CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	Bydureon (EQW): NDA 022200 Supplement 031 Bydureon BCise (EQWS): NDA 209210 Supplement 017
Priority or Standard	Priority
Submit Date(s)	January 22, 2021
Received Date(s)	January 22, 2021
PDUFA Goal Date	July 21, 2021
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Reviewer Name(s)	Mahtab Niyyati
Review Completion Date	June 29, 2021
Established/Proper Name	BYDUREON (exenatide extended-release) injectable suspension BYDUREON BCISE (exenatide extended-release) injectable suspension
Trade Name	Bydureon Bydureon BCise
Applicant	AstraZeneca
Dosage Form(s)	Bydureon 2 mg subcutaneously (SC) administered via a vial and prefilled syringe single-dose tray (SDT) Or a prefilled dual chamber pen (DCP) Bydureon BCise 2 mg SC administered via an autoinjector
Applicant Proposed Dosing Regimen(s)	2 mg once weekly SC
Applicant Proposed Indication(s)/Population(s)	Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus (T2DM)
Recommendation on Regulatory Action	Approval

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
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
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
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 or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Exenatide is a synthetic glucagon like peptide-1 (GLP-1) receptor agonist; its approved formulations include Byetta (dosed as a twice daily subcutaneous [SC] injection), Bydureon (dosed once weekly and packaged as a lyophilized powder to be mixed with an aqueous diluent prior to injection via either a single dose tray or a single dose dual-chamber pen), and Bydureon BCise (dosed once weekly and packaged as an oil-based pre-mixed suspension in an autoinjector).

The three exenatide products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The marketed dose of Bydureon and Bydureon BCise for glycemic control in adults with T2DM is 2 mg subcutaneously once weekly. The Applicant has proposed this same dosing regimen for the proposed pediatric population.

Bydureon and Bydureon BCise would be the first once-weekly treatment for glycemic control in the pediatric T2DM population aged 10 years and older.

In this supplemental New Drug Application (sNDA), AstraZeneca submitted a pediatric study (BCB114) to address the PREA-mandated post-marketing requirement 1860-1 for Bydureon (EQW) NDA 022000 (approval date January 27, 2012) and Bydureon BCise (EQWS) NDA 209210 (approval date October 20, 2017) issued on January 27, 2012, following approval of Bydureon. Study BCB114 also serves to fulfill the terms of the Written Request (WR) for exenatide for pediatric studies issued under the Best Pharmaceuticals for Children Act (BPCA).

With this submission, the Applicant is requesting to expand the indication for Bydureon and Bydureon BCise to "as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus" based on a single adequate and well controlled study (BCB114) evaluating Bydureon as monotherapy or in combination with oral antidiabetics (metformin, sulfonylurea) and/or insulin in pediatric patients 10 years and older with T2DM.

As detailed below the Agency has concluded that clinical data submitted is sufficient to fulfill PMR 1860-1.

The Pediatric Exclusivity Board agreed that study BCB114 fulfilled the Written Request for exenatide issued on March 29, 2006, and last amended on July 16, 2020, in accordance with the

Best Pharmaceuticals for Children Act (BPCA). Pediatric exclusivity was granted for studies conducted with exenatide effective April 1, 2021.

In this review the products will be referred to with the following abbreviations: Bydureon= EQW and BCise=EQWS, unless noted otherwise.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness for EQW and EQWS as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus (T2DM). The substantial evidence of effectiveness provided by the Applicant consisted of one adequate and well-controlled trial and confirmatory evidence.

The single pediatric study (BCB114) was a randomized, placebo-controlled trial that investigated the effect of EQW in lowering HbA1c as an adjunct to diet and exercise in pediatric patients with T2DM inadequately controlled on oral antidiabetic agents and/or insulin. HbA1c is considered by the FDA as a validated surrogate endpoint allowing use for regulatory decisions, as the HbA1c is a standardized assay and a causal link between glucose control via HbA1c and reductions in microvascular diabetic complications has been established. While the statistical superiority of EQW over placebo was borderline using a conservative approach for missing data and inclusion of data regardless of adherence or rescue, the prespecified MMRM analysis that included data regardless of rescue or discontinuation demonstrated superiority. Given the similar trend in treatment effect in either analysis (and generally a similar safety profile to the adult population as demonstrated in study BCB114), the collective evidence from the prespecified (MMRM) and more conservative (washout imputations) analysis of the primary endpoint supports effectiveness of EQW in the pediatric population 10 years of age and older. In addition, the treatment effect of a 0.7% placebo adjusted reduction in HbA1c is clinically meaningful.

As EQW and EQWS are approved to improve glycemic control in adults with T2DM, the establishment of efficacy in adults provides confirmatory evidence of effectiveness (i.e., pediatric extrapolation). FDA guidance[1] states, "if the FDA determines based on relevant science that data from one adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to establish effectiveness, FDA may consider such data and evidence to constitute substantial evidence."

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

There is an unmet need for new treatment options for pediatric patients with T2DM as the approved therapies are limited to metformin, liraglutide (once-daily SC injections), and insulin. Pediatric T2DM is a serious disease with recent clinical trials suggesting some pediatric patients may experience a rapid progression of disease or an accelerated development of diabetes complications and comorbidities. Pediatric T2DM trials are very difficult to conduct, however, because of severe recruitment challenges. Based on this, the single adequate and well-controlled pediatric trial plus confirmatory evidence from adequate and well controlled trials in adults serve as an appropriate regulatory pathway for providing substantial evidence of effectiveness for EQW.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The prevalence of pediatric type 2 diabetes mellitus (T2DM) has been increasing in the United States over the past 20 years. Recent clinical trials in pediatric T2DM suggest some pediatric patients may experience a rapid progression of disease or an accelerated development of diabetes complications and comorbidities. Treatment options for pediatric T2DM are limited, and include metformin, liraglutide, and insulin. Therefore, there is an unmet need for new treatment options for pediatric patients with T2DM.

On January 22, 2021, AstraZeneca submitted supplemental new drug application (sNDA) for EQW (Bydureon) and EQWS (Bydureon BCise) proposing a pediatric indication based on results of a single adequate and well-controlled pediatric phase 3 study (BCB114). BCB114 was a randomized (5:2) multicenter study that enrolled 82 patients aged 11 to < 18 years old with T2DM, with 59 patients randomized to EQW and 23 patients randomized to placebo, administered once weekly subcutaneously. The study consisted of 4 periods; a screening period for 5 weeks, a 24-week double-blind placebo-controlled assessment period, a 28-week open-label uncontrolled extension period where patients randomized to placebo switched to EQW, and a post-treatment follow-up period for 10 weeks. In addition to receiving study medication, all patients were to participate in a lifestyle intervention program encompassing diet and physical activity modification. The patient population exposed to EQW generally reflects the real-world target population and consists of pediatric patients aged 11 to 17 years old with T2DM (mean T2DM duration of about 2.2 years and mean HbA1c at baseline of 8.13%) and obesity (72.4% in the ≥ 97% percentile Body Mass Index [BMI] category; mean BMI 36.8 kg/m^2). Most patients were treated at baseline with either metformin (22 [37.9%]) or insulin and metformin (21 [36.2%]). Most were White (39.7%) and Black or African American (29.3%), and 46.3% were Hispanic or Latino. 60.3% were from North America.

Study BCB114 demonstrated that EQW 2 mg once weekly reduced HbA1c vs. placebo; using a conservative approach (washout imputations) for analyzing the primary endpoint, the point estimate difference in the HbA1c % reduction between EQW and placebo was -0.71; 95% CI -1.42, 0 (borderline superiority), while the pre-specified MMRM approach that included all patients irrespective of adherence or rescue patients demonstrated a point estimate difference of -0.87; 95% CI -1.51, -0.23 (demonstrated superiority). The observed HbA1c reduction as evidenced by the prespecified (MMRM) and more conservative (washout imputations) analysis of the primary endpoint at Week 24 supports effectiveness of EQW in the proposed pediatric population and is clinically meaningful. HbA1c is considered by the FDA as a validated surrogate endpoint allowing use for regulatory decisions, as the HbA1c is a standardized assay and a causal link between glucose control via HbA1c and reductions in microvascular diabetic complications has been established. Therefore, the improved glycemic control as demonstrated in study BCB114 is expected to result in clinical benefit of lower risk of chronic complications of persistent hyperglycemia such as microvascular disease risk reduction.

In patients randomized to EQW, the Applicant's descriptive analysis (excluding data after rescue or premature discontinuation) shows the mean HbA1c change from baseline gradually increased over 52 weeks returning to approximate baseline levels by Week 52 (-0.1%) suggesting a possible lack of durability of glycemic control with EQW treatment in study BCB114, although more likely suggesting rapid disease progression given the notable increase in HbA1c at 24 weeks in the placebo arm. Lack of a control arm over the entire 52-week period limits conclusions.

A subgroup analysis measuring the treatment effect in change in HbA1c for age, gender, race, and region (United States and outside of United States) demonstrated consistency of effect.

The overall safety profile for EQW in study BCB114 is generally similar to the known and labeled risks in adults with T2DM and no new safety issues were identified in the study that warrant Contraindications or Warnings and Precautions beyond what are already in the label. In general, the incidence of treatment-emergent serious adverse events (SAE) in study BCB114 was low; during the controlled assessment period 2 (3.4%) patients on EQW compared to 1 (4.3%) patient on placebo experienced a SAE. In the controlled assessment period, the most frequent adverse reactions were related to gastrointestinal events, hypoglycemia, and injection site reactions.). During the controlled assessment period 1 (1.7%) patient on EQW reported an event of severe hypoglycemia (requiring assistance) versus 0 on placebo. Consistent with the label, most of the patients (6 [21.4%]) who experienced an event of hypoglycemia were treated at baseline with insulin compared to 2 (6.5%) patients who were not treated with insulin at baseline.

Antibodies to exenatide (anti-drug antibodies [ADA]) were observed in most of the patients (93%) in the EQW group over 52 weeks and up to 10-week follow-up period during the study; more patients (63.2%) developed high antibody titers (≥ 625) compared to 29.8% who developed low antibody titers (< 625). Acknowledging the limitations of cross-comparing immunogenicity assessments across programs, the overall immune response to exenatide appears higher in pediatric patients compared to adults with T2DM and antibody titers in ADA positive pediatric patients appear to be higher than in ADA positive adult patients. Consistent with labeled information from adult studies, pediatric patients with high titer antibody to EQW showed a lower reduction in mean HbA1c from baseline (0.07%) compared to those with low titer antibody (-0.73%). The attenuation of HbA1c reduction in patients with high titer antibodies suggest an interference of ADA with drug effect. This may include a possible cross-reaction with endogenous GLP-1 that neutralizes its function. The Applicant did not assess cross-reactivity to endogenous GLP-1 or neutralizing antibodies in study BCB114 but has evaluated cross-reaction to GLP-1 and glucagon in the samples from adult trials evaluating EQWS which demonstrated a potential for development of antibodies cross-reactive with endogenous GLP-1 and glucagon in patients with high titer antibody. The incidence was low (1 [0.8%]) of 118 patients with high-titer antibody) and the clinical significance of these antibodies is currently not known. Due to the possible difference in the overall immune response between adult and

pediatric patients, the cross-reactivity results in the T2DM adult patients may not be applicable to the pediatric patients. However, an assessment of cross-reactivity to GLP-1/glucagon in the pediatric patients may not be needed at this time as no serious safety concern with clinical consequence was observed in the study and the possible impact on efficacy observed in study BCB114 is consistent with the labeled information in adults.

The incidence of injection site reactions during the controlled assessment period was low and generally balanced between the treatment arms. None were serious or led to study drug discontinuation. In the controlled assessment period, all the injection site reactions (except 1 event of injection site pruritus) in the EQW arm occurred in patients who at any point during the study developed high titer ADA.

Over 70% of randomized patients were in the later stages of puberty and had nearly completed linear growth at baseline therefore an evaluation of a possible drug effect on pubertal progression and growth is limited. Residual uncertainties include a possible long-term effect on growth and development (e.g., through a possible effect on pathways such as the hypothalamic-pituitary-adrenal axis as generally described in the literature for GLP-1 receptor agonists[2]). Given that patients in the postmarket setting treated with EQW will likely include pediatric patients with advanced pubertal status and near completed growth, a potential effect on growth may not be clinically significant. As T2DM rarely occurs in pediatric patients < 10 years old, a growth and development study in less mature T2DM patients is not necessary at this time.

Overall, most of the adverse events identified in the BCB114 study had no serious clinical consequence. These risks appear to be acceptable when taking the expected benefits into consideration and can be adequately communicated with product labeling. Some residual uncertainties include a possible lack of durability of effect on HbA1c lowering and/or possible unidentified risks that may be reported postmarket.

Of note, the population PK and exposure-response analysis demonstrate the exenatide plasma concentrations and HbA1c measurements at steady state following administration of EQW were both comparable in adolescent and adults with T2DM (with anti-drug antibody [ADA] titer ≤ 625). Because the previous population PK analysis showed similarity between EQW and EQWS in adults, the PK behavior of EQWS in adolescent patients with T2DM is expected to be similar to that of EQW. This suggests that the effect of EQWS on HbA1c is expected not to be different from the observed effect of EQW on HbA1c in study BCB114. In addition, the overall safety profile for EQWS was shown to be consistent with EQW in the adult population . Therefore, information from study BCB114 could be included in the EQWS label.

[2] Am J Physiol Endocrinol Metab. 2013 May 15;304(10):E1105-17; Clin Endocrinol Metab 104: 202–208, 2019.

The Applicant, however, has not completed human factors validation testing of EQWS in pediatric patients to support the proposed pediatric indication for EQWS. Division of Medication Error Prevention and Analysis (DMEPA) recommended that a Human Factor validation study to identify usability requirements, analyze residual risk with the autoinjector, and demonstrate optimization of the interface is needed to adequately support the safe and effective use of EQWS in the pediatric patients. As there is an unmet need for therapies in pediatric patients with T2DM and the possible risk of medication errors could be addressed through labeling, the Division and DMEPA concluded the Human Factors study could be conducted as a Postmarketing Commitment.

I recommend approval for the sNDA submitted to both NDA 022200 and 209210. My recommendation is consistent with the recommendations of all review disciplines. This recommendation is contingent on agreement on labeling to replace the HbA1c results based on MMRM proposed by the Applicant with HbA1c results based on washout imputations and analysis of covariance model (ANCOVA).

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The prevalence of pediatric type 2 diabetes (T2DM) has been increasing in the United States. • Pediatric T2DM is similar to adult T2DM but with more rapid disease progression. Recent clinical trials in pediatric T2DM suggests that while a subset of patients achieve glycemic control on metformin monotherapy, many patients experience rapid progression of beta-cell dysfunction and glycemic failure.	Pediatric patients with T2DM are at risk of microvascular complications and comorbidities because of lack of adequate glycemic control. Full extrapolation from adults is not appropriate because efficacy should be demonstrated in pediatrics due to differences in disease process.
Current Treatment Options	• Metformin, liraglutide, and insulin are current therapeutic options for youth with T2DM.	There are limited treatment options for pediatric patients with T2DM.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Liraglutide (pediatric approval in 2019) appears to provide ~ 1% reduction in HbA1c compared to placebo.	There is an unmet need for therapies in pediatric patients with type 2 diabetes mellitus.
Benefit	• The primary efficacy endpoint was change from baseline in hemoglobin A1c (HbA1c) after 24 weeks of treatment. The prespecified primary efficacy analysis excluding post-rescue and post-discontinuation data and utilized the longitudinal repeated measures (MMRM) analysis with missing at random assumption (MAR) demonstrated superiority of EQW over placebo at Week 24. • The statistical superiority of EQW over placebo was borderline (-0.71; 95% CI (-1.42, 0]) when the Agency's recommended methodology considered to be the most appropriate analysis technique (including data regardless of adherence or rescue and placebo-based multiple washout imputations to impute for patients without HbA1c data at Week 24) was utilized. • The MMRM analysis that included data regardless of rescue or discontinuation demonstrated superiority (-0.87; 95% CI [-1.51, -0.2]). • The sample size for this trial was small (prespecified power of 74%), especially the small number of patients on placebo (the randomization ratio was 5:2). Therefore, the confidence interval for the change in HbA1c was large.	The observed reduction in HbA1c at Week 24 with EQW treatment in study BCB114 is clinically meaningful. The -0.71 (95% CI [0-1.42, 0]) placebo-adjusted HbA1c reduction in the pediatric population is comparable to the placebo-adjusted HbA1c reduction (-0.64 95% CI [-0.83, -0.45]) observed in the adult population at Week 28 when EQW was added on to insulin glargine and/or metformin. A causal link between glucose control via HbA1c (a validated surrogate endpoint) and reductions in microvascular diabetic complications has been established. Therefore, the improved glycemic control as demonstrated in study BCB114 is expected to result in clinical benefit of a lower risk of chronic complications of hyperglycemia such as microvascular disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The numerical results for the secondary endpoint of change in Fasting Plasma Glucose (FPG) did not demonstrate superiority of EQW over placebo: -25.58 (-55.77, 4.61) 95% confidence interval. • Patients on EQW experienced some reductions in body weight while patients on placebo did not experience weight changes. The treatment effect estimates for patients on EQW were larger, and the 95% CIs overlapped at each visit (similar to results for FPG). The numerical results for the secondary endpoint of change in body weight did not demonstrate superiority of EQW over placebo: -0.99 (-3.44, 1.46) 95% confidence interval. • In the controlled assessment period, most of the subgroup-based results did not show superiority of EQW over placebo. The superiority was only observed among female study participants and patients outside of the United States. • During the controlled assessment period, the Applicant states 1 of 58 patients required rescue due to the failure to maintain glycemic control at Week 24 (ITT population). A review of the data suggests additional patients may have met the pre-defined rescue criteria but not recorded as rescue. • The population PK and exposure-response analysis demonstrate the exenatide plasma concentrations and HbA1c measurements at steady	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	state following administration of EQW were both comparable in adolescent and adults with T2DM. Because the previous population PK analysis showed similarity between EQW and EQWS in adults, the PK behavior of EQWS in adolescent patients with T2DM is expected to be similar to that of EQW. This suggests that the effect of EQWS on HbA1c is expected not to be different from the observed effect of EQW on HbA1c in study BCB114. In addition, the safety profiles of EQWS in T2DM adults was consistent with the known risks with EQW.	
Risk and Risk Management	• No deaths occurred in study BCB114. • The frequency of serious adverse events was generally low with no clinically relevant imbalances between treatment arms during the controlled assessment period. • The frequency of severe hypoglycemia as defined by ADA was low during the controlled assessment period. An increased risk of hypoglycemia was generally observed when EQW was used along with background insulin therapy, however none of these events were serious adverse events and the overall frequency during the controlled assessment period was low (i.e. 6 (21.4%) of patients on EQW treated at baseline with insulin experienced an event of hypoglycemia compared to 2 (6.5%) who were not treated with insulin at baseline. • Antibodies to exenatide were observed in most of the patients (93%) in the EQW group over 52 weeks and up to 10-week follow-up period during	The safety profile of EQW has been well characterized in the adult patients with T2DM, and the safety issues observed in study BCB114 were generally similar to those reported in adult studies. The label adequately informs of the possible risks of treatment with EQW in the pediatric population. Due to the possible difference in the overall immune response between adult and pediatric patients, the cross-reactivity results in the T2DM adult patients may not be applicable to the pediatric patients. However, an assessment of cross-reactivity to GLP-1/glucagon in the pediatric patients may not be needed at this time as no serious safety concern was observed in the study and the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the study; most patients (63.2%) developed high antibody titers (≥ 625) compared to 29.8% who developed low antibody titers (< 625). The immunogenicity data suggests that exenatide was highly immunogenic in the pediatric patients evaluated in study BCB114. No serious potential immune related adverse event with clinical consequence was observed in the study. The attenuation of HbA1c in patients with high titer antibodies suggest an interference of anti-drug antibody (ADA) with drug effect. This may include a possible cross-reaction with endogenous GLP-1 that neutralizes its function too. The Applicant has not assessed cross-reactivity or neutralizing antibodies in study BCB114 but has evaluated cross-reaction to GLP-1 and glucagon in the samples from adult trials. • While the data clearly suggests a trend exists between the change in mean HbA1c and the level of the ADA titer, due to variability of HbA1c response within each titer category, a reliable prediction of the HbA1c response per ADA titer level for an individual patient cannot be determined. • Over 70% of randomized patients were in the later stages of puberty and had nearly completed linear growth at baseline, therefore an evaluation of a possible drug effect on pubertal progression and growth is limited.	possible impact on efficacy observed in study BCB114 is consistent with the labeled information in adults. As T2DM rarely occurs in pediatric patients < 10 years old, a growth and development study in less mature T2DM patients is not necessary at this time.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric type 2 diabetes mellitus (T2DM) has been increasing over the past 20 years[3]. The prevalence of pediatric T2DM appears to be higher in certain racial and ethnic groups (including Hispanic, American Indian and African American adolescents) and in adolescent girls. Over 80% of pediatric patients with T2DM are overweight or obese. The onset of pediatric T2DM often coincides with pubertal insulin resistance. While the pathophysiology of pediatric T2DM is similar to adults (non-autoimmune beta cell failure along with insulin resistance), the degree of insulin resistance in pediatric appears to be more severe compared to adults even at the same degree of adiposity. Data from the TODAY study suggested a heterogeneity in T2DM progression in pediatric patients with some experiencing a rapid progression of disease. While the predictors of treatment response in pediatric T2DM is currently unclear, intrinsic differences in beta cell function may in part contribute to the observed heterogeneity[4].

Pediatric patients with T2DM are at risk for developing microvascular complications (nephropathy, retinopathy, and neuropathy), which are caused by chronic hyperglycemia. In both adults and children with T2DM, the risk of microvascular complications increases with poor glycemic control and duration of the disease. Some authors suggest that youth with T2DM have a higher risk for vascular complications compared with those with type 1 diabetes (after adjustment for age, disease duration, glycemic control, and obesity[5]). Youth with T2DM are at high risk for clinically important cardiovascular disease earlier in adult life than generally expected[6]. Diabetic ketoacidosis and hyperosmolar hyperglycemic state are acute complications that occasionally develop in adolescent patients with T2DM. Identifying and treating children and adolescents with T2DM will improve long-term outcomes.

2.2. Analysis of Current Treatment Options

There is an unmet need for T2DM pediatric therapeutics. The current treatment options approved for pediatric T2DM is limited and include metformin hydrochloride (pediatric approval in 2000), liraglutide (pediatric approval in 2019), and insulin.

Metformin products with an indication for use in pediatric T2DM 10 years and older include metformin hydrochloride immediate release tablets, immediate release oral solution and extended release oral suspension. Liraglutide is a GLP-1 receptor agonist available as an injection for subcutaneous use in pre-filled single patient-use pens delivering doses of 0.6 mg, 1.2 mg or 1.8 mg. Pediatric dosing instructions recommend initiating liraglutide at 0.6 mg daily for at least one week, to increase the dose to 1.2 mg daily if additional glycemic control is

[3] Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. Diabetes Care. 2016;39 (9):1635-1642.
[4] Zeitler P. Progress in understanding youth-onset type 2 diabetes in the United States: recent lessons from clinical trials. World J Pediatr. 2019;15(4):315-321.
[5] JAMA. 2017;317(8):825.
[6] Diabetes Care. 2013;36(12):3863.

required, and to increase to 1.8 mg daily after at least 1 week of treatment with the 1.2 mg dose if additional glycemic control is still required.

Some of the subcutaneous insulin products with an indication "to improve glycemic control in adults and children with diabetes mellitus" include Humulin R, Novolin R, Humulin N, Novolin N, Novolin 70/30, Humulin R U-500, Apidra, FIASP, Humalog, Levemir, Novolog, Ryzodeg 70/30 (insulin degludec and insulin aspart), Toujeo (insulin glargine), and Tresiba (insulin degludec).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Exenatide is marketed in the United States under 3 trade names: Byetta, Bydureon (EQW), and Bydureon BCise (EQWS), all indicated as an adjunct to diet and exercise for glycemic control in adult patients with T2DM. The latter two products are long-acting GLP-1 agonists and are marketed with the same dose and regimen (2 mg once weekly subcutaneous injection).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was conducted with the marketed EQW product to fulfill PMR 1860-6 issued to NDA 022200 (EQW) to evaluate the long-term effects of EQW on cardiovascular events and some other safety variables. The Agency concluded that the data from EXSCEL supported a conclusion that EQW and EQWS are not associated with an unacceptable increase in the risk of major adverse cardiovascular event (MACE), but did not provide sufficient evidence to support the conclusion that these products are superior to placebo in reducing the risk of MACE. Therefore Section 14 of the Prescribing Information of both EQW and EQWS was updated with the MACE data from EXSCEL (the data was used to update the label for EQWS based on similarity of the PK, population PK, and PD profiles of the two products in adults).

3.2. Summary of Presubmission/Submission Regulatory Activity

The presubmission regulatory communications pertaining to the Statistical Analysis Plan, the agreed initial Pediatric Study Plan, and the toxicology signal of accelerated/delayed sexual maturation are addressed in Section 6.1.1, Section 4.6, and Section **Error! Reference source not found.** of this review respectively.

The pre-sNDA Type B meeting (Written Responses dated September 14, 2020) mainly addressed the content and format of the proposed supplement to both NDA 022200 for EQW and NDA 209210 for EQWS.

3.3. Foreign Regulatory Actions and Marketing History

The Applicant states EQW and EQWS are approved in the European Union for use in adults 18 years and older with T2DM to improve glycemic control in combination with other glucose-lowering products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycemic control. The Applicant states the single dose tray (approved in the European Union on June 17, 2011) and the dual chamber pen presentations (approved in European Union on October 1, 2014) of EQW have been approved in over 90 countries, including Canada, Australia, 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)

There were no efficacy/safety or scientific misconduct concerns identified during the review that resulted in a request for an OSI review.

4.2. Product Quality

There are no new chemistry, manufacturing and controls (CMC) or sterility data. Dr. Thammana, the CMC reviewer, recommends approval and states the supplement is adequate from CMC perspective. Dr. Thammana recommends granting the Applicant's request for categorical exclusion from preparation of environmental assessment.

4.3. Clinical Microbiology

There are no new data with regards to microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

There are no new data with regards to pharmacology/toxicology information in the submission.

4.5. Clinical Pharmacology

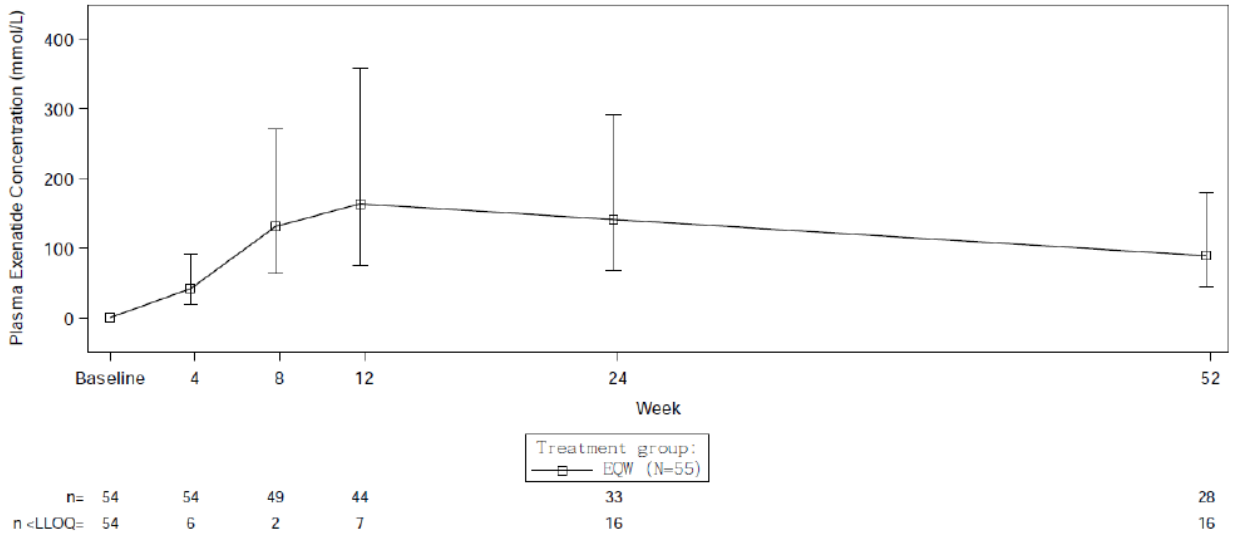
Dr. Johnny Lau and Dr. Yangbing Li reviewed the clinical pharmacology data in the submission and recommend approval. Office of Study Integrity and Surveillance (OSIS) inspections were not requested for this application.

Clinical pharmacology stated that overall, the bioanalytical assay for measuring exenatide in plasma samples was acceptable for study BCB114. In addition, the bioanalytical methods for studies used in the exenatide population PK and exposure-response analysis were comparable.

The Applicant states the 2 mg weekly dose of EQW (approved dose in adults) was selected based on information from a previous study with exenatide (immediate-release formulation) conducted in adolescents (study 2993-124) and the results of previous studies with EQW conducted in adults.

Clinical pharmacology states in study BCB114 (for measurable PK samples) the geometric mean plasma exenatide concentrations increased between randomization and Week 8, then remained relatively constant from Week 8 to Week 52 suggesting that steady-state concentrations were reached in the pediatric population in study BCB114.

Figure 1: Geometric Mean plasma exenatide concentration versus time profile in study BCB114



Source: BCB114 CSR

The Applicant submitted population PK and exposure-response for efficacy analyses of exenatide in adolescent patients with T2DM. The PK profile at steady state of EQW in pediatric patients aged 11 to < 18 years old were comparable with that in adult patients with T2DM. In addition, because the previous population PK analysis showed similarity between EQW and EQWS in adults (Clinical Pharmacology review, NDA 209210 dated December 4, 2018), the PK behavior of EQWS in adolescent patients with T2DM is expected to be similar to that of EQW.

Exposure-response analysis indicated HBA1c measurements at steady state following administration of EQW were comparable between adolescent and adults with T2DM, suggesting that the effect of EQWS on HbA1c is expected not to be different from the observed effect of EQW on HbA1c.

Note that consistent with previous analysis in adults with T2DM, the population PK and the

exposure-response model only evaluated measurable samples[7] at steady state with ADA ≤ 625.

