CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209210Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	209210
Priority or Standard	Standard
Submit Date(s)	December 21, 2016
Received Date(s)	December 21, 2016
PDUFA Goal Date	October 21, 2017
Division/Office	CDER/DMEP
Reviewer Name(s)	Mahtab Niyyati, MD
Review Completion Date	October 5, 2017
Established Name	Exenatide Once-Weekly Suspension
(Proposed) Trade Name	Bydureon BCise
Applicant	Astra Zeneca
Formulation(s)	Injectable suspension
Dosing Regimen	2 mg Once weekly
Applicant Proposed Indication(s)/Population(s)	To improve glycemic control in adult patients with type 2 diabetes mellitus
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with type 2 diabetes

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Glossary

AC	Advisory committee
ADA	Anti-drug antibody
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEC	Clinical Events Classification Committee
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
DMC	Data monitoring committee
DMEP	Division of metabolism and endocrinology products
DMEPA	Division of medication error prevention and analysis
DPP-4	Dipeptidyl-peptidase-4
ECG	Electrocardiogram
eCTD	Electronic common technical document
EOP2	End of Phase 2
ETASU	Elements to assure safe use
EQWS	Exenatide Once-Weekly Suspension
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	Fasting plasma glucose
GCP	Good clinical practice
GLP-1	Glucagon-like peptide-1

GPP	Graphical patient profile
GRMP	Good review management practice
HLGT	Higher level group term
HLT	Higher level term
HF	Human factors
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
IRT	Interdisciplinary Review Team
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
IV	Intravenous
LLT	Lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MCT	Medium chain triglycerides
mITT	Modified intent to treat
ITT	Intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NME	New molecular entity
OBP	Office of Biologic Products
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing information
PK	Pharmacokinetics
PLG	Poly D, L-lactide-co-glycolide
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PMC	Postmarketing commitment
PP	Per protocol
PPI	Patient package insert
PREA	Pediatric Research Equity Act
PT	Preferred Term
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
REMS	Risk evaluation and mitigation strategy

SAE	Serious adverse event
SAP	Statistical analysis plan
SDTM	Study data tabulation model
SGE	Special government employee
SMBG	Self monitored blood glucose
SOC	Standard of care
SOC	System organ class
SC	Subcutaneously
SU	Sulfonylurea
TEAE	Treatment-emergent adverse event
T2DM	Type-2 Diabetes Mellitus
TZD	Thiazolidinedione

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1 Executive Summary

1.1. Product Introduction

Astra Zeneca submitted a New Drug Application (NDA) for a glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide once-weekly suspension (EQWS), a new drug-device combination product with the proposed trade name 'Bydureon BCise'. The Applicant is seeking the indication of adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM).

Exenatide, the active drug ingredient of EQWS, is currently marketed as two formulations administered subcutaneously (SC) for the indication of: adjunct to diet and exercise to improve glycemic control in patients with T2DM: Bydureon (exenatide extended-release once weekly) and Byetta (exenatide twice-daily). EQWS is a different formulation of Bydureon. The Applicant has also developed a single use, fixed-dose auto-injector device for the administration of EQWS.

The Applicant states the only difference between the Bydureon and EQWS formulations is the vehicle and the presentation. EQWS's vehicle is the nonaqueous medium chain triglycerides (MCT), as opposed to the aqueous diluent utilized in Bydureon. The Applicant states the nonaqueous MCT diluent allows for pre-mixed administration of the drug in an auto-injector (as opposed to the vial/syringe system developed for Bydureon) without a need for reconstitution. The Applicant states the biodegradable polymeric microspheres used as the drug delivery system for exenatide in EQWS, are the same as those in Bydureon, and the dosing regimen of 2 mg weekly is also the same as for Bydureon.

Reviewer Comment: The Agency agreed with the EQWS drug development program's leveraging of safety and efficacy data from the Byetta and Bydureon NDAs (End of Phase 2 [EOP2] meeting, December 14, 2011).

1.2. Conclusions on the Substantial Evidence of Effectiveness

This review concludes that there is adequate evidence to recommend approval of EQWS for the proposed indication of an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

This recommendation is based on two Phase 3 clinical trials BCB118 and BCB120, and leveraging of information from the drug development programs for Byetta and Bydureon. The Phase 3 study designs were generally adequate based on the protocols and randomization of baseline demographics.

However, the Phase 3 study designs had caveats. The two EQWS Phase 3 clinical studies did not have a rigorous plan for follow-up of subjects who discontinued treatment. The lack of rigorous follow-up resulted in a high proportion of subjects with missing data[1] after discontinuation of study drug.

Also, the design of the Phase 3 studies underestimated the withdrawal rate when determining the sample size. This is particularly evident in the small pool of 61 placebo subjects in study BCB120. At the end of study BCB120, 37.7% of the 61 placebo subjects had missing HbA1c data at Week 28 resulting in a limited estimation of treatment difference between EQWS, placebo and the active comparator sitagliptin.

The Applicant has demonstrated the superiority of EQWS to Byetta and placebo. Despite the limitations mentioned above, the claim of superiority to Byetta and placebo remained in place after accounting for all randomized subjects regardless of adherence to study drug or initiation of rescue, albeit with a weaker yet still statistically significant association.

The claim of non-inferiority or superiority to sitagliptin is unsubstantiated because of failure to show a placebo-adjusted treatment effect for sitagliptin.

I recommend the approval of EQWS contingent on agreement on labeling. I have summarized my rationale for this recommendation in section 1.3 below.

1.3. Benefit-Risk Assessment

[1] The high rate of missing data at Week 28 reflects missing HbA1c measurements regardless of adherence to drug. So the rate of withdrawal from the Phase 3 studies is lower than missing efficacy data at Week 28.

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Benefit-Risk Summary and Assessment

EQWS is a new drug-device formulation of the glucagon-like peptide-1 (GLP-1) receptor agonist Bydureon, an injectable antidiabetic drug administered once-weekly subcutaneously, approved for treatment of type 2 diabetes mellitus (T2DM) in adults. The active drug substance in EQWS is exenatide. Exenatide is approved and marketed as Byetta (short-acting) and Bydureon (long-acting) formulations. EQWS's vehicle is a nonaqueous Medium Chain Triglycerides (MCT), as opposed to the aqueous diluent utilized in Bydureon. The microsphere drug delivery system for exenatide and the proposed dose and regimen for EQWS (2 mg SC weekly) are the same as in Bydureon. Unlike Bydureon which requires reconstitution before administration, EQWS is administered pre-mixed via an autoinjector.

Diabetes mellitus is a serious disease affecting 22 million people in the United States. Diabetes mellitus is associated with serious morbidities and mortality affecting the quality of life and longevity of diabetic patients. Currently, 12 classes of medications are approved for the treatment of type 2 diabetes mellitus, including GLP-1 agonists.

With respect to the evaluation of Benefit, this review concludes that substantial evidence of clinical efficacy was met in this application. This relies on two Phase 3 clinical studies BCB118 and BCB120, as well as the Bydureon and Byetta clinical development programs and postmarketing experience. These studies show EQWS's benefit in improved glycemic control in patients with type 2 diabetes mellitus inadequately treated with oral antidiabetic medications. The primary endpoint for establishing the efficacy of EQWS was a demonstration of an HbA1c reduction from baseline at Week 28. HbA1c reduction is an acceptable surrogate for improved clinical outcomes (i.e., reduction in microvascular complications).

EQWS 2 mg once-weekly by subcutaneous injection resulted in a statistically significant decrease in HbA1c at Week 28 compared to Byetta and placebo, demonstrating superiority to Byetta and placebo in the two Phase 3 studies. The claim of superiority to Byetta and placebo remained after accounting for all randomized subjects regardless of adherence to study drug or initiation of rescue, albeit with a weaker yet still statistically significant association. The Applicant's claim for EQWS's noninferiority or superiority to sitagliptin is not clinically meaningful because of the failure to demonstrate a placebo-adjusted treatment effect for sitagliptin in study BCB120.

With respect to Risk (including safety and efficacy risks), note the following:

- The overall safety profile for EQWS is consistent with Bydureon and does not raise additional safety concerns.
- The proposed EQWS label adequately conveys the risks known with GLP-1 agonists, i.e., Bydureon and Byetta, either identified during the clinical trials or postmarketing.

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- A clear imbalance in injection site reactions driven by the adverse event injection site nodule occurred in EQWS-treated subjects compared to Byetta. No serious injection site reactions occurred in the two Phase 3 EQWS clinical studies. The proposed label adequately informs of possible severe injection site reactions that may require surgical or medical intervention.
- 74% of EQWS-treated subjects in both Phase 3 studies were anti-exenatide antibody positive during the controlled period. Exploratory analyses suggest a possible smaller reduction in HbA1c with increasing antibody titers at Week 28 and Week 52. However, the sample size of these sub-group exploratory analyses is small limiting data interpretation. Also, more subjects with injection site reactions had positive anti-exenatide antibodies, especially high-titer antibodies. The EQWS development program did not assess possible cross-reactivity of anti-exenatide antibodies with endogenous GLP-1/glucagon, or neutralizing antibody activity. The OBP reviewers states the presence of cross-reactive anti-exenatide antibodies to endogenous GLP-1/glucagon may pose a clinical risk.
- The EQWS drug development program did not assess the cardiovascular safety profile of EQWS.
- The two EQWS Phase 3 clinical studies did not have a rigorous plan for follow-up of patients who discontinued treatment. The lack of rigorous follow-up resulted in a high proportion of patients with missing data after discontinuation of study drug. Also, the design of the Phase 3 studies underestimated the withdrawal rate when determining the sample size. This is particularly evident in the small pool of 61 placebo subjects. At the end of study BCB120, 37.7% of the 61 placebo subjects had missing data resulting in a limited estimation of placebo-adjusted treatment effect for EQWS and the active comparator sitagliptin.

Evaluation of the EQWS database in conjunction with the Bydureon and Byetta clinical trials and postmarketing information suggests that the risks are acceptable at this time and that a favorable Risk/Benefit profile has been presented for EQWS for the intended indication. Overall, I believe the Risk/Benefit considerations favor approval with postmarketing surveillance and adequate labeling. EQWS may rely on the Bydureon NDA's cardiovascular outcome study BCB109, as suggested by the Agency during End of Phase 2 meeting dated December 14, 2011. (b) (4)

[redacted]

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes is associated with multiple comorbidities including macrovascular and microvascular complications affecting the longevity and quality of life of diabetic patients	• Diabetes is a serious condition associated with chronic morbidity and mortality. • Glycemic control of diabetes improves microvascular complications.
Current Treatment Options	• Twelve classes of drugs are FDA-approved in the United States to improve glycemic control in type 2 diabetes patients. • Among these classes are glucagon-like peptide-1 (GLP-1) receptor agonists, e.g., Byetta, Bydureon, Victoza, and lixisenatide.	• Multiple effective treatment options are available for the treatment of type 2 diabetes mellitus. • EQWS is a new drug-device formulation of the GLP-1 agonist Bydureon allowing for administration of the pre-mixed drug via an auto-injector (as opposed to the vial/syringe system developed for Bydureon) without a need for reconstitution.
Benefit	• The two Phase 3 studies show EQWS's benefit in improved glycemic control in patients with type 2 diabetes mellitus inadequately treated with oral antidiabetic medications. • EQWS 2 mg once-weekly by subcutaneous injection resulted in a statistically significant decrease in HbA1c compared to Byetta and placebo at Week 28, demonstrating superiority to Byetta (study BCB118) and placebo (study BCB120).	• The claim of EQWS's superiority to Byetta and placebo remained after accounting for all randomized subjects regardless of adherence to study drug or initiation of rescue, albeit with a weaker yet still statistically significant association. o The Applicant's claim for EQWS's noninferiority or superiority to sitagliptin is not clinically meaningful because of the failure to demonstrate a placebo-adjusted treatment effect for sitagliptin in study BCB120.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• EQWS could be an additional option for treatment of T2DM patients inadequately treated with oral antidiabetic medications.
Risk	• A clear imbalance in injection site reactions driven by the adverse event injection site nodule is seen in the EQWS-treated subjects compared to Byetta. • 74% of the EQWS-treated subjects in the two Phase 3 studies developed anti-exenatide antibodies during the controlled period. • Cross-reactivity of anti-exenatide antibodies to endogenous GLP-1 and glucagon and neutralizing activity were not assessed in the EQWS clinical program. The OBP reviewers states the presence of cross-reactive anti-exenatide antibodies to endogenous GLP-1/glucagon may pose a clinical risk. • The two EQWS Phase 3 clinical studies did not have a rigorous plan for follow-up of patients who discontinued treatment. The lack of rigorous follow-up resulted in a high proportion of patients with missing data after discontinuation of study drug. • The design of the Phase 3 studies underestimated the withdrawal rate when determining the sample size. This is particularly evident in the small pool of 61 placebo subjects. At the end of study BCB120, 37.7% of the small pool of placebo subjects had missing data resulting in a limited estimation of placebo-adjusted comparisons with EQWS and the active comparator sitagliptin.	• No serious injection site reactions occurred in the two Phase 3 EQWS clinical studies. The proposed label adequately informs of possible severe or serious injection site reactions with EQWS that may require surgical or medical intervention. • Exploratory analyses suggest subjects with higher titer antibodies may have an attenuated HbA1c response. However, the sample size of these sub-group exploratory analyses is small limiting data interpretation. More subjects with injection site reactions had positive anti-exenatide antibodies, especially high-titer antibodies. The Office of Biological Product (OBP) reviewer states the assays developed for assessing Bydureon's possible cross-reactivity with endogenous GLP-1 or glucagon were not adequately sensitive. • The statistical reviewer re-analyzed the primary endpoint by including all randomized subjects regardless of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		adherence to treatment or rescue. The Applicant's claim for EQWS's noninferiority or superiority to sitagliptin is not clinically meaningful because of the failure to demonstrate a treatment effect for sitagliptin in study BCB120.
Risk Management	• The overall safety profile for EQWS is consistent with Bydureon and does not raise additional safety concerns. • The OBP reviewers states the possible presence of cross-reactive anti-exenatide antibodies to endogenous GLP-1/glucagon may pose a clinical risk. • The EQWS drug development program was not designed to assess the cardiovascular safety profile of EQWS. • The lack of rigorous follow-up resulted in a high proportion of patients with missing data after discontinuation of study drug.	• The proposed EQWS label 'Warnings and Precautions' adequately conveys the risks known with GLP-1 agonists, i.e., Bydureon and Byetta, either identified during the exenatide clinical trials or in postmarketing. • (b) (4) • EQWS may rely on Bydureon's ongoing cardiovascular outcome study BCB109. • The claim of superiority to Byetta and placebo remained in place after accounting for all randomized subjects regardless of adherence to study drug or initiation of rescue, albeit with a weaker yet still statistically significant association.

2 Therapeutic Context

Analysis of Condition

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes are:

- Biguanides (i.e., metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues
- SGLT2 inhibitor
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e., bromocriptine)
- Insulin and insulin analogs
- Bile acid sequestrant (i.e., colesevelam hydrochloride)

2.2. Analysis of Current Treatment Options

Currently approved GLP-1 agonists for the indication of adjunct to diet and exercise to improve glycemic control in adults with T2DM are Byetta, Bydureon, liraglutide, albiglutide, dulaglutide, and lixisenatide. The GLP-1 agonists other than liraglutide are not recommended as a first-line therapy due to the risk of medullary thyroid carcinoma.

3 Regulatory Background

An immediate-release formulation of exenatide (Byetta) administered twice daily subcutaneously is the first approved GLP-1 receptor agonist (April 28, 2005).

Subsequently, the single-dose tray and the dual-chamber pen presentation for Bydureon, a long-acting exenatide formulation, were first approved in the United States on February 28, 2014.

Both exenatide formulations (Byetta and Bydureon) are approved for the indication of adjunct to diet and exercise to improve glycemic control in T2DM patients.

3.1. Summary of Presubmission/Submission Regulatory Activity

After Pre-IND interactions between the Agency and the Applicant (October 15, 2007), Amylin Pharmaceuticals, Inc. opened the IND for EQWS on September 19, 2008.

Amylin Pharmaceuticals, Inc. initially pursued the EQWS drug development program by requesting a Type B EOP2 (December 14, 2011) meeting for exenatide (b) (4) (b) (4)

During the EOP2 meeting, the Applicant sought the Agency's input on cross-referencing to Bydureon and Byetta NDA's for the EQWS drug development program.

The Applicant inquired about the sufficiency of the QT study BCB112 for Bydureon, and the cardiovascular safety profile of the approved exenatide drug products for satisfying a pre-marketing cardiovascular risk evaluation for EQWS. The Applicant also inquired if the ongoing cardiovascular outcomes study BCB109 for Bydureon is sufficient for satisfying the postmarketing cardiovascular evaluation requirements for EQWS.

Reviewer Comment: The Agency agreed that a separate cardiovascular outcome study will not be planned for EQWS. The Agency suggested transitioning a subset of Bydureon subjects in the cardiovascular outcome study to EQWS. The Agency stated BCB109 may be listed as a PMR under EQWS for regulatory reasons; however determination of whether the postmarketing cardiovascular study BCB109 will fulfill the PMR will be a review issue. Refer to Section 8.5 (page 148) of this review for details.

Other points of discussion were regarding the Applicant's approach to the safety of EQWS in mild to moderate renal impairment, given the Applicant intends to retain labeling language used for exenatide products in the Warning and Precautions section cautioning against the use of EQWS in severe renal impairment and end-stage renal disease.

Reviewer Comment: The Applicant excludes subjects with severe renal failure in the EQWS development program.

End of Phase 2 discussion for the Phase 3 study designs

The Agency agreed with a proposed Phase 3 study for bridging EQWS to the exenatide clinical program with a 28-week, 2-arm (175 T2DM subjects per arm) study comparing EQWS with Byetta.

For the design of the second Phase 3 study where the Applicant intended to assess the safety and efficacy of EQWS compared to sitagliptin, the Agency recommended incorporating a third placebo arm powered based on a non-inferiority margin of 0.3. The Agency recommended allocating a larger number of subjects to EQWS and the active control, and a smaller number of

subjects to the placebo arm.

Reviewer Comment: The design of the two Phase 3 studies conform to the Agency's recommendations during EOP2 meeting.

Pre-NDA (February 8, 2016) clinical guidance for adverse event presentation and subject narratives for the EQWS drug development program provided by the Agency has been applied across the submission.

Withdrawal/missing data:

During the EOP2 meeting, the Agency recommended supportive analysis using last observation carried forward as the imputation method for discontinuations and hyperglycemic rescues.

Reviewer Comment: The Applicant excluded post-rescue and discontinued subjects for the primary endpoint analysis, and used only observed data from completed subjects at Week 28 in the primary endpoint analysis. The caveat of the study design leading to a high rate of missing data at Week 28 for the primary efficacy analysis is discussed in Section 6 (efficacy) of this review.

3.2. Foreign Regulatory Actions and Marketing History

EQWS is not currently approved for use outside or in the United States. Byetta and Bydureon were approved in the European Union on November 20, 2006, and June 21, 2011, respectively, to improve glycemic control in adults with T2DM. The Applicant states, besides the European Union, Byetta is also approved in ~80 countries including Canada, Australia, Japan, Switzerland, and China, and Bydureon is approved in Japan and Switzerland.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Refer to the OSI review by Dr. Cynthia Kleppinger dated August 29, 2017.

DMEP requested an OSI inspection of clinical sites involved in conducting pivotal studies BCB118 and BCB120. Sites were chosen based on the OSI site selection tool. The OSI reviewer states only domestic sites were chosen as both studies were performed in the United States. Sites were chosen that had larger than average enrollment, large efficacy effect size, and no inspectional history or no recent inspectional history. In summary, seven domestic sites representing eight study sites and the monitoring contract research organization were

inspected.

The OSI reviewer states the inspections of three clinical investigators revealed regulatory violations. However, the regulatory violations are unlikely to significantly impact primary safety and efficacy analyses and the data from the respective sites are acceptable for use in support of the indication for NDA 209210. These inspections were classified as No Action Indication.

The inspection of the contract research organization and the remaining clinical investigators revealed no regulatory violations. OSI states overall the inspection findings support the validity of the data as reported by the Applicant under NDA 209210. The inspections were classified as No Action Indicated.

4.2. Product Quality

Refer to the CMC review by Dr. Su Tran.

Manufacturing Process

The drug substance, exenatide, is a 39-amino acid peptide manufactured by (b) (4)
The Applicant states the information for the exenatide drug substance, manufactured by the commercial manufacturers (b) (4) was originally approved in the NDA 021-773 for Byetta and the NDA 022-200 for Bydureon.

Drug Product

The Applicant states the EQWS drug product is an oily suspension of exenatide microspheres in the excipient medium chain triglycerides (MCT), packaged in 2 mL glass cartridges sealed at one end with (b) (4) cap (b) (4) and (b) (4) plunger at the other.

Medium Chain Triglycerides (MCT)

The Applicant states the use of MCT as the vehicle in the EQWS drug product (b) (4)
(b) (4)
(b) (4) The Applicant states the MCT is inert with respect to the microspheres and exenatide.

Reviewer Comment: MCT has not been approved in any FDA-approved drug products for administration through a parenteral route. I defer to the CMC reviewer for the adequacy of the CMC program to support the EQWS drug development program.

Formulation changes in the Phase 2 and three changes

The Applicant states the formulation administered in the Phase 2 study differed from the formulation used in the Phase 3 studies (BCB118 and BCB120). The difference in formulation

(b) (4)

Also, a syringe and vial were used for administration of study drug and not the to-be-marketed autoinjector for the Phase 2 study.

Reviewer Comment: The Phase 3 studies (BCB118 and BCB120) were used for the safety and efficacy assessment of EQWS.

4.3. Clinical Microbiology

Refer to the overall quality review.

4.4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology and Toxicology review dated September 28, 2017, by Dr. Huiquing Hao for details. Below is a high-level summary of the nonclinical program supporting the EQWS development program as stated by the Applicant.

Table 1: Summary of the EQWS nonclinical program

Type	Category	Duration or sub-category	Species (strain)	Regimen / route	Study number
PK	PK	Single dose	Rat (SD)	SC	REST080666*
Toxicology	Repeated dose	1-month 3-month	Monkeys Monkeys	QW / SC QW / SC	REST080663* REST080799*
Special Toxicology	PK of MCTs Repeat dose toxicity of Miglyol 812	Single dose 4 Week	Rat (SD) Rat (Wistar)	Oral/SC Oral	8342572 3113KR

*Study conducted in compliance with GLP regulations.
Abbreviations: PK=pharmacokinetic; QW=once weekly, SC=subcutaneous, SD=Sprague-Dawley, MCT=Medium Chain Triglyceride.
Source: Excerpted from the nonclinical overview, page 9.

The Applicant states the EQWS nonclinical program is supported by data from the nonclinical evaluation of Byetta and Byduroen animal studies, as well as specific animal studies for testing EQWS and the vehicle MCT.

The specific animal studies for EQWS characterize the following:

1. Impact of the EQWS formulation on the PK and toxicology of exenatide
2. Local tolerance (injection site reaction)
3. Anti-exenatide antibodies
4. Assessment of the potential effects on the cardiovascular (ECGs and blood pressure) system

5. Bridge systemic and oral exposures of MCTs, and assess safety and disposition of MCT (4-week repeat dose oral toxicity study with Miglyol 812, an MCT)

The Applicant states the rat PK data show that MCT reduces the early release of exenatide from the microsphere drug delivery system. Otherwise, the Applicant states the PK profile for EQWS is comparable to Bydureon in the nonclinical studies.

Byetta and Bydureon's nonclinical program in support of EQWS:

1. Exenatide causing acute or chronic pancreatitis, or proliferative changes in pancreas
2. Thyroid-related postmarketing requirements for Bydureon

MCT

The Applicant states MCTs (as Miglyol 812 which is primarily caprylic and capric acid) are present in food products such as coconut, palm, and kernel oils. The Applicant states MCTs are approved in Europe as lipid emulsions for adult and pediatric parenteral nutrition, and also used in pharmaceutical and cosmetic products administered via oral, intravenous, intraperitoneal, intramuscular and dermal routes. In the United States, MCTs are available as supplements and nutritional protein based powders.

The Applicant states once ingested, MCTs are absorbed intact across the intestine. Once MCTs are in the systemic circulation MCT is transported mainly to the liver where they are catabolized and metabolized to acetoacetate and beta hydroxybutyrate both of which may be further metabolized to carbon dioxide and water.

The Applicant states nonclinical studies with EQWS were conducted to demonstrate that the safety profile of Bydureon is unaffected by the addition of MCTs in the EQWS formulation (single dose PK and local tolerance in rats, 1- and 3-month repeat dose toxicity in monkeys, and single dose PK study in rats for bridging subcutaneous MCT to oral, and a 4-week repeat dose oral toxicity study with MCT).

The Applicant states the total weekly subcutaneous dose of MCTs in 2 mg EQWS is 0.774 mg (equivalent to 0.0097 mg/kg/week in an 80 kg human).

Reviewer Comment: The nonclinical reviewer states while there are no approved products in the United States with MCT as an excipient, SMOFLIPID, an MCT-containing lipid suspension for parenteral (intravenous) nutrition was recently approved in the US (7/13/2016) as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. Per product label, SMOFLIPID contains 20 gram of lipid per 100 mL, 6 gram of which are MCT. The labeled maximum recommended dose of SMOFLIPID is 2.5 gram/kg/day, or 150 mg of lipid per day (for a 60 kg adult), 45 gram of which represents MCT. This gives a maximum weekly dose of 315 gram of MCT, which compared to the 0.77

gram/week of MCT that patients treated with EQWS will receive is a significantly higher dosage. Refer to the nonclinical review dated September 28, 2017 for details.

4.5. Clinical Pharmacology

Refer to the Clinical Pharmacology review by Dr. Johnny Lau. The information in section 4.5 is derived from the Clinical Pharmacology review dated August 21, 2017.

4.5.1. Mechanism of Action

Exenatide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl-cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Exenatide enhances glucose-dependent insulin secretion under fed and fasting conditions and enhances first and second phase insulin secretion. Exenatide suppresses glucagon secretion in a glucose-dependent manner. Exenatide slows gastric emptying resulting in slower absorption of glucose. Exenatide enhances splanchnic glucose uptake and reduces caloric intake.

4.5.2. Pharmacodynamic

See section 4.5.3 below.

4.5.3. Pharmacokinetics

The geometric mean steady-state average plasma exenatide concentration as measured in both Phase 3 studies was lower compared to Bydureon's steady-state concentration. Also, study BCB120 had a lower[2] steady state exenatide concentration compared to study BCB118 by 14%, after accounting for renal function.

In an attempt to explain the reasoning for the different exenatide concentrations in the two Phase 3 trials, the demographics of both Phase 3 trials were studied for possible differences. The following major differences in the population of the two Phase 3 trials were noted:

1. Renal impairment: BCB118's population has a lower mean eGFR compared to BCB120 because of enrollment of moderate renal impairment subjects only in BCB118.
2. Ethnicity: 60% of the randomized subjects to BCB120 were of Hispanic ethnicity, as opposed to 24% of subjects with Hispanic ethnicity randomized to BCB118.
3. Body weight: The BCB120 subjects have a lower body weight compared to BCB118.

[2] Geometric mean (SE) of plasma exenatide concentration in BCB120 is 153 (9.8) pg/mL, in BCB118 is 208 (9) pg/mL, and for Bydureon (historical data) is 265.8 (20.9) pg/mL.

The clinical pharmacology reviewer states the PK model showed the main variables affecting exenatide concentrations are the eGFR, body weight, and antibody titers. Ethnicity did not fully explain the difference in the steady-state concentrations of exenatide.
Reviewer Comment: The Applicant excluded exenatide plasma concentration samples corresponding to high titers of anti-exenatide antibodies. However, the clinical pharmacology reviewer states the exclusion of the antibody titer outliers did not meaningfully affect estimates of parameters in the population PK model.

Reviewer Comment: The clinical pharmacology reviewer states because exenatide's elimination is through glomerular filtration, it appears that eGFR has the most effect on the average steady-state plasma exenatide concentration. A higher eGFR in BCB120's population leads to higher clearance of exenatide and subsequently, lower average steady-state plasma exenatide concentration compared to BCB118.

On the other hand, the lower body weight in BCB120 may lead to higher average steady state plasma exenatide concentration in BCB120 compared to 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 body weight partly explaining the net lower average steady state plasma exenatide concentration of BCB120 compared to BCB118.

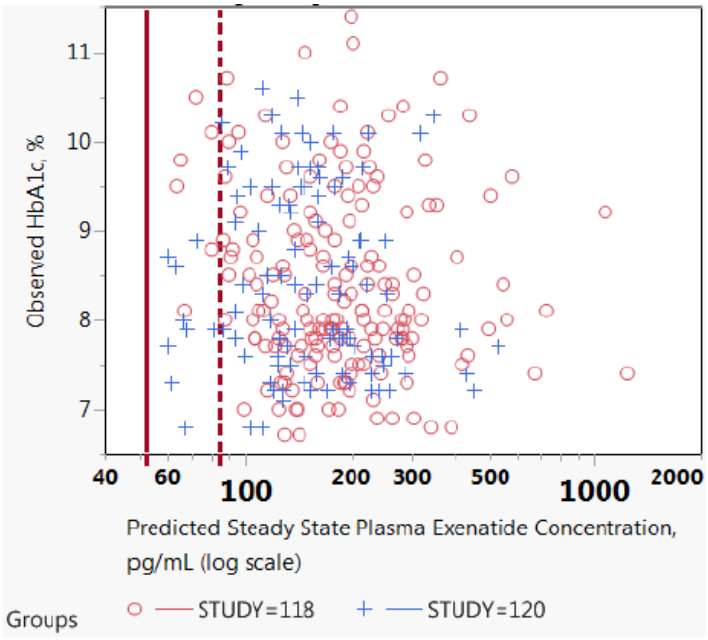
To support the efficacy of the EQWS, especially in BCB120 where the steady state mean exenatide concentrations are lower compared to BCB118, the Applicant assessed the PK and PD relationship of exenatide in a population exposure-response modeling using pooled data from EQWS, and the Bydureon clinical studies.

Reviewer Comment: The clinical pharmacology review states based on the PK modeling, the predicted exenatide EC50 estimates for BCB120 is at least 3-5 times greater than the established exenatide EC50[3]. Thus, a clinical relevance in the exenatide exposure differences from studies BCB118 and BCB120 on HbA1c reduction was not shown.

Figure 1 shows the graph of observed HbA1c versus the predicted average steady-state plasma exenatide concentrations from the population PK modeling. Figure 2 shows the percent change in HbA1c from baseline versus the predicted average steady-state plasma exenatide concentrations from the population PK modeling.

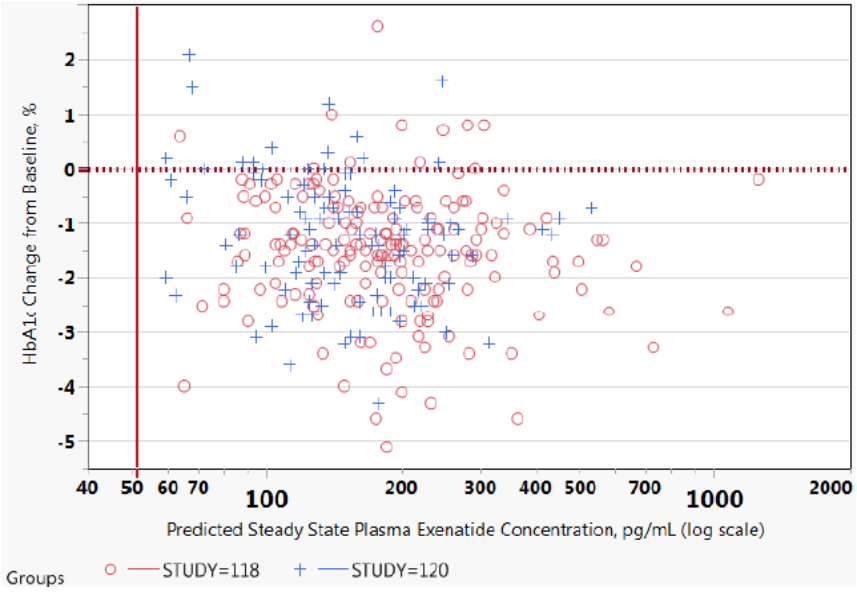
[3] The established exenatide EC50 is estimated at 51.4 pg/mL when exenatide antibody titers are < 125 and 84 pg/mL when exenatide antibody titers are >125.

Figure 1: Plot of observed HbA1c versus individual average steady-state plasma exenatide concentrations during multiple dose administration of EQWS



Source: Excerpted from Clinical Pharmacology review, page 13

Figure 2: Plot of observed HbA1c change from baseline versus individual average steady-state plasma exenatide concentrations during multiple dose administration of EQWS



Source: Excerpted from Clinical Pharmacology review, page 14

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/1.73m2, ideal body weight=64 kg, ADA titer <125) is ≤0.12%. Thus, in support of EQWS's efficacy, despite the differences in the steady-state exenatide concentrations in BCB120 and BCB118, and lower exenatide concentrations compared to the Bydureon clinical program, the population PK and the exposure-response models adequately describe the exenatide plasma concentration and HbA1c data relationship in both Phase 3 EQWS studies. Refer to clinical pharmacology review dated August 21, 2017, for details.

Dose selection:

The Applicant selected the same EQWS dose and regimen (2 mg SC weekly) as the approved dose of Bydureon. PK/PD modeling and simulations confirmed that the 2 mg EQWS dose was efficacious as compared to the established EC50 for exenatide. Clinical pharmacology supports the dosing for EQWS (refer to the clinical pharmacology review dated August 21, 2017).

4.6. Devices and Companion Diagnostic Issues

Division of Medication Error Prevention and Analysis (DMEPA) was consulted to evaluate the human factors (HF) validation study report, the labeling comprehension study, and the Applicant's proposed name. Refer to their review dated September 8, 2017, for details. Center for Devices and Radiological Health (CDRH), reviewed the device component (autoinjector) of the EQWS combination product. Refer to their review dated September 15, 2017, for details.

Reviewer Comment: DMEPA states (September 8, 2017) "the human factor validation study showed failures on critical tasks. The root cause analysis and subjective feedback indicated that additional changes to the proposed labeling are necessary to improve the clarity of the product labeling. However, the changes do not require additional human factor validation studies". DMEPA has provided recommendations for revising the Prescribing Information, Instructions for use, and medication guide (review dated September 8, 2017).

EQWS is presented as a single use, fixed-dose autoinjector for subcutaneous injection of 2 mg of exenatide once-weekly. The autoinjector is the device constituent part of the EQWS combination product (drug-device). The EQWS-filled cartridge is assembled into the autoinjector. To prepare a dose with the autoinjector, the microspheres are re-suspended by shaking the autoinjector before subcutaneous administration.

(b) (4)

The Applicant states the formulation and autoinjector used in the Phase 3 studies represent the

to-be-marketed products.

Reviewer Comment: Following completion of the Phase 3 studies, the Applicant states (b) (4) (b) (4) (b) (4) *Also, several minor design improvements were made to the autoinjector. The CDRH reviewer states "the autoinjector design changes did not affect the essential performance requirements,* (b) (4) (b) (4) *The clinical autoinjector is comparable to the to-be-marketed presentation in terms of performance requirements".*

The CDRH reviewer recommends approval based on the review of the device constituent part of the combination product for EQWS. For details refer to the CDRH review dated September 15, 2017.

5 Sources of Clinical Data and Review Strategy

5.1.1. Table of Clinical Studies

Table 2: Listing of Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Countries
Controlled Studies to Support Efficacy and Safety							
BCB118	Non-inferiority, open-label, randomized, 2-arm study testing EQWS with active comparator Byetta	2 mg weekly subcutaneously	HbA1c change from baseline to Week 28	28-week controlled period + 24-week uncontrolled extension period + 10 week follow-up	229 EQWS and 146 Byetta	T2DM	United States
BCB120	Non-inferiority, open-label, randomized, 3-arm study testing EQWS with active comparator sitagliptin and placebo arm	2 mg weekly subcutaneously	HbA1c change from baseline to Week 28	28-week controlled period + 10-week follow-up	181 EQWS, 120 sitagliptin and 61 placebo	T2DM	United States

5.1.2. Review Strategy

This review will focus primarily on the efficacy and safety findings from the two Phase 3 studies, BCB118 and BCB120. For a discussion of the CMC, nonclinical findings, and clinical pharmacology please refer to the brief discussion above, and the respective primary reviews.

In BCB118 efficacy and safety was evaluated compared to Byetta in adult patients with T2DM who have inadequate glycemic control (i.e., HbA1c ≥7.0% to ≤10.5%) on maximum tolerated doses of metformin, thiazolidinedione (TZD), and sulfonylurea (SU) or a combination of any two. The trial consisted of a 28-week, randomized, open-label treatment period, followed by a 24-week safety extension period where the subjects on Byetta switched to EQWS (i.e., 52-week total treatment duration).

Trial BCB120 is intended to provide efficacy and safety data comparing EQWS to sitagliptin and placebo in a 28-week, randomized, open-label, parallel-group trial in patients with T2DM who had inadequate glycemic control (i.e., HbA1c ≥8.0% to ≤12.0%) on metformin therapy (≥1500 mg/day).

For efficacy and safety, the emphasis of the review is in the 28-week controlled period of the Phase 3 studies to estimate incidence rates of adverse reactions. The reviewer examined the uncontrolled extension period of BCB118 for potential identification of rare safety signals.

6 Review of Relevant Individual Trials Used to Support Efficacy

The review of the EQWS program was done by individual trial and by comparison of treatment arms.

For the individual trial review, the reviewer focused on the individual trial clinical study reports, protocols, and statistical analysis plan. For the review across trials, the reviewer used the summary of clinical efficacy.

Both Phase 3 trials were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization (ICH) Good Clinical Practice (GCP). The trials were monitored by the Applicant using on-site visits, telephone calls, regular inspections of the case report forms and audits.

Study Design

1. STUDY BCB118

Study BCB118 title: a Randomized, Open-Label, Long-Term, Parallel-Group, Comparator-Controlled, Multi-center Study To Compare The Glycemic Effects, Safety, And Tolerability Of

Clinical Review
Mahtab Niyyati, MD
NDA 209210
BCise, Exenatide Once-Weekly Suspension (EQWS)

Exenatide Once Weekly Suspension To Exenatide Twice Daily In Subjects With Type 2 Diabetes Mellitus.

This section discusses BCB118 comparing the efficacy of EQWS with Byetta in T2DM subjects treated inadequately with metformin, SU, pioglitazone or any two combinations using a non-inferiority design.

The review of BCB118 focuses on the 28-week controlled treatment period because the Applicant presents the 28-week efficacy trial results in the proposed label. The 24-week uncontrolled extension period is reviewed for supplemental exploratory analyses.

BCB118 began January 28, 2013, and was completed August 19, 2014. The study was conducted at 65 sites in the United States. The Applicant screened 681 subjects and randomized 377 subjects to the two treatment arms (Byetta and EQWS).

General Design Characteristics

BCB118 is a randomized, open-label, multi-center, 2-arm study. T2DM subjects were randomly randomized in a 3:2 fashion to EQWS SC once weekly or Byetta SC twice daily. The randomization was stratified by previous treatment (diet/exercise, SU, or non-SU), HbA1c and renal function at baseline.

Reviewer Comment: BCB118 is an open-labeled study. In general, un-blinded trials may be susceptible to bias. The Applicant states the subjects, investigator, site staff and the Applicant involved with the data review and analysis were blinded to the key efficacy data throughout the 28-week treatment period.

After 28 weeks of randomization, the subjects were invited to enter an additional 24 weeks of treatment. In the extension arm, the EQWS group continued on EQWS, while the Byetta group switched to EQWS.

Reviewer Comment: During the EOP2 meeting (December 14, 2011) the Agency recommended a controlled extension period especially if the Applicant planned on relying on data from the extension period for labeling purposes. The label focuses on the 28-week controlled period for efficacy.

At selected sites, a meal test cohort of 40 subjects was enrolled in a sub-study and was tested with a standardized meal test along with postprandial glucose, insulin, and triglyceride, and PK assessments.

Study objective and primary efficacy endpoint

The primary objective of BCB118 is confirming the efficacy of EQWS in controlling glycemia in subjects with T2DM. The primary efficacy endpoint is change in HbA1c from baseline (Visit 3 [Day 1]) to Week 28 (Visit 16).

The Applicant states the values at the time of randomization was considered as baseline. If the randomization visit value was missing, then the screening value was used as the baseline value (if available)[4].

Secondary efficacy endpoints

- Proportion of subjects achieving HbA1c target value of <7% at Week 28[5]
- Change in Fasting Plasma Glucose (FPG) from baseline (Visit 3, Day 1) to Week 28
- Change in body weight from baseline (Visit 3, Day 1) to Week 28
- Change in 2-hour postprandial plasma glucose from baseline (Day 1) to Week 16 (Visit 13) for subjects in the meal test cohort

Reviewer Comment: The Applicant only includes the 28-week primary and secondary efficacy results in the proposed label, including results on body weight. The review will not discuss the tertiary endpoints or the exploratory endpoints at Week 52.

Population

T2DM subjects inadequately controlled with diet or exercise or with 1 or 2 oral antidiabetic drugs (metformin, SU, TZD). The enrolled T2DM population is without severe or end-stage renal disease or severe congestive heart failure. The subjects are not enriched for cardiovascular disease; however, subjects with stable heart disease are not excluded.

Key Inclusion Criteria

- Adult ≥ 18 year old diagnosed with T2DM, HgA1c 7.1-11% (inclusive) and FPG < 280 mg/dL twice (screening and Visit 2 [Day -7])
- Background medication (any of the below or combination of two):
  - Diet and exercise
  - Metformin (≥1500 mg/day for at least two months before screening)
  - SU for two months before screening
  - Pioglitazone (≥ 30 mg/day for three months before screening)

[4] The Applicant states the efficacy analyses in the clinical study report used the screening HbA1c values. However, because baseline HbA1c were specified in the statistical analysis plan for use in the primary, secondary and subgroup analyses, these analyses was rerun for the summary of clinical efficacy using the baseline HbA1c for the primary endpoint, secondary endpoints, and subgroup analyses as pre-specified in the statistical analysis plan.

[5] The Applicant states any intent-to-treat (ITT) subject who only had baseline HbA1c value but no post-baseline HbA1c value was considered as not achieving HbA1c of <7% at Week 28.

