CLINICAL PHARMACOLOGY REVIEW

NDAs	022200, Sequences 573, 588, and 597; 209210, Sequence 544
Submission Dates	January 22, 2021, March 12, 2021, and April 30, 2021; January 22, 2021
Brand Names	BYDUREON and BYDUREON BCISE
Generic Name	Exenatide
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
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OCP Division	Cardiometabolic and Endocrine Pharmacology
OND Division	Diabetes, Lipid Disorders, and Obesity
Sponsor	AstraZeneca Pharmaceuticals LP
Formulation; Strength	Extended-release injectable suspension; 2 mg/0.65 mL
Submission Type	Priority review submission
Relevant IND	107,815
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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1 Executive Summary

On January 22, 2021, the sponsor submitted via the 505(b)(1) regulatory pathway for the supplemental New Drug Applications (sNDAs) 022200 for BYDUREON and 209210 for BYDUREON BCISE. Study BCB114 supports these sNDAs and addresses post-marketing requirement 1860-1 under the Pediatric Research Equity Act:

- *1860-1: A randomized and controlled pediatric study under PREA to evaluate the safety and efficacy, and pharmacokinetics of BYDUREON for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).*
- and proposes applicable updates to the US labeling

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data of NDA 022200 Sequences 573, 588, and 597 as well as NDA 209210 Sequence 544. OCP/DCEP finds the data acceptable. See this review's section on "Preliminary Labeling Recommendations" for label recommendations.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

The BYDUREON formulation used in pediatric Study BCB114 (EQW, 2 mg) is identical to the commercial BYDUREON formulation.

The key results of sponsor's population pharmacokinetics (PK) and exposure-response analysis are the following:

- Exenatide plasma concentrations at steady state following administration of BYDUREON were comparable in adolescents and adults with T2DM as well as across the covariate subpopulations.
- HbA1c measurements at steady state following administration of BYDUREON were comparable between adolescents and adults with T2DM.

2 Question-Based Review

2.1 What is the difference between the clinically-tested formulation of exenatide once-weekly suspension and the marketed formulation of BYDUREON in Study BCB114?

No difference. The BYDUREON formulation used in Study BCB114 (EQW, 2 mg) is the same as the commercial BYDUREON formulation originally approved in the US under NDA 022200. Study BCB114's study code is D5551C00002.

2.2 Key Clinical Pharmacology Questions

2.2.1 What are the design features of Study BCB114 for exenatide once-weekly BYDUREON?

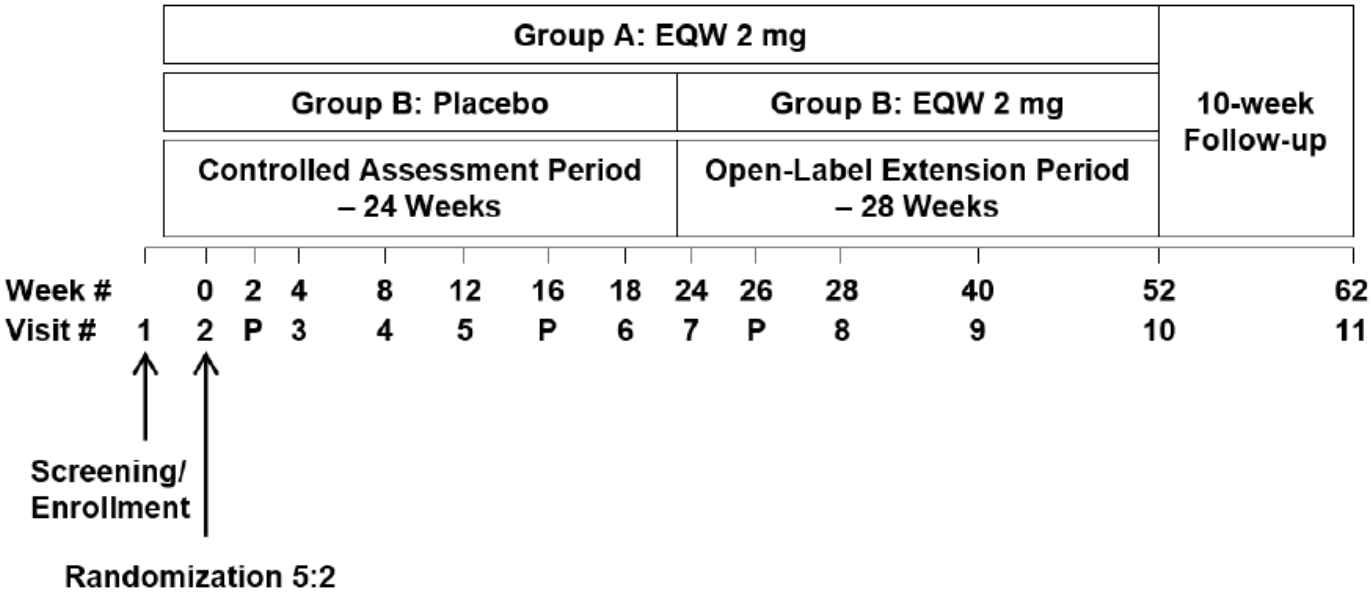
This was a multicenter, randomized, parallel-group, Phase 3 study in adolescent (11 – 17 years) patients with type 2 diabetes mellitus (T2DM) treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and or insulin. The study had 4 periods as shown in Figure 1:

- Screening period (5 weeks)
- Controlled assessment period (24 weeks): double-blind, placebo-controlled period to examine the efficacy and safety of exenatide once weekly (BYDUREON) compared with placebo. About 77 patients were randomly assigned in a 5:2 ratio to receive either BYDUREON 2 mg (Group A) or placebo (Group B).
- Open-label extension period (28 weeks): open-label, uncontrolled period to examine the long-term safety and efficacy of BYDUREON. Patients assigned to the BYDUREON 2 mg treatment (Group

A) were continually treated with BYDUREON 2 mg during the open-label extension period (through Week 52). Patients randomized to placebo (Group B) were to receive BYDUREON 2 mg beginning at the start of the open-label extension period through Week 52.

- Post-treatment follow-up period (10 weeks).

