mg and 1.5-mg dose.

1.4 Final Model

The parameter estimates for the final PopPK model are listed in **Table 4**. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 2**. The VPC plot for the final covariate model with all data is shown in **Figure 3**. The structural model for the final PPK model was a 2-compartmental model as parameterized with CL, V1, V2, V3, Q2 and Q3 for dulaglutide. An exponential error model was used for inter-individual variability, and proportional error model was used for intra-individual variability.

Baseline body weight and patient sex were identified as statistically significant covariates on CL and age was also identified as a statistically significant covariate on KA in the final population PK model.

- A male pediatric T2DM patient weighing 70 kg is expected to have 48.4% higher CL than a female patient of the same body weight.

- Faster absorption occurred in younger T2DM patients, where the mean KA for a 10-year old (0.0127 h^{-1}) would be higher than adult T2DM patients, but the absorption rate gradually reduced towards a plateau by age of 17 years (0.00261 h^{-1}) (**Figure 4)**
- The body weight was identified as a statistically significant covariate on CL, which was estimated to be 0.0578 L/h and 0.147 L/h for body weights at the lower and upper end of the weight range, corresponding to 50.5 kg and 175 kg, respectively. Highest PK exposures would be expected from pediatric T2DM patients weighing approximately 50 kg and lowest PK exposures would be expected from pediatric T2DM patients weighing approximately 175 kg (**Figure 7)**

Table 4 . Population Pharmacokinetic Parameter Estimates for the Base and Final Models

	Mean (%SEE, 95% CI)			
	Base Model		Final Model	
Parameter Description	Population Estimates	IIV[a]	Population Estimates	IIV[a]
Absorption Rate Constant (1/h)				
First-order absorption rate, KA	0.00433 (15.2%, 0.00262 – 0.00602)	92.2 (25.9%, 57.1 - 146)	0.00379 (16.3%, 0.00211 – 0.00555)	74.1 (25.1%, 42.6 - 108)
Age effect on KA[b]			-2.98 (24.2%, -5.44 - -1.53)	
Clearance (L/h)				
Total clearance, CL	0.0979 (5.00%, 0.0880 – 0.108)	57.8 (18.5%, 45.5 – 68.9)	0.0738 (6.22%, 0.0655 – 0.0825)	47.2 (21.4%, 35.5 – 56.2)
Body weight effect on CL[c]	-	-	0.75 Fixed	-
Patient sex effect on CL[d]	-	-	0.484 (27. 9%, 0.258 – 0.752)	-
Intercompartmental clearance, Q	0.011 (43%, 0.00392 – 0.0182)	-	0.00986 (76.9%, 0.00345 – 0.0178)	-
Volume (L)				
Central volume, V2	1.68 (19.6%, 0.997 – 2.64)	92.7 (53.2%, 28.0 - 164)	1.58 (21.0%, 0.918 – 2.47)	71.2 (123%, 13 - 140)
Peripheral volume, V3	3.55 (9.80%, 3.22 – 3.85)	-	3.51 (14.2%, 3.17 – 3.83)	-
Bioavailability (%)				
Absolute bioavailability, F1	0.47 Fixed	-	0.47 Fixed	-
Proportional Residual Error (%)[e]	0.342 (7.31%, 0.292 – 0.387)	-	0.344 (7.33%, 0.298 – 0.387)	-

Abbreviations: CI = bootstrap derived confidence interval; %CV = coefficient of variation; IIV = inter-individual variability; SEE = standard error of the estimate.

[a] Reported as %CV, calculated using the equation = $100\% \cdot \sqrt{e^{OMEGA(N)} - 1}$, where OMEGA(N) is the NONMEM estimate of the variance for the interindividual variability.

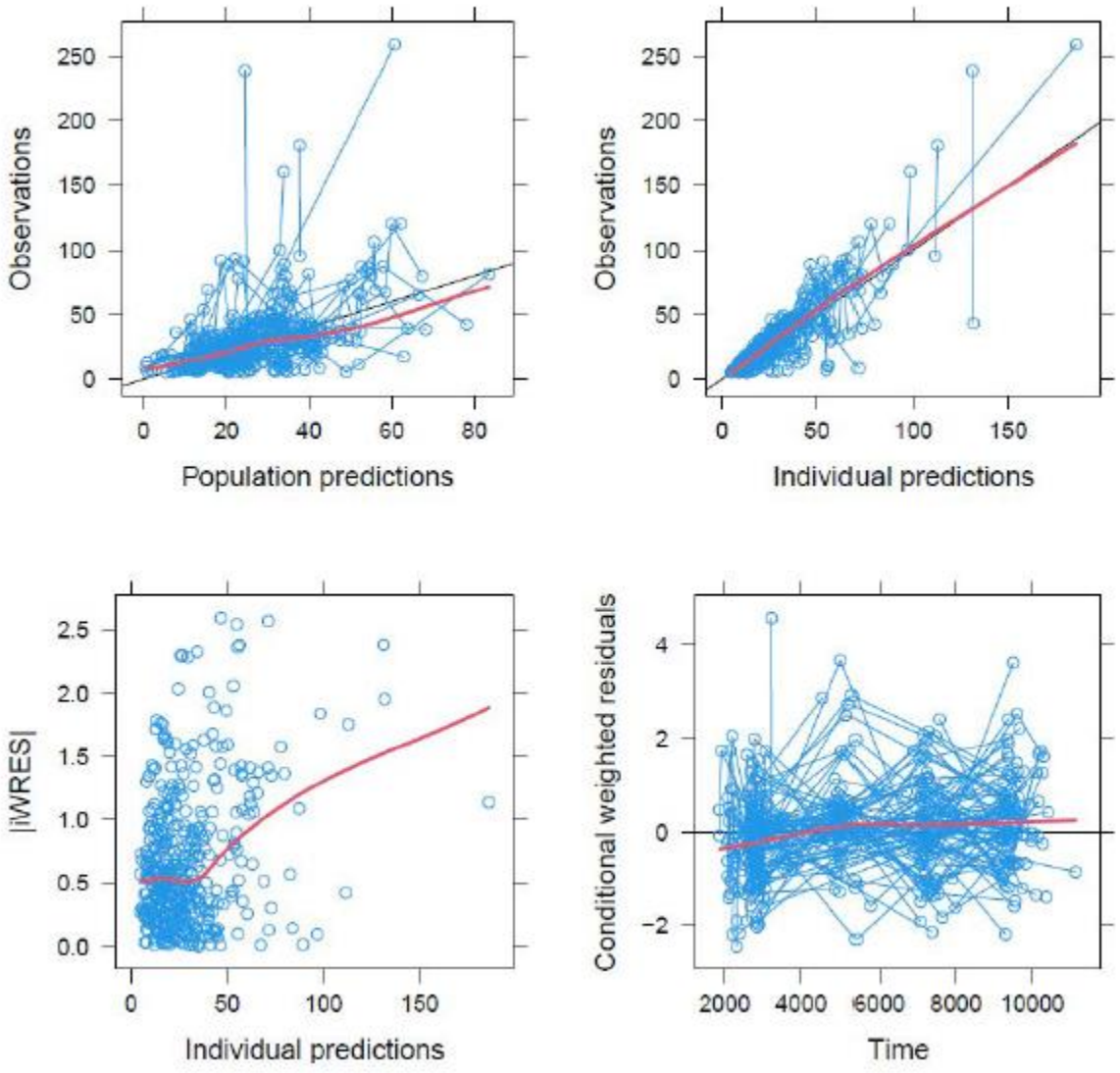
[b] $KA_{inidividual} = KA_{typical} \cdot \left(\frac{Age}{15}\right)^{\theta}$, where 15 years old is the median age of the population