- Stable body weight (not varying by >3%) for last three months before screening with BMI ≤ 45 kg/m2
- Stable treatment for at least two months or no treatment with:
  - Hormone replacement therapy for females
  - Antihypertensive
  - Lipid-lowering
  - Thyroid hormones
  - Antidepressant
- No lactation or pregnancy or must use birth control during the study (subjects exposed to EQWS must extend using birth control for ten weeks after the last dose of EQWS).
- No clinically significant lab, ECG, or physical examination abnormality

Key Exclusion Criteria

- Pancreatitis (past diagnosis or current)
- Triglyceride level ≥ 500 mg/dL at screening
- Personal or family history of medullary carcinoma or multiple endocrine neoplasia
- Renal transplant, dialysis or severe renal insufficiency (eGFR < 30 mL/min/1.73m2)[6]
- Severe congestive heart failure (New York Heart Association Class IV)
- Active cardiovascular disease[7] within three months of screening. Subjects with stable cardiac disease are not excluded.
- Severe hypoglycemia ≥ two within six months before screening
- Serum calcitonin ≥ 100 pg/mL at screening
- Known contraindication, allergies, or hypersensitivity to any component of study drug (including poly D, L-lactide-co-glycolide [PLG] and MCT)
- Prior exposure to exenatide (Byetta, Bydureon or EQWS)
- Exposure to dipeptidyl-peptidase-4 (DPP-4) inhibitors within three months, Alpha-glucosidase inhibitor, meglitinide, nateglinide, or pramlintide within 30 days, or insulin within two weeks or for more than one week within three months before screening

Reviewer's comment: The inclusion and exclusion criteria attempt to limit risk to subjects. In general, the selection criteria exclude subjects with advanced comorbid conditions. Also, the proposed background oral antidiabetic drug doses are optimal or near-optimal doses of approved therapies, which is in line with clinical practice.

Study treatment and Regimen, 28-week controlled treatment period

- EQWS group: 2 mg SC once weekly (± two days) with the autoinjector, SC injection in the abdomen, thigh, or upper arm. The site of injection rotated regularly.

[6] calculated using the Modification of Diet in Renal Disease (MDRD) formula
[7] Such as myocardial infarction, clinically significant arrhythmia, unstable angina, coronary artery bypass surgery, or angioplasty

    - A missed EQWS dose should be administered as soon as possible if the next dose is due at least the next day. Thereafter, subjects can resume with the dosing schedule.
- Byetta group: 5 µg for four weeks followed by 10 µg upto Week 28 of the controlled treatment period; injected SC within 60 minutes before meal time in the morning and evening. If a meal was skipped, Byetta was still administered and followed by a snack within 60 minutes, with at least 6 hours till the next dose. SC injection in the abdomen, thigh, or upper arm. The site of injection is rotated regularly.

Reviewer Comment: After the 28-week period the EQWS group continued on the same regimen of EQWS, and the Byetta group switched to EQWS for an additional open-label uncontrolled 24-weeks extension period.

Reviewer Comment: The trial adheres to the approved Byetta dose and titration regimen in the active comparator arm as labeled.

The investigator assesses the subject's compliance by reviewing subject's glycemic control and adherence to schedule. The compliance data is collected using a dosing log.

Assignment to treatment (randomization)

Randomization to Byetta or EQWS is carried out in a 3:2 fashion at Visit 3 (Day 1) by the interactive web response system (IWRS). The randomization is stratified by:

- Diabetes management at screening
    - Diet or exercise
    - SU or non-SU use[8]
- HbA1c at screening
    - < 9 or ≥ 9 %
- Renal function; estimated glomerular filtration rate (eGFR)
    - Normal: ≥ 90 mL/min/1.73 m2
    - Mild: 60-89 mL/min/1.73 m2
    - Moderate: 30-59 mL/min/1.73 m2

Reviewer Comment: In BCB118, ~37% of the enrolled subjects have normal renal function, 50% mild renal impairment, and 13% moderate renal impairment.

Choice of Byetta as the control group

[8]The protocol states ~ 30% of the subjects will be on SU alone or in combination with metformin or pioglitazone.

During the EOP2 meeting (December 14, 2011) the Agency agreed to Byetta as the comparator for bridging the EQWS drug product to the existing exenatide clinical program. Byetta, Bydureon, and EQWS all share the same active ingredient exenatide.

Concurrent medications

The Applicant states the study entry dosages of the background medications should be maintained unless instructed otherwise by the investigator. Subjects are not permitted to start medication during the study, and change in regimen for any concomitant medication must be reported to the Applicant.

The protocol allowed background oral antidiabetic medications as described in the inclusion criteria[9] and a stable medication regimen for two months for comorbidities[10]. The protocol prohibited the use of exenatide containing GLP-1 agonist, or any GLP-1 analog, an alpha-glucosidase inhibitor, or meglitinide, nateglinide, or pramlintide within 30 days before screening, insulin within two weeks or for > 1 week within three months before screening, and DPP-4 inhibitors within three months before screening. The protocol also prohibited systemic corticosteroids within three months before screening[11] and prescription or over-the-counter weight loss medications within three months before screening.

Rescue medications

The protocol states if the subjects meet the criteria for loss of glucose control as stated below, rescue medication should be initiated according to local prescribing information

- FPG > 270 mg/dL from Week 4 to 16[12]
- FPG > 240 mg/dL from Week 16 to 28[12]
- HbA1c ≥9.0% at any visit after Week 28

The clinical study report states during the 28-week treatment period, 22 subjects (15%) in the Byetta group and 23 subjects (10%) in the EQWS group received new antidiabetic medications. Of the subjects who received new antidiabetic medication, 6 (4.1%) in the Byetta group and 5 (2.2%) in the EQWS group received rescue medications during the 28-week controlled period.

During the 52-week period, 41 (28.1%) in the Byetta group, and 47 (20.5%) in the EQWS group received new antidiabetic medication. Of the subjects who received new antidiabetic medication 22 (14.9%) in the Byetta group and 20 (83.7%) in the EQWS group received rescue

[9] Subjects should continue study entry dosages and time of administration daily unless instructed otherwise by the investigator, except that any morning dose of oral antidiabetic therapy should be delayed on the morning of study-site visits.
[10] Hormone replacement therapy for females, antihypertensive, lipid-lowering medication, thyroid hormones, antidepressant
[11] By oral, intravenous, intra-articular, or intramuscular route; or potent, inhaled, or intrapulmonary (including Advair) steroids known to have a high rate of systemic absorption.
[12] By lab measurement at 2 consecutive visits.

medications during the 52-week period. The most common rescue medications used were insulin (Lantus or Levemir) and SUs.

In response (August 16, 2017) to an Information Request (August 2, 2017), the Applicant clarified that the clinical study report is incorrect; at Week 52, 21 (9.2%) subjects in the EQWS group and 20 (13.7%) subjects in the Byetta group received rescue medications..

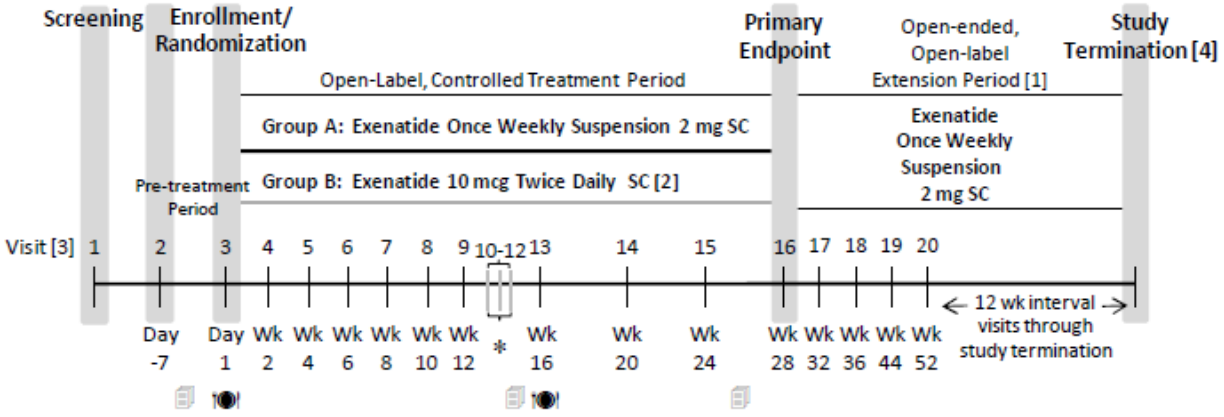
In response (August 16, 2017) to an Information Request (August 2, 2017) asking for clarification on the difference between rescue medication vs. new antidiabetic medication, the Applicant stated subjects may start 'new antidiabetic medication' during the study treatment period, without meeting the criteria for loss of glucose control mentioned above. The 'new antidiabetic medication' is chosen based on an algorithm, while rescue medication is not chosen based on an algorithm.

Because the criteria for initiation of 'new antidiabetic medication' was still unclear, and because subjects who did not meet rescue criteria were started on new antidiabetic medication, another Information Request (August 28, 2017) was sent asking for clarification. The Applicant responded (September 13, 2017) the initiation of new antidiabetic medication outside of rescue criteria was done by the investigators on their own initiative. This is a protocol violation and leads to exclusion from the evaluable population.

Reviewer Comment: The use of 'new antidiabetic medication' underestimates the true incidence of EQWS subjects who may have required rescue.

The efficacy population for labeling includes all randomized subjects regardless of initiation of rescue or adherence to treatment and not just the 'evaluable subjects' excluding the subjects who received new antidiabetic medication.

Figure 3: Procedure and schedule, BCB118:



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.
* Study site visits for PK assessments for a subset of subjects at select study sites.

Source: Excerpted from BCB118 Clinical Study Report, page 36.

The study consists of screening, controlled treatment, and uncontrolled open-ended extension period and a meal test cohort. The controlled treatment period started on Day 1 (Visit 3)[13]. Subjects had site visits every two weeks, followed by every four weeks from Visit 3-9 and Visit 10-15, respectively. The uncontrolled extension period started at Week 32 (Visit 17). The subjects returned to site on Visit 18 (Week 36), Visit 19 (Week 44), and Visit 20 (Week 52). Subsequent visits occurred at 12-week intervals. All subjects returned for a follow-up visit ten weeks after the final treatment visit, no matter when. The meal test cohort attended Visits 3, 10, 11, and 12 for postprandial assessments.

Statistical analysis plan

The Applicant states only endpoints derived after 28 weeks of treatment were statistically analyzed.

Sample Size determination

The Applicant's sample size calculation was powered at > 95% power to demonstrate that EQWS is non-inferior to Byetta within a 0.4% non-inferiority margin assuming a common standard deviation of 1.15% and 91% power to show the superiority of EQWS to Byetta.

In the protocol, the Applicant anticipated an early withdrawal rate of 15% at Week 28 and 20% at Week 52.

[13] If the subjects did not continue on to the extension period, the last day of the 28-week controlled period was 7 days after the last EQWS dose or 1 day after the last Byetta dose.

Reviewer Comment: The statistical reviewer states in BCB118, a moderate power was sustained because of a high rate of missingness at Week 28, i.e., 23% (EQWS) and 26% (Byetta).

Handling of missing data

Details are discussed in section 7.3 of this review.

Interim Analyses

No interim analysis was planned for this study.

Protocol Amendments

BCB118 underwent two protocol amendments. In the first amendment, the main changes include specifying the percentage of renally impaired subjects and changing the eGFR measurements from Cockcroft-Gault to Modification of Diet in Renal Disease (MDRD). The Applicant added an adjudication process for malignancies and pancreatitis and stated that injection site reactions would be reported only if qualified as an adverse event. Injection site biopsy is considered only if the injection site reaction is severe and needed.

Also, the Applicant stated post-rescue data or post-treatment follow-up, whichever occurs first, will be excluded and not carried forward in the summaries and analyses of efficacy endpoints in the 28-week assessment period. Safety data collected post-rescue or after the last dose of study medication, whichever occurs first, will be summarized separately.

During Amendment 2 the main changes were the addition of adjudication of thyroid cancer and pancreatic cancer and reporting Serious Adverse Events (SAE) for three months after the last dose of study drug.

Reviewer Comment: The protocol amendments were evaluated for potential to change the outcome of the analysis. The exclusion of the post-rescue or non-adherent subjects from the primary analysis as proposed in the protocol amendment 1 is addressed in Section 7 of this review. Otherwise, the proposed amendments are unlikely to have significantly affected the integrity of the trial.

Data Quality and Integrity

The statistical reviewer noted discrepancies in the primary results between the clinical study report for BCB118 and the integrated summary of efficacy report and resolved the issue through Information Request (the Applicant clarified the datasets used for analysis).

The statistical reviewer removed six subjects from the efficacy analysis datasets: one miscoded EQWS subject (b) (6), four subjects enrolled twice in different

treatment arms (b) (6) and one EQWS subject who did not have baseline measurement (b) (6) The revised analysis of the primary endpoint by the statistical reviewer reflects the amended efficacy population.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Clinical Study Report for BCB118 states that this study was conducted in accordance with the Declaration of Helsinki (1964), including the current Seoul revision (2008), and consistent with Good Clinical Practice and applicable laws and regulations.

Patient Disposition

Of 881 subjects screened, 304 were screen failures. In total, 375 subjects were randomized to either Byetta (148) or EQWS (229). 2 subjects withdrew before being exposed to Byetta. Thus, 146 were randomized to Byetta and 229 randomized to EQWS.

Reviewer Comment: The SDTM dataset identifies the two subjects who were excluded because of not receiving study drug. The two subjects are eliminated from the actual treatment arm in ADSL.

Note the observed number of subjects at Week 28 for estimating the treatment effect including all randomized subjects regardless of adherence to study drug or initiation of rescue therapy is 119 in the Byetta group and 182 in the EQWS group (Table 3).

Reviewer Comment: The rate of missing efficacy data at Week 28 was 26.7% for Byetta and 23.1% for EQWS. In section 7 'Integrated Review of Effectiveness' the statistical handling of missing data is reviewed.

A higher percentage of subjects in the EQWS group completed 28 weeks (84.3%) compared to the Byetta group (79.5%).

Table 3: Analysis population for study BCB118, mITT

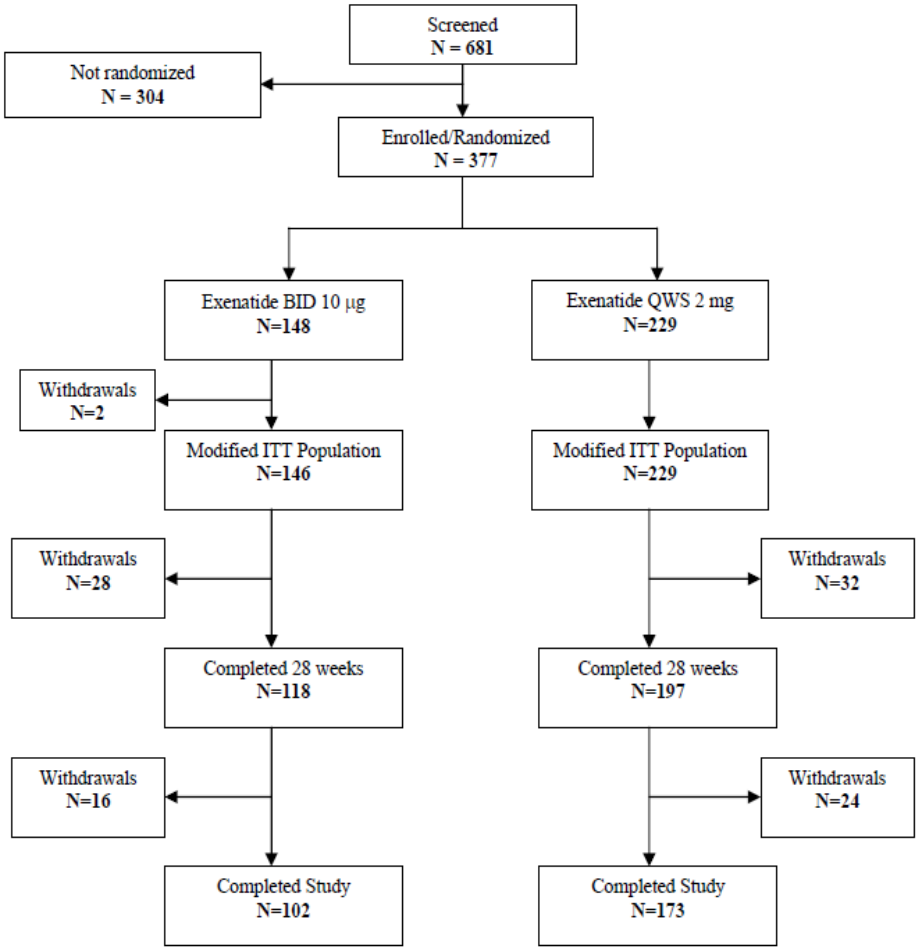
	BID	*EQWS*
	≤ 28 weeks	
Randomized	148	229
Randomized & Treated (ITT population)	**146 (100%)**	**229 (100%)**
Completed 28 week	116 (79.5%)	193 (84.3%)
Observed N (%) at Week 28 for HbA1c		
mITT population (de-jure)	107 (73.3%)	176 (76.9%)
Percent Dropouts	26.7 %	23.1 %
mITT + retrieved dropouts (de-facto)	119 (81.5%)	182 (79.5%)
Percent Dropouts	18.5 %	20.5 %

Source: Excerpted from CDER's statistical review dated September 14, 2017, page 16.

Note the following observations in the 28-week assessment period of study BCB118:

- 14% of the EQWS group withdrew vs. 19% from Byetta group.
- 10% of the EQWS group required additional new antidiabetic medication, of which 2.2% met rescue criteria. The majority of the new antidiabetic medication was SUs, followed by metformin, followed by insulin (note 15% of the Byetta group required new antidiabetic medication). The administration of new antidiabetic medication without meeting rescue criteria is a protocol violation (Response to Information Request; September 13, 2017).
- At Week 28, 23% of the EQWS subject vs. 26.7% of the Byetta subjects have missing values for the primary efficacy estimand.
- When including all randomized subjects regardless of therapy adherence or initiation of rescue medication, a similar proportion of subjects in the EQWS and the Byetta group are included in the primary efficacy estimation.

Figure 4: Disposition, BCB118



Source: Excerpted from Clinical Study Report, BCB118, page 63.

Table 4: Disposition, BCB118

Parameter	EQWS 2 mg (N=229)	BYETTA BID 10 µg (N=148)
Completed 28-week controlled treatment period	197 (86.0)	118 (79.7)
Completed 52 weeks	173 (75.5)	102 (68.9)
Withdrawal prior to Week 28	32	30
Reason for withdrawal		
Withdrawal by subject	17 (7.4)	11 (7.4)
Adverse event	6 (2.6)	8 (5.4)
Investigator decision	1 (0.4)	1 (0.7)
Protocol violation	2 (0.9)	1 (0.7)
Lost to follow-up	5 (2.2)	7 (4.7)
Administrative	0	2 (1.4)
Loss of glucose control	1 (0.4)	0
All withdrawals on/after Week 28	24	16
Withdrawal by subject	16 (7.0)	7 (4.7)
Adverse event	1 (0.4)	2 (1.4)
Investigator decision	0	3 (2.0)
Protocol violation	0	0
Lost to follow-up	7 (3.1)	4 (2.7)
Administrative	0	0
Loss of glucose control	0	0

Source: Excerpted from Summary of Clinical Efficacy, Table 6, page 36.
Abbreviations: BID: twice daily; N=number

Reviewer Comment: After stratifying by the primary reason for discontinuation before Week 28, subject choice occurred in both the EQWS and the Byetta groups at a similar frequency but at a higher incidence compared to other listed reasons. The Byetta group dropped out from adverse events at a higher frequency compared to EQWS (2.6% in EQWS vs. 5.4% Byetta). Drop-out due to adverse events is discussed in Section 8 of this review (safety).

Protocol Violations/Deviations

A summary listing of the relevant protocol deviations reported in BCB118 is presented in Table 5. The Applicant states of the 375 randomized subjects 136 (36.1%) had protocol deviations during the 28-week treatment period. 163 subjects (42.3%) had protocol deviations during the 52-week study period, with similar proportions in each treatment group.

Table 5: Protocol deviations during the 28-week treatment period, BCB118, randomized population

Deviation Type	Exenatide BID 10 mcg N = 148	Exenatide QWS 2 mg N = 229
ALL DEVIATION TYPES DURING THE 28-WEEK ASSESSMENT	53 (35.8)	83 (36.2)
INCLUSION/EXCLUSION CRITERIA	5 (3.4)	9 (3.9)
CONCOMITANT MEDICATION CHANGE	14 (9.5)	17 (7.4)
STUDY DRUG INCORRECT TREATMENT OR DOSE	1 (0.7)	3 (1.3)
OTHER	40 (27.0)	70 (30.6)

The Applicant states subjects may have > 1 protocol deviation. Each subject is counted only once in the total row and in each category.
Source: Excerpted from Clinical Study Report BCB118, page 61, Table 4.3-1.

Reviewer Comment: The initiation of new antidiabetic medication without meeting rescue criteria is a protocol violation and discussed on page 34 of this review under 'Rescue Medication'.

Note two subjects were screened, randomized, and treated in the study twice, once in each treatment group. The narratives are discussed in the safety section 8.

One subject was initially assigned to EQWS, but later enrolled at a second site and assigned to Byetta. The subject was terminated from both sites early after it was determined that he was double-enrolled.

The second subject was initially assigned to Byetta but later enrolled at a second site and was assigned to EQWS. He was lost to follow-up at the first site and was later withdrawn from the second site as per Investigator's Decision after the site learned that he was adjusting his anti-diabetes regimen.

Reviewer Comment: The Applicant states the data from these two subjects are treated in the primary analysis as if four subjects were enrolled, randomized, and treated in the study. (First subject: (b) (6) *and the second subject* (b) (6) (b) (6) *The statistical reviewer excluded the double enrollments from the ITT efficacy population. The narratives of the double-enrollments are discussed in section 8 (safety).*

Table of Demographic Characteristics

In study BCB118, the demographics between the treatment arms appear balanced. Overall, randomization appears successful with study groups having similar baseline characteristics.

Notable observations include:

- The majority of the population is White obese males < 64 years of age: 80% < 64 years old, 74% White, 64% male and mean weight is 214 Lbs., 70% BMI ≥ 30-45 kg/m^2.

- 29 (12.7%) of the exposed population has moderate renal impairment.
- 12.8% do not take background anti-diabetic medication and were treated with diet and exercise alone at screening.
- 40% were treated with SU at screening, and most of them received SU in combination with metformin.

Reviewer Comment: The demographics in BCB118 reasonably represent the general T2DM population who may be prescribed EQWS as a second-line therapy. Baseline characteristics were balanced between treatment groups, suggesting appropriate randomization.

Efficacy Results by the Applicant – Primary Endpoint

In this section, the Applicant's efficacy results are discussed. In Section 7 the Agency's efficacy analysis is discussed.

The Applicant compared the change in HbA1c from baseline to Week 28 between the EQWS group and the Byetta group using MMRM in the mITT population (observed data; de jure population) excluding post-rescue or post-treatment discontinuation observations. No imputation of missing data was performed, and no retrieved dropout subjects were included in the Applicant's primary analysis.

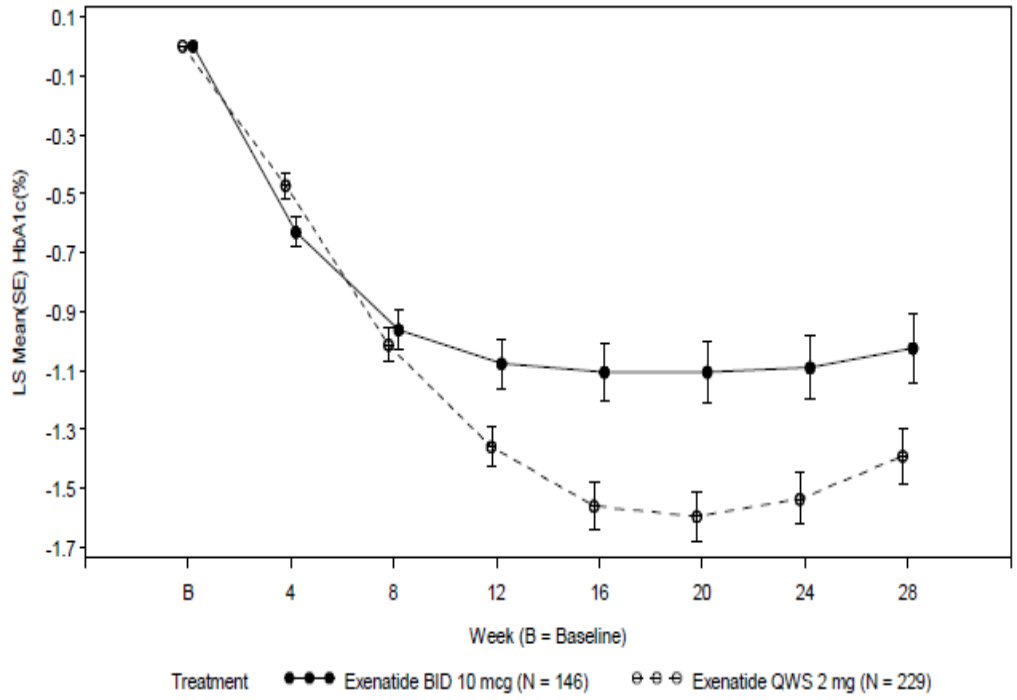
The Applicant concluded non-inferiority of EQWS to Byetta if the upper limit of the 2-sided 95% CI was less than the non-inferiority margin (b) (4)%. Superiority was concluded if this upper limit was less than zero.

Applicant's primary efficacy analyses results

The mean HbA1c at baseline was 8.44 % in Byetta group and 8.45% in the EQWS group. The LS mean change from baseline (SE) at Week 28 was -1.02% (0.11%) and -1.39% (0.09%) in the Byetta and EQWS groups respectively.

The Applicant states the 28-week change in HbA1c of EQWS compared to Byetta met the non-inferiority and the superiority endpoint. The superiority of EQWS compared to Byetta was confirmed since the 95% confidence interval for the treatment difference of the change in HbA1c was entirely below 0%; the upper limit of the CI was -0.12. Numerically, EQWS was superior to Byetta. (b) (4)

Figure 5: HbA1c (%) after 28 weeks of treatment, change from baseline, confirmatory statistical analysis, mITT population, Applicant's analysis



Source: Excerpted from Clinical Study Report BCB118 page 78

Table 6: Efficacy data at 28 weeks, BCB118, mITT, [redacted] (b) (4) as monotherapy or as add-on to metformin, an SU, a TZD, or combination of oral agents

	BYDUREON BCISE 2 mg QW	BYETTA 10 mcg twice daily[1]
Intent-to-Treat Population (N)[76]	229	146
HbA_{1c} (%)[77]		
Mean Baseline	8.5	8.4
Mean Change at Week 28[1]	-1.5	-1.1
Difference from BYETTA[1] [95% CI]	-0.38 (-0.64, -0.12)*	
Percentage Achieving HbA_{1c} <7% at Week 28 (%)[2] [78]	40	36
Fasting Plasma Glucose (mg/dL)[79]		
Mean Baseline	179	186
Mean Change at Week 28[1]	-32	-22
Difference from BYETTA[1] [95% CI]	-10 (-21.5, 1.7)	
2-hour postprandial plasma glucose change from baseline (mg/dL)[3] [80]		
Standard Meal Test Population (N)	37	31
Mean Baseline	254	291
Mean Change at Week 28[1]	-78	-105
Difference from BYETTA[1] [95% CI]	27 (-5.2, 58.9)	

N=number of patients in each treatment group, CI-unadjusted confidence interval, QW=once weekly; *p-value=< 0.01; 1=least square mean; 2=subjects with missing values at Week 28 counted as not achieving goal; 3=data extracted from the standard meal test, which occurred at baseline and week 16.
Source: Excerpted from the proposed label, Section 14, page 21-22.

52-week data, uncontrolled extension period

Reviewer Comment: The additional 24-week extension is mentioned below for purposes of completeness, and for exploratory analysis for the durability of glycemic efficacy in this trial.

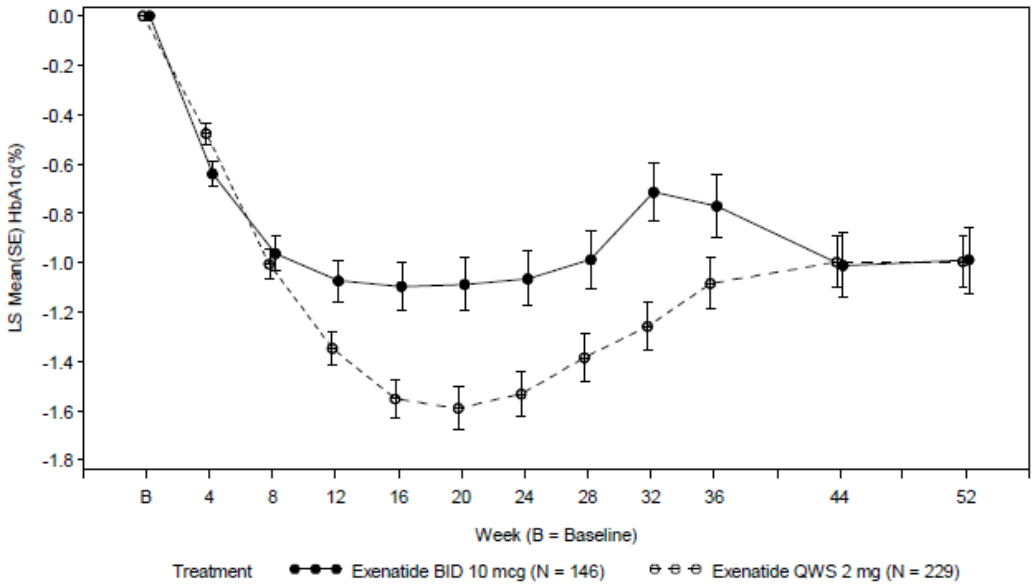
Of note, there was no pre-specified analysis for change in HbA1c at the end of the extension period (i.e., for superiority or noninferiority), and the Applicant does not seek to include the extension data in the label.

All subjects received EQWS in the exploratory long-term extension phase. The Applicant states the HbA1c reductions remained clinically significant over 52 weeks; however the HbA1c effect partially diminished over time especially in the group that had initially received EQWS.

The Applicant states the LS mean change from baseline (SE) at Week 52 was -0.99% (0.13%) and -1.00% (0.11%) in the Byetta and EQWS treatment groups, respectively.

The Applicant states similar proportions of subjects in both groups achieved HbA1c <7% or ≤6.5% at Week 52 and the mean reductions in FPG concentration at Week 52 in both EQWS and Byetta groups were similar. The reductions in body weight were sustained at Week 52.

Figure 6: LS mean (SE) change from baseline to Week 52 in HbA1c, BCB118, mITT



Source: Excerpted from CSR BCB118 page 79

The Applicant states although both groups received EQWS after Week 28, the pattern of HbA1c change over time differed between the Byetta and EQWS group during the long-term extension period. HbA1c levels briefly increased from Week 28 to Week 32 and then gradually declined through Week 44 in subjects who had were randomized to Byetta followed by a switch to EQWS, reflecting the time required to achieve steady-state concentration.

In contrast, HbA1c continued to progressively increase over time in the EQWS group from the nadir achieved at Week 20 to Week 44. At Week 44, the change in HbA1c converged for both groups and appeared to reach a plateau.

Reviewer Comment: The possible effect of antibodies, especially higher titer antibodies, on decreasing efficacy at Week 28 and Week 52 is discussed in Section 8.5 (immunogenicity).

Efficacy Results by the Applicant – Secondary endpoints (Table 6)

The Applicant states because hypothesis tests for primary endpoints in BCB118 were all

statistically significant, hypothesis testing for secondary endpoints were conducted in the following per-specified order:

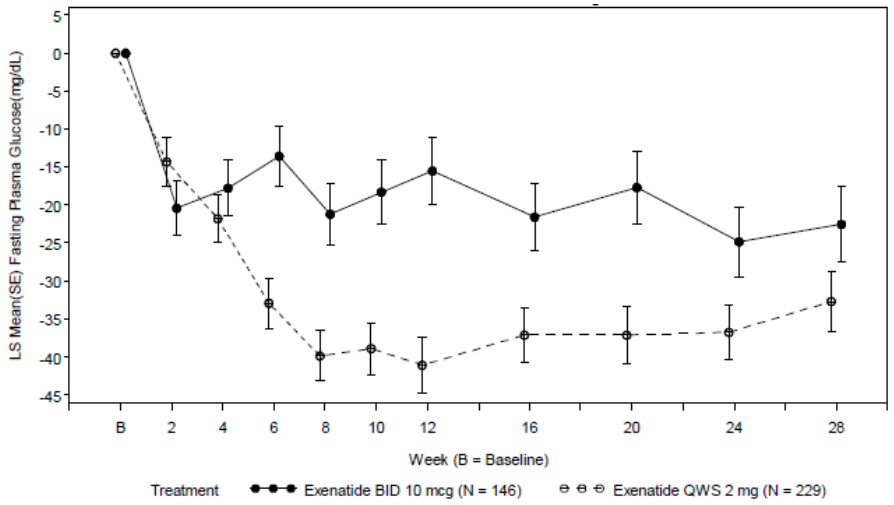
- Proportion of patients achieving HbA1c < 7.0% at Week 28
- Change in FPG from baseline to Week 28
- Change in weight from baseline to Week 28
- Change in 2-hour post-prandial glucose from baseline to Week 28

The Applicant states at Week 28 (Table 6):

- A numerically greater proportion of subjects achieved HbA1c <7%
- The FPG reduction from baseline was greater in the EQWS group than in the Byetta group
- The reduction in LS mean in body weight from baseline to Week 28 was -1.39 (0.0287) kg in the EQWS group and -1.76 (0.365) kg in the Byetta group.
- Numerically greater reduction in LS mean 2-hour PPG concentration in the Byetta group: -104.71 mg/dL (5.769) than in the EQWS group -77.86 mg/dL (-4.29)

Reviewer Comment: The Applicant states none of the between-group differences in the secondary endpoints were statistically significant.

Figure 7: LS mean (SE) change from baseline to Week 28, fasting blood glucose, mITT, Applicants data



Source: Excerpted from CSR BCB118 page 84

Durability of Response and Persistence of Effect

Refer to Section 7.1.5 and 8.5 of this review for a discussion on the possible effect of antibodies, especially higher titer antibodies, on efficacy.

6.1.3. Study BCB120

6.1.4. Study Design

2. STUDY BCB120

Study BCB120 title: A Randomized, Long-Term, Open-Label, 3-Arm, Multicenter Study to Compare the Glycemic Effects, Safety, and Tolerability of Exenatide Once Weekly Suspension to Sitagliptin and Placebo in Subjects With Type 2 Diabetes Mellitus

BCB120 began February 8, 2013, and was completed April 4, 2014. A total of 752 subjects were screened, and 365 subjects were randomized. The proposed label presents the 28-week primary and secondary endpoint results.

For the sections with similarities to BCB118, I will refer to the relevant section of BCB118 and only discuss the differences between the two Phase 3 studies.

General Design Characteristics, BCB120

BCB120 is a Phase 3, randomized, open-label, multicenter, comparator- and placebo-controlled, 3-arm study designed to compare the safety and efficacy of EQWS to sitagliptin and placebo in T2DM subjects inadequately controlled on metformin over 28 weeks. Study BCB120 is designed as a non-inferiority study.

Randomization is carried out in 3:2:1 randomization ratio at Visit 3 (Day 1) by the interactive web response system. The randomization is stratified by HbA1c at screening (< 9 or ≥ 9 %).

BCB120 is an open-label study; however, the Applicant states the subjects, the investigators, study-site personnel, and the Applicant were blinded to oral sitagliptin and oral placebo, and to the key efficacy data for the three treatment groups throughout the 28-week treatment period.

Reviewer Comment: At the EOP2 meeting (December 14, 2011) the Applicant discussed conducting a Phase 3 study comparing EQWS to sitagliptin. The Agency suggested a 3-arm study including a placebo arm to estimate the placebo-adjusted effect of sitagliptin. The Agency stated the inclusion of a placebo arm supports the evaluation of EQWS compared to sitagliptin in the proposed un-blinded study. The Applicant complied with the Agency's recommendation.

Study objective and primary efficacy endpoint, BCB120

The primary objective of BCB120 is confirming the efficacy of EQWS in controlling glycemia in subjects with T2DM. The primary efficacy endpoint is change in HbA1c from baseline (Visit 3 [Day 1]) to Week 28 (Visit 11).

Secondary efficacy endpoints, BCB120

- Proportion of subjects achieving HbA1c target value of <7% at Week 28
- Change in FPG from baseline (Visit 3, Day 1) to Week 28
- Change in body weight from baseline (Visit 3, Day 1) to Week 28
- Change in 2-hour postprandial plasma glucose from baseline (Day 1) to Week 16 (Visit 13) for subjects in the meal test cohort

Treatment and Regimen, BCB120

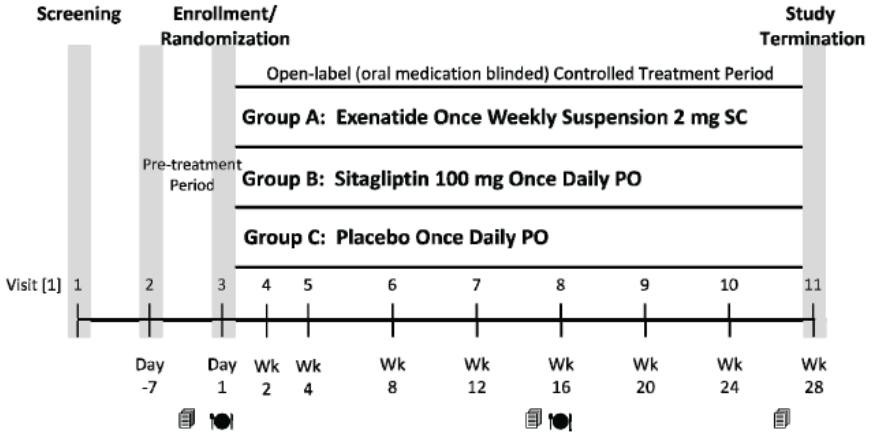
- EQWS: 2 mg SC once weekly (± two days) with the autoinjector, SC injection in the abdomen, thigh, or upper arm. The site of injection rotated regularly within or across regions.
- Sitagliptin and Placebo oral drugs: subjects should continue administering oral study drug at the same time each day (in the morning).

Reviewer Comment: The trial adheres to the approved sitagliptin dose as labeled in the active comparator arm.

The key inclusion and exclusion criteria, population, permitted concurrent medications, and rescue medication criteria are similar to study BCB118 with some differences highlighted below. For details refer to the study design section 6.1.1 for BCB118.

- In BCB120, EQWS was added to the background antidiabetic medication metformin ≥1500 mg/day for at least two months before screening.
- Subjects with eGFR < 60 mL/min/1.73m2 were excluded.
- Subjects exposed to SU or TZD within three months of screening and subjects with an allergy to sitagliptin were excluded.
- Exposure to SU or TZD was prohibited within three months before screening, and GLP-1 agonists and DPP-4 inhibitors were not prescribed during the 10-week safety follow-up period.

Figure 8: Procedure and schedule, BCB120



Indicates 6-point self-monitored blood glucose profiles performed on any 3 days in the week prior to subsequent visit.
Indicates meal test and postprandial assessments for a subset of subjects at select sites.

Abbreviations: PO=by mouth, SC=subcutaneous, Wk=week
1=Visit 2 will occur within 14 days following Visit 1. Visit three will occur 7 (±2) days following Visit 2. Visit 4 through study termination will occur at the indicated interval (±2) days relative to Visit 3. 2=Subjects will return to the study site for a follow-up visit 10 weeks after the final treatment visit.
Source: Excerpted from BCB120 Protocol Amendment 2 page 13

BCB120 consisted of a screening visit (Visit 1) and ten additional study-site visits, occurring at approximately 2- to 4-week intervals through Visit 11 (Week 28/Study Termination). Subjects will return to the study site for a follow-up visit ten weeks after the final treatment visit.

At selected sites, a meal test cohort of 100 subjects (50 subjects from EQWS, 33 subjects from sitagliptin, and 17 subjects from placebo groups) was enrolled in a sub-study and was tested with a standardized meal test along with postprandial glucose, insulin, and triglyceride, and PK assessments.

Statistical analysis plan:

Sample Size determination:

The Applicant's sample size was powered at > 95% power to show superiority of sitagliptin (n=122) to placebo (n=61) assuming a difference of -0.7% with a common standard deviation of 1.15% along with power at > 95% to show the EQWS (n=181) is non-inferior to sitagliptin with the population mean difference of 0.7% between sitagliptin and placebo and a 0.3% non-inferiority margin.

The protocol anticipated an early withdrawal rate of 10% at Week 28, ~162 from EQWS and ~108 from sitagliptin group, and 54 from the placebo group were expected to complete 28 weeks.

Reviewer Comment: The drop-out rate was underestimated at the time of designing the protocol. Refer to section 7.3 for a review on missing data at Week 28 in BCB120.

Handling of missing data:

Refer to section 7.3 for a review on the handling of missing data.

Interim Analyses

No interim analysis was planned for this study.

Protocol Amendments:

The two protocol amendments were evaluated for potential to change the outcome of analysis. The amendments were similar to the amendments made for BCB118 and discussed in Section 6.1.2 (Protocol Amendments for BCB118).

6.1.5. Study Results

Compliance with Good Clinical Practices

The Clinical Study Report for BCB120 states that this study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

Patient Disposition

Of 752 subjects screened, 365 subjects were randomized, of which 182 were randomized to EQWS (181 exposed to EQWS[14]), 122 to sitagliptin, and 61 to placebo.

The statistical reviewer states the observed number of subjects at Week 28 for estimating the treatment effect including all randomized subjects regardless of adherence to study drug or initiation of rescue therapy is 153 in the EQWS group, 106 in sitagliptin group, and 48 in the placebo group (Table 7).

[14] 1 subject did not receive study drug, and was excluded from mITT and safety population.

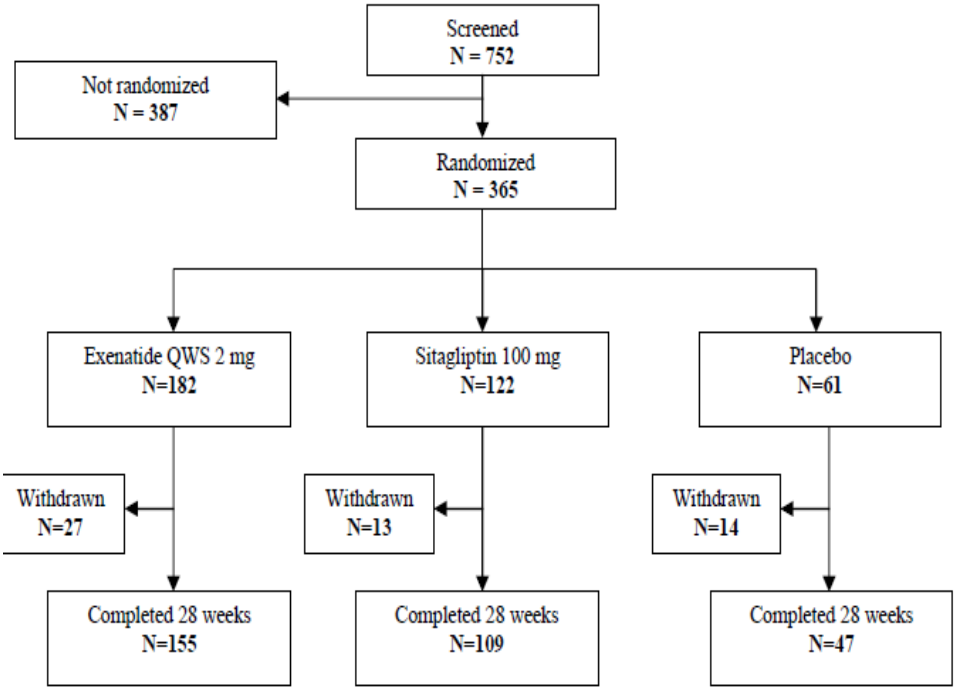
Table 7: Analysis of efficacy population, mITT, BCB120

	EQWS 2 mg	Sitagliptin	Placebo
Randomized	182	122	61
Randomized & Treated (ITT population)	**181 (100%)**	**122 (100%)**	**61 (100%)**
Completed 28-week	155 (85.6%)	109 (89.3%)	47 (77.0%)
Observed N (%) at Week 28 for HbA1c			
mITT population (de-jure)	141 (77.9%)	98 (80.3%)	38 (62.3%)
Percent Dropouts	22.1%	19.7%	37.7%
mITT + retrieved dropouts (de-facto)	153 (84.5%)	106 (86.8%)	48 (78.7%)
Percent Dropouts	15.5%	13.2%	21.3%

Source: Excerpted from CDER's statistical review, page 17.