Figure 1. Study BCB114's schematic

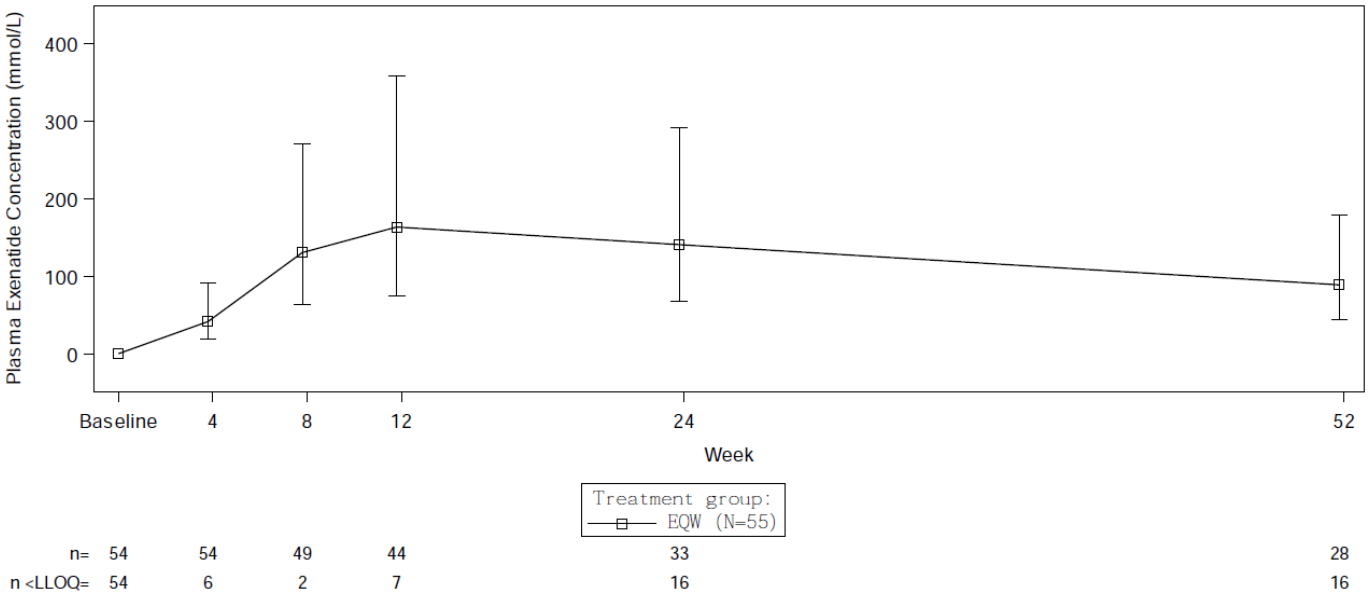


Source: Study BCB114 report's Figure S1

2.2.2 What are the pharmacokinetic (PK) characteristics of exenatide once-weekly BYDUREON in Study BCB114?

For measurable samples, the geometric mean plasma exenatide concentrations over time increased between randomization and Week 8 then remained relatively constant from Week 8 to Week 52 suggesting that steady-state concentrations had been reached. Figure 2 shows the exposure data of Study BCB114. The proportion of exenatide plasma concentrations below limit of quantitation (BLOQ) were higher in adolescents (17%) compared to that in adults (9%) and appeared to correlate to the higher presence of anti-drug antibody (ADA) titer > 625 in adolescents (16%) compared to that in adults (7%). For both adult and adolescent samples, the BLOQ rate is 8-12 fold higher for samples with ADA titer > 625 than that for samples with no ADA or ADA titer ≤ 625 (52-72% vs. 6%, see Table 8).

Figure 2. Geometric Mean (GSD interval) plasma exenatide concentration versus time profile of Study BCB114.



Source: Study BCB114 report's Figure 14.2.2.11

2.2.3 How does the exposure of exenatide in adolescents for Study BCB114 compared with that of adults for exenatide once-weekly as BYDUREON or BYDUREON BCISE?

Population PK analysis indicated that the PK profile of BYDUREON in the pediatric subjects (ages of 11 to less than 18 years old) was consistent with that in adult subjects for those with ADA titer ≤ 625, however the rate of ADA high titer and concentration below LLOQ was high in adolescents (see 2.2.2). Because the previous population PK analysis showed similarity between BYDUREON and BYDUREON BCISE in adults (Clinical Pharmacology review of NDA 209210 dated December 4, 2018 DARRTS Reference ID: 4358137), the PK behavior of BYDUREON BCISE in adolescent subjects is expected to be similar to that of BYDUREON.

2.2.4 What are the effects of anti-drug antibody on exenatide PK and pharmacodynamics (PD) for Study BCB114?

Based on the population PK analysis and exposure-response analysis, the anti-drug antibody effect on exenatide PK and PD is less distinct for those with ADA titer ≤625 in Study BCB114 and similar between adolescents and adults. However, however the rate of ADA high titers (titer > 625) rate and concentration below LLOQ was high in adolescents (see 2.2.2). And patients with higher titers (titer > 625) or concentration below LLOQ had an attenuated HbA1c response.

2.3 Bioanalytical

2.3.1 Is the bioanalytical method properly validated to measure exenatide for Study BCB114?

The sponsor used the immunoenzymetric (IEMA) assay to determine exenatide concentration in plasma samples. Briefly, this was a 2-site, sandwich assay, which used EXE4:2-8.4 monoclonal antibody for capture and biotinylated glucagon-like peptide (GLP):3-3.1 monoclonal antibody for detection of exenatide captured on the enzyme-linked immunosorbent assay (ELISA) plates. Table 1 details the bioanalytical validation of exenatide in plasma samples for Study BCB114.

Table 1. Bioanalytical method validation of plasma exenatide concentrations for Study BCB114.

Cross Validation Study Number:	8360-719
Method Type:	ELISA
Curve Fit; Weighting Factor	Five Parameter Logistic Curve Fit (Marquardt) with $1/Y^2$ weighting
Analyte Name(s):	Exenatide
Species Matrix:	Human K2EDTA Plasma
Sample Volume:	0.5 mL requested (0.2 mL minimum)
Minimum Required Dilution (MRD)	1/2
Calibrator/Control:	Exenatide
Capture Reagent:	EXE4:02-08.04
Detection Reagents:	Biotinylated muGLP1:03-03.01, Streptavidin HRP
Substrate:	TMB one component
Lower Limit of Quantitation (LLOQ):	20.000 pg/mL
Upper Limit of Quantitation (ULOQ):	500.000 pg/mL
Sample Storage Temperature:	-60 to -80°C
Freeze/Thaw Stability:	Up to 8 cycles at -60 to -80°C*
Room Temperature Stability:	Up to 23 hours and 29 minutes at -60 to -80°C*
Refrigerated Temperature (2 to 8ºC) Stability:	Up to 45 hours and 45 minutes*
Long Term Stability:	Up to 1388 days at -60 to -80°C*
3% BSA Working Stock Long Term Stability:	1449 days at -60 to -80°C*
3% BSA working standard stability:	1108 days at -60 to -80°C*
Dilutional Linearity:	1/8000*
Method Developed By:	Sponsor, validated at (b) (4)

*As referenced under Sponsor provided validation reports (b) (4)
Source: Clinical Study Report Appendix 16.1.13 AstraZeneca Exenatide - BCB114 Page 12 of 345.

The bioanalytical assay for measuring exenatide in plasma samples is acceptable for Study BCB114.

2.3.2 Are the bioanalytical methods for studies used in the exenatide population pharmacokinetic and exposure-response analysis comparable?

Yes. Table 2 details the bioanalytical method specifications for the studies used in the exenatide population pharmacokinetic and exposure-response analysis.