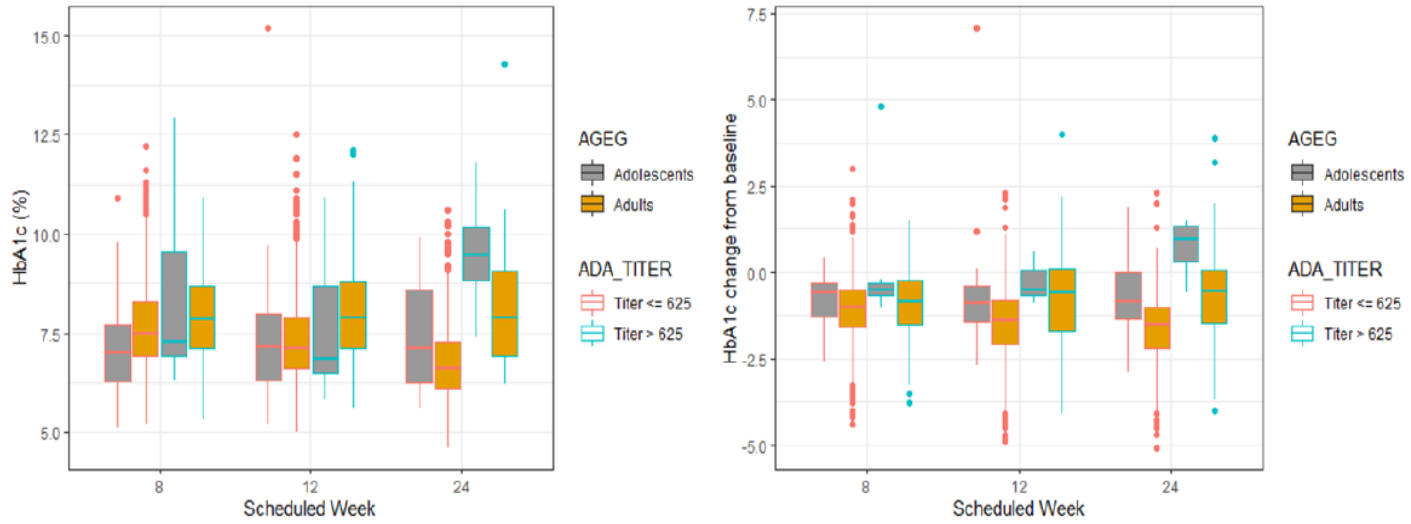
Some of the differences between the adult and pediatric data as noted by the clinical pharmacology reviewer is the higher incidence of the exenatide concentration below limit of quantification (BLOQ) in adolescents with T2DM (17%) compared to adults with T2DM (9%) which appeared to correlate to the higher incidence of high titer ADA titer in adolescents compared to that in adults.

Other differences between the adult and pediatric data in the exposure-response analysis include a slightly lower baseline HbA1c for the adolescents compared to adults. Also, although the predicted HbA1c in adolescents was comparable to data from adults with T2DM, the predicted absolute HbA1c change from baseline was lower in adolescents than adults. This might be explained by the higher incidence of antibody titer in adolescents compared to adults.

In addition, as shown in Figure 2**Error! Reference source not found.** clinical pharmacology notes that adolescent T2DM patients with higher titers (> 625) or concentration BLOQ had an attenuated HbA1c response. This finding corroborates Office of Biotechnology Products (OBP) conclusions that patients with high titer ADA generally experienced an attenuation of HbA1c at Week 24 suggesting a possible interference of ADA with drug effect. Immunogenicity will be further discussed in Section 8.4.3 of this review.

[7] The clinical pharmacology reviewer states a total of 365 plasma PK samples from 58 subjects were provided. Overall, 209 (57.3%) concentrations with non-steady state measurements (prior to week 8 or after week 30), 8 (2.19%) concentrations below the LLOQ and 25 (6.8%) concentrations with antibody titer > 625 were excluded, resulting in a total of 123 (33.7%) quantifiable concentrations from 47 subjects in the population PK analysis.

Figure 2: Observed HbA1c (right figure) and HbA1c change from baseline (left figure) at steady state stratified by population (adolescents and adults) and anti-exenatide antibody titer



Source: Clinical pharmacology review; AGEG: age group; ADA: anti-drug antibody

4.6. Devices and Companion Diagnostic Issues

EQWS/autoinjector

Study BCB114 was originally designed to address PREA PMR 1860-1 for both the EQW and EQWS products. The Applicant amended the Agreed initial Pediatric Study Plan (May 18, 2018) and proposed removal of the EQWS arm from study BCB114 based generally on PK similarity between the two products. The Agency recommended considering whether any differences in product presentation may require additional data, e.g., Human Factors for the intended use of the EQWS product (Advice Letter dated November 6, 2018). However, the Applicant did not complete a Human Factors validation testing to support the proposed pediatric indication for EQWS.

The Applicant's rationale to support the safe and effective use of the autoinjector is in part based on the expectation that the caregiver/health care provider will decide on the child's capability for a successful self-administration. In addition, the Applicant submitted a User Related Risk Analysis reviewing user and design input requirements for the autoinjector dimensions (size and shape that is easy to handle and transport, or enable the user to easily carry out a successful delivery), the autoinjector's max width, force, torque, vertical twisting strength, minimum and maximum required forces, comprehension and compliance, injection depth, and mixing. The Applicant referenced data from a previous Human Factor validation study in adult patients and caregivers and specifications of some other devices currently on the market (e.g., benralizumab autoinjector subassembly) approved for 12 year and older patients to support the safe and effective use of the device in the pediatric population.

The risks identified by the Applicant were generally related to dimensions (e.g., unable to grip or trigger the injection), torque and force (e.g., unable to fully depress needle shield or generate force to unlock), comprehension and compliance (e.g., forgets to take weekly dose, package not stored out of reach of children, or unable to hold shield steady on the skin), injection depth (selects wrong injection site or the same each week), package opening (e.g., package design not intuitive), or mixing (does not mix with enough force, or long enough, or discontinues mixing due to discomfort). The Applicant proposes these risks could generally be mitigated by patient labeling, including the Instructions for Use.

The Division of Medical Error Prevention and Analysis (DMEPA) did not agree with the Applicant's proposed justification and User Related Risk Analysis conclusions that the EQWS design input requirements are acceptable for the new user population and that the device will fulfill the user requirements without increase in severity or likelihood of occurrence for any of the identified risks.

Note that DMEPA requested a consult from Center for Diagnostic and Radiologic Health (CDRH) to provide feedback on whether the device specifications are suitable for a new indication and pediatric user group. CDRH reviewed the device description and design verification and assessed the specifications for pediatric use. CDRH concluded the device constituent parts of the combination product are approvable for the proposed indication. As the essential performance requirements for the device were not validated for the new user population CDRH deferred the acceptability of the lack of Human Factors to DMEPA. Refer to the CDRH consult dated June 8, 2021, for details.

DMEPA concluded that pediatric patients are a distinct user group and the referenced adult HF data is not a sufficient comparator for pediatric patients due to differences that may impact usability, such as differences in cognitive abilities and anthropometry. Therefore, the Applicant should provide HF human factor validation study data to demonstrate the EQWS combination product user interface has been optimized to support safe and effective self-administration by intended pediatric patients, for the product's intended uses and under the expected use conditions.

Reviewer Comment: As there is an unmet need for therapies in pediatric patients with T2DM and the possible risk of medication errors such as improper mixing, dosing errors, or administration errors could be addressed through labeling, DMEPA and the Division agreed that the Human Factor study validation study to demonstrate that the user interface is optimized to support the safe and effective self-administration of EQWS in pediatric patients 10 to < 18 years old and to analyze residual risk with the user interface design may be conducted as a Postmarketing Commitment.

EQW

Study BCB114 was initiated in May 2016 proposing to administer EQW with the prefilled syringe SDT presentation. As expiration of study medication was expected prior to completion of the study, the protocol was amended (amendment # 4 dated August 2018) to allow use of the EQW single-dose dual-chamber pen (DCP) presentation.

Reviewer Comment: Per the FDA guidance on marketing status notification, the Applicant informed the Agency (September 14, 2020) that on March 2021 the EQW dual-chamber pen was permanently discontinued from the United States market for business reasons. Therefore, Human Factor validation data for the EQW presentations is not required. The EQW label should be updated to include instructions to generally reflect the protocol instructions on administration of EQW to the pediatric patients during the trial.

4.7. Consumer Study Reviews

This section is not applicable to this submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary efficacy and safety data to substantiate the proposed labeling claims and updates are based on a single adequate and well-controlled phase 3 trial i.e., study BCB114.

5.2. Review Strategy

In this submission, I consider substantial evidence for efficacy to be based on results of the 24-week placebo-controlled assessment period of the phase 3 study BCB114. The established efficacy in the adult T2DM population can provide confirmatory evidence. Dr. Anna Kettermann conducted a detailed analysis of efficacy and independently evaluated the Applicant's claims. Dr. Kettermann recommends approval of the sNDA.

The safety analysis is based on the 24-week placebo-controlled assessment period of study BCB114. I evaluated safety data from the open-label uncontrolled extension period for potential rare or idiosyncratic events. Where applicable, I reviewed the safety data using the submitted datasets. Additional analysis of interest was requested from the Applicant in Information Requests.

6. Review of Relevant Individual Trials Used to Support Efficacy

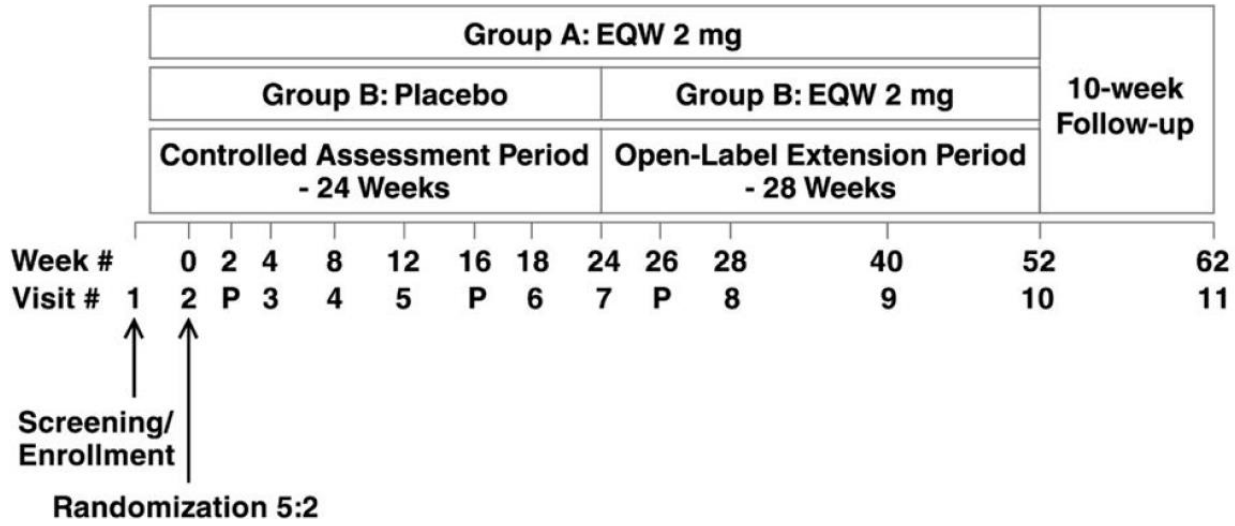
6.1. BCB114

6.1.1. Study Design

General Design Characteristics

Study BCB114 was a multicenter randomized study to assess safety, tolerability, efficacy and PK of EQW as monotherapy and adjunctive therapy to oral antidiabetic agents (metformin/sulfonylurea) and/or insulin in pediatric patients aged 10-17 with T2DM. As shown in Figure 3, the study consisted of 4 periods; a screening period for 5 weeks, a 24-week double-blind, placebo-controlled parallel design assessment period; a 28-week open-label uncontrolled extension period where patients randomized to placebo switched to EQW and patients randomized to EQW continued on EQW, and a post-treatment follow-up period for 10 weeks.

Figure 3: Study BCB114 design



Source: BCB114 CSR

Patients were to return to the study site at 4- or 12-week intervals for safety, efficacy, PD and PK assessments over 52 weeks. All patients had to complete study termination procedures at Visit 11 (Week 62), 10 weeks after administration of last dose of EQW. The investigator contacted patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address questions, and review adverse events. Over 80% of patients administered EQW using the prefilled syringe, and the remainder used the dual chamber pen.

Primary objectives

- To evaluate the effect on glycemic control, as measured by HbA1c, of EQW following 24 weeks of treatment compared to placebo in pediatric patients (10-17, inclusive)

with T2DM.

- To evaluate the safety and tolerability of EQW compared to placebo following 24 weeks of treatment in pediatric patients (10-17, inclusive) with T2DM.

Secondary objectives

To compare the effects of EQW following 24 weeks of treatment with placebo in pediatric patients (10-17, inclusive) with T2DM on:

- Fasting plasma glucose (FPG)
- Proportion of patients achieving HbA1c goals
- Body weight and Tanner pubertal stage
- Blood pressure and lipids

To assess the effects of long-term EQW therapy (~1 year) in pediatric patients (10-17, inclusive) with T2DM on:

- Safety and tolerability
- HbA1c, fasting plasma glucose, and proportion of patients achieving HbA1c goals
- Body weight and Tanner pubertal stage
- Blood pressure and lipids
- Beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostatic model assessment (HOMA) in patients not on insulin

Population

The patient population randomized to EQW in study BCB114 generally reflects the real-world target population and is adequately representative of the United States population with a broad range of demographic and disease characteristics. The population consisted of pediatric patients aged 11 to 17 years old with T2DM (mean T2DM duration of about 2.2 years and mean HbA1c at baseline of 8.13%) and obesity (72.4% in the ≥ 97% percentile BMI category; mean BMI 36.8 kg/m2). Most patients were treated at baseline (stable dose for at least 2 months) with either metformin (22 [37.9%]), insulin and metformin (21 [36.2%]), and insulin only (6 [10.3%]). 8 (13.8%) were not treated with any oral antidiabetic medication or insulin at baseline. Most were White (39.7%) and Black or African American (29.3%), and 25 (46.3%) were Hispanic or Latino. 60.3% were from North America. All patients were to participate in a lifestyle intervention program encompassing diet and physical activity modifications from Week -2 to Week 52.

Reviewer Comment: As about 60% of the randomized patients were from North America, the applicability of the data to the United States is acceptable.

Key Inclusion Criteria

- Child or an adolescent of 10 to < 18 years of age, at screening.
- Diagnosed with T2DM per American Diabetes Association (ADA) diagnostic criteria.
- HbA1c of 6.5% to 11%, inclusive, in patients not taking insulin/sulfonylurea, and of 6.5% to 12%, inclusive, in patients taking insulin/sulfonylurea at screening.
- C-peptide of > 0.6 ng/mL at screening.
- Treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (e.g., metformin and/or sulfonylurea) and/or insulin for at least 2 months prior to screening.
- Fasting plasma glucose < 280 mg/dL at screening.
- Physical examination and electrocardiogram (ECG) results deemed not clinically significant by the investigator at randomization.

Reviewer Comment: The youngest age randomized to EQW and placebo was 11 and 12 years old respectively.

Key Exclusion Criteria

- A clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator, such as aspartate or alanine transaminase > 3 × the upper limit of normal (ULN), renal disease or serum creatinine > 1.5 mg/dL (males) or > 1.4 mg/dL (females), gastrointestinal disease deemed significant by the investigator, organ transplantation, chronic infection, malignancy (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of screening.
- A personal or family history of elevated calcitonin, calcitonin > 100 ng/L, medullary thyroid carcinoma, or multiple endocrine neoplasia 2.
- Past use of exenatide or any GLP-1 receptor agonist.
- Known allergies or hypersensitivity to any component of study treatment.

Study Endpoints

The primary efficacy endpoint was change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24).

The key efficacy endpoints included in the hierarchical testing procedure are listed below. All measured change from baseline Week 0 (Visit 2) to Week 24 (Visit 7):

- Change in HbA1c (primary endpoint)
- Change in fasting plasma glucose (FPG)

- Change in body weight
- Change in fasting insulin

Secondary endpoints not included in the testing procedure are listed below. All measured change from baseline Week 0 (Visit 2) to Week 52 (Visit 10) and intermediate visits as applicable:

- HbA1c
- FPG
- HbA1c < 6.5%, ≤ 6.5%, < 7%
- Body weight
- Fasting insulin
- Change in beta cell function and insulin sensitivity
- Lipids
- Blood pressure
- Proportion of patients requiring rescue due to failure to maintain glycemic control and number of rescues episodes
- BMI
- Body weight percentile and height percentile

This review generally focuses on the endpoints included in the hierarchal testing procedure. Some of the exploratory endpoints such as effect on blood pressure will be discussed during the review.

Statistical Analysis Plan (SAP)

- ***Primary efficacy analysis***

Refer to Section 6.1.2 of this review for a discussion on the SAP's prespecified method for the primary efficacy analysis.

- ***Sample size justification***

The SAP prespecified that based on an estimated drop-out rate of 10%, a true treatment difference of -0.7% between EQW and placebo in change from baseline for HbA1c, standard deviation of 1%, two-sided significance of 0.05, and 74% power to detect a treatment difference, 77 eligible patients were to be randomized in a 5:2 ratio to the EQW and placebo treatment groups on Week 0 (Visit 2). Randomization was stratified by screening HbA1c strata (< 9% or ≥ 9%).

The Applicant states the study was powered only to 74% for the prespecified MMRM analysis which excluded post rescue or premature discontinuation data and imputed missing data at

Week 24 based on the Missing at Random (MAR) assumption. The study was not powered for the more conservative Missing Not at Random (MNAR) analysis as later requested by the Agency because of recruitment challenges stemming from socioeconomic and eligibility factors amongst adolescents with T2DM.

At least 40% and not more than 60% of the randomized patients were to be females. At least 40% of patients were to be recruited from areas with similar ethnicity and lifestyle to those of the European Union states.

Reviewer Comment: The sample size for study BCB114 is underpowered (74%) for the conservative Missing Not at Random analysis with a very small comparator group (5:2 randomization ratio).

The efficacy of EQW in adults has been documented and evaluated in the clinical development program for exenatide, which could be used as supportive evidence.

- ***Populations***
  - Randomized: all randomized patients.
  - Intent-to-treat (ITT): all randomized patients who received at least 1 dose of randomized study medication.
  - Evaluable: all randomized patients who received at least 1 dose of randomized study medication and have at least 1 baseline and post-baseline HbA1c assessment.
  - Safety: all patients who received at least one dose of study medication.
  - PK: all patients who received at least 1 dose of EQW with at least 1 post-dose PK measurement and who did not deviate from the protocol in ways that would significantly affect the PK analyses as determined at the final protocol deviation meeting prior to unblinding of the study.

- ***Definition of study periods***
  - Controlled assessment period: date of the first dose of randomized study medication to date of the Week 24 visit or the Early Termination visit for patients who discontinue the study prior to Week 24.

  - Extension period: date of first dose of open-label EQW + 1 day to date of Week 52 visit, or the Early Termination visit for patients who discontinue the study prior to Week 52. The extension period will only be defined for patients who enter the extension period and receive at least one dose of open-label EQW.

  - Treatment period: controlled assessment period and extension period combined i.e., date of first dose of randomized study medication to date of Week 52 visit or

Early Termination visit for patients who discontinue the study prior to Week 52.

- ***Definition of baseline***

For the controlled assessment period, the SAP describes baseline as the last non-missing value (including unscheduled visit) collected on or prior to the first dose of study medication[8].

The SAP states for change from baseline summaries of data collected during the extension period, the baseline value will not be rederived.

- ***Early Termination Visit***

If a patient discontinued after randomization but prior to completion of the study treatment period, the patient was to be invited to return to the study site as soon as possible for an early termination visit to collect HbA1c, fasting plasma glucose, body weight, and safety laboratory measures.

Protocol Amendments

The protocol for study BCB114 was amended 4 times. The first 3 amendments occurred before study initiation and generally included clarifications and updates to the protocol and procedures to implement changes requested by the European Medicine Agency Pediatric Committee. Amendment 4 (December 14, 2017) occurred after 43 patients were randomized. 40 additional patients were randomized to the study following Amendment 4. Some of the amendments (#4) are outlined below:

- Injection site reaction assessment was added as a safety endpoint.
- The bone turnover marker was updated from deoxypyridinoline to N-telopeptide.
- Addition of the dual chamber pen presentation for use in all patients recruited from August 2018 and after. This was because the single dose tray formulation was expected to expire before study completion.
- Instructions for study medication administration was amended to state caregivers were to administer study medication to the patient and patients were to self-administer only if deemed appropriate by a qualified study staff. This was to minimize risk that a patient could self-administer in cases when their capabilities may make self-administration

[8] Per the SAP, assessments carried out on the date of first dose are assumed to have been done pre-dose unless time information indicates otherwise. In case of multiple measurements for a given variable with tied collection date or date/time, the mean of the values will be calculated for baseline. If the baseline value is missing for a given variable, change from baseline will be missing.

inappropriate.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states study BCB114 was performed in accordance with the ethical principles stated by the Declaration of Helsinki and that are consistent with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Financial Disclosure

The Applicant adequately disclosed financial interests of the investigators. The Applicant states despite due diligence efforts, a signed investigator financial disclosure form was not collected from 4 investigators (from 3 sites). 2 of these sites did not randomize any patients, and the third site randomized 4 patients to the study. The Applicant's submitted financial disclosure shows none of the other investigators had information to disclose.

Reviewer Comment: Overall, the investigator financial disclosures do not raise questions about the data integrity; furthermore, the study was double-blinded, and the primary endpoint was an objective laboratory measurement (HbA1c) minimizing possible bias.

Patient Disposition

A total of 159 patients enrolled in study BCB114 from 36 centers. 76 (47.8%) failed to meet the randomization criteria and 83 (52.2%) were randomized to the double-blind placebo-controlled assessment period in a 5:2 fashion across 27 study centers: 59 to EQW and 24 to placebo. 1 (1.2%) patient randomized to EQW did not receive study medication due to adverse event of vomiting leading to study discontinuation prior to the first dose of study treatment. This randomized patient was not counted as completing or discontinuing treatment.

Disposition, controlled assessment period

Since the randomization ratio in this trial was 5:2, a much larger number of patients (~72%) were randomized to EQW.

9 (15.3%) patients prematurely discontinued study treatment and the study during the controlled assessment period; 8 patients from the EQW group and 1 patient from placebo. These 9 patients had missing Week 24 HbA1c measurements. 1 (1.7%) additional patient from the EQW group discontinued study treatment due to a protocol deviation of noncompliance but

remained in the study. This patient is counted as retrieved dropout (prematurely discontinued treatment but had a nonmissing Week 24 HbA1c measurement).

Of the 82 patients who entered the controlled assessment period, 72 (86.7%) completed the controlled assessment period, 49 (83.1%) patients from EQW and 23 (95.8%) from placebo. Reasons for discontinuation from study and study treatment from the controlled assessment period are shown below.

Table 1: Disposition, randomized population, controlled assessment period

	EQW (N=59)	Placebo (N=24)
	n (%)	n (%)
COMPLETED	49 (83.1)	23 (95.8)
DISCONTINUED from STUDY	8 (13.5)	1 (4.2)
Lost to follow-up	2 (3.4)	1 (4.2)
Withdrawal by subject	6 (10.2)	0
DISCONTINUED from STUDY TREATMENT	9 (15.3)	1 (4.2)
Protocol deviation	1 (1.7)	0
Lost to follow-up	2 (3.4)	1 (4.2)
Withdrawal by subject	6 (10.2)	0

Created by reviewer, Analysis Studio, ADaM dataset

Disposition, open-label extension period

From the 72 (86.7%) patients who completed the controlled assessment period, all but 1 patient entered the open-label extension period: 49 (83.1%) randomized to the EQW arm continued on EQW and 23 (95.8%) randomized to placebo switched to EQW. Of these 5 (10.2%) from the EQW arm and 5 (21.7%) from the "placebo to EQW" arm discontinued study treatment and study. Reasons for discontinuations from study and study treatment are shown below.

Table 2: Disposition, randomized population, open-label extension period

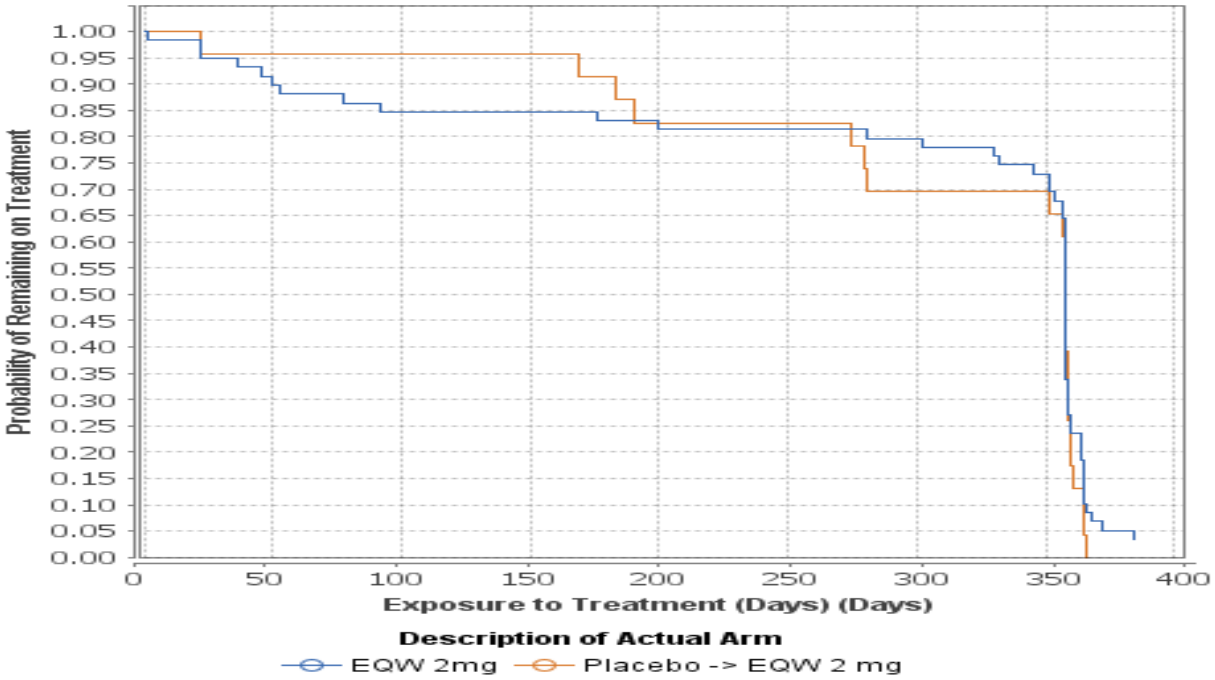
	EQW 2mg (N=49)	Placebo -> EQW 2 mg (N=23)
	n (%)	n (%)
COMPLETED	44 (89.8)	18 (78.3)
DISCONTINUED from STUDY and STUDY TREATMENT	5 (10.2)	5 (21.7)
Lost to follow-up	1 (2.0)	1 (4.3)
Other	0	1 (4.3)
Withdrawal by subject	4 (8.2)	3 (13.0)

Created by reviewer, Analysis Studio, ADaM dataset

Note the discontinuation due to "other" from the "placebo to EQW" arm in Table 3 refers to a 16-year-old who per the Applicant reportedly was in a detention facility during the treatment period and was not granted access to the study medication. The investigator withdrew the patient from the study.

The Kaplan-Meier plot shown below (Figure 4) depicts the difference in follow-up between the treatment arms and shows the higher discontinuation in the EQW arm compared to placebo. Most discontinuations from the EQW arm occurred earlier in the trial.

Figure 4: Kaplan-Meier plot for follow-up, controlled assessment period and open-label extension period, randomized population



Created by reviewer, JReview, ADaM dataset

In summary, a higher proportion of patients from the EQW arm (9 [15.3]) prematurely withdrew from the study compared to placebo (1 [4.2]). The most common reason for premature study withdrawal from the EQW arm was "withdrawal by subject".

The Applicant states none of the discontinuations occurred due to an adverse event. The Applicant submitted (regulatory response dated April 16, 2021) brief narratives of patients who prematurely discontinued the study due to the reason "withdrawal by subject". A review of these narratives suggest that some of the reasons that may have contributed to "withdrawal by subject" from the EQW arm may have included gastrointestinal symptoms (1 patient), not liking EQW injections or not able to handle the pain from injections (2 patients), and noncompliance (about 3 patients). Two patients who switched from placebo to EQW dropped out after

receiving the first dose of EQW (no reason stated).

Reviewer Comment: It is expected that exenatide-related gastrointestinal symptoms or injection site reactions may result in intolerability in some pediatric patients.

Protocol Violations/Deviations

The SAP prespecified that the Applicant use ICH (E3) terminology for protocol deviations related to study inclusion or exclusion criteria, conduct of trial, patient management, or patient assessment. Important protocol deviations were to be identified and documented by the study physicians and statisticians prior to unblinding of data.

The Applicant's data shows the proportion of patients with at least 1 important protocol deviation was in favor of placebo: 59.3% vs 50% in the EQW and placebo arms respectively. Of these, a higher proportion of patients in the EQW group did not adhere to the protocol specific visit schedule compared to placebo: 22% vs. 8.3%, and a slightly higher proportion did not comply with protocol-specified assessment criteria for efficacy or safety: 6 (10.2%) vs. 2 (8.3%) in the EQW and placebo arms respectively.

Some issues listed below were noted during the review:

- The CSR suggests there may have been some issues with the interactive voice response system (IVRS[9]) with assigning multiple unique subject IDs to the same patient. The CSR suggests this issue affected a low number of patients (~2), and only one patient was randomized and treated.

- The Applicant states one patient ((b) (6)) on EQW was unblinded in error during the controlled assessment period due to incorrect reporting by the study site of an SAE that was subsequently downgraded to a TEAE. The study team was not unblinded and the patient[10] completed the 52-week study.

- Following database lock and unblinding, the Applicant noted one patient randomized to placebo ((b) (6)) had received EQW for 175 days during the controlled assessment period; therefore, the patient was assigned to EQW for safety and PK analysis and to placebo for efficacy analysis.

[9] The CSR notes the E-codes (b) (6) were captured in the interactive voice response system twice for the same patient. E-code (b) (6) was incorrectly randomized and screen failed, while (b) (6) was captured as a screen failure. E-codes (b) (6) were captured in the interactive voice response system twice for the same patient. E-code (b) (6) was captured as a screen failure, while (b) (6) was screened, randomized, and treated

[10] The narrative states the patient was a 15-year female with T2DM for < 1 year randomized to EQW who experienced 4 nonserious adverse events of abdominal pain related to injection site and 1 nonserious hypoglycemia all of which resolved.

- The initial database lock for study BCB114 occurred on June 11, 2020, but errors were noted on a quality check of anti-drug antibody data requiring a new data transfer. Therefore, the final database lock with the corrected data occurred on August 6, 2020. The Applicant states the risk to the integrity of study results was mitigated by re-running the immunogenicity analysis using the corrected data. OBP reviewed the corrected data and concluded no negative impact is expected on the immunogenicity assessment for EQW.

Reviewer Comment: The protocol violations/deviations described above are generally not expected to significantly impact the study results.