Reviewer Comment: 85.6% of the EQWS group, 89.3% of the sitagliptin group, and 77% of the placebo group completed the 28 weeks treatment period. The rate of drop-outs is 22.1% for the EQWS group, 19.7% for the sitagliptin group, and 37.7% for the placebo group.

Figure 9: Disposition, BCB120



Source: Excerpted from Clinical Study Report BCB120, page 51.

Table 8: Disposition, BCB120, randomized population

Disposition	Exenatide QWS 2 mg N = 182	Sitagliptin 100 mg PO N = 122	Placebo N = 61	All Subjects N = 365
COMPLETED THE STUDY	155 (85.2)	109 (89.3)	47 (77.0)	311 (85.2)
ALL WITHDRAWALS FROM THE STUDY	27	13	14	54
REASON FOR WITHDRAWAL				
WITHDRAWAL BY SUBJECT	14 (7.7)	7 (5.7)	7 (11.5)	28 (7.7)
ADVERSE EVENT	4 (2.2)	0	3 (4.9)	7 (1.9)
INVESTIGATOR DECISION	1 (0.5)	0	1 (1.6)	2 (0.5)
PROTOCOL VIOLATION	1 (0.5)	0	0	1 (0.3)
LOST TO FOLLOW-UP	7 (3.8)	6 (4.9)	3 (4.9)	16 (4.4)
STUDY TERMINATED BY SPONSOR	0	0	0	0
ADMINISTRATIVE	1 (0.5)	0	0	1 (0.3)
LOSS OF GLUCOSE CONTROL	0	0	0	0

Source: Excerpted from Clinical Study Report, BCB120, page 52.

Reviewer Comment: In all three treatment groups, most of the withdrawals were by subject choice (7.7% in EQWS, 5.7% in sitagliptin, and 11.5% in placebo) followed by lost to follow-up (3.8% EQWS vs. 4.9% in sitagliptin and 4.4% in placebo). The withdrawal rate due to adverse events was higher in the Placebo group (4.9%) compared to the EQWS group (1.7%) and the sitagliptin group (0%). The withdrawals due to adverse events are discussed in Section 8 (safety).

Note the following observations in the 28-week treatment period of study BCB120:

- 27 (15%) of the EQWS group withdrew vs. 13 (10.65%) subjects from the sitagliptin group, and 14 (23%) from the placebo group.
- Seven subjects (3.9%) in the EQWS group, 11 (9.0%) in the sitagliptin group, and 11 subjects (18.0%) in the placebo group received new antidiabetic medications, including rescue medication. 6 (3.3%) subjects in the EQWS group and nine subjects each in the sitagliptin (7.4%) and placebo (14.8%) groups received rescue medication during the 28-week treatment period (all were SUs).
- On average, the placebo subjects were started earlier on rescue medication compared to EQWS and sitagliptin subjects.
- At Week 28, 22% of the EQWS subject vs. 19.7% of the sitagliptin, and 37.7% of the placebo subjects had missing HbA1c values.
- When including all randomized subjects regardless of therapy adherence or initiation of rescue medication, a similar proportion of subjects in the EQWS and the Byetta group are included in the primary efficacy estimation.

Protocol Violations/Deviations

The Applicant states the proportion of protocol deviations in BCB120 was similar between the three arms (45% in EQWS group vs. 41% in sitagliptin and placebo each). 'Study drug incorrect dose' was the most frequent violation in the EQWS group compared to sitagliptin and placebo

(8.2% vs. 4.1% vs. 3.3%).

Table 9: Protocol deviations during the 28-week treatment period, BCB120, randomized population

Deviation Type	Exenatide QW8 2 mg N = 182	Sitagliptin 100 mg PO N = 122	Placebo N = 61	All Subjects N = 365
ALL DEVIATION TYPES	82 (45.1)	50 (41.0)	25 (41.0)	157 (43.0)
INCLUSION/EXCLUSION CRITERIA	11 (6.0)	7 (5.7)	1 (1.6)	19 (5.2)
CONCOMITANT MEDICATION CHANGE	11 (6.0)	4 (3.3)	5 (8.2)	20 (5.5)
STUDY DRUG INCORRECT TREATMENT OR DOSE	15 (8.2)	5 (4.1)	2 (3.3)	22 (6.0)
OTHER	64 (35.2)	38 (31.1)	19 (31.1)	121 (33.2)

The Applicant states subjects may have > 1 protocol deviation. Each subject is counted only once in the total row and in each category. Source: Excerpted from Clinical Study Report, BCB120, page 49.

One subject was enrolled twice at different sites and assigned two Unique Subject Identifiers (b) (6) The subject was randomized to EQWS both times and withdrew from the study both times. The subject was lost to follow-up at the first site and terminated early for protocol violation at the second site. This subject was counted only once in the randomized population. The narrative is provided in the Section 8 (safety).

Demographic Characteristics

Demographics were well balanced between the three treatment arms in BCB120. Some notable observations:

1. BCB120 did not enroll moderate or severe renal impairment subjects.
2. The only background antidiabetic medication is metformin.
3. In BCB120, 65% of the enrolled population is of Hispanic ethnicity compared to the 23% Hispanic population in BCB118.
4. The population in BCB120 is younger and less obese compared to BCB118.

Reviewer Comment: The demographics in this study reasonably represent the general population with T2DM who may be prescribed EQWS. Baseline characteristics were balanced between treatment groups, suggesting appropriate randomization. The major difference in baseline characteristics between BCB120 and BCB118 is baseline renal function status.

Efficacy Results by the Applicant– Primary Endpoint

In this section, the Applicant's efficacy results are discussed. In section 7 the Agency's efficacy analysis is discussed.

The Applicant compared the change in HbA1c from baseline to Week 28 between the EQWS group and the comparators (sitagliptin and placebo) using MMRM in the mITT population

(observed data; de jure population) excluding post-rescue or post-treatment discontinuation observations. No imputation of missing data was performed, and no retrieved dropout subjects were included.

The Applicant pre-specified hypothesis testing was concluding the superiority of EQWS to placebo at alpha= 0.05, followed by non-inferiority and superiority of EQWS to sitagliptin at alpha= 0.05. Non-inferiority to sitagliptin was concluded if the upper limit of the 2-sided 95% CI was less than the non-inferiority margin 0.3%. Superiority was concluded if this upper limit was less than zero.

Applicant's primary efficacy analyses results:

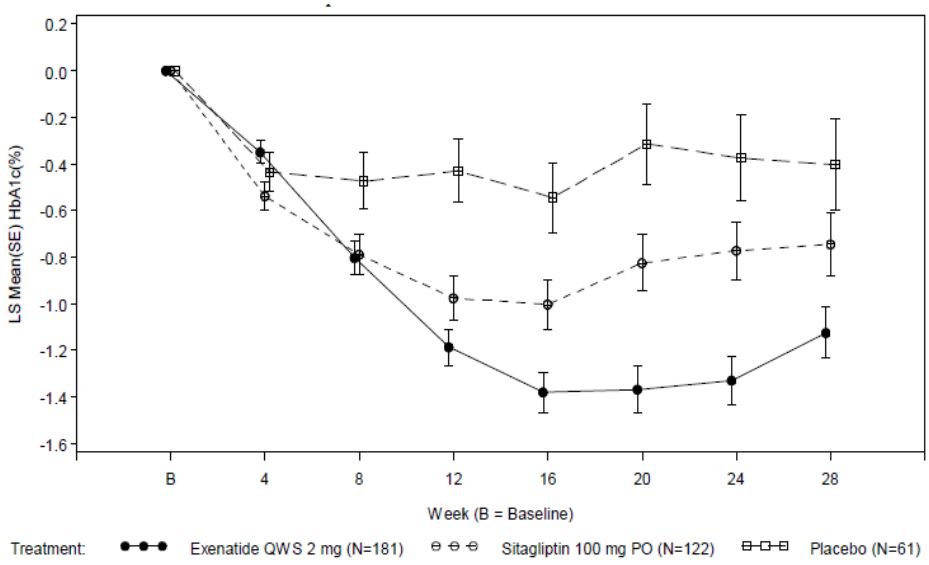
The mean HbA1c at baseline was 8.42%, 8.5%, and 8.5 % in the EQWS, sitagliptin and the placebo groups, respectively. The Applicant's efficacy analysis shows the LS mean change from baseline (95% CI) at Week 28 was -1.13% (-1.34, -0.91), -0.75% (-1.01, -0.49), and -0.40 (-0.79, -0.02) for the EQWS, sitagliptin and placebo treatment groups, respectively.

The Applicant states the 28-week change in HbA1c of EQWS compared to placebo met the pre-specified superiority endpoint. The superiority of EQWS compared to placebo was confirmed since the 95% confidence interval for the treatment difference of the change in HbA1c was entirely below 0%; the upper limit of the CI was -0.3. Numerically, EQWS was superior to placebo.

The pre-specified statistical plan then moved on to test non-inferiority to sitagliptin followed by superiority to sitagliptin. The Applicant states for the primary efficacy endpoint, there was a statistically significantly larger reduction in HbA1c from baseline to Week 28 in the EQWS group compared with the sitagliptin group (p = 0.0209). The Applicant concluded that there was a statistically significantly larger reduction in HbA1c from baseline to Week 28 in the EQWS group compared with the sitagliptin group (p = 0.0209) and the placebo group (p=0.0010). Numerically, EQWS was superior to placebo and sitagliptin.

The figure below shows the mean change in HbA1c from baseline (week 0) to week 28. There was a steeper decrease in HbA1c in EQWS seen in the first 16 weeks of treatment followed by a plateau till week 24, and a slight increase from week 24-28.

Figure 10: HbA1c (%) by treatment week- change from baseline- mean plot- mITT, BCB120:



Source: Excerpted from the Clinical Study Report, BCB120, page 64.

Table 10: HbA1c (%), Week 28, change from baseline, mITT, BCB120

	BYDUREON BCISE 2 mg QW	Sitagliptin 100 mg/day	Placebo once daily
Intent-to-Treat Population (N)[88]	181	122	61
HbA_{1c} (%)[89]			
Mean Baseline	8.4	8.4	8.4
Mean Change at Week 28[1]	-1.0	-0.6	-0.3
Difference from sitagliptin[1] [95% CI]	-0.40 (-0.73, -0.07)*		
Difference from placebo[1] [95% CI]	-0.75 (-1.18, -0.32)**		
Percentage Achieving HbA_{1c} <7% at Week 28 (%)[2 90]	39*	31	21
Mean fasting plasma glucose (mg/dL)[91]			
Mean Baseline	174	175	164
Mean Change at Week 28[1]	-20.2	-10.1	10.7
Difference from sitagliptin[1] [95% CI]	-10.1 (-21.7, -1.6)		
Difference from placebo[1] [95% CI]	-30.8 (-46.6, -15.1)		
Mean 2-hour postprandial plasma glucose change from baseline (mg/dL)[3 92]			
Standard Meal Test Population (N)	44	31	15
Mean Baseline	257	278	222
Mean Change at Week 28[1]	-66	-31	-41
Difference from sitagliptin[1] [95% CI]	-36.0 (-67.9, -3.3)		
Difference from placebo[1] [95% CI]	-25.6 (-65.7, -14.6)		

N=number of patients in each treatment group, CI-unadjusted confidence interval, QW=once weekly; *p-value=< 0.05**p-value < 0.01;1=least square mean; 2=subjects with missing values at Week 28 counted as not achieving goal; 3=data extracted from the standard meal test, which occurred at baseline and week 16.

(b) (4)

Efficacy Results - Secondary endpoints

To further assess the superiority of EQWS vs. sitagliptin and placebo, four secondary endpoints were compared between treatments in BCB120. The Applicant states only if non-inferiority of EQWS to sitagliptin for the primary endpoint is established at the significance level $\alpha = 0.05$, the secondary endpoints are tested with multiplicity adjustments.

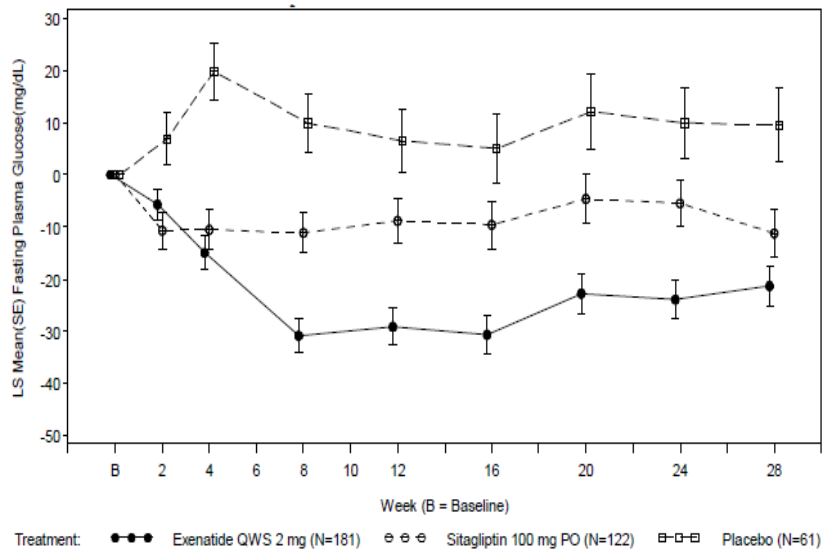
- Proportion of patients achieving HbA1c < 7.0% at Week 28
- Change in fasting plasma glucose concentrations from baseline to Week 28
- Change in weight from baseline to Week 28
- Change in 2-hour post-prandial glucose from baseline to Week 28

The Applicant states:

- A statistically significantly higher proportion of subjects in the EQWS group achieved HbA1c < 7% at Week 28 than in the sitagliptin and placebo groups[15].
- The FPG reduction from baseline between the EQWS and placebo groups reached statistical significance (p=0.00001), while the difference between the EQWS and sitagliptin groups did not reach statistical significance (p = 0.0924)[16].
- The LS mean (SE) changes from baseline in body weight were -1.12 (0.26) kg, -1.19 (0.31) kg, and 0.15 (0.48) kg in the EQWS, sitagliptin, and placebo groups, respectively. The LS mean difference (SE) between the EQWS group and the sitagliptin group was 0.07 (0.41) (nominal p=0.8625). The LS mean difference (SE) between the EQWS group and the placebo group was -1.27 (0.54) (nominal p=0.0198).
- The LS mean (SE) reduction in 2-hour postprandial plasma glucose from baseline to Week 16 was 60 (10) mg/dL in the EQWS group, 24 (13) mg/dL in the sitagliptin group (nominal p=0.0248), and 39 (17) mg/dL in the placebo group (nominal p=0.2914).

Reviewer Comment: The Applicant presents the secondary endpoints in the proposed label.

Figure 11: Plot of LS mean (SE) change from baseline in fasting blood glucose over time, mITT, BCB120



Source: Excerpted from the Clinical Study Report for BCB120, page 67

[15] 78 of 181 subjects (43.1%) in the EQWS group, 39 of 122 subjects (32.0%) in the sitagliptin group (p=0.0489), and 15 of 61 subjects (24.6%) subjects in the placebo group (p=0.0103).
[16] The Applicant states the mean baseline FPG concentrations were 178, 177, and 173 mg/dL in the EQWS, sitagliptin and placebo groups, respectively. At Week 28, the LS mean (SE) change in FPG from baseline in the EQWS, sitagliptin, and placebo groups were -21.3 (3.9), -11.3 (4.6), and 9.6 (7.1) mg/dL, respectively.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoint

The efficacy of the two Phase 3 trials was tested at 28-week of treatment; trial BCB118 had an additional uncontrolled 52-week safety extension with no pre-specified statistical testing. The efficacy data of the two Phase 3 EQWS studies are not pooled as the two studies have different control groups (Byetta in BCB118; sitagliptin and oral placebo in BCB120).

In summary, BCB118 is a 2-arm non-inferiority study comparing EQWS with the active control Byetta. BCB120 is a 3-arm non-inferiority trial comparing EQWS with oral sitagliptin and oral placebo (3:2:1).

To demonstrate EQWS's efficacy, the Applicant used Mixed Model for Repeated Measures (MMRM) as a primary statistical analysis excluding post-rescued and/or discontinued observations and Last Observation Carried Forward (LOCF) as a sensitivity analysis. The Applicant analyses using only observed data (de jure population) at 28-weeks showed EQWS is superior to Byetta in study BCB118 and superior to placebo and sitagliptin in study BCB120.

The Applicant states in study BCB118, the reduction in HbA1c from baseline to Week 28 was statistically significantly larger in the EQWS group compared with the Byetta group (difference of -0.38%, p=0.0050). The adjusted mean change from baseline (SE) at Week 28 was -1.48% (0.100%) in the EQWS group and -1.10% (0.117%) in the Byetta group.

The Applicant states in study BCB120, the reduction in HbA1c from baseline to Week 28 was statistically significantly larger in the EQWS group compared with the sitagliptin group (difference of -0.40%, p=0.0169) and the placebo group (difference of -0.75%, p=0.0008). The adjusted mean change from baseline (SE) at Week 28 was -1.03% (0.118) for EQWS, -0.63% (0.142) for sitagliptin, and -0.29% (0.204) for placebo.

Table 11: Summary statistics for HbA1c results across Phase 3 trials from baseline to Week 28, mITT population (de jure), Applicant's analysis

Phase 3 trials	Treatment group	N mITT	Baseline Mean HbA1c (SD)	End of Trial LS Mean HbA1c (SE)	LS Mean Change in HbA1c	Treatment difference (95% confidence interval)	p-value
BCB118	EQWS Byetta	175 108	8.45 (1.060) 8.44 (0.982)	7.01 (1.093) 7.37 (1.380)	-1.44 (1.169) -1.08 (1.244)	-0.38 (0.134) (-0.64,-0.12)	0.0050
BCB120	EQWS Sitagliptin Placebo	141 98 38	8.40 (1.024) 8.43 (1.042) 8.38 (1.052)	7.28 (1.306) 7.56 (1.393) 7.74 (1.436)	-1.12 (1.209) -0.87 0.1360) -0.64 (1.295)	EQWS-sitagliptin: -0.40 (0.166) (-0.73, -0.07) -0.75 (0.220) EQWS-placebo: -0.75 (0.220) (-1.18, -0.32)	0.0169 0.0008

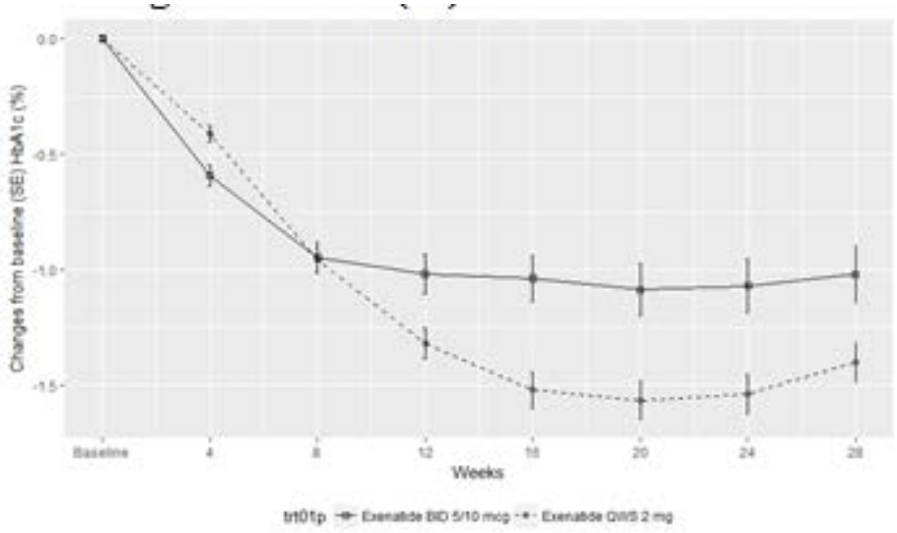
Statistical reviewer analysis:

Excluding rescued or/and discontinued subjects does not reflect the real clinical world. Follow-up data, rescued subjects, and drop-outs should all be considered as relevant efficacy information.

The statistical reviewer re-calculated the estimand for both Phase 3 studies by including all randomized subjects regardless of discontinuation of study medication or starting rescue. The rationale is that all potential outcomes that would have been observed under different exposures regardless of adherence to treatment, use of rescue therapy or discontinuation of study drug in the T2DM patient's group are clinically relevant and should be taken into consideration for estimation of EQWS's effectiveness.

In study BCB118, the upper limit of 95% confidence interval for the difference between EQWS and Byetta was below the pre-specified non-inferiority margin of 0.4. Thus EQWS was non-inferior to EQWS. The superiority of EQWS to Byetta was also demonstrated with significant p-values. The LS means (SE) of changes of HbA1c (%) from baseline at Week 28 including all randomized subjects regardless of adherence or post-rescue (de-facto population) were -1.39 (0.09) and -1.03 (0.12) for EQWS and Byetta respectively.

Figure 12: Longitudinal Changes of HbA1c (%) in BCB118



Excerpted from CDER's statistical review dated September 14, 2017, page 20.

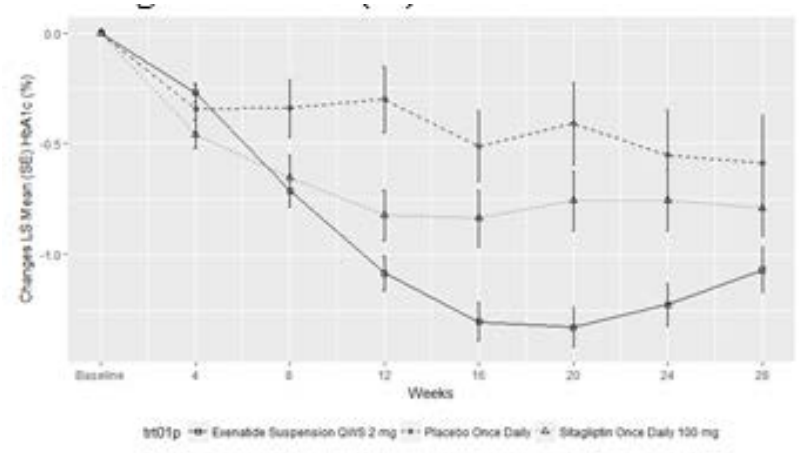
In study BCB120, the statistical reviewer re-analyzed the primary estimand by including all randomized subjects regardless of adherence, or initiation of rescue therapy. The re-analysis shows EQWS was superior to placebo and non-inferior to sitagliptin. EQWS failed to show superiority to sitagliptin. The LS means (SE) changes of HbA1c from baseline at Week 28 were -1.07 (0.10) %, -0.79 (0.13) % and -0.58 (0.21) % for EQWS, sitagliptin, and placebo respectively.

Of note, sitagliptin failed to show superiority to placebo. Sitagliptin showed a weaker placebo-adjusted treatment effect in study BCB120 (-0.19%) than the already established placebo-adjusted effect of -0.7% for sitagliptin.

The lack of treatment effect for sitagliptin means EQWS's claim (non-inferiority or superiority) to sitagliptin is unsubstantiated. However, the efficacy of EQWS is established by superiority to the placebo arm in the same clinical trial.

Reviewer Comment: The placebo treatment arm was added in the noninferiority trial design by the recommendation of the Agency at the EOP2 meeting (December 14, 2011).

Figure 13: Longitudinal Changes of HbA1c (%) in BCB120



Excepted from CDER's statistical review dated September 14, 2017, page 21.

Study limitations:

A limitation of the Phase 3 program is the high rate of missing efficacy (HbA1c) data at Week 28.

At Week 28, in study BCB118, 23% of the EQWS group vs. 26.7% of the Byetta group have missing HbA1c data. At Week 28, in study BCB120, 22% of the EQWS group, 19.7% of the sitagliptin group, and 37.7% of the placebo group have missing HbA1c values.

In study BCB118, 14% of the EQWS group withdrew vs. 19% from the Byetta group. In study BCB120, 15% of the EQWS group withdrew vs. 10.65% from the sitagliptin group, and 23% from the placebo group.

In the EQWS Phase 3 program at Week 28, the rate of missingness is high. The Phase 3 studies did not have a rigorous plan for follow-up of patients who discontinued treatment. The Applicant states continued follow-up of discontinued subjects was not practiced at the time of agreement on the design of the Phase 3 with the Agency. This led to a high proportion of patients with missing data after discontinuation of study drug, which by design was equal to discontinuation from the study. Also, the design of the study underestimated the withdrawal rate when determining the sample size.

Despite the above limitations, the statistical reviewer was able to establish noninferiority and superiority of the EQWS to Byetta in study BCB118, and the superiority of EQWS to placebo in study BCB120, after including all randomized subjects subject regardless of adherence to study drug or initiation of rescue.

7.1.2. Secondary and Other Endpoints

The pre-specified hypothesis testing for both Phase 3 studies is shown below. Both Phase 3 studies made adjustments for multiplicity.

Figure 14: Hypothesis testing procedures in study BCB118 and BCB120

	Study BCB118	Study BCB120
Primary endpoint	H_{01}: Noninferiority of EQWS to BYETTA BID on the primary endpoint at α=0.05	H_{01}: Superiority of EQWS to placebo on the primary endpoint at α=0.05
	H_{02}: Superiority of EQWS to BYETTA BID on the primary endpoint at α=0.05	H_{02}: Noninferiority of EQWS to sitagliptin on the primary endpoint at α=0.05
		H_{03}: Superiority of EQWS to sitagliptin on the primary endpoint at α=0.05
Secondary endpoints	H_{11} and H_{12}: Superiority of HbA1c goal and FPG for EQWS vs. BYETTA BID at α=0.05	H_{11}: Superiority of HbA1c goal for EQWS vs. sitagliptin at α=0.05
	H_{21} :Superiority of weight for EQWS vs. BYETTA BID at α=0.05	H_{21}: Superiority of FPG for EQWS vs. sitagliptin at α=0.05
	H_{31}: Superiority of 2h PPG for EQWS vs. BYETTA BID at α=0.05	H_{31}: Superiority of weight for EQWS vs. sitagliptin at α=0.05
		H_{41}: Superiority of 2h PPG for EQWS vs. sitagliptin at α=0.05

BID twice daily; EQWS exenatide once weekly suspension; FPG fasting plasma glucose; HbA1c hemoglobin A1c; PPG postprandial plasma glucose

Source: Excerpted from the Summary of Clinical Efficacy page 22.

The statistical reviewer states because hypothesis tests for primary endpoints were all statistically significant in BCB118, hypothesis testing for secondary endpoints were conducted in the following order to control the family-wise error rate at 0.05:

1) Proportion of patients achieving HbA1c < 7.0% at Week 28
2) Change in fasting plasma glucose concentrations from baseline to Week 28

The statistical reviewer states for descriptive purpose, the proportions of subjects who achieved HbA1c < 7.0% at Week 28 were 40% in EQWS group compared to 38% in the Byetta group. Subjects with missing values at Week 28 were counted as non-responders. The difference in the proportions did not reach statistical significance. Any further formal hypothesis testing was stopped.

The mean changes from baseline to Week 28 for fasting serum glucose were -35 mg/dL and -27mg/dL for EQWS and Byetta, respectively.
In BCB120, no further hypothesis testing for secondary endpoints was performed by the statistical reviewer because hypothesis testing for primary endpoints failed to show the superiority of EQWS to sitagliptin.

For descriptive purpose, 41%, 31%, and 26% of subjects achieved HbA1c < 7.0% at Week 28 in EQWS, sitagliptin and placebo groups respectively. Subjects with missing values at Week 28 were counted as non-responders. The mean changes from baseline to Week 28 for fasting serum glucose were -24 mg/dL, -19 mg/dL and 3.9 mg/dL for EQWS, sitagliptin, and placebo respectively.

Reviewer Comment: The proportions of subjects who achieved HbA1c < 7.0% and mean changes from baseline to Week 28 for fasting serum glucose (b) (4)

7.1.3. Subpopulations

The statistical reviewer states subgroup analyses for the primary endpoint of change in HbA1c (%) from baseline to Week 28 was performed across subgroups defined by race (White vs. Black or African American vs. Others), gender (Female vs. Male), and age (≥ 65 vs. < 65). Also, subgroup analyses by ethnicity (Hispanic/Latino vs. Non-Hispanic/Latino) and renal function at baseline (Normal vs. Impairment (normal, mild, and moderate)) were explored.

Majority of subgroups (White, both sexes, and age <65) showed favorable results of EQWS compared to control consistent with the results from the primary analysis for HbA1c changes from baseline to Week 28 in BCB118.

Subgroups with a small number of subjects showed the wider 95% Confidence Interval. In BCB120, most subgroups were favorable for EQWS compared to placebo like the primary analysis results, except three subgroups (Black/African America, Other race groups, and Age ≥65).

No interaction terms between the subgroups and treatment group were significant.

Numerically significant interaction between normal renal function and treatment group and interaction between ethnicity and treatment group were detected in BCB118. Numerically significant interaction between mild/moderate renal function and sitagliptin treatment group and interaction between non-Hispanic ethnicity and sitagliptin treatment group were detected in BCB118.

Reviewer Comment: The clinical relevance of these findings is unclear, and interpretation of results is limited by small patient numbers in several subgroups. Refer to the Agency's statistical review for details of subgroup analyses.

7.1.4. Dose and Dose-Response

Refer to Section 4.5 of this review, clinical pharmacology. The EQWS dose and regimen 2 mg subcutaneously weekly are the same as Bydureon's dose and regimen.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Refer to Section 6.1.2 '52 week data, uncontrolled extension period, BCB118'.

7.2. Additional Efficacy Considerations

7.2.1. Other Relevant Benefits

This drug product may allow for the patient convenience of eliminating mixing with water before injection.

7.3. Integrated Assessment of Effectiveness

The Applicant evaluated the 28-week efficacy of EQWS in two Phase 3 trials in patients with T2DM including an add-on to oral anti-diabetic drugs, as well as monotherapy.

BCB118 includes a subset of subjects exposed to EQWS as monotherapy (33 subjects in EQWS group, and 16 in Byetta group) and study BCB120 contains the placebo-controlled safety data (61 subjects in the placebo group).

The Phase 3 studies did not have a rigorous plan for follow-up of patients who discontinued treatment. The Applicant states continued follow-up of discontinued subjects was not practiced at the time of agreement on the design of the Phase 3 with the Agency. This led to a high proportion of subjects with missing data after discontinuation of study drug, which by design was equal to discontinuation from the study. Also, the design of the study underestimated the withdrawal rate when determining the sample size.

The high rate of missingness at Week 28 appeared to affect the robustness of the evidence for EQWS's effectiveness compared to the comparators.

The statistical reviewer's analysis includes rescued and discontinued subjects and reflects the real world clinical scenario more compared to the Applicant's analysis of primary endpoint.

For BCB118, the evidence suggests the drug has effectiveness in patients with T2DM in the United States as compared to Byetta. After including all randomized subjects despite adherence or initiation of rescue therapy, the estimand weakened but maintained statistical significance. Thus numerically, EQWS is superior to Byetta.
For study BCB120, the evidence suggests the drug has effectiveness in patients with T2DM in the United States as compared to placebo.

Sitagliptin showed a weaker placebo-adjusted treatment effect (-0.19%) than the already established placebo-adjusted effect of -0.7% for sitagliptin. EQWS was superior to placebo and non-inferior to sitagliptin. EQWS was noninferior to sitagliptin but failed to show superiority to sitagliptin.

The lack of treatment effect for sitagliptin means EQWS's claim (non-inferiority or superiority) to sitagliptin is not meaningful. However, the efficacy of EQWS is established by superiority to the placebo arm in the same clinical trial.

Taken together the totality of the data, and considering the EQWS drug development program is an abbreviated program relying on the Bydureon and Byetta, I believe the Applicant has provided adequate evidence of an effect of EQWS in the treatment of T2DM.

8 Review of Safety

Safety Review Approach

Section 8.1 discusses the overall presentation of the safety data and pooling strategy.

The EQWS clinical development program includes three completed studies, i.e., one Phase 2 study (BCB112), and two Phase 3 studies (BCB118 and BCB120). All three studies were conducted in the United States. The Applicant states there are no ongoing studies for EQWS at this time. In the 120-day submitted Safety Update, the Applicant identified October 1, 2011, as the cutoff date for the safety data.

The Applicant states the safety population is comprised of all subjects exposed to at least one dose of the study drug.

Table 12: Safety sets proposed by the Applicant for NDA 209210

Analysis set code	Analysis set name	Groupings of subjects and/or studies	Description
SF-1	Phase 3 controlled	Phase 3 clinical studies (BCB118 and BCB120): 28-week controlled period	First 28 weeks of studies BCB118 and BCB120: All treatment groups will be presented individually plus all EQWS subjects pooled.
SF-2	Phase 3 uncontrolled extension	Phase 3 clinical study (BCB118): uncontrolled extension period	Weeks 29-52 of study BCB118: All subjects were administered EQWS 2 mg once weekly during the extension period. Results will be presented by original group of randomization and pooled.
SF-3	Phase 2	Phase 2 Study BCB110	Cohort 1 (healthy volunteers) and Cohort 2 (T2DM subjects): All treatment groups presented individually.
SF-4	EQWS 2 mg, Phase 3	EQWS 2 mg subjects from Phase 3 studies (BCB118, BCB120)	Pool of all subjects receiving EQWS 2 mg once weekly in studies BCB118 (controlled or extension period) and BCB120.

Source: Excerpted from Page 12 of EQWS SAP ISS edition 1.

The Applicant's main data pool for analysis of the Phase 3 integrated safety database was the Phase 3 controlled safety set (SF-1) comprised of the pool of the two 28-week controlled periods of the two Phase 3 studies (BCB118 and BCB120). The Applicant used the uncontrolled Phase 3 extension safety dataset (SF-2) from study BCB118, and the Phase 2 (SF-3) study BCB110 to provide supplemental safety information. The Applicant used SF-4 (pool of all Phase 3 EQWS- treated subjects) safety set to present an exposure-adjusted analysis of selected adverse events of special interest.

The safety data presented by the Applicant in the Phase 3 clinical study reports also include an additional pool of all Phase 3 subjects (all EQWS-treated subjects and all comparators in one pool).

Reviewer Comment: I do not believe clinically meaningful data is derived from this pool because the interpretation of safety data related to EQWS is difficult. Thus I did not discuss this pool in my review.

The proposed label mainly presents the pooled data from the two 28-week controlled periods (SF-1), except the treatment-emergent adverse reactions where the SF-4 (pool of all Phase 3 EQWS-treated subjects) safety dataset is presented.

Reviewer Comment: The pool of all Phase 3 EQWS-treated subjects (SF-4) comprises of the largest pool of T2DM subjects exposed to EQWS from the two Phase 3 studies. I used the EQWS pool (SF-4) mainly for exploratory analysis and identification of rare adverse events. However, interpretation of safety data derived from this pool is difficult because it represents safety data

from the controlled and uncontrolled extension periods and subjects switching from Byetta to EQWS.

Safety analysis sets used by the reviewer and the reviewer's rationale:

I performed the primary safety review of NDA 209210 by evaluating the safety of each pivotal Phase 3 trial individually to estimate and compare the incidence of adverse events. The rationale for evaluating each Phase 3 study individually is because study BCB118 allows for comparison of EQWS to Byetta and study BCB120 to placebo. For evaluation of rare adverse events an exploratory analysis of the overall balance of the EQWS safety data for the proposed indication by using the all EQWS pool (SF-4) as well as the uncontrolled extension arm (Week 29-52) of study BCB118 was performed.

In each section of the safety review, I describe my approach to the evaluation of the adverse events. For example, to estimate and compare the incidence of injection site reactions I focused on the controlled treatment arm of study BCB118 with Byetta as the comparator. Study BCB120 is limited in estimating the risk of injection site reactions because the comparators are oral treatments as opposed to subcutaneous injections (sitagliptin and oral placebo).

I also performed multiple exploratory analyses using the Applicant's submitted safety database to evaluate safety areas of interest. These results are mentioned, as pertinent throughout the review.

All submitted narratives for deaths, nonfatal SAEs, and discontinuations due to adverse events were reviewed.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 13: Size of Phase 3 exposure to EQWS, BCB118 and BCB120

Study (duration)	Number of subjects	Number of subjects exposed*				
		EQWS		BYETTA	Placebo	Sitagliptin
		10 mg single dose	2 mg once weekly	10 µg BID		100 mg/day PO
Phase 2 study:						
Study BCB110:						
- Cohort 1: Healthy subjects (single dose)	30	30	-	-	-	-
- Cohort 2: T2DM patients (repeated doses)	35	-	23	-	12	-
Phase 3 studies:						
Study BCB118						
- 28-week controlled period	375	-	229	146	-	-
- Uncontrolled extension period: subjects switching from BYETTA to EQWS			116			
Study BCB120	364	-	181	-	61	122
Total (all studies)	**804**	**30**	**549**	**146**	**73**	**122**

*safety population.
Abbreviations: BID: twice daily, PO: by mouth, T2DM: type 2 diabetes mellitus
Source: Adapted from the ISS Summary of Clinical Safety; page 21.

Total Size of Exposure

The one Phase 2 and two Phase 3 EQWS clinical studies enrolled a total of 804 subjects, and EQWS was administered to a total of 579 unique subjects, of which 549 were T2DM subjects.

The total exposure for EQWS in the T2DM subjects in the two Phase 3 studies is 526 (354.97 patient-years).

During the 28-week active-controlled treatment period of study BCB118, 229 subjects received EQWS, and 146 subjects received Byetta. One hundred sixteen subjects from the Byetta group and 193 from the EQWS group (total 309 subjects) continued to the uncontrolled extension period lasting up to 52 weeks. All 309 subjects who entered the uncontrolled extension period were treated with EQWS.

During the 28-week placebo-controlled period of study BCB120, 181 subjects received EQWS, and 61 subjects received placebo. In a third active-control arm, 121 subjects received sitagliptin.

Reviewer Comment: During the EOP2 meeting (December 14, 2011), the Agency agreed with at least 250 subjects exposed to EQWS for six months and 150 subjects exposed to EQWS for one year in study BCB118.

For study BCB120, during the EOP2 meeting, the Applicant initially proposed a 2-arm study with ~175 T2DM subjects per arm comparing EQWS to sitagliptin. The Agency recommended including an oral placebo arm (to estimate the placebo-adjusted effect of sitagliptin) with a larger number of subjects allocated to EQWS and the active control arm and a smaller number to the oral placebo arm, and to power the 3-arm study based on the non-inferiority margin of 0.3%.

In general, the number of subjects exposed to EQWS adheres to pre-submission agreements.

Total Duration of Exposure

Of the 526 T2DM subjects exposed to EQWS during Phase 3, 226 (43%) subjects received EQWS for at least six months (in studies BCB118 and BCB120), and 158 (30%) subjects received EQWS for at least 12 months (in study BCB118).

Table 14: Duration of exposure to EQWS (number of weeks) in BCB118 and BCB120

Study Treatment	Number of Subjects n(%)	Number (%) of Subjects by Total Weeks of Exposure [a] <12	>=12 to <24	>=24 to <36	>=36 to <48	>=48 to <52	>=52
Phase 3 Study BCB118							
EQWS	345 (100)	28 (8.1)	27 (7.8)	74 (21.4)	43 (12.5)	15 (4.3)	158 (45.8)
EQWS-->EQWS Group	229 (100)	19 (8.3)	8 (3.5)	13 (5.7)	16 (7.0)	15 (6.6)	158 (69.0)
BYETTA-->EQWS Group[b]	116 (100)	9 (7.8)	19 (16.4)	61 (52.6)	27 (23.3)	NA	NA
BYETTA	146 (100)	22 (15.1)	9 (6.2)	115 (78.8)			
Phase 3 Study BCB120							
EQWS	181 (100)	19 (10.5)	10 (5.5)	152 (84.0)			
Sitagliptin	122 (100)	10 (8.2)	2 (1.6)	110 (90.2)			
Placebo	61 (100)	8 (13.1)	6 (9.8)	47 (77.0)			
All EQWS 2 mg (Phase 3)	526 (100)	47 (8.9)	37 (7.0)	226 (43.0)	43 (8.2)	15 (2.9)	158 (30.0)

[a] Duration of EQWS exposure=(Date of the Last Injection of Study Medication - Date of First Injection of Study Medication + 7)/7;
Duration of BYETTA exposure= (Date of the Last Injection of Study Medication - Date of First Injection of Study Medication + 1)/7;
[b] Only includes number of weeks of EQWS dosing after switching from Byetta to EQWS at Week 29.
Source: Excerpted from the ISS listings Table1.1, page1.

Reviewer Comment: The duration of exposure to EQWS in T2DM subjects (158 ≥ one year; 226 ≥ six months) does not meet the minimum ICH guidance recommendations (minimum 1500 total, 300 subjects for six months and 100 for one year at clinically relevant doses). Also, the EQWS total exposure is less than the 2,500 exposed subjects (300-500 for ≥1.5 year) recommended in the draft February 2008 diabetes mellitus guidance. However, because EQWS is a different formulation with the same active ingredient (exenatide), the EQWS NDA makes appropriate references to the Byetta and the Bydureon NDAs (21-773 and 02-022). The Applicant states as of March 31, 2009, over 1 million patients have been exposed to exenatide in the United States,

and over 6000 T2DM subjects and healthy volunteers have been exposed to exenatide in clinical trials. Thus, from a safety perspective, the exposure in the EQWS development program appears adequate.

Study completion and withdrawal in the Phase 3 studies

For details regarding overall study completion and withdrawal in the Phase 3 studies refer to Sections 6.1.2 and 6.1.5 of this review. For discontinuations due to adverse event refer to Section 8.4.3 of this review.