Table 2. Plasma Exenatide Bioanalytical Assay Specifications

Study number	LLQ (pg/mL)	Linear range (pg/mL)	Recovery (%)	Assay accuracy (%)		Assay precision (%)		Stability	
				Inter	Intra	Inter	Intra	Freeze-thaw (N cycles)	Long term plasma (days at -70°C)
(b) (4)	10	10 to 400	86.2 to 127.0	-5.6 to 7.6%	-14.6 to 21.7	5.8 to 13.6	0.4 to 30.1	3	Not found[o]
	10	10 to 400	86.2 to 127.0	-5.6 to 7.6	-14.6 to 21.7	5.8 to 13.6	0.4 to 30.1	6	≥ 12 m at -20°C
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	716
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	229
	20	20 to 500	66.8 to 169.6	-13.8 to 9.5	-18.4 to 25.0	3.2 to 8.7	1.1 to 10.0	5	716
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	716
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	1388
	20	20 to 500	Not tested[n]	-6.8 to 7.6	-15.5 to 20.3	5.6 to 13.9	1.4 to 18.6	8	1388
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	1388
	20	20 to 500	Not tested[n]	-6.8 to 7.6	-15.5 to 20.3	5.6 to 13.9	1.4 to 18.6	8	1388
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	716
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	716
	20	20 to 500	78.0 to 117.6	-5.3 to 14.3	-20.4 to 21.8	3.1 to 15.0	1.1 to 20.4	8	1388

(b) (4)

[n] Due to partial validation from a transfer of the assay to an additional testing site

[o] Not found in referenced report (b) (4)

LLQ, lower limit of quantification; m, months; N, number.

Source: NDA 022200 Serial 597 submitted on April 30, 2021.

3 Preliminary Labeling Recommendations

NDA 022200 (BYDUREON):

6.2 Immunogenicity

In the pediatric study [see Clinical Studies (14.3)], the maximum antibody titer obtained at any time during the study was low (<625) for approximately 30% of patients and high (≥625) for approximately 63% of patients. The percentage of patients with positive antibody titers peaked at approximately Weeks 12 (high titer) to 24 (low titer) of dosing and then decreased to approximately 31% and 40%, respectively, by the end of the treatment period. Patients with higher titers had an attenuated HbA1c response.

12.3 Pharmacokinetics

Specific Populations

Pediatric Patients

The clinical pharmacology of BYDUREON has been evaluated in the population pharmacokinetic study in adolescent patients with type 2 diabetes mellitus between ages of (b) (4) 11 to less than 18 years old. The pharmacokinetic profile of BYDUREON in the pediatric population was consistent with (b) (4) the adults.[7]

NDA 209210 (BUDUREON BCISE):

6.2 Immunogenicity

In the pediatric study [see Clinical Studies (14.3)], the maximum antibody titer obtained at any time during the study was low (<625) for approximately 30% of patients and high (≥625) for approximately 63% of patients. The percentage of patients with positive antibody titers peaked at approximately Weeks 12 (high titer) to 24 (low titer) of dosing and then decreased to approximately 31% and 40%, respectively, by the end of the treatment period. Patients with higher titers had an attenuated HbA1c response.[6]

12.3 Pharmacokinetics

Specific Populations

Pediatric Patients

The clinical pharmacology of BYDUREON, another formulation of exenatide extended release, has been evaluated in the population pharmacokinetic study in adolescent patients with type 2 diabetes mellitus between ages of (b) (4) 11 to less than 18 years old. ~~The pharmacokinetic profile of BYDUREON (b) (4) in the pediatric population is (b) (4) in adults.~~ The pharmacokinetic behavior of BYDUREON BCISE in adolescent patients is expected to be consistent with (b) (4) that of BYDUREON ~~in adolescent patients~~.

Appendix 4.1 Pharmacometric Review

4.1.1 Population PK analysis

Population PK analysis was conducted based on previously developed model estimated on Phase 3 data in adults to assess the PK of exenatide plasma concentrations at steady state in adolescents with T2DM from study BCB114. BCB114 was a random, double blinded, parallel-group, placebo-controlled, multi-center Phase 3 study to evaluate the effect of exenatide on HbA1c of EQW (2 mg) versus placebo for 24 weeks. The details are shown in Table 3.

Table 3. Summary of dataset from study 5551C00002.

Study	Population	Exenatide dose (mg)	Exenatide (b) (4) manufacturing scale	PK sample collection	PD (HbA1c) sample collection
EQW					
D5551C00002 (Phase 3)	Adolescents with T2DM (n = 59)	2	(b) (4)	Predose Day 1 and week 4, 8, 12, 24, and 52 (end of study)	Day 1 and week 4, 8, 12, 18, 24, 28, 40, and 52 (end of study)

EQW, exenatide once weekly; HbA1c, glycosylated haemoglobin; PD, pharmacodynamic, PK, pharmacokinetic; T2DM, type 2 diabetes mellitus.

Source: Population PK and ER Report, Page 11, Table 1.

Table 4 shows a summary of exenatide plasma concentration data from study BCB114. A total of 365 plasma PK samples from 58 subjects were provided. Overall, 209 (57.3%) concentrations with non-steady state measurements (prior to week 8 or after week 30), 8 (2.19%) concentrations below the LLOQ and 25 (6.8%) concentrations with antibody titer > 625 were excluded, resulting in a total of 123 (33.7%) quantifiable concentrations from 47 subjects in the population PK analysis. Therefore, the analysis (consistent with previous analysis in adults) only evaluated measurable samples at steady state with ADA titer $\leq$ 625.

Table 4. Summary of Data in population PK analysis of Exenatide in Adolescents with T2DM.

Type	Subjects [n]	Samples [n (%)]
Below LLOQ	8	8 (2.19)
Antibody titre > 625	12	25 (6.85)
Used in PK analysis	47	123 (33.7)
Non-steady state measurement	58	209 (57.3)
Overall in dataset	58	365 (100)

LLOQ, lower limit of quantification; n, number of subjects; PK, pharmacokinetic; T2DM, type 2 diabetes mellitus.

Source: Population PK and ER Report, Page 20, Table 5.

Demographic data for adolescents in Study BCB114 and adults from Phase 3 studies are shown in Table 5. The majority of the adolescent subjects were Caucasian (38.3%) and Black/African American (25.5%), while the majority of the adult subjects were Caucasian (81.0%). The median age of adolescent subjects

was 15 years old (range: 11 - 17) and 53.2% were females. The median body weight and ideal body weight in adolescents were 102 kg (range: 48 - 201) and 59 kg (range: 34 – 83), which are similar to adult subjects 90 kg (range: 47 - 181) and 62 kg (range: 34- 102), respectively. Median eGFR in adolescents is 109 mL/min/1.73 m^2 (range: 68, 150), which is slightly higher than adults 88 mL/min/1.73 m^2 (range: 34 - 217). The proportion with different levels of baseline antibody titers were comparable between adolescent and adult subjects.

Table 5. Demographics and Baseline Characteristics of Adolescents and adults with T2DM from Phase 3 Studies In the population PK analysis.

Variable	Adolescents T2DM	Adults T2DM Ph3
n	47	1064
Age [years]	15 [11, 17]	56 [23, 83]
Body mass index [kg/m^2]	37 [18, 71]	32 [19, 65]
Body weight [kg]	102 [48, 201]	90 [47, 181]
eGFR [mL/min/1.73 m^2]	108 [68, 150]	89 [34, 217]
Ideal body weight [kg]	59 [34, 83]	62 [34, 102]
Females	25 (53.2)	503 (47.3)
Race		
Caucasian	18 (38.3)	862 (81.0)
Black/African American	12 (25.5)	121 (11.4)
Asian	2 (4.3)	37 (3.5)
Native American	4 (8.5)	5 (0.5)
Hispanic	0 (0.0)	30 (2.8)
Other	11 (23.4)	7 (0.7)
Hawaiian/Pacific Islander	0 (0.0)	2 (0.2)
Antibody titre		
0	46 (97.9)	1007 (94.6)
25	1 (2.1)	41 (3.9)
125	0 (0.0)	15 (1.4)
625	0 (0.0)	1 (0.1)

Values are median [range] or n (%)
eGFR, estimated glomerular filtration rate; Ph 3, phase 3; n, number of subjects; T2DM, type 2 diabetes mellitus; PK, pharmacokinetics.