[c,d] $CL_{inidividual} = CL_{typical} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot (1 + \theta)$, where θ = 0 for female and θ = 0.484 for male

[e] Reported as standard deviation

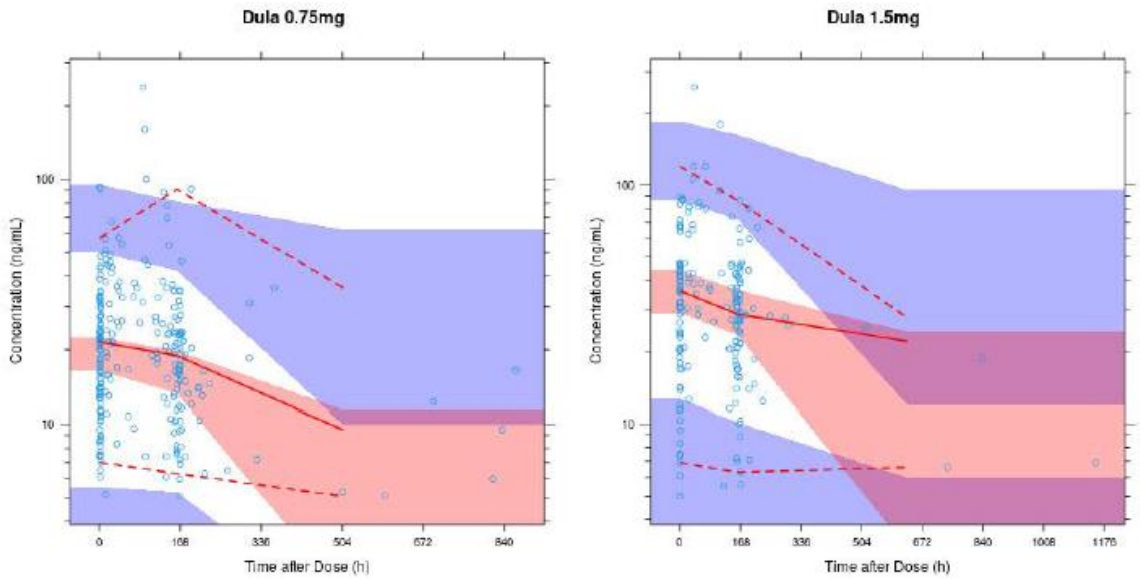
Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 35-36 (link).

Figure 2. Goodness-of-fit plots for final covariate model



Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 109 (link).

Figure 3. VPC plots for final covariate model

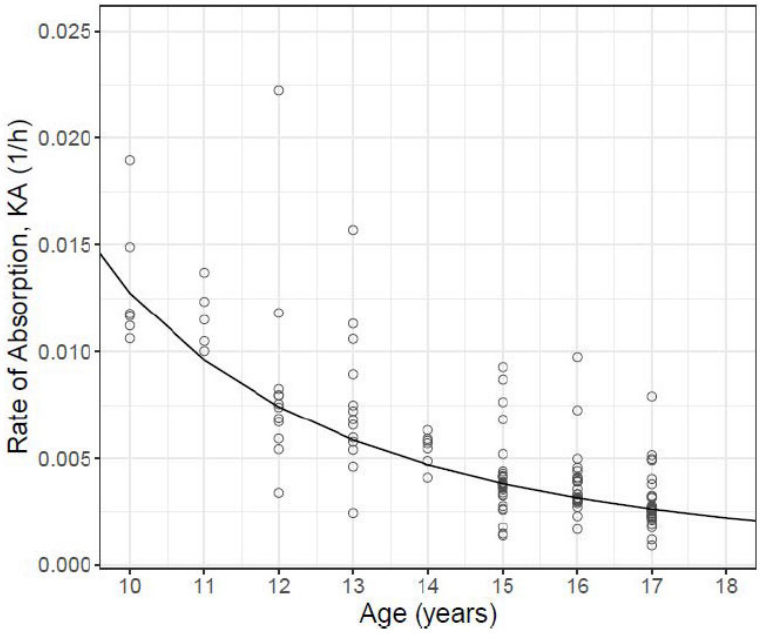


Notes:

- Blue circles denote observed dulaglutide concentrations.
- Solid red lines denote median of the observed concentrations.
- Dotted red lines denote 2.5th and 97.5th percentiles of the observed concentrations while the width of the colored bands corresponds to the model-simulated 95% CIs of the predicted 2.5th, 50th, and 97.5th percentiles.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 36 (link).

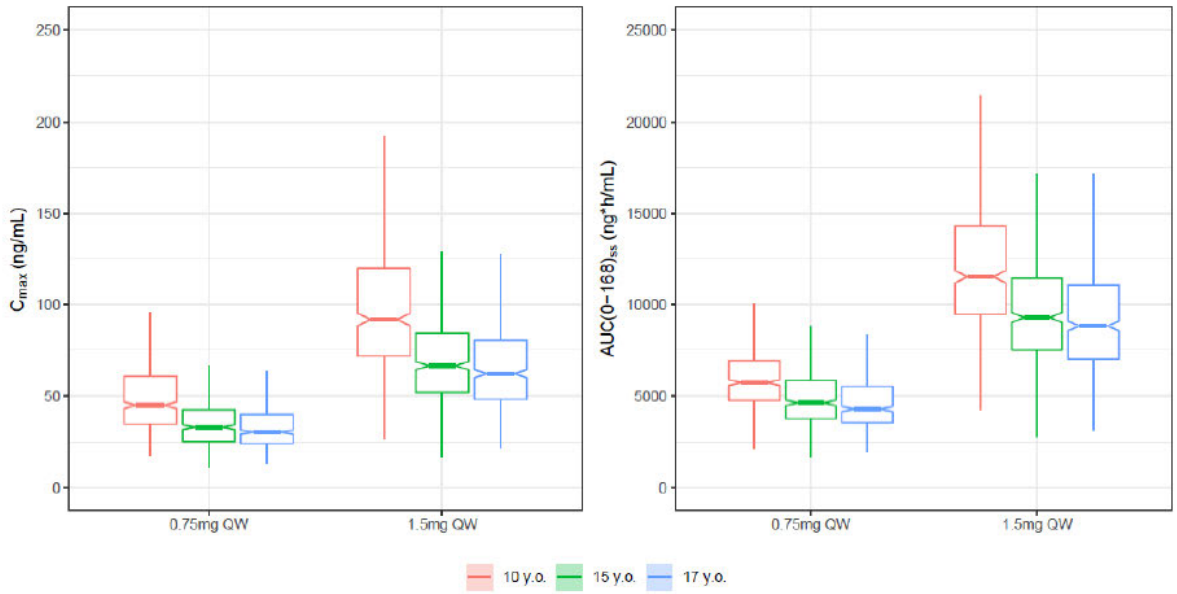
Figure 4. Relation of pediatric T2DM patients with different age and rate of absorption



Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 56 (link).

