CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209210Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	209-210 Serials 0000; 0018
Submission Dates	December 21, 2016; August 8, 2017
Brand Name	To-be-determined
Generic Name	Exenatide
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
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OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	AstraZeneca Pharmaceuticals LP
Formulation; Strength	Extended-release injectable suspension; 2 mg/0.85mL
Submission Type	Standard 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

The sponsor submitted NDA 209-210 through the 505(b)(1) regulatory pathway to seek approval for the exenatide once-weekly suspension (EQWS) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

EQWS is a subcutaneously injected extended-release non-aqueous suspension that was developed as an extension to the currently marketed BYETTA (NDA 21-919 approved on October 30, 2009) and BYDUREON (NDA 22-200 approved on January 27, 2012).

The sponsor submitted the following 3 clinical studies to support NDA 209-210:

- Phase 2: Study BCB110 was a 2-cohort, single- and repeat-dose study to examine the pharmacokinetics (PK), tolerability, and safety of exenatide once weekly non-aqueous suspension in healthy volunteers and in patients with type 2 diabetes mellitus (T2DM)
- Phase 3: Study BCB118 was a randomized, open-label, long-term, parallel-group, comparator controlled, multicenter study to compare the glycemic effects, safety, and tolerability of exenatide once weekly non-aqueous suspension to exenatide twice daily in patients with T2DM
- Phase 3: Study BCB120 was a randomized, long-term, open-label, 3-arm, multicenter study to compare the glycemic effects, safety, and tolerability of exenatide once weekly non-aqueous suspension to sitagliptin and placebo in patients with T2DM

This document reviews the Clinical Pharmacology data for NDA 209-210 Serials 0000 and 0018. For simplicity, this review refers the following:

- EQWS for the to-be-marketed exenatide once-weekly non-aqueous suspension
- BYETTA for the approved and marketed exenatide immediate-release aqueous solution
- BYDUREON for the approved and marketed exenatide once-weekly aqueous suspension

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the clinical pharmacology data of NDA 209-210 Serials 0000 and 0018. OCP/DCP2 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

Following a single subcutaneous dose of 10 mg exenatide non-aqueous suspension, plasma exenatide concentrations increased slowly over time and peaked at about Weeks 6 to 7. No early-release exenatide peak was observable within the first 8 hours postdose. The highest geometric mean (SE) plasma exenatide concentration within the first 8 hours postdose was 34.9 (8.33) pg/mL compared with the corresponding value of 124.4 (15.41) pg/mL on Day 1 for a 10 mg dose of BYDUREON.

Plasma exenatide concentrations increased between Day 1 and Week 10 with once weekly 2 mg EQWS subcutaneous (SC) injection. From Weeks 10 thru 28, plasma exenatide concentrations remained stable, indicating steady state achievement. The geometric mean (SE) steady state average plasma exenatide concentration between Week 10 and Week 28 was 208 (8.99) pg/mL.

In another study, plasma exenatide concentrations were not assessed between Day 1 and Week 8 with once weekly 2 mg EQWS SC injection. From Week 8 thru 28, the plasma exenatide concentration remained stable, indicating that steady-state achievement. The geometric mean steady state average plasma exenatide concentration was 153 (9.75) pg/mL between Week 16 and Week 28.

The key results of sponsor's population PK and exposure-response analyses are the following:

- The eGFR, IBW, and antibody titer are main covariates that affect exenatide exposure.

- After accounting for differences in eGFR and IBW between studies, the average steady state plasma exenatide concentration from Study BCB120 was estimated to be 14% lower than that of Study BCB118.
- The efficacy of EQWS for primary endpoint of change from baseline in HbA1c was established with the 2 mg weekly SC administration in Studies BCB118 and BCB120 and pooled exposure-HbA1c response analysis supported these findings.

Patients with mild and moderate renal function receiving 2 mg EQWS weekly showed a 28% and 70% increase in exenatide exposure, respectively, than that with healthy renal function; but dose adjustment is unnecessary.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the formulation of the to-be-marketed EQWS?

Tables 1 and 2 detail the components and unit formula, respectively, of the to-be-marketed EQWS.

Table 1. Components for the EQWS

Component	Function	Standard
Exenatide microspheres		
Exenatide	Active pharmaceutical ingredient	AstraZeneca
5050[a] DL (b) (4) Polymer (poly(D,L-lactide-co-glycolide))	(b) (4)	AstraZeneca
Sucrose		NF
Vehicle		
Medium chain triglycerides		AstraZeneca
(b) (4)		NF[b]
		USP
		NF

[a] Represents ratio (b) (4)
[b] Commercially available (b) (4) which meets NF requirements
Source: Sponsor's O.1.1P QOS Table 1

Table 2. Unit formula for the EQWS

Component	% w/w (of microspheres)	Unit formula[a]	Nominal quantity per cartridge (mg)[b]	Nominal quantity per 0.85 mL dose delivered (mg)[a]
Exenatide microspheres containing:			(b) (4)	
Exenatide				2.0
Sucrose				0.8
5050 DL (b) (4) Polymer				37.2
Medium chain triglycerides (MCT)				774.4[c]

[a] Based on a nominal exenatide content of (b) (4) w/w in the exenatide microspheres
[b] The cartridge fill volume is (b) (4) mL, including an overfill to account for autoinjector priming and hold up requirements
[c] Drug product density is nominally (b) (4)
Source: Sponsor's O.1.1P QOS Table 2

2.1.2 What is the difference between EQWS and the approved BYDUREON formulation?
EQWS formulation contains the same active ingredient, exenatide that is contained in BYDUREON and BYETTA. EQWS contains the same exenatide load (b) (4) and extended-release microspheres as BYDUREON (an aqueous formulation), but with a non-aqueous medium-chain triglycerides (MCT) vehicle for use with an autoinjector.

2.1.3 What are the differences between the clinically-tested formulation of exenatide once-weekly non-aqueous suspension and the to-be-marketed formulation of EQWS?
For Study BCB110, the sponsor used the to-be-marketed representative microspheres and the Phase 3 and to-be-marketed MCT suspension vehicle, but the formulation differed from that used in the Phase 3 EQWS studies in terms of the (b) (4), and administration device (extemporaneous preparation; syringe and vial for Study BCB110). For Studies BCB118 and BCB120, the sponsor used the to-be-marketed representative microspheres, (b) (4) in MCT suspension, and administered via a to-be-marketed representative autoinjector device. The sponsor studied the to-be-marketed formulation of EQWS in Studies BCB118 and BCB120. Table 3 compares the formulation between Phase 2 and Phase 3 studies.

Table 3. Comparison of the formulation used in Studies BCB110, BCB118, and BCB120.

Formulation	Loading	Microsphere Concentration*	Injection Volume	Dose
Study BCB110, Cohort 1			(b) (4)	10 mg
Study BCB110, Cohort 2				2 mg
Studies BCB118 & BCB120				2 mg

*P.2.2 uses the term suspension concentration, whereas 2.7.1 uses the term microsphere concentration.
Source: Reviewer's compilation of P.2.2 Pages 5/27 & 12/27

For example, the injected exenatide dose is calculated as (b) (4) 2 mg.

2.2 Key Clinical Pharmacology Questions

Readers of this review may refer to the clinical pharmacology reviews of BYDUREON by Drs. Jayabharathi Vaidyanathan and Manoj Khurana (NDA 22-200) in DARRTS.

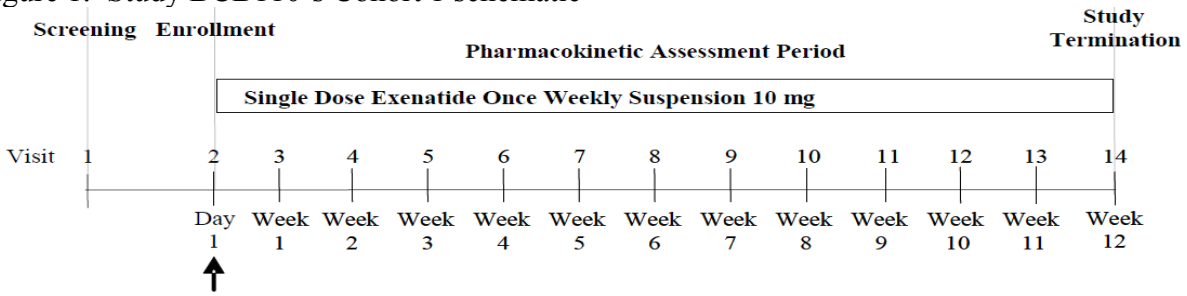
2.2.1 What are the design features of Studies BCB110, BCB118, and BCB120 for exenatide once-weekly non-aqueous suspension?

Study BCB110

This was a 2-cohort, single- and repeat-dose study conducted to assess the PK, tolerability, and safety of exenatide once-weekly non-aqueous suspension administered as a single dose and once weekly over a 12-week assessment period.

Cohort 1: Healthy participants (N=30) received a single SC dose of 10 mg exenatide once-weekly non-aqueous suspension, which was followed by a 12-week assessment period during which PK, tolerability, and safety were evaluated. Blood samples for plasma exenatide concentration measurement were drawn 15 minutes before single-dose EQWS administration and at 1, 1.5, 2, 3, 4, 6, and 8 hours following administration. A single sample was taken at subsequent visits on Weeks 1 to 12. Figure 1 shows the schematic of Study BCB110 Cohort 1.