Source: Population PK and ER Report, Page 20-21, Table 6.

The model was estimated with first-order conditional estimation method in the nonlinear mixed effects modeling software (NONMEM), version 7.3.0. PsN. pirana and R were used for the exploratory analysis, executing NONMEM runs and post-processing of NONMEM output. The previous developed population PK model for EQW and EQWS Phase 3 data is shown below:

$$C_{ss,avg,ij} = ((\theta_1 \cdot \left(\frac{baseline\ eGFR_i}{81.6}\right)^{\theta_2} + \theta_3 \cdot (\text{IBW-64.1}) + \theta_4 \cdot T_{125,625,ij}) \cdot F_{rel}) \cdot exp^{\eta_i}$$

Where:

- $C_{ss,avg,ij}$ is the individually predicted steady-state concentration (pg/mL) for the i^{th}

subject at the j^{th} measurement.

- Baseline $eGFR_i$ is the baseline eGFR for the i^{th} subject.
- IBW is the ideal body weight for the i^{th} subject.
- $T_{125,625,ij}$ is an indicator variable for antibodies to exenatide for the i^{th} subject at the j^{th} measurement
- η_i is the inter-individual variability (IIV) estimate for the i^{th} subject.
- F_{rel} is the relative bioavailability for the suspension formulation of EQWS relative to EQW

Exenatide plasma concentrations had been modeled on a log-transformed scale. The residual variability was modeled as additive on the logarithmic scale. Parameter estimates from the final model is presented in Table 6.

Table 6. Parameter Estimates of the Exenatide Population PK Model Using (b) (4) Manufacturing Scale Phase 3 Study Data Only.

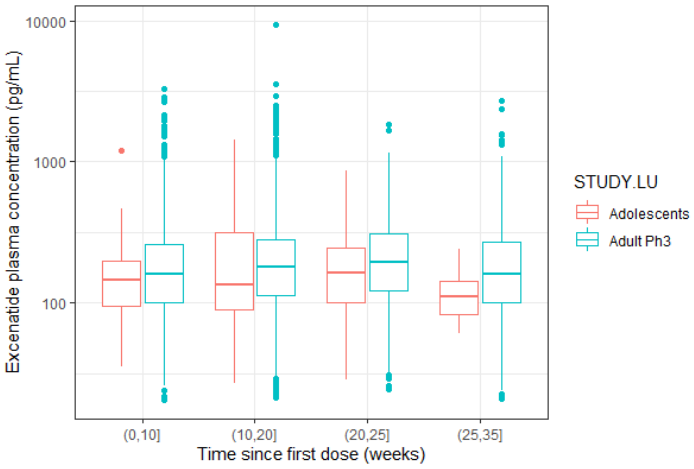
Parameter	Description	Mean	%RSE
θ_1	Mean $C_{ss,avg}$ for 2 mg dose	161	2.8
θ_2	eGFR effect on $C_{ss,avg}$ as a power model: $(eGFR/81.6)^{\theta 3}$	-0.85	9.2
θ_3	IBW effect on $C_{ss,avg}$ as an additive (shift) model θ_4*(IBW-64.1)	-1.38	14.8
θ_4	Antibody titre ≥ 125 as an additive (shift) effect on $C_{ss,avg}$	39	11.1
θ_5	EQWS as a proportional effect on $C_{ss,avg}$ for autoinjector delivery	1.01	3.8
ω^2	Variance of interindividual variability for $C_{ss,avg}$	0.285	7.5
σ^2	Variance of residual error for Tandem assay	0.284	4.6

Parameter names have been adapted from source to simplify and exclude parameters not needed.
θ, fixed-effects parameter; ω, variance of inter-individual variability; σ, variance of residual variability; $C_{ss,avg}$, average exenatide concentration at steady state; eGFR, estimated glomerular filtration rate; EQWS, exenatide once weekly suspension; IBW, ideal body weight; PK, pharmacokinetic; RSE, relative standard error.

Source: Population PK and ER Report, Page 17, Table 3.

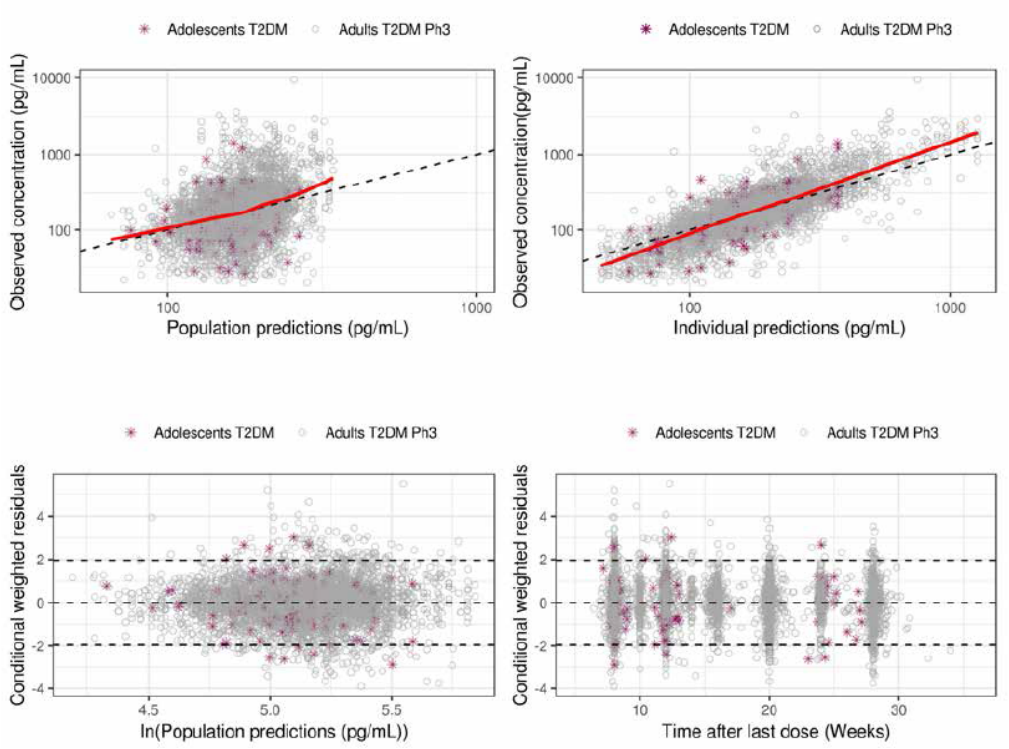
The previous population PK model were based on a large number of samples from >1000 adults with T2DM. Addition of relatively few data points from study BCB114 was therefore not anticipated to have a major impact on the parameter estimates if re-estimated. Therefore, external model evaluations were performed. No obvious differences were observed between exenatide plasma concentrations in adolescents and adults with T2DM with measurable PK and ADA titer ≤ 625.(Figure 3) Goodness-of-fit plots and VPC showed no unacceptable bias in model performance.(Figure 4 Figure 5)

Figure 3. Exenatide Plasma Concentrations Versus Time After First Dose at Steady State Stratified by Population (Adolescents (BCB114) and Adult Patients with T2DM.