Boxplots of simulated Cmax and AUC(0-168) at steady state following once weekly SC from 10, 15 and 17 year old T2DM patients are shown in **Figure 5** which showed that there are exposure difference between different ages. Meanwhile, boxplots of simulated FG and HbA1c change from baseline following once-weekly subcutaneous dosing in pediatric T2DM patients aged from 10, 15 and 17 year old T2DM patients showed that there is no obvious different ΔFG and ΔHbA1c between age groups in **Figure 6**.

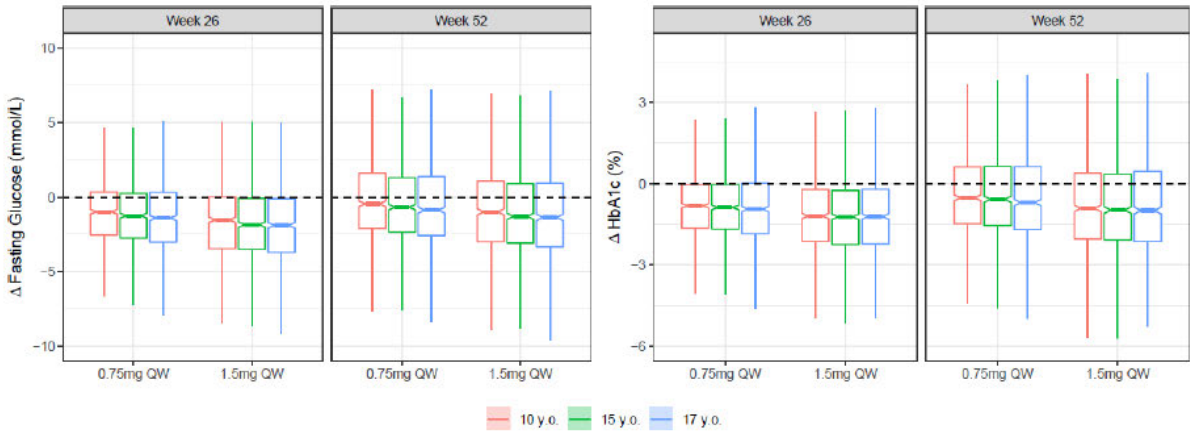
Figure 5. Simulated dulaglutide Cmax and AUC(0-168)ss at steady-state following once-weekly subcutaneous dosing in pediatric T2DM patients aged between 10 and less than 18 years



Abbreviations: AUC(0-168)ss = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; Cmax,ss = steady state maximum concentration.

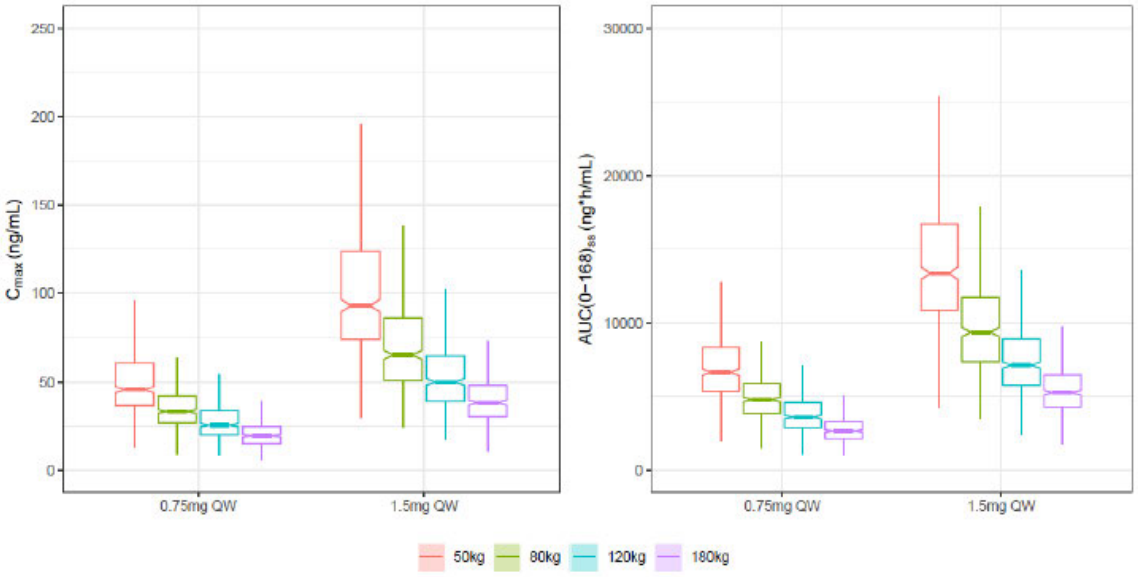
Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 57 (link).

Figure 6. Simulated fasting glucose and HbA1c change from baseline at Week 26 and Week 52 following once-weekly subcutaneous dosing in pediatric T2DM patients aged between 10 and less than 18 years.



Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 58 (link).

Figure 7. Effect of body weight on dulaglutide PK

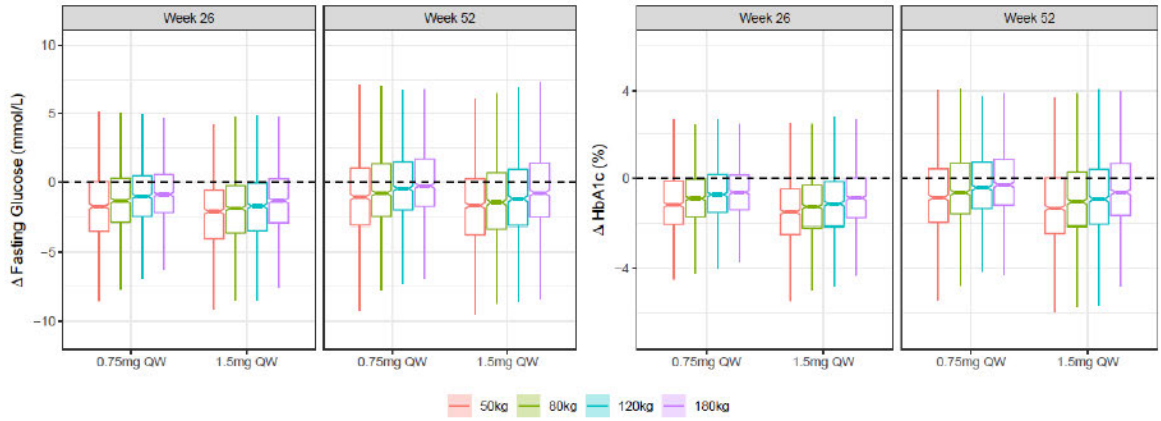


Abbreviations: AUC(0-168)ss = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; Cmax,ss = steady state maximum concentration.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 50 (link).

The body weight range of pediatric T2DM patients (50.5-175 kg) is similar to that of adult T2DM patients (52.5 - 171 kg, Phase 3 GBGL Population PK/PD Report, page 39, link; 44 – 166 kg GBCF, GBCJ, GBCK, GBCZ, and GBDN PK/PD Report, page 38, link). In the approved adult T2DM patient labeling, body weight was not identified as a factor for dosage. In addition, although body weight has an effect on dulaglutide CL, model-predictions of changes from baseline FG and HbA1c over a range of body weights showed that there is no obvious difference in **Figure 8.**

Figure 8. Simulated fasting glucose and HbA1c changes from baseline at Week 26 and Week 52 following once-weekly subcutaneous dosing of dulaglutide in pediatric T2DM patients over a range of baseline body weights.



Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 51 (link).

1.5 Pharmacokinetic Exposure Comparison Between Pediatric and Adult Type 2 Diabetes Patients

Comparison of the population mean PK parameter estimates between pediatrics and adults in **Table 5** showed that pediatrics have lower mean Ka and higher CL than those of adult patients.

- Population mean CL was slightly (24.5%) higher in pediatric patients, but this difference is lower than the IIV for CL.
- Population mean KA in pediatric patients was lower, at 49.3% of that in adults, but this difference is also within the IIV for KA.

In addition, comparison of mean exposures between pediatrics and adults in **Table 6** showed that pediatric patients have lower exposure than those of adult patients per dose. The mean AUC at steady state in pediatric patients was approximately 37% lower than that in adult patients. However, this difference was not determined to be clinically meaningful since clinical results in Study GBGC supported clinical efficacy and safety of dulaglutide in pediatric patients (10 years old and older).

Table 5. Exposure Comparison Between Pediatric and Adult Type 2 Diabetes Patients

Abbreviations: IIV = inter-individual variability; NA = not applicable because not estimated. a: Population PK and PD analyses of studies: GBCF, GBDA, and GBDC

Parameter	Pediatric Population Estimate (IIV%)	Adult Population Estimate (IIV%)[a]
First-order absorption rate constant, KA (h^{-1})	0.00379 (74.1%)	0.00769 (40.5%)
Total clearance, CL (L/h)	0.0738 (47.2%)	0.0593 (33.8%)
Intercompartmental clearance, Q (L/h)	0.00986 (NA)	0.0201 (NA)
Central volume, V2 L)	1.58 (71.2%)	2.25 (55.6%)
Peripheral volume, V3 (L)	3.51 (NA)	3.75 (NA)
Absolute bioavailability	0.47	0.476

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 44-45 (link).

Table 6. Summary Table of The Mean (95% CI) Steady-State Pharmacokinetic Exposures for Pediatric and Adult T2DM Patients Receiving Subcutaneous 0.75 mg and 1.5 mg of Dulaglutide Once-weekly

	0.75 mg QW		1.5 mg QW	
	Mean (95% CI)			
	Pediatric	Adult	Pediatric	Adult
AUC(0-168)ss (ng*h/mL)	4170 (3770, 4510)	6650 (6220, 7080)	8350 (7640, 9070)	13100 (12300, 14000)
Cmax,ss (ng/mL)	31 (28.4, 33.5)	48.3 (45, 51.6)	62 (56.9, 67.2)	94.6 (88.8, 102)

Abbreviations: AUC(0-168)ss = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; CI = confidence interval; Cmax,ss = steady state maximum concentration; QW = once weekly. Note: Summarized from simulation of 200 trials with 150 patients per dose

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 46 (link).

Reviewer comment:

The exposures between pediatrics and adults are not comparable. Despite this difference in exposure, the dosing recommendations have not changed in part because of the pediatric clinical efficacy information.

Simulation of 50 trials with 150 patients per dose showed that mean male pediatric exposure is 36% lower than that of female pediatrics, ***Table 7****. However, these difference may not be clinically meaningful (See Clinical and Statistics Division review for final conclusion on safety and efficacy between male and female pediatric patients).*

Table 7. Exposure comparison between male and female pediatrics by simulation

Dose	AUC(0-168)ss	female AUC(0-168)ss	male AUC(0-168)ss	Difference
0.75	4173	4643	2991	36%
1.5	8363	9305	6018	36%

Reviewer's assessment

1.6 PD model development

Data

PK/PD models were developed based on Study H9X-MC-GBGC (GBGC), a phase 3 multicenter, randomized double-blind parallel arm placebo-controlled superiority trial with an open-label extension (**Figure 1)**, to characterize the PK/PD of dulaglutide following subcutaneous weekly doses of 0.75 and 1.5 mg doses in children and adolescents with type 2 diabetes mellitus (T2DM or T2D). The PK/PD data incudes 1019 FG and 1006 HbA1c measurements from 154 patients with individual post hoc PK parameters obtained from PopPK model. Clinical study included analysis was summarized in **Table 2** and demographic covariates for analysis were summarized in **Table 3**.

Base model

The base model was based on previous models developed in adult T2DM patients and adapted to fit the individual post hoc PK parameters with the full time-course of fasting glucose (FG) and glycated hemoglobin (HbA1c) observations via NONMEM by implementing the importance sampling assisted by mode a posteriori (MAP) estimation method. In this model, the time course of the HbA1c response was driven by FG concentration through a linked concentration-response model that fitted both FG and HbA1c data jointly. A disease progression model together with an offset compartment where dulaglutide and placebo effects were introduced was utilized to describe FG concentration over time.

The model has 2 components, the progression of disease and an offset term for the symptomatic effect of dulaglutide therapy. Fasting glucose level is determined by the disease progression and the delayed dulaglutide effect (Equation 1 to Equation 3, **Figure 9**). The model will be parameterized in terms of baseline FG (E0G), baseline HbA1c (E0H), disease progression (kDis), offset rate constant (kOff), turnover rate for HbA1c (kout), placebo response (PLAC), lower HbA1c limit (HLIM), concentration of half-maximal response (EC50), hill coefficient (γ), and FG exponent (φ) with a steady-state approximation and an assumption that the effect of disease progression for an Emax model is negligible**.**

Figure 9. FG-HbA1c model equations

$$\frac{d(Disease)}{dt} = k_{Dis} \quad \text{Equation 1}$$

$$\frac{d(Offset)}{dt} = k_{off} \cdot (Effect - Offset) \quad \text{Equation 2}$$

$$FG = Disease \cdot (1 - Offset) \quad \text{Equation 3}$$

Where Disease is the projected FG value in the absence of therapy, k_{Dis} is the rate of disease progression, Offset is the therapy effect, Effect is the magnitude of drug effect, k_{off} is the rate constant for delay in drug effect and FG is fasting glucose.

The time-course of HbA1c will be described by a turnover model, with the rate of formation driven by FG (Equation 4).

$$\frac{d(HbA1c)}{dt} = k_{in} \cdot FG^{\varphi} - k_{out} \cdot HbA1c \quad \text{Equation 4}$$

Where k_{in} is the formation rate of HbA1c, φ is the FG exponent, FG is fasting glucose and k_{out} is the degradation rate constant of HbA1c.

The maximum response to therapy will be parameterized in terms of a physiological lower limit on HbA1c. Using the steady-state approximation, and assuming that the effect of disease progression is negligible, an Emax parameter will be derived from this limit (Equation 5).

$$Emax = 1 - PLAC - \left(\frac{HLIM}{E0_H}\right)^{\frac{1}{\varphi}} \quad \text{Equation 5}$$

Where PLAC is the placebo response, HLIM is the lower limit for HbA1c, $E0_H$ is the baseline HbA1c and φ is the FG exponent

A concentration response model will be used to describe the effect of dulaglutide therapy on the offset term (Equation 6).

$$Effect = \frac{Emax \cdot C_p^{\gamma}}{EC50^{\gamma} + C_p^{\gamma}} \quad \text{Equation 6}$$

Where C_p is the dulaglutide plasma concentration, Emax is the maximum response, EC50 is the concentration at half-maximal response for dulaglutide and γ is the hill coefficient.