8.2.2. Relevant characteristics of the safety population

Table 15: Demographics, baseline, and disease characteristics, randomized population, Phase 3 studies

		BCB118		BCB120		
Characteristics		Byetta n (%) n=146	EQWS n(%) n=229	EQWS n (%) n=181	Placebo n (%) n=61	Sitagliptin n (%) n=122
Age group	< 65	118 (80.8)	182 (79.5)	154 (85.1)	54 (88.5)	106 (86.9)
	>=65	28 (19.2)	47 (20.5)	27 (14.9)	7 (11.5)	16 (13.1)
Sex	F	54 (36.99%)	81 (35.37%)	92 (50.83%)	24 (39.34%)	56 (45.90%)
	M	92 (63.01%)	148 (64.63%)	89 (49.17%)	37 (60.66%)	66 (54.10%)
Race	American Indian or Alaskan	3 (2.05%)	2 (0.87%)	0	1 (1.64%)	2 (1.64%)
	Asian	8 (5.48%)	17 (7.42%)	9 (4.97%)	3 (4.92%)	2 (1.64%)
	Black or African American	23 (15.75%)	38 (16.59%)	24 (13.26%)	7 (11.48%)	18 (14.75%)
	Native Hawaiian	0	1 (0.44%)	0	0	1 (0.82%)
	Other	2 (1.37%)	3 (1.31%)	0	0	1 (0.82%)
	White	110 (75.34%)	168 (73.36%)	148 (81.77%)	50 (81.97%)	98 (80.33%)
Ethnicity	Hispanic or Latino	34 (23.29%)	54 (23.58%)	111 (61.33%)	32 (52.46%)	77 (63.11%)
	Not Hispanic or Latino	112 (76.71%)	174 (75.98%)	70 (38.67%)	29 (47.54%)	45 (36.89%)
BMI Category	<30	44 (30.14%)	68 (29.69%)	74 (40.88%)	28 (45.90%)	55 (45.08%)
	>=30	102 (69.86%)	161 (70.31%)	107 (59.12%)	33 (54.10%)	67 (54.92%)
Baseline Strata Renal Function	Mild Impairment	76 (52.05%)	115 (50.22%)	78 (43.09%)	26 (42.62%)	54 (44.26%)
	Moderate Impairment	15 (10.27%)	29 (12.66%)	1 (0.55%)	0 (0.00%)	4 (3.28%)
	Normal	55 (37.67%)	85 (37.12%)	102 (56.35%)	35 (57.38%)	64 (52.46%)
Duration of Diabetes	<3	26 (17.81%)	40 (17.47%)	30 (16.57%)	7 (11.48%)	15 (12.30%)
	>=10	51 (34.93%)	81 (35.37%)	65 (35.91%)	24 (39.34%)	43 (35.25%)
	>=3 to <10	69 (47.26%)	108 (47.16%)	86 (47.51%)	30 (49.18%)	64 (52.46%)
Baseline Strata HbA1c	< 9.0%	97 (66.44%)	161 (70.31%)	125 (69.06%)	42 (68.85%)	83 (68.03%)
	>= 9.0%	49 (33.56%)	68 (29.69%)	56 (30.94%)	19 (31.15%)	39 (31.97%)
Diabetes Management Method	Diet and Exercise	17 (11.64%)	31 (13.54%)	0	0	0
	Metformin	65 (44.52%)	102 (44.54%)	181 (100.00%)	61 (100.00%)	121 (99.18%)
	Metformin + SU	52 (35.62%)	76 (33.19%)	0	0	1 (0.82%)
	Metformin + TZD	4 (2.74%)	5 (2.18%)	0	0	0
	Metformin + TZD + SU	2 (1.37%)	4 (1.75%)	0	0	0
	SU	6 (4.11%)	8 (3.49%)	0	0	0
	SU + TZD	0	1 (0.44%)	0	0	0
	TZD	0	2 (0.87%)	0	0	0

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In BCB118 more males were exposed to EQWS compared to females. In BCB120, exposure was evenly distributed between sexes (except placebo). When exposure was evaluated by age, most of the exposure was in the group < 65 years old in both studies (80-85%). When comparing across racial groups, the largest exposure occurred across White patients, with 75-80% of the total exposure in both studies. Most exposures to EQWS occurred in subjects with a duration of diabetes ≥ 3 and < 10 years, followed by ≥ ten years in both studies. There were more obese subjects in both studies compared to non-obese subjects (Body Mass Index [BMI] < 30 kg/m^2).

Reviewer Comment: In the Phase 3 Studies BCB118 and BCB120, the demographic and the baseline characteristics were generally balanced across the randomized treatment groups and adequately represents the overall population with T2DM. The older age group has a smaller but still reasonable exposure.

Note the following observations on the Phase 3 population demographics:

1. BCB120 had a higher percentage of Hispanic/ Latino subjects in the EQWS group (61.3%) compared to BCB118 (23.6%); however, the baseline diabetes characteristics (HbA1c and diabetes duration) was similar between study BCB118 and BCB120.
2. BCB118 had a higher percentage of subjects with moderate renal impairment in the EQWS group (12.7%) compared to the EQWS group in study BCB120 (0.6%).
3. BCB118 had a higher percentage of EQWS subjects with BMI ≥ 30 kg/m2 (70.3%) compared to EQWS subjects in study BCB120 (59.1%).

Reviewer Comment: In general, review of the safety database of BCB120 showed a lower incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation of study or treatment compared to BCB118. The observed difference in the risk profile between study BCB118 and BCB120 may be partly explained by the differences in the baseline renal function leading to lower exenatide concentrations measured in BCB120 compared to BCB118. Also, a normal variation of manifestations of adverse events within a population is a possibility too. For details regarding the difference in steady-state exenatide concentrations between BCB118 and BCB120 refer to Section 4.5 clinical pharmacology of this review.

8.2.3. Adequacy of the safety database

The size and adequacy of the safety database are overall reasonable considering the duration of treatment, demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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The organization and data quality of the safety section was generally adequate. Throughout the safety review, the reviewer sent several Information Requests to the Applicant for clarification of safety issues. In particular, the reviewer requested additional analyses for antibody titer categorization and effect of antibody titers on safety and efficacy at a granular level. Also, the reviewer requested re-analysis of hypoglycemia adverse events according to the American Diabetes Association definitions.

Note in BCB118 two subjects was enrolled twice, and in BCB120 one subject was enrolled twice. The narratives of these double-enrolled subjects are as below:

BCB118: (b) (6) 43-year-old African/American male with a history of 6.4 years of T2DM on glipizide and metformin was enrolled twice at two different sites. The subject was randomized to Byetta (b) (6) however missed the Byetta doses frequently and administered Byetta daily instead of twice daily. The subject continued to the extension period on EQWS and was lost to follow-up. The only adverse event reported after study termination from the second was a low hematocrit.

Review of the graphical patient profile shows while on Byetta in the first center, the subject was randomized to EQWS in the second center (b) (6) The adverse event profile during the double-enrollment period include an asymptomatic injection site nodule, mild worsening back pain, and four episodes of moderate hypoglycemia (capillary glucose ranging from 36-44 mg/dL with resolution with oral carbs without the need for assistance). The subject was terminated by the investigator for self-adjusting hypoglycemic medications.

BCB118: (b) (6) 61-year-old White male with past medical history significant for 5-year history of T2DM on metformin, coronary stent with history of angina, proteinuria, and hypertension was enrolled twice at two different sites and exposed to both EQWS and Byetta for about 1 month along with metformin and glyburide. 4 months later, the subject was terminated after discovery of double-enrollment. During the time of the study, the reported adverse event was mild hypoglycemia (55 mg/dL) after an upper respiratory infection requiring oral antibiotics. A month after termination of the study, during the follow-up period, he developed the SAEs of osteomyelitis requiring toe amputation followed by the SAE severe congestive heart failure. The event of heart failure was confirmed by adjudication.

Reviewer Comment: The SAE of heart failure occurred after hospitalization for osteomyelitis requiring intravenous antibiotics thus attribution of causality to EQWS is unlikely.

BCB120: (b) (6) 71-year-old African American male with an about a ten-year history of T2DM on metformin was enrolled as (b) (6) first and was exposed to 3 doses of EQWS over six weeks. The narrative states the subject had the adverse event of fall/trip with laceration of leg requiring antibiotics. He then enrolled as

(b) (6) in a different site and was randomized to EQWS and received four doses. The subject was dosed twice on one day at each site without adverse events. The adverse events during the study include mild hyperkalemia and mild hypocalcemia (before being dosed twice on one day) and mild thrombocytopenia towards the end of the study. The subject was lost to follow-up for the first site and was terminated from the second site for double enrollment.

Reviewer Comment: Overall, based on a review of the adverse events of the above double-enrolled subjects, the inclusion of the double-enrolled subjects in the safety population does not appear to have a significant impact on the risk assessment of EQWS or labeling purposes.

8.3.2. Categorization of Adverse Events

The Applicant defines an adverse event as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment".

The Applicant states the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 was used for the integrated safety analyses (ISS). However, the MedDRA version at the time of the database lock for study BCB118 was 16.1, and for study BCB120 was 17.0.

According to the MedDRA dictionary, each adverse event is coded to the lowest level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary System Organ Class (SOC).

Treatment-emergent adverse events (TEAEs) were defined as adverse events with the date of onset on or after the first day of treatment and no later than seven days after the last day of treatment. All the adverse events reported in the ISS were TEAEs.

Adverse events of special interest (AESI) were defined for the 2 Phase 3 trials. These events were selected based on the known and potential risks of Bydureon and Byetta. The AESIs are discussed in section 8.5.

For tabulations of adverse events by severity, analyses were based on the investigator's judgment of severity grade. Pre-specified definitions of severity grades (mild, moderate, severe) were provided to the investigators in the protocols. In both Phase 3 studies, the severity of the adverse event was rated by using three categories:

- Mild (activities of daily living are not disturbed)
- Moderate (activities of daily living are disturbed by the symptom to some extent)
- Severe (activities of daily living are disturbed by the symptom to a great large extent)

Routine Clinical Tests

Routine clinical laboratory evaluations included hematology, biochemistry, and urinalysis. Pregnancy test was performed in women. Amylase and lipase were not routinely measured in the EQWS drug development program. ECGs were not routinely performed during the Phase 3 program.

8.4. Safety Results

Deaths

As reported by the Applicant, there was one death in the EQWS clinical program. A subject who was assigned to treatment with Byetta during the controlled period of study BCB118, and switched to EQWS in the extension period, died during the extension period because of ascites and hepatocellular carcinoma. A summary narrative follows:

Subject (b) (6) was a 64-year-old, White female with a 2-year history of T2DM, gastric ulcer, diabetic neuropathy, and previous heavy use of alcohol. On Day 287, the subject presented at the emergency room with abdominal distension, tenderness, and nausea, and found to have ascites, splenomegaly, and hepatic cirrhosis. She was later hospitalized and diagnosed with primary hepatocellular carcinoma. The last dose of EQWS was on Day 302. On Day 303, the subject returned to the emergency room for a therapeutic paracentesis. The subject died on Day 339 because of the ascites and hepatocellular carcinoma.

Reviewer Comment: The fatal event of liver cirrhosis along with complications of ascites and hepatocellular carcinoma seem unlikely to be due to study drug exposure, especially with a risk factor of previous heavy use of alcohol.

8.4.2. Serious Adverse Events (SAE)

The Applicant defines SAE according to the Code of Federal Regulations (CFR) Title 21 Part 312.32[17]. All SAEs were followed by the investigator until resolution or stabilization. This is acceptable.

Reviewer's approach to SAEs:

To assess for numerical imbalances in treatment-emergent SAEs compared to Byetta, I reviewed the 28-week controlled period of study BCB118. To assess numerical imbalances in treatment-emergent SAEs compared to placebo and sitagliptin, I reviewed study BCB120. To

[17] Any adverse event leading to death, life threatening situation, new or prolongation of inpatient hospitalization, persistent or significant incapacity to conduct normal life functions, congenial anomaly or birth defect, important medical event jeopardizing the subject and may require an intervention to prevent death, be life threatening, or require hospitalization.

assess for possible rare SAEs, I did an exploratory analysis of treatment-emergent SAEs of the uncontrolled extension period of study BCB118, and the follow-up periods for both Phase 3 studies.

Table 16: Treatment-emergent SAEs by PT- safety population, BCB118 and BCB120

	BCB118				BCB120	
	Byetta n (%)	EQWS n (%)	EQWS n (%)		EQWS n (%)	Placebo n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD
Abdominal hernia obstructive	0	0	0	0	1 (0.52%)	0
Abortion spontaneous	0	0	0	0	0	0
Acute kidney injury	1 (0.68%)	0	0	0	0	0
Acute myeloid leukaemia	0	0	0	0	0	0
Acute myocardial infarction	0	0	1 (0.86%)	0	0	1 (1.64%)
Acute pulmonary oedema	1 (0.68%)	0	0	0	0	0
Ascites	0	0	1 (0.86%)	0	0	0
Atrial fibrillation	0	0	1 (0.68%)	0	0	0
Basal cell carcinoma	1 (0.68%)	0	0	0	0	0
Brain stem infarction	0	0	0	0	1 (0.52%)	0
Breast cancer	0	0	0	0	1 (0.52%)	0
Cardiac failure congestive	0	0	0	0	0	0
Carotid artery stenosis	0 (0.00%)	0	1 (0.86%)	0	0	0
Cellulitis	1 (0.68%)	0	0	0	0	0
Chest pain	0	0	1 (0.86%)	0	0	0
Coronary artery disease	0	0	1 (0.86%)	0	0	1 (1.64%)
Deep vein thrombosis	0	0	0	0	0	0
Diarrhoea	0	0	0	0	1 (0.52%)	0
Diverticular perforation	1 (0.68%)	0	0	0	0	0
Drug withdrawal syndrome	1 (0.68%)	0	0	0	0	0
Dyspnoea	0	0	1 (0.86%)	0	0	0
Fall	0	0	0	0	0	1 (1.64%)
Hepatocellular carcinoma	0	0	1 (0.86%)	0	0	0
Hidradenitis	0	1 (0.44%)	0	0	0	0
Humerus fracture	0	0	0	0	0	0
Infectious colitis	0	0	0	1 (0.44%)	0	0
Lactic acidosis	1 (0.68%)	0	0	0	0	0
Localised infection	0	1 (0.44%)	0	0	0	0
Lower limb fracture	0	0	0	1 (0.44%)	0	0
Malignant melanoma	0	0	0	1 (0.44%)	0	0
Myocardial infarction	0	1 (0.44%)	0	0	0	0
Osteoarthritis	0	0	0	1 (0.44%)	0	0
Osteomyelitis	0	0	0	0	0	0
Pancreatic carcinoma	0	0	0	0	0	0
Pancreatitis	0	1 (0.44%)	0	1 (0.44%)	0	0
Postoperative respiratory failure	0	0	0	0	0	0
Postoperative wound infection	0	0	0	0	0	0
Pyelonephritis	0	0	0	0	0	0
Rheumatoid arthritis	0	0	0	0	1 (0.52%)	0
Salmonellosis	0	0	0	1 (0.44%)	0	0
Septic shock	1 (0.68%)	0	0	0	0	0
Skin infection	0	0	0	0	0	0
Syncope	0	1 (0.44%)	0	0	0	0
Toxic encephalopathy	1 (0.68%)	0	0	0	0	0
Umbilical hernia	0	0	0	1 (0.44%)	0	0
Uterine leiomyoma	1 (0.68%)	0	0	0	0	0
Subjects(filtered)	7 (4.79%)	5 (2.18%)	6 (4.11%)	7 (3.06%)	5 (2.76%)	2 (3.28%)
1stColItemSubjects	146 (100.00%)	229 (100.00%)	116 (100.00%)	193 (100.00%)	181 (100.00%)	61 (100.00%)

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A. Controlled treatment arm, study BCB118 and BCB120:

Overall, in the Phase 3 controlled treatment periods of BCB118 and BCB120, the incidence of treatment-emergent SAEs was highest in the Byetta group (4.8%) followed by the placebo group (3.3%), and the EQWS group (2.18% in BCB118 and 2.76% in BCB120).

Reviewer Comment: All the MedDRA PTs for SAEs in the controlled periods of both Phase 3 studies were single events, and no concerning pattern was observed.

Reviewer Comment: JReview's graphical patient profiles of the SAE PTs 'hidradenitis' (arm pit) and 'localized infection' (the lower level term is infected toe) from the EQWS group of study BCB118 did not show a relationship to injection site reactions.

Reviewer Comment: The SAE PTs lactic acidosis, septic shock, toxic encephalopathy, acute kidney injury are related to one subject in the Byetta group of study BCB118 who developed septic shock, likely unrelated to the study drug.

The SAEs of obstructive abdominal hernia, diarrhea, and breast cancer in the EQWS group of BCB120, and the SAE of pancreatitis in the EQW group of BCB118 led to the withdrawal of treatment during the 28-week controlled periods.

B. 24-week extension arm, study BCB118 (including follow-up period):

Reviewer Comment: Similar to the controlled period, the SAEs during the 24-week uncontrolled extension period were single digits without a concerning pattern.

The most common SAE SOC in the 24-week extension period belonged to Cardiac disorders (3/309; 1%) and Gastrointestinal disorders (3/309; 1%).

Two of the PTs (hepatocellular carcinoma and ascites) that occurred during the 24-week extension period were fatal (refer to Death section 8.4.1).

In the follow-up period of BCB118, the following SAE PTs occurred in 7 subjects from the EQWS group: pancreatic carcinoma (narrative below), atrial fibrillation, abortion spontaneous, cardiac failure congestive, coronary artery disease, deep vein thrombosis, osteomyelitis, skin infection, humerus fracture, and postoperative respiratory failure.

During the follow-up period of study BCB120, 3 SAEs occurred in the EQWS group (acute myeloid leukemia, atrial fibrillation, and pyelonephritis), 1 SAE in the sitagliptin, and 1 SAE in the placebo group.

Reviewer Comment: Review of the graphical patient profile for the SAE 'humerus fracture' (BCB118) did not show a relationship to hypoglycemia. The reported term for the PT skin infection is 'subcutaneous abdominal fluid collection/infection'.

In general, review of the SAEs in the follow-up periods appears to be unrelated to study drug.

Narrative for the SAE of pancreatic cancer (follow-up period, BCB118):

Subject (b) (6): A 59-year-old female with an 8-year history of T2DM and past medical history of hypertension, irritable bowel syndrome, and positive family history of pancreatic cancer (from which mother died at age 81) was randomized to the Byetta group (BCB118), and later switched to EQWS during the extension period. On Day 309 during the extension period, the subject experienced the adverse events of moderate weight loss and mild stomach pain. About four months after study completion (Day 456), the subject continued to have nausea, stomach pain, weight loss and was diagnosed on CT scan and Fine Needle Aspiration with pancreatic adenocarcinoma (7x4.9x4.8 cm) deemed surgically unresectable due to encasement of the superior mesenteric artery. The adverse event of pancreatic carcinoma was confirmed by Adjudication.

Reviewer Comments: A direct relationship between GLP-1 therapy and pancreatic cancer is not settled yet. The positive family history of pancreatic cancer in the mother and the latency of the occurrence of an approximately 7 cm mass confound establishing a direct causal relationship to study drug.

Reviewer's Summary of SAEs:

Overall a total of 38 SAEs occurred in both Phase 3 trials (controlled, extension, and follow-up periods) in subjects exposed to EQWS; 30 SAEs from study BCB118 (controlled, extension and follow-up periods) and 8 SAEs from study BCB120 (controlled and follow-up period).

The incidence of SAEs was generally low on treatment and was in single digits. Most SAEs seem unrelated to study drug. No specific pattern emerged of a single type of serious adverse event, or grouping of serious adverse events, which occurred with greater frequency among EQWS patients compared to the comparators in the two pivotal trials.

Of note, in the EQWS clinical development program, there were no treatment-emergent SAEs coded to the following PTs in the EQWS group: aplastic anemia, agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute liver failure, rhabdomyolysis, angioedema, or anaphylaxis.

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SAE Narratives:

Review of the narratives did not raise a significant concern for a specific SAE occurring as a result of EQWS treatment. Selected narratives of EQWS subjects with additional comments are summarized below.

SAE Narratives, BCB118

Subject (b) (6): 51-year-old African-American male with a 14-year history of T2DM on oral antidiabetic medication and past medical history of hypertension, hypocholesteremia, and obesity hospitalized for abdominal pain (mid-lower), constipation and nausea without fever or vomiting on Day 45 of study. Physical exam was negative for abdominal tenderness. Lipase was elevated 759 U/L (normal range 23-300). CT scan showed mild low-attenuation/heterogeneous enhancement of the pancreatic head with associated minimal peri-pancreatic fat stranding (nonspecific but suggesting an inflammatory process). EQWS was discontinued, and adjudication confirmed the case as pancreatitis.

Reviewer Comment: The temporal association of onset of acute pancreatitis after initiation of EQWS suggests possible causality. Pancreatitis is a labeled risk for GLP-1 agonists.

(b) (6) 56-year-old male with a four-year history of T2DM on metformin and occasional alcohol use with a family history of coronary artery disease in father developed pressure type substernal chest pain with negative troponins and negative ECG on Day 79 of the study. Despite the negative workup subject was catheterized due to typical symptomatology and found to have 50% LAD and 99% PDA stenosis with thrombosis requiring stent intervention. He was diagnosed with NSTEMI myocardial infarction. The subject continued the study into the extension period and withdrew due to personal reasons. This event was confirmed by adjudication.

Reviewer Comment: The adjudication confirmation appears reasonable. The contribution of the underlying risk factors confounds attribution of causality to EQWS.

(b) (6) 65-year-old white male with 11 history of T2DM on metformin and glipizide, psoriasis, and proteinuria who was randomized to Byetta. The subject was diagnosed with basal cell carcinoma on Day 104 on Byetta which was confirmed by adjudication. The subject entered the extension period and after five doses of EQWS developed a papular rash for 15 days over the entire body except for the head, face, palms, soles, and genitals.

Reviewer Comment: The event of basal cell carcinoma is unlikely related to study drug. Hypersensitivity reactions are labeled risks for GLP-1 therapy.

(b) (6) 49-year-old white male with three years of T2DM on no medication with a history of hypertension and bilateral lower extremity rash at study entry, who on Day 301 had

a motor vehicle accident driving under blizzard conditions. The narrative states the subject felt fine before the accident but had a brief loss of consciousness after the accident. Blood glucose measured at the emergency room was 150 mg/dL.

(b) (6) A 55-year-old female with a one-year history of T2DM on no medication and history of obesity, hyperlipidemia, hypertension, and fatty liver who on Day 287 developed acute abdominal pain, nausea, vomiting and diarrhea, and leukocytosis. Lipase was >3000 U/L (11-59 U/L), and amylase 1869 U/L (0-105 U/L). Computed tomography (CT) of the abdomen performed that same day showed inflammatory changes around the pancreatic head and body consistent with pancreatitis, without evidence of pancreatic necrosis or portal vein thrombosis, but with some suspicion of a pancreatic pseudocyst; A repeat abdominal CT scan showed changes consistent with acute pancreatitis with significant pancreatic phlegmon and significantly increased free fluid surrounding the pancreas, but no definitive pancreatic necrosis. Another follow-up abdominal CT with contrast revealed diffuse homogeneous enhancement of the pancreas, with significant relatively organized peripancreatic fluid without a defined pseudocyst or abscess. The adjudication confirmed this case as pancreatitis.

Reviewer Comment: The temporal association of onset of acute pancreatitis after initiation of EQWS suggests possible causality. Pancreatitis is a labeled risk for GLP-1 agonists.

(b) (6) 43-year-old Hispanic female with seven-year history of T2DM on metformin with past medical history of hyperlipidemia, elevated ALT, nephropathy, anemia, and prior cholecystectomy randomized to Byetta initially and continued to the extension period. The subject required rescue medication for hyperglycemia during the study. A week after study termination the subject had a positive urine pregnancy test and ten days later had a spontaneous abortion.

(b) (6) 64-year-old African-American male with five-year history of T2DM on metformin, pioglitazone, and glimepiride, and history of hypertension, hyperlipidemia, peripheral neuropathy, and paresthesia of legs. On day 179, two days following the subject's 26th dose of EQWS, the subject lost consciousness while driving home and ran into a pole. No glucose measurements are available from the time of motor vehicle accident. The narrative states the subject did not have previous episodes of hypoglycemia before the motor vehicle accident. The fingerstick glucose the day before was 108 mg/dL. A comprehensive workup of the syncope revealed no major abnormality. Subject's glucose values while hospitalized ranged from 108 - 190 mg/dL and no arrhythmias were detected on telemetry. He was discharged with syncope of unknown etiology. Adjudication did not confirm ventricular tachycardia or ventricular fibrillation.

Reviewer Comment: An etiology for the syncopal event was not found despite a generally comprehensive syncope workup in the hospital. Pre-accident glucose values are not available

from the narrative. However one cannot rule out a possible hypoglycemia event leading to syncope, considering four antidiabetic medications were on board. There is no information regarding the presence or absence of symptoms surrounding the unconsciousness (e.g., dizziness, hypoglycemic symptoms).

SAE Narratives, BCB120

(b) (6) is a 55-year old male with a 3-year history of T2DM on metformin randomized to EQWS with a history of hypertension and hypercholesterolemia. On Day 16 the subject was diagnosed with brainstem infarct after experiencing right sided numbness, dizziness, and unsteady gait, and an MRI showed a focal area of acute ischemia in the brain stem and a possible area of adjacent lacunar infarct.

Reviewer Comment: The contribution of the underlying risk factors confounds attribution of causality to EQWS.

(b) (6) An SAE of diarrhea occurred in a subject in the EQWS group who had a concomitant urinary tract infection that eventually progressed to pyelonephritis.

(b) (6) 74-year old white Hispanic/Latino male with a 10-year history of T2DM on metformin with past medical history of hypertension, chronic obstructive pulmonary disease, valvular cardiomyopathy, moderate aortic stenosis, and a systolic murmur on physical examination who was randomized to the EQWS arm. On Day 212 after completion of study dosing subject developed asymptomatic atrial fibrillation and diastolic dysfunction requiring hospitalization.

Reviewer Comment: The contribution of the underlying risk factors described in the narrative confounds attribution of causality to EQWS.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Events

Reviewer's approach to discontinuations due to TEAEs

To assess for numerical imbalances in the incidence of TEAEs leading to the withdrawal of treatment or study compared to Byetta, I reviewed the 28-week controlled period of BCB118. To assess numerical imbalances in the incidence of TEAEs leading to the withdrawal of treatment or study compared to sitagliptin and placebo, BCB120 was reviewed. The uncontrolled extension period of BCB118 and follow-up periods for both Phase 3 studies were also reviewed for longer term possible safety signals leading to discontinuation of treatment or study.

An Information Request was sent (August 2, 2017) asking the Applicant to clarify and summarize the subject discontinuations of study or treatment in both Phase 3 studies. The

information in section 8.4.3 is derived from the Applicants response (August 16, 2017) to the Information Request (August 2, 2017).

The following two tables stratifies the TEAEs leading to treatment and study discontinuation by MedDRA PT for the controlled treatment and extension period of the two Phase 3 studies:

Table 17: Treatment discontinuation due to TEAE by PT- safety population, BCB118 and BCB120

	BCB118				BCB120	
	Byetta n (%)	EQWS n (%)			EQWS n (%)	Placebo n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD
Nausea	3 (2.05%)	3 (1.31%)	0	0	0	0
Injection site nodule	0	2 (0.87%)	1 (0.86%)	0	0	0
Diarrhoea	0	2 (0.87%)	0	0	1 (0.55%)	0
Vomiting	0	2 (0.87%)	0	0	0	0
Pancreatitis	0	1 (0.44%)	0	1 (0.52%)	0	0
Pyrexia	0	1 (0.44%)	0	0	0	0
Abdominal pain	0	1 (0.44%)	0	0	0	0
Supraventricular tachycardia	0	1 (0.44%)	0	0	0	0
Insomnia	0	1 (0.44%)	0	0	0	0
Pain in extremity	0	1 (0.44%)	0	0	0	0
Chest discomfort	0	1 (0.44%)	0	0	0	0
Weight decreased	1 (0.68%)	1 (0.44%)	0	0	0	0
Injection site urticaria	1 (0.68%)	1 (0.44%)	0	0	0	0
Pyelonephritis	0	0	0	0	0	0
Abdominal hernia obstructive	0	0	0	0	1 (0.55%)	0
Hepatocellular carcinoma	0	0	1 (0.86%)	0	0	0
Breast cancer	0	0	0	0	1 (0.55%)	0
Muscle spasms	0	0	1 (0.86%)	0	0	0
Weight increased	0	0	1 (0.86%)	0	0	0
Rash generalised	0	0	0	0	0	0
Lower gastrointestinal haemorrhage	0	0	0	0	1 (0.55%)	0
Oedema peripheral	0	0	0	0	0	1 (1.64%)
Urinary tract infection	0	0	0	0	0	0
Urticaria	0	0	0	0	1 (0.55%)	0
Acute myocardial infarction	0	0	0	0	0	1 (1.64%)
Angioedema	0	0	0	0	0	1 (1.64%)
Feeling abnormal	0	0	0	0	0	1 (1.64%)
Hypoaesthesia	0	0	0	0	0	1 (1.64%)
Ascites	0	0	1 (0.86%)	0	0	0
Visual impairment	0	0	0	1 (0.52%)	0	0
Acute myeloid leukaemia	0	0	0	0	0	0
Toxic encephalopathy	1 (0.68%)	0	0	0	0	0
Septic shock	1 (0.68%)	0	0	0	0	0
Procedural nausea	1 (0.68%)	0	0	0	0	0
Lip swelling	1 (0.68%)	0	0	0	0	0
Lactic acidosis	1 (0.68%)	0	0	0	0	0
Hypoglycaemia	1 (0.68%)	0	0	0	0	0
Gastritis haemorrhagic	1 (0.68%)	0	0	0	0	0
Diverticular perforation	1 (0.68%)	0	0	0	0	0
Atrial fibrillation	1 (0.68%)	0	0	0	0	0
Acute kidney injury	1 (0.68%)	0	0	0	0	0
Abdominal discomfort	1 (0.68%)	0	0	0	0	0 (0.00%)
Subjects(filtered)	12 (8.22%)	11 (4.80%)	2 (1.72%)	2 (1.03%)	5 (2.76%)	3 (4.92%)
1stColItemSubjects	146 (100.00%)	229 (100.00%)	116 (100.00%)	193 (100.00%)	181 (100.00%)	61 (100.00%)

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Table 18: Study discontinuation due to TEAE by PT- safety population, BCB118 and BCB120

	BCB118				BCB120	
	Byetta n (%)	EQWS n (%)			EQWS n (%)	Placebo n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD
Abdominal hernia obstructive	0	0	0	0	1 (0.55%)	0
Acute myeloid leukaemia	0	0	0	0	0	0
Acute myocardial infarction	0	0	0	0	0	1 (1.64%)
Angioedema	0	0	0	0	0	1 (1.64%)
Ascites	0	0	1 (0.86%)	0	0	0
Breast cancer	0	0	0	0	1 (0.55%)	0
Diarrhoea	0	1 (0.44%)	0	0	0	0
Diverticular perforation	1 (0.68%)	0	0	0	0	0
Feeling abnormal	0	0	0	0	0	1 (1.64%)
Hepatocellular carcinoma	0	0	1 (0.86%)	0	0	0
Hypoaesthesia	0	0	0	0	0	1 (1.64%)
Hypoglycaemia	1 (0.68%)	0	0	0	0	0
Injection site nodule	0	1 (0.44%)	0	0	0	0
Injection site urticaria	1 (0.68%)	1 (0.44%)	0	0	0	0
Lip swelling	1 (0.68%)	0	0	0	0	0
Lower gastrointestinal haemorrhage	0	0	0	0	1 (0.55%)	0
Nausea	2 (1.37%)	1 (0.44%)	0	0	0	0
Pancreatitis	0	1 (0.44%)	0	1 (0.52%)	0	0
Rash generalised	0	0	0	0	0	0
Septic shock	1 (0.68%)	0	0	0	0	0
Vomiting	0	2 (0.87%)	0	0	0	0
Weight decreased	1 (0.68%)	0	0	0 (0.00%)	0	0
Subjects(filtered)	8 (5.48%)	5 (2.18%)	1 (0.86%)	1 (0.52%)	3 (1.66%)	3 (4.92%)
1stColItemSubjects	146 (100.00%)	229 (100.00%)	116 (100.00%)	193 (100.00%)	181 (100.00%)	61 (100.00%)

Created by reviewer using JReview, ADAM dataset ISS.

A. Controlled treatment period, BCB118 and BCB120: TEAEs leading to Treatment Withdrawal

In BCB118, a total of 22 subjects (11 each in the EQWS and the Byetta groups) discontinued treatment because of adverse events during the controlled period.

Reviewer Comment: In BCB118, during the controlled treatment period, the incidence of treatment discontinuation (Table 17) due to TEAE was higher in the Byetta group compared to EQWS (8.2% vs. 4.8%).

The most common PTs leading to treatment discontinuation during the controlled treatment period of BCB118 in the EQWS group was nausea (1.3% EQWS vs. 2.05% Byetta), followed by injection site nodule, diarrhea, and vomiting (0.87% each in EQWS vs. 0 in Byetta).

The PT supraventricular tachycardia leading to treatment withdrawal does not appear to have occurred on the background of elevated heart rate. The subject had a history of supraventricular tachycardia. Adjudication committee did not confirm the supraventricular tachycardia as ventricular tachycardia or fibrillation.

In BCB120, the highest rate of treatment discontinuation was in the placebo group (4.92% vs. 2.76% EQWS). The PTs leading to treatment discontinuation in the EQWS group are abdominal hernia obstructive, abdominal pain, diarrhea, lower gastrointestinal hemorrhage, breast cancer, and urticaria. There were no treatment discontinuations due to TEAEs in the sitagliptin group.

Reviewer Comment: Subject [redacted] (b) (6) *(BCB120, EQWS group) withdrew treatment and the study due to moderate urticaria. The graphical patient profile shows this subject had mild injection site rash and mild trunk rash simultaneously, followed by injection site pain and erythema. After developing general urticaria around Day 40, subject withdrew from treatment and study. The reason for withdrawal is stated as "subject felt awful for months, and had hives that he thought was related to the drug". The subject carries a past medical history of seasonal allergies and rash on lower extremities.*

TEAEs leading to study withdrawal

Of the 22 subjects who discontinued study treatment in study BCB118 during the controlled treatment period, 12 subjects (5 in the EQWS group and 7 in the Byetta group) also discontinued the study because of adverse events during the 28-week controlled treatment arm.

In the controlled arm of study BCB118, the most common SOC leading to the withdrawal of study in the EQWS group belonged to the SOC Gastrointestinal disorders (1.3 %), compared to Byetta (2.7%). The second most common SOC belonged to the SOC General disorders and administration site conditions (0.9% in EQWS vs. 0.7% in Byetta).

In BCB120, a total of 8 subjects (5 in the EQWS group and 3 in the placebo group) discontinued treatment because of TEAEs during the study. Of the total eight subjects who discontinued study treatment because of an adverse event, three from the EQWS group and three from the placebo group also discontinued the study because of an adverse event.

In BCB120, the most common SOC leading to the withdrawal of study due to TEAE in the EQWS group was SOC Gastrointestinal (1.1% in EQWS, vs. 0 in placebo and sitagliptin), followed by the SOC Neoplasms benign, malignant and unspecified (0.6% EQWS vs. 0 in sitagliptin and placebo).

Reviewer Comment: Study withdrawal due to gastrointestinal events was less in the EQWS group compared to Byetta, but more in EQWS compared to sitagliptin.

Reviewer Comment: In comparing treatment groups, there was a lower premature study discontinuation rate due to adverse events in the EQWS-treated patients (2.18%) than in the comparator Byetta (5.48%) in the controlled period of study BCB118.

In study BCB120, the incidence of study withdrawal due to an adverse event was highest in the placebo group, followed by EQWS, and sitagliptin (4.92% vs. 2.18% vs. 1.6% respectively).

B. 24-week extension arm, study BCB118:

During the extension period of study BCB118, an additional four subjects withdrew treatment due to TEAE, 2 of which discontinued the study. The PTs injection site nodule and pancreatitis leading to treatment withdrawal were likely related to the study drug.

In BCB118, during the follow-up period, the following PTs led to study withdrawal in the EQWS group: abdominal pain, injection site nodule, nausea, vomiting, and generalized rash.

In BCB120, during the follow-up period, the following PTs led to study withdrawal in the EQWS group: acute myeloid leukemia, pyelonephritis, and urinary tract infection.

Reviewer Comment: Although the incidence of treatment discontinuation due to TEAE is higher in the Byetta group compared to the EQWS group, note that the following PTs led to treatment discontinuation only in the EQWS group (both Phase 3 studies, all periods): injection site nodule, diarrhea, vomiting, abdominal pain, pancreatitis, urticaria, and rash generalized.

Label:

In the proposed label, the Applicant presents the incidence of TEAEs leading to discontinuation of 'therapy' from the pooled EQWS arms of the 28-week controlled treatment periods of BCB118 and BCB120.

Reviewer Comment: In the label, the Applicant states the pooled incidence of discontinuation from the therapy due to adverse events is (b)(4)% in the two 28-week trials. This is not accurate. The pooled incidence of discontinuation from the study due to adverse events is (b)(4)%, but the pooled incidence of discontinuation due to treatment (therapy) due to TEAE is 3.9% in the two 28-week trials.

In response (August 16, 2017) to an Information Request (August 2, 2017) the Applicant clarified that during the 28-week controlled period, the incidence of treatment discontinuation due to TEAE in the EQWS group was 11 (4.8%) in BCB118 and 5 (2.76%) in BCB120. Thus the pooled incidence of discontinuation due to treatment due to TEAE is 3.9% in the two 28-week trials.

(b) (4) the following two tables show the incidence of treatment discontinuation due to TEAE by SOC and PT for the pooled 28-week EQWS group of the two Phase 3 studies (n=410).

Table 19: Treatment discontinuation due to TEAE by SOC- safety population, pooled 28-week EQWS groups of BCB118 and BCB120

SOC	EQWS n (%)	Byetta n (%)	Placebo n (%)
Gastrointestinal disorders	8 (1.95%)	7 (4.79%)	0
General disorders and administration site conditions	5 (1.22%)	1 (0.68%)	2 (3.28%)
Skin and subcutaneous tissue disorders	1 (0.24%)	0	1 (1.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.24%)	0	0
Cardiac disorders	1 (0.24%)	1 (0.68%)	1 (1.64%)
Musculoskeletal and connective tissue disorders	1 (0.24%)	0	0
Psychiatric disorders	1 (0.24%)	0	0
Investigations	1 (0.24%)	1 (0.68%)	0
Renal and urinary disorders	0	1 (0.68%)	0
Infections and infestations	0	1 (0.68%)	0
Nervous system disorders	0	1 (0.68%)	1 (1.64%)
Injury, poisoning and procedural complications	0	1 (0.68%)	0
Metabolism and nutrition disorders	0	2 (1.37%)	0
Subjects(filtered)	16 (3.90%)	12 (8.22%)	3 (4.92%)
1stColItemSubjects	410 (100.00%)	146 (100.00%	61 (100.00%)

Created by reviewer using JReview, ADAM dataset ISS.

Table 20: Treatment discontinuation due to TEAE by PT- safety population, pooled 28-week EQWS groups of BCB118 and BCB120

Dictionary Derived Term	EQWS n (%)	Byetta n (%)	Placebo n (%)
Diarrhoea	3 (0.73%)	0	0
Nausea	3 (0.73%)	3 (2.05%)	0
Injection site nodule	2 (0.49%)	0	0
Vomiting	2 (0.49%)	0	0
Pain in extremity	1 (0.24%)	0	0
Lower gastrointestinal haemorrhage	1 (0.24%)	0	0
Insomnia	1 (0.24%)	0	0
Pyrexia	1 (0.24%)	0	0
Supraventricular tachycardia	1 (0.24%)	0	0
Chest discomfort	1 (0.24%)	0	0
Breast cancer	1 (0.24%)	0	0
Injection site urticaria	1 (0.24%)	1 (0.68%)	0
Abdominal pain	1 (0.24%)	0	0
Abdominal hernia obstructive	1 (0.24%)	0	0
Pancreatitis	1 (0.24%)	0	0
Weight decreased	1 (0.24%)	1 (0.68%)	0
Urticaria	1 (0.24%)	0	0
Toxic encephalopathy	0	1 (0.68%)	0
Procedural nausea	0	1 (0.68%)	0
Lip swelling	0	1 (0.68%)	0
Lactic acidosis	0	1 (0.68%)	0
Hypoglycaemia	0	1 (0.68%)	0
Gastritis haemorrhagic	0	1 (0.68%)	0
Diverticular perforation	0	1 (0.68%)	0
Atrial fibrillation	0	1 (0.68%)	0
Acute kidney injury	0	1 (0.68%)	0
Abdominal discomfort	0	1 (0.68%)	0
Oedema peripheral	0	0	1 (1.64%)
Hypoaesthesia	0	0	1 (1.64%)
Feeling abnormal	0	0	1 (1.64%)
Angioedema	0	0	1 (1.64%)
Septic shock	0	1 (0.68%)	0
Acute myocardial infarction	0	0	1 (1.64%)
Subjects(filtered)	16 (3.90%)	12 (8.22%)	3 (4.92%)
1stColItemSubjects	410 (100.00%)	146 (100.00%)	61 (100.00%)

Created by reviewer using JReview, ADAM dataset ISS.

Reviewer Comment: The incidence of discontinuation of treatment due to adverse events was 3.9% for EQWS-treated subjects in the two comparator-controlled 28-week trials. The most common SOC leading to discontinuation of treatment for EQWS-treated subjects were Gastrointestinal Disorders (1.95%) and General Disorders and Administration Site Conditions (0.68%). For EQWS-treated patients, the most frequent PTs leading to discontinuation of treatment within each of these respective classes were diarrhea (0.73%), nausea (0.73%), vomiting (0.5%) and injection-site nodule (0.5%), and injection site urticaria (0.24%).

Reviewer's summary of discontinuation due to TEAE:

In the Byetta-controlled study BCB118, the incidence of treatment discontinuation due to adverse events was higher in the Byetta group compared to EQWS group.

In BCB118, the most frequent adverse events leading to treatment discontinuation in the controlled period of the EQWS group were nausea, vomiting, diarrhea, injection site nodule, and pancreatitis. These are known safety risks for GLP-1 agonists.

In the placebo-controlled study BCB120, the incidence of treatment discontinuation due to an adverse event was higher in the placebo group compared to EQWS.

Of note In the EQWS clinical development program, there were no TEAEs coded to the following PTS in the EQWS group leading to premature treatment or study discontinuation: aplastic anemia, agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute liver failure, acute renal failure, rhabdomyolysis, angioedema, or anaphylaxis.

There were two SAEs of acute pancreatitis in the EQWS group that led to treatment withdrawal, and two moderate PTs of rash generalized and urticaria in the EQWS group leading to treatment withdrawal.