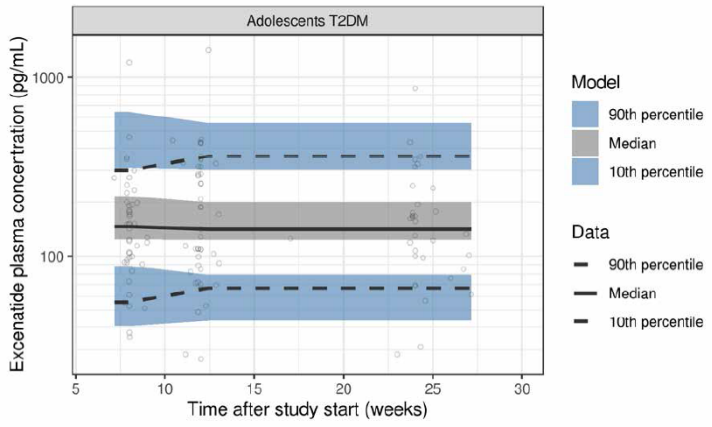
Source: Reviewer's analysis

Figure 4. Goodness-of-Fit Plot for Exenatide Adult T2DM Model Population PK Model.



Source: Population PK and ER Report, Page 66, Figure F4.

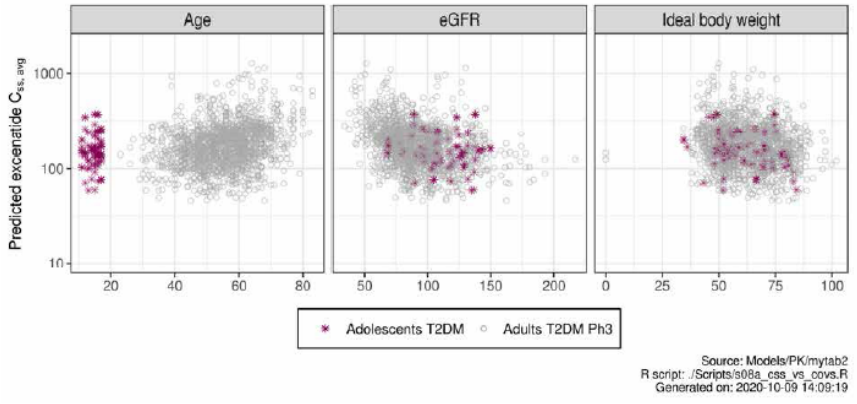
Figure 5. External Evaluation of Adult T2DM Population Pharmacokinetic Phase 3 Model for the Use in Adolescents with T2DM Comparing Observed and Predicted Exenatide Plasma Concentrations Versus Time After First Dose.



Source: Population PK and ER Report, Page 24, Figure 4.

Model-predicted exenatide $C_{ss,avg}$ stratified by population and different levels of covariates age, antibody titer, sex, race, eGFR, and IBW is summarized in Figure 6 and Table 7. Exenatide $C_{ss,avg}$ in adolescents with T2DM (median (5^{th}-95^{th} percentiles): 149.8 (75.9-359)) overlap with the data from adults with T2DM (172.1 (74.3-414.3). As expected from the covariates in the model, $C_{ss,avg}$ increases with increasing age, as a result of decreasing renal function. The adolescent data aligns with these patterns on the lower age and upper eGFR range. The effect of IBW and antibody titer is similar between adults and adolescents. The differences in median values across the categories of race for adults and adolescents may be explained by the low number of observations in each category.

Figure 6. Predicted Average Exenatide at Steady State Versus Different Continuous Covariates and Stratified by Population.



$C_{ss,avg}$, average concentration at steady state; eGFR, estimated glomerular filtration rate; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

Source: Population PK and ER Report, Page 26, Figure 6.

Table 7. Descriptive Statistics for Predicted Average Exenatide Plasma Concentrations at Steady State in Adolescents and Adults, Stratified into Different Subpopulations.

Variable	Adolescents T2DM	Adults T2DM Ph3
Overall	149.8 [121.7-215] (75.9-359)	172.1 [121.7-236.3] (74.3-414.3)
Antibody titre		
0	143.5 [109.1-166.2] (78.4-168.7)	140.6 [100.1-203.3] (62.3-316.2)
25	111.7 [76.1-129.1] (59.3-262.3)	157.9 [116.7-207.3] (75.1-389.3)
125	165.4 [137.2-242.8] (107.2-370.1)	196.3 [138.9-255] (85.3-407.3)
625	154.5 [142.4-193.4] (91.1-293.6)	207 [143.6-284.8] (92.8-540.8)
Sex		
Female	158.2 [135.4-197.3] (76.8-338.7)	181.4 [134-246.5] (79-435.2)
Male	142.7 [107.5-236] (75.9-347)	160 [114.6-227.2] (68.9-384.7)
Race		
Caucasian	182.2 [136.1-244.3] (76-370.3)	167.7 [120.1-229.6] (75-411)
Black/African American	142.5 [121.8-149.9] (75.7-170.8)	167.1 [112.9-244.7] (69.5-424.4)
Asian	163.7 [139.4-188.1] (119.9-207.5)	185.8 [139.9-248.9] (114-382.5)
Native American	158.7 [146.4-255.4] (103.1-345.6)	253.7 [209.2-278.5] (121.2-455.4)
Other	130.2 [107.5-145.8] (73-237.4)	182.5 [122.4-221.1] (88.2-250.6)
Hispanic		254.3 [211.5-294.3] (94.1-477)
Hawaiian/Pacific Islander		201.3 [170.9-231.7] (146.6-255.9)

Values are median [interquartile range] (5th-95th percentile)
Ph3, phase 3; T2DM, type 2 diabetes mellitus.

Source: Population PK and ER Report, Page 28, Table 7.

Reviewer's comments:
The population PK analyses by the sponsor were checked by the reviewer. It's acceptable to use the previous model due to the good agreement between observations and predictions for adolescent subjects, while the model was limited to exenatide concentration data with antibody titer ≤ 625, as samples with antibody titer > 625 were excluded from the analysis. As shown in the following table, the proportion of exenatide plasma concentrations below limit of quantitation (BLOQ) were higher in adolescents (17%) compared to that in adults (9%) and appeared to correlate to the higher presence of anti-drug antibody (ADA) titer > 625 in adolescents (16%) compared to that in adults (7%). For both adult and adolescent samples, the BLOQ rate is 8-12 fold higher for samples with ADA titer > 625 than that for samples with no ADA or ADA titer ≤ 625 (52-72% vs. 6%).

Table 8. Summary of steady state measurements of exenatides below LLOQ.