For all PK/PD models, a patient will be considered to be on a concomitant medication if they took the medication without interruption for >75% of the study duration. The focus on concomitant medications for this study includes basal insulin and metformin.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 90 (link).

Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. The inter-individual variability was considered for baseline fasting glucose (E0G), baseline HbA1c (E0H), first-order rate constant on HbA1c loss (KOUT), offset rate constant (kOff), disease progression (kDis), lower HbA1c limit (HLIM), and hill coefficient (γ).

Intra-individual variability was tested as proportional on the dependent variable.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0) by bootstrap, successful model convergence, and diagnostic visual predictive check (VPC).

Covariate analysis

Covariate parameters include body weight, body mass index, sex, baseline fasting glucose, baseline HbA1c, ethnic origin, rescue therapy (overall), rescue therapy (time-varying), baseline duration of diabetes in years, screening anti-dulaglutide antibody status, anti-dulaglutide antibody titer, treatment-emergent antidrug antibody (TE-ADA) and neutralizing antibody status. In the final population PD model, the covariate for patients administered rescue therapy was found to be significant on HLIM. Meanwhile, TE-ADA was not found to be a statistically significant time-varying covariate on the final PD model.

Covariates (power model, piece-wise linear model, power + linear combination model and multiplicative model) were assessed for covariates with forward selection criteria of the significant level of 0.01 based on $\chi 2$ test ($p < 0.01$, a decrease in OBJ > 6.64 for one degree of freedom) and backward deletion criteria with the significance level of 0.001 based on $\chi 2$ test ($p < 0.001$, an increase in OBJ > 10.83 for one degree of freedom)

Final Model

The parameter estimates for the final fasting glucose-HbA1c model are listed in **Table 8**. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 10** and **Figure 11** The VPC plot for the final covariate model with all data is shown in and **Figure 13** The final PD model was an exponential error model for inter-individual variability, and proportional error model for intra-individual variability.

- Based on the covariate screening process conducted via stepwise covariate modelling (SCM), the covariate for patients administered rescue therapy was found to be significant on HLIM.

- Patients who required rescue therapy were estimated to have a 39.1% higher mean HLIM of 7.47% versus patients who did not require any rescue therapy 5.37%.
- Pediatric T2DM patients were found to have a faster disease progression than adult T2DM patients concurring with literature reports.

Table 8. Dulaglutide Pharmacokinetic-fasting glucose-HbA1c Parameters from the Population Base and Final Models

	Mean (%SEE, 95% CI)			
	Final Base		Final Model	
Parameter Description	**Population Estimates**	**IIV[a]**	**Population Estimates**	**IIV[a]**
Baseline				
Fasting Glucose, E0G (mmol/L)	8.68 (3.02%, 8.27 – 9.12)	28.5 (17.4%, 25.2 – 31.7)	8.64 (2.94%, 8.25 – 9.04)	27.9 (17.4%, 24.8 – 30.4)
HbA1c, E0H (%)	7.95 (1.48%, 7.78 – 8.14)	14.1 (17.8%, 12.7 – 15.4)	8.00 (1.41%, 7.82 – 8.18)	13.7 (17.2%, 12.2 – 15.0)
Correlation between E0G and E0H[b]	0.843 (18.4%)	-	1.00 (17.0%)	-
Placebo Effect				
Placebo effect, PLAC (fraction)	0 Fix	22.6 (26.4%, 17.6 – 28.1)	0 Fix	23.2 (27.1%, 17.8 – 27.4)
Rate Constants				
Delay in drug effect on glucose reduction, KOFF (1/h)	0.00456 (9.02%, 0.00318 – 0.0103)	226 (51.7%, 159 - 390)	0.00654 (13.0%, 0.00347 – 0.0104)	254 (55.2%, 158 - 358)
First-order rate constant on HbA1c loss, KOUT (1/h)	0.000959 (2.25%, 0.000755 – 0.00134)	61.4 (71.3%, 47.5 - 107)	0.000912 (2.29%, 0.000671 – 0.00120)	69.0 (73.0%, 54.6 - 114)
Disease progression rate constant, KDIS (mmol/L/h)	0.000188 (2.20%, 0.000119 – 0.000243)	175 (26.0%, 143 - 269)	0.000168 (2.26%, 0.000121 – 0.000238)	189 (27.5%, 132 - 249)
Lower HbA1c Limit				
Lower limit on HbA1c, HLIM (%)	5.61 (4.67%, 5.34 – 5.96)	26.8 (22.2%, 20.4 – 31.1)	5.37 (4.84%, 5.06 – 5.66)	24.6 (22.2%, 17.0 – 29.0)
Rescue therapy effect on HLIM[c]	-	-	0.391 (24.3%, 0.159 – 0.648)	-
Drug Effect				
Drug concentration at half maximal effect, EC50 (ng/mL)	10.8 (6.89%, 9.67 – 10.9)	15 Fixed	11.9 (7.02%, 11.0 – 12.3)	15 Fixed
Hill coefficient, HILL (unitless)	1.11 (17.7%, 1.09 – 1.20)	15 Fixed	1.11 (18.7%, 1.09 – 1.16)	15 Fixed
Glucose Effect on HbA1c				
Glucose effect on HbA1c coefficient, GGAM (unitless)	0.691 (5.82%, 0.638 – 0.767)	26.2 (37.6%, 15.4 – 32.4)	0.685 (4.86%, 0.621 – 0.789)	34.7 (26.5%, 23.8 – 46.4)
Proportional residual error glucose (mmol/L)[d]	0.213 (2.43%, 0.194 – 0.228)	-	0.232 (2.83%, 0.217 – 0.252)	-
Proportional residual error HbA1c (%)[d]	0.0634 (3.19%, 0.0550 – 0.0697)	-	0.0664 (3.39%, 0.0588 – 0.0745)	-

Abbreviations: CI = bootstrap derived confidence interval; %CV = coefficient of variation; IIV = inter-individual variability; SEE = standard error of the estimate.

[a] Reported as %CV, calculated using the equation = $100\% \cdot \sqrt{e^{OMEGA(N)} - 1}$, where OMEGA(N) is the NONMEM estimate of the variance for the interindividual variability.