Demographics

Table 3: Baseline demographic characteristic, safety population

	EQW 2 mg n=59	Placebo n=23
Age Group years old	n (%)	n (%)
mean and standard deviation (SD)	14.9 (1.87)	15.6 (1.7)
median	15	16
range	11-17	12-17
Age Group years old		
>=10 to <=12	8 (13.6%)	3 (13%)
>=13 to <=16	37 (62.7%)	11 (47.8%)
>16	14 (23.7%)	9 (39.1%)
Age Group years old		
< 12 years	4 (6.8%)	0
>=12 years	55 (93.2%)	23 (100.0%)
Sex		
Female	32 (54.2%)	16 (69.6%)
Male	27 (45.8%)	7 (30.4%)
Race		
WHITE	23 (39%)	12 (52.2%)
BLACK OR AFRICAN AMERICAN	18 (30.5%)	7 (30.4%)
OTHER	12 (20.3%)	2 (8.7%)
AMERICAN INDIAN OR ALASKA NATIVE	4 (6.8%)	1 (4.3%)
ASIAN	2 (3.4%)	1 (4.3%)
Ethnicity		
NOT HISPANIC OR LATINO	30 (50.8%)	12 (52.2%)
HISPANIC OR LATINO	25 (42.4%)	8 (34.8%)
Baseline Height cm		
mean (SD)	165.7 (9.6)	165.3 (8.7)
range	140-185.3	142.6-176.7
Baseline Height Percentile		

<3	0	1 (4.3%)
>=3 to <85	44 (74.6%)	18 (78.3%)
>=85 to <97	11 (18.6%)	2 (8.7%)
>=97	4 (6.8%)	2 (8.7%)
Baseline Body Mass Index (BMI) kg/m2		
mean and SD	36.9 (9.2)	34.7 (6.4)
median	36.8	33.8
range	18.5-71.2	25.4-50.3
Baseline Weight kg		
mean and SD	102.5 (29.9)	95.5 (22.4)
median	101.7	93.1
range	47-201.4	61.7-152.4
Baseline Weight Percentile		
<3	1 (1.7%)	0
>=3 to <85	4 (6.8%)	1 (4.3%)
>=85 to <97	11 (18.6%)	10 (43.5%)
>=97	43 (72.9%)	12 (52.2%)
Tanner Stage at Baseline		
Stage 5	40 (67.8%)	17 (73.9%)
Stage 4	9 (15.3%)	5 (21.7%)
Stage 3	7 (11.9%)	0
Stage 2	2 (3.4%)	1 (4.3%)
Stage 1	1 (1.7%)	0
Device Type		
Pre-filled syringe	52 (88.1%)	19 (82.6%)
Dual chamber pen	7 (11.9%)	4 (17.4%)

Created by reviewer, JReview, ADaM dataset

At baseline, the mean age of the patients randomized to placebo was older (15.6 years old) compared to EQW (14.9 years old). Most (62.7% in the EQW group and 47.8% in the placebo group) were in the ≥ 13 to ≤ 16 years age group. The lowest age randomized to EQW and placebo was 11 and 12 years old respectively.

The mean baseline weight was higher in the EQW arm (102.18 kg) compared to placebo (96.7 kg). A higher proportion of patients randomized to EQW (72.4%) were severely obese compared to placebo (54.2%).

Most patients were White (39% on EQW and 52% on placebo) or Black or African American (30.5% on EQW and 30.4% on placebo). 45.5% on EQW and 40% on placebo were Hispanic or Latino. Most patients were from North America (63.4%). A higher proportion (22.4%) of patients on EQW were from South America compared with placebo (8.3%).

At baseline most patients were Tanner stage 5 (67.8% in the EQW arm and 73.9% in the

placebo arm), followed by Tanner stage 4 (15.3% in the EQW arm and 21.7% in the placebo arm), as expected based on the age of the study population.

Baseline disease characteristics

Table 4: Baseline disease characteristics, safety population

	EQW 2 mg n=59	Placebo n=23
Baseline systolic blood pressure mmHg		
mean and standard deviation (SD)	122.69 (13.03)	121.78 (9.62)
median	123	122
range	95-149	108-144
Baseline diastolic blood pressure mmHg		
mean and SD	74.46 (10.52)	72.87 (7.84)
median	74	72
range	48-97	62-86
HbA1c at Baseline %		
mean and SD	8.12 (1.21)	8.31 (1.53)
median	8	7.6
range	6.3-11.2	6.6-11.2
HbA1c baseline %		
< 9 %	45 (76.3%)	16 (69.6%)
>=9 %	14 (23.7%)	7 (30.4%)
Fasting Plasma Glucose mg/dL		
mean and SD	164.13 (59.20)	172.91 (60.47)
median	146	150
range	71-342	90-301
eGFR at Baseline mL/min/1.73m2		
mean and SD	108.54 (21.51)	105.81 (23.7)
median	108.15	106.92
range	68.4-149.8	57.3-145.9
eGFR at Baseline mL/min/1.73m2		
< 125	43 (72.9%)	18 (78.3%)
>=125	16 (27.1%)	5 (21.7%)
Duration of Diabetes years		
mean and SD	2.23 (2.16)	2.53 (2.01)
median	1.40	2.31
range	0.04-10.3	0.24-9.6
Duration of Diabetes years		
>=1 to <=5	35 (59.3%)	19 (82.6%)
<1	18 (30.5%)	3 (13%)
>5	6 (10.2%)	1 (4.3%)

Created by reviewer, JReview, ADaM dataset

At baseline, the mean baseline HbA1c was slightly higher in patients randomized to placebo (8.31%) compared to EQW (8.12%), and a higher proportion of patients on placebo had a HbA1c

≥ 9% (7 [30.4%]) compared to EQW (14 [23.7%]). The mean duration of T2DM was longer in the placebo arm (2.5 years) compared to EQW arm (2.2 years).

Reviewer Comment: Overall, patients randomized to placebo were older and more mature with generally worst glycemic control as assessed by mean HbA1c at baseline (8.31% in patients randomized to placebo vs. 8.12% in patients randomized to EQW) and % patients with HbA1c >=9% at baseline (30.4% in patients randomized to placebo vs. 23.7% in patients randomized to EQW) The patients randomized to EQW were generally more obese.

The primary analysis using the ANCOVA model contained baseline HbA1c as a covariate controlling for the baseline group differences. In addition, subgroup analyses conducted by the FDA statistical reviewer demonstrated no effect of baseline HbA1c category (greater than or less than 9%) on efficacy. The difference in body weight at baseline is not expected to significantly impact the primary analysis.

The interpretation of measures such as mean weight, systolic, diastolic measures is difficult across the age ranges in the study; it would have been more helpful to collect SDS (or Z scores) to better assess these measures across different age groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Per the SAP, treatment compliance for the controlled assessment period was calculated for each patient using the total number of doses received divided by the number of planned doses. The SAP defined the number of planned doses as the duration of treatment exposure (in days) / 7, rounded to the highest integer. The total number of doses received was calculated as the total number of used/partially used vials returned, based on returned used/unused study medication data collected in the drug accountability eCRF page at each visit.

The Applicants data shows that during the controlled assessment period, most (95.1%) used 80% to < 120% of dispensed study medication: 57 patients (96.6%) in the EQW group and 21 patients (91.3%) in the placebo group.

Table 5: Study medication compliance, % of dispensed study medication use, controlled assessment period, safety population

		EQW	Placebo	Total
	Statistic	**(N = 59)**	**(N = 23)**	**(N = 82)**
Percent of dispensed EQW/Placebo used[a]	n	59	23	82
	Mean	97.58	99.75	98.19
	SD	8.019	11.352	9.056
	Median	100.00	100.00	100.00
	Min	83.3	87.5	83.3
	Max	133.3	135.7	135.7
Percent of dispensed EQW/Placebo used, n (%)	< 80%	0	0	0
	≥ 80% to < 120%	57 (96.6)	21 (91.3)	78 (95.1)
	≥ 120%	2 (3.4)	2 (8.7)	4 (4.9)

a= Total number of doses received defined as the total number of used vials returned for EQW/placebo treatment group, based on the drug accountability CRF.
Source: BCB114 CSR

Reviewer Comment: Estimates of compliance based on reliance on patients to return used/unused study medication may have limited accuracy.

SAP's definition for rescue

The SAP definitions of rescue as well as the Applicant's data on the proportion of patients requiring rescue in study BCB114 is discussed in this section.

Definition of rescue in trial BCB114
The SAP states the following criteria led to initiation of rescue medication:
A loss of glycemic control by:

- An increase from baseline in HbA1c values by ≥ 1 % confirmed at a subsequent clinic visit scheduled at the investigator's discretion

  OR

- FPG ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home SMBG, and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit (to take place within 2 weeks).

Increases in insulin from baseline in patients receiving insulin at baseline was to be reviewed by the clinical team prior to unblinding. Increases identified as potential rescue episodes were to be queried at the site-level and therapy reason updated to "rescue" per the investigator judgement.

The SAP defined a new concomitant antidiabetic medication for the controlled assessment period as medications started on or after the first randomized dose. The SAP also stated for patients entering the extension period, any medication started at Week 24 was to be recorded as rescue for the extension period and not the controlled assessment period.

Reviewer Comment: The pre-specified definition for "new concomitant antidiabetic medication" may lead to underestimation of rescue for the controlled assessment period because practically Week 24 rescue should be counted towards the controlled assessment period.

Applicant's data on rescue
Table 6 shows the Applicant's data on the frequency of "new concomitant antidiabetic medication" and Table 7 shows the frequency of rescue during the study.

Table 6: New concomitant antidiabetic medications, controlled assessment period and open-label extension period, ITT population

	Controlled assessment period		Open-label extension period	
	EQW n=58	Placebo n=24	EQW n=49	Placebo to EQW n=23
Patients with any antidiabetic medications	8 (13.8%)	7 (29.2%)	11 (22.4%)	5 (21.7%)
Biguanides	4 (6.9%)	1 (4.2%)	3 (6.1%)	0
Insulins fasting acting	4 (6.9%)	4 (16.7%)	3 (6.1%)	3 (13%)
Insulin long acting	4 (6.9%)	6 (25%)	7 (14.3)	4 (17.4)

Adapted from the BCB114 CSR

The data above show during the controlled assessment period, patients randomized to placebo had a higher frequency (29.2%) of requiring a new antidiabetic concomitant medication compared to patients randomized to EQW (13.8%).

Table 7: Frequency of rescue, controlled assessment and open-label extension period, ITT population

	Controlled assessment period		Open-label extension period	
	EQW n=58	Placebo n=24	EQW n=49	Placebo to EQW n=23
Patients with any rescue medications	1 (1.7%)	0	5 (10.2%)	2 (8.7%)
Biguanides	0	0	1 (2%)	0
Insulins fasting acting	1 (1.7%)	0	2 (4.1%)	1 (4.3%)
Insulin long-acting	1 (1.7%)	0	3 (6.1%)	2 (8.7%)

Adapted from the BCB114 CSR

Table 6 shows in the ITT population, 8 (13.8%) and 7 (29.2%) of patients in the EQW and placebo groups received "new concomitant antidiabetic medication" during the controlled assessment period. From these patients, 1 (1.7%) patient on EQW was recorded as rescue (Table 7) by the Applicant. The Applicant was queried (May 4, 2021) to clarify why patients started on new antidiabetic medication during the controlled assessment period did not meet the criteria for rescue. The Applicant responded one additional patient on EQW (b) (6)) was likely not appropriately recorded as rescue in the eCRF during the controlled assessment period and the remaining 7 patients in the EQW group who the Applicant states received new antidiabetic medication but were not counted as rescue does not appear to have met the rescue criteria because they didn't meet the glycemic worsening threshold. Review of the data suggests that one additional patient in the EQW arm appears to have initiated insulin therapy as a new concomitant medication during the controlled assessment period but not captured as rescue or new concomitant medication.

In conclusion, the Applicant's data shows that overall, 8 (13.8%) of patients in the EQW arm and 7 (29.2%) of patients in the placebo arm received new antidiabetic therapy during the controlled assessment period (whether defined as 'rescue' or just 'additional concomitant medications').

We note that the primary efficacy analysis considers all patients irrespective of rescue or premature discontinuation.

The Applicant's data (Table 6) shows the proportion of patients who met the criteria for rescue at Week 52 was higher in patients randomized to EQW 5 [10.2%]) compared to patients randomized to placebo who switched to EQW (1 [4.3%]).

Efficacy Results – Primary Endpoint

The SAP prespecified the population level summary for the primary endpoint as the least square (LS) mean difference in change from baseline at Week 24 between EQW and placebo measured in the "evaluable population" (defined as all randomized patients with at least one post-baseline efficacy measurement). The SAP pre-specified that the intercurrent events i.e., data after rescue, study treatment discontinuation, and study withdrawal will be excluded from the efficacy analysis and a mixed model repeated measures (MMRM) analysis based on data collected prior to rescue or discontinuation of treatment with missing at random assumption (MAR) will be conducted.

The Agency provided feedback (July 16, 2020) on the proposed Statistical Analysis plan (SAP) submitted on June 4, 2020, for study BCB114. The Agency disagreed with the Applicant's approach for the primary analysis based on MMRM and the "evaluable population" and recommended using an intent-to-treat approach (i.e., treatment policy estimand) in an ANCOVA model with missing data handled based on placebo-based multiple washout and requested tipping point analysis to examine the robustness of the imputations.
The Applicant proposed (regulatory response dated July 30, 2020) performing the requested re-analyses as posthoc since the study was already unblinded. The Agency responded (August 6, 2020) with one additional comment recommending using the same imputation method for the tipping point analysis as the primary analysis.

Dr. Anna Kettermann re-analyzed the primary endpoint using the Agency's recommended strategy to include all available data (post-rescue and premature discontinuation) regardless of adherence and utilized a placebo-based multiple washout imputation to impute for patients without HbA1c data at Week 24. In addition, De. Kettermann used the pre-specified MMRM method to estimate the change in HbA1c from baseline at Week 24, but in contrast to the Applicant's approach, Dr. Kettermann performed the MMRM analyses using all data points obtained prior to and after the rescue/discontinuation.

Reviewer Comment: I agree with Dr. Kettermann that including all available data in the primary analysis more appropriately describes real world outcomes and excluding post-discontinuation/rescue data is not representative of the randomized population. I agree that patients who discontinue treatment may not experience a similar outcome as patients who complete treatment. I also agree that examining the effect of Week 24 HbA1c under the assumption that no patient experienced rescue during the trial may be contrary to clinical practice.

The Applicant's prespecified primary efficacy analysis excluding post-rescue and post-discontinuation data and utilizing the longitudinal repeated measures (MMRM) analysis with missing at random assumption demonstrated superiority of EQW over placebo at Week 24 (-0.85%; 95% CI [-1.51, -0.19]; p=0.012).

Table 8 shows the primary analysis outcome in an ANCOVA model performed by Dr. Kettermann.

Table 8: Primary analysis outcomes, ANCOVA with placebo-based washout imputations, controlled assessment period, ITT population, FDA analysis

	Change in HbA1c at week 24	
Treatment	**Estimate**	**95%CI**
EQW	-0.25	(-0.66, 0.16)
Placebo	0.45	(-0.11, 1.02)
EQW-Placebo	-0.71	(-1.42, 0.00)

CI= confidence interval
Source: statistical review dated June 2, 2021

Dr. Kettermann's analysis shows that the statistical superiority of EQW over placebo was borderline (-0.71; 95% CI [-1.42, 0]; p-value 0.052) when the Agency's recommended methodology considered to be the most appropriate analysis technique was utilized.

The Applicant conducted a 2-way tipping point analysis using a base model with a placebo washout imputation approach. According to their findings, a change of -0.2% HbA1c units for EQW (while leaving imputed placebo values the same) led to a p-value of 0.041 (change from a p value of 0.052 in the primary analysis) for the placebo washout analysis with a LS mean of -0.74%.

Dr. Kettermann's analysis utilizing the pre-specified MMRM method but including data regardless of rescue/discontinuation (Table 9) demonstrated superiority (-0.87; 95% CI [-1.51, -0.23]).

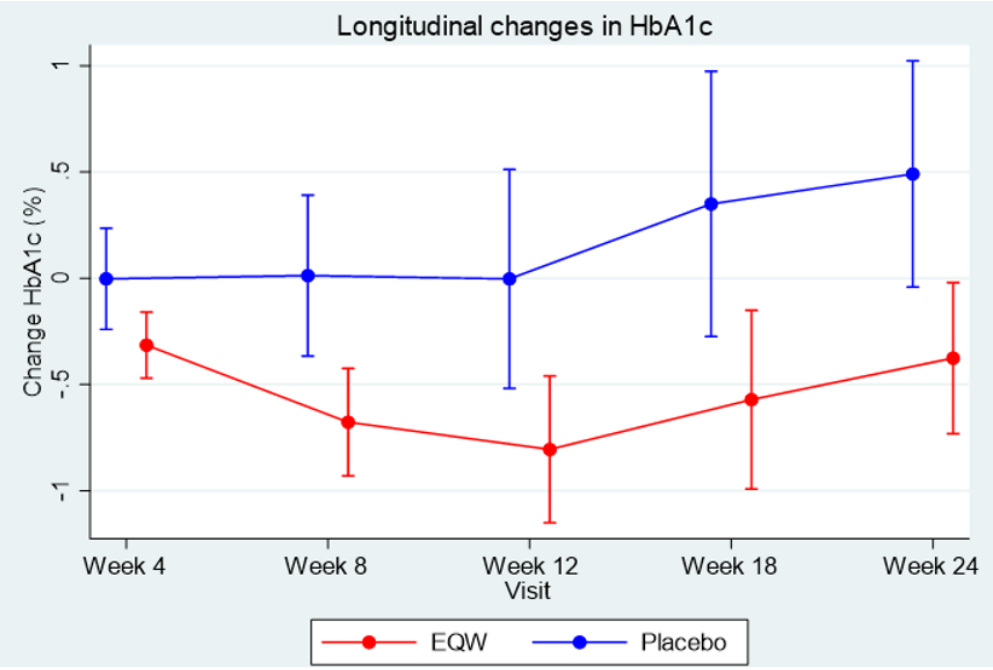
Table 9: MMRM analysis results, controlled assessment period, ITT population, FDA analysis

MMRM results	Change in HbA1c at week 24	
Treatment	**Estimate**	**95%CI**
EQW	-0.38	(-0.73, -0.02)
Placebo	0.49	(-0.04, 1.02)
EQW-Placebo	-0.87	(-1.51, -0.23)

CI=confidence interval
Source: statistical review dated June 2, 2021

Dr. Kettermann graphed the longitudinal changes with HbA1c (adjusted for baseline HbA1c and country without imputations for missing data) shown in Figure 5.

Figure 5: Longitudinal changes in HbA1c, Least Square mean with 95% confidence interval, controlled assessment period, ITT population, FDA analysis

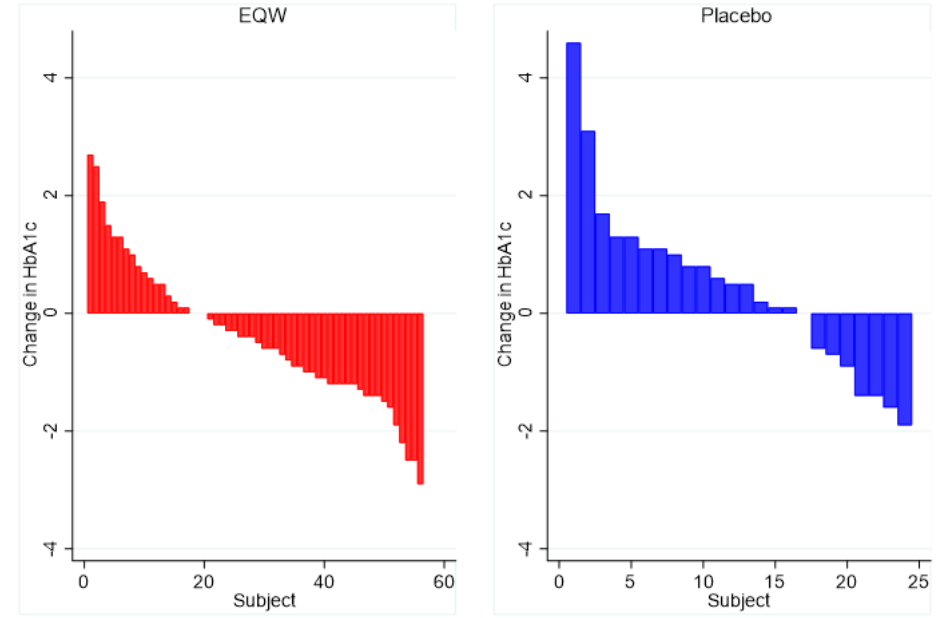


Source: statistical review dated June 2, 2021

The graph suggests the estimates of HbA1c change from baseline in patients on EQW were larger, but the 95% confidence intervals were overlapping. One of the possible explanations for the overlapping confidence interval could be the small sample size, especially the small group of patients on placebo.

Dr. Kettermann also performed an unadjusted waterfall plot of change in HbA1c shown below (Figure 6).

Figure 6: Waterfall plots, HbA1c change from baseline, controlled assessment period, ITT population, FDA analysis

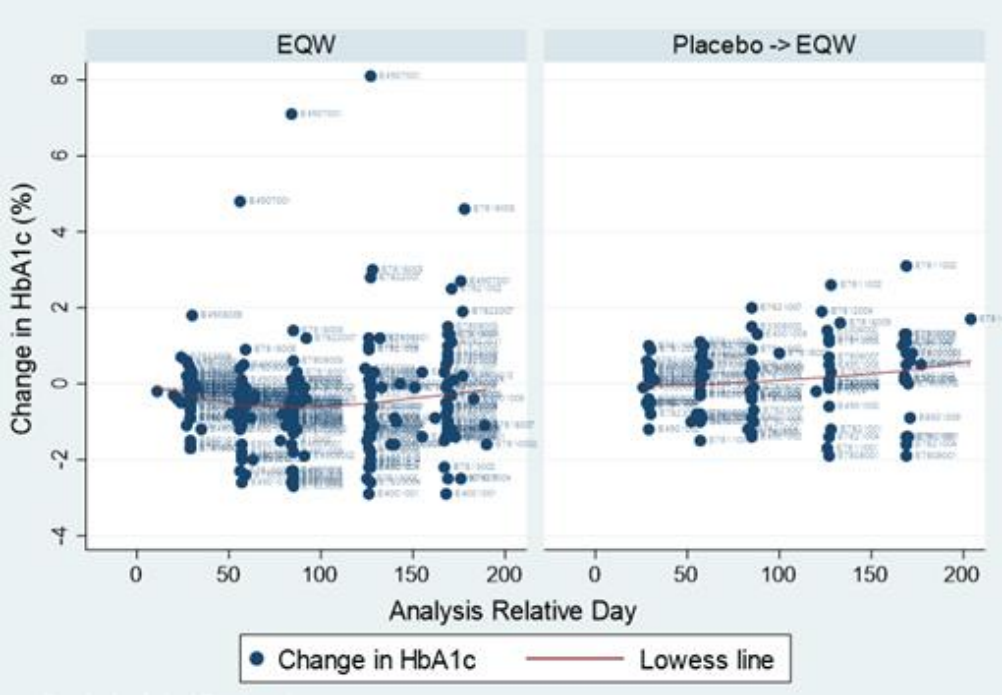


Each waterfall plot shows individual unadjusted changes in HbA1c. Each vertical bar represents an individual patient. Values above zero represent an individual's increase in HbA1c during 24-week treatment. Values below zero represent an individual's reduction of HbA1c during treatment period. Source: statistical review dated June 2, 2021

The waterfall plot suggests that a larger percentage of patients on EQW compared to placebo experienced lowering of HbA1c during the trial. A maximum HbA1c increase of > 4% was observed in patients on placebo, while the maximum increase on EQW was > 2%.

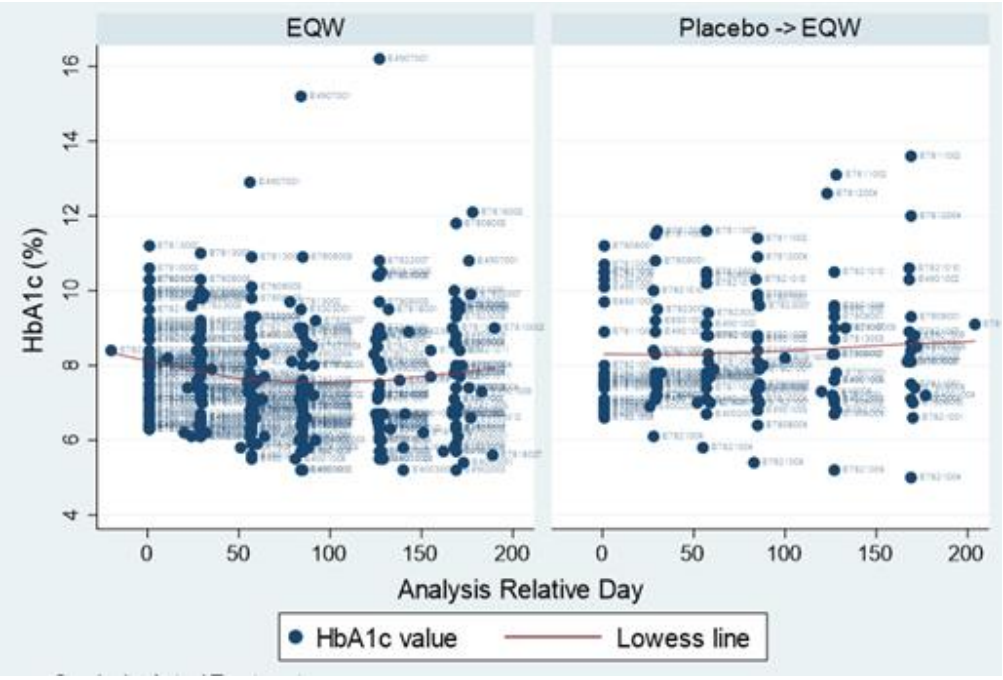
Dr. Kettermann also graphed individual HbA1c by treatment arm using the ITT population as shown below (Figure 7 and Figure 8).

Figure 7: Plot of HbA1c change from baseline by visit and treatment arm, controlled assessment period, ITT population, FDA analysis



Source: statistical review dated June 2, 2021

Figure 8: Plot of HbA1c by visit and treatment arm, controlled assessment period, ITT population, FDA analysis

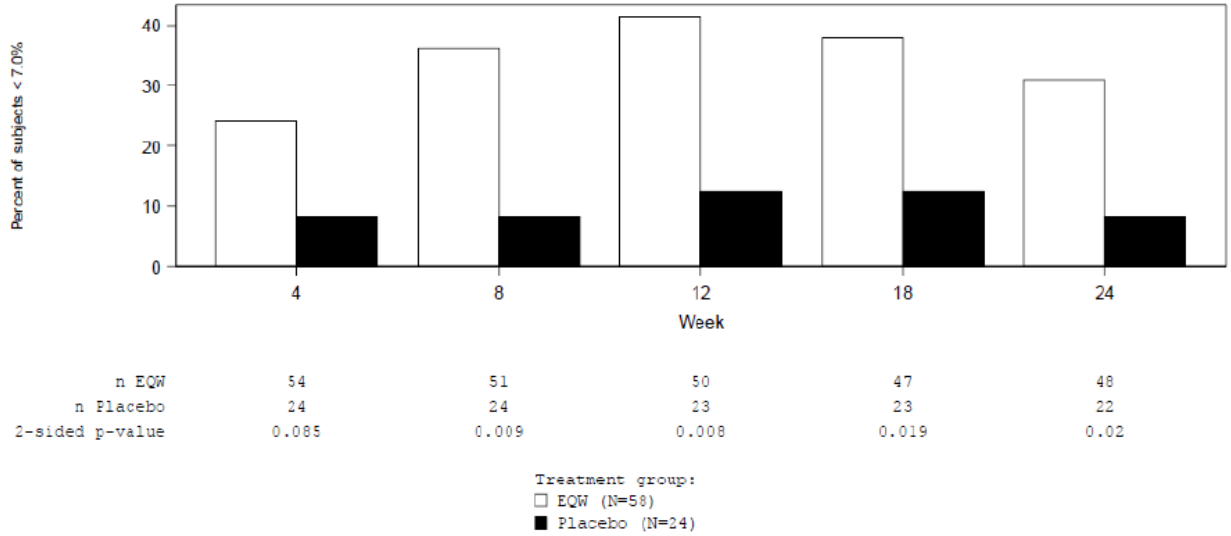


Source: statistical review dated June 2, 2021

The plots above suggest while there were more patients with larger HbA1c elevations on EQW compared to placebo, the mean HbA1c reduction appeared to be in favor of EQW.

The Applicant's data (Figure 9) based on Cochran-Mantel-Haenszel (CMH) analysis (stratified by baseline HbA1c [< 9.0% or ≥ 9.0%]) with missing data treated as non-responder in the evaluable population shows numerically greater proportions of EQW patients versus placebo patients achieved HbA1c goals of < 7%. The Applicant's data show the proportions of patients achieving HbA1c < 7% at Week 24 were 31% and 8.3% in the EQW and placebo groups, respectively (22.7%, 95% CI [6.5, 39], nominal p = 0.020). Data collected on or after initiation of rescue medication or after premature discontinuation of study medication were excluded.

Figure 9: Bar graph of proportion of patients meeting HbA1c < 7% at Week 24 and intermediate visits, Cochran-Mantel-Haenszel analysis with missing data treated as non-responder, ITT population, Applicant's data



Source: BCB114 CSR

Data Quality and Integrity

The data quality was generally adequate to allow for a substantive review.

The Applicant states the quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. The Applicant states the study was carried out in accordance with GCP guidelines. The Applicant states a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures was conducted by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures.

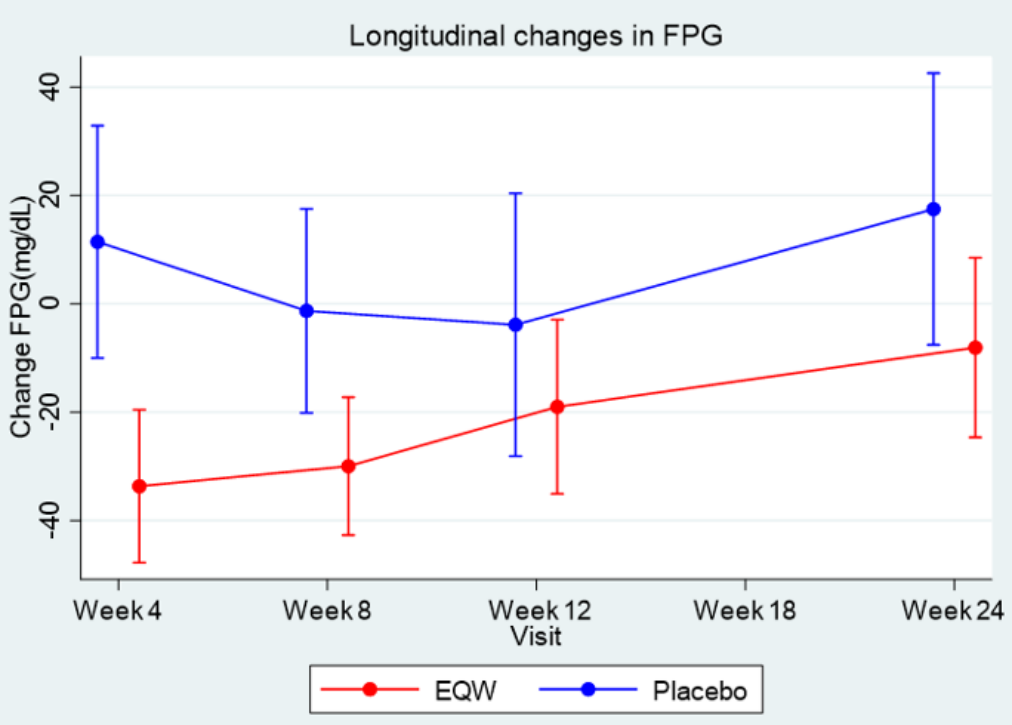
Efficacy Results – Secondary and other relevant endpoints

Dr. Kettermann analyzed the key secondary endpoints included in the testing hierarchy: fasting plasma glucose (FPG) and body weight.