	ADOLESCENT		ADULTS	
Total	156	Below LLOQ	7681	Below LLOQ
		26 (17%)		718 (9%)
Titer ≤ 625	131 (84%)	Below LLOQ	7133 (93%)	Below LLOQ
		8 (6%)		432 (6%)
Titer > 625	25 (16%)	Below LLOQ	548 (7%)	Below LLOQ
		18 (72%)		286 (52%)

Source: Reviewer's analysis.

4.1.2 Exposure-Response Analysis

Table 9 provides a summary of the HbA1c measurements data from Study BCB114. A total of 154 HbA1c measurements from 47 subjects (with available plasma PK samples) treated with exenatide were collected. Overall, 51 (33.1%) measurements were non-steady state measurements (prior to week 12), 19 (20.8%) measurements were missing, 1 (0.64%) measurement was an outlier, resulting in a total of 70 (45.5%) measurements from 39 subjects were included in the exposure-response analysis.

Table 9. Summary of Data in Exposure-Response Analysis of Exenatide in Adolescents with T2DM.

Type	Subjects [n]	Samples [n (%)]
Used in HbA1c analysis	39	70 (45.5)
Missing HbA1c	19	32 (20.8)
Non-steady state HbA1c	40	51 (33.1)
Outlier	1	1 (0.649)
Overall in dataset	47	154 (100)

HbA1c, glycosylated haemoglobin; n, number of subjects; T2DM, type 2 diabetes mellitus

Source: Population PK and ER Report, Page 29, Table 8.

The exposure-response model was estimated with based on Hb1Ac data using an E_{max} model. The previous developed model for EQW and EQWS Phase 3 data is shown below:

$$HbA1c_{ij} = \text{Baseline } HbA1c_i\ (\%) - \left(\frac{E\max_i(\%) \cdot C_{ss,avg,ij}}{EC_{50,i} + C_{ss,avg,ij}}\right)$$

$$\text{EC}_{50,i}\ (\text{pg/mL}) = \left(\theta_2 + \theta_4 \cdot (\text{if } Titer_{ij} \geq 125)\right) \cdot exp^{\eta_i}$$

$$E_{max,i}(\%) = \left(\theta_1 + \theta_3 \cdot (\text{Baseline } HbA1c_i\text{-}8.2)\right) \cdot exp^{\eta_i}$$

Where:

- $HbA1c_{ij}$ is the individually predicted HbA1c (%) value for the i^{th} subject at the j^{th} measurement
- Baseline $HbA1c_i$ is the baseline HbA1c value for the i^{th} subject
- $Titer_{ij}$ is an indicator variable for antibody to exenatide of 125 or 625 independent of assay lab for the i^{th} subject at the j^{th} measurement
- η_i is the IIV random effect estimate for the i^{th} subject.
- $C_{ss,avg,ij}$ is the individually predicted predose steady-state concentration (pg/mL) for the i^{th}
- subject at the j^{th} measurement with the population PK model

Parameter estimates from the final exposure-response model is presented in

Table 10. Parameter Estimates of the Final EQWS Exenatide Population Exposure-Response Model

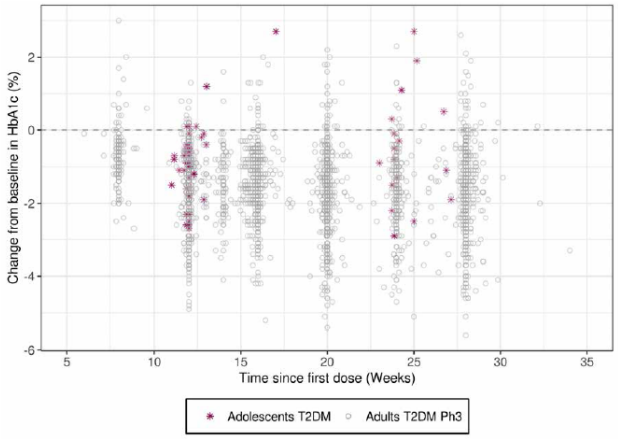
Parameter	Description	Mean	%RSE
θ_1	E_{max} at a baseline HbA1c of 8.2%	1.89	6.5
θ_2	EC_{50} for titre < 125 (pg/mL)	52.1	31.3
θ_3	Change in E_{max} for each 1% of deviation of baseline HbA1c from 8.2%	0.67	7.7
θ_4	Increase of EC_{50} for titre ≥ 125 (pg/mL)	33.3	33.7
ω, E_{max}^2	Variance of inter individual variability for E_{max}	0.039	26
ω, EC_{50}^2	Variance of inter individual variability for EC_{50}	2.9	25
σ^2	Variance of residual error for HbA1c	0.0039	8.6

EQWS, Exenatide once weekly suspension; EC_{50}, exenatide concentration generating 50% of E_{max}; E_{max}, maximum effect; HbA1c, glycosylated haemoglobin; RSE, relative standard error.

Source: Population PK and ER Report, Page 18, Table 4.

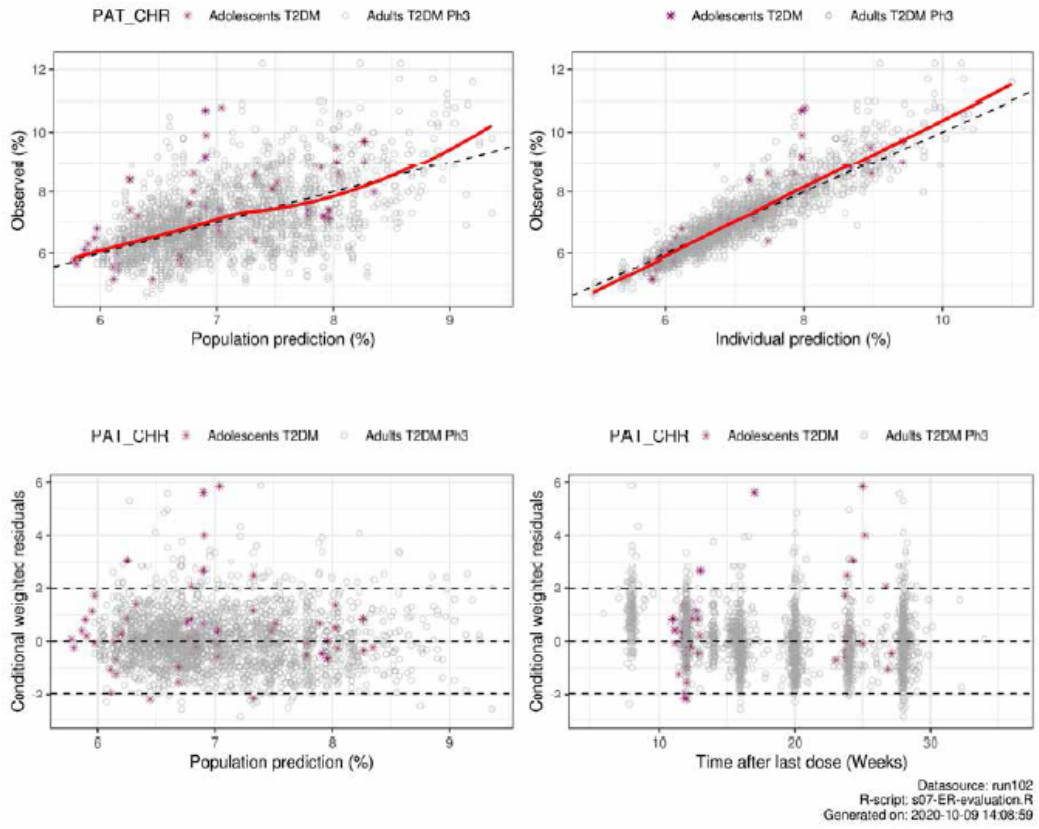
The previous exposure-response model was estimated based on a large number of samples from adults. It was anticipated that the addition of relatively few data points from study BCB114 would not have major impact on the parameter estimates. Therefore, external model evaluations were performed. No obvious differences between HbA1c measurements versus time were observed between adolescents and adult subjects with T2DM (Figure 7). Goodness-of-fit plots was shown in Figure 8 and no unacceptable bias was observed in model performance.