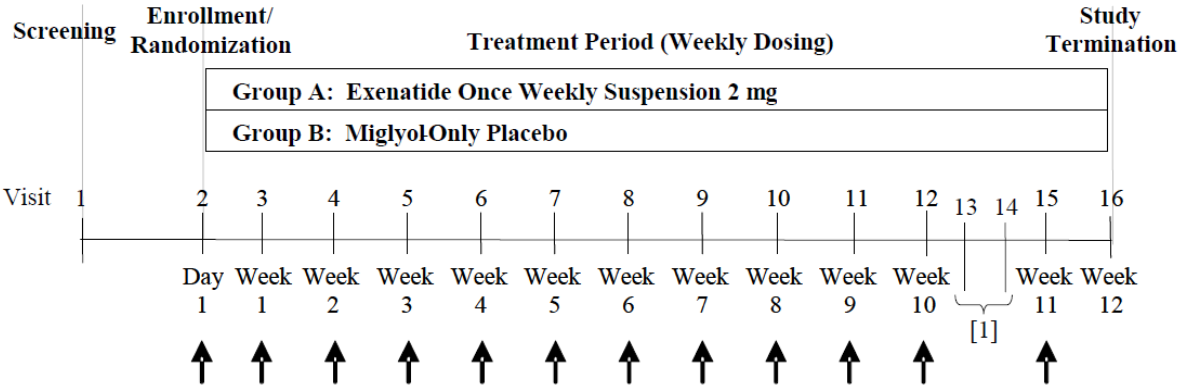
Figure 1. Study BCB110's Cohort 1 schematic



Note: Arrow indicates administration of single 10-mg dose of exenatide once weekly suspension.
Source: Modified from Study BCB110's report Figure 1

Cohort 2: Patients with T2DM were randomized to 2 mg exenatide once-weekly non-aqueous suspension (N=23) or MCT placebo (N=12) in a 2:1 ratio and administered weekly injections of study medication (exenatide once-weekly non-aqueous suspension or placebo) for 12 weeks, during which PK, pharmacodynamics (PD), efficacy, tolerability, and safety assessments were performed. Blood samples for plasma exenatide measurement were drawn at enrollment and at Weeks 2, 4, 6, 8, 10, and 12. At Week 10, samples were drawn 15 minutes before exenatide once-weekly non-aqueous suspension administration and at 1, 1.5, 2, 3, 4, and 6 hours following administration. Figure 2 shows the schematic of Study BCB110 Cohort 2.

Figure 2. Study BCB110's Cohort 2 schematic



Note: Arrows indicate administration of study medication.
Source: Modified from Study BCB110's report Figure 2

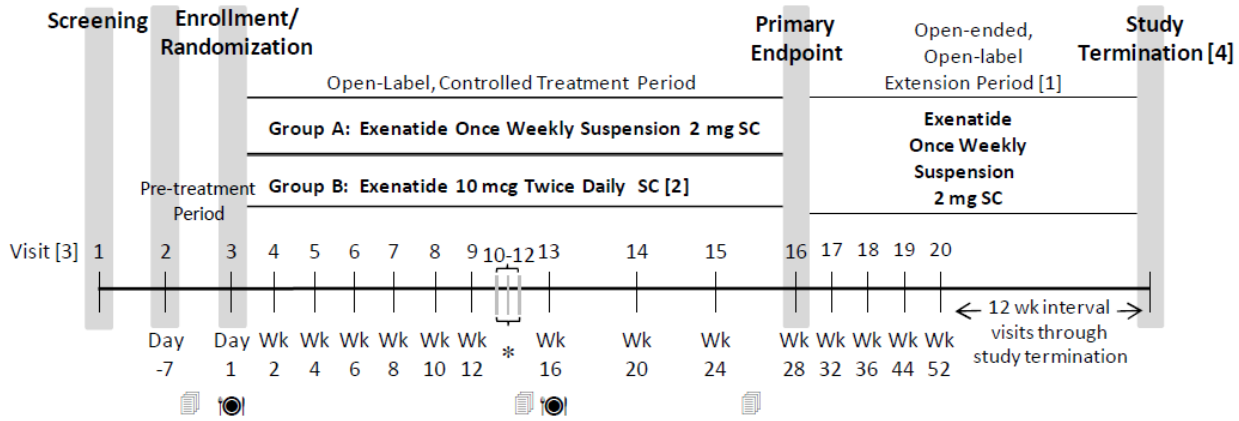
Study BCB118

This was a randomized, open-label, long-term, multicenter, comparator-controlled study. Patients with T2DM were randomly assigned in a ratio of 3:2 to treatment with 2 mg EQWS once weekly for 28 weeks (N=229) or 5 µg BYETTA twice daily for 4 weeks followed by 10 µg twice daily for the remaining 24 weeks of the controlled treatment period (N=146).

Randomization was stratified by diabetes management method at screening (diet/exercise alone, sulfonylurea use, or non-sulfonylurea use), screening glycosylated hemoglobin (HbA1c) stratum (<9% or ≥9%) and renal function (normal [estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2], mild renal impairment [eGFR 60 to 89 mL/min/1.73 m^2], or moderate renal impairment [eGFR 30 to 59 mL/min/1.73 m^2).

Ninety-nine patients were enrolled in a meal test cohort to participate in a standardized meal test and undergo postprandial glucose and PK assessments. Blood samples for plasma exenatide measurement were drawn at baseline and at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28. Following the 28-week primary assessment period, patients entered an extension period during which all patients received 2 mg EQWS from Week 29 through Week 52. Figure 3 shows the schematic of Study BCB118.

Figure 3. Study BCB118's schematic



6 point self-monitored blood glucose profiles performed on any three days in week prior to subsequent visit.

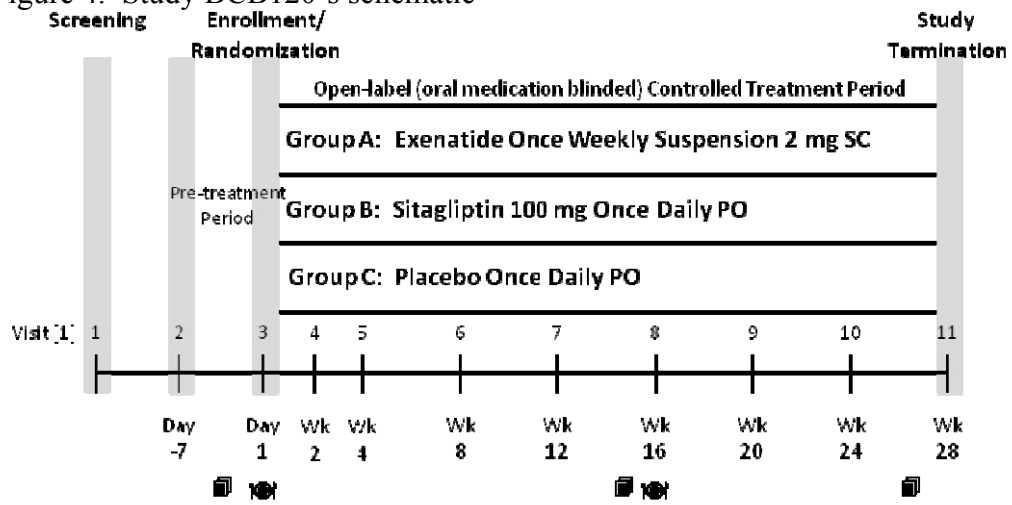
Indicates meal test and postprandial assessments for a subset of subjects at select sites.

Source: Modified from Study BCB118's report Figure 3.1-1

Study BCB120

This was a randomized, open-label (oral agents blinded), long-term, multicenter, comparator- and placebo-controlled study designed to compare the efficacy, safety, and tolerability of EQWS with that of sitagliptin and placebo, and to characterize the PK of EQWS over 28 weeks. Patients with T2DM and inadequate glycemic control while taking ≥1500 mg metformin daily were randomly assigned to treatment with 2 mg EQWS once weekly (N=181), 100 mg sitagliptin once daily (N=122), or oral placebo once daily (N=61) in a ratio of 3:2:1, with randomization stratified by screening HbA1c (<9% or ≥9%). A subset of patients in each treatment group at select study sites were enrolled in a meal test cohort and participated in a standardized meal test. Blood samples for plasma exenatide measurement were drawn at baseline and at Weeks 8, 16, and 28, and at 10 weeks after the final visit. Figure 4 shows the schematic of Study BCB120.

Figure 4. Study BCB120's schematic



6 point self-monitored blood glucose profiles performed on any three days in the week prior to subsequent visit.

Indicates meal test and postprandial assessments for a subset of subjects at select sites.

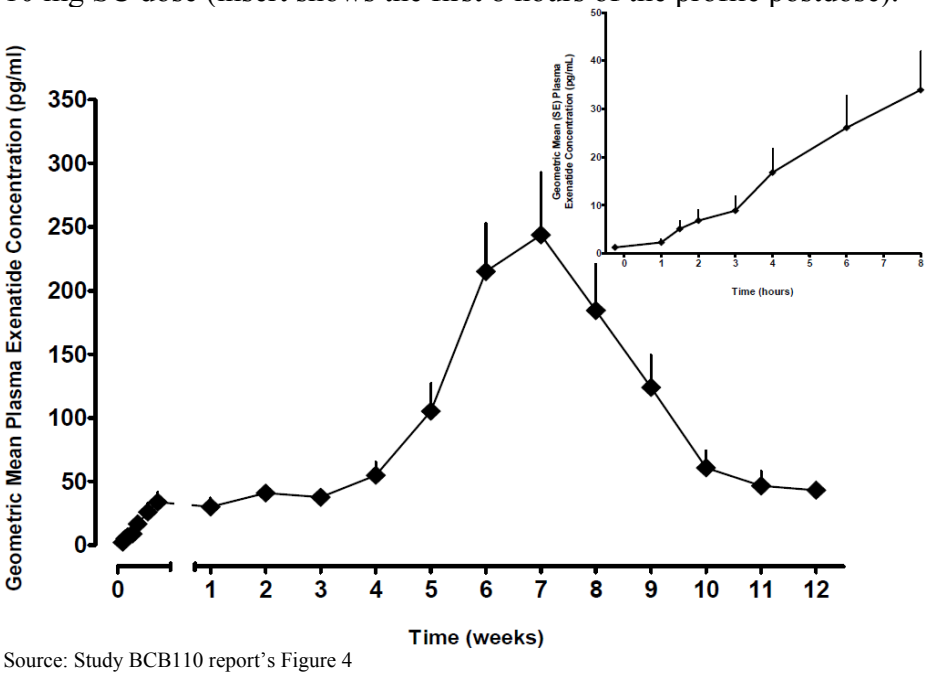
Source: Modified from Study BCB120's report Figure 3.1-1

2.2.2 What are the PK characteristics of exenatide once-weekly non-aqueous suspension in Studies BCB110, BCB118, and BCB120?