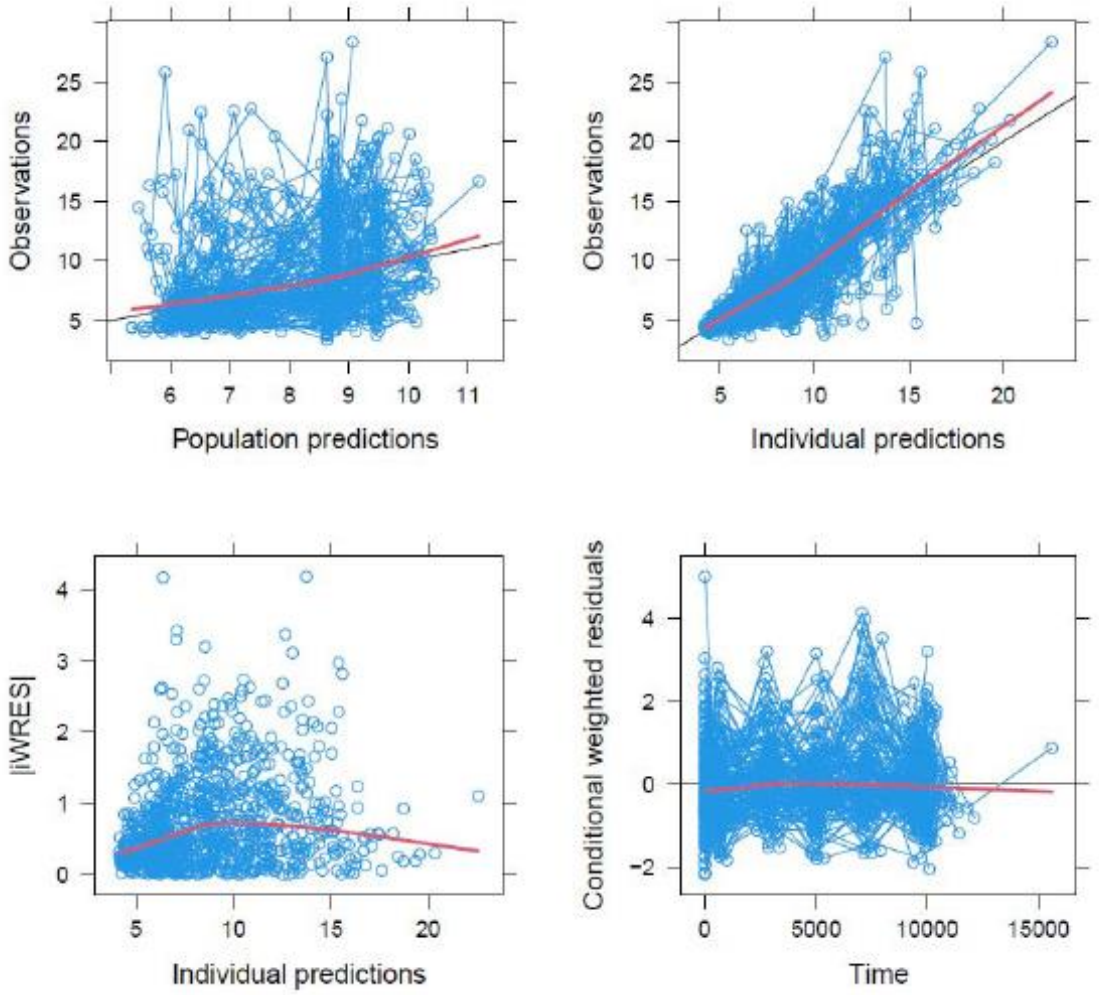
[b] correlation coefficient, calculated using the equation = $\frac{COV(M,N)}{\sqrt{OMEGA(M) \cdot OMEGA(N)}}$, where COV(M,N) is the NONMEM estimate of the covariance between parameters M and N, OMEGA(M) and OMEGA(N) are the NONMEM estimate of the variance for the interindividual variabilities for parameters M and N.

[c] $HLIM_{individual} = HLIM_{typical} \cdot (1 + \theta)$ where θ = 0.391 for patients who received rescue therapy and θ = 0 otherwise

[d] Reported as standard deviation.

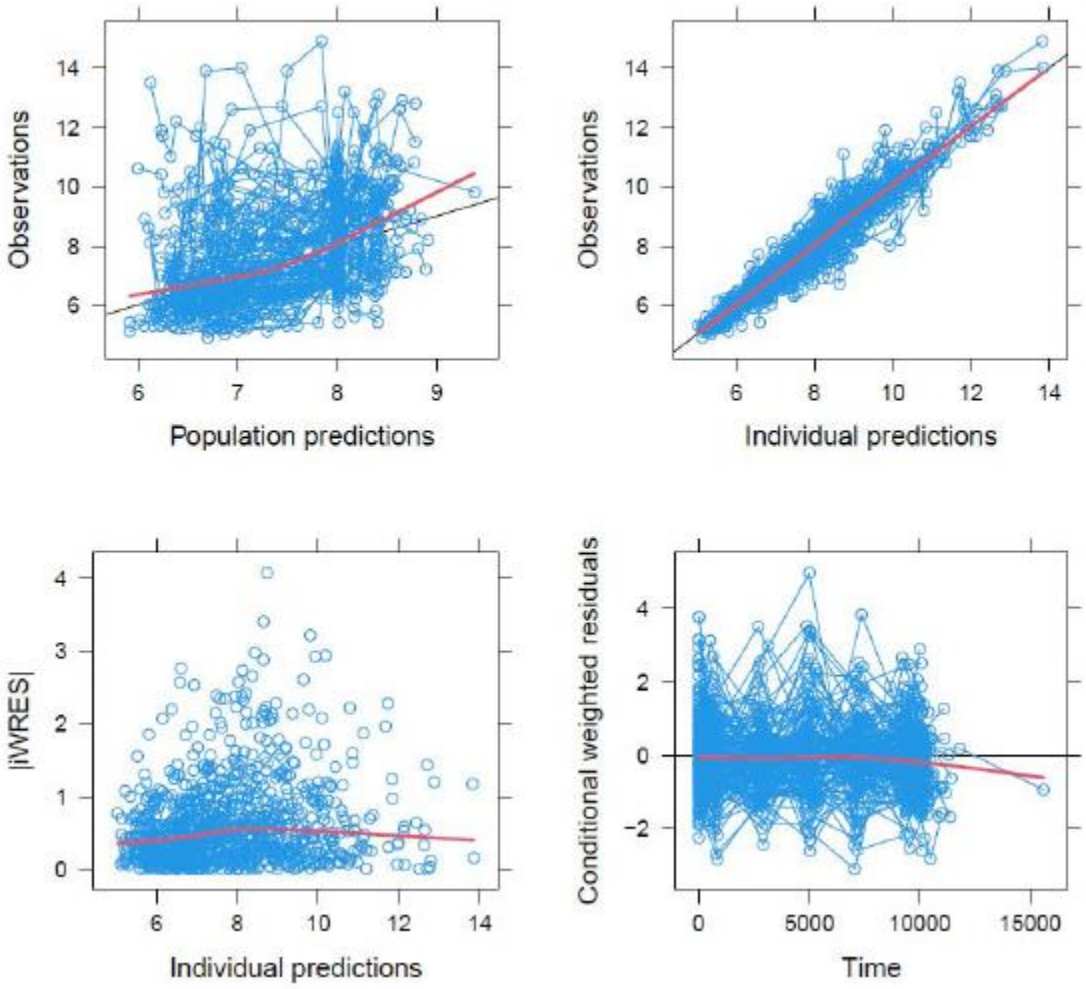
Abbreviations: E0G = baseline fasting glucose; E0H = baseline HbA1c; HbA1c = glycated hemoglobin; HLIM =lower limit of HbA1c; KDIS = disease progression rate constant; KOUT = first-order rate constant on HbA1c loss; MOF = minimum objective function; SEE = standard error of the estimate; TE-ADA = treatment-emergent anti-drug antibody. Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 38-39 (link).