Figure 7. HbA1c Versus Time After First Dose at Steady State Stratified by Population (Adolescents (BCB114) and Adult Patients with T2DM.



Source: Population PK and ER Report, Page 33, Figure 10.

Figure 8. Goodness-of-Fit Plot for Exenatide Adult T2DM Model Exposure-Response Model for HbA1c.



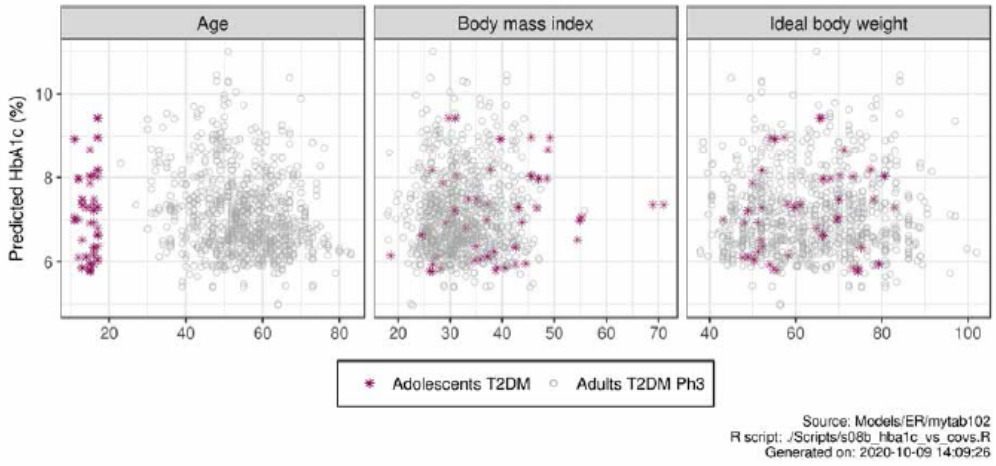
Upper row: red line is a smoother, black dashed line is line of identify. Bottom row: black dashed lines indicate mean of zero and 95% confidence interval for a normal distribution.
HbA1c, glycosylated haemoglobin; T2DM, type 2 diabetes mellitus; Ph3, Phase 3.

Source: Population PK and ER Report, Page 68, Figure F6.

Potential differences in HbA1c between different subpopulations were evaluated by comparing distributions of HbA1c. Model-predicted HbA1c stratified by population, and different levels of covariates age, antibody titer, sex, race, eGFR, and IBW is summarized in Figure 9 and Table 11.

HbA1c in adolescents with T2DM (median (5th-95th percentiles): 7.1 (5.8-9)) was comparable to data from adults with T2DM (6.9 (5.9-9)). Similar HbA1c effect for the different titers was observed in adolescents. No major differences were seen for different sex or race.

Figure 9. Predicted HbA1c at Steady State Versus Different Continuous Covariates and Stratified by Population.



HbA1c, glycosylated haemoglobin; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

Source: Population PK and ER Report, Page 38, Figure 15.

Table 11. Descriptive Statistics for Predicted HbA1c Concentrations at Steady State in Adolescents Stratified into Different Subpopulations.

Variable	Adolescents T2DM	Adults T2DM Ph3
Overall	7.1 [6.2-8] (5.8-9)	6.9 [6.4-7.6] (5.9-9)
Antibody titre		
0	7 [7-7] (7-7)	6.8 [6.4-7.4] (5.9-8.8)
25	6.6 [6-7] (5.9-7.4)	7 [6.4-7.6] (5.9-8.9)
125	7.3 [6.3-8] (5.8-9)	7 [6.4-7.6] (5.9-9)
625	7.3 [6.2-8.2] (6-9.4)	7.2 [6.6-7.8] (6.2-9)
Sex		
Female	7.2 [6.2-7.4] (5.9-8.9)	6.9 [6.4-7.5] (6-8.8)
Male	7.1 [6.3-8] (5.8-9.4)	7 [6.5-7.7] (5.9-9.1)
Metformin		
No	6.7 [5.9-7.7] (5.8-9)	6.5 [6.2-6.8] (5.8-8.3)
Yes	7.1 [6.3-8] (5.9-9.1)	7 [6.5-7.6] (5.9-9)
Sulfonamides		
No	7 [6.2-7.9] (5.8-9)	6.9 [6.4-7.6] (5.9-8.9)
Yes	8.4 [8.2-8.5] (8.1-8.6)	7 [6.5-7.9] (6-9.2)
Thiazolidinediones		
No	7.2 [6.2-8] (5.8-9)	6.9 [6.5-7.6] (5.9-8.9)
Yes	7 [7-7] (7-7)	6.6 [6.3-7.4] (6-9)
Race		
Caucasian	7.2 [6.2-7.5] (5.8-9.4)	6.9 [6.4-7.6] (6-8.9)
Black/African American	8 [7.2-8.3] (6.5-8.9)	7.2 [6.5-7.9] (5.9-9.3)
Asian	7.9 [7.9-7.9] (7.9-7.9)	7.2 [6.3-7.6] (5.9-8.4)
Native American	6.1 [6.1-7] (5.9-7)	6.6 [5.4-6.9] (5.4-7)
Other	7 [6.1-8] (5.9-8.1)	6.6 [6.5-7.4] (6.4-8.2)
Hispanic		7 [6.5-7.4] (6.3-9.2)
Hawaiian/Pacific Islander		6.5 [6.5-6.5] (6.5-6.5)

Values are median [interquartile range] (5th-95th percentile).
HbA1c, glycated haemoglobin; Ph3, phase 3; T2DM, type 2 diabetes mellitus.

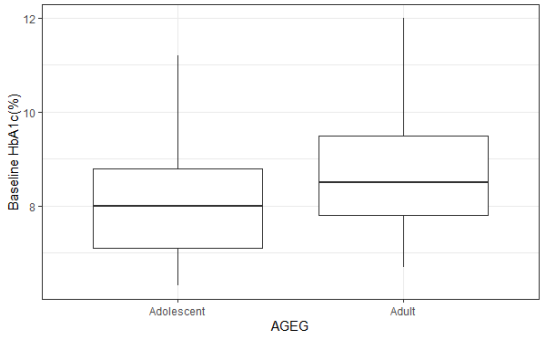
Source: Population PK and ER Report, Page 40, Table 10.