Study BCB 110 Cohort 1

Exenatide PK was dose proportional for BYDUREON up to 10 mg. Accordingly, the sponsor chose to study 10 mg exenatide once-weekly non-aqueous suspension to ensure that the plasma exenatide concentrations were high enough to be measured after a single SC dose. Figure 5 shows the geometric mean plasma exenatide concentration versus time profile of the single 10 mg SC dose of exenatide once-weekly non-aqueous suspension. Plasma exenatide concentrations increased slowly over time upon injection and peaked at about Weeks 6 to 7. No early-release exenatide peak was observable within the first eight hours postdose. The highest geometric mean (SE) plasma exenatide concentration within the first 8 hours postdose was 34.9 (8.33) pg/mL compared with the corresponding value of 124.4 (15.41) pg/mL on Day 1 for a 10 mg dose of BYDUREON.

Figure 5. Plasma exenatide concentration versus time profile for Study BCB110 Cohort 1 after a single 10 mg SC dose (insert shows the first 8 hours of the profile postdose).

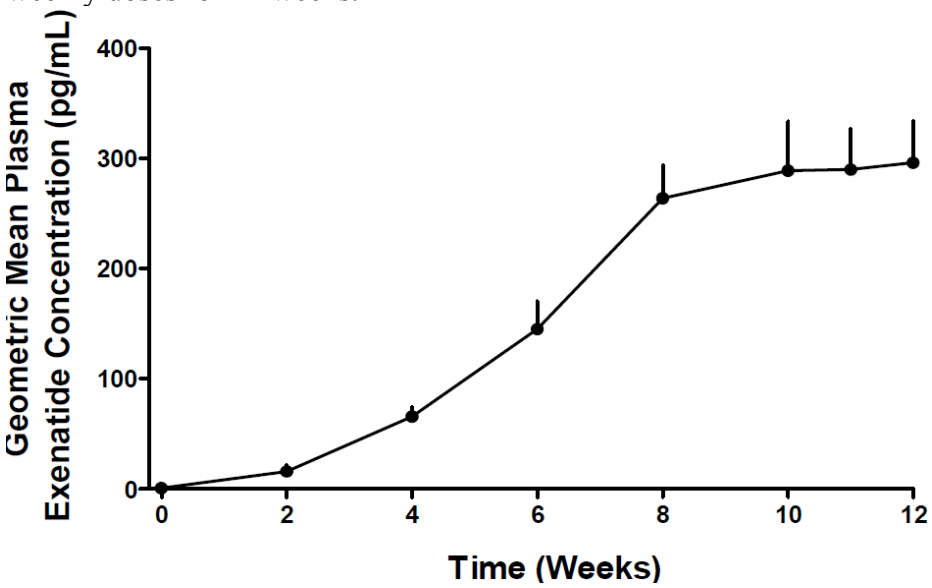


Source: Study BCB110 report's Figure 4

Study BCB 110 Cohort 2

Figure 6 shows the geometric mean plasma exenatide concentration versus time profile of the multiple 2 mg dose once weekly for the exenatide once-weekly non-aqueous suspension. Plasma exenatide concentrations increased over time upon multiple dosing and peaked at about Week 10 and achieved a geometric mean concentration of 310.0 (49.80) pg/mL.

Figure 6. Plasma exenatide concentration versus time profile for Study BCB110 Cohort 2 after 2 mg weekly doses for 12 weeks.

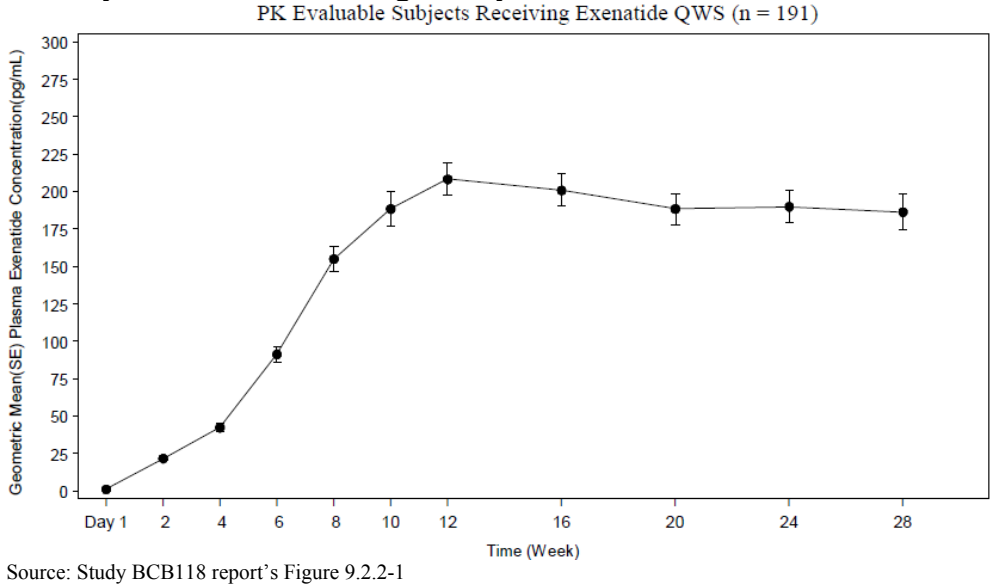


Source: Study BCB110 report's Figure 5

Study BCB 118

Plasma exenatide concentrations increased between Day 1 and Week 10 with once weekly 2 mg EQWS SC injection. From Weeks 10 thru 28, plasma exenatide concentrations remained stable, indicating steady state achievement. The geometric mean (SE) steady state average plasma exenatide concentration between Weeks 10 and 28 was 208 (8.99) pg/mL. Figure 7 shows the geometric mean plasma exenatide concentration versus time profile for Study BCB118 for samples with antibody titers ≤ 625.

Figure 7. Plasma exenatide concentration versus time profile for Study BCB118 for samples with antibody titers ≤ 625 after 2 mg weekly SC doses for 28 weeks.

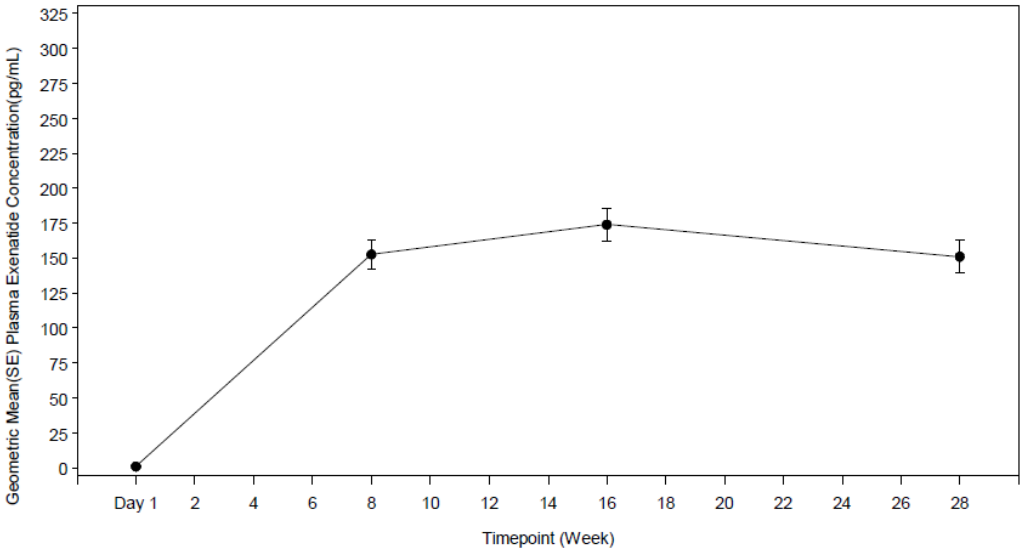


Source: Study BCB118 report's Figure 9.2.2-1

Study BCB 120

Plasma exenatide concentrations were not assessed between Day 1 and Week 8 with once weekly 2 mg EQWS SC injection. From Week 8 thru the remainder of Study BCB120, the plasma exenatide concentration remained stable, indicating that steady-state achievement (Figure 8). The geometric mean steady state average plasma exenatide concentration was 153 (9.75) pg/mL between Week 16 and Week 28.

Figure 8. Plasma exenatide concentration versus time profile for Study BCB120 for samples with antibody titers ≤ 625. Population: PK Evaluable Subjects (N = 134)



Source: Study BCB120 report's Figure 9.2.2-1

This reviewer noticed a relatively lower average steady state plasma exenatide concentration for Study BCB120 when compared to Study BCB118. The sponsor conducted a population PK analysis thru a model developed with BYDUREON clinical studies data and pooled data from exenatide once-weekly non-aqueous suspension studies. During the population PK model development, the sponsor estimated different parameters for the relative bioavailability of Studies BCB118 and BCB120. Table 4 lists the parameter estimates of the final EQWS exenatide population PK model. See Appendix 4.1 for the details of the population PK analysis. Briefly, the key results are the following:

- eGFR, IBW, and antibody titer are main covariates that affect exenatide exposure
- After accounting for differences in eGFR and IBW between studies, the average steady state plasma exenatide concentration from Study BCB120 was estimated to be 14% lower than that of Study BCB118.