Dr. Kettermann utilized an MMRM model in analysis of change in FPG and change in body weight based on observed data without imputations for missing data.

Figure 10 shows a graphical exploration of the changes in fasting plasma glucose in the controlled assessment period.

Figure 10: Longitudinal changes in fating plasma glucose, Least Square mean with 95% confidence interval, controlled assessment period, ITT population, FDA analysis



Source: statistical review dated June 2, 2021

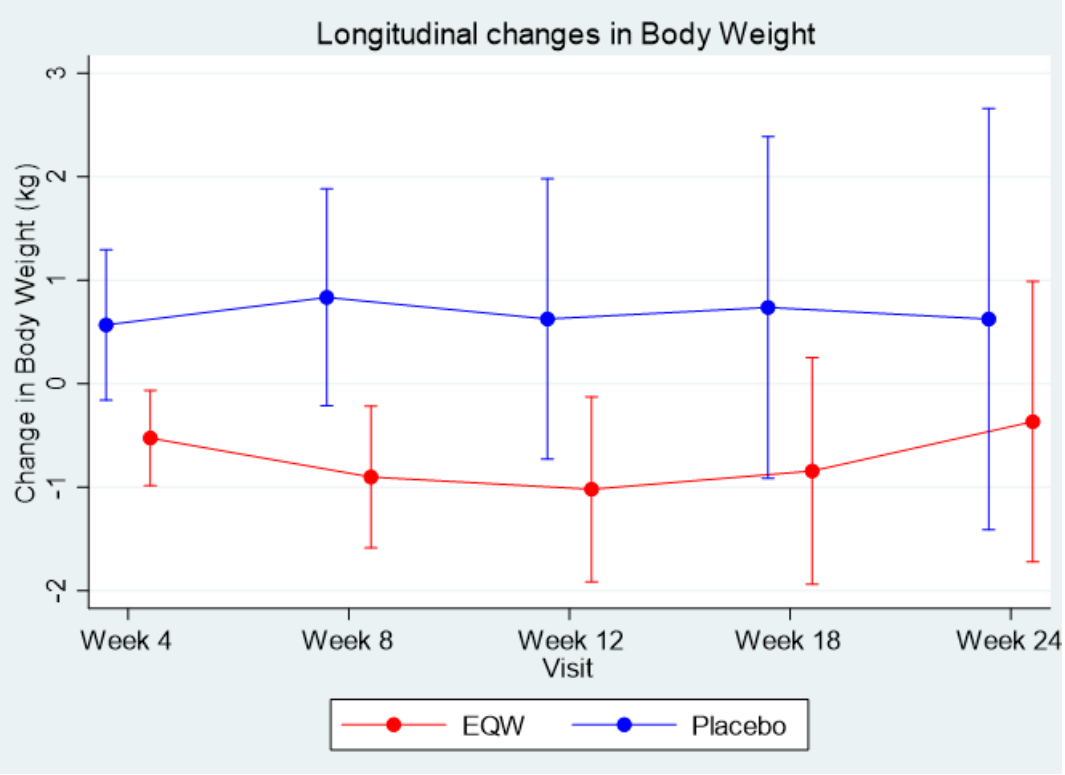
Table 10: Fasting plasma glucose analysis, MMRM, controlled assessment period, ITT population, FDA analysis

Change in FPG	EQW N=58	Placebo N=24	Difference (EQW versus Placebo) at Week 24
Estimate	-8.08	17.5	-25.58
95%CI	(-24.67, 8.51)	(-7.58, 42.58)	(-55.77, 4.61)

Source: statistical review dated June 2, 2021

Although the estimates of the change in fasting plasma glucose had a larger magnitude in patients on EQW, the 95% confidence intervals had a large overlap starting at Week 8. The numerical results for change in FPG adjusted for baseline FPG, treatment, geographic region, baseline and treatment-by-visit interactions do not demonstrate superiority of EQW over placebo.

Figure 11: Longitudinal changes in body weight, Least Square means with 95% CI, controlled assessment period, ITT population, FDA analysis



Source: statistical review dated June 2, 2021

Table 11: Outcomes of body weight analysis, MMRM, controlled assessment period, ITT population, FDA analysis

Change in weight	EQW N=58	Placebo N=24	Difference (EQW versus Placebo) at Week 24
Estimate	-0.37	0.63	-0.99
95%CI	(-1.72, 0.99)	(-1.41, 2.66)	(-3.44, 1.46)

Source: statistical review dated June 2, 2021

Patients on EQW experienced some reductions in body weight while patients on placebo did not experience weight changes. The treatment effect estimates for patients on EQW were larger, and the 95% confidence intervals overlapped at each visit.

Similar to FPG, the numerical results for change in body weight adjusted for baseline weight, treatment, geographic region, baseline, and treatment-by-visit interactions do not demonstrate superiority of EQW over placebo.

Durability of Response

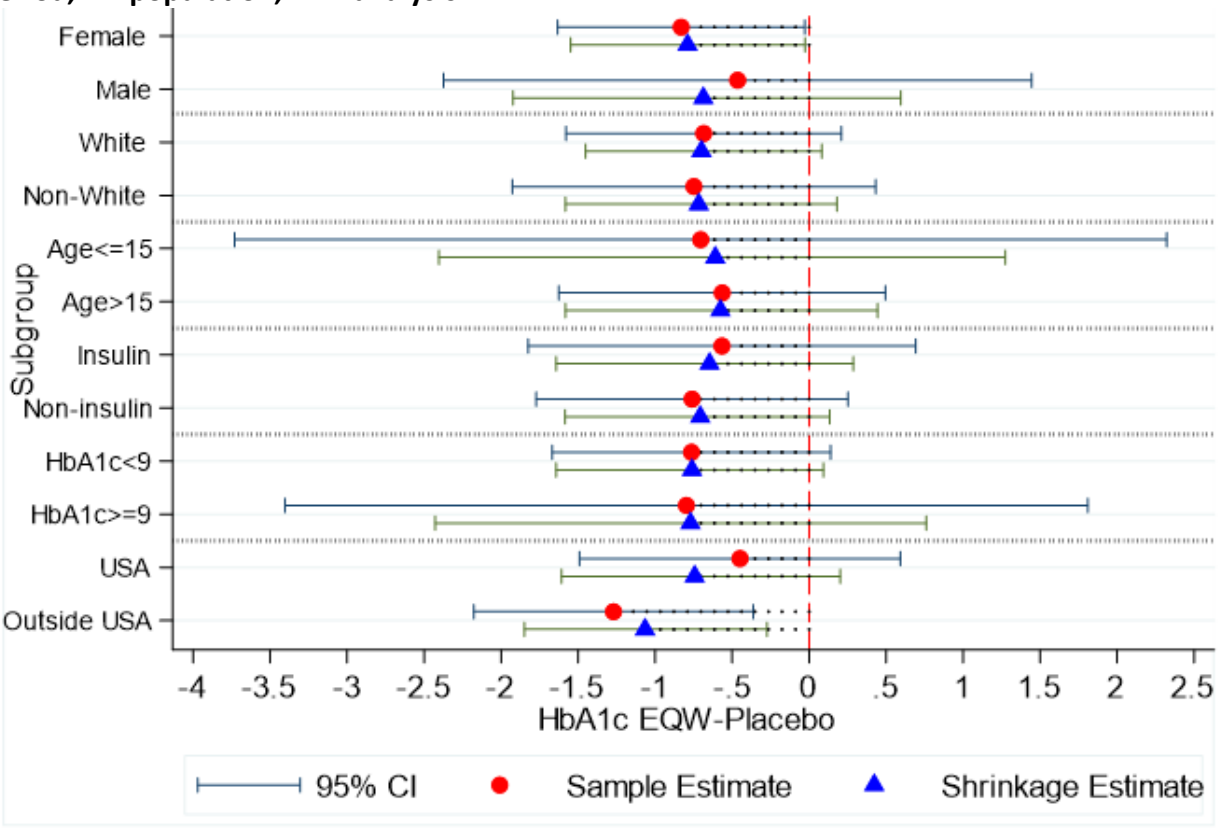
In patients randomized to EQW, the Applicant's descriptive analysis (excluding data after rescue or premature discontinuation) shows the mean HbA1c change from baseline gradually increased over 52 weeks returning to approximate baseline levels by Week 52 (-0.1%) suggesting a possible lack of durability of glycemic control with EQW treatment in study BCB114, although more likely suggesting rapid disease progression given the notable increase in HbA1c at 24 weeks in the placebo arm. Lack of a control arm over the entire 52-week period limits conclusions.

Subpopulations

Dr. Kettermann measured the estimates of treatment effect in change in HbA1c for subgroups including age, gender, and race by using the same ANCOVA model as for the primary analysis. Since most of the patients were from the United States, the subgroup analysis by region included only two categories: United States and outside of United States. Additionally, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates. Refer to the statistical review for the Bayesian hierarchical model assumptions.

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups are presented in Figure 12 below. A subgroup analysis demonstrated consistency of effect.

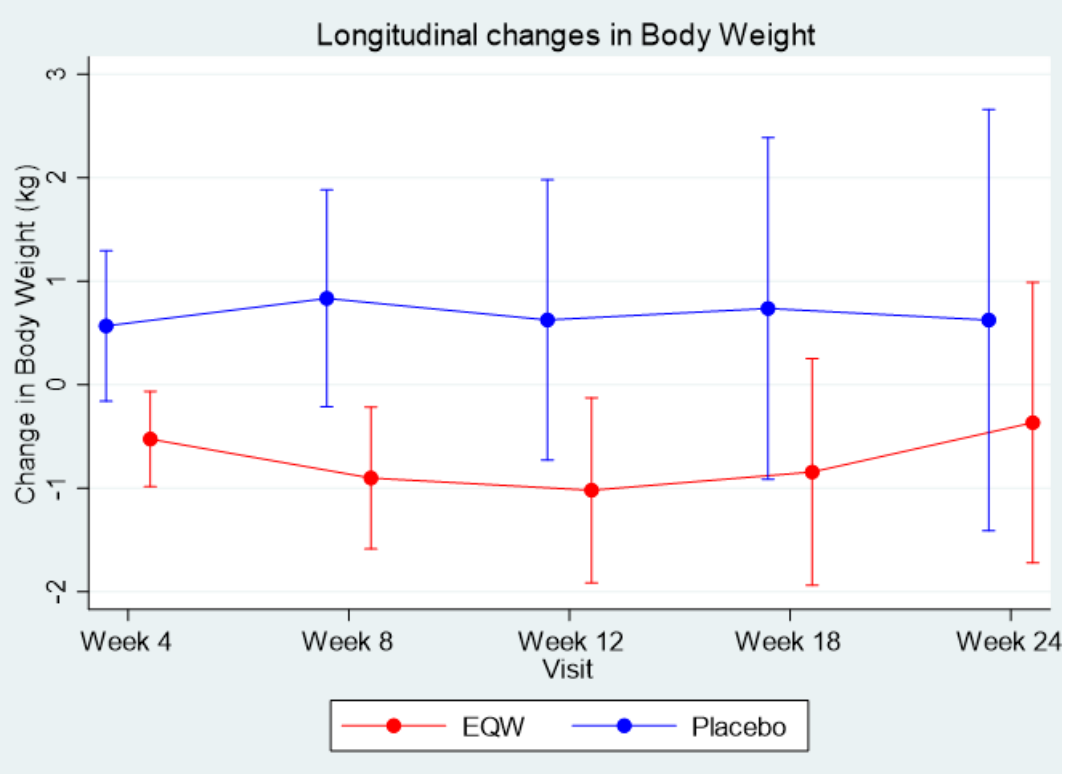
Figure 12: Results of subgroup analysis by treatment arm, ANCOVA, controlled assessment period, ITT population, FDA analysis



Source: statistical review dated June 2, 2021

Figure 11 and Table 11 show the FDA analysis of the secondary endpoint of change in body weight at Week 24 from baseline utilizing MMRM based on observed data without imputations for missing data.

Figure 11: Longitudinal changes in body weight, Least Square means with 95% CI, controlled assessment period, ITT population, FDA analysis



Source: statistical review dated June 2, 2021

Table 11: Outcomes of body weight analysis, MMRM, controlled assessment period, ITT population, FDA analysis

Change in weight	EQW N=58	Placebo N=24	Difference (EQW versus Placebo) at Week 24
Estimate	-0.37	0.63	-0.99
95%CI	(-1.72, 0.99)	(-1.41, 2.66)	(-3.44, 1.46)

Source: statistical review dated June 2, 2021

Patients on EQW experienced some reductions in body weight while patients on placebo did not experience weight changes. The treatment effect estimates for patients on EQW were larger, and the 95% confidence intervals overlapped at each visit.

Similar to FPG, the numerical results for change in body weight adjusted for baseline weight, treatment, geographic region, baseline, and treatment-by-visit interactions do not demonstrate superiority of EQW over placebo.

Durability of Response

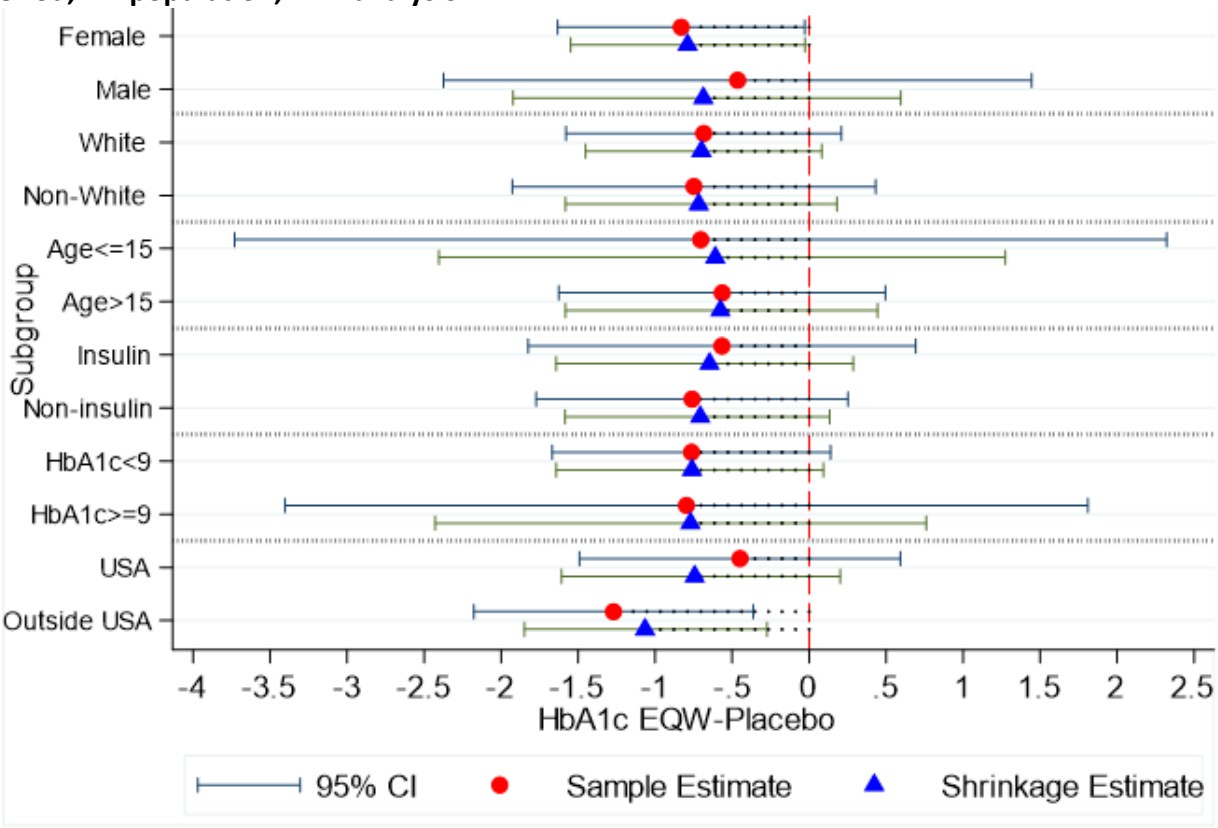
In patients randomized to EQW, the Applicant's descriptive analysis (excluding data after rescue or premature discontinuation) shows the mean HbA1c change from baseline gradually increased over 52 weeks returning to approximate baseline levels by Week 52 (-0.1%) suggesting a possible lack of durability of glycemic control with EQW treatment in study BCB114, although more likely suggesting rapid disease progression given the notable increase in HbA1c at 24 weeks in the placebo arm. Lack of a control arm over the entire 52-week period limits conclusions.

Subpopulations

Dr. Kettermann measured the estimates of treatment effect in change in HbA1c for subgroups including age, gender, and race by using the same ANCOVA model as for the primary analysis. Since most of the patients were from the United States, the subgroup analysis by region included only two categories: United States and outside of United States. Additionally, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates. Refer to the statistical review for the Bayesian hierarchical model assumptions.

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups are presented in Figure 12 below. A subgroup analysis demonstrated consistency of effect.

Figure 12: Results of subgroup analysis by treatment arm, ANCOVA, controlled assessment period, ITT population, FDA analysis



Source: statistical review dated June 2, 2021

7. Integrated Assessment of Effectiveness

Since there was only one trial submitted for review, subsections not applicable to this submission have been deleted.

7.1. Integrated Assessment of Effectiveness

The primary efficacy endpoint was change from baseline in hemoglobin A1c (HbA1c) after 24 weeks of treatment. The prespecified primary efficacy analyses utilized the longitudinal repeated measures (MMRM) analysis in the evaluable population excluding post-rescue and discontinuation data and demonstrated superiority of EQW over placebo at Week 24. The statistical superiority of EQW over placebo was borderline (-0.71; 95% CI [-1.42, 0]) when the

Agency's recommended methodology considered to be the most appropriate analysis technique (including data regardless of adherence or rescue and placebo-based multiple washout imputations to impute for patients without HbA1c data at Week 24) was utilized. The MMRM analysis that included data regardless of rescue demonstrated superiority (-0.87; 95% CI [-1.51, -0.23]). The sample size for this trial was small, especially the small number of patients on placebo (the randomization ratio was 5:2). Therefore, the confidence interval for the change in HbA1c was large.

Nonetheless, given the similar trend in treatment effect in either analysis and generally similar safety profile to the adult population, the collective evidence from the prespecified (MMRM) and more conservative (washout imputations) analysis of the primary endpoint supports effectiveness of EQW in pediatric population.

Although the Applicant intended to enroll pediatric patients aged 10 years and older, the youngest patient enrolled in the study was 11 years old. The submitted data support the use of EQW for the proposed indication for pediatric subjects aged 10 and older, as there is no reason to believe that efficacy would differ between patients 10 and 11 years old.

In patients randomized to EQW, the Applicant's descriptive analysis (excluding data after rescue or premature discontinuation) shows the mean HbA1c change from baseline gradually increased over 52 weeks returning to approximate baseline levels by Week 52 (-0.1%) suggesting a possible lack of durability of glycemic control with EQW treatment in study BCB114, although more likely suggesting rapid disease progression given the notable increase in HbA1c at 24 weeks in the placebo arm. Lack of a control arm over the entire 52-week period limits conclusions.

The prespecified secondary endpoints of change in fasting plasma glucose and change in weight did not demonstrate superiority of EQW over placebo.

A subgroup analysis measuring the treatment effect in change in HbA1c for age, gender, race, and region (United States and outside of United States) demonstrated consistency of effect.

I believe the Applicant has provided adequate evidence of an effect of EQW in the treatment of T2DM in the proposed pediatric population.

8. Review of Safety

8.1. Safety Review Approach

The safety of EQW has been well studied in T2DM adult patients. The Applicant did not prespecify any adverse events of special interest for study BCB114. Adverse events were captured on the adverse event eCRF. Hypoglycemia events were captured on a hypoglycemia eCRF. The safety population was comprised of all randomized patients who received at least one dose of study medication regardless of planned treatment.

My safety review was in part focused on previously identified risks and included a review of data quality and integrity[11], adverse events, and laboratory datasets. Adverse events were analyzed by MedDRA Preferred Term Version 23 and by pooling of the similar adverse events referred to as the FDA Medical Dictionary for Regulatory Activities (MedDRA) Query (FMQ).

The safety profile of EQW was assessed via review of the safety data from the placebo-controlled assessment period of study BCB114. To assess longer-term safety e.g., possible effect of drug on puberty progression, growth, and possible rare or idiosyncratic events I reviewed the 52-week data of patients randomized to EQW who continued to the open-label extension period for an additional 28 weeks. However, due to lack of a comparator the interpretation of the 52-week safety data is limited.

I reviewed the Applicant's safety data presented in the BCB114 CSR. When appropriate, the safety data was verified by analysis of the submitted tabulation or analysis datasets and additional evaluations were performed on these datasets to investigate potential signals or patient level data.

Some of the safety data were explored for signals in specific demographics. This was achieved by either evaluating descriptive statistics or through a graphic analysis. When appropriate, Information Requests were sent to the Applicant for clarifications or additional analyses. Except where noted, safety analyses used the safety population and the on-treatment data. In general, the key safety findings were reproducible and able to be confirmed using the submitted datasets.

8.2. Review of the Safety Database

8.2.1. Overall exposure

The mean duration of EQW exposure in BCB114 during the controlled assessment period was

[11] Data integrity, including traceability of SDTM to ADaM data was done by the Office of Computational Science Core Data Fitness team.

157.3 days or about 5 months (Table 12**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**). The mean duration of EQW exposure in BCB114 during the controlled assessment period and open-label extension period combined was 356.7 days or 1 year. Duration of exposure to EQW was defined by the Applicant as last dose of EQW date - first dose of EQW date + 7 days.

Table 12: Duration of exposure, controlled assessment period, safety population

Duration of exposure (days)*	EQW n=59	Placebo N=23	Total N=82
Mean	157.3	165.6	159.6
SD	44.4	18.26	38.94
Min	170	168	168.5
Max	210	180	210
Median	170	168	168.5

*Defined as last dose date-first dose date + 7 days.
Source: BCB114 CSR.

A total of 59 patients received EQW in study BCB114 during the controlled assessment period. Among these patients, 50 (84.7%) were exposed to a least 24 weeks. 38 (64.4%) patients who continued into the uncontrolled period were exposed for 52 weeks (Table 13).

Table 13: Patients treated by duration, controlled assessment period and open-label extension period, safety population

Exposure category (weeks)	EQW N=59	Placebo N=23	Placebo to EQW N=22
	n (%)	n (%)	n (%)
≥ 1	59 (100)	23 (100)	22 (100)
≥ 6	57 (96.6)	23 (100)	19 (86.4)
≥ 12	52 (88.1)	23 (100)	19 (86.4)
≥ 24	50 (84.7)	20 (87)	16 (72.7)
≥ 36	48 (81.4)	-	-
≥ 42	47 (79.7)	-	-
≥ 48	46 (78)	-	-
≥ 52	38 (64.4)	-	-

Source: Regulatory Response dated April 16, 2021.

Reviewer Comment: As EQW's safety profile has been previously evaluated in adults, the

exposure and size of the safety database is considered generally adequate and similar to the exposure obtained in the liraglutide pediatric trial that supported expanding Victoza's indication to patients ages 10 years and older.

8.2.2. Relevant characteristics of the safety population

Demographic and baseline characteristics of the trial population have been previously discussed in Section 6.1.2 of this review.

8.2.3. Adequacy of the safety database

Discussed above under Section **Error! Reference source not found.**.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The JumpStart Service was consulted to review data quality for this sNDA, including an SDTM assessment and SDTM to ADaM traceability. The overall data and submission quality are reasonable. Adverse event coding was evaluated using the JumpStart output in which a matching score was calculated comparing the verbatim term to the coded preferred term (PT). The adverse event coding was reasonable.

8.3.2. Categorization of Adverse Events

The SAP specified that treatment-emergent adverse events (TEAE) in study BCB114 are defined as adverse events occurring after the first dose of study medication through the end of the treatment plus 7 days or plus 90 days for SAEs (or other clinically significant events judged as related to drug), including adverse events collected after patients initiate possible glycemic rescue therapy.

Reviewer Comment: Considering that plasma exenatide concentrations generally fall below the minimal detectable concentration approximately 10 weeks after discontinuation of EQW, the proposed cut-offs for identification of treatment-emergent adverse events may be short; however, the protocol was designed with a follow-up visit 10 weeks after end of study treatment. A review of the ADAE dataset set to "10-week follow-up phase" did not identify adverse events.

For patients who entered the extension period, adverse events, hypoglycemia, and concomitant medications recorded at the Week 24 visit were assigned to the open-label extension period, and the remainder of the safety assessments at the Week 24 visit were assigned to the controlled assessment period.

8.3.3. Routine Clinical Tests

In study BCB114, the Applicant assessed safety by examination of adverse events, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide.

8.4. Safety Results

8.4.1. Deaths

The Applicant did not report any deaths during study BCB114.

8.4.2. Serious Adverse Events (SAE)

Controlled assessment period
In the controlled assessment period, the incidence of on-treatment SAEs was low: 1 (4.3%) in the placebo group and 2 (3.4%) in the EQW group. Results of the MedDRA Preferred Term (PT) analysis is shown in Table 14 below. In general, a review of the narratives (described below) of these SAEs did not suggest causality to EQW.

Table 14: Incidence of on treatment SAEs by SOC and PT, controlled assessment period, safety population

	EQW 2 mg n= 59	Placebo n= 23
Patients with any SAEs n (%)	**2 (3.4%)**	**1 (4.3%)**
Psychiatric disorders	**1 (1.7%)**	**0**
Major depression	1 (1.7%)	0
Infections and infestations	**1 (1.7%)**	**0**
Abscess limb	1 (1.7%)	0
Gastrointestinal disorders	**0**	**1 (4.3%)**
Irritable bowel syndrome	0	1 (4.3%)

Created by reviewer, JReview, ADaM dataset

All SAEs PTs during the controlled assessment period were single events. The SAE PT major depression in the EQW group and irritable bowel syndrome in the placebo group were severe in intensity and PT abscess limb was moderate in intensity. None of the SAEs led to study or study drug withdrawal.

The SAE PT abscess limb in the EQW arm occurred in the thigh and was not related to an injection site reaction.

Narrative for SAE PT major depression (b) (6)

SAE PT major depression occurred 6 weeks following EQW discontinuation due to "withdrawal by subject". The narrative states the patient is a 15-year-old biracial male with history of T2DM for 6 months treated with metformin at baseline, obesity (baseline BMI= 45 kg/m2), insomnia, attention deficit hyperactivity disorder, learning disability, and headaches. Patient was noncompliant and discontinued study treatment on study day 181. While on EQW, the TEAEs (all mild in severity) gingival pain, diarrhea, abdominal pain upper (led to temporary study drug interruption), upper respiratory tract infection, and ligament sprain were captured on the eCRF. On study day 223 the patient presented to the emergency department with suicidal ideation and was diagnosed with major depression requiring hospitalization. The narrative states prior to hospitalization the patient had issues with complex family dynamics. Patient was also diagnosed with asthma during the hospitalization. The patient was discharged on study day 239. This patient also had an event of hypoglycemia classified as Level 3 hypoglycemia which is discussed in Section 8.4.4 of this review.

Open-label extension period

During the open-label extension period, 3 (6%) in the EQW group and 1 (4.5%) patient in the "placebo to EQW" group experienced an SAE (Table 15). None of the SAEs led to study or study drug withdrawal. The SAE PT suicidal ideation (severe intensity) led to drug interruption. Due to lack of comparative data, interpretation of data from the open-label extension period is limited.

Table 15: Incidence of treatment-emergent SAEs by SOC and PT, open-label extension period, safety population

	EQW 2 mg n= 50	Placebo to EQW n= 22
Patients with any SAEs n (%)	**3 (6%)**	**1 (4.5%)**
Psychiatric disorders	**1 (2%)**	**1 (4.5%)**
Suicidal ideation	1 (1%)	1 (4.5%)
Infections and infestations	**2 (4%)**	**0**
Cellulitis	1 (2%)	0
Pneumonia	**1 (2%)**	0
Gastrointestinal disorders	**1 (2%)**	**0**
Gastritis	1 (2%)	0

Created by reviewer, JReview, ADAM dataset

The SAE PT cellulitis in the EQW arm occurred in the lower extremity and was not related to an injection site reaction.

The SAE PT suicidal ideation (severe intensity) occurred in a 17-year-old White and Mexican male (b) (6) with a history of T2DM on metformin, depression on Zoloft, aggression/mood on Trileptal, attention deficit hyperactivity disorder, asthma, hypertension, hyperlipidemia and no family history of depression or suicide. Patient was randomized to EQW and on day 281 developed suicidal ideation/plan (for the first time with no identified personal or environmental

trigger) with no requiring a referral to a mental facility.
The SAE PT (b) (6)) suicidal ideation in the "placebo to EQW" arm (severe intensity) occurred in a 16-year-old Black or African American female with history of T2DM on metformin at baseline, hypertension, with no documented medical history of depression at the time of screening. On study day 414 (Week 59) the patient developed suicidal ideation/plan (predisposing factor was conflict with parents) requiring hospitalization and treatment. The narrative suggests that the increased feeling of depression coincided with the initiation of insulin therapy as rescue at Week 52.states

Narrative for SAE gastritis (b) (6)
The patient was a 16-year-old White female with T2DM for 2 months at baseline, hypertension, polycystic ovary syndrome, and hypothyroidism randomized to EQW with onset of SAE gastritis (moderate intensity) on study day 200 for 4 days requiring hospitalization and treatment. EQW was continued and the vital signs remained normal. An abdominal ultrasound showed mild hepatic steatosis and an X-ray showed a cascade stomach with hypersecretion and mucosal inflammation. The narrative suggests diet led to the gastrointestinal symptoms as the patient consumed a large meal with incompatible food types and similar symptoms were experienced by the sister).

Two SAEs occurred off-treatment: diabetic ketoacidosis and dengue fever and unlikely related to EQW.

Narrative for SAE diabetic ketoacidosis
The patient was a 17-year-old female randomized to "placebo to EQW" group with history of T2DM for almost 10 years treated with insulin and metformin at baseline. HbA1c at baseline was 10.7% which increased to 11.7% at Week 52. Patient was treated with EQW from day 169 to 280. Per the narrative, the event of diabetic ketoacidosis (severe intensity) occurred on study day 410, about 6 weeks after study completion and 18 weeks after last dose of drug, requiring hospitalization for a day. The narrative states the investigator reported non-compliance with insulin regimen and clarified the patient's family received diabetes education regarding diabetes and sick day management.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant states there were no dropouts or discontinuation of study treatment due to adverse events.

A review of the submitted ADAE dataset shows 3 (5.1%) and 1 (2%) of patients on EQW vs. 0 on placebo experienced a treatment-emergent adverse event that led to study drug interruption during the controlled assessment period and open-label extension periods respectively (Table 16).

Table 16: Treatment-emergent adverse events requiring study drug interruption, controlled assessment period, safety population

Dictionary Derived Term	Unique Subject Identifier	EQW
Abdominal pain	D5551C00002 (b) (6)	1 (1.7%)
Abdominal pain upper	D5551C00002	1 (1.7%)
Acne	D5551C00002	1 (1.7%)
Dyspepsia	D5551C00002	1 (1.7%)
Abdominal distension		1 (1.7%)
	Subjects(filtered)	3 (5.1%)
	1stColItemSubjects	59 (100.0%)

Created by reviewer, JReview, ADaM dataset

A narrative for patient (b) (6)) randomized to EQW who discontinued EQW as "withdrawal by subject" due to gastrointestinal symptoms (PTs abdominal pain, dyspepsia, and abdominal distension) is described under Section 8.4.2 of this review. Intolerability due to drug-related gastrointestinal events is expected in some patients.