Figure 10. Goodness-of-fit plots for final PD FPG model



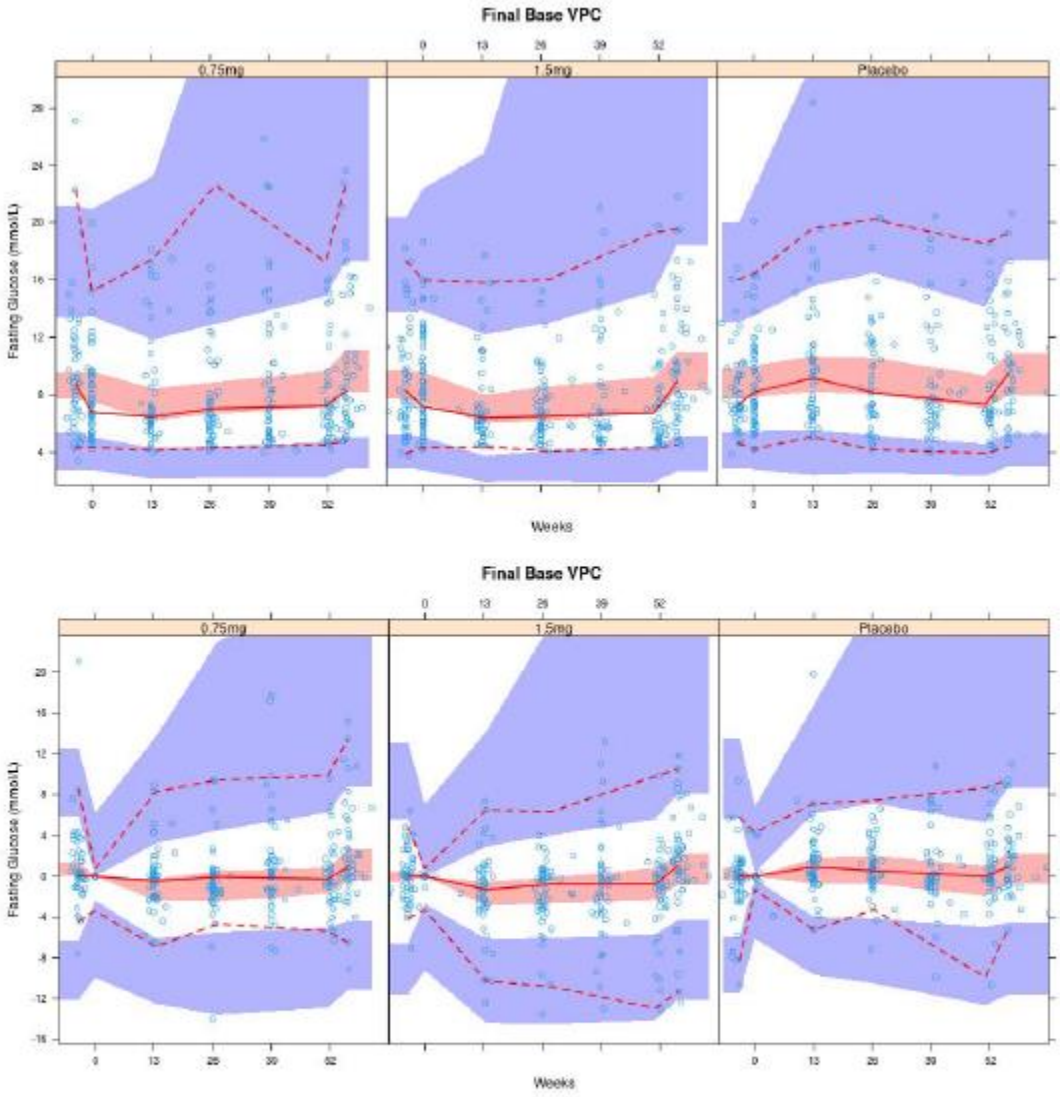
Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 125 (link).

Figure 11. Goodness-of-fit plots for final PD HbA1c model



Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 126 (link).

Figure 12. Visual predictive check for fasting glucose (top panel) and change from baseline fasting glucose (bottom panel) from the pharmacodynamic final base model for placebo and dulaglutide doses of 0.75 mg and 1.5 mg.

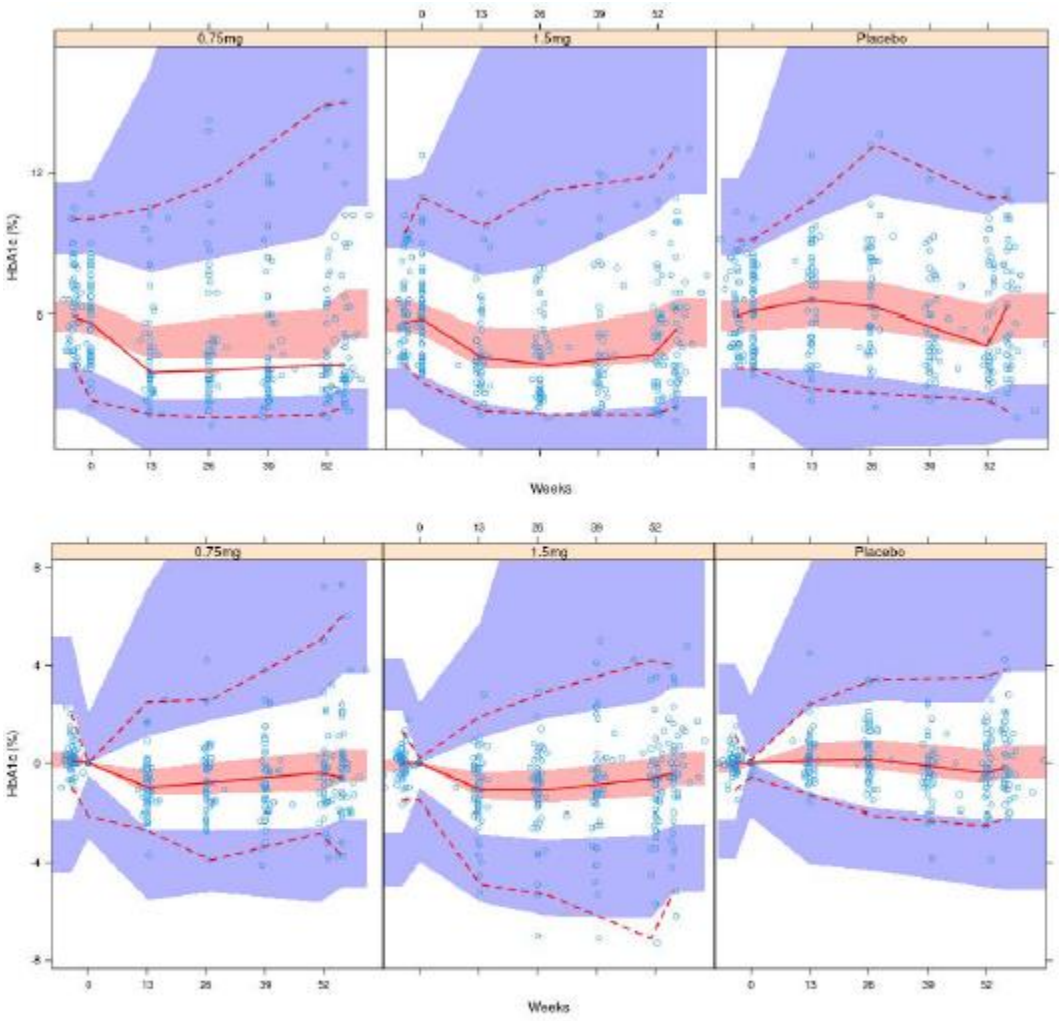


Notes:

- Circles denote observed fasting glucose values
- Solid red lines denote median of the observed values
- Dotted red lines denote 2.5th and 97.5th percentiles of the observed values while the width of the colored bands correspond to the model-simulated 95% CIs of the predicted 2.5th, 50th and 97.5th percentiles.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 117 (link).