Table 4. Parameter estimates of the final EQWS exenatide population PK model

Parameter	Description	Mean	%RSE
θ1	Mean $C_{ss,av}$ for 0.8 mg dose	87.8	8.6
θ2	Mean $C_{ss,av}$ for 2 mg dose	148	6.8
θ3	eGFR effect on $C_{ss,av}$ as a power model : $(EGFR/81.6)^{\theta 3}$	-0.83	10.0
θ4	Manufacture scale (b) (4) as an additive (Shift) effect on $C_{ss,av}$	106.0	21.0
θ5	IBW effect on $C_{ss,av}$ as an additive (shift) model θ4*(IBW-64.1)	-1.74	17.1
θ6	High antibody as an additive (Shift) effect on Css,ave	42.4	15.7
θ7	EQWS as a proportional effect on $C_{ss,av}$ for Study BCB110	1.22	9.0
θ8	EQWS as a proportional effect on $C_{ss,av}$ for Study BCB118 & BCB120	0.70	4.1
ω^2	Variance of between subject variability for $C_{ss,av}$	0.218	8.1
σ^2	Variance of residual error for (b) (4) assay	0.199	8.3
σ^2	Variance of residual error for (b) (4) assay	0.247	7.0
σ^2	Variance of residual error for (b) (4) assay	0.0849	21.0

Source: Sponsor's Population Pharmacokinetic Report Table 2

The Division of Metabolism and Endocrinology sent an information request letter to the sponsor seeking explanation for the observed differences between Studies BCB118 and BCB120. The sponsor responded on August 8, 2017 explaining the likely reasons for the observed differences. The mean patient characteristics in Studies BCB118 and BCB120 appear similar. The distributions of some demographics between Study BCB118 and Study BCB120 differ and may partly explain the difference in average steady state plasma exenatide concentration. However, these covariates (demographics) were accounted for in the final model and did not fully explain the differences. These demographics are the following:

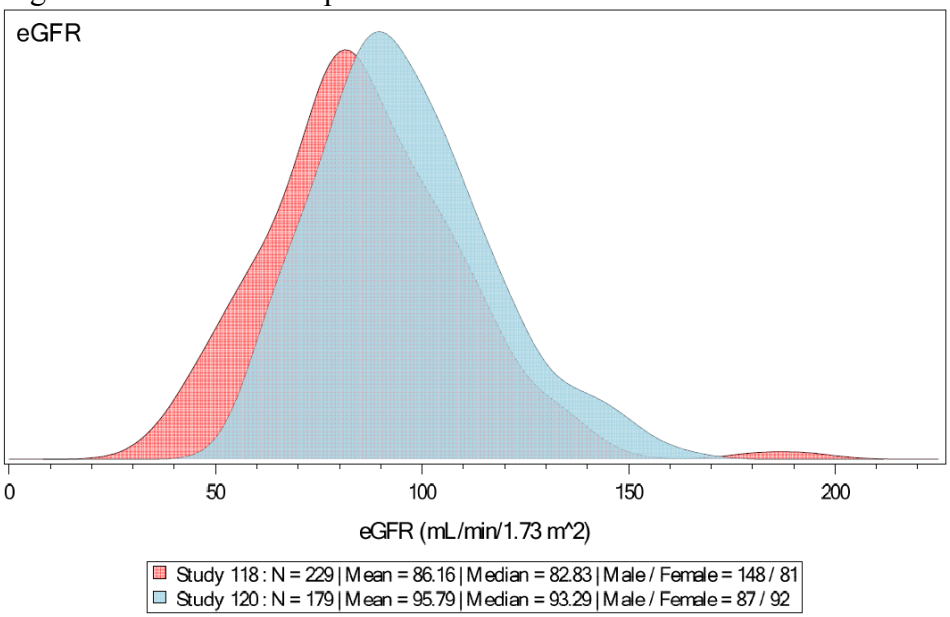
- estimated glomerular filtration rate (eGFR)
- ideal body weight (IBW)
- age
- body weight

In Study BCB118, patients with mild and moderate renal function showed a 28% and 70% increase in exenatide exposure than that with healthy renal function. However, EQWS dose adjustment is not necessary for patients with moderate and mild renal impairment because patients with moderate and mild renal impairment receiving 2 mg BYDUREON showed a 62% and 33% increase in exenatide exposure without dose adjustment (BYDUREON label recommendation).

Figures 9 – 12 show the distribution of eGFR, IBW, age, and body weight of the patients, respectively, of Studies BCB118 and BCB120.

Figure 9 shows that patients in Study BCB120 had higher renal function, namely eGFR than those of Study BCB118.

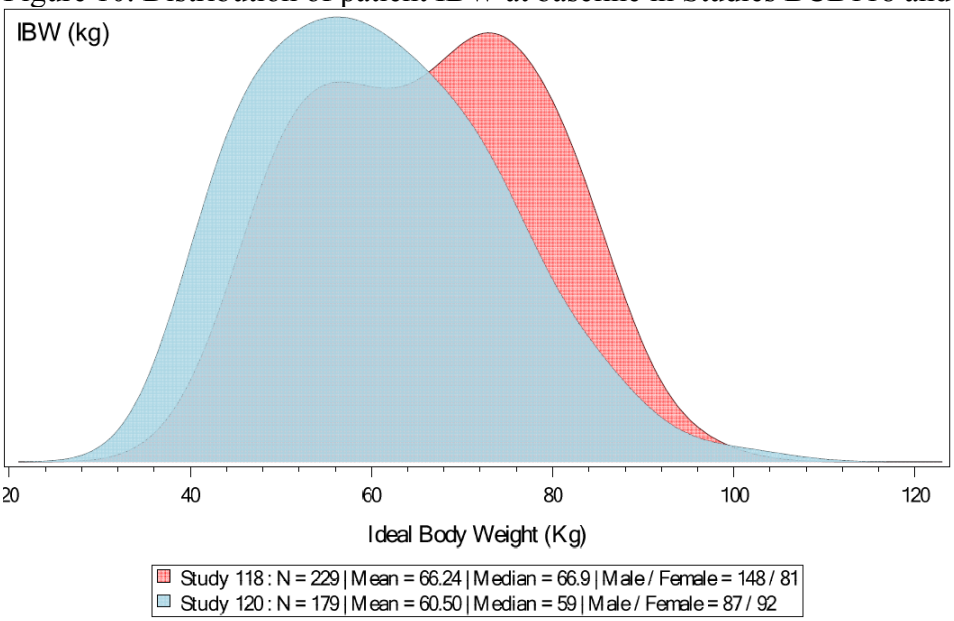
Figure 9. Distribution of patient eGFR at baseline in Studies BCB118 and BCB120.



Source: Modified from NDA 209-210 Serial 0018 Figure 1

Figure 10 shows that patients in Study BCB120 had lower IBW than those of Study BCB118.

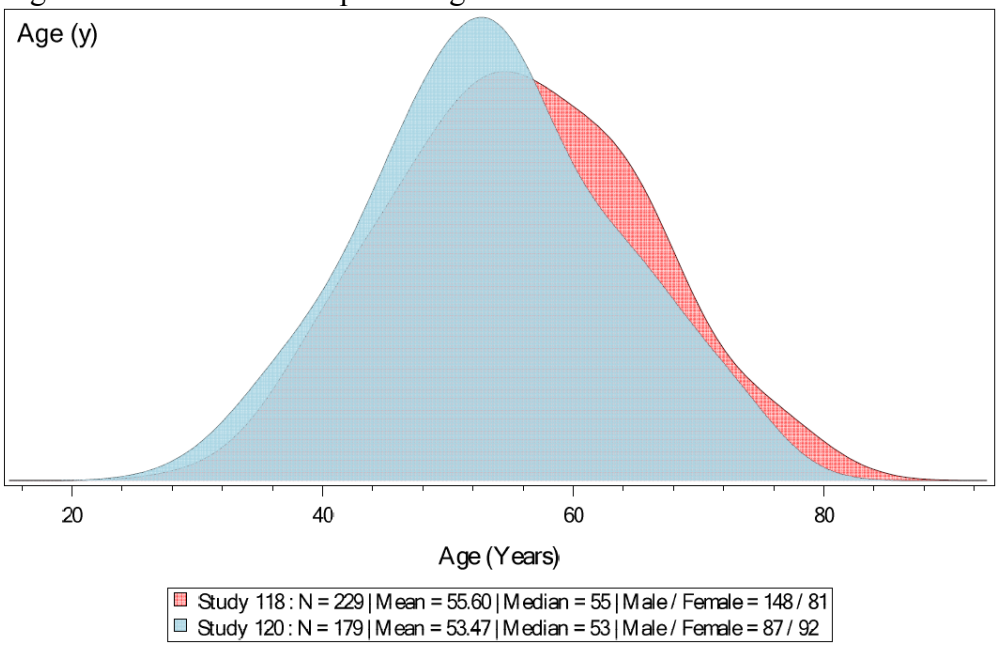
Figure 10. Distribution of patient IBW at baseline in Studies BCB118 and BCB120.



Source: Modified from NDA 209-210 Serial 0018 Figure 2

Figure 11 shows that the age distribution of patients in Study BCB118 and Study BCB120 is similar.