The PT abdominal pain (b) (6) requiring study drug interruption occurred about 20 days prior to premature withdrawal from the study by the patient due to "withdrawal by subject". A narrative of this patient is provided in Section 8.4.2 of this review.

In the open-label extension period the treatment-emergent adverse event impulsive behavior and SAE suicidal ideation in a patient (b) (6) randomized to "placebo to EQW " led to EQW interruption. Refer to Section 8.4.2 for a narrative.

8.4.4. Significant Adverse Events

Gastrointestinal treatment-emergent adverse events and hypoglycemia events are discussed in this section.

Gastrointestinal events

In the controlled assessment period, the incidence of gastrointestinal treatment-emergent adverse events was 13 (22%) in the EQW group and 6 (26.1%) in the placebo group. However, the PTs nausea, vomiting, diarrhea, and abdominal pain were reported in a higher proportion of patients in the EQW group compared with the placebo group as shown in Table 17 below.

Table 17: SOC Gastrointestinal disorders, controlled assessment period, safety population

Dictionary Derived Term	EQW 2 mg	Placebo
Diarrhoea	5 (8.5%)	1 (4.3%)
Nausea	4 (6.8%)	1 (4.3%)
Abdominal pain upper	3 (5.1%)	0
Vomiting	3 (5.1%)	0
Abdominal pain	2 (3.4%)	3 (13%)
Abdominal distension	1 (1.7%)	0
Gastrointestinal pain	0	1 (4.3%)
Gastrooesophageal reflux disease	0	1 (4.3%)
Irritable bowel syndrome	0	1 (4.3%)
Decreased appetite	0	1 (4.3%)
Subjects(filtered)	13 (22%)	6 (26.1%)
1stColItemSubjects	59 (100%)	23 (100%)

Created by reviewer, JMPClinical, ADaM dataset

During the controlled assessment period, none of the treatment-emergent gastrointestinal adverse events led to permanent study drug withdrawal, none were severe in intensity or serious.

In the controlled assessment period, one severe gastrointestinal TEAE (PT gastroesophageal reflux) and one SAE (PT irritable bowel syndrome) occurred in patients on placebo.

In the open-label extension period a generally similar proportion of patients in the EQW (6 [12%]) and "placebo to EQW" arms (3 [13.6%]) experienced gastrointestinal events. None led to study drug interruption or study drug or study withdrawal. None were severe in intensity. One SAE gastritis (b) (6) in the "placebo to EQW" group (moderate in intensity) was observed. Refer to Section 8.4.2 for a narrative of this patient. Overall, the frequency of gastrointestinal events in the open-label extension period was lower (9 [12.5%]) than the frequency of gastrointestinal events in the EQW arm during the controlled assessment period (13 [22%]).

Hypoglycemia

Per the SAP, hypoglycemic events were to be captured during the treatment period plus 7 days on a hypoglycemia event eCRF. Patients were instructed to report hypoglycemia symptoms along with a blood glucose and the investigators were to complete the hypoglycemia eCRF if the symptoms were consistent with hypoglycemia. If an asymptomatic blood glucose value of < 54 mg/dL was noted, the investigator had to complete the hypoglycemia eCRF if in his/her judgment the circumstances around the glucose value were consistent with hypoglycemia.

The Applicant clarified (regulatory response dated April 16, 2021) that the investigators were to use medical judgment to consider whether to document an asymptomatic event with a glucose value of < 54 mg/dL as hypoglycemia. Consequently, although some investigator-reported cases of asymptomatic hypoglycemia with glucose < 54 mg/dL were captured, it is possible that not all events of glucose < 54 mg/dL in asymptomatic patients were documented if the investigator believed the event to not be a true case of hypoglycemia. The Applicant also stated by definition, the Level 2 hypoglycemia data presented in the BCB114 clinical study report captures all the < 54 mg/dl hypoglycemia events reported by the investigators, regardless of symptoms, during the study treatment period.

Reviewer Comment: Per the Applicant's response, it is possible that some asymptomatic < 54 mg/dL events were not captured by the investigators in study BCB114.

The Applicant used several classification systems for characterizing hypoglycemia events i.e., mild/moderate/severe, major/minor/other and Level 1/2/3 defined by the 2016 American Diabetes Association (ADA) Position Statement and the 2018 International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical guidelines.

The Applicant's data shows a total of 13 hypoglycemic events in 8 (13.6%) patients on EQW and 7 events in 1 (4.3%) patient on placebo (in favor of placebo) was captured on the hypoglycemia eCRF during the controlled assessment period (3 hypoglycemia events were captured on both the adverse events and the hypoglycemia eCRF). None of the hypoglycemia events required hospitalization and none were serious.

The Agency requested (Information Request dated April 6, 2021) that the Applicant classify severe hypoglycemia according to the ADA definition.

In response (April 23, 2021), the Applicant noted 2 (3.4%) and 0 patients experienced severe hypoglycemia (ADA 2013 definition) in the EQW and placebo groups respectively during the controlled assessment period. In a subsequent response (May 13, 2021) to a follow-up Information Request (May 4, 2021), the Applicant clarified that due to a programming error, one of the patients was incorrectly identified (b) (6) as severe hypoglycemia. The Applicant further clarified (regulatory response dated May 24, 2021) this patient did not require assistance of another person to obtain treatment. Therefore, only 1 patient (b) (6) on EQW vs 0 in the placebo group experienced severe hypoglycemia by the ADA definition[13] during

[12] The patient is a 14-year-old female randomized to EQW who experienced an event of asymptomatic hypoglycemia (SMBG= 38 mg/dL) on study day 90 while awake. The ADHYPO dataset indicated the event was "severe" in intensity while the narrative stated the intensity was "mild". The Applicant clarified (regulatory response dated May 21, 2021) the reason for the discrepancy was because this event was reported as "missing severity" in the hypoglycemia eCRF; therefore, the intensity was imputed as "severe". The discrepancy between the adverse event and hypoglycemia eCRF was queried but could not be resolved because of site closure as a result of the COVID-19 pandemic.

[13] Defined by American Diabetes Association and the Endocrine Society; Diabetes Care, v.36 (5); 2013 May

the controlled assessment period. Below is a narrative related to the event categorized by the Applicant as severe hypoglycemia. Refer to Section 8.4.2 for this patient's (b) (6) full narrative.

15-year-old male (b) (6) with T2DM for 6 months treated with metformin at baseline and obesity (baseline BMI= 45 kg/m2) experienced an event of hypoglycemia about 2 weeks after starting EQW. The event occurred for a duration of 8 hours while the patient was awake. Reported symptoms were confusion, dizziness, drowsiness, hunger and feeling shaky and required third party assistance (type of assistance not documented). The fingerstick blood glucose was 84 mg/dL. No history of severe hypoglycemia was documented in the medical history. The investigator reported the cause of severe hypoglycemia event was "fasting before sedation for a medical test". The narrative states the reported clinical course was not consistent with true hypoglycemia given the 8-hour duration of the episode and the blood glucose of 84 mg/dL.

The Applicant states in study BCB114 severe hypoglycemia was defined as an event with severe cognitive impairment requiring external assistance for recovery consistent with the ADA's definition. Therefore, severe hypoglycemia was defined by requiring a "Yes" response on the Hypoglycemic Event eCRF for the question "Symptomatic Hypoglycemia Event?" and also a "Yes" response on the question "Did this Event Require Assistance to resolve because of severe impairment in consciousness or behavior?". Any patients answering "yes" to each of these questions on the eCRF was considered to have had an event of "severe hypoglycemia" per the ADA definition (regardless of blood glucose values reported). Therefore, by definition the patient above was categorized as severe hypoglycemia based on requiring external assistance to recover and symptom of confusion, even though the blood glucose was reported as 84 mg/dL at the time of the event.

Table 18Table 19 shows the severe hypoglycemia incidence and rate by age group during the controlled assessment period.

Table 18: Hypoglycemia incidence and rate by age groups, controlled assessment period, safety population

		EQW			Placebo			
Age Group (years)		Number (%) of patients [a]	Number of Events	Exposure adjusted event rate [b]	Number (%) of patients [a]	Number of Events	Exposure adjusted event rate [b]	Estimate of difference between treatment groups (CI) [c]
		(N=59) (Patient-years=25.4)			(N=23) (Patient-years=10.4)			
All ages	Patients with any hypoglycemia	8 (13.6)	13	0.51	1 (4.3)	7	0.67	
	Blood glucose < 54 mg/dL with or without symptoms	2 (3.4)	2	0.08	1 (4.3)	1	0.10	-0.01 (-0.178, 0.079)
	Severe hypoglycemia [d]	1 (1.7)	1	0.04	0	0	0.00	0.02 (-0.127, 0.090)
	Severe hypoglycemia and Blood glucose < 54 mg/dL with or without symptoms	0	0	0.00	0	0	0.00	
		(N=19) (Patient-years=8.5)			(N=5) (Patient-years=2.1)			
10-14	Patients with any hypoglycemia	2 (10.5)	3	0.35	0	0	0.00	
	Blood glucose < 54 mg/dL with or without symptoms	1 (5.3)	1	0.12	0	0	0.00	0.05 (-0.384, 0.246)
	Severe hypoglycemia [d]	0	0	0.00	0	0	0.00	
	Severe hypoglycemia and Blood glucose < 54 mg/dL with or without symptoms	0	0	0.00	0	0	0.00	
		(N=40) (Patient-years=16.9)			(N=18) (Patient-years=8.3)			
> 14	Patients with any hypoglycemia	6 (15.0)	10	0.59	1 (5.6)	7	0.84	
	Blood glucose < 54 mg/dL with or without symptoms	1 (2.5)	1	0.06	1 (5.6)	1	0.12	-0.03 (-0.234, 0.083)
	Severe hypoglycemia [d]	1 (2.5)	1	0.06	0	0	0.00	0.03 (-0.152, 0.129)
	Severe hypoglycemia and Blood glucose < 54 mg/dL with or without symptoms	0	0	0.00	0	0	0.00	

CI=Confidence Interval; N Number of patients in treatment group and age group.
a Patients with multiple events in the same category are counted only once in that category.
b For exposure-adjusted event rate calculation, the numerator is the number of events, and the denominator is the total exposure during the controlled assessment period from patients in the analysis set by treatment group and age group.
c The confidence intervals for the difference in proportions were computed using the Newcombe method.
d As defined by American Diabetes Association and the Endocrine Society; Diabetes Care, v.36 (5); 2013 May.
Note the Applicant has not provided a definition for "any hypoglycemia".
Source: Regulatory response dated May 24, 2021.

To examine a relationship between insulin use, hypoglycemia, and treatment with EQW the Applicant analyzed hypoglycemia events with and without insulin/and or sulfonylurea use at baseline during the controlled assessment period (Table 19).

Table 19: Incidence of hypoglycemia in patients using insulin and/or a sulfonylurea at baseline, controlled assessment period, safety population

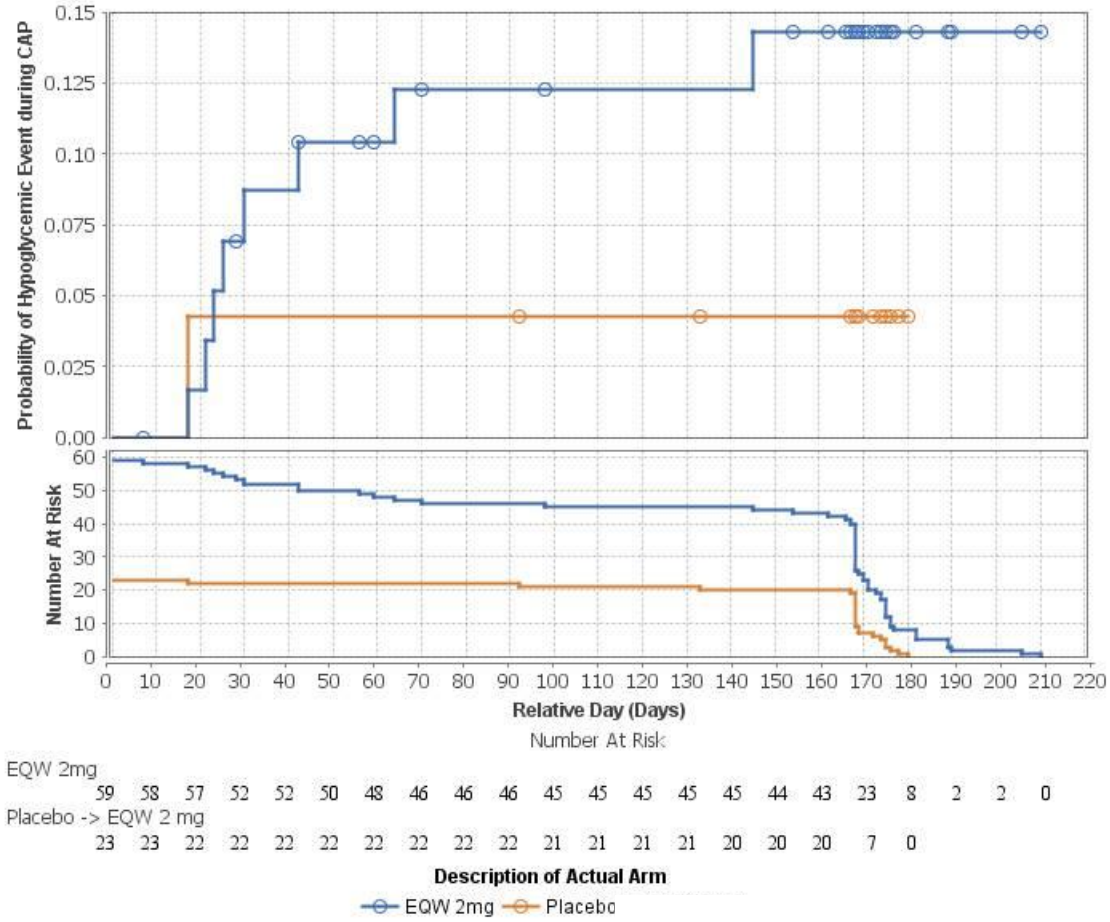
		Number (%) of patients with events		
Background insulin and/or Sulfonylurea use		**EQW**	**Placebo**	**Estimate of difference between treatment groups (CI) [b]**
All patients		**N=59**	**N=23**	
	Patients with any hypoglycemia	8 (13.6)	1 (4.3)	
	Blood glucose < 54 mg/dL with or without symptoms	2 (3.4)	1 (4.3)	-0.01 (-0.178, 0.079)
	Severe hypoglycemia [a]	1 (1.7)	0	0.02 (-0.127, 0.090)
Not on background insulin and/or sulfonylurea		**N=31**	**N=12**	
	Patients with any hypoglycemia	2 (6.5)	0	
	Blood glucose < 54 mg/dL with or without symptoms	0	0	
	Severe hypoglycemia [a]	1 (3.2)	0	0.03 (-0.212, 0.162)
On background insulin and/or sulfonylurea		**N=28**	**N=11**	
	Patients with any hypoglycemia	6 (21.4)	1 (9.1)	
	Blood glucose < 54 mg/dL with or without symptoms	2 (7.1)	1 (9.1)	-0.02 (-0.311, 0.153)
	Severe hypoglycemia [a]	0	0	

CI, Confidence Interval; N, Number of patients in treatment group and background insulin and/or sulfonylurea use.
a As defined by ADA and the Endocrine Society; Diabetes Care, v.36 (5); 2013 May.
b The confidence intervals were computed using the Newcombe method.
Source: Regulatory response dated May 21, 2021.

In general, the Applicant's data suggests the frequency and rate of Level 2 and severe hypoglycemia events (ADA definition) during the controlled assessment period was low. Consistent with the labeled information, most of the patients (6 [21.4%]) who experienced an event of hypoglycemia were treated at baseline with insulin compared to 2 (6.5%) patients who were not treated with insulin at baseline.

Figure 13 shows time to first event of (any) hypoglycemia during the controlled assessment period, suggesting that most patients on EQW experienced hypoglycemia earlier in the trial.

Figure 13: Time to first event of hypoglycemia, controlled assessment period, safety population



Source: Created by JReview analyst, JReview, ADaM dataset

During the open-label extension period the Applicant's data shows a total of 4 (8%) patients had 5 hypoglycemia events in the EQW group and 1 (4.5%) patient in the "placebo to EQW" group had 8 events. 2 (4%) patients on EQW had 2 events of Level 3 hypoglycemia compared to 0 in the "placebo to EQW" group. The Applicant states 3 of the 4 patients with hypoglycemic events on EQW and the 1 patient with 8 hypoglycemia events in the "placebo to EQW" group were treated with insulin at baseline.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Results from the MedDRA Preferred Term analysis and FDA MedDRA Query (FMQ) Analysis were generally consistent.

In the controlled assessment period, 17 (73.9%) patients on placebo compared to 36 (61%) patients on EQW experienced a TEAE (in favor of EQW). But the frequency of most SOCs were

higher in the EQW arm compared to placebo.

Table 20 shows the incidence of TEAEs by SOC (≥ 10% in frequency) and PT during the controlled assessment period. The most common SOC in the EQW arm was Infection and Infestations 16 (27.1%) in favor of placebo 5 (21.7%). This SOC was driven by PTs upper respiratory tract infection and nasopharyngitis in the EQW arm. The second most common SOC Gastrointestinal disorders in the EQW arm is discussed under Section 8.4.4 of this review. The third most common SOC was Metabolism and nutrition disorders in EQW arm 7 (11.9%) in favor of placebo 2 (8.7%). The PTs hypoglycemia and dyslipidemia drove this SOC in the EQW arm.

Table 20: Incidence of patients with TEAE by SOC (≥ 10% on EQW) and PT, controlled assessment period, safety population

	EQW 2mg n=59	Placebo n=23
Patients with at least 1 TEAE n (%)	**36 (61.0%)**	**17 (73.9%)**
Infections and infestations	**16 (27.1%)**	**5 (21.7%)**
Upper respiratory tract infection	6 (10.2%)	0
Nasopharyngitis	4 (6.8%)	2 (8.7%)
Urinary tract infection	3 (5.1%)	2 (8.7%)
Abscess limb	1 (1.7%)	0
Ear infection	1 (1.7%)	0
Sinusitis	1 (1.7%)	1 (4.3%)
Vaginal infection	1 (1.7%)	0
Pharyngitis bacterial	1 (1.7%)	0
Influenza	0	1 (4.3%)
Staphylococcal skin infection	0	1 (4.3%)
Tonsillitis	0	1 (4.3%)
Gastrointestinal disorders	**13 (22.0%)**	**6 (26.1%)**
Diarrhoea	5 (8.5%)	1 (4.3%)
Nausea	4 (6.8%)	1 (4.3%)
Abdominal pain upper	3 (5.1%)	0
Vomiting	3 (5.1%)	0
Abdominal pain	2 (3.4%)	3 (13.0%)
Dyspepsia	1 (1.7%)	0
Gingival pain	1 (1.7%)	0
Abdominal distension	1 (1.7%)	0
Gastrointestinal pain	0	1 (4.3%)
Gastrooesophageal reflux disease	0	1 (4.3%)
Irritable bowel syndrome	0	1 (4.3%)
Salivary gland mucocoele	0	1 (4.3%)
Metabolism and nutrition disorders	**7 (11.9%)**	**2 (8.7%)**
Hypoglycaemia	3 (5.1%)	0
Dyslipidaemia	2 (3.4%)	0
Hyperglycaemia	1 (1.7%)	1 (4.3%)
Hypertriglyceridaemia	1 (1.7%)	0
Increased appetite	1 (1.7%)	0
Decreased appetite	0	1 (4.3%)
Respiratory, thoracic and mediastinal disorders	**6 (10.2%)**	**1 (4.3%)**
Cough	4 (6.8%)	1 (4.3%)
Respiratory tract congestion	2 (3.4%)	0
Oropharyngeal pain	2 (3.4%)	0
Nasal congestion	2 (3.4%)	0
Dyspnoea	1 (1.7%)	0
Nervous system disorders	**6 (10.2%)**	**3 (13.0%)**
Headache	4 (6.8%)	2 (8.7%)
Memory impairment	1 (1.7%)	0
Dizziness postural	1 (1.7%)	0
Syncope	0	1 (4.3%)
General disorders and administration site conditions	**6 (10.2%)**	**2 (8.7%)**
Injection site erythema	3 (5.1%)	1 (4.3%)
Injection site pruritus	2 (3.4%)	1 (4.3%)
Injection site swelling	1 (1.7%)	0
Injection site pain	1 (1.7%)	0
Injection site nodule	1 (1.7%)	0
Injection site induration	1 (1.7%)	1 (4.3%)
Non-cardiac chest pain	1 (1.7%)	0
Injection site bruising	1 (1.7%)	0
Skin and subcutaneous tissue disorders	**6 (10.2%)**	**2 (8.7%)**
Dermatitis contact	1 (1.7%)	0
Acne	1 (1.7%)	0
Ingrowing nail	1 (1.7%)	0
Night sweats	1 (1.7%)	0
Dermal cyst	1 (1.7%)	0
Urticaria	1 (1.7%)	0
Skin odour abnormal	1 (1.7%)	0
Skin ulcer	0	1 (4.3%)
Onychoclasis	0	1 (4.3%)

Created by reviewer, JReview, AdaM dataset; TEAE: treatment-emergent adverse event

Table 21: Incidence of adverse reaction by PT (≥ 2% and > 1 event on EQW), controlled assessment period, safety population

Dictionary Derived Term	EQW	Placebo
Diarrhoea	5 (8.5%)	1 (4.3%)
Nausea	4 (6.8%)	1 (4.3%)
Injection site erythema	3 (5.1%)	1 (4.3%)
Vomiting	3 (5.1%)	0
Hypoglycaemia	3 (5.1%)	0
Abdominal pain upper	3 (5.1%)	0
Injection site pruritus	2 (3.4%)	1 (4.3%)
Subjects(filtered)	14 (23.7%)	3 (13.0%)
1stCollItemSubjects	59 (100.0%)	23 (100.0%)

Created by reviewer, JReview, ADaM dataset.

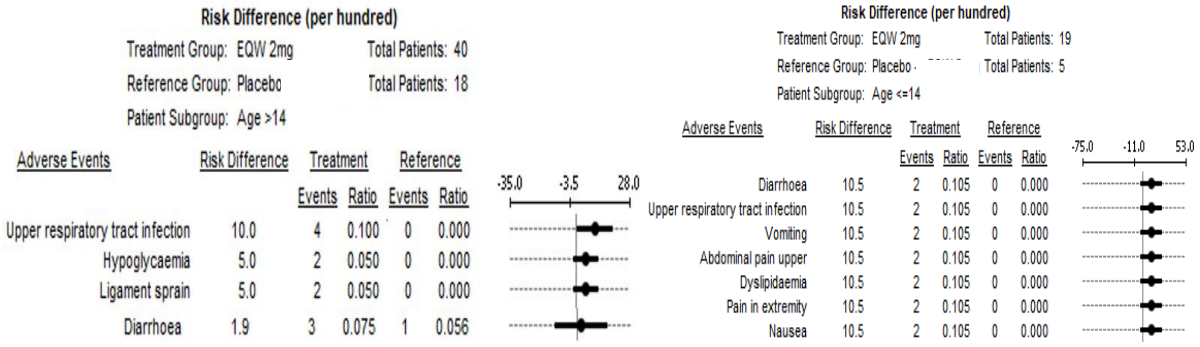
In the controlled assessment period, 61% of patients reported at least one adverse event in the EQW arm compared to 73.9% in the placebo arm. In the EQW arm, the most frequent likely drug-related adverse reactions were related to gastrointestinal events, hypoglycemia, and injection site reactions (Table 21). Hypoglycemia and gastrointestinal events are discussed in Section 8.1. of this review. Some other singular PTs such as hyperglycemia and ketonuria are probably drug related too.

Demographic subgroup analyses of treatment-emergent adverse events:

In the controlled assessment period, a subgroup analysis by race of TEAEs suggested most TEAEs in the EQW arm occurred in the American Indian or Alaska Native race (4 [100%]) patients followed by Black or African American patients (14 [77.8%]). In the EQW arm a similar incidence of TEAEs occurred in the Hispanic or Latino vs. Not Hispanic or Latino ethnicity.

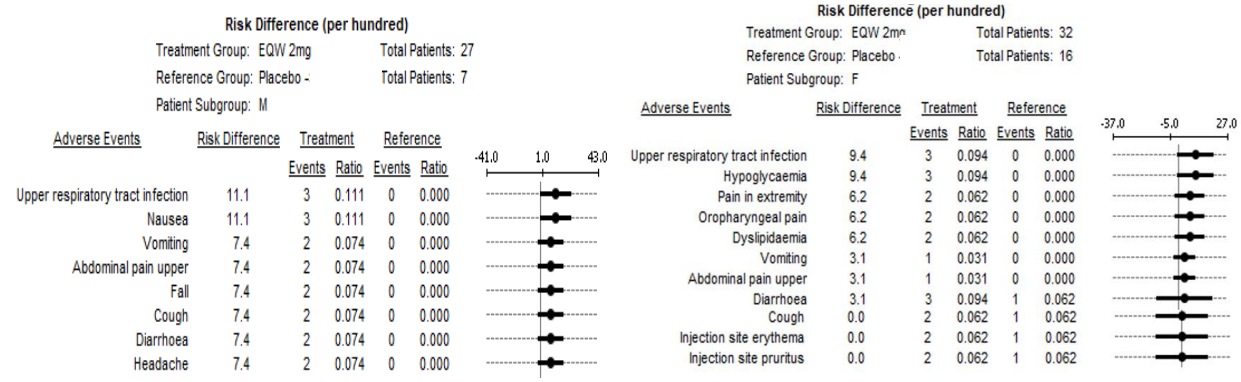
A descriptive subgroup analysis by age (<=14 years old and > 14 years old) and by sex is shown in Table 22 and Table 23, respectively.

Table 22: Risk difference (per 100), subgroup analysis by age (<=14 years old and > 14 years old), controlled assessment period, safety population (including only events with n >1)



A higher risk difference (per 100) between EQW and placebo is observed for GI-related TEAEs in the <=14 years old compared to > 14 years old. Due to small number of patients in each subgroup (especially in the <=14 years old) and small number of events in each subgroup, any conclusions are limited.

Table 23: Risk difference (per 100), subgroup analysis by sex, controlled assessment period, safety population (including only events with n >1)



In the subgroup analysis shown above by sex, no meaningful differences are observed between the two subgroups.

Open-label extension period
In the open-label extension period, treatment-emergent adverse events reported were qualitatively similar to those reported during the controlled period and consistent with the known safety profile of exenatide.

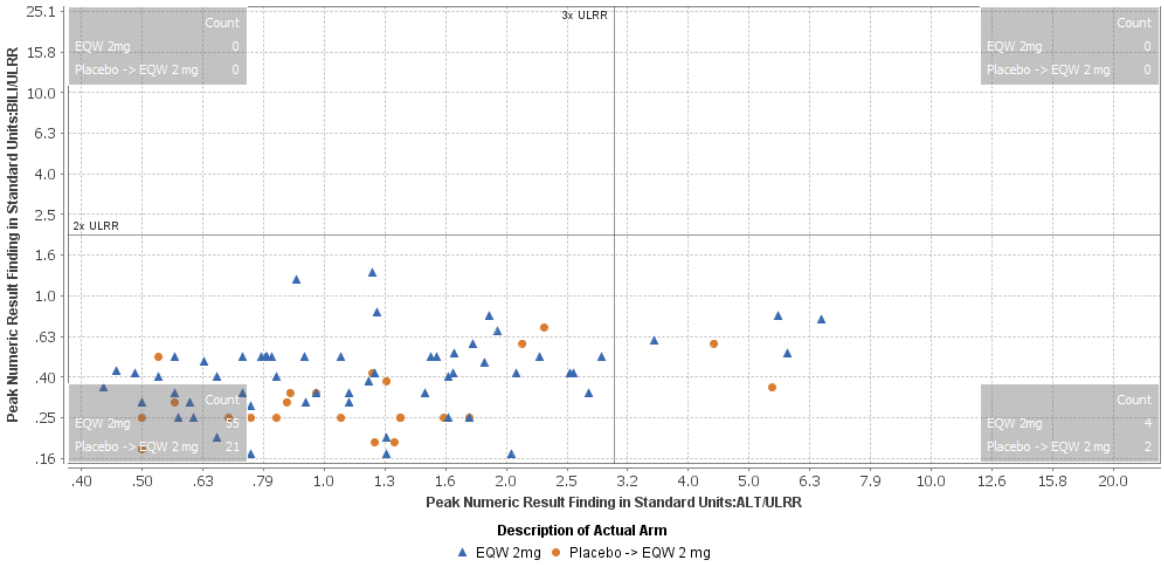
Reviewer's comment: In general, based on the TEAEs reported in study BCB114 no new safety concern with EQW treatment was observed. Section 6 of the Prescribing Information can be updated to state the safety of EQW in pediatric patients age 10 to <18 years old with T2DM was similar to that observed in adults with T2DM.

8.4.6. Laboratory Findings

The protocol specified that abnormal laboratory (and vital signs) were to be reported as an adverse event if deterioration from baseline was observed. Also, laboratory and vitals were reported as adverse events if they fulfilled any of the SAE criteria or led to discontinuation of study drug. The protocol defined the baseline value for laboratory as the last non-missing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

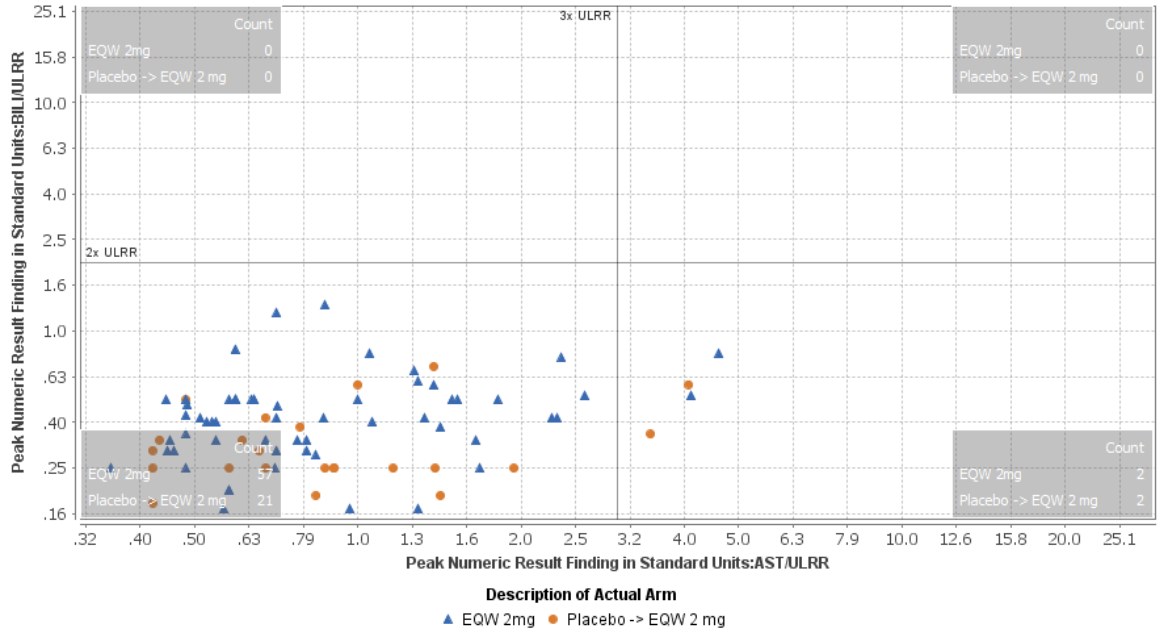
Hepatic enzymes
The submitted data shows that no hepatic event fulfilled Hy's Law criteria during the trial i.e., aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x upper limit of normal (ULN) and total bilirubin ≥ 2 x ULN.