Figure 13. Visual predictive check for HbA1c (top panel) and change from baseline HbA1c (bottom panel) from the pharmacodynamic final base model for placebo and dulaglutide doses of 0.75 mg and 1.5 mg.



Notes:

- Circles denote observed HbA1c values
- Solid red lines denote median of the observed values
- Dotted red lines denote 2.5th and 97.5th percentiles of the observed values while the width of the colored bands correspond to the model-simulated 95% CIs of the predicted 2.5th, 50th and 97.5th percentiles.

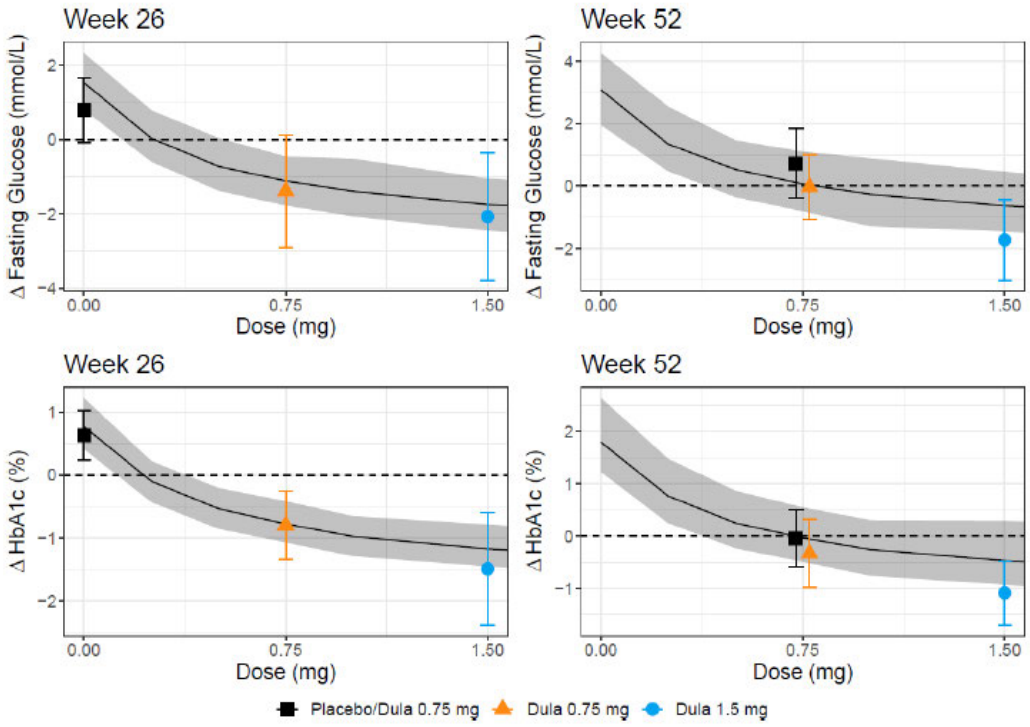
Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 118 (link).

1.7 Model-predicted Dulaglutide Dose-Response for Fasting-glucose and HbA1c

Model-predicted dose-response relationships for dulaglutide based on the exposure-response FG-HbA1c model, in **Figure 14**, showed the following:

- At Week 26, prediction of the observed changes from baseline in FG and HbA1c for placebo and both dulaglutide doses were noted, with the observed data generally falling closer to or within the 95% CI of the predictions.
- At Week 52, the PK/PD model predicted FG and HbA1c of the dulaglutide 0.75 mg dose well, but slightly under-predicted mean changes from baseline in FG and HbA1c for the 1.5 mg dose with some overlaps in the observed and predicted CIs.
- Patients originally assigned to placebo treatment up to Week 26, when switched to dulaglutide0.75 mg, demonstrated HbA1c reduction was close to patients who received dulaglutide 0.75 mg throughout, by Week 52.

Figure 14. Model-predicted and observed dulaglutide dose-response relationships for change from baseline fasting glucose (top) and HbA1c (bottom) at Week 26 (left) and Week 52 (right).



Abbreviation: HbA1c = glycated hemoglobin.
Notes:

- Simulation was performed with 200 trials of 150 virtual patients for each dose at mean baseline HbA1c of 8.07% (95%CI: 7.84%, 8.26%).
- Solid black lines denote the mean of 200 trials and the shaded areas denote the 95% confidence interval of the mean.
- Colored symbols and error bars denote mean observed data and 95% confidence interval.

Source: Applicant's pop-pk-gbgc-02-legacy-report, Page 59 (link).

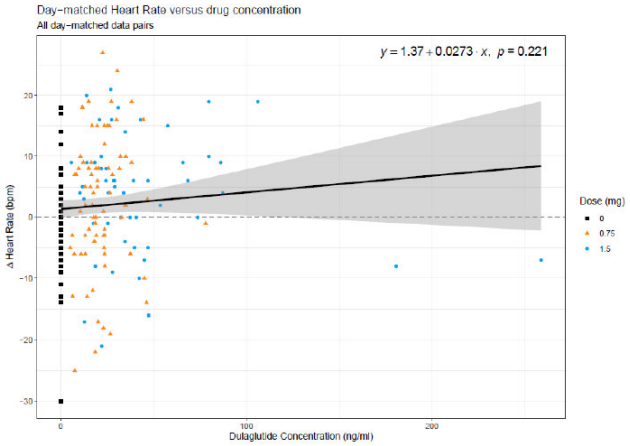
Reviewer comments:

For the most part, the applicant's goodness-of-fit plots and VPC plots suggest that the model captures the central tendency of the data. Of importance is the variability observed in pharmacodynamic response as this suggest the 37% difference in mean exposure between adults and pediatrics may not be clinically meaningful. Differences in exposure at the low dose may also be resolved by titration to the 1.5mg dose based on the patient's response. The modeling may be challenged for the highest dose at week 52. The observed data suggest the model is underpredicting both fasting plasma glucose and ΔHbA1c. The mean observed changes from baseline in HbA1c of 1.5 mg dosage at week 26 is at the margin of 95% CI of PK/PD prediction. Meanwhile, the mean observed changes from baseline in HbA1c of 1.5 mg dosage at week 52 is out of 95% CI of PK/PD model prediction. While this is a concern of the limits of the model, the observations suggest a more favorable therapeutic response which is adjustable per titration between the 0.75 and 1.5 mg dose levels.

1.7 Drug exposure and safety

Correlation between change from baseline heart rate and dulaglutide concentrations from study GBGC was assessed by the applicant, **Figure 15**.

Figure 15. Correlation between change from baseline lipase and dulaglutide concentrations from Study GBGC.



Abbreviation: Δ = change from baseline.
Note: Symbols represent the observed change from baseline data grouped by randomized treatment group; solid black line represents the slope of the exposure-response relationship; shaded band represents the 95% confidence interval.

Source: Applicant's gbgc-04-body, page 170 (link)

Reviewer comments:

Based on the codes and dataset for the heart-rate analysis, correlation between change from baseline heart rate and dulaglutide concentrations is as shown in Figure 15.

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/s/

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