8.4.4. Significant Adverse Events

Treatment-Emergent Adverse Events (TEAE)

Reviewer's approach to TEAEs

To assess for numerical imbalances in TEAEs compared to Byetta, the controlled arm of study BCB118 was reviewed. To assess numerical imbalances in TEAEs compared to placebo and sitagliptin, study BCB120 was reviewed. To assess rare safety signals or adverse events that may occur with longer duration of treatment, the 24-week extension period of study BCB118 was reviewed. Also, the Applicant's pool of all EQWS subjects for the proposed labeling was reviewed and replicated.

The risk assessment tool (JReview) was used to illustrate the risk difference (per 100) between the Byetta and EQWS groups during the controlled period of study BCB118.

Table 21: TEAE by PT > 2 % in frequency- safety population, BCB118 and BCB120

	BCB118				BCB120		
	Byetta n (%)	EQWS n (%)			EQWS n (%)	Placebo n (%)	Sitagliptin n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD
Injection site nodule	1 (0.68%)	36 (15.72%)	5 (4.31%)	1 (0.51%)	14 (7.73%)	0 (0.00%)	0 (0.00%)
Nausea	30 (20.55%)	22 (9.61%)	5 (4.31%)	1 (0.51%)	16 (8.84%)	0 (0.00%)	2 (1.64%)
Upper respiratory tract infection	5 (3.42%)	13 (5.68%)	3 (2.58%)	2 (1.03%)	4 (2.21%)	2 (3.28%)	0 (0.00%)
Headache	9 (6.16%)	13 (5.68%)	0 (0.00%)	2 (1.03%)	8 (4.42%)	1 (1.64%)	2 (1.64%)
Diarrhoea	17 (11.64%)	12 (5 24%)	2 (1.72%)	3 (1.55%)	5 (2.76%)	1 (1.64%)	2 (1.64%)
Injection site pruritus	1 (0.68%)	10 (4.37%)	2 (1.72%)	0 (0.00%)	5 (2.76%)	0 (0.00%)	0 (0.00%)
Injection site erythema	1 (0.68%)	8 (3.49%)	0 (0.00%)	0 (0.00%)	3 (1.66%)	0 (0.00%)	0 (0.00%)
Constipation	4 (2.74%)	8 (3.49%)	1 (0.68%)	0 (0.00%)	2 (1.10%)	1 (1.64%)	1 (0.82%)
Pain in extremity	5 (3.42%)	8 (3.49%)	0 (0.00%)	3 (1.55%)	2 (1.10%)	1 (1.64%)	0 (0.00%)
Dizziness	6 (4.11%)	8 (3.49%)	0 (0.00%)	2 (1.03%)	4 (2 21%)	0 (0.00%)	1 (0.82%)
Vomiting	9 (6.16%)	8 (3.49%)	2 (1.72%)	1 (0.51%)	6 (3.31%)	0 (0 00%)	0 (0 00%)
Injection site pain	0 (0.00%)	7 (3 06%)	2 (1.72%)	0 (0.00%)	3 (1.66%)	0 (0 00%)	0 (0 00%)
Injection site bruising	0 (0.00%)	7 (3 06%)	3 (2.58%)	0 (0.00%)	5 (2.76%)	0 (0 00%)	0 (0 00%)
Abdominal distension	1 (0.68%)	6 (2.62%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0 00%)	0 (0 00%)
Muscle spasms	2 (1.37%)	6 (2.62%)	1 (0.68%)	1 (0.44%)	1 (0.55%)	2 (3 28%)	0 (0 00%)
Gastrooesophageal reflux disease	2 (1.37%)	6 (2.62%)	0 (0.00%)	2 (1.03%)	2 (1.10%)	0 (0 00%)	1 (0.82%)
Back pain	5 (3.42%)	6 (2.62%)	0 (0.00%)	1 (0.51%)	2 (1.10%)	1 (1.64%)	3 (2.46%)
Nasopharyngitis	6 (4.11%)	6 (2.62%)	3 (2.58%)	7 (3.62%)	1 (0.55%)	4 (6.56%)	0 (0 00%)
Cough	0 (0.00%)	5 (2.18%)	2 (1.72%)	1 (0.51%)	1 (0.55%)	0 (0 00%)	1 (0.82%)
Blood creatine phosphokinase increased	2 (1.37%)	5 (2.18%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0 00%)	1 (0.82%)
Urinary tract infection	3 (2.05%)	5 (2.18%)	0 (0.00%)	5 (2.18%)	3 (1.66%)	2 (3 28%)	3 (2.46%)
Fall	5 (3.42%)	5 (2.18%)	2 (1.72%)	3 (1.55%)	2 (1.10%)	2 (3 28%)	0 (0 00%)
Subjects(filtered)	110 (75.3%)	162 (70.7%)	64 (55 2%)	95 (49 2%)	101 (55.8%)	29 (47.5%)	40 (32.8%)
1stColItemSubjects	146 (100.00%)	229 (100 00%)	116 (100 00%)	193 (100.00%)	181 (100.00%)	61 (100 00%)	122 (100.00%)

Created by reviewer using JReview, ADAM dataset ISS.
Note the total number of subjects filtered represent the total number of TEAEs in each treatment arm, but the table presents TEAEs > 2% in frequency.

A. Controlled treatment arm, study BCB118 and BCB120:

During the controlled period of BCB118, the incidence of TEAEs was highest in the Byetta group (75.3%) compared to the EQWS group (70.7%).

During the controlled period of BCB120, the incidence of TEAEs was highest in the EQWS group (55.8%) followed by the placebo group (47.5%), and the sitagliptin group (32.8%).

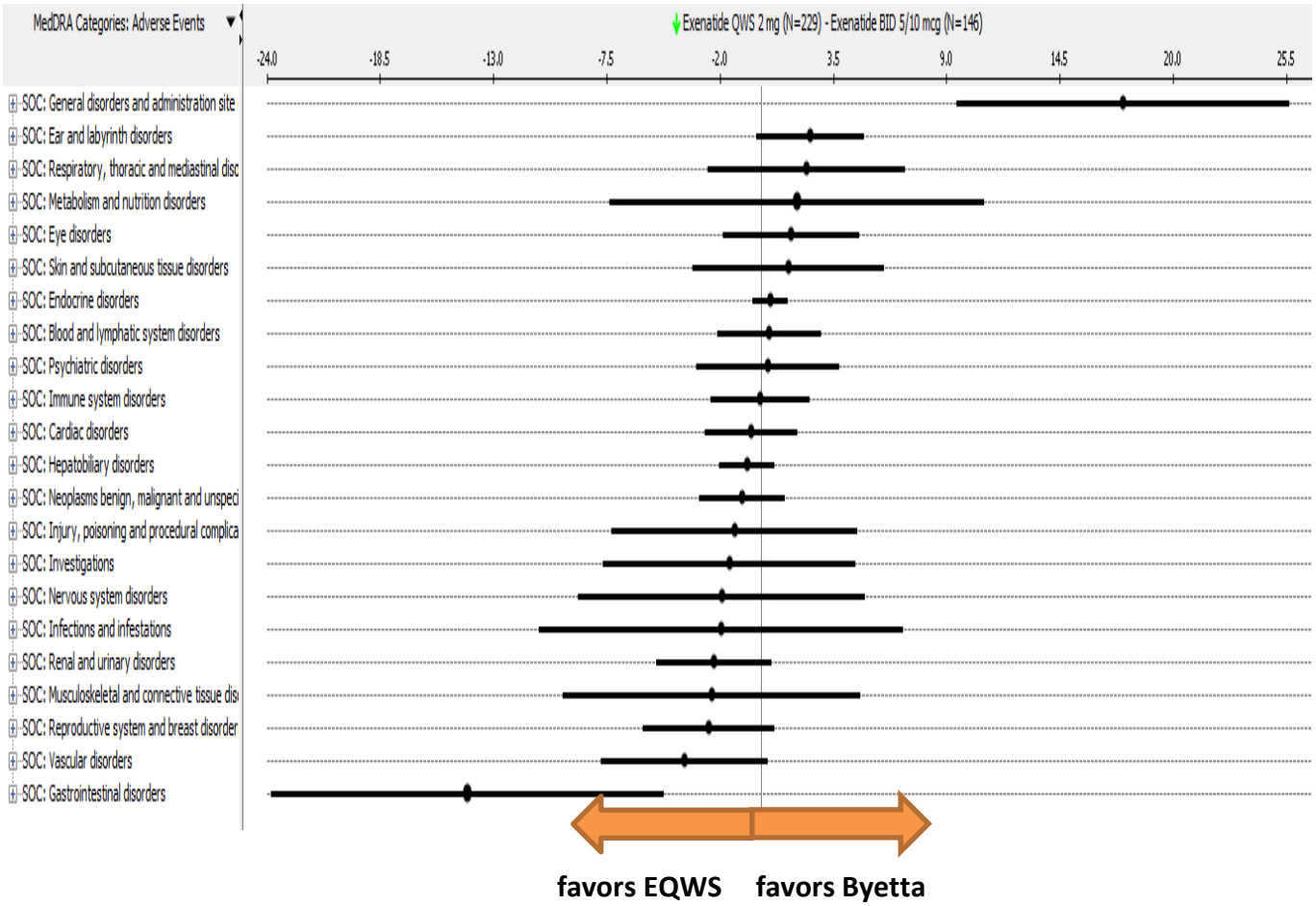
The most common TEAE SOC during the controlled periods of BCB118 and BCB120 in the EQWS group belonged to the SOC General disorders and administration site conditions (30.6% BCB118 and 21% BCB120), followed by the SOC Gastrointestinal disorders (22.7% BCB118 and 17.7% BCB120), and the SOC Infections and infestations (22.7% BCB118 and 11.6% BCB120).

The most frequent TEAE PTs during the controlled period of BCB118 in the EQWS group are injection site nodule, followed by nausea, headache, and upper respiratory tract infection. The most frequent PTs in BCB120 in the EQWS group are nausea followed by injection site nodule and headache.

The PTs occurring in favor of Byetta compared to EQWS in the controlled period of BCB118 are upper respiratory tract infection, injection site pruritus, constipation, injection site erythema, bruising, pain, abdominal distension, gastrointestinal reflux disease, and increased creatine phosphokinase (CPK).

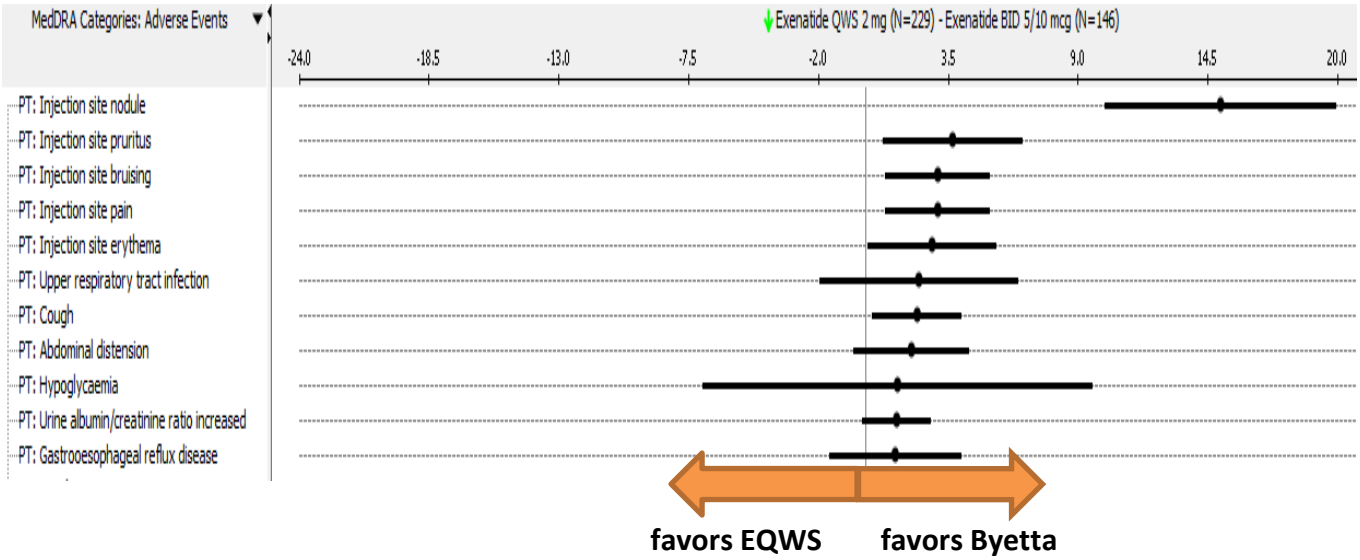
The figures below show the risk difference (per 100) by SOC and PT for EQWS vs. Byetta during the controlled period of study BCB118.

Figure 15: TEAE Risk Difference (per 100) by SOC, EQWS vs. Byetta, safety population, controlled period, BCB118



Created by reviewer using JReview, ADAM dataset ISS.

Figure 16: TEAE Risk Difference (per 100) by PT, EQWS vs. Byetta, safety population, controlled period, BCB118



Created by reviewer using JReview, ADAM dataset ISS.

Reviewer Comment: A clear imbalance is observed in the SOC General Disorders and Administration Site driven by the PT injection site nodule in the controlled period of BCB118 in the EQWS group compared to Byetta. Injection site reaction TEAEs are discussed in section 8.5. Note the SOC Gastrointestinal disorder has the least risk difference in favor of EQWS compared to Byetta. Gastrointestinal TEAEs are discussed in section 8.5.

Reviewer Comment: Refer to injection site reactions in Section 8.5. for a discussion on possible splitting of injection site PTs (nodule, granuloma, induration, mass).

B. 24-week extension arm, BCB118

51.5% of subjects developed a TEAE during the 24-week extension period of study BCB118.

The most frequent SOC was Infections and Infestations (17.8%), followed by the SOC Musculoskeletal and connective tissue disorders (8.1%) and SOC Gastrointestinal disorders (7.8%).

Label:

In the proposed label, the Applicant presents the TEAEs using the 'All EQWS' pool. The All EQWS pool contains all subjects exposed to EQWS during the controlled, uncontrolled, and follow-up period and all subjects who switched from Byetta to EQWS during the extension

period (n=526).

Reviewer Comment: The TEAE table (Table 22) (b) (4) *was replicated by requesting the formula from the Applicant (Information Request; August 2, 2017).*

Table 22: TEAE by PT > 1% in frequency- safety population, BCB118 and BCB120, pooled EQWS as presented in the label

Dictionary Derived Term	All EQWS
Injection site nodule	55 (10.46%)
Nausea	43 (8.17%)
Upper respiratory tract infection	22 (4.18%)
Headache	22 (4.18%)
Diarrhoea	21 (3.99%)
Injection site pruritus	17 (3.23%)
Vomiting	17 (3.23%)
Injection site bruising	15 (2.85%)
Nasopharyngitis	15 (2.85%)
Urinary tract infection	13 (2.47%)
Pain in extremity	13 (2.47%)
Dizziness	13 (2.47%)
Injection site pain	12 (2.28%)
Hypertension	12 (2.28%)
Fall	12 (2.28%)
Injection site erythema	11 (2.09%)
Influenza	11 (2.09%)
Constipation	11 (2.09%)
Dyspepsia	10 (1.90%)
Gastrooesophageal reflux disease	10 (1.90%)
Cough	9 (1.71%)
Hyperlipidaemia	9 (1.71%)
Sinusitis	9 (1.71%)
Arthralgia	9 (1.71%)
Injection site induration	9 (1.71%)
Back pain	9 (1.71%)
Muscle spasms	8 (1.52%)
Fatigue	8 (1.52%)
Bronchitis	8 (1.52%)
Abdominal distension	7 (1.33%)
Contusion	6 (1.14%)
Blood creatine phosphokinase increased	6 (1.14%)
Rash	6 (1.14%)
Gastroenteritis viral	6 (1.14%)
Abdominal pain	6 (1.14%)
Hyperkalaemia	6 (1.14%)
Subjects(filtered)	348 (66.16%)
1stColItemSubjects	526 (100.00%)

Created by reviewer using JReview, ADAM dataset ISS and formula provided in the response (August 16, 2017) to Information Request (August 2, 2017)

Reviewer Comment: The interpretation of the safety pool 'all EQWS' may be clinically difficult because this pool is comprised of controlled, uncontrolled, and Byetta to EQWS switch subjects. This pool may also dilute the incidence of adverse events. It may be more informative to present the data as a pool of the two 28-week controlled periods of the two Phase 3 studies (b) (4) (b) (4) *(Table 23).*

Table 23: TEAE by PT > 1 % in frequency- safety population, pool of the two 28-week controlled periods of BCB118 and BCB120

Dictionary Derived Term	EQWS n (%)	Byetta n (%)	Placebo n (%)	Stagliptin n (%)
Injection site nodule	50 (12.20%)	1 (0.68%)	0 (0.00%)	0 (0.00%)
Nausea	38 (9.27%)	30 (20.55%)	0 (0.00%)	2 (1.64%)
Headache	21 (5.12%)	9 (6.16%)	1 (1.64%)	2 (1.64%)
Diarrhoea	17 (4.15%)	17 (11.64%)	1 (1.64%)	2 (1.64%)
Upper respiratory tract infection	17 (4.15%)	5 (3.42%)	2 (3.28%)	0 (0.00%)
Injection site pruritus	15 (3.66%)	1 (0.68%)	0 (0.00%)	0 (0.00%)
Vomiting	14 (3.41%)	9 (6.16%)	0 (0.00%)	0 (0.00%)
Dizziness	12 (2.93%)	6 (4.11%)	0 (0.00%)	1 (0.82%)
Injection site bruising	12 (2.93%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site erythema	11 (2.68%)	1 (0.68%)	0 (0.00%)	0 (0.00%)
Constipation	10 (2.44%)	4 (2.74%)	1 (1.64%)	1 (0.82%)
Pain in extremity	10 (2.44%)	5 (3.42%)	1 (1.64%)	0 (0.00%)
Injection site pain	10 (2.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	8 (1.95%)	2 (1.37%)	0 (0.00%)	1 (0.82%)
Urinary tract infection	8 (1.95%)	3 (2.05%)	2 (3.28%)	3 (2.46%)
Injection site induration	8 (1.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Back pain	8 (1.95%)	5 (3.42%)	1 (1.64%)	3 (2.46%)
Abdominal distension	7 (1.71%)	1 (0.68%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis	7 (1.71%)	6 (4.11%)	4 (6.56%)	0 (0.00%)
Fall	7 (1.71%)	5 (3.42%)	2 (3.28%)	0 (0.00%)
Muscle spasms	7 (1.71%)	2 (1.37%)	2 (3.28%)	0 (0.00%)
Fatigue	7 (1.71%)	4 (2.74%)	0 (0.00%)	0 (0.00%)
Dyspepsia	7 (1.71%)	7 (4.79%)	0 (0.00%)	1 (0.82%)
Cough	6 (1.46%)	0 (0.00%)	0 (0.00%)	1 (0.82%)
Hypertension	6 (1.46%)	5 (3.42%)	2 (3.28%)	1 (0.82%)
Hyperlipidaemia	6 (1.46%)	3 (2.05%)	0 (0.00%)	1 (0.82%)
Blood creatine phosphokinase increased	6 (1.46%)	2 (1.37%)	0 (0.00%)	1 (0.82%)
Ear pain	5 (1.22%)	1 (0.68%)	0 (0.00%)	0 (0.00%)
Subjects(filtered)	263 (64.15%)	110 (75.34%)	29 (47.54%)	40 (32.79%)
1stColItemSubjects	410 (100.00%)	146 (100.00%)	61 (100.00%)	122 (100.00%)

Created by reviewer using JReview, ADAM dataset ISS

The Applicant's subgroup analysis by age show the verall incidence of adverse events was similar in EQWS-treated subjects aged <65 years (63.7%) and those aged ≥65 years (66.2%). At the SOC level, adverse events were generally similar between the <65 years and ≥65 years EQWS-treated age groups.

The most notable between-group differences for these 2 age groups were higher incidence rates in the ≥65 years age group of Eye disorders (6.8% vs 1.2%), Gastrointestinal disorders (27.0% vs 19.0%), General disorders and administration site conditions (32.4% vs 25.0%), Musculoskeletal and connective tissue disorders (16.2% vs 9.2%), and Skin and subcutaneous tissue disorders (9.5% vs 3.3%).

In the age group ≥65 years, 18.9% developed the PT injection site nodule compared to 10.7% in the age group < 65 years old. The incidence of gastrointestinal PTs nausea, diarrhea, and vomiting was higher in the the age group ≥65 years compared to the age group < 65 years old (12.2 vs. 8.6%, 8.1 vs. 3.3%, 5.4 vs. 2.4% respectively).

Reviewer Summary of TEAEs:

The incidence of TEAEs was highest in the Byetta group, followed by the EQWS group, the placebo group (47.5%), and the sitagliptin group (32.8%) during the controlled period of both studies. In the EQWS group, a clear imbalance is observed in the SOC General disorder and administration site driven by the PT injection site nodule in the controlled period of the Phase 3 studies. The SOC Gastrointestinal disorder has the least risk difference in favor of EQWS compared to Byetta.

8.4.5. Laboratory Findings

For laboratory safety analysis, the Applicant analyzed subjects with at least one post-baseline lab value. The Applicant states the worst lab value was used if a subject had multiple scheduled or unscheduled safety laboratory values within the same visit.

Table 24: Criteria for potentially clinical important laboratory values in the EQWS clinical program

Analyte	Values of potential clinical importance
Clinical chemistry analytes	
Albumin	<2.5 g/dL
Bicarbonate (serum)	<18 mEq/L; >35 mEq/L
Blood urea nitrogen	>45 mg/dL
Calcium (serum)	<8 mg/dL; >11 mg/dL
Creatine kinase (total)	>3× ULN (IU/L)
Creatinine (serum)	≥1.5X baseline
Phosphorus	<1.0 mg/dL
Potassium (serum)	<3.0 mEq/L; >5.5 mEq/L
Sodium (serum)	<130 mEq/L; >150 mEq/L
Uric acid (serum)	Males: >10.0 mg/dL; Females: >8.0 mg/dL
Hematology	
Hematocrit	Males: <36%; Females: <30%
Hemoglobin	Males: <12 g/dL; Females: <10 g/dL
Platelets	<75,000 /µL; > 500,000 /µL
White blood cell count	< 1,500 cells/µL; > 18,000 cells/µL
Lipid Profile	
Cholesterol, total	>350 mg/dL
Triglycerides	>500 mg/dL

Source: Excerpted from Statistical analysis plan for ISS edition 1, Appendix 2, page 44.

The Applicant states the incidence of potentially clinically significant laboratory abnormalities in EQWS-treated subjects was ≥ 1% and at least twice the rate for placebo only for bicarbonate <18 mEq/L, triglycerides > 500 mg/dL and creatinine ≥ 1.5 mg/dL. Creatinine lab abnormality is discussed in section 8.5.

Bicarbonate lab abnormalities:
The Applicants data show during the controlled period of BCB118 and BCB120, post-baseline bicarbonate values of < 18 mEq/L were seen in 6.6% of the pooled EQWS subjects, 8.2% of the Byetta subjects, 4.1% of the sitagliptin subjects and 3.3% of the placebo subjects. The Applicant states most of these subjects had baseline bicarbonate values that were at the lower end of the normal range, and the bicarbonate changes were not judged as clinically significant by the investigator.

This reviewer examined the following selected adverse events: blood bicarbonate decreased, hypotension, lactic acidosis, and metabolic acidosis, and also reviewed the outlier bicarbonate data in a box-whisker presentation (JReview).

Reviewer Comment: Lactic acidosis is the only SAE of severe intensity reported in a subject from the Byetta group who developed lactic acidosis in the setting of septic shock. The remainder of the other PT adverse events stated above were either mild or moderate in severity.

Below are select graphical patient profile reviews of the bicarbonate-related adverse events stated above:

1. PT 'Blood bicarbonate decreased':
   Subject (b) (6): 46-year-old African-American obese male with eight-year duration of T2DM and HgA1c of 10% at baseline treated with metformin, with past medical history significant for hypertension and mild renal impairment at baseline randomized to EQWS treatment (BCB118). The GPP shows increased CPK (up to 700 IU/L from baseline of 250 IU/L), increased creatinine (1.29 mg/dl baseline to 1.52 mg/dL), and decreased bicarbonate (down to 13 mEq/L). The bicarbonate level returned to baseline, with a later second decline to 16 mEq/L. Adjudication did not confirm the increased CPK as an acute coronary syndrome. The study was terminated due to subject withdrawal.

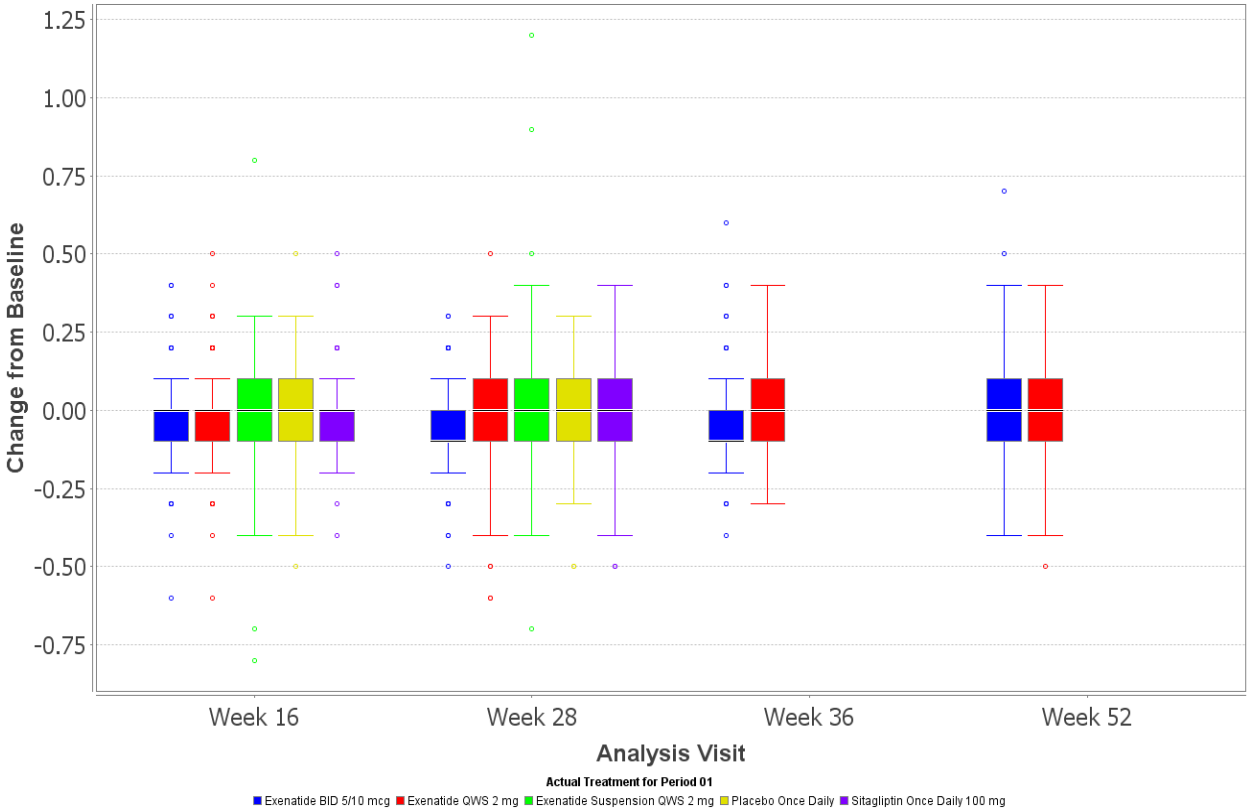
Reviewer Comment: The etiology of the transient biochemical changes of increased CPK, low bicarbonate, and increased creatinine is unknown. The subject withdrew by choice, and longer-term follow-up is not available.

2. PT 'metabolic acidosis':
   Subject (b) (6): a 43-year-old obese female, HbA1c 7.6% at baseline on metformin randomized to the EQWS group (BCB118, who developed the adverse event of mild metabolic acidosis (bicarbonate 16 from baseline 25 mEq/L) during the extension period along with the adverse event abdominal pain. The bicarbonate levels returned to baseline on the next visit. About a month earlier the subject had the adverse event of urinary tract infection. The subject's GPP does not show other significant vital sign or lab abnormality. No nausea or vomiting adverse events are reported.

Review of the bicarbonate measurement outliers in JReview's box-whisker presentation (Figure 17) shows a transient decrease of bicarbonate level in some subjects. In some subjects, the transient bicarbonate decrease coincided with transient creatinine increases.

Overall, the bicarbonate lab abnormalities appear transient and the bicarbonate measurements central tendencies appear similar in the EQWS group compared to the comparators in the box whiscker bicarbonate presentation (Figure 17).

Figure 17: Box-whisker presentation of bicarbonate central tendency and change from baseline, and outliers per visit- controlled and extension periods, safety population, BCB118 and BCB120



Generated by the reviewer, JReview, ADAM dataset, ISS
Note the Week 36 and Week 52 data represent EQWS treated subjects only.

Creatine phosphokinase (CPK) lab abnormalities:
Review of the chemistry labs with JReview show the following outlier for CPK:

Subject (b) (6) a 49-year-old Asian male with past medical history of intermittent hypertension, hyperlipidemia, and polio, with diet-controlled T2DM and mild renal impairment at baseline randomized to the Byetta group (BCB118), had a baseline elevated CPK value of 1001 IU/L. The graphical patient profile shows that during the extension phase on EQWS, the CPK increased to ~6000 IU/L, followed by a later return to the baseline value. A concurrent aspartate aminotransferase (AST) increase to 91 U/L from baseline of 27 U/L was seen. No other concurrent adverse event was reported.

Reviewer Comments: The event triggering the CPK increase up to ~6000 IU/L (in the setting of an elevated baseline CPK level and a history of polio) is unknown.

Review of Applicant's data shows 4.4% of the EQWS subjects, 4.8% of the Byetta subjects, 2.5% of the sitagliptin subjects and no placebo subjects had post-baseline triglyceride levels of >500 mg/dL during the controlled periods of the Phase 3 studies.

Note in BCB120, mean triglyceride levels at baseline were higher in the EQWS group (174.4 mg/d [49 to 798 mg/dL]) than in placebo subjects (155.9 mg/dL [61 to 348 mg/dL]) and several of the EQWS subjects with post-baseline triglyceride levels of >500 mg/dL also had baseline values near or above this threshold.

Evaluation of the hematology, biochemistry, and urine analysis central tendencies and outlier analysis by JReview were generally comparable between EQWS and the comparators.

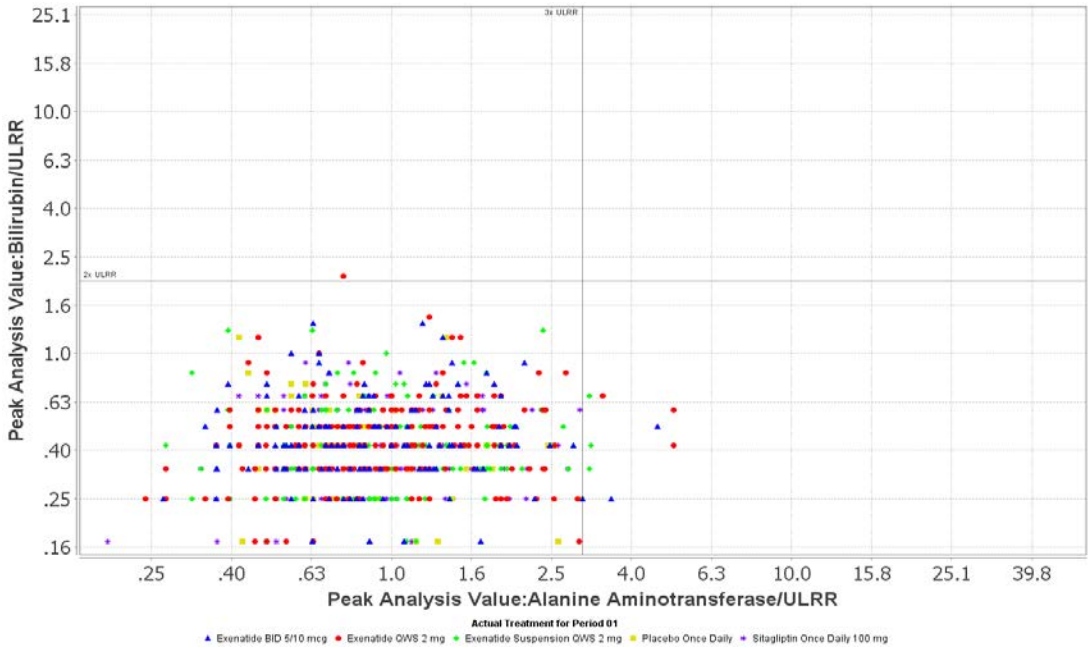
Evaluation of hepatic function:

There were no patients who met Hy's law.

The Applicant states the only potentially clinically significant hepatic laboratory abnormalities with an incidence at least twice the rate for placebo were ALT >3 x ULN (1.0% versus 0%, placebo), ALT >5 x ULN (0.5% versus 0%, placebo), and AST >3 x ULN (0.5% versus 0%, placebo).

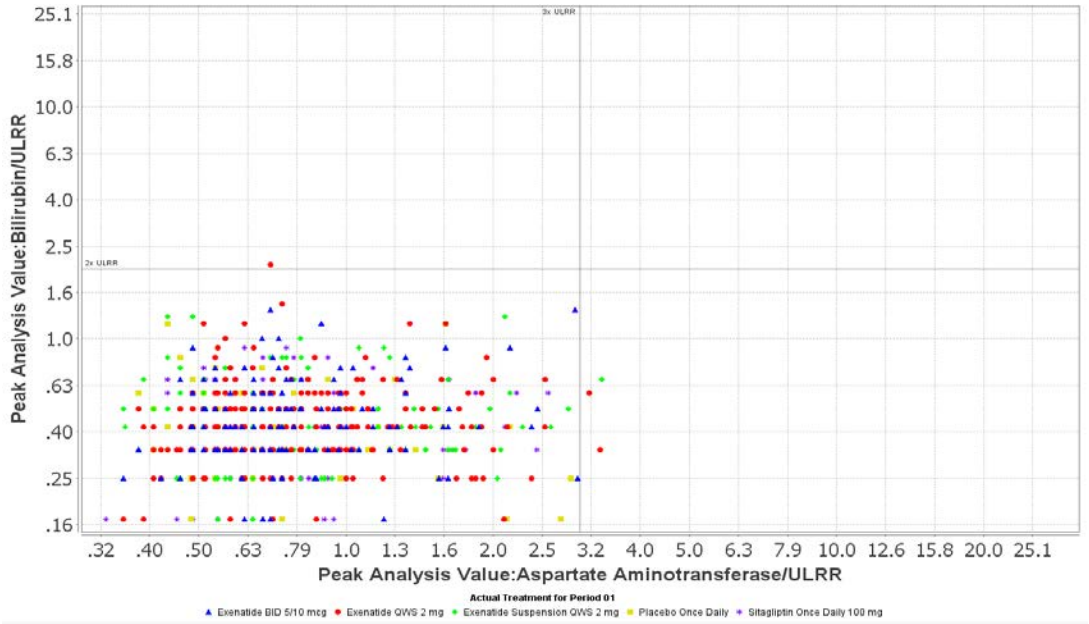
The Applicant states these transaminase elevations were transient, and none were associated with a hepatobiliary adverse event.

Figure 18: Potential Hy's law plot, alanine transferase (ALT) vs. bilirubin, controlled period, safety population, BCB118 and BCB120



Generated by the reviewer, JReview, ADAM dataset, ISS.

Figure 19: Potential Hy's law plot, aspartate aminotransferase (AST) vs. bilirubin, controlled period, safety population, BCB118 and BCB120



Generated by the reviewer, JReview, ADAM dataset, ISS.
The graphical patient profiles of the outliers for ALT > 3 ULN and ALT > 2 ULN, as well as AST > 3 ULN and AST > 2 ULN from the EQWS group as shown in the graphs above were reviewed.

In general, the transaminase increases were transient with a return to baseline in the majority of cases. The Applicant reported no adverse events for these outlier subjects.

A few subjects had mild elevations of CPK and creatinine in addition to the elevations in transaminases, but the majority did not have a concomitant vital sign or lab abnormality.

One subject [redacted] (b) (6) GPP below) had a double peak in the transaminases (mild elevation, with normal bilirubin levels) and no adverse events (61-year-old white female with baseline mild renal impairment, and HbA1c 7.6% on metformin, BMI 27.8).

Subject [redacted] (b) (6) Graphical Patient Profile, randomized to the EQWS group, 52-week data, BCB118:

(b) (6)

The subject (b) (6) with the highest rise in bilirubin (and subsequent return to baseline) was identified in the outlier evaluation of bilirubin measurements (see below).

Subject (b) (6) Graphical Patient Profile, randomized to EQWS group, 28-week data, BCB120:

(b) (6)

Reviewer's comments: There were no subjects with ALT or AST values >10 x ULN. The highest transaminase elevations identified in the Hy's plot graph (Figure 20 and 21) are two subjects in the EQWS group with > 5 X ALT compared to 0 in the Byetta group in BCB118. No elevations in bilirubin >1.5 x ULN or cases meeting possible Hy's Law criteria were reported in the EQWS clinical studies.

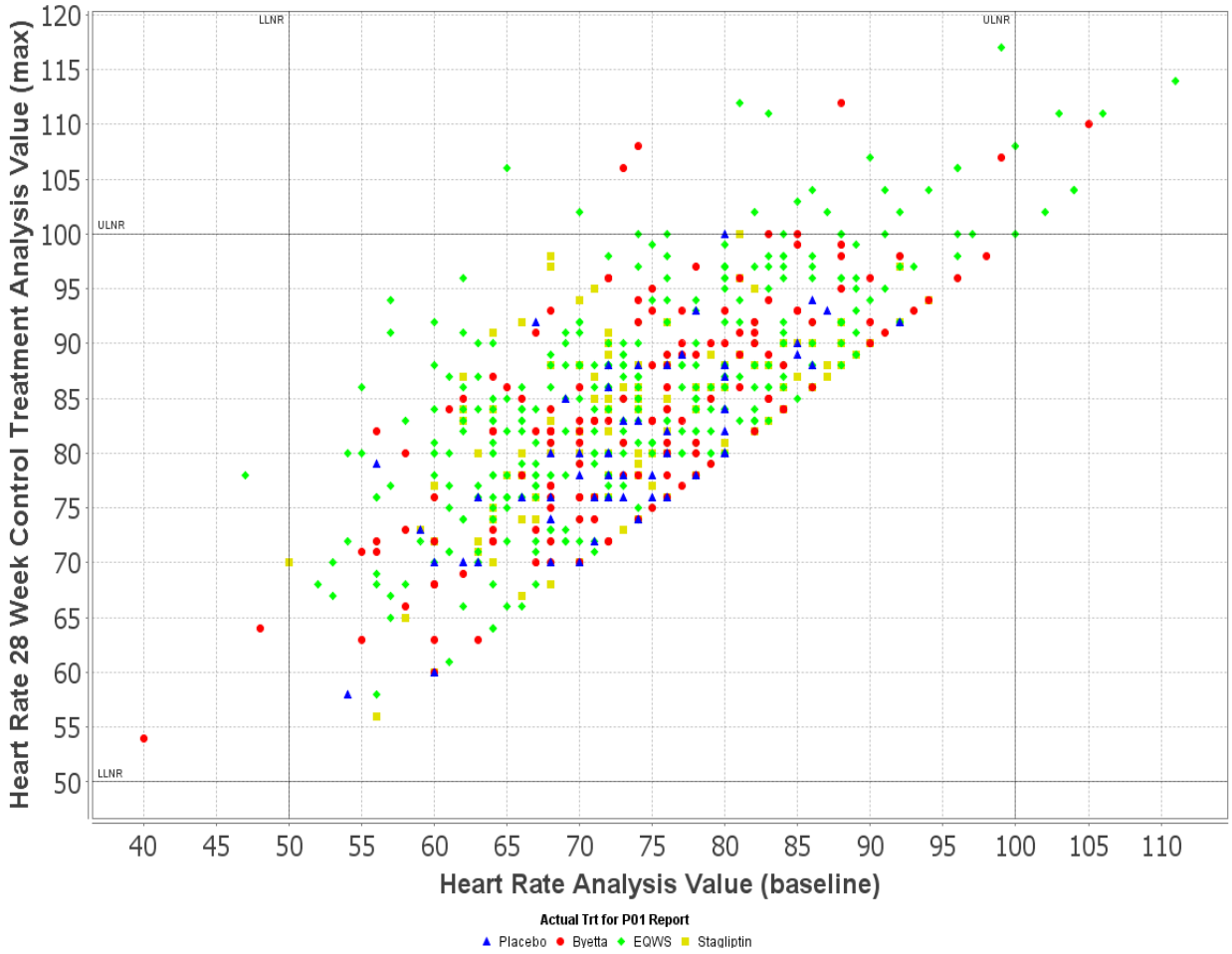
8.4.6. Vital Signs

The Applicant's states between the baseline and the last on-treatment assessment during the Phase 3 controlled study periods, there were no clinically meaningful effects on heart rate, or systolic and diastolic blood pressure in the EQWS-treated subjects.

Review of the Applicant's data shows the mean heart rate increase (SD) from baseline to last on-treatment visit during the pooled 28-week controlled periods in the EQWS group is 2.4 (9.0) beats per minute.

Review of the Applicant's data shows sitting systolic blood pressure fell by a mean (SD) of 1.6 mmHg from a baseline value of 128.9 mmHg, and sitting diastolic blood pressure increased by a mean (SD) of 0.14 mmHg from a baseline value of 77.8 mmHg in the EQWS group of both Phase 3 studies.

Figure 20: Heart rate baseline vs. maximum value at 28-weeks- pooled 28-week EQWS arms-scatter plot, BCB118 and BCB120



Generated by the reviewer, JReview, ADAM dataset, ISS

The scatter plot above shows that at 28-weeks, 16 (3.9%) EQWS subjects (pool of 28-week treatment periods of BCB118 and BCB120) shifted from a baseline of normal (50-100 beats/minute) to high (> 100 beats/minute) vs. 4 (2.73%) in Byetta and none in placebo.

Review of the Applicant's data shows in BCB118 the maximum mean heart rate change (SD) from baseline is 4.1 (8.79) at week 10, and in BCB120 the maximum mean heart rate change (SD) from baseline is 3.5 (8.58) at the early termination visit.

8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were not routinely collected during the Phase 3 studies.

QT
The effect of EQWS on QTc has not been studied.

A thorough QT study to examine the effects of therapeutic and supratherapeutic concentrations of exenatide on the QT interval was conducted for Bydureon (BCB112). The QT-Interdisciplinary Review Team (IRT) reviewed the thorough QT study report for Bydureon and concluded BCB112 as a negative thorough QT study with no concentration-QT relationship observed within the range of exenatide exposures.

Reviewer Comment: During the EOP2 meeting (December 14, 2011) the Agency agreed with reliance on the Bydureon QT studies to support the NDA for EQWS. On December 6, 2011, the Agency consulted the QT-IRT to opine on the sufficiency of Bydureon's thorough QT study (BCB112) for satisfying EQWS's pre-marketing requirements for possible EQWSs' QT/QTc interval prolongation and proarrhythmic potential. QT-IRT agreed that the thorough QT Study BCB112 is sufficient to meet the premarketing requirements for EQWS.