Figure 14: Potential Hy's law plot, alanine transferase vs. bilirubin, controlled assessment period and open-label extension period, safety population



The upper limit of normal for ALT used in the graph is defined by the Applicant with varying cut-offs i.e. 30-41 U/L.
Note patients in the placebo arm (red dots) switched to EQW at Week 24. This plot does not differentiate placebo from placebo to EQW (all shown in red dots).
Created by reviewer, JReview, ADaM dataset

Figure 15: Potential Hy's law plot, aspartate aminotransferase vs. bilirubin, controlled assessment period and open-label extension period, safety population

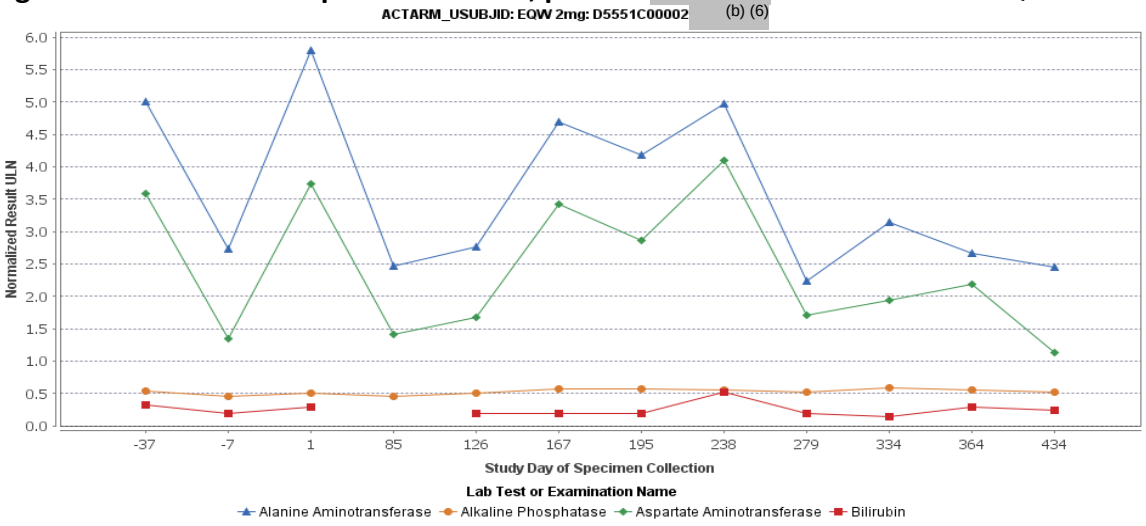


The upper limit of normal for AST used in the graph is defined by the Applicant with varying cut-offs i.e. 31-36 U/L.
Note patients in the placebo arm (red dots) switched to EQW at Week 24. This plot does not differentiate placebo from placebo to EQW (all shown in red dots).

Created by reviewer, JReview, ADaM dataset

The graphical patient profiles (JReview) of patients shown in the left lower quadrant of Figure 14 and Figure 15Figure 14 with transaminase levels > 3 ULN were reviewed as narratives were not available for most. In general, most patients with transaminase > 3 ULN (left lower quadrant of Figure 14 and Figure 15 either had baseline abnormal liver function tests or were diagnosed with non-alcoholic steatohepatitis (NASH) during the study (i.e., 2 patients). The figures below show the patient-level patterns of liver function tests (LFT) for some of these patients.

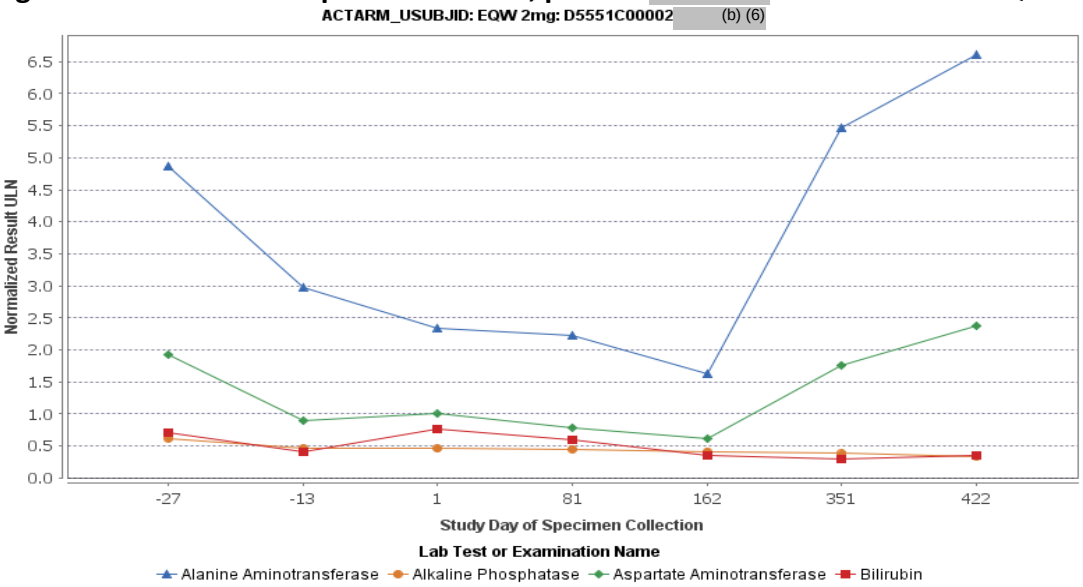
Figure 16: Liver function panel over time, patient (b) (6) randomized to EQW



Source: created by reviewer, JReview, ADaM dataset

The narrative of this patient (b) (6) is provided in Section 8.4.2 of this review. The LFTs show fluctuations of the transaminases during the study with elevated baseline transaminases. The liver ultrasound performed during the study suggested mild hepatic steatosis. The TEAEs (not serious or severe) 'alanine aminotransferase increased' and 'aspartate aminotransferase increased' were captured on eCRF.

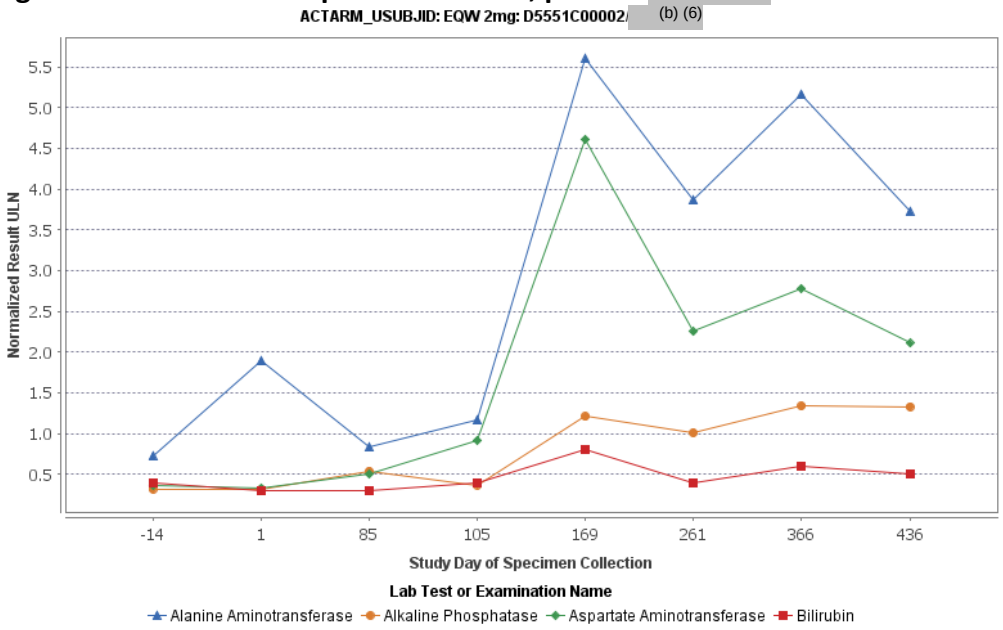
Figure 17: Liver function panel over time, patient (b) (6) randomized to EQW



Source: created by reviewer, JReview, ADaM dataset

13-year-old male with baseline weight 125.1 kg and baseline HbA1c 6.6% on no antidiabetic medications with history of T2DM diagnosed for 1 year and asthma. Patient was exposed to amoxicillin for tonsillitis around day 220 (transaminase elevation starts at day 162). No follow-up lab available after day 432. The patient had elevated transaminases at baseline.

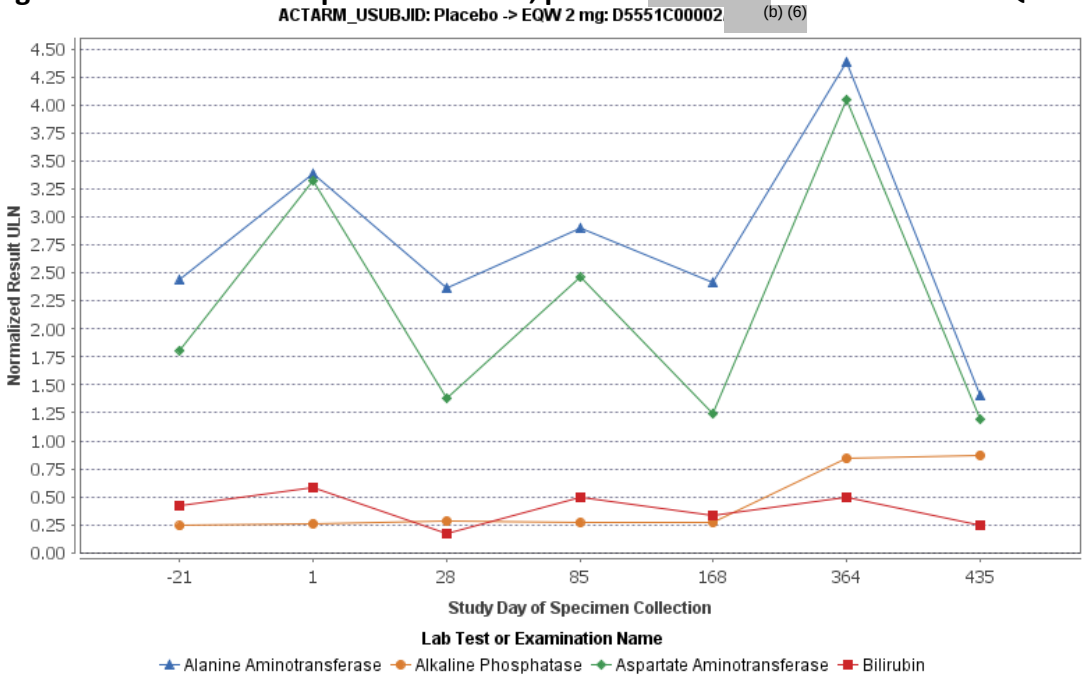
Figure 18: Liver function panel over time, patient (b) (6) randomized to EQW



Source: created by reviewer, JReview, ADaM dataset

11-year-old White female from Mexico on insulin for T2DM (1.1 years duration) with past medical history of subclinical hypothyroidism was diagnosed with hepatic steatosis and dyslipidemia during the study and started on ursodeoxycholic acid and simvastatin/fenofibrate.

Figure 19: Liver function panel over time, patient (b) (6) randomized to EQW



Source: created by reviewer, JReview, ADaM dataset

17-year-old Hispanic White male from United States on insulin and metformin for T2DM (2-year duration). Baseline transaminases were elevated.

Reviewer Comment: These patient-level data suggest that most patients who developed an increase in transaminases had elevated liver function test at baseline or were diagnosed with hepatic steatosis during the trial. No Hy's law event was observed in this study and no TEAE was observed suggestive of liver failure during the study. The Applicant limited enrollment in this trial to patients with transaminase elevation < 3 ULN; conclusions on possible effect of EQW on liver function especially in patients with abnormal liver function at baseline is limited.

The incidence of elevated liver function tests in the treatment groups were evaluated as shown in Table 24 below.

Table 24: Incidence of elevated liver function tests, controlled assessment and open-label extension period, safety population

		Controlled assessment period		Open-label extension period	
		EQW N=59	Placebo N=23	EQW N=50	Placebo to EQW N=22
		n (%)	n (%)	n (%)	n (%)
ALT ukat/L	> 3 ULN	4 (6.8%)	2 (9%)	3 (6%)	0
	> 5 ULN	2 (3.4%)	1 (4%)	3 (6%)	1 (4.5%)
AST ukat/L	> 3 ULN	2 (3.4%)	1 (4%)	1 (2%)	1 (4.5%)
	> 5 ULN	0	0	0	0
Total bilirubin mg/dL	> 2 ULN	0	0	0	0

Created by Office of Computational Service, custom analysis, ADaM data. The upper limit of normal for ALT was considered 0.5 ukat/L (=30 U/L) and for AST 0.6 ukat/L (=36 U/L) in this custom analysis.

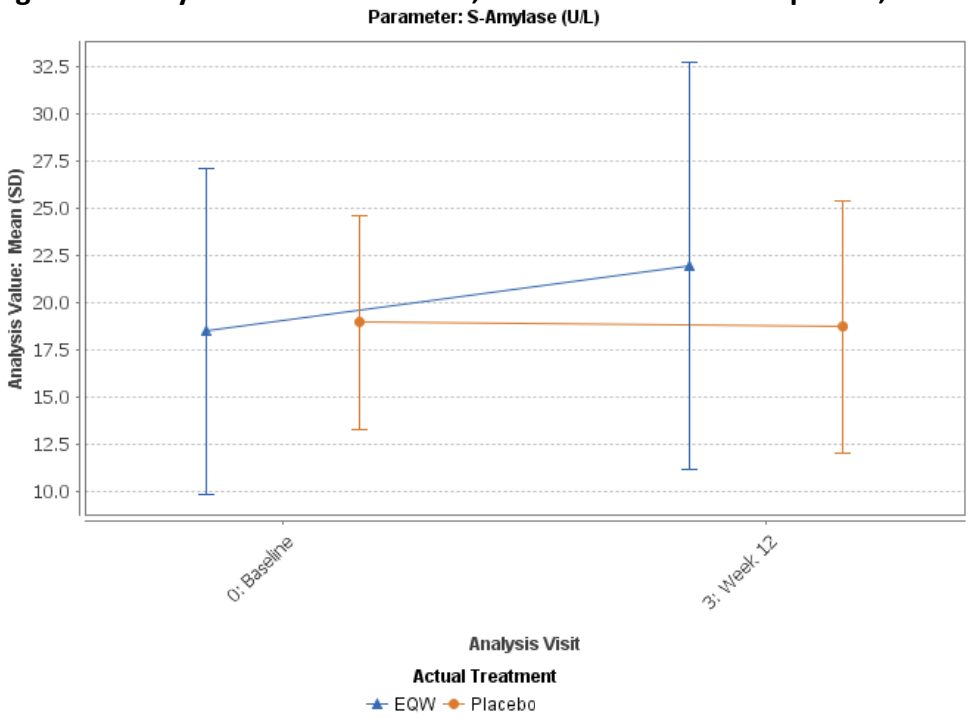
The analysis above shows that no patients developed ALT or AST values > 10 x ULN during the controlled assessment period. In general, the transaminase elevation > 3 ULN or > 5 ULN appears balanced between the treatment groups during the controlled assessment period.

Pancreatic enzymes

The Applicant did not report TEAEs suggestive of acute pancreatitis, a labeled risk for exenatide products. In study BCB114 amylase and lipase were measured at baseline, Week 12, and Week 52. The comparative safety data is limited for pancreatic enzymes as only one measurement was done at Week 12 during the controlled assessment period. Patients with a history of acute pancreatitis were not excluded from the study.

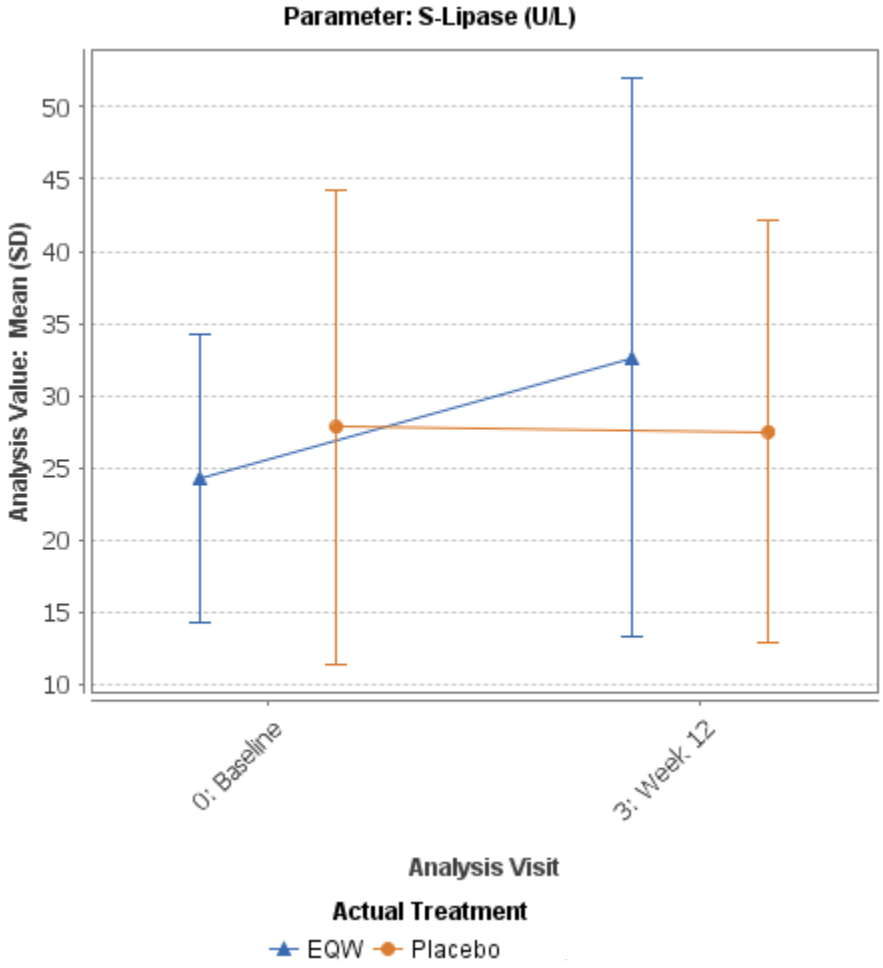
In the controlled assessment period, the mean change from baseline to Week 12 for pancreatic amylase was 3.6 U/L on EQW compared to 0.5 U/L on placebo. The mean change from baseline to Week 12 for lipase was 8.4 U/L on EQW compared to -1.1 U/L on placebo.

Figure 20: Amylase values over time, controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

Figure 21: Lipase values over time, controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

Table 25: Pancreatic enzymes, controlled assessment period, safety population

		EQW N=59	Placebo N=23
U/L		n (%)	n (%)
Amylase	> 1.5 X baseline	5 (8.5%)	0
	> 2 X baseline	3 (5.1%)	0
	> 3 X baseline	1 (1.7%)	0
Lipase	> 1.5 X baseline	11 (18.6%)	2 (8.7%)
	> 2 X baseline	6 (10.2%)	0
	> 3 X baseline	1 (1.7%)	0
	> 2 ULN	1 (1.7%)	0
	> 5 ULN	0	0

Created by Office of Computational Service, ADaM dataset

Table 25 shows a higher frequency of elevated pancreatic enzymes in the EQW group during the controlled assessment period. A review of the TEAE database for the patients with elevated pancreatic enzymes generally did not show treatment-emergent adverse events suggestive of acute pancreatitis, gallstone disease, or gastrointestinal symptoms. Most patients on EQW with elevated pancreatic enzymes trended back towards baseline at Week 52 but some did not.

The above data shows during the controlled assessment period patients treated with EQW experienced pancreatic enzymes elevations while patients on placebo generally did not. While narratives of these events were not available, a review of the TEAE and graphical patient profile of these patients did not suggest a diagnosis of pancreatitis for these patients. The clinical significance of routine amylase and lipase monitoring is not clear at this time. The label informs based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. The label adequately informs the risk of possible pancreatitis with exenatide.

Kidney function

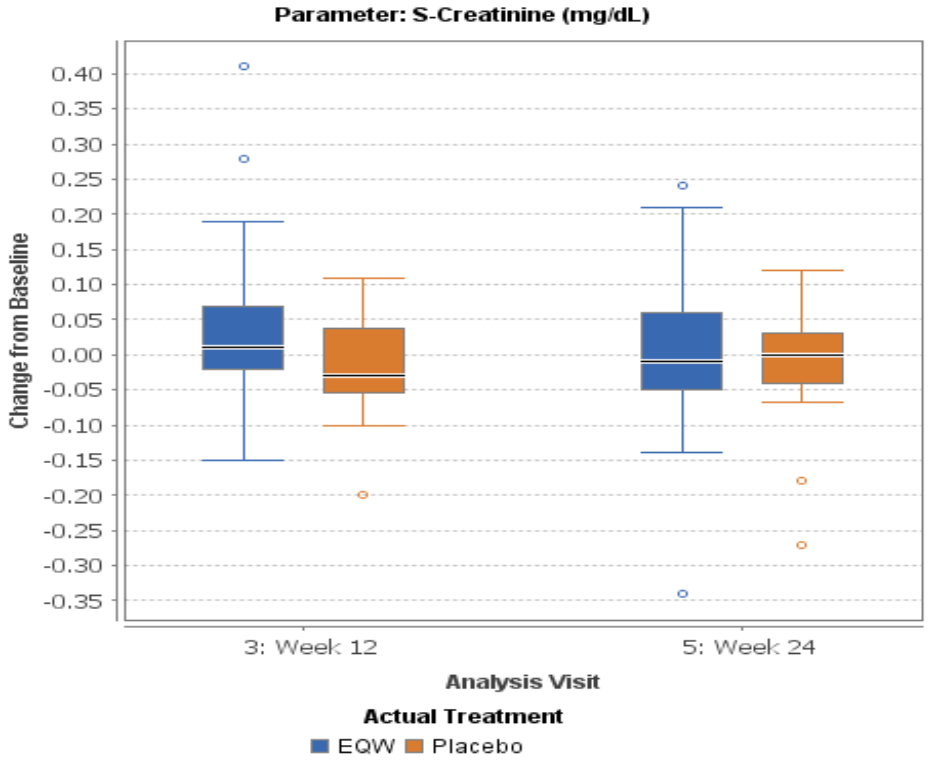
The label informs exenatide may induce nausea and vomiting with transient hypovolemia and may worsen renal function. Postmarketing increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation has been reported. Exenatide is not recommended for use in patients with eGFR below 45 mL/min/1.73m^2.

In this study, patients with renal disease or serum creatinine > 1.5 mg/dL in males and > 1.4 mg/dL in females were excluded. The baseline mean and median eGFR were both about 107 mL/min/1.73m^2. The estimated glomerular filtration rate (eGFR) was derived based on the Bedside Schwartz formula: eGFR = 41.3 × (Height in meters/Serum creatinine in mg/dL).

Kidney function in study BCB114 was evaluated by a review of adverse events and laboratory such as creatinine and eGFR measurements. In study BCB114 chemistry laboratory was measured at baseline, Week 12, 24, 52, and 62.

Figure 22 below shows the pattern of mean serum creatinine (mg/dL) change from baseline with outliers (relative to the box whisker presentation).

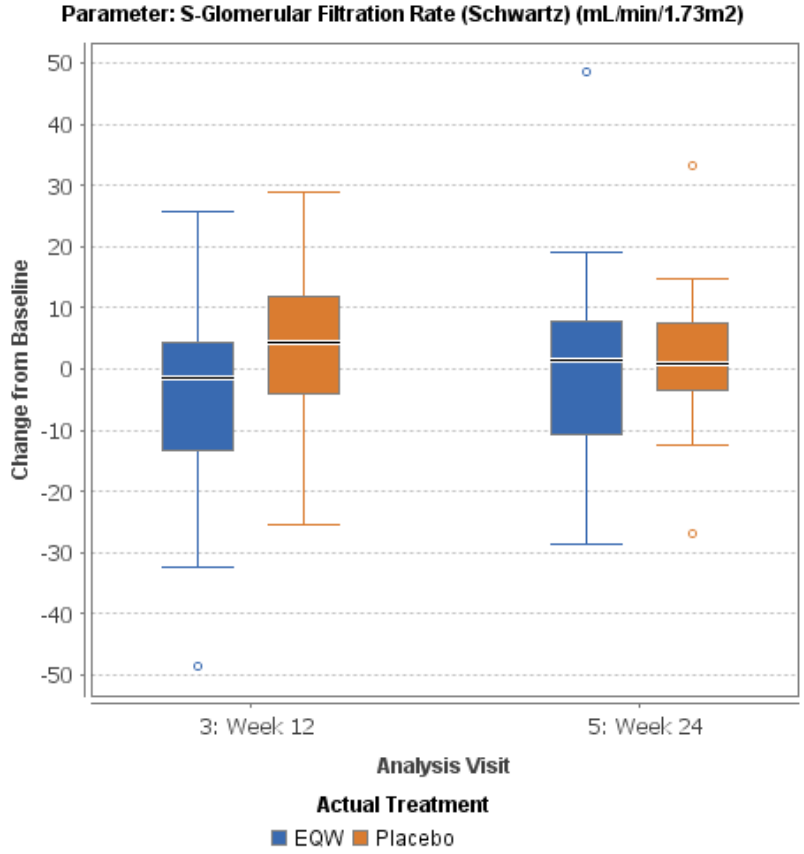
Figure 22: Creatinine (mg/dL), change from baseline and outliers (relative to the box whisker plot), controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

During the controlled assessment period the mean change from baseline for creatinine (mg/dL) was slightly higher in the EQW arm (0.02 mg/dL) compared to placebo (-0.01 mg/dL) at Week 12.
Figure 23 and Table 26 below show the mean eGFR (mL/min/1.73m^2) change from baseline.

Figure 23: eGFR (mL/min/1.73m2), change from baseline and outliers (relative to the box whisker plot), controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

Table 26: eGFR mL/min/1.73m2, change from baseline, controlled assessment period, safety population

		eGFR mL/min/1.73m2	
		Mean (SD)	**Min/median/max**
EQW n=59	Week 12	-2.5 (13.7)	-48.5/0/25.7
	Week 24	0.4 (13.5)	-28.6/0.9/48.5
Placebo n=23	Week 12	3.9 (13.3)	-25/4.3/28.9
	Week 24	0.9 (11.6)	-26/0.3/33

Min=minimum; Max=maximum; SD= Standard deviation
Source: adapted from BCB114 CSR

During the controlled assessment period (Table 29), the mean change from baseline for eGFR (mL/min/1.73m2) at Week 12 was lower on EQW (-2.6 mL/min/1.73m2) compared to placebo

(3.9 mL/min/1.73 m2). In the EQW arm, the mean eGFR increased to 0.4 mL/min/1.73m2 at Week 24 compared to Week 12 but still was lower than the mean eGFR at Week 24 in the placebo arm (0.9 mL/min/1.73m2).

Table 27: Creatinine (mg/dL) change from baseline and eGFR (mL/min/1.73m2) decrease from baseline at any time during the study, controlled assessment period, safety population

		Controlled assessment period	
		EQW N=59	Placebo N=23
		n (%)	n (%)
Creatinine mg/dL	≥ 1.5 X baseline	8 (13.5%)	3 (13.04%)
	≥ 2 X baseline	1 (1.69)	0
	≥ 3 X baseline	0	2 (8.7%)
eGFR mL/min/1.73m^2	Decreased by 20% from baseline	3 (5.08%)	0
	Decreased by 50% from baseline	0	1 (4.3%)
	Decreased by 75% from baseline	3 (5.08%)	0

Created by Office of Compuational Service

The adverse event profiles of patients on EQW with a decrease in eGFR or increase in creatinine as shown in Table 27 were reviewed. No TEAE suggestive of acute renal failure, volume depletion, or gastrointestinal symptoms were reported for these patients. No clear pattern of increased creatinine or decreased eGFR from baseline between the treatment arms is observed during the controlled assessment period. In general the small number of events limit conclusions.

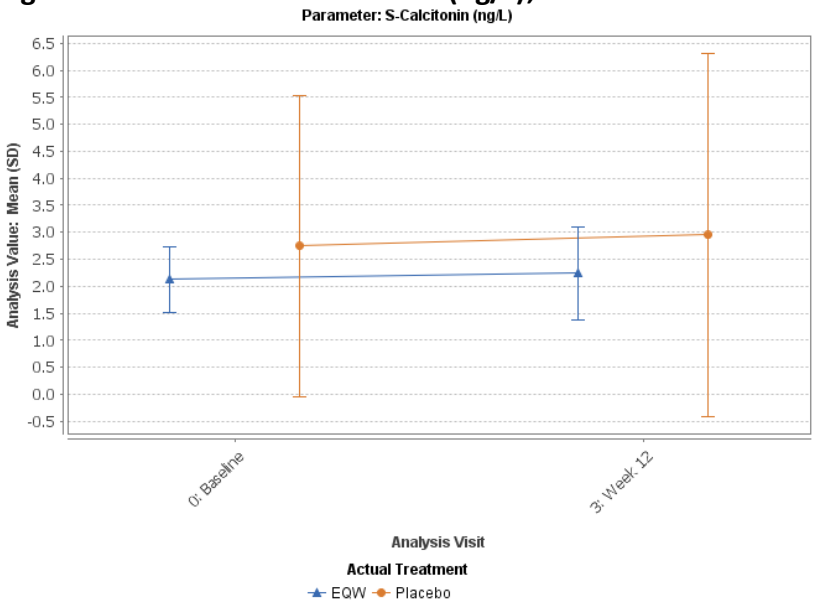
Exenatide labeling informs of the risk of possible acute renal events with EQW based on postmarketing reports.The reviewer's query of the TEAE database did not show PTs suggestive of an acute renal event during the controlled assessment period.

Calcitonin and Carinoembryonic Antigen (CEA)

Patients with a personal or family history of elevated calcitonin or calcitonin > 100 ng/L, medullary thyroid cancer or multiple endocrine neoplasia-2 were excluded from the study. Calcitonin was measured at baseline, Week 12, and Week 52 in study BCB114.