Reviewer's Comments:

The exposure-response analysis by the sponsor was checked by the reviewer. The exposure-response model was limited to exenatide concentration data with ADA titer ≤ 625, as samples with ADA titer > 625 were not available from population PK analysis. It was noticed that the baseline HbA1c for adolescents involved in the analysis is slightly lower than adults (Figure 10). Although the predicted HbA1c in adolescents was comparable to data from adults with T2DM, HbA1c change from baseline is lower in adolescents than adults (Figure 11). This might be explained by higher ratio of antibody titer (≥125) in adolescent than adult.

For patients with PK sample BLOQ or with ADA titer > 625, a trend of an attenuated HbA1c response was observed (Figure 12 and Figure 13).

Figure 10. Baseline HbA1c for subjects in the model Stratified by Population.



Source: Reviewer's analysis

Figure 11. Observed and Predicted HbA1c, HbA1c change from baseline at Steady State Stratified by Population.

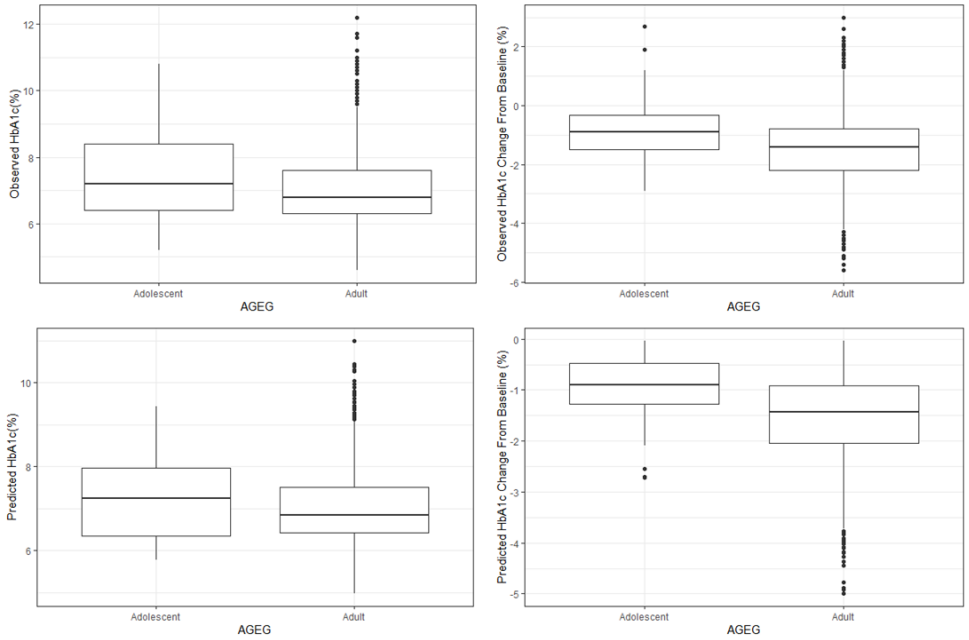
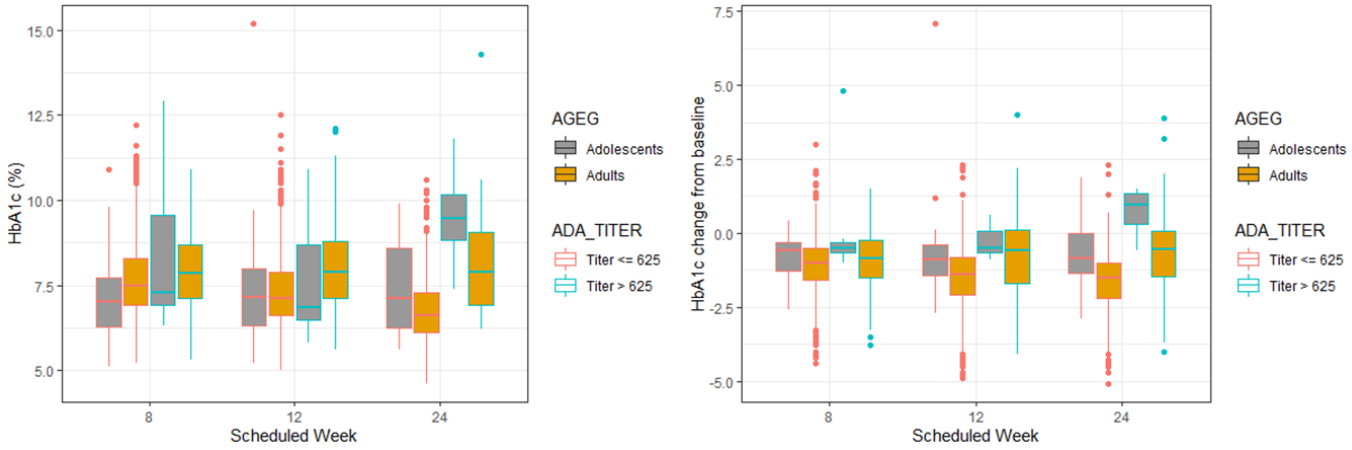
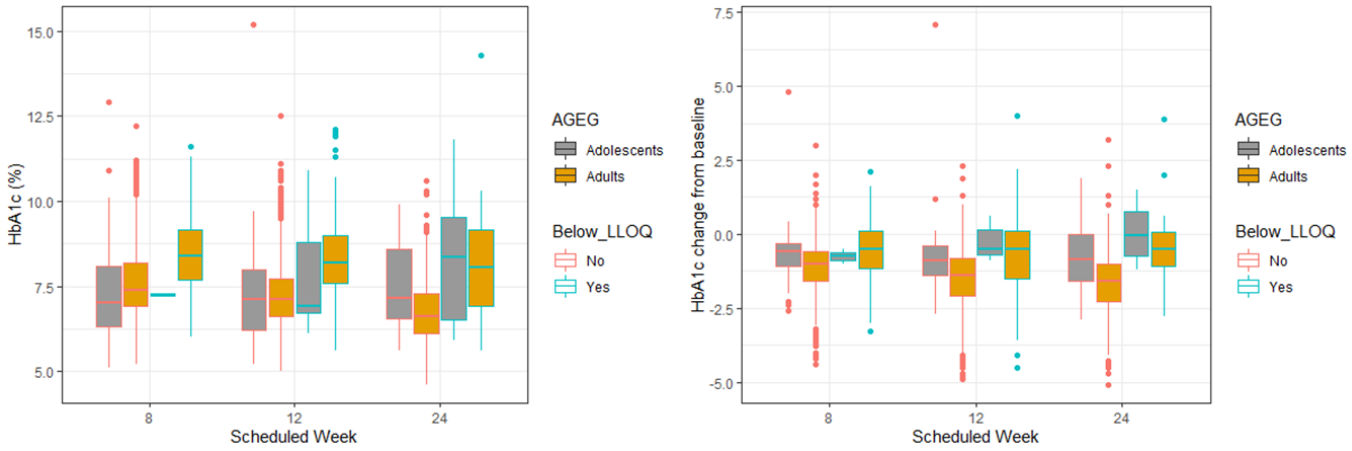


Figure 12. Observed HbA1c, HbA1c change from baseline at Steady State Stratified by Population and antibody titer.



Source: Reviewer's analysis

Figure 13. Observed HbA1c, HbA1c change from baseline at Steady State Stratified by Population and exenatide concentration below LLOQ.



Source: Reviewer's analysis

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