8.4.8. Immunogenicity

Refer to section 8.5.

8.5. Analysis of Submission-Specific Safety Issues

In section 8.5 the submission-specific safety issues in the order of the proposed labeling for EQWS is discussed.

Note the Applicant identified the following adverse events as major safety issues for EQWS:

- Gastrointestinal
- Injection site related
- Hypoglycemia
- Loss of consciousness (potential indicator of a hypoglycemia event)
- Road traffic accidents (potential indicator of a hypoglycemia event)
- Cardiovascular (adjudicated)
- Thyroid neoplasms (adjudicated)
- Pancreatic Cancer(adjudicated)
- Pancreatitis (adjudicated)
- Renal failure
- Overdose

Clinical Review
Mahtab Niyyati, MD
NDA 209210
BCise, Exenatide Once-Weekly Suspension (EQWS)

Reviewer Comment: My review focuses on the labeled risks as below:

- *Thyroid C-cell tumors*
- *Acute pancreatitis*
- *Hypoglycemia with concomitant use of insulin secretagogues or insulin*
- *Renal impairment*
- *Gastrointestinal disease*
- *Immunogenicity*
- *Hypersensitivity*
- *Injection site reactions*

Thyroid Medullary Neoplasm:

All currently labeled long-acting GLP-1 analogs, including EQWS, have a black box warning for the risk of thyroid C-cell tumors in rats and mice. However, at this time, the risk of thyroid C-cell tumors in humans is uncertain.

The Applicant adjudicated events of thyroid neoplasms. For adjudication purposes, the MedDRA search term for the Applicant's Custom MedDRA Query (CMQ)/PT search of the database belonged to the SOC 'Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)'.

No adverse event of thyroid medullary neoplasm occurred in the EQWS development program.

Applicant's analysis

The Applicant's evaluation of calcitonin levels was performed at baseline, Week 16, 28, 36, and 52, and reported by gender. There was no independent calcitonin monitoring committee for the EQWS development program. The Applicant's evaluation of the calcitonin measurements did not show a significant change in mean calcitonin concentrations during the Phase 3 studies.

In BCB118 at Week 28, the mean (SD) calcitonin concentrations were 3.58 (3.50) pg/mL and 3.49 (3.91) pg/mL in the Byetta and EQWS groups, respectively.

At Week 52 the mean (SD) calcitonin concentrations were 3.44 (2.97) pg/mL and 3.57 (3.66) pg/mL in the Byetta and EQWS groups, respectively.

In BCB120, the mean (SD) changes from baseline to Week 28 in the EQWS, sitagliptin, and placebo groups were -0.06 (0.86), -0.02 (1.20), and -0.04 (0.70) pg/mL, respectively. In BCB120, no EQWS subject had calcitonin > 20 pg/mL at Week 28.

When evaluated by the magnitude of increase, the proportion of subjects with any post-baseline calcitonin value ≥20 pg/mL was low in BCB118. In BCB118, two male subjects in the

EQWS group had calcitonin values of > 20 pg/mL both at baseline and at Week 28. One female subject had calcitonin > 20 pg/mL at Week 52.

Reviewer Comment: One of the male subjects mentioned above had a baseline calcitonin value of 25.3 pg/mL and a peak calcitonin value of 34.2 pg/mL, with a later decline to 15.4 pg/mL. The other male subject had a baseline calcitonin of 27.3 pg/mL with subsequent calcitonin measurements of 19 pg/mL and 28 pg/mL during the study.

Reviewer's analysis:

A. MedDRA search

In addition to the Applicant's analysis, I performed a custom MedDRA query search of the submitted Phase 3 TEAE dataset for the adverse event of 'thyroid disease' and 'abnormal blood calcitonin levels'. The following PTs were identifed in the extension period of BCB118: blood thyroid stimulating hormone increased, goitre, and hypothyroidism.

The PT 'blood thyroid stimulating hormone increased' occurred in a subject randomized to Byetta who switched to EQWS in the extension period with a past medical history of hyperthyroidism. The PT 'goitre' occurred in a EQWS-treated subject with a past medical history of hypothyroidism.

B. Calcitonin labs

I reviewed the calcitonin labs in subjects with a calcitonin shift from normal to abnormal levels at any time during the Phase 3 studies.

9 Byetta subjects (7 of which shifted from normal to abnormal after switching to EQWS), and 5 EQWS subjects had a calcitonin shift from normal to abnormal during BCB118. Generally, most subjects had transient calcitonin shifts from normal to < 10 pg/mL, and a few subjects had abnormal baseline calcitonin values. No thyroid medullary carcinoma was seen in the EQWS program.

Only one subject had an increase in calcitonin to 20.1 pg/mL on Day 368 of EQWS exposure with a later return to baseline calcitonin value.

Reviewer's Summary

No medullary thyroid neoplasm was identified in the Phase 3 studies. No subject had calcitonin values >100 pg/mL at Week 28 or 52 in the Phase 3 studies. Most calcitonin shifts from normal to abnormal were < 10 pg/mL with a subsequent reversal. Review of the thyroid neoplasms by custom MedDRA query searches and laboratory assessments do not reveal a significant abnormal trend in the Phase 3 EQWS studies.

Pancreatitis

The Applicant adjudicated pancreatitis events in the EQWS development program. Potential pancreatitis events were identified by adverse events in the clinical database using the MedDRA search criteria (HGLT: exocrine pancreatic disorders). Clinical Events Classification Committee (CEC) adjudicated each suspected pancreatitis event using pre-specified endpoint criteria and was blinded to study treatment.

CEC defined pancreatitis as symptoms of abdominal pain or vomiting and objective evidence of pancreatic inflammation (amylase or lipase > 3X ULN or >2 x ULN in subjects with chronic pancreatitis) or evidence of pancreatitis by imaging. The confirmed pancreatitis was classified as mild or severe (based on evidence of organ failure or local complications).

Reviewer Comment: Amylase and lipase labs were not routinely collected during the Phase 3 EQWS studies. Thus there could be an under-estimation of events in the EQWS development program.

A total of 3 cases of acute pancreatitis occurred in the EQWS development program in BCB118. 2 treatment-emergent SAE events of pancreatitis occurred in the EQWS group and 1 in the Byetta group (not an SAE). All 3 adverse events of pancreatitis led to withdrawal from the treatment and study. No adverse event of pancreatitis occurred in BCB120.

Pancreatitis Narratives

Subject (b) (6) 51-year-old African-American male with T2DM presented with abdominal pain, constipation, and nausea, but no fever or vomiting on Day 43 of EQWS treatment during the controlled period of BCB118. The serum lipase level was 759 U/L (23 to 300 U/L). The pancreatitis was of moderate intensity and resolved after 15 days.

Subject (b) (6) 55-year-old White female subject with T2DM had an onset of severe abdominal pain, nausea, vomiting, and diarrhea on Day 287 of EQWS treatment during the extension period of BCB118. The serum lipase level was >3000 U/L (11 to 59 U/L), and the serum amylase level was 1869 U/L (0 to 105 U/L). The pancreatitis was severe in intensity.

Reviewer Comment: Review of the two narratives above suggest the SAEs of pancreatitis in BCB118 were possibly related to EQWS because of a temporal association with EQWS initiation and recovery after EQWS withdrawal. Adjudication confirmed both of the above SAEs of pancreatitis.

Subject (b) (6) 53-year-old Asian female was randomized to the Byetta group during the controlled period of BCB118. The subject presented with an increase in lipase to 679 U/L on Day 173 with no fever, chills, nausea, vomiting, and no abdominal tenderness with a normal abdominal exam. CT imaging did not show acute pancreas inflammation or obstruction.

The increased lipase was resolved on Day 194; however, the investigator decided to withdraw the subject due to the event pancreatitis and classified the event as severe.

Reviewer Comment: The adjudication committee did not confirm the above adverse event of pancreatitis. The narrative describes an elevation in pancreatic enzyme without any imaging or clinical evidence of pancreatitis. I agree with the adjudication committee's decision. This case may be referred to as an asymptomatic lipase elevation.

Reviewer Comment: Because of lack of routine measurement of amylase and lipase in the Phase 3 studies similar events may have been missed and the incidence of asymptomatic pancreatic enzyme elevations in the EQWS-treated subjects is unknown.

The reviewer independently performed a post-hoc search for the event 'pancreatitis' using the submitted TEAE database. This exploratory analysis was consistent with the Applicant's results discussed above.

Reviewer's summary of pancreatitis events

Two SAEs of pancreatitis occurred in EQWS-treated subjects. The label adequately informs the risk of possible pancreatitis with EQWS. The label states based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.

Hypoglycemia

Severe hypoglycemia may occur when GLP-1 receptor agonists are used with an insulin secretagogue (e.g., a sulfonylurea [SU]) or insulin. In the Warning and Precautions section of the approved GLP-1 receptor agonist labels lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia is advised.

Thus, the most relevant assessment of hypoglycemia in the EQWS development program is derived from BCB118 because the background antidiabetic medication included SUs.

Subjects with a recent history of severe hypoglycemia were excluded from the Phase 3 EQWS studies.

In this section hypoglycemia adverse events are discussed as below:

1. Methods of capturing, subject reporting, and definitions of hypoglycemia in the EQWS development program
2. Applicant's exploratory analysis of hypoglycemia submitted to the NDA and proposed in the label
3. Re-analysis of hypoglycemia adverse events based on the American Diabetes Association (ADA) hypoglycemia classification

4. Reviewer's analysis of hypoglycemia

Capturing hypoglycemia events in the EQWS development program

- The investigator determines if a subject's symptoms are consistent with hypoglycemia symptoms. If so, the investigator documents an adverse event of hypoglycemia in the hypoglycemia adverse event eCRF and source document.
- The investigator assesses any asymptomatic plasma glucose ≤ 54 mg/dL and determines if it is consistent with an asymptomatic hypoglycemia event. If so, the investigator documents a hypoglycemia adverse event in the hypoglycemia adverse event eCRF.
- The investigator informs the Applicant of any severe hypoglycemia adverse event.

Reviewer Comment: Because the method of capturing hypoglycemia adverse events is different from other treatment-emergent adverse events, the hypoglycemia adverse events are analyzed separately from the TEAEs.

Subject reporting of hypoglycemia

Subjects were instructed to perform 6-point Self Monitored Blood Glucose (SMBG) profiles on Day 1, Week 16 and 28 of the study and record in a diary. Each 6-point SMBG consists of 3 pre-prandial (15 minutes premeal) and three post-prandial (1.5-2 hours postmeal) glucose measurements obtained in one day. Fasting blood glucose was measured at almost all visits.

Definitions of hypoglycemia in the EQWS development program

In the EQWS clinical program, the Applicant classified hypoglycemia as major, minor, or symptoms of hypoglycemia:

- Major hypoglycemia:
    - An event that resulted in the loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia in the judgment of the Investigator or physician) that resolved after administration of glucagon or glucose.
    - An event that required third-party assistance to resolve because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycemia were detected by subject) and was associated with glucose < 54 mg/dL.

- Minor hypoglycemia is an event with symptoms consistent with hypoglycemia and a blood glucose < 54 mg/dL.

- Symptoms of hypoglycemia: An event which does not meet the criteria for either a major or minor event described above.

Reviewer Comment: The hypoglycemia classification submitted to the EQWS NDA does not follow the ADA definitions. Using the Applicant's classification maybe a reasonable approach for exploratory analyses, however, it is not acceptable for labeling purposes.

Applicant's exploratory analyses of hypoglycemia

The Applicant states no major hypoglycemia events occurred in the EQWS development program.

Reviewer Comment: I identified one subject in the Byetta group with the adverse event of hypoglycemia and unconsciousness requiring assistance and treated with oral glucose. The Applicant acknowledged re-categorizing this subject from minor to major hypoglycemia (Information Request August 2, 2017, and Applicant's Response August 16, 2017).

In the 28-week controlled period of BCB118, a higher proportion of subjects developed minor hypoglycemia in the EQWS group (26.1%) compared to the Byetta group (17.7%) with SU as the background oral antidiabetic drug. Without SU on board, Byetta had a higher incidence of minor hypoglycemia (4.8%) compared to EQWS (2.1%). Note these results include rescued subjects (Table 25).

In diet-controlled T2DM subjects of BCB118, minor hypoglycemia occurred in 1 subject from the EQWS group and one subject from the Byetta group.

In BCB120, no events of major or minor hypoglycemia were reported. In BCB120 metformin was the background antidiabetic medication.

Table 25: Hypoglycemia during the 28-week controlled treatment periods, stratified by background antidiabetic medication (SU, metformin, monotherapy)-safety population, BCB118 and BCB120

	Study BCB118 Controlled Period		Study BCB120 Controlled Period				
Parameter	EQWS N=229 n (%)	Byetta N=146 n (%)	EQWS N=181 n (%)	Sitagliptin N=122 n (%)	Placebo N=61 n (%)	All EQWS[a] N=410 n (%)	All Phase 3 Subjects[b] N=739 n (%)
All subjects							
Major hypoglycaemia	0	0	0	0	0	0	0
Minor hypoglycaemia	26 (11.4)	15 (10.3)	0	1 (0.8)	0	26 (6.3)	42 (5.7)
Symptoms of hypoglycaemia	37 (16.2)	22 (15.1)	4 (2.2)	7 (5.7)	2 (3.3)	41 (10.0)	72 (9.7)
On Sulfonylurea at baseline	88	62	0	1	0	88	151
Major hypoglycaemia	0	0	0	0	0	0	0
Minor hypoglycaemia	23 (26.1)	11 (17.7)	0	0	0	23 (26.1)	34 (22.5)
Symptoms of hypoglycaemia	25 (28.4)	16 (25.8)	0	0	0	25 (28.4)	41 (27.2)
No Sulfonylurea at baseline	141	84	181	121	61	322	588
Major hypoglycaemia	0	0	0	0	0	0	0
Minor hypoglycaemia	3 (2.1)	4 (4.8)	0	1 (0.8)	0	3 (0.9)	8 (1.4)
Symptoms of hypoglycaemia	12 (8.5)	6 (7.1)	4 (2.2)	7 (5.8)	2 (3.3)	16 (5.0)	31 (5.3)
Metformin only at baseline	101	65	181	121	61	282	529
Major hypoglycaemia	0	0	0	0	0	0	0
Minor hypoglycaemia	1 (1.0)	3 (4.6)	0	1 (0.8)	0	1 (0.4)	5 (0.9)
Symptoms of hypoglycaemia	7 (6.9)	4 (6.2)	4 (2.2)	7 (5.8)	2 (3.3)	11 (3.9)	24 (4.5)
Diet and exercise only at baseline	33	16	0	0	0	33	49
Major hypoglycaemia	0	0	0	0	0	0	0
Minor hypoglycaemia	1 (3.0)	1 (6.3)	0	0	0	1 (3.0)	2 (4.1)
Symptoms of hypoglycaemia	5 (15.2)	1 (6.3)	0	0	0	5 (15.2)	6 (12.2)

[a]=all EQWS subjects in BCB118 controlled period + all EQWS subjects in BCB120; [b]= all subjects in BCB118 controlled period + all subjects in BCB120
Source: Excerpted from ISS narrative summary, Table 13, page 46.

Reviewer Comment: I was able to replicate the above table with JReview using the submitted ADAM dataset for the 28-week controlled period of BCB118 and BCB120.

(b) (4)

According to the Applicant's hypoglycemia definitions and analyses, no serious or severe hypoglycemia, or withdrawal due to a hypoglycemic event during the 28-week controlled periods of the EQWS-treated subjects occurred.

In the Byetta group, one severe hypoglycemic event (not leading to withdrawal), and one

withdrawal due to moderate hypoglycemia occurred. The Applicant classified both as minor hypoglycemia, and both subjects were on an SU as background antidiabetic therapy.
Reviewer Comment: The subject with severe hypoglycemia in the Byetta group is the subject with unconsciousness who the Applicant agreed to re-categorize from minor to major hypoglycemia. ADA-defined severe hypoglycemia is discussed further below.

Re-analysis of hypoglycemia adverse events based on the American Diabetes Association hypoglycemia classification:

Reviewer Comment: Following an Information Request (August 18, 2017), the Applicant submitted (September 13, 2017) the hypoglycemia adverse events analyzed by the ADA-defined hypoglycemia classification.

Table 26 shows the Applicant's re-analysis of the hypoglycemic adverse events according to the Joint position statement of the American Diabetes Association and the European Association for the study of diabetes[18]. Table 27 shows the Applicant's re-analysis of the hypoglycemia adverse events according to the ADA classification[19].

[18] Diabetes Care Volume 40, January 2017
[19] American Diabetes Association and the Endocrine Society (Diabetes Care, v.36 (5); 2013 May.

Table 26: Hypoglycemia classified as three levels[18] with onset during the 28-week controlled periods, overall and by concomitant anti-diabetic therapy including data after rescue therapy-safety population, BCB118 and BCB120

	Study BCB118 Controlled Period		Study BCB120 Controlled Period				All Phase 3
	EQW8	Byetta	EQW8	Sitaglipton	Placebo	All EQW8[b]	Subjects[c]
Subpopulation	N=229	N=146	N=181	N=122	N=61	N=410	N=739
Hypoglycemia Classification [a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one hypoglycemic adverse event	47 (20.5)	28 (19.2)	4 (2.2)	7 (5.7)	2 (3.3)	51 (12.4)	88 (11.9)
All subjects							
Level 1 Hypoglycemia	33 (14.4)	17 (11.6)	1 (0.6)	4 (3.3)	1 (1.6)	34 (8.3)	56 (7.6)
Level 2 Hypoglycemia	26 (11.4)	15 (10.3)	0	1 (0.8)	0	26 (6.3)	42 (5.7)
Level 3 Hypoglycemia	0	1 (0.7)	0	0	0	0	1 (0.1)
Non-definable	8 (3.5)	6 (4.1)	3 (1.7)	3 (2.5)	1 (1.6)	11 (2.7)	21 (2.8)
On Sulfonylurea at baseline	88	62	0	1	0	88	151
Level 1 Hypoglycemia	22 (25.0)	12 (19.4)	0	0	0	22 (25.0)	34 (22.5)
Level 2 Hypoglycemia	23 (26.1)	11 (17.7)	0	0	0	23 (26.1)	34 (22.5)
Level 3 Hypoglycemia	0	1 (1.6)	0	0	0	0	1 (0.7)
Non-definable	7 (8.0)	4 (6.5)	0	0	0	7 (8.0)	11 (7.3)
No Sulfonylurea at baseline	141	84	181	121	61	322	588
Level 1 Hypoglycemia	11 (7.8)	5 (6.0)	1 (0.6)	4 (3.3)	1 (1.6)	12 (3.7)	22 (3.7)
Level 2 Hypoglycemia	3 (2.1)	4 (4.8)	0	1 (0.8)	0	3 (0.9)	8 (1.4)
Level 3 Hypoglycemia	0	0	0	0	0	0	0
Non-definable	1 (0.7)	2 (2.4)	3 (1.7)	3 (2.5)	1 (1.6)	4 (1.2)	10 (1.7)

Source: Excerpted from the response to Information Request dated September 13, 2017.

According to the Joint Position classification[18], the proposed glucose levels when reporting hypoglycemia in clinical trials are as follows:

- Level 1 is a glucose level ≤ 70 mg/dL.
- Level 2 is a glucose level < 54 mg/dL; which is sufficiently low to indicate serious clinically important hypoglycemia
- Level 3 is severe hypoglycemia indicating severe cognitive impairment requiring external assistance for recovery (as defined by the ADA)

Table 27: Hypoglycemia with onset during the 28-week controlled period according to the American Diabetes Association[19], overall and by concomitant anti-diabetic therapy including post-rescue subjects, safety population, BCB118 and BCB120

	Study BCB118 Controlled Period		Study BCB120 Controlled Period				
Subpopulation Hypoglycemia Classification [a]	EQWS N=229 n (%)	Byetta N=146 n (%)	EQWS N=181 n (%)	Sitaglipton N=122 n (%)	Placebo N=61 n (%)	All EQWS[b] N=410 n (%)	All Phase 3 Subjects[c] N=739 n (%)
Patients with at least one hypoglycemic adverse event	47 (20.5)	28 (19.2)	4 (2.2)	7 (5.7)	2 (3.3)	51 (12.4)	88 (11.9)
All subjects							
Severe Hypoglycemia	0	1 (0.7)	0	0	0	0	1 (0.1)
Documented Symptomatic Hypoglycemia	29 (12.7)	19 (13.0)	1 (0.6)	1 (0.8)	1 (1.6)	30 (7.3)	51 (6.9)
Asymptomatic Hypoglycemia	23 (10.0)	10 (6.8)	0	4 (3.3)	0	23 (5.6)	37 (5.0)
Probable Symptomatic Hypoglycemia	3 (1.3)	5 (3.4)	1 (0.6)	1 (0.8)	0	4 (1.0)	10 (1.4)
Pseudo-Hypoglycemia	3 (1.3)	2 (1.4)	1 (0.6)	0	1 (1.6)	4 (1.0)	7 (0.9)
Non-Definable	3 (1.3)	0	1 (0.6)	2 (1.6)	0	4 (1.0)	6 (0.8)
On Sulfonylurea at baseline	88	62	0	1	0	88	151
Severe Hypoglycemia	0	1 (1.6)	0	0	0	0	1 (0.7)
Documented Symptomatic Hypoglycemia	22 (25.0)	15 (24.2)	0	0	0	22 (25.0)	37 (24.5)
Asymptomatic Hypoglycemia	16 (18.2)	7 (11.3)	0	0	0	16 (18.2)	23 (15.2)
Probable Symptomatic Hypoglycemia	2 (2.3)	4 (6.5)	0	0	0	2 (2.3)	6 (4.0)
Pseudo-Hypoglycemia	3 (3.4)	1 (1.6)	0	0	0	3 (3.4)	4 (2.6)
Non-Definable	3 (3.4)	0	0	0	0	3 (3.4)	3 (2.0)
No Sulfonylurea at baseline	141	84	181	121	61	322	588
Severe Hypoglycemia	0	0	0	0	0	0	0
Documented Symptomatic Hypoglycemia	7 (5.0)	4 (4.8)	1 (0.6)	1 (0.8)	1 (1.6)	8 (2.5)	14 (2.4)
Asymptomatic Hypoglycemia	7 (5.0)	3 (3.6)	0	4 (3.3)	0	7 (2.2)	14 (2.4)
Probable Symptomatic Hypoglycemia	1 (0.7)	1 (1.2)	1 (0.6)	1 (0.8)	0	2 (0.6)	4 (0.7)
Pseudo-Hypoglycemia	0	1 (1.2)	1 (0.6)	0	1 (1.6)	1 (0.3)	3 (0.5)
Non-Definable	0	0	1 (0.6)	2 (1.7)	0	1 (0.3)	3 (0.5)

Source: Excerpted from the response to information request dated September 13, 2017.

Reviewer Comment: For labeling purposes, ADA-defined severe hypoglycemia, and the Level 2 (glucose < 54 mg/dL regardless of symptoms) are the most clinically relevant measures for hypoglycemia risk assessment.

In the controlled period of BCB118, the overall hypoglycemia events are generally balanced between the EQWS and the Byetta group (19-20%). In BCB120 the incidence of hypoglycemia was lower compared to BCB118 (background oral antidiabetic medication in BCB120 is metformin), and more subjects in the sitagliptin group (5.7%) had a hypoglycemia event compared to placebo (3.3%) and EQWS (2.2%).

In the controlled period of BCB118 symptomatic hypoglycemia appears balanced between EQWS and Byetta. When categorized by baseline SU use, the overall incidence of symptomatic

hypoglycemia seems generally balanced in subjects on baseline SU treatment (25% EQWS and 24.2% Byetta) and slightly in favor of Byetta subjects with no SU at baseline (5% EQWS vs. 3.6% Byetta) (Table 27).

The Applicant considers a hypoglycemic event to be severe if the subject requires assistance for severe neuroglycopenia symptoms such as loss of consciousness, seizures, coma, severe impairment in consciousness or behavior, encephalopathy, and shock. According to this definition of severe neuroglycopenia, during the controlled period of BCB118 and BCB120, no EQWS subjects had severe hypoglycemia, and one subject in the Byetta group had severe hypoglycemia (Table 27).

Reviewer Comment: Refer to the reviewer's exploratory analysis of hypoglycemia below for more details.

In the controlled period of BCB118, the overall number of subjects with glucose < 54 mg/dL also appears balanced between the Byetta and EQWS group, but when categorized by background SU use, more subjects in the EQWS group developed glucose < 54 mg/dL compared to Byetta. In subjects not on SU at baseline, more subjects in the Byetta group developed glucose < 54 mg/dL compared to the EQWS group (Table 26).

EQWS has not been studied in combination with insulin therapy to estimate risk of hypoglycemia; however the Bydureon approved label informs that during a 26-weeks add-on to metformin or metformin + SU trial, 66 Bydureon-treated subjects were tested on the background of SU and glargine (44% developed minor hypoglycemia) and 157 Bydureon-treated subjects were tested with glargine and no SU on board (19% developed minor hypoglycemia[20]).

Reviewer's exploratory analysis of hypoglycemia: MedDRA search

1. The following submitted flags (ADAM dataset; ISS) were reviewed: 'Hypo treatment IM glucagon',' hypo treatment IV glucose', and 'Hypoglycemia outcome', and 'require assistance hypoglycemia'.

In BCB118, ten subjects in the EQWS group and five subjects in the Byetta group, and in BCB120 one subject in the EQWS group and one subject in the sitagliptin group requiring assistance for a hypoglycemia event were identified by the reviewer (Table 28).

Also, a subject in the Byetta group with "unconsciousness" requiring assistance was identified,

[20] Minor hypoglycemia in the Bydureon studies was defined as symptoms of hypoglycemia with a glucose < 54 mg/dL. and patient was able to self-treat.

and the Applicant was queried as mentioned above.

Table 28: Subjects with hypoglycemic adverse event requiring assistance, safety population, BCB118 and BCB120

		BCB118			BCB120	
		Byetta n (%)	EQWS n (%)		EQWS n (%)	Sitagliptin n (%)
Hypoglycemia Symptom	Severity Intensity	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	
NONE	M LD	0	3 (1.31%)	0	0	0
CONFUSION, DIZZINNESS, FEELING JITTERY		0	1 (0.44%)	0	0	0
CONFUSION, FEEL NG JITTERY		0	1 (0.44%)	0	0	0
CONFUSION		0	1 (0.44%)	0	0	0
DIZZ NNESS		0	1 (0.44%)	1 (0.86%)	0	0
Missing data		0	1 (0.44%)	0	0	0
DIZZ NNESS, FEEL NG JITTERY		0	1 (0.44%)	0	0	0
FEELING JITTERY, TACHYCARDIA	MODERATE	0	1 (0.44%)	0	0	0
FEELING JITTERY, OTHER: NAUSEA		0	1 (0.44%)	0	0	0
DIZZ NESS	M LD	0	0	0	1 (0.55%)	1 (0 82%)
FEELING JITTERY		2 (1.37%)	0	0	0	0
DIZZ NNESS, FEEL NG JITTERY, TACHYCARDIA	MODERATE	1 (0.68%)	0	0	0	0
OTHER: SHIVER NG AND FEEL NG WEAK		1 (0.68%)	0	0	0	0
NONE	SEVERE	1 (0.68%)	0	0	0	0
	Subjects(filtered)	5 (3.42%)	10 (4.37%)	1 (0.68%)	1 (0.55%)	1 (0 82%)
	1stColItemSubjects	146 (100.00%)	229 (100.00%)	116 (100 00%)	181 (100.00%)	122 (100.00%)

Generated by the reviewer using JReview ADAM dataset, ISS

All the EQWS subjects who required assistance for hypoglycemia (Table 24) were treated with oral glucose, and most were on SU as background antidiabetic medication. None discontinued the study or treatment. The ranges of blood glucose in these subjects were 47-69 mg/dL (3 subjects had glucose value < 54 mg/dL).

However three subjects who required assistance had confusion as the hypoglycemia symptom (b) (6)

Reviewer Comment: An Information Request (August 2, 2017) was sent for clarification on why the subjects who required assistance for hypoglycemia were not categorized as major (severe) hypoglycemia. The Applicant responded (August 16, 2017) that none of these subjects qualified as major (severe) hypoglycemia because of lack of severe neuroglycopenic symptoms.

In their response (August 16, 2017), the Applicant also evaluated the hypoglycemic events associated with confusion. Eleven hypoglycemia events in BCB118 and none in BCB120 were associated with confusion; however, the Applicant states none of these hypoglycemia events were categorized as major hypoglycemia because of their mild intensity or because they did not

meet all of the criteria for major hypoglycemia as per the Applicant's definition.
Reviewer Comment: The three subjects identified in Table 28 who required assistance associated with the symptom confusion qualify as severe hypoglycemia according to the ADA hypoglycemia classification. The proposed label should be revised to include the three subjects mentioned above as severe hypoglycemia.

The Applicant confirmed that subject (b) (6) on Byetta (who experienced unconsciousness and required assistance with oral glucose) met the clinical study protocol definition of major hypoglycemia and will be re-categorized as major (severe) hypoglycemia.

Reviewer Comment: The Applicant states the programming algorithm used for identifying cases of major hypoglycemia had an error.

2. I reviewed the graphical patient profiles of the following adverse events in the EQWS group that may be related to a hypoglycemia event: Contusion, fibula Fracture, Humerus Fracture, Gait Disturbances, Fall, Fatigue, Concussion, Road Traffic accident.

Reviewer Comment: Some of the subjects experiencing the above adverse events also experienced the adverse event hypoglycemia; however a review of the graphical patient profiles in JReview did not show that the above-mentioned adverse events occurred as a result of hypoglycemia. *However, note the below narrative:*

Subject (b) (6) from the EQWS group, suffered from the SAE syncope followed by a road traffic accident on Day 179, two days following the subject's 26th dose of EQWS. The narrative states a comprehensive workup for syncope was negative for any significant cardiovascular etiology. It is plausible that the subject suffered from a possible hypoglycemia before the accident leading to syncope, given the subject was on four antidiabetic medications at the time of the syncope/accident.

Reviewer's Summary of hypoglycemia

The overall incidence of hypoglycemia is balanced between the EQWS and Byetta group. More subjects developed symptomatic hypoglycemia in the EQWS group on the background of SU therapy.

The Applicant's revised hypoglycemia classification according to the ADA does not identify any subjects with severe hypoglycemia. However, three EQWS-treated subjects with hypoglycemia and confusion requiring assistance were identified during the review. The proposed label should include these three subjects as severe hypoglycemia.

Renal Impairment:

In the EQWS development program, acute renal failure was considered an AESI; however, the

Applicant did not adjudicate acute renal failure in the EQWS program and excluded subjects with GFR < 30 mL/min/1.73m2 from the study.

Non-clinical studies have not shown direct nephrotoxicity; however GLP-1 receptor agonists may potentially cause renal impairment. This may be secondary to gastrointestinal side effects and volume depletion resulting in acute renal failure.

Reviewer Comment: The proposed label adequately informs that EQWS should not be used in patients with severe renal impairment (eGFR <30 mL/min /1.73m^2) or end-stage renal disease and should be used with caution in patients with renal transplantation.

Reviewer Approach to abnormal renal function

Note the population enrolled in the two Phase 3 studies differed in baseline renal function. Study BCB118 enrolled 85 (37%) normal renal function, 115 (50.2%) mild, and 29 (12.7%) moderate renal impairment subjects in the EQWS group, while BCB120 enrolled 102 (56.4%) normal renal function, 78 (43%) mild, and 1 (0.6%) moderate renal impairment subjects in the EQWS group. The number of subjects in each renal category is generally balanced across treatment arms in each study.

Thus for assessing renal events in the EQWS group compared to the Byetta group, I reviewed the controlled period of BCB118. I also reviewed renal events and abnormal renal function by using custom post-hoc PT search of the submitted TEAE database and reviewed creatinine lab abnormalities.

The Applicant did not submit post-baseline eGFR measurements in the ADAM datasets. An Information Request was sent requesting (September 1, 2017) eGFR shift tables for the Phase 3 studies.

Applicant's analysis:

The Applicant assessed renal function in the Phase 3 studies by serum creatinine and custom query of acute renal events.

The Applicant's submitted pre-defined CMQ for Acute Renal Failure identifies two subjects with a renal event (PTs 'renal failure' and 'acute kidney injury') in BCB118 (graphical patient profiles below), and no renal events in the EQWS group in BCB120.

- PT renal failure: Subject (b) (6) 40-year-old male subject with baseline HbA1c 8.6% and past medical history of obesity, hyperlipidemia, hypertension, and sleep apnea was randomized to the Byetta group. Baseline creatinine was 0.82 mg/dL and remained relatively stable throughout the study with a maximum increase to 0.97

mg/dL on Day 100 while still on Byetta. During the extension phase (all normal creatinine levels) the PTs renal failure, microalbuminuria and hyperuricemia were coded to the subject (urate up to 8.6).

Reviewer Comment: It is unclear why the PT 'renal failure' was coded to this subject with a normal creatinine.

- PT Acute kidney failure: subject (b) (6) a subject in the Byetta group developed acute renal failure in the setting of septic shock. The event septic shock is likely unrelated to Byetta.

Subgroup analysis by the Applicant:

Of the 410 EQWS-treated subjects in the Phase 3, controlled study periods, 187 had normal renal function at baseline (eGFR ≥90 mL/min/1.73m2), 193 had mild impairment (eGFR ≤60 to ≤89 mL/min/1.73m2), and 30 had moderate impairment (eGFR 30 to ≤59 mL/min/1.73m2).

Because of the relatively low number of subjects with moderate renal impairment, comparisons between this subgroup and the normal renal function and mild renal impairment subgroups should be made with caution.

The overall incidence of adverse events was similar in subjects with normal renal function (64.2%), mild renal impairment (64.2%), and moderate renal impairment (63.3%).

Compared with the subgroups with mild or moderate renal impairment, the incidence of adverse events was lower in the normal renal function subgroup for the SOCs Gastrointestinal disorders (16.6% vs 23.8 and 23.3%, respectively), General disorders and administrative site conditions (23.5% vs 28.5% and 30.0%, respectively), and Musculoskeletal and connective tissue disorders (6.4% vs 13.5% and 16.7%, respectively).

In subjects with moderate renal impairment, the incidence of Eye disorders was greater than in subjects with normal renal function or mild impairment (6.7% vs 2.1% and 1.6%, respectively).

The incidence of adverse events was lower in the moderate renal impairment subgroup compared with the normal renal function and mild impairment subgroups for the SOCs Investigations (0% vs 6.4% and 9.3%, respectively) and Nervous system disorders (3.3% vs 9.6% and 11.9%, respectively).

In the Byetta treatment group of BCB118, gastrointestinal adverse events were reported in 38.2%, 34.2%, and 46.7% of subjects with normal, mildly impaired, and moderately impaired renal function respectively.

Table 29: Adverse events in ≥ 5% of the EQWS treated subjects in the controlled periods by renal function status, BCB118 and BCB120

Preferred Term	Number (%) of subjects		
	Normal renal function (N=187)	Mild renal impairment (N=193)	Moderate renal impairment (N=30)
Injection site nodule	16 (8.6)	30 (15.5)	4 (13.3)
Nausea	14 (7.5)	22 (11.4)	2 (6.7)
Injection site pruritus	3 (1.6)	9 (4.7)	3 (10.0)
Diarrhea	4 (2.1)	10 (5.2)	3 (10.0)
Upper respiratory tract infection	6 (3.2)	8 (4.1)	3 (10.0)
Vomiting	2 (1.1)	10 (5.2)	2 (6.7)
Injection site bruising	5 (2.7)	5 (2.6)	2 (6.7)
Pain in extremity	3 (1.6)	5 (2.6)	2 (6.7)
Muscle spasms	1 (0.5)	4 (2.1)	2 (6.7)
Cough	2 (1.1)	2 (1.0)	2 (6.7)
Headache	9 (4.8)	11 (5.7)	1 (3.3)

Source: Excerpted from ISS narrative summary page 73.

Reviewer's MedDRA analysis

1. Review of the renal PTs mapped to the SOC Renal and urinary disorders to assess imbalances in renal events:

Table 30: SOC Renal and urinary disorders, controlled and extension periods, safety population, BCB118 and BCB120

	BCB118				BCB120		
	Byetta n (%)	EQWS n (%)			EQWS n (%)	Placebo n (%)	Sitagliptin n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD
Acute kidney injury	1 (0.68%)	0	0	0	0 (0.00%)	0	0
Glycosuria	0	0	0	0	0	0	1 (0.82%)
Haematuria	1 (0.68%)	0	0	3 (1.55%)	1 (0.55%)	0	0
Microalbuminuria	1 (0.68%)	0	0	1 (0.52%)	0	0	0
Nephrolithiasis	1 (0.68%)	0	2 (1.72%)	1 (0.52%)	0	1 (1.64%)	0
Nephropathy	0	0	0	0	0	0	0
Pollakiuria	0	0	1 (0.86%)	0	0	0	0
Proteinuria	0	0	1 (0.86%)	0	0	0	0
Renal failure	0	0	1 (0.86%)	0	0	0	0
Renal impairment	0	0	0	1 (0.52%)	0	0	0
Urinary incontinenc	0	1 (0.44%)	0	0	0	0	0
Urine flow decrease	0	0	0	1 (0.52%)	0	0	0
Subjects(filtered)	4 (2.74%)	1 (0.44%)	5 (4.31%)	5 (2.59%)	1 (0.55%)	1 (1.64%)	1 (0.82%)
1stColItemSubjects	146 (100.00%)	229 (100.00%)	116 (100.00%)	193 (100.00%)	181 (100.00%)	61 (100.00%)	122 (100.00%)

Generated by the reviewer using JReview ADAM dataset, ISS

During the controlled treatment period of BCB118, the incidence of renal events mapped to the SOC Renal disorders was low, and compared to Byetta was favorable for EQWS. Most renal PTs occurred during the extension period. Other than the two renal PTs identified with the Applicant's pre-defined MedDRA CMQ search, the following PT was noted:

- PT 'renal impairment' during the extension period of BCB118: Subject (b) (6) (b) (6) is a 67-year-old White male with a baseline HbA1c of 9.5% and baseline moderate renal impairment with past medical history of renal stone and lithotripsy. Subject developed the adverse event renal impairment and urine flow decreased, along with a creatinine value which peaked to 1.97 mg/dL from baseline of 1.4 mg/dL after the adverse event toe puncture nail wound..

2. Post-hoc CMQ search for renal events in the submitted TEAE dataset, ISS:

Table 31: Post-hoc custom query search for renal events (ISS TEAE dataset), controlled and extension periods, safety population, BCB118 and BCB120

	Study BCB118		Study BCB120		
Dictionary Derived Term	Byetta n (%)	EQWS n (%)	EQWS n (%)	Placebo n (%)	Sitagliptin n (%)
Urinary tract infection	3 (2.05%)	12 (5.24%)	6 (3.31%)	2 (3.28%)	3 (2.46%)
Blood creatinine increased	1 (0.68%)	4 (1.75%)	0	0	0
Hyperkalaemia	3 (2.05%)	4 (1.75%)	1 (0.55%)	0	1 (0.82%)
Metabolic acidosis	0	2 (0.87%)	0	0	0
Dehydration	0	2 (0.87%)	0	0	0
Hyperuricaemia	1 (0.68%)	2 (0.87%)	1 (0.55%)	0	0
Urine flow decreased	0	1 (0.44%)	0	0	0
Renal impairment	0	1 (0.44%)	0	0	0
Urinary incontinence	0	1 (0.44%)	0	0	0
Blood urine present	0	1 (0.44%)	0	0	0
Microalbuminuria	1 (0.68%)	1 (0.44%)	0	1 (1.64%)	0
Proteinuria	1 (0.68%)	1 (0.44%)	0	0	0
Blood potassium increased	3 (2.05%)	1 (0.44%)	1 (0.55%)	0	1 (0.82%)
Nephropathy	0	0	1 (0.55%)	0	0
Blood urea increased	1 (0.68%)	0	0	0	0
Renal failure	1 (0.68%)	0	0	0	0
Kidney infection	1 (0.68%)	0	1 (0.55%)	0	0
Acute kidney injury	1 (0.68%)	0	0	0	0
Subjects(filtered)	12 (8.22%)	27 (11.79%)	10 (5.52%)	3 (4.91%)	5 (4.10%)
1stColItemSubjects	146 (100.00%)	229 (100.00%)	181 (100.00%)	61 (100.00%)	122 (100.00%)

Generated by the reviewer using JReview ADAM dataset, ISS

The graphical patient profiles for the PT 'blood creatinine increased' from the above post-hoc CMQ was reviewed. Most of the PT 'blood creatinine increased' occurred during the extension period of BCB118 in subjects with baseline mild or moderate renal impairment. The etiology for these mostly transient creatinine increases is unknown. Select graphical patient profiles reviews are presented below:

Subject (b) (6) 46-year-old African-American obese male with eight-year duration of T2DM and HgA1c of 10% at baseline treated with metformin, with past medical history of hypertension and mild renal impairment at baseline was randomized to the EQWS arm of BCB118. Review of the graphical patient profile shows increased CPK (up to 700 from baseline of 250 IU/L), increased creatinine (1.29 baseline to 1.52 mg/dL), and decreased bicarbonate (down to 13 mEq/L). Adjudication did not confirm the increased CPK as an acute coronary syndrome. It is unclear what led to these biochemical abnormalities. The study was terminated due to subject withdrawal.

Subject (b) (6) 71-years-old Hispanic male with T2DM, HbA1c 8.3%, and mild renal impairment at baseline was randomized to the EQWS treatment arm of BCB118. Review of the graphical patient profile shows the subject had an increase of creatinine from baseline on study day 143, (1.12 to 1.43 mg/dL) with a return to baseline creatinine level.

Subject (b) (6) with a past medical history of hypocholesteremia and hypertension had an increase in creatinine from baseline of 1.27 to 1.71 mg/dL at the end of the study with subsequent resolution.

Laboratory assessments of renal function:

The Applicant's analysis of abnormal renal function shows 5 (1.2%) EQWS subjects (3 from the controlled period of BCB118, and 2 from BCB120), 1 (0.7%) Byetta subject, 2 (1.6%) sitagliptin subjects and no placebo subject had an increase ≥1.5 x baseline in serum creatinine during the controlled period of the Phase 3 studies. The Applicant states these creatinine increases were modest in magnitude; most creatinine increases were slightly above the ULN range, and all peak levels were < 2 mg/dL. None of these changes were considered clinically significant by the investigator or reported as adverse events.

In response (September 8, 2017) to an Information Request (September 1, 2017), the Applicant provided eGFR shift tables on renal function status between baseline and Week-28 of the two Phase 3 studies. The Applicant states in BCB118, one subject shifted from moderate to severe renal impairment at Week-28, and 3.8% shifted from mild to moderate renal impairment. In BCB120, no shifts to severe renal impairment occurred, and 2.5% of mild shifted to moderate renal impairment.