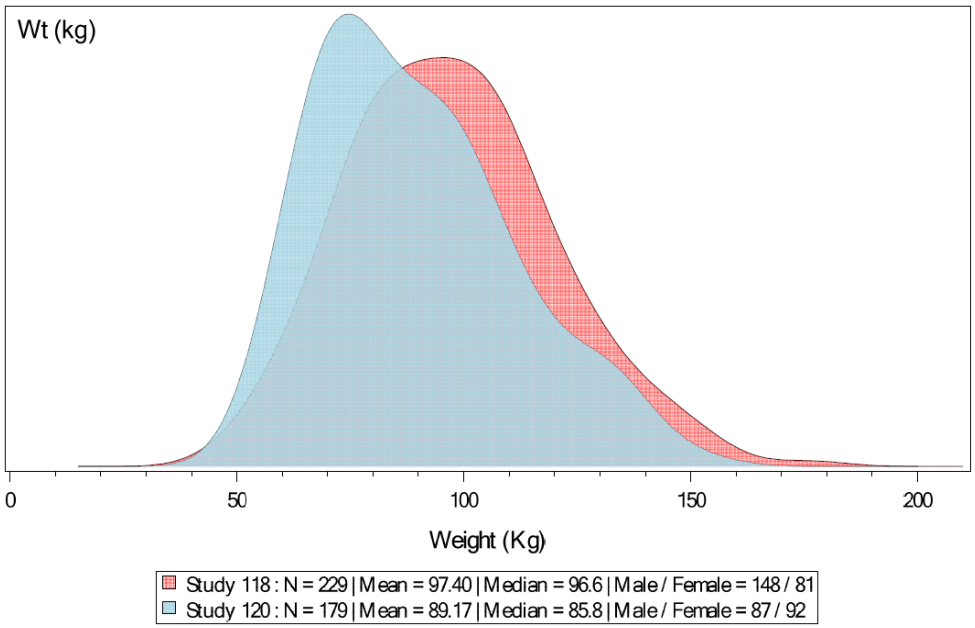
Figure 11. Distribution of patient age at baseline in Studies BCB118 and BCB120.



Source: Modified from NDA 209-210 Serial 0018 Figure 3

Figure 12 shows that the body weight distribution of patients in Study BCB118 and Study BCB120 is consistent with that of the IBW.

Figure 12. Distribution of patient body weight at baseline in Studies BCB118 and BCB120.



Source: Modified from NDA 209-210 Serial 0018 Figure 4

Exenatide is predominantly eliminated by glomerular filtration. Thus, higher eGFR will lead to higher clearance of exenatide and subsequently lower average steady state plasma exenatide concentration for Study BCB120 than that of Study BCB118. Lower IBW of patients in Study BCB120 may lead to higher average steady state plasma exenatide concentration in Study BCB120 than that of Study BCB118 because of decreased volume of distribution. However, the effect of eGFR on average steady state plasma

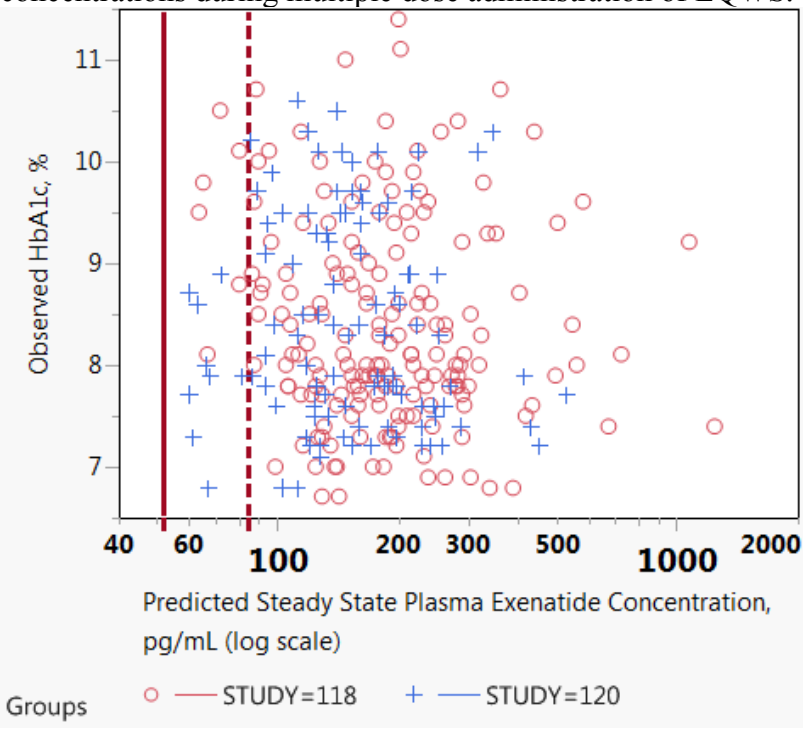
exenatide concentration seems to be larger than that of the effect of IBW partly explaining in the net lower average steady state plasma exenatide concentration of Study BCB120 than Study BCB118.

2.2.3 What is the clinical relevance for the difference in average steady state plasma exenatide concentration between Study BCB118 and Study BCB120?

The efficacy of EQWS for primary endpoint of change from baseline in HbA1c was established with the 2 mg weekly SC administration in Studies BCB118 and BCB120 (see Statistical and Clinical Reviews by Drs. Yoonhee Kim and Mahtab Niyyati, respectively, for further details). The sponsor performed population exposure-response analysis for EQWS, which serves as the supportive evidence of efficacy and rules out any clinical relevance in the observed exenatide exposure differences from Studies BCB118 and BCB120 on HbA1c reduction.

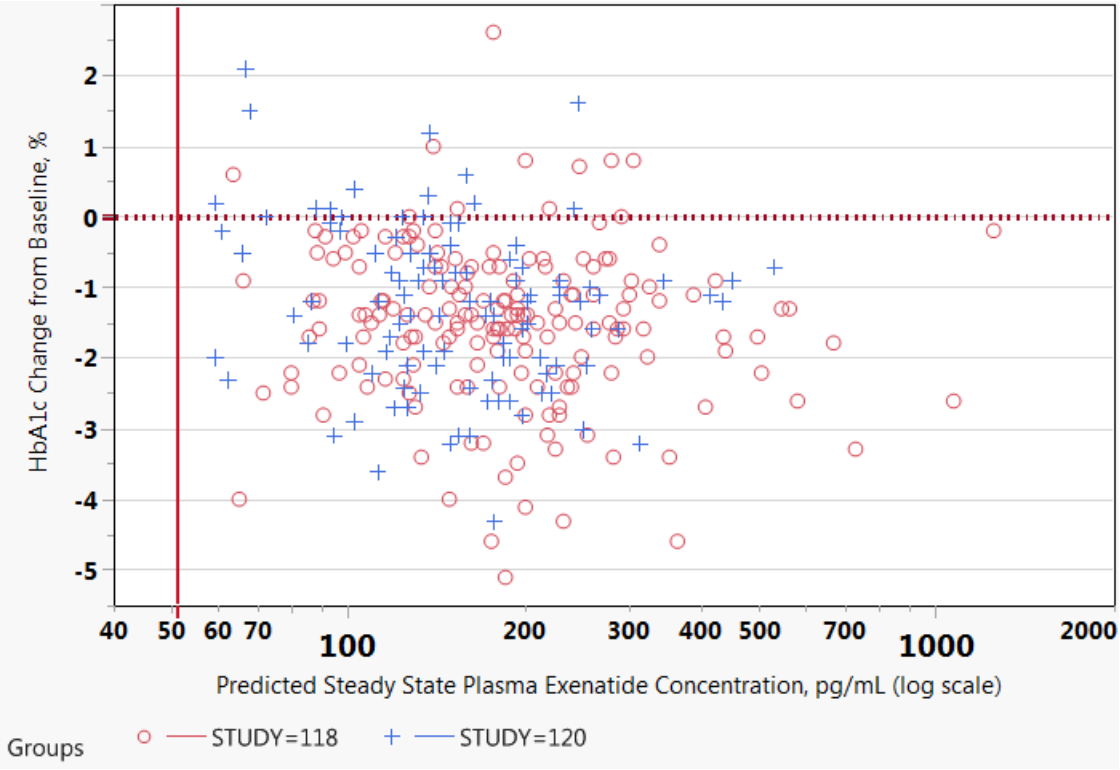
The estimated exenatide EC_{50} is 51.4 pg/mL when exenatide antibody titers are < 125 and 84 pg/mL when exenatide antibody titers are ≥ 125. These exenatide EC_{50} estimates are consistent with the exenatide EC_{50} estimate, 83.5 pg/mL, from the Clinical Pharmacology review of BYDUREON (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf). Figures 13 and 14 show the graph of observed HbA1c versus the predicted average steady-state plasma exenatide concentrations from the population PK modeling and the percent change of HbA1c from baseline versus the predicted average steady-state plasma exenatide concentrations from the population PK modeling, rrespectively. These graphs show that exenatide exposure-response relationship from Study 118 is similar to that observed from Study 120. The geometric mean of the the average steady-state plasma exenatide concentration of Study 120 is 153 pg/mL and is abot 3 times or 2 times higher than the exenatide EC_{50} for titers < 125 and ≥ 125, respectively. Thus, the difference in average steady state plasma exenatide concentration between Study BCB118 and Study BCB120 may not be clinically relevant.

Figure 13. Plot of observed HbA1c versus individual average steady-state plasma exenatide concentrations during multiple dose administration of EQWS.



Source: Reviewer's analysis

Figure 14. Plot of observed HbA1c change from baseline versus individual average steady-state plasma exenatide concentrations during multiple dose administration of EQWS.



Source: Reviewer's analysis

2.3 Bioanalytical

2.3.1 Are the bioanalytical methods properly validated to measure exenatide?

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.

The capture antibody was specific for exenatide, because it recognized a C-terminal epitope of exenatide and did not cross-react with GLP-1(7-36) or glucagon. The detection antibody recognized an N-terminal epitope on exenatide, GLP-1(7-36), and glucagon. The assay was specific for exenatide because of the selectivity of the capture antibody. Since binding of both antibodies was necessary to generate a signal, cross-reactivity with other peptides or metabolites was minimized. The assay determined exenatide plasma concentration according to the exenatide standard curve (a set of exenatide standards prepared in negative control human plasma). To ensure longitudinal performance of the assay, each new lot of exenatide plasma standards was calibrated against exenatide "gold standards," which was a set of exenatide standards prepared in buffer (see REST100200 and the document entitled "Re-Establishment of Consistent Exenatide Immunoassay Recalibration"). Table 5 details the bioanalytical validation of exenatide.