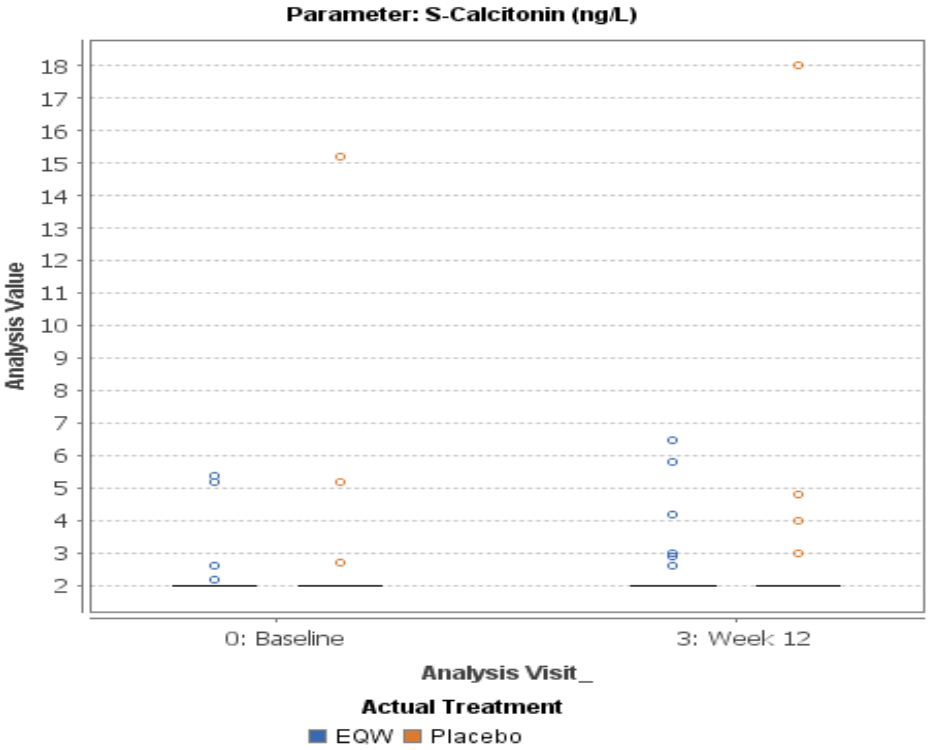
There was no meaningful difference in serum calcitonin change from baseline mean values to Week 12 between treatment groups (0.11 ng/L and 0.21 ng/L for EQW and placebo groups at Week 12, respectively).

Figure 24: Mean serum calcitonin (ng/L), controlled assessment period, , safety population



Created by reviewer, JReview, ADaM dataset

Figure 25: mean serum calcitonin (ng/L), controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

The calcitonin outliers identified in the box whisker analysis in the EQW arm (Figure 25) were not associated with an adverse event. Lack of comparator at Week 52 limits conclusions.

No meaningful change from baseline for carcinoembryonic antigen between the treatment arms was observed at Week 12.

The Applicant states patient [redacted] (b) (6) (11 years old, female) experienced an adverse event of carcinoembryonic antigen increased on Study Day 382, 25 days after the last dose of EQW which was considered related to study medication by the investigator. The patients baseline CEA was high at 10.9 µg/L (normal range: 0.8 to 5 µg/L); however, an unscheduled repeat of the baseline measurement was 7.1 µg/L. At the Week 52 visit (Study Day 380), the patient had a carcinoembryonic antigen value of 11.3 µg/L which was a change of 0.4 µg/L from baseline. All other measurements taken during the study were below the baseline value, including an unscheduled measurement of 8.4 µg/L taken on Study Day 503 (a change of -2.5 µg/L from baseline). Serum calcitonin levels were undetectable (< 2 ng/L) throughout the study, and per the investigator, the patient had no evidence of any medical condition that would result in elevated carcinoembryonic antigen.

Reviewer Comment: The clinical significance of the high CEA values in this patient is unclear. The patient appears to have a high baseline CEA level with fluctuations throughout the study which does not appear to be causally associated with drug.

Thyroid hormone, prolactin, cortisol

These laboratories were measured at baseline, Week 12, 24, and 52. No meaningful differences in mean prolactin and thyroid stimulating hormone between the treatment arms was seen over the controlled assessment period the outliers. Overall, the number of outliers for these labs are low and with no consistent pattern. The TEAEs 'blood prolactin increased' and 'thyroid stimulating hormone increased' was reported for 2 patients on EQW during the controlled assessment period. Narratives are not available, but the graphical patient profiles suggest the following:

- TEAE blood prolactin increased (b) (6)): 11-year-old American Indian or Alaska Native obese male Tanner stage 1 at baseline with an increase of prolactin from a normal baseline of 4.8 microgram/L to 36.7 microgram/L at Week 24 and return to almost baseline (6.5 microgram/L) at Week 52. The etiology and clinical significance of this transient increase in prolactin is not clear. Notably this patient remained at Tanner stage 1 throughout the trial; it's unknown if the increased prolactin interfered with pubertal progression or not.

- The TEAE thyroid stimulating hormone increase occurred in a patient with a history of subclinical hypothyroidism requiring an increase in the levothyroxine dose.

Cortisol

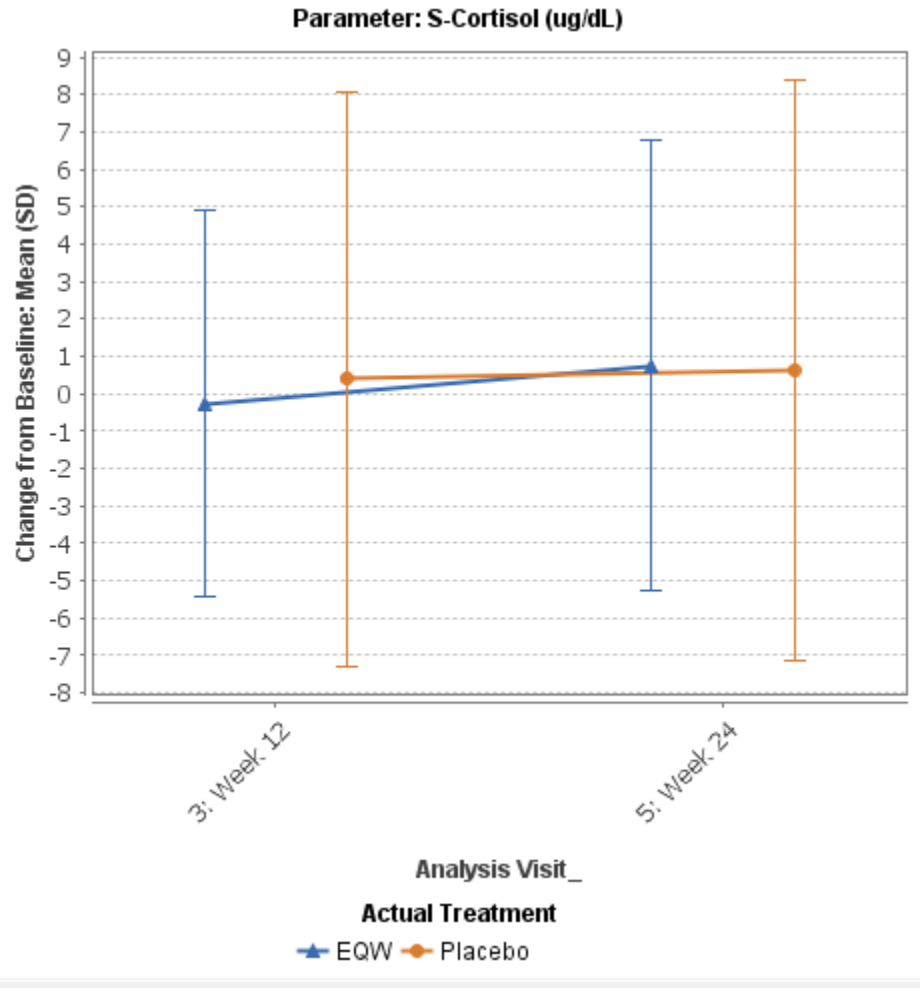
Serum or urine cortisol/corticosterone were not measured in animals in any of the approved GLP1 agonists. However published studies in animals and human suggest that GLP-1 receptor agonists may have an effect on the HPA axis by increasing ACTH and cortisol levels. Treatment with GLP-1 receptor agonists exenatide (10 µg/kg twice daily) or liraglutide (1200 µg/kg once daily) for 2 weeks increased corticosterone levels in mice under basal conditions as well as under stress. Some authors suggest these alterations may lead to disruption of the corticosterone circadian rhythm, hypertrophy of the adrenal gland, impaired pituitary-adrenal stress responses, and reductions in food intake and body weight. The chronic impact of possible HPA axis activity with chronic GLP-1 receptor agonist therapy and clinical implications is unknown.[14,15]

In this study serum cortisol was measured at baseline, Week 12, 24, and 52. The mean serum cortisol change from baseline in the EQW arm increased by 0.75 mcg/dL in the EQW arm compared to 0.39 mcg/dL in the placebo arm. It is unclear if this small increase of mean serum

[14] Am J Physiol Endocrinol Metab. 2013 May 15;304(10):E1105-17.
[15] Clin Endocrinol Metab 104: 202–208, 2019.

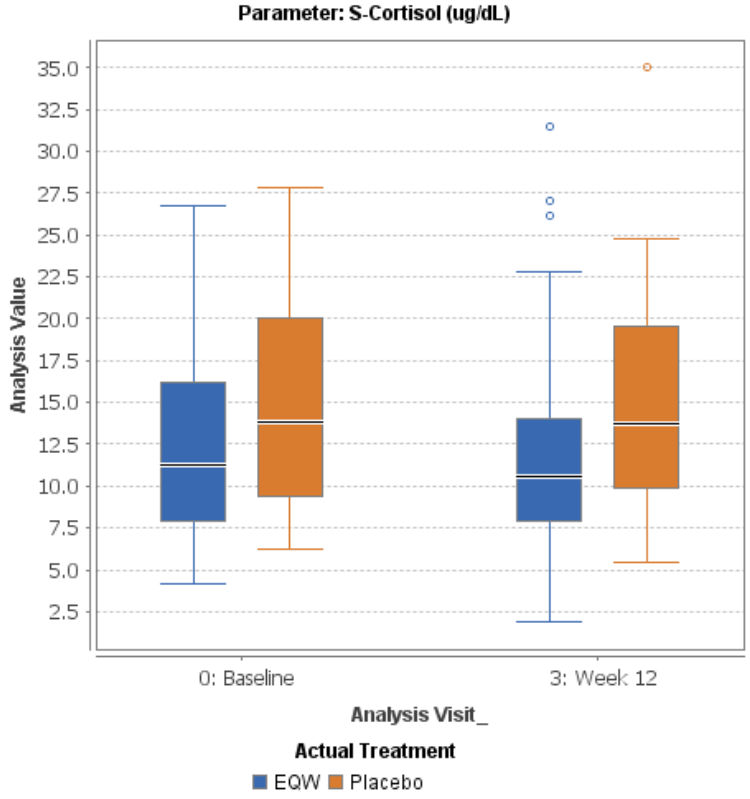
cortisol at Week 24 compared to placebo is meaningful and conclusions on possible clinical implications based on a single serum cortisol measurement at Week 24 is challenging.

Figure 26: Serum cortisol, change from baseline, controlled assessment period and open-label extension period, safety population



Source: Created by reviewer, JReview, ADaM dataset

Figure 27: Serum cortisol, controlled assessment period and open-label extension period, safety population

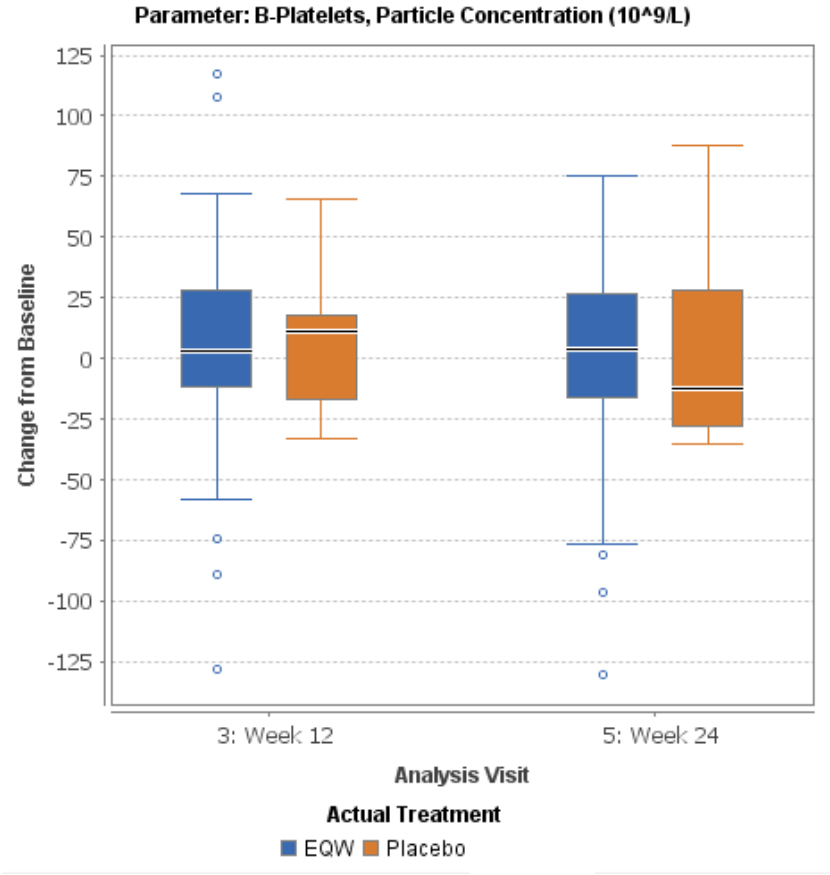


Source: Created by reviewer, JReview, ADaM dataset

Hematology

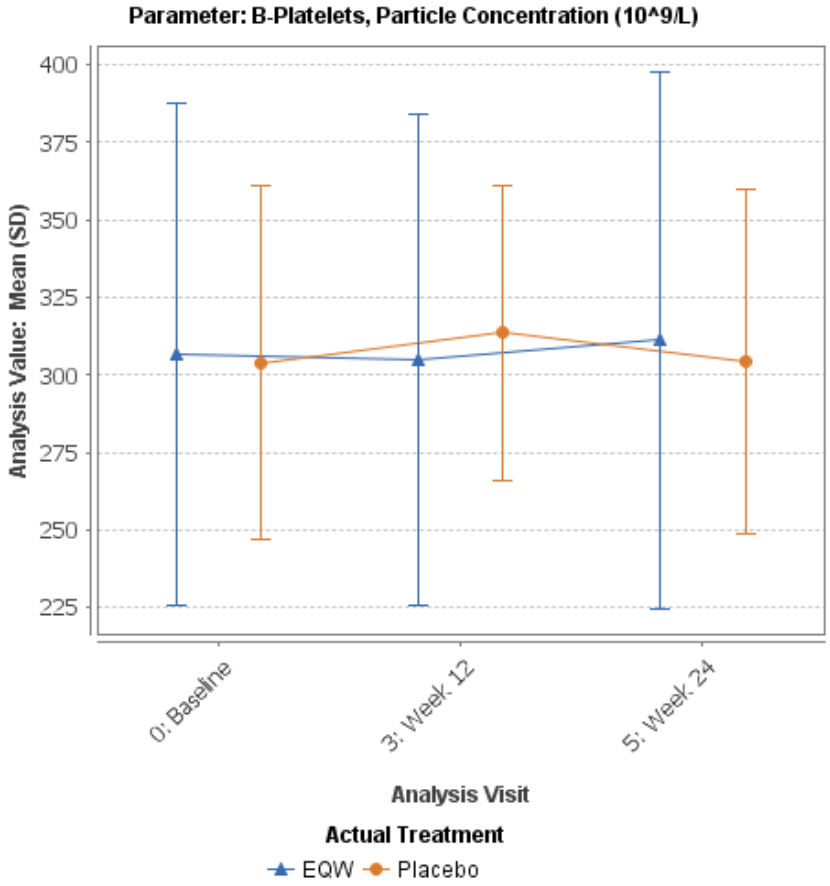
Exenatide-induced thrombocytopenia is an uncommon, labeled risk for long-acting exenatide products which could potentially be fatal and cause serious bleeding. No adverse event of thrombocytopenia or bleeding was reported in study BCB114. The Applicant's data shows no patient in the EQW group had a platelet value below the lower limit of normal during the controlled asssment and open-label extension period. The central tendency analysis did not show meaningful differences between treatment arms during the controlled assessment period.

Figure 28: Change from baseline, platelet count, controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

Figure 29: Platelet count, controlled assessment and open-label extension period, safety population



Created by reviewer, JReview, ADaM dataset

8.4.7. Vital Signs

Blood pressure and heart rate are parameters of interest for exenatide products. In general, GLP-1 receptor agonists including EQW very modestly lower blood pressure while increasing heart rate. The overall effect on cardiovascular outcomes is thought to be neutral or favorable. The EXSCEL trial demonstrated no excess cardiovascular risk in adults with T2DM and cardiovascular disease, with a point estimate for MACE that leaned favorably but was not statistically significant.

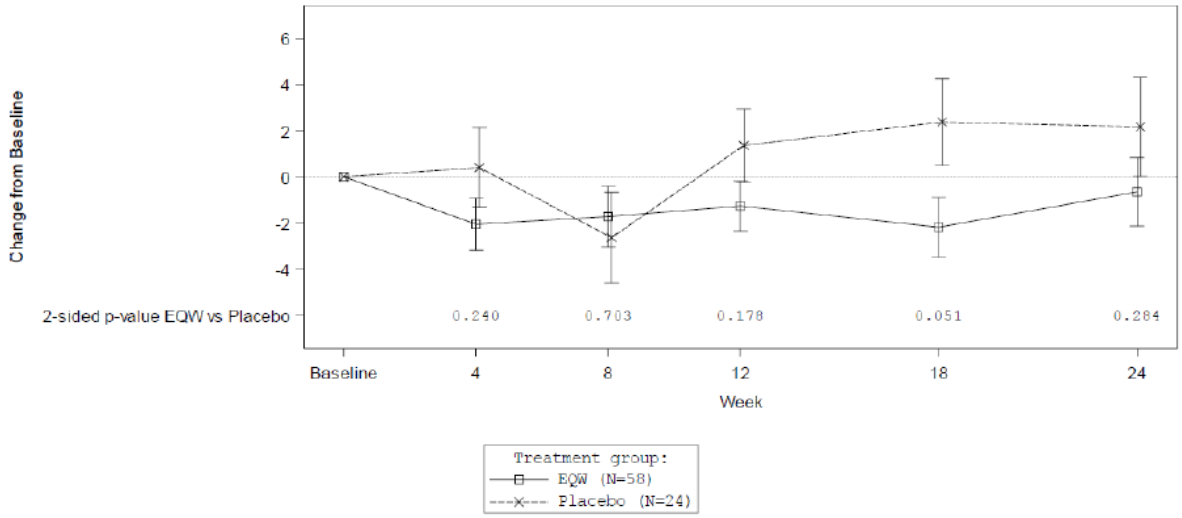
Blood pressure

The Applicant evaluated the blood pressure change from baseline at Week 24 as a secondary efficacy endpoint by MMRM (excluding post rescue or discontinuation data) in the ITT

population (in patients with a baseline and Week 24 value). The Applicant's data shows the LS mean change from baseline at Week 24 for SBP was -0.7 mmHg in the EQW arm and 2.2 mmHg in the placebo arm. The difference in LS mean change between the EQW and placebo at Week 24 was -2.8 mmHg (nominal p=0.284).

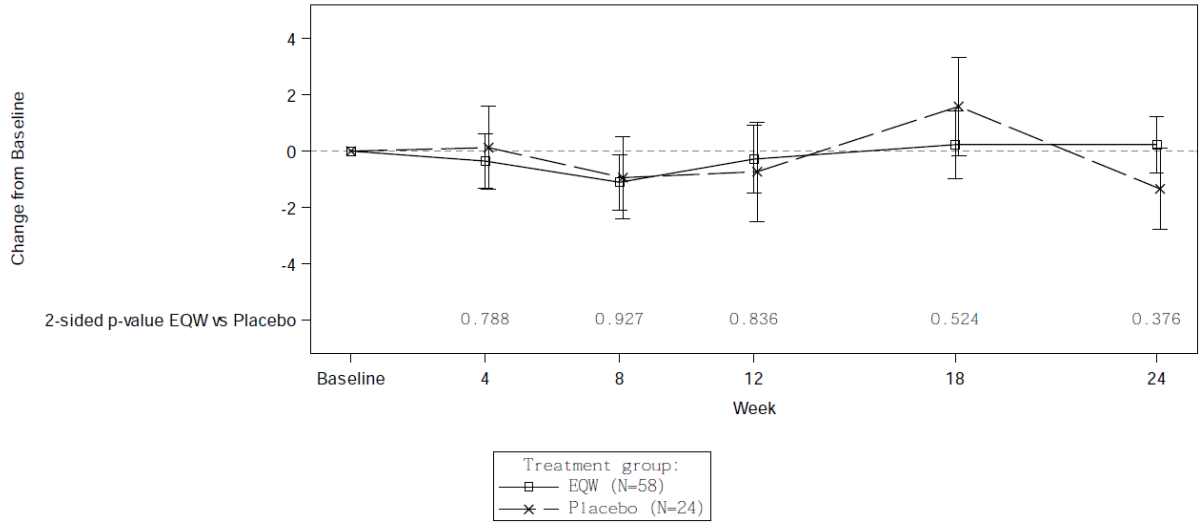
The LS mean change from baseline at Week 24 for DBP was 0.2 mmHg in the EQW arm and -1.3 in the placebo arm. The difference in LS mean change between the EQW and placebo at Week 24 was 1.6 mmHg, nominal p=0.376.

Figure 30: Change in systolic blood pressure (mmHg) from baseline, controlled assessment period, MMRM analysis, LS Mean (standard error), ITT population



Source: BCB114 CSR

Figure 31: Change in diastolic blood pressure (mmHg) from baseline, controlled assessment period, MMRM analysis, LS Mean (standard error), ITT population



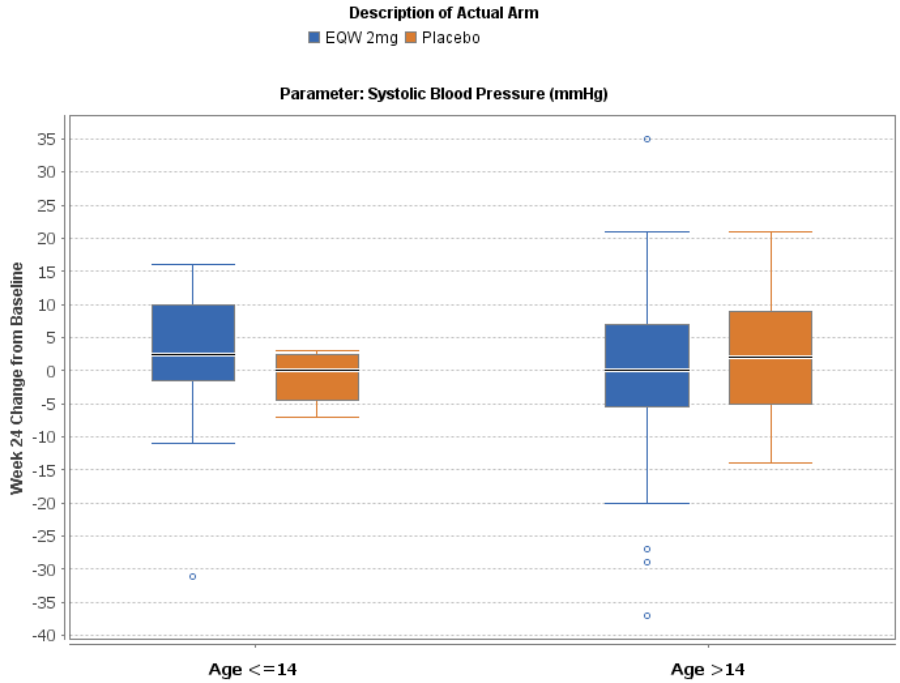
Source: BCB114 CSR

Subgroup analysis of systolic blood pressure by age and sex

Subgroup analysis of systolic blood pressure by sex did not show significant differences in change from baseline during the controlled assessment period in the EQW group between male and female patients. In general, female patients in the EQW arm experienced a placebo adjusted lower systolic blood pressure change from baseline by about -2.5 to -5 mmHg during the controlled assessment period. In general, no difference was seen in change from baseline in

systolic blood pressure in male patients in EQW arm compared to placebo. Due to small number of patients in each subgroup the conclusions may not be reliable. Below (Figure 32) is a subgroup analysis for systolic blood pressure at Week 24 by age group <=14 and > 14 years old.

Figure 32: Subgroup analysis for systolic blood pressure at Week 24 by age group <=14 and > 14 years old, safety population



In the age group <=14 years old at Week 24: EQW N=17 and placebo N=4
In the age group >14 years old at Week 24: EQW N=34 and placebo N=18
Only patients with a baseline and post-baseline value are included.

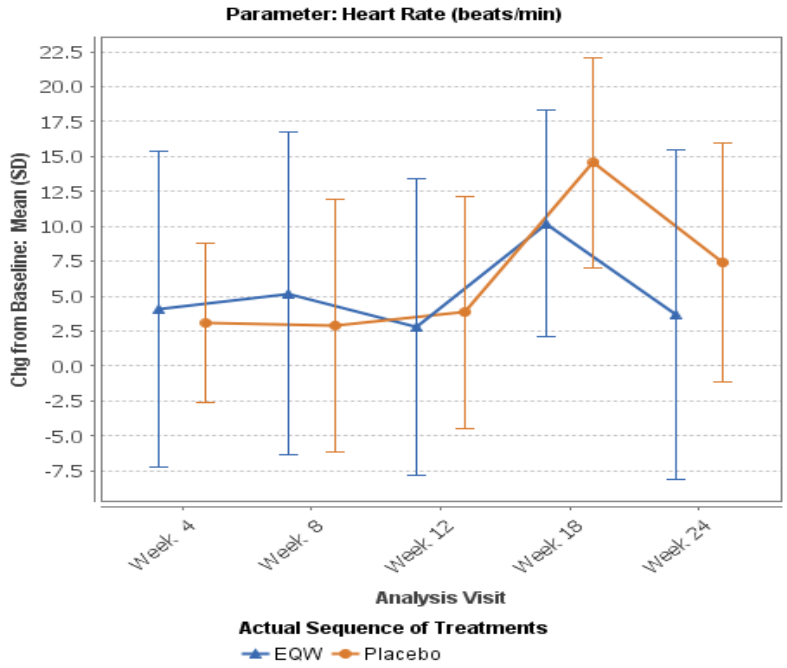
Figure 32 shows patients randomized to the EQW group in the <=14 years old age group had a lower change from baseline in mean systolic blood pressure from baseline compared to placebo at Week 24 (-2 mmHg compared to -8 mmHg, in the EQW group vs placebo respectively at Week 24), however the mean change from baseline for systolic blood pressure in patients > 14 years old age was generally comparable between the EQW and placebo arm. Note that the number of placebo patients in the age group <=14 years old with a baseline and postbaseline SBP value is n=4, making conclusions limited.

Heart Rate

While a similar frequency of patients had a heart rate > 95 bpm between the two arms during the controlled assessment period, a higher frequency of patients in the EQW arm had a heart rate > 85 in the EQW arm (72.9%) compared to placebo (56.5%) (data not shown).

Figure 33 shows the mean change from baseline in heart rate and Figure 34 shows a trend of heart rate values with outliers (relative to the box whisker presentation) during the controlled assessment period.

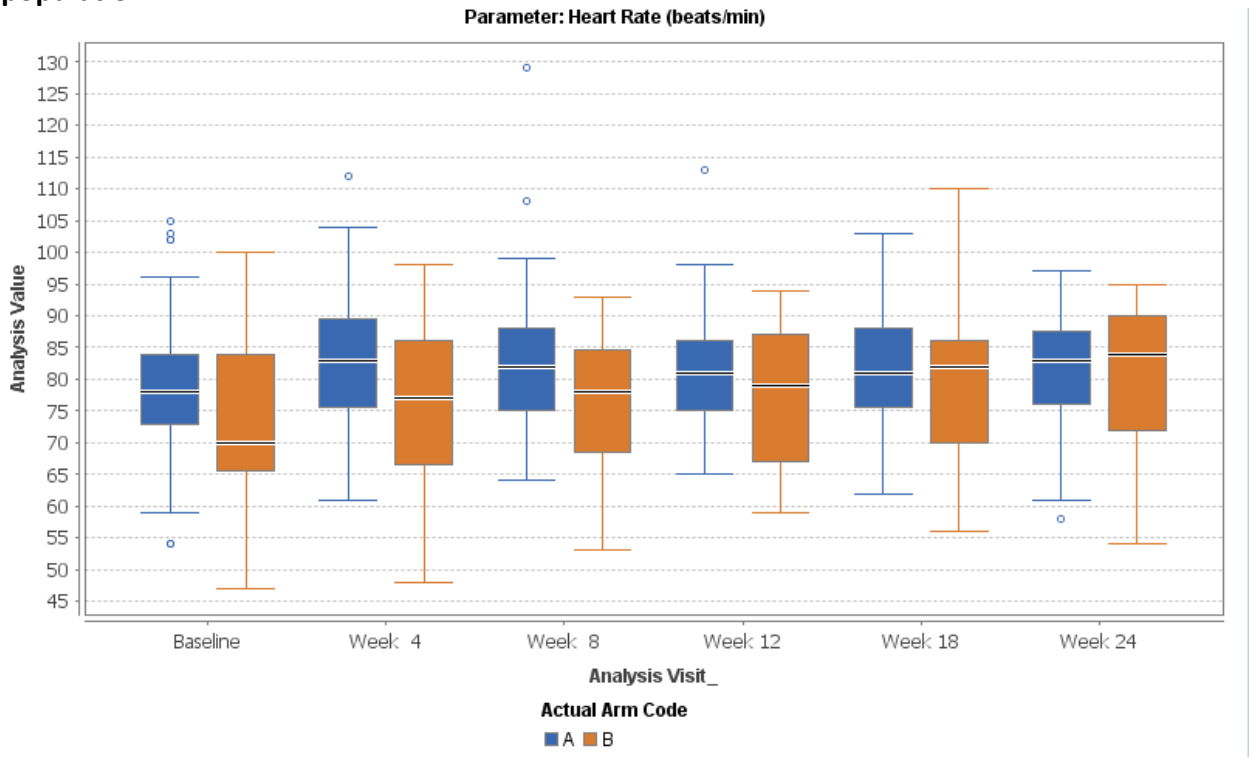
Figure 33: Change in heart rate (beat per minute) from baseline, controlled assessment period, safety population



Created by reviewer, JReview, ADaM dataset

Figure 33 shows that patients in the controlled assessment period, the EQW group experienced an increase in mean heart rate by about + 5 bpm earlier in the trial compared to placebo i.e., up to Week 8. During the controlled assessment period, the mean heart rate after Week 8 in the EQW arm is generally similar to placebo. The reason for the observed increased heart rate in the placebo arm is unclear.