Reviewer's analysis of renal function labs:

Table 32: Abnormal renal labs- safety population, controlled and extension periods, BCB118

	Byetta n (%)		EQWS n (%)			
Abnormal renal labs	CONTROLLED TREATMENT PERIOD	FOLLOW-UP PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	FOLLOW-UP PERIOD
Inc SCr from Base>=0.3 mg/dL	9 (6.47%)	3 (2.16%)	15 (6.67%)	4 (2.88%)	13 (5.78%)	1 (0.44%)
Increase in SCr from Baseline >=1 mg/dL	9 (6.47%)	3 (2.16%)	15 (6.67%)	4 (2.88%)	13 (5.78%)	1 (0.44%)
Increase in SCr>=1.5x Baseline	3 (2.16%)	0	6 (2.67%)	1 (0.72%)	3 (1.33%)	0
Increase in SCr>=2.0x Baseline	1 (0.72%)	0	0	1 (0.72%)	0	0
SCr >=2.5mg/dL	1 (0.72%)	0	0	1 (0.72%)	1 (0.44%)	0
Subjects(filtered)	9 (6.47%)	3 (2.16%)	17 (7.56%)	4 (2.88%)	14 (6.22%)	1 (0.44%)
1stColItemSubjects	139 (100.00%)	139 (100.00%)	225 (100.00%)	139 (100.00%)	225 (100.00%)	225 (100.00%)

Generated by the reviewer using JReview ADAM dataset, BCB118

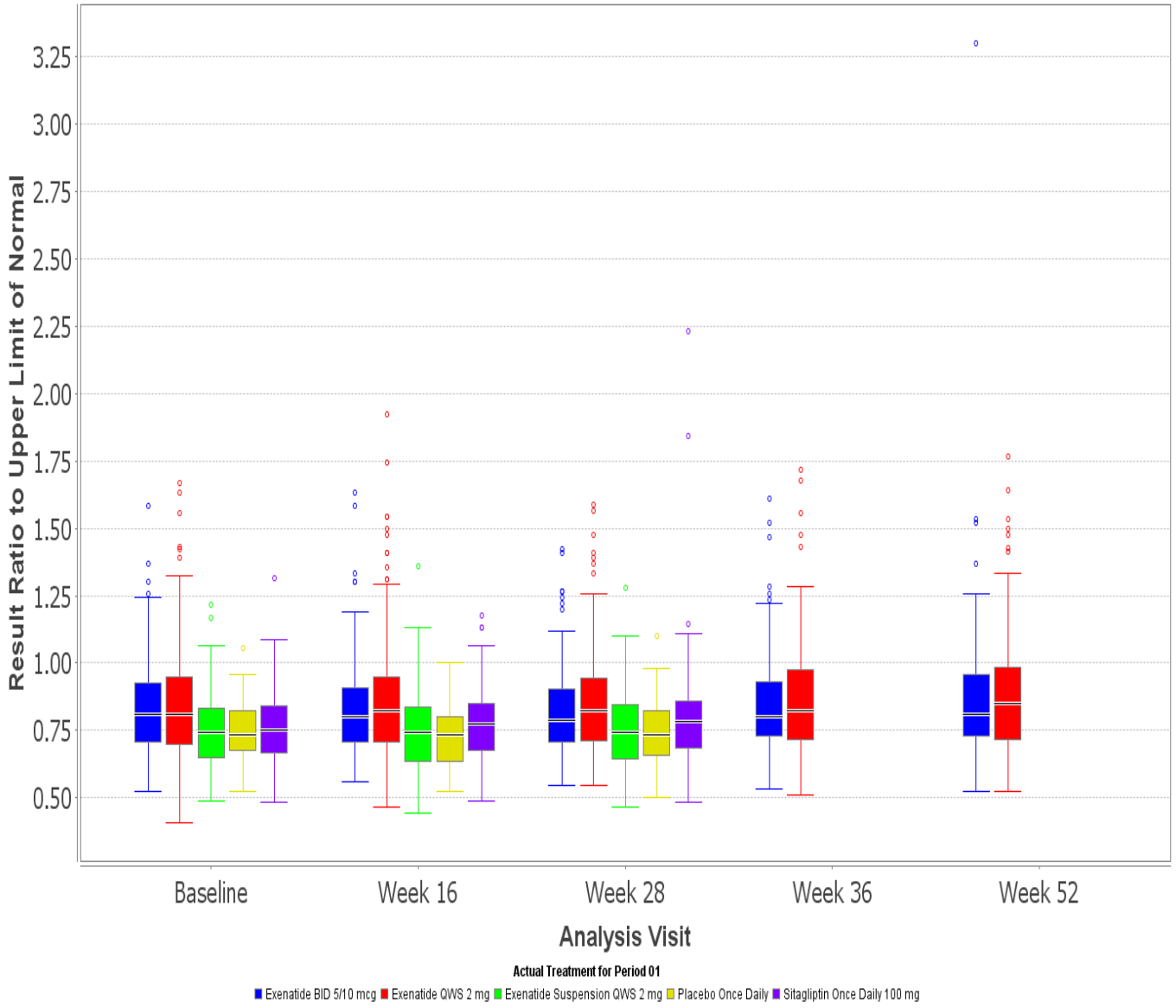
During the controlled period of BCB118, increase in serum creatinine from baseline was slightly more in favor of Byetta. Six subjects (2.67%) in the EQWS group had a ≥ 1.5 times creatinine

increase from baseline compared to 3 subjects (2.16%) in the Byetta group. One subject in the EQWS program had increased serum creatinine ≥ 2.5 mg/dL, and one subject had a maximum creatinine increase to 2.12 mg/dL. Review of the graphical patient profiles is below:

- Subject (b) (6) 66-year-old White male with seven years duration of T2DM and past medical history of moderate renal failure, congestive heart failure, defibrillator, and cardiomegaly with a baseline creatinine of 1.96 mg/dL had increased creatinine to 2.12 mg/dL by the end of the extension period. The only adverse event reported during the study was blood creatinine increased.

- Subject (b) (6) 65-year-old American Indian/Alaska Native obese male with T2DM, HbA1c 7.3% at baseline on metformin and TZD with a history of moderate renal impairment, hypertension and hyperlipidemia was randomized to the Byetta group with a baseline creatinine of 1.9 mg/dL. Subject developed a severe right foot infection during the extension period after switching to EQWS with an increase in creatinine to 3.96 mg/dL. No follow-up creatinine value is provided. The increase in creatinine appears to be related to underlying infection.

Figure 21: Mean (SD) creatinine levels relative to the upper limit of normal, including outliers, controlled and extension periods, safety population, BCB118 and BCB120



Generated by the reviewer with JReview, ADAM ISS
Note after week 28 the Byetta subjects switched to EQWS.

In the above box whisker presentation the mean creatinine in the EQWS group remains relatively stable throughout the duration of the study. Some of the outliers have been discussed above.

Reviewer summary for renal safety:

In the controlled period of BCB118 subjects with mild and moderate renal impairment were tested with EQWS compared to Byetta. The incidence of TEAEs in the Renal and urinary disorders SOC was higher in the Byetta group compared to EQWS group.

One patient (randomized to Byetta and later switched to EQWS) was reported as having a post-baseline creatinine value of > 3x ULN while on EQWS during the extension period. However, review of the graphical patient profile suggests a concurrent foot infection may have contributed to worsening renal function.

Supportive evidence from the central tendency for creatinine does not suggest a significant worsening renal function with EQWS use, however, due to small numbers a risk assessment of moderate renal impairment is limited in the EQWS program. Outlier evaluation of serum creatinine values ≥ 1.5 x ULN revealed slightly higher incidences for EQWS vs Byetta. Most creatinine increases were transient.

The data suggests that there is no new or worsening signal for renal safety for EQWS. As currently labeled, EQWS should be used cautiously in patients with (b) (4) moderate renal impairment (b) (4)
(b) (4)

Treatment-emergent Gastrointestinal Adverse Events

Reviewer approach:

To assess for numerical imbalances in TEAEs compared to Byetta, I reviewed the controlled arm of study BCB118. To assess numerical imbalances in TEAEs compared to placebo and sitagliptin, I reviewed study BCB120. To assess rare safety signals I looked at the extension period of study BCB118 and the follow-up periods for both Phase 3 studies. I also explored the gastrointestinal TEAES using JReview's Risk Assessment and GPP tool.

Reviewer Comment: During the EOP2 meeting the Agency agreed with relying on Bydureon's gastric emptying study with no plans for a gastric emptying assessment with EQWS. The Applicant stated the observed changes in gastric emptying rates with Bydureon were minimal and less than those observed with Byetta.

A. Controlled treatment arm, study BCB118 and BCB120:

In the controlled period of BCB118, the incidence of gastrointestinal TEAEs (PTs mapped to the SOC Gastrointestinal disorders) is favorable for EQWS compared to Byetta (22.71% in EQWS group vs. 36.99% in Byetta group). For study BCB120, the incidence of gastrointestinal adverse events is 17.68% for EQWS vs. 7.38% for sitagliptin and 3.28% for placebo.

Table 33: Gastrointestinal TEAEs mapped to the SOC Gastrointestinal Disorders by treatment arm, controlled and extension periods, safety population, BCB118 and BCB120

Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	Byetta to EQWS EXTENSION TREATMENT PERIOD	EQWS to EQWS EXTENSION TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD
Nausea	30 (20.55%)	22 (9.61%)	5 (4.31%)	1 (0.51%)	16 (8.84%)	0 (0.00%)	2 (1.64%)
Diarrhoea	17 (11.64%)	12 (5.24%)	2 (1.72%)	3 (1.55%)	5 (2.76%)	1 (1.64%)	2 (1.64%)
Constipation	4 (2.74%)	8 (3.49%)	1 (0.86%)	0 (0.00%)	2 (1.10%)	1 (1.64%)	1 (0.82%)
Vomiting	9 (6.16%)	8 (3.49%)	2 (1.72%)	1 (0.51%)	6 (3.31%)	0 (0.00%)	0 (0.00%)
Abdominal distension	1 (0.68%)	6 (2.62%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	2 (1.37%)	6 (2.62%)	0 (0.00%)	2 (1.03%)	2 (1.10%)	0 (0.00%)	1 (0.82%)
Abdominal pain	3 (2.05%)	3 (1.31%)	1 (0.86%)	1 (0.51%)	1 (0.55%)	0 (0.00%)	1 (0.82%)
Dyspepsia	7 (4.79%)	3 (1.31%)	0 (0.00%)	3 (1.55%)	4 (2.21%)	0 (0.00%)	1 (0.82%)
Abdominal pain upper	2 (1.37%)	1 (0.44%)	1 (0.86%)	1 (0.51%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Acquired oesophageal web	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aphthous ulcer	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dental caries	1 (0.68%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hiatus hernia	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatitis	0 (0.00%)	1 (0.44%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toothache	1 (0.68%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal discomfort	3 (2.05%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal hernia obstructive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Abdominal pain lower	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	2 (1.64%)
Abdominal symptom	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Ascites	0 (0.00%)	0 (0.00%)	1 (0.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breath odour	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Colitis ulcerative	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Diverticular perforation	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diverticulum	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Flatulence	2 (1.37%)	0 (0.00%)	1 (0.86%)	0 (0.00%)	0 (0.00%)	1 (1.64%)	2 (1.64%)
Food poisoning	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	1 (0.68%)	0 (0.00%)	1 (0.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis haemorrhagic	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal sounds abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.82%)
Haemorrhoids	1 (0.68%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inguinal hernia	0 (0.00%)	0 (0.00%)	1 (0.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Large intestine polyp	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lip swelling	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lower gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Mouth ulceration	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Odynophagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Pancreatitis acute	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rectal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)	0 (0.00%)
Umbilical hernia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Subjects(filtered)	54 (36.99%)	52 (22.71%)	10 (8.62%)	14 (7.25%)	32 (17.68%)	2 (3.28%)	9 (7.38%)
1stColItemSubjects	146 (100.00%)	229 (100.00%)	116 (100.00%)	193 (100.00%)	181 (100.00%)	61 (100.00%)	122 (100.00%)

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In the controlled period of study BCB118, the PTs nausea, diarrhea, vomiting drive the SOC

gastrointestinal in the EQWS group. Compared to Byetta, the incidence rates of these adverse events were lower (almost half). The PTs abdominal distension, constipation and GERD were more common in EQWS compared to Byetta, which may be explained by the effect of GLP-1 on gastric motility.

In BCB120, except for abdominal pain, all PTs mapped to the SOC Gastrointestinal disorders occurred more commonly in the EQWS group when compared to sitagliptin and placebo (17.68%: EQWS vs. 7.38%: sitagliptin, vs. 3.28%: placebo). This data speaks to the higher frequency of gastrointestinal adverse events with GLP-1 therapies in general.

Withdrawal, SAEs, and Severe gastrointestinal TEAEs:

In the 28-week controlled period of study BCB118 and study BCB120, the SOC gastrointestinal was the most common SOC for treatment and study withdrawals due to TEAE in the EQWS group. Refer to the section 8.4.3. for a discussion of withdrawal from treatment and study due to gastrointestinal TEAEs.

Reviewer Comment: Even though there is a lower incidence of nausea, vomiting, diarrhea in the EQWS group, more adverse events of diarrhea and vomiting lead to withdrawal in the EQWS group compared to Byetta in study BCB118.

In the 28-week period of study BCB118, there is one SAE of pancreatitis. During the extension period, the PT umbilical hernia was an SAE. In study BCB120, there are two SAEs: diarrhea and abdominal hernia obstructive.

In the controlled period of study BCB118 the percentage of severe gastrointestinal TEAEs was in the single digits (1.3% in EQWS vs. 2.05% in Byetta). In the EQWS group during the controlled period the PTs diarrhea, nausea, abdominal pain was severe. In the Byetta group during the controlled period, diarrhea, acute pancreatitis, and vomiting, abdominal discomfort was severe PTs. In study BCB120, abdominal hernia obstructive and colitis ulcerative were severe PTs (1.1% EQWS vs. 0.82% sitagliptin).

I reviewed the majority of the graphical patient profiles using JReview and did not find a concerning pattern or a significant clinical consequence such as irreversible renal failure, or severe renal failure. Most subjects developed a mild increase in creatinine following severe nausea, vomiting, and diarrhea with later resolution.

B.24-week extension arm, study BCB118:

During the 24-week extension period of Study BCB118, the incidence of gastrointestinal TEAEs was 7.8% with the PTs nausea, diarrhea, dyspepsia, and vomiting driving the SOC. It is noted that most gastrointestinal TEAEs during the extension period occurred in the Byetta group who had switched to EQWS.

In study BCB118 extension period one subject with SAE of pancreatitis withdrew treatment and study, and another subject had an SAE of umbilical hernia. The severe gastrointestinal PTs were umbilical hernia, diarrhea, and pancreatitis.

Reviewer Comment: In addition to the gastrointestinal TEAEs mapped to the SOC Gastrointestinal I reviewed the graphical patient profiles of the following selected PTs by the reviewer that may be related to a gastrointestinal adverse event. Review of the following PTs by using the graphical patient profile did not raise a concerning pattern related to an gastrointestinal TEAE: Gastroenteritis, Gastroenteritis viral, Gastrointestinal viral infection, Infectious colitis, helicobacter infection, blood creatinine increased, renal failure, dehydration.

Reviewer Comment: Overall, the rate of withdrawal, SAEs and severe gastrointestinal TEAEs are low, and most are known safety risks associated with GLP-1 therapy.

Reviewer's Summary of gastrointestinal TEAEs:

Overall, subjects exposed to EQWS experienced a lower incidence rate of gastrointestinal TEAEs compared to Byetta during the controlled period of study BCB118. However compared to placebo and sitagliptin subjects exposed to EQWS experienced a higher rate of gastrointestinal TEAEs. The rate of withdrawal, SAEs, and severe gastrointestinal TEAEs are low, and most are known safety risks associated with GLP-1 therapy.

Immunogenicity

Overview

Immunogenicity is a concern with all injectable peptides and has been observed with the approved products in the GLP-1 receptor agonist class.

Development of antibodies with neutralizing activity or cross-reactivity to endogenous GLP-1/glucagon may result in reduced efficacy or potential safety issues due to interferences with normal glucose regulation.

Reviewer Comment: Office of Biological Products (OBP) requested (August 18, 2017) the Applicant to submit the neutralization assay results for EQWS, and validation reports for evaluating the cross-reactivity of anti-exenatide antibody to GLP-1, glucagon, and sequence irrelevant peptides. The Applicant responded (September 1, 2017) that ADA was not tested for neutralizing activity or the cross-reactivity with GLP-1 and glucagon in the EQWS clinical program.

The OBP reivewer states while detection of neutralizing activity may be of mechanistic interest, possible cross-reactivity to endogenous GLP-1 may pose a clinical risk. OBP's reviewer states the Bydureon assays for evaluating the cross-reactivity of anti-exenatide antibody to GLP-1 and

glucagon were not adequately sensitive. Thus, OBP issued three postmarketing commitments as below:

1. [redacted] (b) (4)
2. *Test samples from clinical trials BCB118 and BCB120 for the presence of anti-GLP-1 and anti-glucagon antibodies using* [redacted] (b) (4)
3. *Validate the sensitivity of the version of ELISA-0308 method used for the detection of anti-exenatide antibodies (ADA) in patient samples collected in NDA 209210 clinical studies BCB118 and BCB120.*

The immunogenicity assessment in the EQWS submission is based on anti-exenatide antibody data collected in the two Phase 3 studies.

Antibody assessments for EQWS and Byetta were performed at baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and Week 28 and in the extension period Week 36 and Week 52, plus follow-up visit (Only EQWS antibodies were measured at Week 2, 6, 10, 15 and not Byetta).

In BCB120, antibody assessment was done at baseline, week 8, Week 16, Week 28, and follow-up visit for the EQWS group.

Reviewer's Approach to immunogenicity

In the EQWS drug development program, the most clinically relevant information about antibody response is derived from the Byetta comparator-controlled study, BCB118. Thus the focus for an effect of the antibody on safety and efficacy parameters was the controlled period of BCB118, where Byetta is the comparator. In BCB120, the anti-exenatide antibody formation is not relevant for the comparators placebo and sitagliptin. Also, I reviewed the extension period of BCB 118 for long-term effect on antibody formation and the possible effect on safety and efficacy. I also reviewed the HbA1c, and potentially immunogenic adverse events that occurred in the higher titer antibody group.

OVERALL ANTIBODY RESULTS:

Definitions:

The Applicant defines a subject with TEABs if the antibody test was positive after the first dose of study drug following a negative or missing antibody measurement on or before the first dose of treatment, or the titer was increased at least three dilutions from a detectable measurement before the first dose of randomized study drug.

The Applicant defines TEAB titers ≥ 625 as high titers and TEAB titer < 625 as low titers, and TEAB titer ≥25 is identified as positive.

In the 28-week controlled period of study BCB118, the incidence of treatment-emergent antibody (TEAB) positive subjects was higher in the EQWS group (76.2%) compared with the Byetta group (50.3%). At Week 52, 52.1% of subjects initially randomized to EQWS and 61.8% of subjects initially randomized to Byetta were antibody positive.

In BCB118 by Week 4, 23% of subjects on EQWS were antibody-positive compared to 25% of Byetta subjects. In BCB120 by week 4, 33% of EQWS subjects were antibody positive. The incidence of EQWS treated antibody-positive subjects continued to increase after week four until week 16 and appeared to decrease after week 16. The incidence in Byetta-treated subjects was generally lower but with a similar pattern.

Table 34: Incidence of treatment-emergent antibodies to exenatide by post-baseline visit, 28-week controlled period, safety population, BCB118 and BCB120

	Study BCB118 Controlled Period						Study BCB120 Controlled Period					
	EQWS N=229			Byetta N=146			EQWS N=181			All Phase 3 EQWS[a] N=410		
Parameter	Eval	Pos n (%)	Neg n (%)	Eval	Pos n (%)	Neg n (%)	Eval	Pos n (%)	Neg n (%)	Eval	Pos n (%)	Neg n (%)
Antibody status at baseline	213	6 (2.8)	207 (97.2)	141	1 (0.7)	140 (99.3)	134	7 (5.2)	127 (94.8)	347	13 (3.7)	334 (96.3)
Highest TEAB status at any post baseline visit (Weeks 2-28) [b]	227	173 (76.2)	54 (23.8)	143	72 (50.3)	71 (49.7)	166	118 (71.1)	48 (28.9)	393	291 (74.0)	102 (26.0)
Highest TEAB status at individual post baseline visits (Weeks 2-28) [b]												
Week 2	199	7 (3.5)	192 (96.5)	20	1 (5.0)	19 (95.0)	14	1 (7.1)	13 (92.9)	213	8 (3.8)	205 (96.2)
Week 4	210	48 (22.9)	162 (77.1)	133	33 (24.8)	100 (75.2)	6	2 (33.3)	4 (66.7)	216	50 (23.1)	166 (76.9)
Week 6	212	89 (42.0)	123 (58.0)	13	3 (23.1)	10 (76.9)	0	0	0	212	89 (42.0)	123 (58.0)
Week 8	206	110 (53.4)	96 (46.6)	121	43 (35.5)	78 (64.5)	144	84 (58.3)	60 (41.7)	350	194 (55.4)	156 (44.6)
Week 10	200	121 (60.5)	79 (39.5)	16	8 (50.0)	8 (50.0)	0	0	0	200	121 (60.5)	79 (39.5)
Week 12	194	121 (62.4)	73 (37.6)	121	52 (43.0)	69 (57.0)	4	2 (50.0)	2 (50.0)	198	123 (62.1)	75 (37.9)
Week 14	4	2 (50.0)	2 (50.0)	1	0	1 (100.0)	0	0	0	4	2 (50.0)	2 (50.0)
Week 15	32	22 (68.8)	10 (31.3)	5	3 (60.0)	2 (40.0)	0	0	0	32	22 (68.8)	10 (31.3)
Week 16	195	136 (69.7)	59 (30.3)	111	42 (37.8)	69 (62.2)	139	90 (64.7)	49 (35.3)	334	226 (67.7)	108 (32.3)
Week 20	196	118 (60.2)	78 (39.8)	114	42 (36.8)	72 (63.2)	2	0	2 (100.0)	198	118 (59.6)	80 (40.4)
Week 24	189	107 (56.6)	82 (43.4)	115	39 (33.9)	76 (66.1)	1	1 (100.0)	0	190	108 (56.8)	82 (43.2)
Week 28	182	97 (53.3)	85 (46.7)	112	31 (27.7)	81 (72.3)	127	80 (63.0)	47 (37.0)	309	177 (57.3)	132 (42.7)

Source: Excerpted from ISS narrative summary, Table 17, page 57
[a]=All EQWS subjects in BCB118 (controlled period) + all EQWS subjects in BCB120
[b]=All subjects in BCB118 (controlled period) + all subjects in BCB120

Reviewer Comment: The label for the other approved GLP-1 agonists informs that the incidence of ADA formation for Byetta was 20-38%, liraglutide 8.6%, Bydureon 49%, and lixisenatide 70%.

Note cross-comparing the incidence of ADA formation across different drugs is generally limited because of different assay methodology, the timing of sampling and different patient populations. However, it is noticed that in the EQWS drug development program, the incidence of ADA is in the higher range compared to the majority of the approved GLP-1 agonists.

In BCB118, among the 182 subjects with an evaluable ADA measurement at Week 28, the proportion of EQWS subjects with positive antibodies was 53.3% (97/182). In BCB120 among the 127 subjects with an evaluable ADA measurement at Week 28, the proportion of EQWS subjects with positive antibodies was 63% (80/127). In the Byetta group, at Week 28 a lower proportion of subjects (27.7%) had positive antibodies compared to EQWS.

An Information Request (August 22, 2017) was sent asking for a breakdown of exenatide antibody-positive subjects by titer category, including the outliers for a more granular exploratory analyses.

Table 35: Summary of antibody titer data at Week 28, safety population, BCB118 and BCB120

	BCB118 - 28 Weeks	BCB118 - 28 Weeks	BCB118 - Weeks 29-52	BCB120
Visit	EQWS 2mg N=229	Byetta N=146	EQWS 2mg N=309	EQWS 2mg N=181
Week 28	182/229 (79.5)	112/146 (76.7)		127/181 (70.2)
Negative	85/182 (46.7)	81/112 (72.3)		47/127 (37.0)
Positive (total)	97/182 (53.3)	31/112 (27.7)		80/127 (63.0)
25	41/97 (42.3)	16/31 (51.6)		29/80 (36.3)
125	32/97 (33.0)	10/31 (32.3)		32/80 (40.0)
625	13/97 (13.4)	3/31 (9.7)		11/80 (13.8)
3125	9/97 (9.3)	2/31 (6.5)		6/80 (7.5)
15625	2/97 (2.1)	0		1/80 (1.3)
78125	0	0		1/80 (1.3)

Source: Excepted from Response to Information Request dated August 31, 2017

Reviewer Comment: In general, in BCB118, at Week 28 of the controlled period, a relatively similar proportion of antibody-positive subjects peaked to the 125 antibody titer category in the EQWS and Byetta groups. However, a higher proportion of EQWS subjects peaked to the higher titers of 625, 3125 and 15625 compared to Byetta.

Possible effect of antibodies on efficacy

The effect of antibodies on efficacy was assessed by exploratory sub-group analyses. BCB118 was primarily used to examine the impact of antibodies on reduction in HbA1c and fasting

blood glucose at 28 and 52 weeks in the EQWS group compared to the Byetta group.

Table 36: Mean change from baseline in HbA1c at 28 weeks for EQWS treated subjects in study BCB118 by antibody status and titer, Week 28, safety population

Antibody Status/Titer	Statistics	BCB118 EQWS 28 weeks (N=229)	BCB118 Byetta 28 weeks (N=146)
Negative	n/N	85/179 (47.5)	77/105 (73.3)
	LS Mean	-1.45	-1.15
	SE	0.121	0.127
	95% CI	(-1.69, -1.21)	(-1.40, -0.90)
Positive(total)	n/N	94/179 (52.5)	28/105 (26.7)
	LS Mean	-1.42	-0.95
	SE	0.104	0.191
	95% CI	(-1.62, -1.21)	(-1.33, -0.57)
25	n/N	41/94 (43.6)	15/28 (53.6)
	LS Mean	-1.79	-1.41
	SE	0.141	0.233
	95% CI	(-2.07, -1.50)	(-1.88, -0.95)
125	n/N	30/94 (31.9)	9/28 (32.1)
	LS Mean	-1.44	-0.59
	SE	0.170	0.312
	95% CI	(-1.79, -1.10)	(-1.22, 0.05)
625	n/N	12/94 (12.8)	3/28 (10.7)
	LS Mean	-0.81	0.30
	SE	0.265	0.556
	95% CI	(-1.38, -0.23)	(-0.92, 1.51)
3125	n/N	9/94 (9.6)	1/28 (3.6)
	LS Mean	-0.61	-1.58
	SE	0.211	0.667
	95% CI	(-1.11, -0.11)	(-3.16, -0.01)
15625[1]	n/N	2/94 (2.1)	0
	LS Mean	-0.40	
	SE	1.000	
	95% CI	(-13.11, 12.31)	

Source: Excerpted from the Applicant's response (August 31, 2017) to Information Request (August 18, 2017).
n: number of patients with specified status/titer at that visit; N: number of patients with status/titer available at that visit[21]
[1]LSMean is replaced by mean for this category as not a sufficient number of patients was available in the Byetta treatment group for performing the ANCOVA.

[21] LS Means are based on ANCOVA performed at week-28 with change from baseline to week-28 in fasting plasma glucose as the dependent variable, treatment as the fixed effect and baseline fasting plasma glucose as the continuous covariate. [1] LSMean is replaced by mean for this category as not sufficient numbers of patients were available in the byetta treatment group for performing the ANCOVA.

Reviewer Comment: Review of Table 35 demonstrates no apparent difference between low titer antibody positive and antibody negative subjects. However, it is noted that high titer subjects had a smaller reduction in HbA1c at 28 weeks in the EQWS arm, and there is a decline in the efficacy response that corresponds with increasing antibody concentrations. However, the sample size of these sub-group analyses is small, and meaningful clinical inferences are difficult to make based on small sample sizes.

At 52 weeks, a similar trend was observed (Table 36). Subjects with higher titer ADA had a reduced efficacy compared to ADA negative subjects. Acknowledging that these are subgroup findings from small numbers of subjects, it seems to suggest that the presence of ADAs (particularly at high concentrations) may adversely impact the efficacy of EQWS. This could be due to chance, but may also indicate the presence of neutralizing antibodies. As mentioned earlier, testing for neutralizing antibodies was not performed in the EQWS program.

Table 37: Mean change from baseline in HbA1c at 52 weeks for EQWS treated subjects in study BCB118 by antibody status and titer, safety population

Antibody Status/Titer	Statistics	BCB118 EQWS 52 weeks (N=193)	BCB118 Byetta 52 weeks (N=116)
Negative	n/N	75/153 (49.0)	33/84 (39.3)
	LS Mean	-1.47	-1.61
	SE	0.098	0.149
	95% CI	(-1.66, -1.27)	(-1.91, -1.32)
Positive(total)	n/N	78/153 (51.0)	51/84 (60.7)
	LS Mean	-1.09	-1.34
	SE	0.124	0.153
	95% CI	(-1.33, -0.85)	(-1.64, -1.04)
25	n/N	39/78 (50.0)	20/51 (39.2)
	LS Mean	-1.47	-1.69
	SE	0.114	0.160
	95% CI	(-1.70, -1.24)	(-2.01, -1.37)
125	n/N	21/78 (26.9)	22/51 (43.1)
	LS Mean	-1.13	-1.15
	SE	0.241	0.235
	95% CI	(-1.62, -0.64)	(-1.62, -0.67)
625	n/N	9/78 (11.5)	8/51 (15.7)
	LS Mean	-0.95	-0.96
	SE	0.313	0.332
	95% CI	(-1.63, -0.28)	(-1.68, -0.25)
3125	n/N	8/78 (10.3)	1/51 (2.0)
	LS Mean	0.59	-0.32
	SE	0.604	1.715
	95% CI	(-0.89, 2.07)	(-4.52, 3.87)
15625[1]	n/N	1/78 (1.3)	0
	LS Mean	-1.10	
	SE		
	95% CI		

Source: Excerpted from the response (August 31, 2017) to Information Request (August 18, 2017); n: number of patients with specified status/titer at that visit; N: number of patients with status/titer available at that visit.

Also, an exploratory analysis for a possible effect of high titer positive anti-exenatide antibodies on HbA1c and fasting blood glucose change from baseline on EQWS subjects who at any time during the study had peaked to ≥ 625 titer was performed by reviewing the individual subject listing.

Specifically, the exploratory analysis was performed to identify whether a concerning pattern with decreased efficacy and high titer antibodies was observed or not.

In the 52-Week study BCB118, a listing provided by the Applicant of 27 subjects with an antibody titer of 3125 and six subjects with an antibody titer of 15625 was reviewed. Some of the subjects with higher titer antibodies showed a trend of an increase of HbA1c at Week 52 or an increase of HbA1c starting around Week 36 to Week 52.

Reviewer Comment: Interpretation of such exploratory analysis is limited.

Possible effect of antibodies on safety parameters

To assess the effect of antibodies on safety parameters, the following analysis was done:

1. Effect of antibody status and titer on common TEAE ≥ 1 % by anti-exenatide antibody status in the Phase 3 controlled periods, safety population
2. Effect of antibody status and titer on potentially immunogenic TEAEs (Applicant's Custom Query); hypersensitivity reactions
3. Exploratory analysis of TEAEs in all subjects who peaked to maximum titer of ≥ 625 including titer outliers

Table 38: Effect of antibody status and titer on common TEAE ≥ 1 % by anti-exenatide antibody status in the BCB118 and BCB120 controlled periods, safety population

	BCB118				BCB120	
	Byetta n (%)		EQWS n (%)		EQWS n (%)	
Dictionary Derived Term	Any Positive	Negative	Any Positive	Negative	Any Positive	Negative
Hypoglycaemia	11 (7.53%)	17 (11.64%)	34 (14.85%)	13 (5.68%)	2 (1.10%)	2 (1.10%)
Injection site nodule	0 (0.00%)	1 (0.68%)	25 (10.92%)	11 (4.80%)	13 (7.18%)	1 (0.55%)
Nausea	14 (9.59%)	16 (10.96%)	19 (8.30%)	3 (1.31%)	11 (6.08%)	4 (2.21%)
Headache	3 (2.05%)	6 (4.11%)	11 (4.80%)	2 (0.87%)	5 (2.76%)	3 (1.66%)
Upper respiratory tract infection	1 (0.68%)	4 (2.74%)	10 (4.37%)	3 (1.31%)	3 (1.66%)	1 (0.55%)
Injection site pruritus	1 (0.68%)	0 (0.00%)	9 (3.93%)	1 (0.44%)	5 (2.76%)	0 (0.00%)
Diarrhoea	8 (5.48%)	9 (6.16%)	8 (3.49%)	4 (1.75%)	3 (1.66%)	1 (0.55%)
Vomiting	2 (1.37%)	7 (4.79%)	7 (3.06%)	1 (0.44%)	3 (1.66%)	2 (1.10%)
Injection site erythema	0 (0.00%)	0 (0.00%)	7 (3.06%)	1 (0.44%)	2 (1.10%)	0 (0.00%)
Constipation	0 (0.00%)	4 (2.74%)	6 (2.62%)	2 (0.87%)	1 (0.55%)	1 (0.55%)
Gastrooesophageal reflux disease	0 (0.00%)	2 (1.37%)	6 (2.62%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
Injection site bruising	0 (0.00%)	0 (0.00%)	6 (2.62%)	1 (0.44%)	3 (1.66%)	2 (1.10%)
Pain in extremity	3 (2.05%)	2 (1.37%)	6 (2.62%)	2 (0.87%)	2 (1.10%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	2 (1.37%)	5 (2.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle spasms	0 (0.00%)	2 (1.37%)	5 (2.18%)	1 (0.44%)	1 (0.55%)	0 (0.00%)
Injection site pain	0 (0.00%)	0 (0.00%)	5 (2.18%)	2 (0.87%)	1 (0.55%)	1 (0.55%)
Back pain	1 (0.68%)	4 (2.74%)	5 (2.18%)	1 (0.44%)	2 (1.10%)	0 (0.00%)
Dizziness	3 (2.05%)	3 (2.05%)	5 (2.18%)	3 (1.31%)	4 (2.21%)	0 (0.00%)
Fall	3 (2.05%)	2 (1.37%)	5 (2.18%)	0 (0.00%)	1 (0.55%)	1 (0.55%)
Abdominal distension	0 (0.00%)	1 (0.68%)	4 (1.75%)	2 (0.87%)	1 (0.55%)	0 (0.00%)
Cough	0 (0.00%)	0 (0.00%)	4 (1.75%)	1 (0.44%)	1 (0.55%)	0 (0.00%)
Hyperlipidaemia	1 (0.68%)	2 (1.37%)	4 (1.75%)	0 (0.00%)	2 (1.10%)	0 (0.00%)
Nasopharyngitis	5 (3.42%)	1 (0.68%)	4 (1.75%)	2 (0.87%)	0 (0.00%)	1 (0.55%)
Abdominal pain	1 (0.68%)	2 (1.37%)	3 (1.31%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
Urinary tract infection	1 (0.68%)	2 (1.37%)	3 (1.31%)	2 (0.87%)	2 (1.10%)	0 (0.00%)
Arthralgia	1 (0.68%)	1 (0.68%)	3 (1.31%)	1 (0.44%)	0 (0.00%)	0 (0.00%)
Blood triglycerides increased	1 (0.68%)	2 (1.37%)	3 (1.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	1 (0.68%)	3 (2.05%)	3 (1.31%)	1 (0.44%)	2 (1.10%)	1 (0.55%)
Ear pain	1 (0.68%)	0 (0.00%)	3 (1.31%)	1 (0.44%)	1 (0.55%)	0 (0.00%)
Oropharyngeal pain	2 (1.37%)	0 (0.00%)	3 (1.31%)	1 (0.44%)	0 (0.00%)	0 (0.00%)
Hypertension	2 (1.37%)	3 (2.05%)	3 (1.31%)	0 (0.00%)	3 (1.66%)	0 (0.00%)
Sinusitis	3 (2.05%)	1 (0.68%)	3 (1.31%)	1 (0.44%)	0 (0.00%)	0 (0.00%)
Rash	3 (2.05%)	1 (0.68%)	3 (1.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspepsia	5 (3.42%)	2 (1.37%)	3 (1.31%)	0 (0.00%)	3 (1.66%)	1 (0.55%)
1stColItemSubjects	146 (100.00%)	146 (100.00%)	229 (100.00%)	229 (100.00%)	181 (100.00%)	181 (100.00%)
Subjects(filtered)	54 (36.99%)	61 (41.78%)	129 (56.33%)	40 (17.47%)	65 (35.91%)	30 (16.57%)

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Review of Table 37 for common TEAEs ≥ 1% by antibody status (28-week controlled periods) shows that injection site nodules and hypoglycemia were reported more frequently in the ADA positive EQWS subjects compared to the antibody-negative EQWS subjects. Imbalances in other common TEAES in the ADA positive EQWS subjects compared to ADA negative EQWS subjects e.g. headache, upper respiratory tract infection, and nausea is noted.

BCB120 generally showed a similar pattern for a relationship between common TEAEs and

antibody status (except for hypoglycemia which had a low incidence in BCB120).
Reviewer Comment: Overall, the clinical significance of these observations is unknown and may be chance findings. Hypoglycemia (see below) and injection site reactions (refer to section 8.5 injection site reactions) possible relationship with antibody status were further explored.

Antibody status and hypoglycemia:

Reviewer Comment: The Applicant provided an exploratory analysis of antibody status and titer on minor hypoglycemia defined as symptoms of hypoglycemia and glucose level < 54 mg/dL in the EQWS program (the ADA defined symptomatic hypoglycemia uses a glucose cut-off of < 70 mg/dL).

Table 39: Number (%) of subjects with minor hypoglycemia by anti-exenatide antibody status and titer categorized by antidiabetic background therapy in BCB118 during controlled period, safety population

	Monotherapy (N=49)		Metformin (N=166)		SU + Metformin (N=131)	
Antibody Status/Titer	EQWS (N=33)	Byetta (N=16)	EQWS (N=101)	Byetta (N=65)	EQWS (N=77)	Byetta (N=54)
Antibody status available at least once at any time during treatment	33	16	101	65	77	54
Always Negative [1]	2/6 (33.3)	1/9 (11.1)	0	4/39 (10.3)	8/19 (42.1)	5/18 (27.8)
At Least Once Positive [1]	0	0	3/78 (3.8)	2/26 (7.7)	13/58 (22.4)	7/36 (19.4)
25[2]	0	0	1/3 (33.3)	0	1/13 (7.7)	0
125	0	0	0	2/2 (100.0)	5/13 (38.5)	5/7 (71.4)
625	0	0	0	0	5/13 (38.5)	1/7 (14.3)
3125	0	0	2/3 (66.7)	0	2/13 (15.4)	1/7 (14.3)
15625	0	0	0	0	0	0
78125	0	0	0	0	0	0

Source: Excerpted from response to Information Request dated August 31, 2017
[1] Numerator: number of patients with minor hypoglycemia in that category; and denominator: number of patients in that category.
[2] For rows equal to a specific titer, numerator: number of patients with minor hypoglycemia in that category; and denominator: the total number of antibody-positive patients with minor hypoglycemia.

Reviewer Comment: In general, a numerical increase in minor hypoglycemia was observed in antibody-negative EQWS subjects compared to antibody positive EQWS subjects in the add-on to SU and metformin group.

A numerical increase in minor hypoglycemia was observed in antibody-positive EQWS subjects compared to antibody positive Byetta subjects in the add-on to SU and metformin group during the 28-week controlled period of study BCB118.

Reviewer Comment: In general, with limiting the population to subjects who have at least one antibody status available during the 28-week treatment period, and who develop minor hypoglycemia, a strong correlation between antibody positivity and hypoglycemia is not observed in the EQWS subjects. These exploratory subgroup analyses are small in number and may be chance findings with unknown clinical significance.

Hypersensitivity reactions:

Cases of anaphylaxis and angioedema has been reported with other GLP-1 receptor agonists. The proposed label adequately informs of the risk of hypersensitiviy with EQWS.

Reviewer Comment: The EQWS program did not adjudicate on-treatment possible allergic events and identification of these events was based on investigator reporting. The impact of lack of adjudication and prospective identification of immune-related adverse events is unknown.

Table 40: Potentially immunogenic adverse events by antibody status-Applicant's custom query, controlled period, safety population, BCB118 and BCB120

		BCB118				BCB120	
		Byetta n (%)		EQWS n (%)		EQWS n (%)	
SOC	Dictionary Derived Term	Any Positive	Negative	Any Positive	Negative	Any Positive	Negative
Blood and lymphatic system disorders	Eosinophilia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.87%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders	Lip swelling	0 (0.00%)	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions	Injection site erythema	0 (0.00%)	0 (0.00%)	7 (3.06%)	1 (0.44%)	2 (1.10%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Injection site hypersensitivity	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Injection site induration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.44%)	5 (2.76%)	2 (1.10%)
	Injection site inflammation	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Injection site nodule	0 (0.00%)	1 (0.68%)	22 (9.61%)	11 (4.80%)	12 (6.63%)	1 (0.55%)
		0 (0.00%)	0 (0.00%)	3 (1.31%)	0 (0.00%)	3 (1.66%)	0 (0.00%)
	Injection site oedema	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Injection site pruritus	0 (0.00%)	0 (0.00%)	5 (2.18%)	1 (0.44%)	5 (2.76%)	0 (0.00%)
		1 (0.68%)	0 (0.00%)	4 (1.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Injection site rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Injection site reaction	0 (0.00%)	0 (0.00%)	2 (0.87%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
	Injection site swelling	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
	Injection site urticaria	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders	Drug hypersensitivity	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Hypersensitivity	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (0.68%)	0 (0.00%)	3 (1.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	1 (0.68%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)
	Arthritis	0 (0.00%)	3 (2.05%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Periarthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders	Asthma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)
	Bronchospasm	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders	Angioedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Dermatitis	0 (0.00%)	0 (0.00%)	2 (0.87%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Dermatitis allergic	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
	Rash	2 (1.37%)	1 (0.68%)	3 (1.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Rash erythematous	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Rash papular	1 (0.68%)	0 (0.00%)	1 (0.44%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Rash pruritic	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Urticaria	0 (0.00%)	0 (0.00%)	2 (0.87%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		8 (5.48%)	7 (4.79%)	50 (21.83%)	15 (6.55%)	24 (13.26%)	3 (1.66%)
		146 (100.00%)	146 (100.00%)	229 (100.00%)	229 (100.00%)	181 (100.00%)	181 (100.00%)

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During the controlled period, an imbalance is noticed in the adverse events arthralgia (3 EQWS

subjects: 0 Byetta subjects), dermatitis (2 EQWS subjects: 0 Byetta subjects), urticaria (2 EQWS subjects: 0 Byetta subjects) in antibody-positive EQWS vs. Byetta subjects. None were severe or serious. These imbalances are low in number. Review of the 52-week data shows a similar trend. No death was attributed to the hypersensitivity reactions.