Table 5. Validation of the exenatide bioanalytical method.

Matrix:	Human K_2EDTA Plasma
Analyte:	Exenatide synonymous with AC2993,
Method of Detection:	ELISA
Analytical Systems Software:	SoftMax® Pro GxP v5.0.1 (Molecular Devices)
LIMS and Regression Software:	Watson Bioanalytical LIMS™ v7.3 (Thermo
Additional Data Analysis and Calculations:	Microsoft® Office Excel 2003
Regression Analysis:	Five Parameter Curve Fit with weighting $1/Y^2$
Validation Samples:	20.0 (VS1), 40.0 (VS2), 50.0 (VS3), 175 (VS4), 375 (VS5), 500 (VS6) and 10,000
Intra-Assay Accuracy (% Bias):	-20.4% to 21.8%
Intra-Assay Precision (% CV):	1.1% to 20.4%
Inter-Assay Accuracy (% Bias):	-5.3% to 14.3%
Inter-Assay Precision (% CV):	3.1% to 15.0%
Quality Control Samples (All Runs):	50.0 (LQC), 175 (MQC), 375 (HQC) pg/mL
Intra-Assay Accuracy (% Bias):	-13.6% to 21.2%
Intra-Assay Precision (% CV):	0.0% to 14.6%
Inter-Assay Accuracy (% Bias):	-0.3% to 11.7%
Inter-Assay Precision (% CV):	5.9% to 9.5%
LLOQ:	The LLOQ based on the Accuracy and Precision data is 20.0 pg/mL
ULOQ:	The ULOQ based on the Accuracy and Precision data is 500 pg/mL
Dilutional Linearity Test:	400,000 pg/mL was linear to 1:8,000 diluted in Human K_2EDTA Plasma
Accuracy (% AR):	106.8 % to 111.6%
Precision (% CV):	0.6% to 1.8%
Matrix Effect (Selectivity):	7 male and 7 female human plasma individuals
Unspiked Plasma Samples:	All samples (100%) were found to be BLOQ
Spiked Plasma Samples:	13 of the 14 individuals (93.0%) were within acceptable %AR limits
Accuracy (% AR):	78.0% to 117.6%
Precision (% CV):	0.3% to 7.0%
Freeze/Thaw Stability:	8 Cycles
Storage Stability in Matrix:	Up to 23 hours and 29 minutes at 5°C and Ambient Temperature
Short-term (ambient temperature and refrigerated)	Stable up to 23.5 hours
Long-term (frozen, -70 ± 10°C)	Stable for at least 1338 days
Long-term gold standard stock (frozen, -70 ± 10°C)	Stable for 1449 days

Source: Modified from Report REST100118R1 Page 11 of 155 and Summary of Biopharmaceutics, 2.7.1 Table 4.

The bioanalytical assay for measuring exenatide in plasma samples is acceptable with reasonable accuracy and precision.

3 Preliminary Labeling Recommendations

Fasting and Postprandial Glucose

(b) (4)

Comment [JL1]: Internal Comment: For this section, we may need to discuss with Stat to see if the reported changes are OK.

(b) (4)

In a (b) (4) study of BYDUREON BCISE (b) (4), 2-hour postprandial glucose levels were measured at Week 16, during a mixed meal tolerance test, in a subset of patients with type 2 diabetes mellitus.[49] The (b) (4) mean change from baseline was −78 mg/dL (b) (4) (b) (4)

Comment [JL3]: Internal Comment: Sponsor used "summary-clin-efficacy-type2-diabetes.pdf" Page 58/100; cannot find these # in Study BCB118's report.

Cardiac Electrophysiology

Absorption

Following a single subcutaneous dose of (b) (4) exenatide non-aqueous suspension there is an initial period of release of surface-bound exenatide followed by a gradual release of exenatide from the microspheres, which results in a peak of (b) (4) plasma exenatide concentration at around ~~w~~Week 6 to Week 7 representing the hydration and erosion of the microspheres.[51]

Comment [JL4]: FDA Comment: Study BCB110 Cohort 1 used an earlier formulation and is not BYDUREON BCISE.

Following initiation of once every 7 days (weekly) administration of 2 mg BYDUREON BCISE in another study, gradual increase in the plasma exenatide concentration is observed up to (b) (4) Week 10.[52] From (b) (4) Week 10 mean plasma exenatide concentrations of approximately 208 pg/mL were maintained over once every 7 days (weekly) dosing intervals to Week 28 indicating that steady state was achieved.[53]

Comment [JL5]: FDA Comment: This is BCB110 Cohort 2's result and not BYDUREON BCISE, which is the to-be-marketed formulation.

Comment [JL6]: FDA Comment: This is Study BCB118's result, which used the to-be-marketedBYDUREONBCISE.

(b) (4)

Appendix 4.1

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following 2 key questions:

- **Why is the average steady state plasma exenatide concentration different between Study BCB118 and Study BCB120?**
- **What is the clinical relevance for the difference in average steady state plasma exenatide concentration between Study BCB118 and Study BCB120?**

The sponsor used the population PK model developed for the BYDUREON submission and updated the model with data from the 3 clinical studies (BCB110, BCB118, and BCB120) with the exenatide once-weekly non-aqueous suspension. The exenatide population PK model and population exposure-response model were thoroughly reviewed by Dr. Manoj Khurana for the BYDUREON submission and the parameter estimates for the exenatide once-weekly non-aqueous suspension (EQWS) are reasonable. Thus, the Clinical Pharmacology Review Team decided to accept the sponsor's population PK and population exposure-response analyses.

EXECUTIVE SUMMARY

Exenatide once weekly suspension (EQWS) in an autoinjector device was developed as a formulation and delivery device change of BYDUREON in which the exenatide-containing microspheres are combined with a non-aqueous medium chain triglyceride diluent o provide a premixed product that is ready to use device following simple agitation of the suspension. EQWS contains a 2 mg dose of exenatide for subcutaneous injection.

The purpose of the present analysis was to update the previously developed population pharmacokinetic (PPK) and exposure-response models for BYDUREON and EQWS with additional data from the Phase 3 studies of EQWS BCB118 and BCB120.

The objectives of these analyses are as follows:

- to update the previously developed PPK model that describes the average steady-state plasma exenatide concentration ($C_{ss,av}$) with phase 3 data for 2 mg EQWS;
- to update the previously developed exposure-response model that describes the relationship between exenatide $C_{ss,av}$ and hemoglobin A1c (HbA1c) with phase 3 data for 2 mg EQWS;
- to evaluate the effect of antibodies to exenatide, subject and organ function descriptors on model-predicted exenatide $C_{ss,av}$ and HbA1c after EQWS treatment.

The data for modeling comprised steady-state exenatide plasma concentrations and HbA1c in 6 studies of BYDUREON and 3 studies of EQWS. For pharmacokinetic modeling there were a total of 4396

steady-state exenatide plasma concentration values from 806 subjects, while there were 1879 concentrations from 383 subjects treated with EQWS. For exposure- response modeling there were a total of 2257 steady-state exenatide plasma concentration and HbA1c value pairs from 654 subjects, while there were 1409 pairs from 353 subjects treated with EQWS. The relationships between exenatide dose and steady-state plasma exenatide centration, and between plasma exenatide concentration and HbA1c, were described with nonlinear mixed-effects regression model accounting for within- and between-subject variability. The models were estimated using nonlinear mixed-effects modeling software, the nonlinear mixed effects software.

The PPK and exposure-response models adequately described data from the Phase 3 EQWS studies BCB118 and BCB120. Exclusion of exenatide plasma concentration samples corresponding to high titers to exenatide antibodies did not meaningfully affect estimates of parameters of the PPK model.

Neither lower estimated mean Css,av of exenatide after administration of EQWS than BYDUREON nor effects on exenatide plasma concentration of patient's parameters body weight, estimated glomerular filtration rate (eGFR) and antibody titer, were predicted to meaningfully impact HbA1c lowering. Modeling results support the conclusion that no dose adjustment is needed for EQWS based on either age, race, gender, ideal body weight, renal function or titer of anti-exenatide antibodies.

Conclusions:

- The updated PPK model of EQWS adequately described steady-state average exenatide plasma concentration data from the Phase 3 EQWS studies BCB118 and BCB120.
- The updated population exposure-response model of EQWS adequately described exenatide plasma concentration – HbA1c data from the Phase 3 EQWS studies BCB118 and BCB120.
- At steady state, the predicted difference in efficacy between EQWS and BYDUREON due to the difference in exposure in the typical patient (eGFR=75.2 ml/min/1.73m^2, ideal body weight=64 kg, ADA titer <125) is ≤0.12%.

2.2.1 Population pharmacokinetic modeling

The final PPK model for BYDUREON and EQWS (Amylin Modeling Report 2011) re-estimated after adding phase 3 EQWS data in the present report is shown below.

$$C_{ss,\,ave_{ij}} = \left(\begin{array}{l} (\theta_1 + \theta_2 \cdot \text{Dose}_i) \cdot \left(\dfrac{\text{baseline eGFR}_i}{81.6} \right)^{\theta_3} + \\ \theta_4 \cdot \text{Scale}_i + \\ \theta_5 \cdot (\text{IBW} - 64.1) + \\ \theta_7 \cdot T_{125,625,\,ij}\,(\text{if Antibody Titer} = 125 \text{ or } 625) \end{array} \right) \cdot F_{rel} \cdot \exp^{\eta_i}$$

Where:

- $C_{ss,ave,ij}$ is the individually predicted predose steady-state concentration (pg/mL) for the ith subject at the jth measurement.
- Dose_i is an indicator variable for the exenatide dose (Dose_i=0 for 0.8 mg dose and Dose_i=1 for 2 mg dose).
- Scale_i is an indicator variable for the 1-kg manufacturing scale for the ith individual (Scale_i=1 when 1 kg manufacturing scale was used).
- baseline eGFR_i is the baseline eGFR for the ith subject.
- IBW is the ideal body weight for the ith subject.
- $T_{125,625,ij}$ is an indicator variable for antibodies to exenatide for the ith subject at the jth measurement ($T_{125,625ij}$=1 if antibody titer to exenatide ≥125).
- η_i is the IIV estimate for the ith subject. It was modelled using a normal distribution with mean of 0 and variance of ω^2.
- F_{rel} is the relative bioavailability for the suspension formulation of EQWS relative to BYDUREON.