Reviewer Comment: In general, except for the injection site reactions (discussed separately), the incidence of potentially immune-related adverse events reported under other SOCs were too few to make meaningful comparisons based on antibody status.

Reviewer Comment: One subject (b) (6) *from the BCB120 EQWS group withdrew treatment and the study due to moderate urticaria. Review of the graphical patient profile shows this subject had mild injection site rash and mild trunk rash, followed by injection site pain and erythema. After developing general urticaria around Day 40, subject withdrew from treatment and study. The reason given is: subject felt awful for months, and had hives that he thought was related to the drug.*

Subject (b) (6) *withdrew during the extension period of BCB118 after developing generalized rash (randomized to Byetta and switched to EQWS during the extension period). The narrative states physical exam showed a papular rash involving the entire body except for the head, face, palms, soles and genitals. The rash resolved 15 days after EQWS discontinuation suggesting causality. The narrative states the event was a serious adverse event of rash, however of moderate intensity. However, this adverse event is not listed as an SAE, nor flagged by the Applicant as an SAE in JReview.*

Lastly, an exploratory analysis of potentially immunogenic TEAEs and hypoglycemia stratified by antibody titer categories ≥ 625 (including the antibody titer outliers) was performed.

The majority of the potentially immunogenic TEAEs in the antibody titer category ≥ 625 in the EQWS group in both Phase 3 studies belong to injection site reactions (nodule, pruritus, erythema, induration, edema, inflammation, and swelling). The other potentially immunogenic adverse events in the EQWS group were rash, rash erythematous, arthralgia, and bronchospasm.

Reviewer Comment: Review of the graphical patient profiles for bronchospasm (b) (6) (b) (6) *demonstrates the adverse event of bronchospasm occurred after the adverse event of upper respiratory tract infection. The lower level term was post-infectious bronchospasm. See below profile:*

Review of the adverse event of hypoglycemia in the subjects with antibody titer ≥ 625 at any time during the study shows a pattern of recurrent hypoglycemic events in ~4 subjects (in contrast to 1 subject exposed to Byetta who had 3 episodes of hypoglycemia). Review of the graphical patient profiles for these subject suggests none of these recurrent hypoglycemic events were serious, severe, or resulted in study withdrawal. Below is the graphical patient profiles of some of these EQWS-treated subjects with recurrent hypoglycemia and positive antibody status.

(b) (6)

Reviewer Comment: In general, these exploratory analyses are limited and difficult to derive clinically meaningful conclusions.

Lastly, the graphical patient profiles for the following selected adverse events were reviewed: Eosinophilia, dermatitis allergic, seasonal allergy, arthritis, pyrexia, rhinorrhea, dermatitis, dermatitis contact, hypersensitivity, cough, bronchospasm, rash erythematous, and blister.

Reviewer Comment: No systemic immune-related respiratory symptoms or anaphylactic reactions were reported with the above adverse events. The adverse event of eosinophilia occurred in antibody-negative subjects. None were categorized as serious or severe.

Reviewer's summary of immunogenicity:

In the Phase 3 studies in the EQWS drug development program about 74% of subjects were anti-exenatide antibody positive during the controlled period.

In general, the incidence of antibodies to exenatide cannot be directly compared with the incidence of antibodies of other products due to different assays and populations across drug development programs. However, it is to be noted that antibody formation occurs in a high percentage of subjects exposed to EQWS.

Anti-drug antibodies that cross-react to endogenous GLP1 or glucagon may affect glucose homeostasis. Antidrug antibodies may also neutralize exenatide and impact efficacy. However, cross-reactivity of anti-exenatide antibodies to endogenous GLP-1 and glucagon, and neutralizing antibodies were not assessed in the EQWS clinical program. The OBP review shows lack of adequate sensitivity of the Bydureon cross-reactivity assay to endogenous GLP1/glucagon. (b) (4)

A higher percentage of subjects with injection site reactions had positive antibodies, especially high titer antibodies. A slightly higher percentage of subjects with positive antibodies had a possible allergic reaction (e.g., rash, dermatitis) in the EQWS group compared to Byetta, but none were serious. This conclusion is limited due to the small number of patients with allergic reactions. Exploratory analyses suggest a possible smaller reduction in HbA1c at Week 28 and Week 52 with increasing antibody titers. However, the sample size of these sub-group exploratory analyses is small limiting data interpretation.

Search for PTs anaphylactic reactions, anaphylactic shock, swollen lips, tongue-uvula, stridor, hypoxemia, or associated symptoms of end-organ dysfunction was negative. I also examined the TEAE database for circulatory collapse as an indicator for anaphylaxis shock and did not identify any.

Narratives

The Applicant submitted six narratives for severe potentially immunogenic events for the following PTs: osteoarthritis, bronchospasm, acute pancreatitis, ulcerative colitis.

Reviewer Comment: Review of the above narratives submitted by the Applicant did not show relevance to the study drug or an immunogenic event.

Injection site reactions:

Injection site reactions have been reported with other members of the GLP-1 receptor agonist class of drugs. They have been reported with an increased incidence in patients with positive ADAs with other GLP-1 agonists, e.g., Bydureon and lixisenatide.

Bydureon's label was updated in 2014 after post-marketing reports of serious injection site

reactions with or without subcutaneous nodules were identified, some requiring surgical intervention (the EQWS proposed label contains similar language)

A. Controlled treatment arm, study BCB118 and BCB120:

For the Phase 3 studies, injection site reactions were defined by searching the PTs of all adverse events including the term “injection site”.

Table 41: Injection Site Related TEAEs by PT mapped to the SOC General, safety population, controlled and extension periods, BCB118 and BCB120

	BCB118				BCB120
	Byetta n (%)		EQWS n (%)		EQWS n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	EXTENSION TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	EXTENSION TREATMENT PERIOD	TREATMENT PERIOD
Injection site nodule	1 (0.68%)	5 (4.3%)	36 (15.72%)	1 (0.5%)	14 (7.73%)
Injection site pruritus	1 (0.68%)	2 (1.7%)	10 (4.37%)	0	5 (2.76%)
Injection site erythema	1 (0.68%)	0	8 (3.49%)	0	3 (1.66%)
Injection site bruising	0	3 (2.6%)	7 (3.06%)	0	5 (2.76%)
Injection site pain	0	2 (1.7%)	7 (3.06%)	0	3 (1.66%)
Injection site reaction	0	0	2 (0.87%)	0	1 (0.55%)
Injection site haemorrhage	0	0	2 (0.87%)	0	1 (0.55%)
Injection site mass	0	0	2 (0.87%)	0	1 (0.55%)
Injection site swelling	0	0	1 (0.44%)	0	2 (1.10%)
Injection site induration	0	1 (0.9%)	1 (0.44%)	0	7 (3.87%)
Injection site inflammation	0	0	1 (0.44%)	0	0
Injection site cyst	0	0	1 (0.44%)	0	0
Injection site urticaria	2 (1.37%)	1 (0.9%)	1 (0.44%)	0	0
Injection site oedema	0	0	1 (0.44%)	0	0
Injection site granuloma	0	0	1 (0.44%)	0	0
Injection site discomfort	1 (0.68%)	0	0	0	0
Injection site hypersensitivity	1 (0.68%)	0	0	0	0
Injection site paraesthesia	0	0	0	0	1 (0.55%)
Injection site rash	0	0	0	0	1 (0.55%)
Injection site haematoma	0	2 (1.37%)	0	0	1 (0.55%)
Injection site adverse events	6 (4.11%)	13 (11.2%)	64 (27.95%)	1 (0.5%)	34 (18.78%)
1stColItemSubjects	146 (100.00%)	116 (100.00%)	229 (100.00%)	193 (100.00%)	181 (100.00%)

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In the controlled period of study BCB118, injection site reactions were reported in 27.95% of the EQWS group versus 4.11% of the Byetta group.

Reviewer Comment: In the controlled period of BCB118, a clear imbalance is seen for injection site reactions favoring Byetta, with the PT injection site nodule driving the SOC as seen below (15.7% injection site nodules in EQWS vs. 0.7% in Byetta).

Reviewer Comment: An Information Request (August 22, 2017) for clarification on the clinical difference between the adverse events "injection site nodule", "injection site granuloma", "injection site induration" and "injection site mass". The Applicant responded (August 31, 2017) that the process of mapping verbatim terms to the lower level term and preferred terms are an automated process without sponsor's input.

In BCB118, 47 events of injection site nodule, 1 event of injection site granuloma, 2 events of injection site induration, and 2 events of injection site mass were reported; In BCB120, 28 events of injection site nodules, 0 events of injection site granuloma, 7 events of injection site induration, 1 event injection site mass were reported.

Reviewer Comment: It is possible that the incidence of the adverse event injection site nodule is underestimated due to splitting.

The SOC General Disorders and Administration Site Conditions have the highest Risk Difference compared to Byetta, driven by the HGLT: Administration Site Reactions, driven by the PT injection site nodule as shown below.

Figure 22: TEAE Risk Difference (per 100) by SOC, EQWS vs. Exenatide, safety population, controlled arm, BCB118

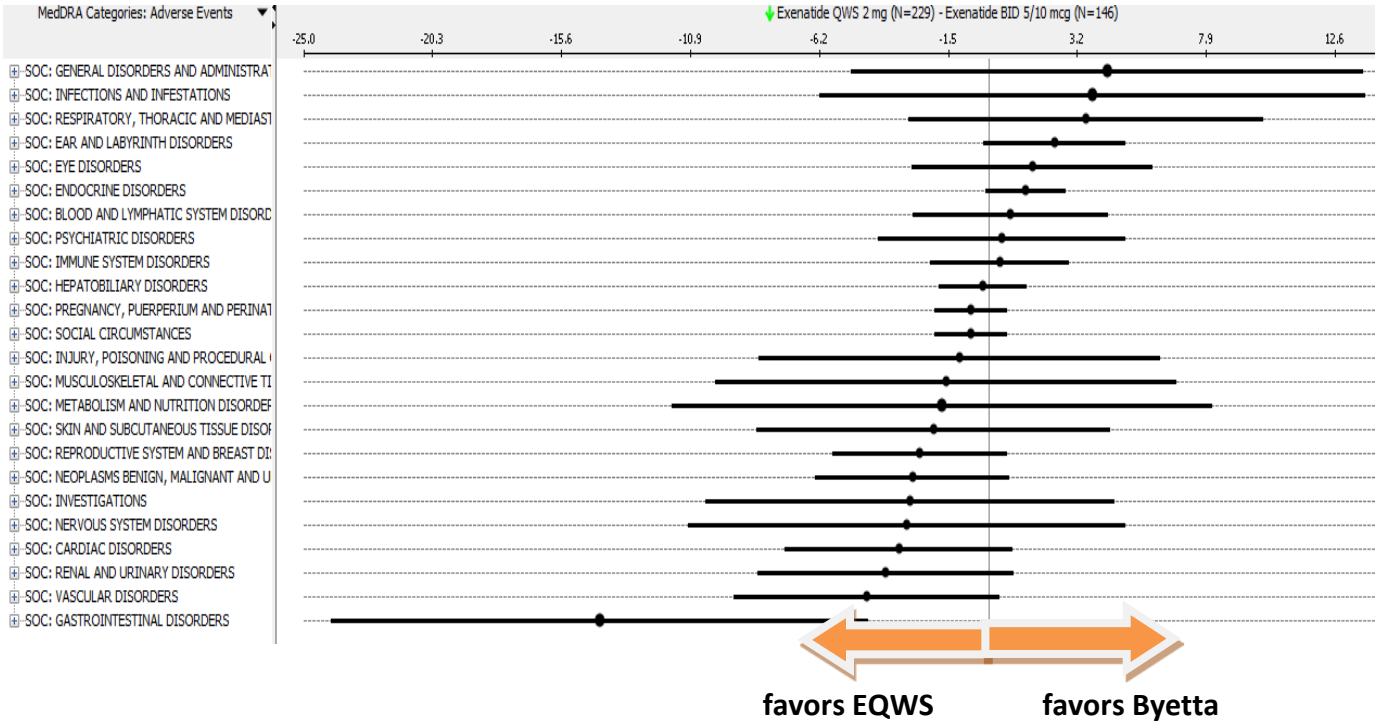

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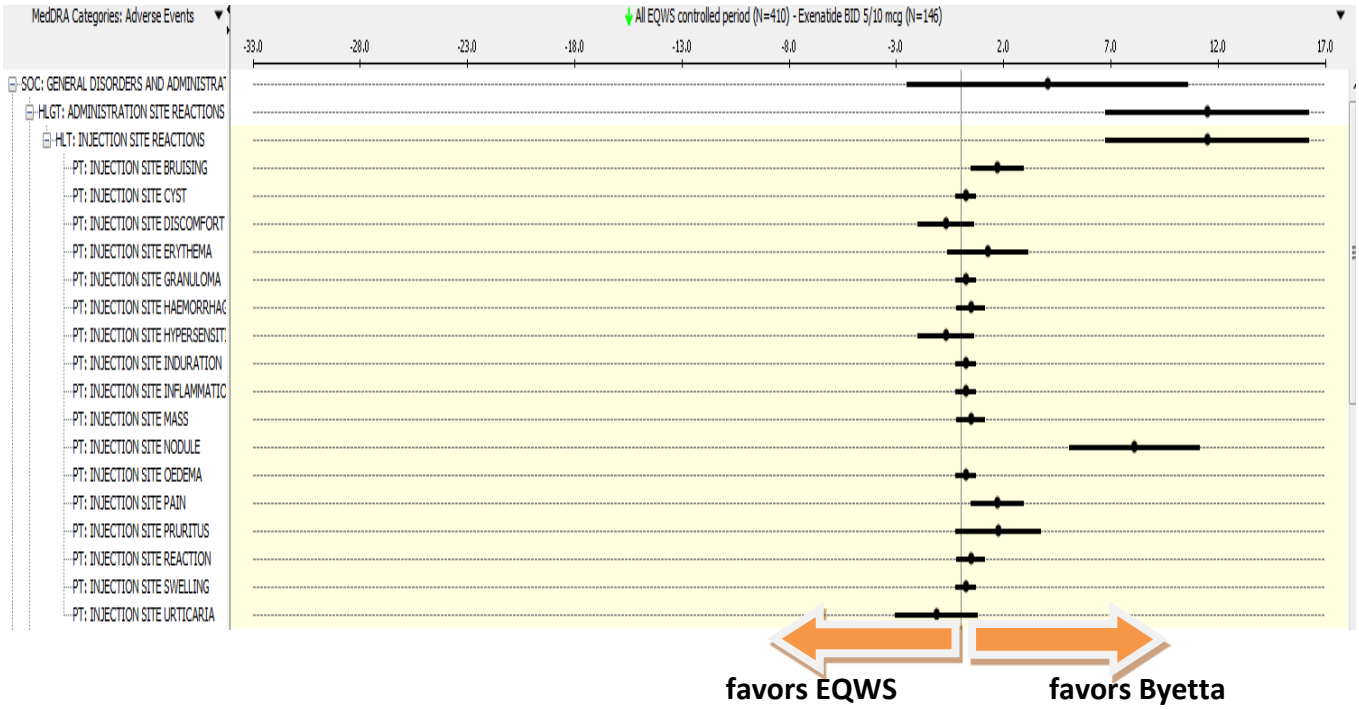
Figure 23: Injection Site TEAEs Risk Difference (per 100) by PT- safety population, 28-week controlled arm, BCB118



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In BCB118 the graphical patient profiles for EQWS-treated subjects with the following selected adverse events were reviewed: aphthous ulcer, blister, cellulitis, dermatitis, dermatitis contact, dermatitis allergic, drug hypersensitivity, erythema, furuncle, hordeolum, and localized infection. A PT of device-related infection occurred in the placebo group.

Reviewer Comment: Review of the graphical patient profiles indicate the adverse events of localized infection (in the toe) and hidradenitis (armpit), localized infection (postop wound infection), hordeolum and furuncle were not related to injection site reactions.

Reviewer Comment: The Applicant responded (August 31, 2017) to an Information Request (August 22, 2017) asking for clarification on the adverse events of skin infection. The Applicant states the subject has an adverse event of injection site nodule which resolved after about one year. About a month later the subjects had an adverse event of superficial skin infection with no specified location. However, it is unlikely the two adverse events are related because the adverse event of the subcutaneous nodule at the injection site was reported as resolved.

Reviewer Comment: 3 subjects with the adverse event cellulitis (b) (6) (b) (6) *were identified. The Applicant response (August 31, 2017)*

to an Information Request (August 22, 2017) sent for clarification states 2 of the subjects cellulitis events were not a result of injection site reactions. However, one subject (b) (6) (b) (6) *had two skin-related adverse events overlapping by one day: injection site reaction, and cellulitis with no specified location. It may be plausible that this event of cellulitis was related to the injection site reaction.*

B.24-week extension arm, study BCB118:

During the Phase 3, uncontrolled extension period, the overall incidence of injection site adverse events in the 309 EQWS-treated subjects was 4.5% with the majority of PTs injection site nodule (1.9%) and injection site bruising (1%).

Almost all of the injection site adverse events (i.e., 13 of the total of 14 subjects) with onset during the extension period occurred in subjects randomized to Byetta during the controlled period.

Reviewer Comment: The between-group difference between EQWS and Byetta during the extension period suggests the injection site reactions are product specific.

Withdrawal, SAEs, and Severe injection site reactions

Three subjects withdrew treatment because of injection site reactions from the EQWS group during the controlled period of study BCB118. 2 subjects withdrew treatment due to mild and moderate nodules, and one subject withdrew treatment due to severe injection site urticaria, compared to 1 treatment discontinuation from moderate injection site urticaria in the Byetta group.

Reviewer Comment: The one severe injection site urticaria occurred in the controlled arm of BCB118 in a subject exposed to EQWS leading to withdrawal. The subject required intramuscular epinephrine (as needed), oral prednisolone, ranitidine, and diphenhydramine.

No SAEs related to injection site reactions were reported during the Phase 3 studies.

The Applicant states there were no withdrawals, SAE, or severe injection site reactions in BCB120.

Table 42: Treatment discontinuation due to injection site reactions, safety population, controlled period, BCB118

		Byetta n (%)		EQWS n (%)	
Dictionary Derived Term	Severity Intensity	CONTROLLED TREATMENT PERIOD	EXTENSION TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	FOLLOW-UP PERIOD
Injection site nodule	MILD	0 (0.00%)	1 (0.68%)	2 (0.87%)	0 (0.00%)
	MODERATE	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.44%)
Injection site urticaria		1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	SEVERE	0 (0.00%)	0 (0.00%)	1 (0.44%)	0 (0.00%)
	Subjects(filtered)	1 (0.68%)	1 (0.68%)	3 (1.31%)	1 (0.44%)
	1stColItemSubjects	146 (100.00%)	146 (100.00%)	229 (100.00%)	229 (100.00%)

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Reviewer Comment: Review of the graphical patient profiles for subjects with the adverse event of injection site reactions appeared to demonstrate a few subjects[22] who withdrew from the study by choice but had injection site nodules at the time of withdrawal. An Information Request was sent asking for clarification for whether these subjects discontinued the study or treatment due to injection site reactions (August 22, 2017). The Applicant responded (August 31, 2017) none of the queried subjects discontinued study or study drug due to an adverse event.

Table 43: Potentially Immune Mediated Treatment-Emergent Injection Site Reactions by Antibody Status and Titer, controlled treatment period in subjects evaluable for TEABs, safety population, BCB118

	BCB118							
	Byetta n (%)				EQWS n (%)			
Dictionary Derived Term	High Positive n(%) n=143	Low Positive n(%) n=143	Any Positive n(%) n=143	Negative n(%) n=143	High Positive n(%) n=227	Low Positive n(%) n=227	Any Positive n(%) n=227	Negative n(%) n=227
Injection site nodule	0	0	0	1 (0.70%)	14 (6.17%)	11 (4.85%)	25 (11 01%)	11 (4 85%)
Injection site pruritus	0	1 (0.70%)	1 (0.70%)	0	6 (2.64%)	3 (1.32%)	9 (3 96%)	1 (0.44%)
Injection site erythema	0	0	0	0	5 (2 20%)	2 (0.88%)	7 (3 08%)	1 (0.44%)
Injection site oedema	0	0	0	0	1 (0.44%)	0 (0.00%)	1 (0.44%)	0
Injection site reaction	0	0	0	0	1 (0.44%)	1 (0.44%)	2 (0 88%)	0
Injection site hypersensitivity	1 (0.70%)	0	1 (0.70%)	0	0	0	0	0
Injection site induration	0	0	0	0	0	0	0	1 (0.44%)
Injection site inflammation	0	0	0	0	0	1 (0.44%)	1 (0.44%)	0
Injection site swelling	0	0	0	0	0	1 (0.44%)	1 (0.44%)	0
Injection site urticaria	1 (0.70%)	0	1 (0.70%)	0	0	1 (0.44%)	1 (0.44%)	0
Subjects(filtered)	2 (1.40%)	1 (0.70%)	3 (2.1%)	1 (0.70%)	21 (9.25%)	18 (7.93%)	39 (17%)	13 (5.73%)
1stColItemSubjects	143 (100 00%)	143 (100.00%)	143 (100.00%)	143 (100.00%)	227 (100.00%)	227 (100.00%)	227 (100.00%)	227 (100.00%)

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22 (b) (6)

(b) (6)

Reviewer Comment: The incidence of potentially immune-related injection site reactions was greater in subjects in the EQWS treatment group compared to Byetta group. These reactions are less commonly observed in antibody-negative patients and patients with low titer antibody compared with those with high titer antibody.

Table 44: Potentially Immune Mediated Treatment-Emergent Injection Site Reactions by Antibody Status and Titer, controlled treatment period in subjects evaluable for TEABs, safety population, BCB120

	BCB120			
	EQWS n (%)			
Dictionary Derived Term	High Positive n(%) n=166	Low Positive n(%) n=166	Any Positive n(%) n=166	Negative n(%) n=166
Injection site nodule	7 (4.22%)	6 (3.61%)	13 (7.83%)	1 (0.60%)
Injection site induration	4 (2.41%)	1 (0.60%)	5 (3.01%)	2 (1.20%)
Injection site pruritus	3 (1.81%)	2 (1.20%)	5 (3.01%)	0 (0.00%)
Injection site swelling	1 (0.60%)	1 (0.60%)	2 (1.20%)	0 (0.00%)
Injection site erythema	1 (0.60%)	1 (0.60%)	2 (1.20%)	0 (0.00%)
Injection site reaction	0 (0.00%)	1 (0.60%)	1 (0.60%)	0 (0.00%)
Subjects(filtered)	13 (7.83%)	9 (5.42%)	22 (13.25%)	3 (1.81%)

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Reviewer summary:

Although injection site nodules had the highest incidence compared to Byetta in the controlled period of BCB118, the rate of withdrawal generally appears low in the Phase 3 program, with no serious events.

Among ADA-positive patients, in the controlled treatment period, the incidence of injection site reactions was higher in patients with positive ADA than in patients with negative ADA.

Cardiovascular Safety:

The Applicant discusses cardiovascular safety as part of the EQWS NDA. However, the EQWS drug development program is not designed to adequately address cardiovascular outcomes. A currently ongoing post-marketing study (BCB109) is evaluating Bydureon's cardiovascular outcomes.

During the EOP2 meeting, the Agency agreed with relying on the cardiovascular safety data obtained to date from the Byetta and Bydureon formulations. The Agency agreed BCB109[23], Bydureon's outcome study, may fulfill the post-marketing cardiovascular risk assessment for EQWS.

[23] A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus

During the EOP2 the Agency encouraged the Applicant to consider testing a subset of EQWS subjects in the BCB109 PMR study to obtain controlled, long-term safety data.

Reviewer Comment: It does not appear that the Applicant has included EQWS subjects in the PMR cardiovascular outcome study for Bydureon.

To rely on the results of the Bydureon outcome study for evaluating EQWS's cardiovascular risk, the Applicant has to sufficiently demonstrate a bridge between EQWS to Bydureon and show similar effectiveness between the two exenatide formulations.

The clinical pharmacology review states through simulation and population PK modeling the Applicant has shown that EQWS at its steady state concentration achieves adequate PD effect relative to the known PD effect of exenatide; in other words, EQWS's EC50 is three times the established EC50 for exenatide.

Thus, relying on Bydureon's PMR study for the cardiovascular safety of EQWS appears reasonable.

The proposed label adequately informs that there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with exenatide.

Reviewer Comment: Exclusion of patients with advanced cardiac disease (i.e., NYHA class III-IV, unstable angina, stroke or myocardial infarction) decreases the overall cardiovascular risk compared to the enriched population in cardiovascular outcomes trials.

Adjudication process for cardiovascular safety

In the EQWS drug development program, the Clinical Events Classification Committee (CEC) was responsible for the adjudication process.

Cardiovascular events were adjudicated using pre-specified criteria by an adjudication committee blinded to study treatment. The following cardiac disorders were selected for evaluation and adjudication by the CEC:

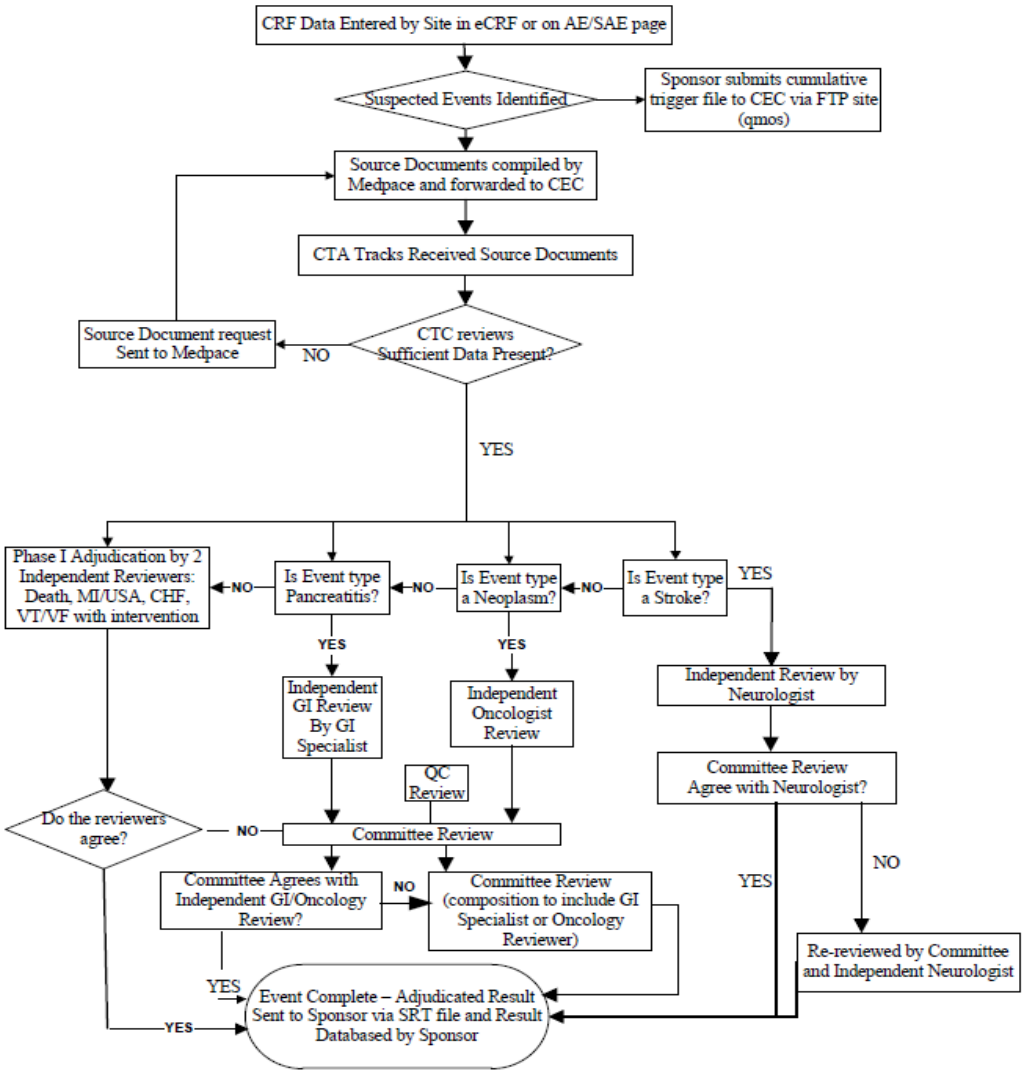
- Death; adjudicated as cardiovascular or non-cardiovascular [24]
- Myocardial infarction
- Unstable angina requiring hospitalization
- Non-fatal stroke

[24] All deaths will be considered cardiovascular unless an unequivocal non-cardiovascular cause of death can be established

- Congestive heart failure requiring hospitalization
- Ventricular tachycardia/ventricular fibrillation requiring intervention

The Applicant states a validated SAS program was used for identifying potential cardiovascular events from the adverse event or SAE data in the clinical database. The Applicant also assessed the clinical dataset with routine internal medical and safety reviews for identification of potential events, and a monthly medical review was conducted by the Physician Medical Monitor. Also, the CEC reviewed triggered event packets for additional possible cardiovascular events.

Figure 24: Adjudication process in the EQWS development program



Source: Excerpted from Clinical Study Report BCb118, page 4829.

Cardiovascular events

The Applicant states the exposure-adjusted cardiovascular event incidence and event rates (95% confidence interval [CI]) in the EQWS-treated subjects during the controlled period of BCB118 were 44.6 (14.5, 91.4) per 1000 patient-years and 44.2 (14.4, 90.6) per 1000 patient-years, respectively. In comparison, the corresponding values for the Byetta group were 29.8 (3.6, 82.9) per 1000 patient-years and 59.4 (16.2, 130.1) per 1000 patient-years.

In BCB120, the corresponding event rates for the placebo subjects was 36.3 (0.9, 134.0) and 72.5 (8.8, 202.1) per 1000 patient-years.

Adjudication of cardiovascular events

The Applicant states no cardiovascular or unknown deaths occurred in the EQWS development program. The Applicant states the CEC confirmed 3 out of 14 possible MACE events sent for adjudication. The confirmed MACE events are highlighted in Table 45.

Table 45: Cardiovascular events, safety population, controlled and extension periods, BCB118 and BCB120

	BCB118 controlled period		BCB118 extension period		BCB120 controlled period		
	Byetta n(%) n=146	EQWS n(%) n=229	EQWS n(%) n=193	Byetta to EQWS n(%) n=116	EQWS n(%) n=181	Sitagliptin n(%) n=122	Placebo n(%) n=61
Acute myocardial infarction	0	0	0	1 (0.86%)	0	0	1 (1.64%)
Angina pectoris	0	0	0	0	0	0	0
Atrial fibrillation	1 (0.68%)	0	0	1 (1.72%)	0	0	0
Bundle branch block bilateral	0	0	1 (0.51%)	0	0	0	0
Cardiac failure congestive	0	0	0	0	0	0	0
Cardiomyopathy	0	0	0	0	0	0	0
Coronary artery disease	0	0	0	2 (2.58%)	0	0	1 (1.64%)
Diastolic dysfunction	0	0	0	0	0	0	0
Dilatation ventricular	1 (0.68%)	0	0	0	0	0	0
Left ventricular dysfunction	1 (0.68%)	0	0	0	0	0	0
Myocardial infarction	0	1 (0.44%)	0	0	0	0	0
Palpitations	0	0	1 (0.51%)	0	0	0	0
Supraventricular tachycardia	0	1 (0.44%)	0	0	0	0	0
Tachycardia	0	0	1 (0.51%)	0	0	0	0
Ventricular extrasystoles	0	0	1 (0.51%)	0	0	0	0
Subjects(filtered)	2 (1.37%)	2 (0.87%)	2 (1.03%)	3 (2.58%)	0	0	1 (1.64%)

Yellow highlights indicate events adjudicated and confirmed as acute Myocardial Infarction.
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Reviewer Comment: No unfavorable cardiovascular imbalance was seen in the EQWS-treated subjects. See narratives below for the two EQWS-treated confirmed cardiovascular event.

- Subject [redacted] (b) (6) is a 56-year-old white male with a 4-year history of T2DM

who presented with sub-sternal, non-radiating, pressure-type chest pain and shortness of breath on Day 79 of the controlled study period. The subject had a family history of coronary artery disease. The troponin level was 1.62 ng/mL (0 to 0.05 ng/mL) consistent with a non-ST-segment elevation myocardial infarction. The subject was discharged from the hospital on Day 80 in a hemodynamically stable state and continued study drug.

- Subject (b) (6) was a 51-year-old white female with a 6-year history of T2DM who presented with upper anterior chest discomfort radiating to the jaw, mid-upper back and shoulder pain, shortness of breath, and mild diaphoresis, without nausea, vomiting or wheezing on study Day 288 (extension period). Pertinent medical history includes hypertension and obesity. ECG showed sinus tachycardia and changes consistent with an inferior wall myocardial infarction. The troponin level was 23.2 uIU/mL (0 to 0.78 uIU/mL) and the creatine kinase MB level was 190.97 ng/mL (0 to 5.0 ng/mL). The subject continued study drug.

Reviewer Comment:The narratives of the 2 adjudicated EQWS-treated subjects confirmed for a MACE event suggests pre-existing cardiovascular risk factors such as hyperlipidemia or hypertension may have contributed to the cardiovascular event.

Table 46: Cardiovascular SAEs, controlled and extension periods, safety population, BCB118 and BCB120

	BCB118		BCB120			
	Byetta n (%)		EQWS n (%)	EQWS n (%)	Placebo n (%)	Sitagliptin n (%)
Dictionary Derived Term	CONTROLLED TREATMENT PERIOD	EXTENSION TREATMENT PERIOD	CONTROLLED TREATMENT PERIOD	TREATMENT PERIOD	TREATMENT PERIOD	FOLLOW-UP PERIOD
Acute myocardial infarction	0	0	0	0	1 (1.64%)	0
	0	1 (0.86%)	0	0	0	0
Acute pulmonary oedema	1 (0.68%)	0	0	0	0	0
Atrial fibrillation	0	1 (0.86%)	0	0	0	0
	0	0	0	0	0	0
	0	0	0	0	0	0
Brain stem infarction	0	0	0	1 (0.55%)	0	0
Cardiac failure congestive	0	0	0	0	0	0
Carotid artery stenosis	0	1 (0.86%)	0	0	0	0
Chest pain	0	1 (0.86%)	0	0	0	0
Coronary artery disease	0	0	0	0	1 (1.64%)	0
	0	0	0	0	0	0
	0	1 (0.86%)	0	0	0	0
	0	0	0	0	0	1 (0.82%)
Dyspnoea	0	1 (0.86%)	0	0	0	0
Myocardial infarction	0	0	1 (0.44%)	0	0	0
	1 (0.68%)	5 (4.31%)	1 (0.44%)	1 (0.55%)	1 (1.64%)	1 (0.82%)
	146 (100.00%)	116 (100.00%)	229 (100.00%)	181 (100.00%)	61 (100.00%)	122 (100.00%)

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Reviewer Comment: Review of the narratives of the cardiac SAEs show the underlying risk factors confounds attribution of causality to EQWS.

Arrhythmias

Most of the arrhythmia PTs are single events. No withdrawal due to arrhythmia occurred. No narratives of arrhythmias have been submitted. Below are two graphical patient profiles for twi two SAE adverse events of atrial fibrillation.

- An SAE of severe atrial fibrillation occurred in a 64-year-old White male with T2DM and baseline HbA1c 7.6% treated with metformin with past medical history of hypertension, hyperlipidemia, obesity, and sleep apnea. Subject was randomized to Byetta and continued on EQWS during the extension period. The SAE of atrial fibrillation occurred during the extension period on EQWS.

- An SAE of moderate atrial fibrilliation occurred in a 70-year-old White male with T2DM and baseline HbA1c 9.9% on metformin, TZD, and SU and mild renal impairment were randomized to Byetta and switched to EQWS during the extension period. Past medical history was significant for obesity, COPD, hypertension, and hyperlipidemia. The subject developed an SAE of moderate atrial fibrillation at around the same time as a COPD exacerbation and bronchitis during the extension period on EQWS. The same subject had an episode of acute pulmonary edema while on Byetta during the first 28 weeks of the study.

8.6. Specific Safety Studies/Clinical Trials

None

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

During the controlled period of BCB118, three confirmed neoplasms by the adjudication committee were reported in the EQWS-treated subjects (breast cancer, fibroadenoma of breast, and benign neoplasm of skin), and an adverse event of basal cell carcinoma was reported in a subject in the Byetta group.

Another three confirmed neoplasms were reported during the extension period of BCB118: 1 advers event each of malignant melanoma, hepatocellular carcinoma, and basal cell carcinoma.

The Applicant states among all of the confirmed adverse events of neoplasm, study treatment was discontinued only in the subjects with breast cancer and hepatocellular carcinoma.

An additional adverse event of acute myeloid leukemia (SAE and severe) was reported in a 49-year-old White female subject during the follow-up period of BCB118, ten days after the last dose of Byetta (Day 115 onset).

The narrative of an adverse event of pancreatic carcinoma is discussed in page 79 of this review.

8.7.2. Human Reproduction and Pregnancy

In BCB118 the following two pregnancies occurred:

Subject [redacted] a 41-year-old White female found pregnant after two month exposure to EQWS. The study treatment was discontinued. The subject gave birth to a normal, healthy baby.

Subject [redacted] (b) (6) a 43-year-old White female in the Byetta group completed the 52-week study. At Week 52 she had a positive serum pregnancy test. The subject had a spontaneous abortion shortly after.

8.7.3. Pediatrics and Assessment of Effects on Growth

The Applicant has been granted a partial waiver for pediatric subjects < 10 years old and a deferral for 10 to < 18 years old for pediatric studies. The Division (May 27, 2016) and PeRC (August 16, 2017) agreed with the pediatric plan proposed in the iPSP (BCB114). The agreed-upon iPSP proposes [redacted] (b) (4)

(b) (4)

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In BCB118 there was one accidental overdose in the Byetta group. No overdoses occurred in the EQWS group in the Phase 3 studies.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Relevant information related to post-marketing safety issues is discussed with each adverse event of special interest in section 8.5.

8.8.2. Expectations on Safety in the Postmarket Setting

Not applicable.

8.9. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Evaluation of the EQWS database suggests that the risks are acceptable at this time and that a favorable risk/benefit profile has been presented for EQWS for the intended indication.

The overall safety profile for EQWS is consistent with Bydureon and does not raise additional safety concerns. Each trial was evaluated individually.

There was no concerning pattern of SAEs for EQWS-treated patients. The risk of SAEs and drop-outs due to adverse events was lower for EQWS than for Byetta or placebo.

The most common adverse events for EQWS included injection site nodules and nausea.

Similar to Bydureon, EQWS had a noticeable imbalance for injection site reactions driven by the adverse event injection site nodules compared to Byetta. No serious injection site reaction occurred in EQWS-treated subjects.

74% of EQWS treated subjects were antibody-positive during the Phase 3 controlled periods. A higher percentage of subjects with injection site reactions had positive antibodies, especially higher titer antibodies. A slightly higher percentage of subjects with positive antibodies had a possible allergic reaction (e.g., rash, dermatitis) in the EQWS group compared to Byetta, but none were serious. This conclusion is limited due to the small number of patients with allergic reactions. Exploratory analyses suggest a possible smaller reduction in HbA1c at Week 28 and Week 52 with increasing antibody titers. However, the sample size of these sub-group exploratory analyses is small limiting data interpretation. Cross-reactivity of anti-exenatide antibodies to endogenous GLP-1 and glucagon and neutralizing antibodies were not assessed in the EQWS clinical program. Refer to Section 12 of this review for the postmarketing commitments issued by OBP (b) (4)

(b) (4)

The Applicant did not report any severe hypoglycemia in the EQWS-treated subjects. However, one subject in the Byetta group (hypoglycemia symptom unconsciousness and requiring assistance) and three subjects in the EQWS group were identified during the review that qualifiy as severe hypoglycemia according to the American Diabetes Association hypoglycemia definitions (hypoglycemia symptom confusion and requiring assistance).

There were no cases of fatal pancreatitis. 2 treatment-emergent SAE events of pancreatitis occurred in the EQWS group leading to treatment and study withdrawal.

One subject originally treated with Byetta who switched to EQWS during the extension period of BCB118 developed pancreatic carcinoma. The patient exposure is too small to assess risk for pancreatic cancer.

No Medullary Thyroid Carcinoma occurred in the EQWS clinical program.

No cases fulfilled the biochemical definition of Hy's law in the EQWS program.

EQWS has not been studied in patients with severe renal impairment.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened, and no external consultations were obtained

10 Labeling Recommendations

10.1.1. Prescribing Information

Prescribing information will be addressed in internal labeling meetings and labeling negotiation with Applicant. Suggestions have been made in the proposed label document.

10.1.2. Patient Labeling

See above.

10.1.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1.1. Safety Issue(s) that Warrant Consideration of a REMS

None

11.1.2. Conditions of Use to Address Safety Issue(s)

None

11.1.3. Recommendations on REMS

None

12 Postmarketing Requirements and Commitments

Office of Biological Products (OBP) requested (August 18, 2017) the Applicant to submit the neutralization assay results for EQWS, and validation reports for evaluating the cross-reactivity of anti-exenatide antibody to GLP-1, glucagon, and sequence irrelevant peptides. The Applicant responded (September 1, 2017) that ADA was not tested for neutralizing activity or the cross-reactivity with GLP-1 and glucagon in the EQWS clinical program.

The OBP reivewer states while detection of neutralizing activity may be of mechanistic interest, possible cross-reactivity to endogenous GLP-1 may pose a clinical risk. OBP's reviewer states the historic Bydureon assays for evaluating the cross-reactivity of anti-exenatide antibody to GLP-1 and glucagon were not adequately sensitive. Thus, OBP issued three postmarketing commitments as below:

1. (b) (4)
2. Test samples from clinical trials BCB118 and BCB120 for the presence of anti-GLP-1 and anti-glucagon antibodies using (b) (4)
3. Validate the sensitivity of the version of ELISA-0308 method used for the detection of anti-exenatide antibodies (ADA) in patient samples collected in NDA 209210 clinical studies BCB118 and BCB120.

Appendix

13.1.1. Financial Disclosure

Covered Clinical Study: BCB118 and BCB120

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified:		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: X Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes: X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes: X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes: X	No ☐ (Request explanation from Applicant)

One investigator received approximately $33,000 honoraria for speaking and for consulting; The Applicant states the investigator enrolled (b) (6) subjects and randomized (b) (6) subjects out of a total of 377 randomized subjects for the trial BCB118, and in BCB120, the same investigator enrolled (b) (6) subjects and randomized (b) (6) subjects out of a total of 365 randomized subjects for the trial. It is unlikely that the integrity of the trial was affected by the investigator's contribution to the studies.

Clinical Review
Mahtab Niyyati, MD
NDA 209210
BCise, Exenatide Once-Weekly Suspension (EQWS)

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAHTAB NIYYATI
10/19/2017

LISA B YANOFF
10/19/2017