In the original BYDUREON model, bioavailability of EQWS in Study BCB110 relative to BYDUREON was estimated:

$$F_{rel} = \theta_7 \text{ (Study BCB110) or}$$
$$= 1 \text{ (BYDUREON)}$$

In the present report where phase 3 EQWS data was added to the PK model, bioavailability of EQWS in either Study BCB118 or BCB120 relative BYDUREON was estimated.

$F_{rel} = \theta_7$ (Study BCB110) or
$= \theta_8$ (Study BCB118 or BCB120) or
$= 1$ (BYDUREON)

To predict individual $C_{ss,av}$ of exenatide for the purpose of exposure-response modeling, bioavailability of EQWS was estimated for Study BCB118 and BCB120 separately.

$F_{rel} = \theta_7$ (Study BCB110) or
$= \theta_8$ (Study BCB118) or
$= \theta_9$ (Study BCB120) or
$= 1$ (BYDUREON)

Exenatide plasma concentrations were modelled after logarithimic transformation. The residual variability was modelled as additive on the logarithmic scale using a normal distribution with mean of 0 and variance of σ^2.

2.2.2 Population Exposure-Response Modeling

The final exposure-response model for BYDUREON and EQWS re-estimated after adding phase 3 EQWS data in the present report is shown below.

$$\text{HbA1c}_{ij} = \text{Baseline HbA1c}_i\,(\%) - \left(\frac{E_{maxi}(\%) \cdot C_{ss,\,avij}}{EC_{50i} + C_{ss,\,avij}} \right)$$

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

$$E_{maxi}\,(\%) = \left(\theta_1 + \theta_3 \cdot (\text{Baseline HbA1c}_i - 8.2)\right) \cdot \text{EXP}^{\eta_i}$$

Where

- HbA1c_{ij} is the individually predicted HbA1c (%) value for the ith subject at the jth measurement;
- Baseline HbA1c_i is the baseline HbA1c value for the ith subject, $C_{ss,avij}$ is the individually predicted exenatide concentration for the ith subject and the jth measurement;
- Titer_{ij} is an indicator variable for antibody to exenatide of 125 or 625 independent of assay lab for the ith subject at the jth measurement (Titer_{ij}=0 if titer<125 and Titer_{ij}=1 if titer≥125);
- η_i is the IIV random effect estimate for the ith subject. It was modelled using a normal distribution with mean of 0 and variance of ω^2.

- $C_{ss,av,ij}$ is the individually predicted predose steady-state concentration (pg/mL) for the ith subject at the jth measurement; these values were computed with individual empiric Bayesian parameter estimates of the PK model with relative bioavailability estimated for each EQWS Study BCB110, BCB118 and BCB120.

The residual variability of HbA1c was modelled as additive using a normal distribution with mean of 0 and variance of σ^2.

3. RESULTS

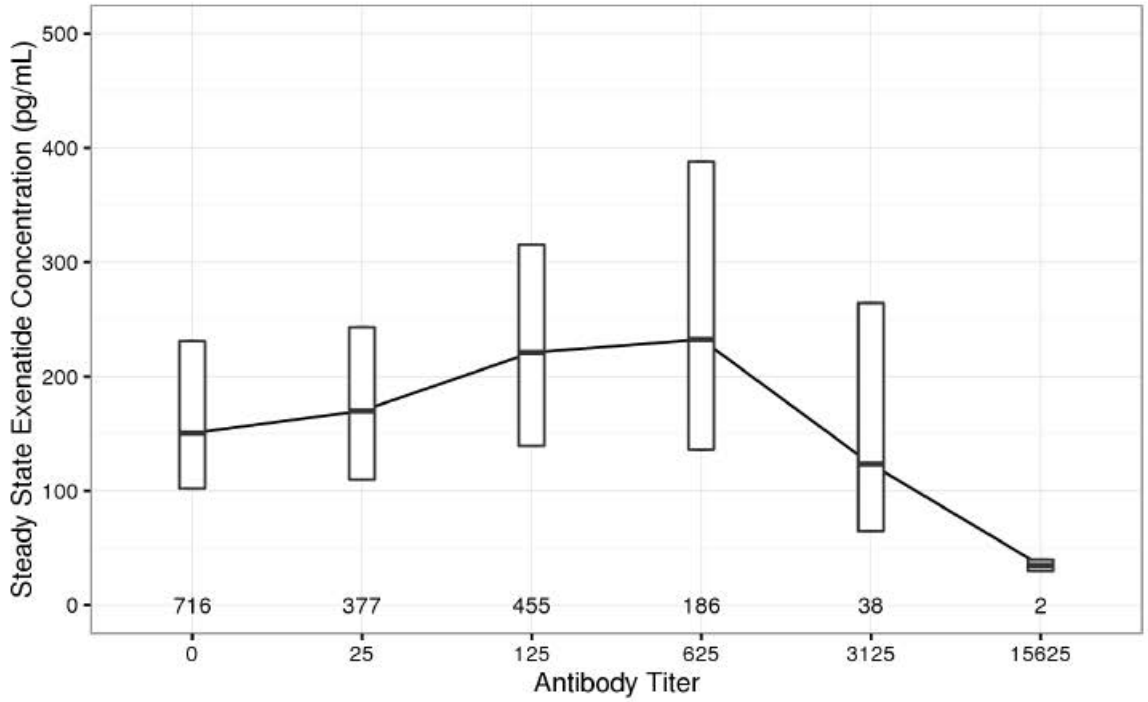
3.1 Population pharmacokinetic model

3.1.1 Data

Graphical evaluations of exenatide steady-state plasma concentrationsin subjects treated with EQWS showed a decrease in measurable exenatide plasma concentration in samples with exenatide antibody titers ≥3125 relative to antibody-negative and low-titer (≤625) antibody samples (Figure 1). As was the case for the original BYDUREON PPK model analysis, exenatide plasma concentrations associated with a higher titer (≥625 when assayed at (b) (4) and ≥3125 when assayed at (b) (4)) for subjects treated with exenatide were excluded from the primary PK analysis. These criteria resulted in exclusion of 7 % of the evaluable exenatide steady-state plasma concentrations from all BYDUREON and EQWS studies in the PK source dataset (source: \models\model-01\output\output-05\20161110\summ-excl-tit.csv).

The final PPK analysis dataset included a total of 4396 steady-state exenatide plasma concentration values from 806 subjects, and there were 1879 concentrations from 383 subjects treated with EQWS (source: \models\model-01\output\output-05\20161110\summ-pk-data.csv). These concentrations corresponded to low antibody titer: less than or equal to 125 (b) (4), or less than or equal to 625 (b) (4).

Figure 1 **Steady-state exenatide plasma concentration in studies BCB118 and BCB120 stratified by titer of antibodies to exenatide (N=1774)**



Notes: Boxes are 25th and 75th percentiles. Trend lines connect medians for each category at each dose. The numbers above the x-axis represent the number of observations for each box.
Source: \models\model-01\output\output-05\20161110\titer.png

For the entire analysis data set, the majority of subjects were male (59%, source: \models\model-01\output\output-05\20161110\summ-subj-sex.csv) and Caucasian (66%, source: \models\model-01\output\output-05\20161110\summ-subj-race.csv). A total of 38%, 27%, 27%, and 8% of exenatide plasma concentrations were associated with antibody to exenatide titers of 0, 25, 125, and 625, respectively (source: \models\model-01\output\output-05\20161110\summ-conc-titer.csv).

3.1.2 Final pharmacokinetic model

Parameter estimates and their precision for the final EQWS PPK model are shown in Table 2. Inspection of model diagnostics showed that the model described the data adequately (Section 7, Appendix 1 and Appendix 2).

Table 2 Parameter estimates of the final EQWS exenatide population PK model

Parameter	Description	Mean	%RSE
θ1	Mean $C_{ss,av}$ for 0.8 mg dose	87.8	8.6
θ2	Mean $C_{ss,av}$ for 2 mg dose	148	6.8
θ3	eGFR effect on $C_{ss,av}$ as a power model : $(EGFR/81.6)^{\theta 3}$	-0.83	10.0
θ4	Manufacture scale (b) (4) as an additive ((b) (4) effect on $C_{ss,av}$	106.0	21.0
θ5	IBW effect on $C_{ss,av}$ as an additive (b) (4) model θ4*(IBW-64.1)	-1.74	17.1
θ6	High antibody as an additive (b) (4) effect on Css,ave	42.4	15.7
θ7	EQWS as a proportional effect on $C_{ss,av}$ for Study BCB110	1.22	9.0
θ8	EQWS as a proportional effect on $C_{ss,av}$ for Study BCB118 & BCB120	0.70	4.1
ω^2	Variance of between subject variability for $C_{ss,av}$	0.218	8.1
σ^2	Variance of residual error for (b) (4) assay	0.199	8.3
σ^2	Variance of residual error for (b) (4) assay	0.247	7.0
σ^2	Variance of residual error for (b) (4) assay	0.0849	21.0

Source: \models\model-01\output\output-07\20161111\par-mod201.txt

The final EQWS exenatide PPK model showed antibody titer as a significant covariate on exenatide steady-state concentrations. As compared to antibody-negative subjects, the model predicted a modest additive increase (by 42.4 pg/mL for BYDUREON, or 29.7 pg/mL after adjustment for bioavailability of EQWS) in mean steady-state exenatide plasma concentrations for titers ≥125.

Mean steady-state exenatide plasma concentration for EQWS for low titer, eGFR 90 mL/min/1.73 m^2 and ideal body weight 64 kg, which are the mean values in studies 118 and 120 (source: \models\model-01\output\output-06\20161110\mean-bw-gfr.txt), was predicted to be 153 pg/mL, while the concentration for BYDUREON was predicted to be 217 pg/mL (source: \models\model-02\output\output-03\20161110\conc-for-eqws-byd.csv). For a subject with ideal body weight 64 kg and eGFR 82 mL/min/1.73 m^2 mean steady state concentration of exenatide after EQWS is predicted to be 165 pg/mL for a low titer; and 195 pg/mL – for a high titer (source: \models\model-02\output\output-03\20161110\conc-for-ab-effect.csv).

3.1.3 Effect of antibody data exclusion

In order to compute individual $C_{ss,av}$ of exenatide for exposure-response modeling a variant of the final PPK model was employed, with separate bioavailability for Study BCB118 and Study BCB120. Parameter estimates of this model are shown in Table 4. These estimates are very similar to the final PPK model.

Parameter estimates were not impacted by exclusion of exenatide plasma concentration samples with high titers (Table 2 and Table 3). Values of parameter estimates are very similar for models with and without high antibody titers. The exception is the relative bioavailability of EQWS in Study BCB110 whose estimation was no longer supported by the data when including high titer samples.

Table 3 Parameter estimates of the final EQWS exenatide population PK model with and without high titer samples

Parameter	Description	Exclude high titers		Include high titers	
		Mean	%RSE	Mean	%RSE
$\theta 1$	Mean Css,av for 0.8 mg dose	89.1	8.6	83	10.9
$\theta 2$	Mean Css,av for 2 mg dose	147	6.9	150.7	7.6
$\theta 3$	eGFR effect on Css,av as a power model : $(EGFR/81.6)^{\theta 3}$	-0.79	10.3	-0.69	13.6
$\theta 4$	Manufacture scale (b) (4) as an additive (b) (4) effect on Css,av	105.7	21.0	106.6	21.3
$\theta 5$	IBW effect on Css,av as an additive (b) (4) model $\theta 4*(IBW-64.1)$	-1.89	15.9	-1.87	16.6
$\theta 6$	High antibody as an additive (b) (4) effect on Css,av	43.0	15.5	36.5	18.6
$\theta 7$	EQWS as a proportional effect $(1+\theta 7)$ on Css,av for Study BCB110	0.22	50.9	-0.01	1315
$\theta 8$	EQWS as a proportional effect $(1+\theta 8)$ on Css,av for Study BCB118	-0.24	14.2	-0.25	14.6
$\theta 9$	EQWS as a proportional effect $(1+\theta 9)$ on Css,av for Study BCB120	-0.38	9.2	-0.38	9.6
ω^2	Variance of between subject variability for Css,av	0.215	8.1	0.26	8.3
σ^2	Variance of residual error for (b) (4) assay	0.199	8.3	0.2	8.1
σ^2	Variance of residual error for (b) (4) assay	0.246	7.0	0.26	6.6

Table 3 **Parameter estimates of the final EQWS exenatide population PK model with and without high titer samples**

Parameter	Description	Exclude high titers		Include high titers	
		Mean	%RSE	Mean	%RSE
σ^2	Variance of residual error for (b) (4) assay	0.085	21.0	0.128	38.0

Source: \models\model-01\output\output-07\20161111\par-mod202.txt for the model excluding high titers; \models\model-01\output\output-07\20161111\par-mod602.txt for the model including high titers

3.2 Population exposure-response model

3.2.1 Data

The final population exposure-response analysis dataset included a total of 2257 steady-state exenatide plasma concentration and HbA1c value pairs from 654 subjects, and there were 1409 pairs from 353 subjects treated with EQWS (source: \models\model-02\output\output-02\20161109\summ-pkpd-data.csv).

3.2.2 Final exposure-response model

Parameter estimates and their precision for the final EQWS population exposure-response model are shown in Table 4. Inspection of model diagnostics showed that the model described the data adequately (Appendix 1 and Appendix 2).

Table 4 **Parameter estimates of the final EQWS exenatide population exposure-response model**

Parameter	Description	Mean	%RSE
$\theta 1$	Emax at baseline HbA1c 8.2%	1.86	7.3
$\theta 2$	EC50 at low titer (pg/mL)	51.4	36.3
$\theta 3$	Change of Emax for each 1% of deviation of baseline HbA1c at baseline from 8.2%	0.64	8.5
$\theta 4$	Increase of EC50 for high titer (pg/mL)	32.6	44.7
ω^2	Variance of between subject variability for Emax	0.043	26
ω^2	Variance of between subject variability for EC50	3	30
σ^2	Variance of residual error for (b) (4) assay	0.0038	10

Source: \models\model-02\output\output-04\20161111\par-mod101.txt

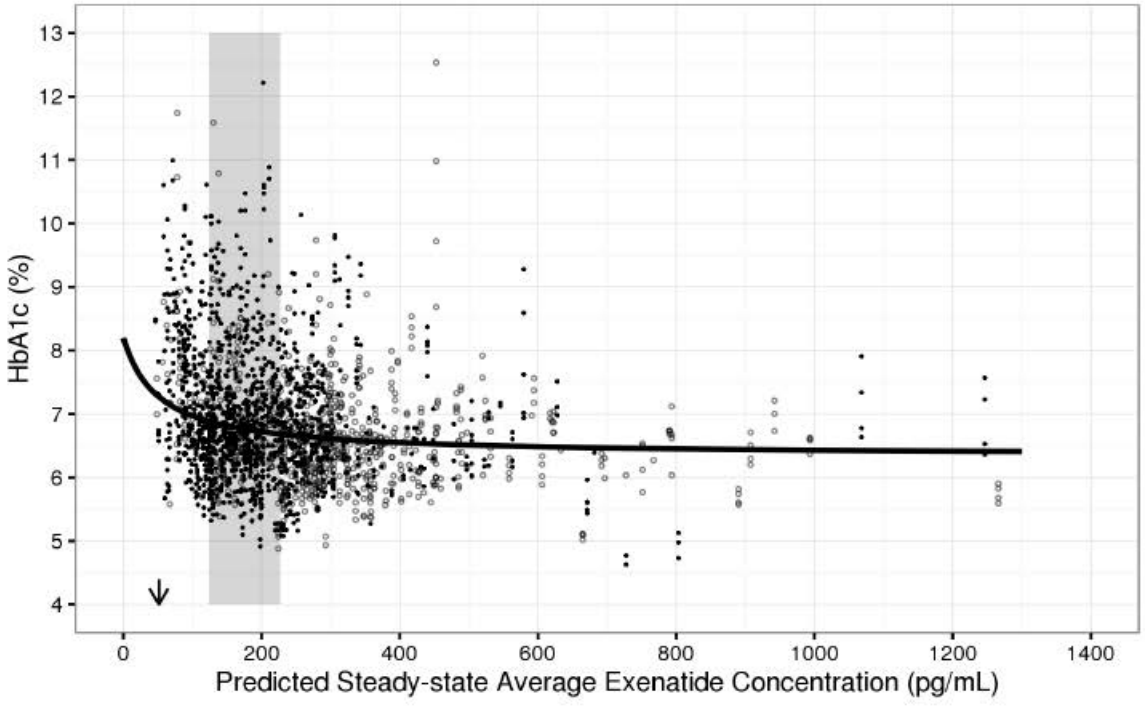
The estimated EC_{50} of the exenatide systemic exposure-response relationship is 51.4 pg/mL when antibody to exenatide titers are <125 and 84 pg/mL when antibody titer levels are ≥125.

Out of all predicted concentrations with the final PPK model 99% of concentrations for low titers (<125) lie above the EC_{50}=51.4 pg/mL, and 97% of concentrations for high titers (≥125) lie above the EC_{50}=84 pg/mL (source: \models\model-01\output\output-06\20161110\ic50-percentiles.txt).

The model also predicts that for a given exenatide plasma concentration, the percent change in HbA1c from baseline is greater for subjects with higher baseline HbA1c values.

Figure 2 illustrates the population mean predicted exenatide systemic exposure-response curve for a typical antibody-negative subject assuming a baseline HbA1c of 8.2%. The observed HbA1c versus exenatide $C_{ss,av}$ is overlaid with shaded regions indicating the 25th to 75th percentiles of the predicted exenatide $C_{ss,av}$ for EQWS 2 mg. For a subject with low titer (<125), ideal body weight 64 kg, eGFR 75.2 mL/min/1.73 m^2 and baseline HBA1c 8.2%, steady state HbA1c is predicted to be 6.75 for EQWS and 6.65 for BYDUREON (source: source: \models\model-02\output\output-03\20161110\hba1c-for-eqws-byd.csv). Plasma concentration of exenatide is predicted to be 177 pg/mL and 253 pg/mL, respectively.

Figure 2 **Observed HbA1c versus individual average steady-state exenatide plasma concentrations following multiple dose administration of EQWS overlaid with the model predicted exposure response curve for antibody-negative data**



Notes: Filled circles represent data from EQWS treated subjects. Open circles represent data from BYDUREON-treated subjects. Baseline HbA1c values were fixed to the population median value. The shaded region represents the 25th to 75th percentiles of the predicted $C_{ss,av}$ for the 2 mg EQWS dose. The arrow at 51.4 pg/mL represents the population mean EC_{50}.

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/s/

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