Figure 34: Heart rate (beat per minute) measurements, controlled assessment period, safety population



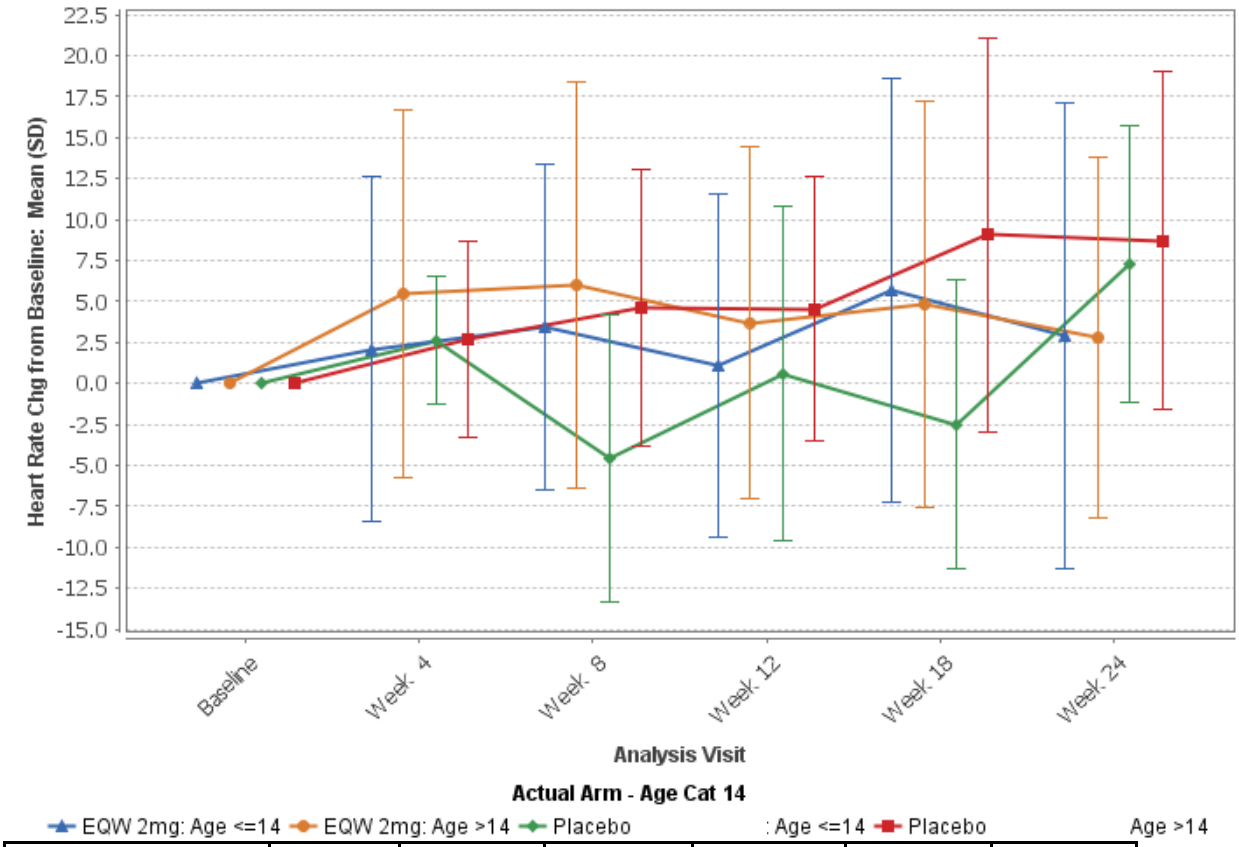
A= EQW; B=Placebo
Created by reviewer, JReview, ADaM dataset

During the controlled assessment period, most outliers (relevant to the box-whisker presentation) as shown in Figure 34 had transient elevations of heart rate above the patient's baseline.

Subgroup analysis for heart rate by age and sex

During the controlled assessment period, patients > 14 years old had an increased heart rate > 95 bpm more frequently compared to <=14 years old: 12 (30%) compared to 4 (21%), respectively, and more frequently compared to placebo: 12 (30%) vs 4 (22%) respectively. Patients <= 14 years old had a higher frequency of heart rate > 20 bpm increase compared to placebo in the same age group: 4 (21.1%) vs. 0 (data not shown).

Figure 35: Subgroup analysis by age group <=14/> 14 years old, change from baseline in mean heart rate (bpm), controlled assessment period, safety population



Actual Arm	Baseline	Week 4	Week 8	Week 12	Week 18	Week 24
EQW Age <=14	19	19	18	18	15	17
EQW Age >14	40	40	35	34	34	34
Placebo: Age <=14	5	5	5	5	4	4
Placebo Age >14	18	18	18	18	18	18
Subjects(filtered)	82	82	76	75	71	73

Only patients with a baseline and postbaseline value are included.
Created by JReview analyst, ADaM dataset

A descriptive subgroup analysis (

Figure 35) suggests that older patients (> 14 years old) generally experienced a higher increase in mean heart rate change from baseline (about + 5 bpm) compared to <= 14 year old (about + 2.5 bpm) up to about Week 12, after which they generally overlap.

Figure 35 also suggests that the younger age group (<=14 years old) on EQW had placebo-adjusted difference of about + 3-7 bpm change from baseline during the initial 18 weeks of the study, and the > 14 years on EQW had a placebo adjusted increase in heart rate by about + 2.5 bpm during the initial 8 weeks of the study. Due to small numbers in each subgroup especially in the lower age group meaningful conclusions are limited.

The subgroup analysis by sex for heart rate generally did not show meaningful differences between male and females in the EQW group. Due to small number of patients in each subgroup conclusions are limited.

In conclusion, while interpretation of the descriptive subgroup analysis is limited (especially because of small number of patients in the lower age groups), it appears that the older patients may experience a higher mean heart rate change from baseline compared to younger patients. The label informs that increases in heart rate from baseline ranging from 1.5 to 4.5 beats per minute have been observed in comparator-controlled clinical trials in the adult patients with T2DM.

8.4.1. Electrocardiograms (ECGs)

No ECGs were performed during the treatment period or follow-up period. This is acceptable as there are no known cardiac concerns with exenatide.

8.4.2. QT

This section was evaluated as part of the original NDA review.

8.4.3. Immunogenicity

Assay
To analyze immunogenicity samples from the pediatric patients with T2DM in study BCB114, the Applicant utilized the anti-exenatide antibody assay that was validated using serum samples

from adult patients with T2DM. Based on the data submitted by the Applicant, the OBP reviewer concluded the assays previously validated for use in the adult T2DM patients were appropriate for the immunogenicity assessment in the pediatric population in study BCB114 and that the use of the validation cut point that was determined using samples from adult patients can be used in analyzing the samples from the pediatric patients in study BCB114.

Definitions
The SAP defined the baseline as ADA measured at Day 1 at the time of randomization. If the antibody measurement was missing it was considered as negative. If the antibody was confirmed positive at baseline, it was considered as "any positive".

The SAP defined a treatment-emergent ADA as:

- if at any visit the ADA is positive after the first dose of EQW following a negative or missing ADA measurement, or
- the ADA titer at any visit is increased by at least 1 titration category from a detectable measurement prior to first dose of randomized study medication.

The SAP defined ADA titers ≥ 625 as high positive and titers < 625 as low positive.

Results
Antibodies to exenatide were observed in 93% of patients on EQW at any time during the 62-week study, with a higher frequency of patients developing high positive ADA (63.2%) compared with low positive ADA (29.8%).

Table 28 shows the frequency of ADA positive patients peaked at Week 12 for high titer ADA (58.8%) and Week 24 for low titer ADA (55.1%) with a gradual decline afterwards.

Table 28: Incidence of antibodies to exenatide by visit, controlled assessment period and open-label extension period, safety population

	EQW (N = 59)			
Analysis Visit	Negative n (%)	High positive n (%)	Low positive n (%)	Any positive n (%)
Baseline (n = 58)	57 (98.3)	0	1 (1.7)	NA
Week 4 (n = 55)	30 (54.5)	9 (16.4)	16 (29.1)	24 (43.6)
Week 8 (n = 52)	4 (7.7)	28 (53.8)	20 (38.5)	48 (92.3)
Week 12 (n = 51)	2 (3.9)	30 (58.8)	19 (37.3)	49 (96.1)
Week 24 (n = 49)	2 (4.1)	20 (40.8)	27 (55.1)	47 (95.9)
Week 52 (n = 45)	13 (28.9)	14 (31.1)	18 (40.0)	32 (71.1)
10-week Follow-up (n = 44)	21 (47.7)	11 (25.0)	12 (27.3)	23 (52.3)
Highest over 52 weeks and Follow-up (n = 57)	4 (7.0)	36 (63.2)	17 (29.8)	53 (93.0)

Percentages were calculated from the number of patients with data by treatment group and visit. Patients in the placebo to EQW group are not included in this table.
Source: BCB114 CSR

In the adult EQW T2DM program (in 5 comparator-controlled studies; n=918), 405 (45%) had had low titer ADA and 107 (12%) EQW-treated patients had high titer antibodies at study endpoint (24-30 weeks). In one of the studies (#105) 74% were overall positive for ADA over 30 weeks. In the EQWS development program, 74% of EQWS-treated patients were ADA positive; 42% developed low-titer and 32% developed high-titer ADA at any time during the 2 phase 2 studies.

Reviewer Comment: Acknowledging the limitations of cross-comparing immunogenicity assessments across programs with different patient populations, the overall immune response to exenatide as well as antibody titers in ADA positive samples appears higher in pediatric patients compared to adults with T2DM. In general, the immunogenicity data suggests that exenatide was highly immunogenic in pediatric patients evaluated in study BCB114. While the Applicant suggests the reason for the difference in immune response in pediatric and adult patients may be due to immune senescence and a decline in qualitative and quantitative immune function, the reason for the possible difference in immune response in pediatric and adult patients is unclear.

Possible effect of ADA on efficacy

Table 29 shows the mean change from baseline in HbA1c by visit and by antibody status and titer during the controlled assessment period.

Table 29: Mean change from baseline in HbA1c % to Week 24 by antibody status and titer, controlled assessment period, evaluable population

		EQW (N=58)			
Analysis visit	HbA1c summary statistics	Negative [a]	High Positive [b]	Low Positive [c]	Treatment Emergent ADA Positive [d]
Week 4	n	28	9	16	24
	Mean	-0.21	-0.53	-0.38	-0.48
	SD	0.526	0.412	0.836	0.681
	Min	-1.1	-1.2	-1.7	-1.7
	Median	-0.20	-0.50	-0.10	-0.35
	Max	1.8	0.0	0.7	0.6
Week 8	n	4	28	19	47
	Mean	-1.03	-0.51	-0.82	-0.63
	SD	0.568	1.235	0.779	1.076
	Min	-1.8	-2.4	-2.6	-2.6
	Median	-0.85	-0.45	-0.60	-0.50
	Max	-0.6	4.8	0.4	4.8
Week 12	n	2	29	19	48
	Mean	-1.10	-0.55	-1.07	-0.76
	SD	0.141	1.687	1.028	1.472
	Min	-1.2	-2.6	-2.7	-2.7
	Median	-1.10	-0.60	-0.90	-0.75
	Max	-1.0	7.1	1.2	7.1
Week 24	n	2	20	26	46
	Mean	-1.15	0.07	-0.73	-0.39
	SD	0.071	1.097	1.226	1.227
	Min	-1.2	-1.4	-2.9	-2.9
	Median	-1.15	-0.05	-0.75	-0.55
	Max	-1.1	2.5	2.7	2.7

Source: BCB114 CSR; evaluable population consists of all randomized patients who received at least 1 dose of randomized study medication and had at least 1 baseline and postbaseline assessment.

Table 29 shows at Week 24, the mean change from baseline in HbA1c in the EQW group was greater in patients with low positive antibodies (-0.73%) compared with those with high positive antibodies (+ 0.07%). Between Week 4 and Week 12, a decrease in the mean HbA1c is observed in the low titer group, while the mean HbA1c remained generally stable in the high titer ADA group. Due to the low number of patients in the EQW group with negative antibody results, no further comparisons could be made. A similar trend was observed at Week 52.

The Applicant summarized (Table 30) the change in mean HbA1c for each ADA titer group in study BCB114 to evaluate the possible impact of the ADA titer on HbA1c per titer group (regulatory response dated May 26, 2021).

Table 30: Mean change from baseline in HbA1c % to Week 24 by antibody status and titer, controlled assessment period, evaluable population

			EQW (N=58)						
Visit	Rs [a]	Summary	Negative	25	125	625	3125	15625	Treatment Emergent ADA Positive
Week 4	-0.12(0.429)	n	28	10	6	6	3	0	24
		Mean	-0.21	-0.49	-0.18	-0.38	-0.83		-0.48
		SD	0.526	0.891	0.773	0.354	0.404		0.681
		Min	-1.1	-1.7	-1.6	-0.9	-1.2		-1.7
		Median	-0.20	-0.15	0.00	-0.40	-0.90		-0.35
		Max	1.8	0.7	0.6	0.0	-0.4		0.6
Week 8	0.13(0.210)	n	4	4	15	20	8	0	47
		Mean	-1.03	-0.60	-0.88	-0.76	0.13		-0.63
		SD	0.568	0.258	0.865	0.771	1.905		1.076
		Min	-1.8	-0.9	-2.6	-2.4	-1.0		-2.6
		Median	-0.85	-0.60	-0.60	-0.50	-0.45		-0.50
		Max	-0.6	-0.3	0.4	0.5	4.8		4.8
Week 12	0.26(0.010)	n	2	3	16	21	5	3	48
		Mean	-1.10	-1.33	-1.03	-0.64	-0.32	-0.27	-0.76
		SD	0.141	1.210	1.029	1.962	0.455	0.777	1.472
		Min	-1.2	-2.7	-2.6	-2.6	-0.8	-0.9	-2.7
		Median	-1.10	-0.90	-0.90	-0.70	-0.50	-0.50	-0.75
		Max	-1.0	-0.4	1.2	7.1	0.3	0.6	7.1
Week 24	0.38(<0.001)	n	2	12	14	10	7	3	46
		Mean	-1.15	-0.92	-0.58	-0.22	0.36	0.33	-0.39
		SD	0.071	1.021	1.398	1.196	0.932	1.258	1.227
		Min	-1.2	-2.5	-2.9	-1.4	-1.0	-1.0	-2.9
		Median	-1.15	-0.85	-0.75	-0.35	0.60	0.50	-0.55
		Max	-1.1	0.8	2.7	2.5	1.3	1.5	2.7

A=Spearman rank-order correlation coefficient Rs between HbA1c and antibody titers at the corresponding visit, the p-value indicating correlation significantly different than 0 is shown in parenthesis. Data collected after rescue or premature discontinuation are excluded.
Source: regulatory response dated May 26, 2021.

Table 30 suggests a trend in reduced magnitude of mean changes from baseline in HbA1c in the higher ADA titer categories during the controlled assessment period. At Week 12 no significant change is observed in mean HbA1c values in patients with low titer antibody (< 625) compared to patients with negative ADA, while at Week 24 there appears to be a linear relationship between titer and an increase in change in HbA1c values.

Consistent with the labeled information, in general an attenuation of mean change in HbA1c is observed in patients with high titer antibody. Evaluation of patient level data indicates a substantial variability of HbA1c response by titer, suggesting prediction of HbA1c response for an individual patient is difficult.

The attenuation of HbA1c in patients with high titer antibodies suggest an interference of ADA with drug effect; this may suggest a possible cross-reaction with endogenous GLP-1 that neutralizes its function too and/or the presence of neutralizing antibodies against exenatide. The Applicant has not assessed cross-reactivity or neutralizing antibodies in study BCB114 but has evaluated cross-reaction to GLP-1 and glucagon in the samples from adult trials evaluating EQWS which demonstrated a potential for development of antibodies cross-reactive with endogenous GLP-1 and glucagon in patients with high titer antibody. The incidence was low (1 [0.8%] of 118 patients with high-titer antibody) and the clinical significance of these antibodies is currently not known. The Applicant states the low level of GLP-1/glucagon cross-reactivity results in adult T2DM patients suggest that cross-reactivity of ADA with GLP-1/glucagon maybe low in pediatric patients.

Reviewer Comment: I agree with OBP that due to the possible difference in the overall immune response between adult and pediatric patients, the cross-reactivity results in the T2DM adult patients may not be applicable to the pediatric patients. However, an assessment of cross-reactivity in the pediatric patients may not be needed at this time as no serious safety concern with observable clinical consequence was reported in the study and the possible impact on efficacy observed in study BCB114 is consistent with the labeled information in adults.

Possible effect of ADA on safety

Due to the high incidence of high titer antibody and low number of patients with negative ADA in study BCB114 conclusions on a possible association of ADA with adverse events is limited.

Table 31 is the reviewer's post hoc query of possible immune-related TEAEs in the safety population during the controlled assessment period.

Table 31: Possible immune related TEAEs, controlled assessment period, safety population

Dictionary Derived Term	EQW	Placebo
Dermatitis contact	1 (1.7%)	0 (0.0%)
Urticaria	1 (1.7%)	0 (0.0%)
Arthralgia	1 (1.7%)	1 (4.3%)
Subjects(filtered)	3 (5.1%)	1 (4.3%)
1stColItemSubjects	59 (100.0%)	23 (100.0%)

Refer to Appendix 1 for a list of pre-specified PTs included in the SAP for potentially immune-related adverse events. Note injection site reactions were pre-specified but not included in this table as they were analyzed separately.
JReview, ADaM dataset

The PT arthralgia occurred in the low titer ADA group and the PT urticaria in the high titer ADA group. The number of events is too small to draw meaningful conclusions on relation to antibody status. None were serious, severe, or led to study drug discontinuation.

During the extension period the following possible immune-related PTs occurred in the EQW group (all single events): Asthma, swelling face, urticaria, arthralgia; the PT asthma (single event) was captured in the placebo to EQW group. None were serious, severe, or led to study drug discontinuation.

The incidence of injection site reactions during the controlled assessment period was similar between the treatment arms (8.5% vs. 8.7%, in EQW vs. placebo, respectively). All the injection site reactions in the EQW arm occurred with use of the single tray presentation. None were serious or led to study drug discontinuation.

In the controlled assessment period, all the injection site reactions (except 1 event of injection site pruritus) in the EQW arm occurred in patients who at any point during the study developed high titer ADA. Based on adult trials, the EQW label currently informs that injection site reactions in patients treated with EQW were more commonly observed in ADA positive patients compared to ADA negative patients, with a greater incidence in those with higher titer antibodies.

Overall, the incidence of possible immune related treatment-emergent adverse events during the controlled assessment period in study BCB114 was low and none were serious, severe, or led to study drug discontinuation or appeared to have clinical consequence.

8.1. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues are discussed thought Section 8.4 of this review.

8.2. Safety Analyses by Demographic Subgroups

Throughout the safety review descriptive subgroup analyses are discussed as pertinent. No meaningful interactions were observed in the descriptive subgroup analysis of TEAEs by age, sex, ethnicity, and race (discussed under Section 8.4.5. of this review) and in the descriptive subgroup analysis by age and sex for systolic blood pressure and heart rate (as discussed under Section 8.4.7. of this review). Note that the small number of patients in each subgroup limits meaningful conclusions.

Formal statistical assessments for interactions on safety signals have not been conducted given the overall small subgroup sizes.

8.3. Specific Safety Studies/Clinical Trials

In response to a request from the European Medicines Agency Committee, the Applicant conducted an extended safety follow-up period designed to allow observation of ongoing development and growth. Patients were instructed to return to the study site at approximately

6-month intervals for a period of up to 3 years, during which certain adverse events, height, weight, and Tanner pubertal stage were to be assessed, and carcinoembryonic antigen and calcitonin concentrations were to be measured. The results are not available yet.

The SAP states patients who discontinued study medication prior to Visit 11 (Week 62/Study Termination) should enter the extended safety follow-up period, unless they have a height difference of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Patients who do not have height assessments at study site visits over a 6-month interval prior to discontinuation of study medication will also enter the follow-up period.

8.4. Additional Safety Explorations

8.4.1. Human Carcinogenicity or Tumor Development

There is no information relevant to this section of the review in the submission.

8.4.2. Human Reproduction and Pregnancy

There is no information relevant to this section of the review in this submission.

8.4.3. Pediatric and Assessment of Effects on Growth

Earlier toxicology studies (2012) conducted in cynomolgus monkeys with multiple long-acting GLP-1 receptor agonists suggested an increase in weight of male reproductive tissue and accelerated sexual maturation in male monkeys. During early development, non-GLP toxicology studies evaluating EQW suggested a delayed sexual development in juvenile rats. Consequently, the Agency recommended (April 16, 2016) that the Applicant conduct a GLP-compliant juvenile study with EQW to support a pediatric trial.

In response, the Applicant stated published literature suggest GLP-1 agonists may have an effect on the Hypothalamo-Pituitary-Gonadal (HPG) axis and therefore the pharmacology could result in subtle endocrine effects in rats. The Applicant suggested the most appropriate assessment of the clinical relevance of the subtle endocrine effects noted in the toxicology studies is by assessing growth and development in the pediatric study. Moreover, the influences of obesity and T2DM on the HPG axis should be considered; e.g., literature suggests the excessive adiposity in the obese T2DM prepubertal population may predispose to a risk of advancing puberty in girls and delaying puberty in boys.

During the review of the liraglutide pediatric supplement, pharmacology/toxicology commented that it is difficult to reconcile the rat findings of developmental delay with the original purpose for conducting the study (which was due to accelerated sexual development in monkeys). Based on a modest degree of an effect seen in juvenile studies and the absence of compelling clinical significance of a slight acceleration/delay in onset or progression through

puberty it was decided there is no noted safety signal that would warrant the labeling of nonclinical data in the liraglutide label.

In study BCB114, growth and development were assessed by measurement of Tanner stage, bone age, height, and sex and growth hormone assessments described below.

Height
The protocol required height to be measured by patient standing with bare feet close together, with legs straight, and arms at side and shoulders relaxed with a stadiometer or other similar device. The Applicant further clarified (regulatory response dated April 16, 2021) to ensure consistency of height measurements, general guidance was provided to the investigators to designate a single study staff member to measure height using the same machine throughout the study.

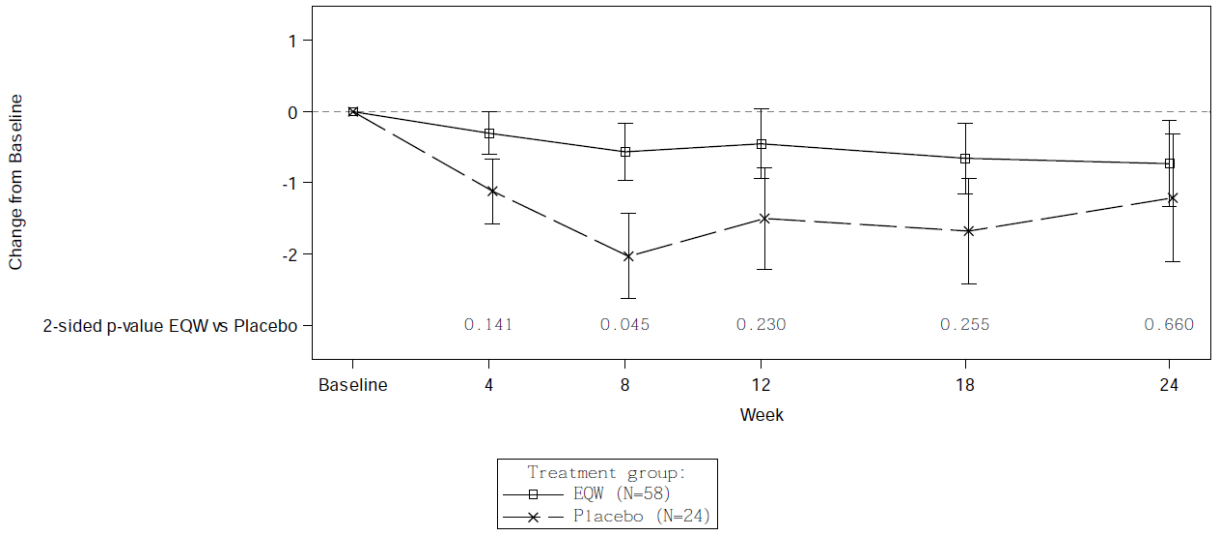
In this trial, height was measured at screening, Week 0, 4, 8, 12, 18, 24, 28, 40, 52, 62 or early termination visit. The SAP states height percentile was determined based on the standardized growth chart for boys and girls developed by the National Center for Health Statistics in collaboration with the National Center for Chronic disease Prevention and Health Promotion. The percentile values for height were calculated using the growth chart tables from Center for Disease Control (CDC) using the raw data available for height by gender.

Reviewer Comment: While some elements of the 2007 FDA Guidance on Growth[16] were followed for height measurements, other elements such as e.g., the duration of the baseline period for height measurement was not followed.

Change in height percentile from baseline was an exploratory efficacy variable in this study. Changes in height percentiles between treatment groups from Visit 2 (Week 0) to Week 24 and each intermediate visit, were compared using an MMRM approach in the evaluable population (Figure 36).

[16] FDA Guidance for Industry, Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. March 2007. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm071968.pdf).

Figure 36: Change from baseline in height percentile by visit, controlled assessment period, MMRM Analysis, LS Mean (standard error), evaluable population



Data collected after initiation of rescue medication or after premature discontinuation of study medication were excluded.
Source: BCB114 CSR.

The Applicant's data (Figure 36) shows the LS mean change in height percentile was -0.73% for the EQW group and -1.21% for the placebo group. The difference in LS mean change between the EQW and placebo groups was 0.48% (nominal p = 0.660). No meaningful between-group differences were noted for change from baseline in height percentile during the controlled assessment period.

Reviewer comment: It doesn't appear that the above analysis excluded patients who did not grow during the trial. These may be patients who had completed their pubertal growth prior to the start of the trial and had fused epiphyses and therefore should be excluded from the analysis. The Applicant's analysis doesn't consider the sex differences on growth trajectory. The timing in the pubertal growth spurt is different for males and females thus males and females undergoing puberty should be analyzed separately.

Patient level height velocity was reviewed in the very small subset of patients who at baseline had a bone age < 14 years suggesting unfused epiphysis at baseline and who also had both baseline and postbaseline data for bone age (discussed below).

Bone age
Bone age assessment was assessed at baseline and week 52 or early termination visit. Radiography of hand and wrist was used to calculate bone age.

The mean bone age at baseline in males randomized to EQW was 16.83 years with a standard deviation (SD) of 1.55 and median bone age of 17 years old. The mean bone age at baseline in

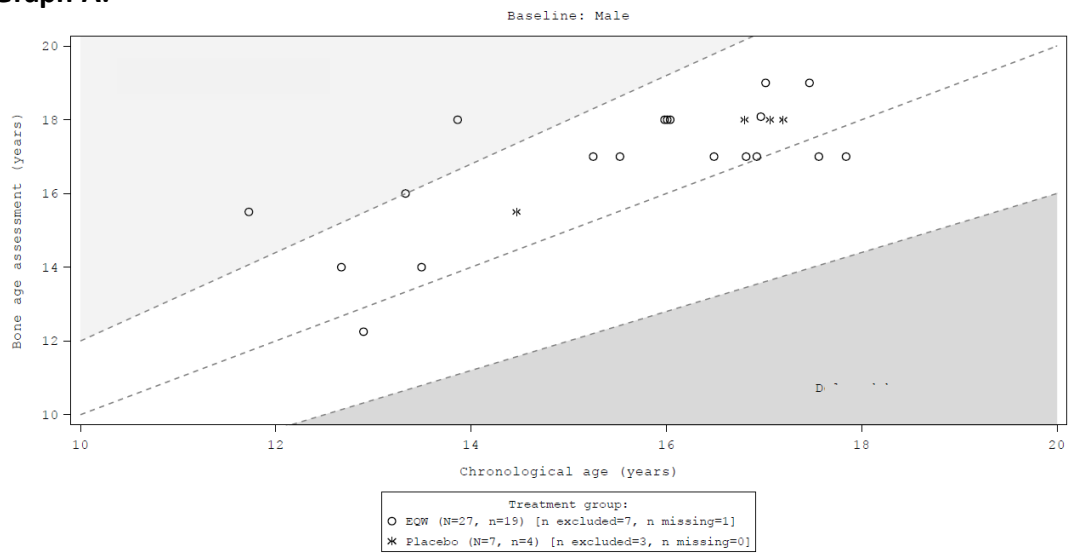
females randomized to EQW was 15.85 with a standard deviation of 1.95 and median of 16 years old, and the median bone age was 17 years old. The number of patients randomized to placebo by gender was small (7 males and 15 females) and the mean (SD) bone age was higher compared to patients randomized to EQW: 16.11 (1.91) years old in males and 16.47 (1.71) years old in females.
In study BCB114 bone age was not assessed at Week 24; because the patients randomized to placebo switched to EQW at Week 24 a comparative assessment to placebo at Week 52 is not reliable; therefore, interpretation of data is limited.

The Applicant (regulatory response dated April 16, 2021) submitted scatterplots of bone age vs. chronologic age by gender at baseline for patients with both a baseline and postbaseline bone age assessment as shown in Figure 37.

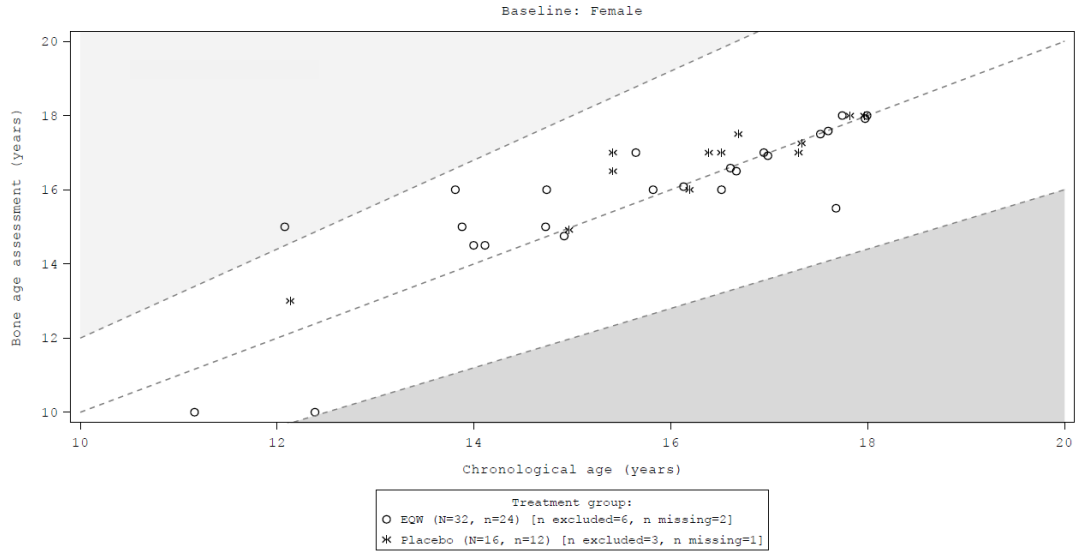
The Applicant also submitted (regulatory response dated May 18, 2021) patient-level data including Tanner stage (genitalia for males and breast for females) and height measurements for the patients identified in Figure 37 who had a bone age of < 14 years old at baseline.

Figure 37: Bone age versus chronologic age at baseline by gender, safety population; Graph A: males; Graph B=females

Graph A:



Graph B:



Patients with bone age data at baseline and post-baseline are included in this graph. Note patients randomized to placebo were switched to EQW at Week 24 and exposed to 28 weeks of EQW by Week 52.
Source: adapted from regulatory response dated May 18, 2021.

Reviewer Comment: The mean bone age of 16.83 and 15.85 years in male and female patients respectively, and the graphs above showing most patients randomized to EQW in study BCB114 (who had a baseline and postbaseline bone age measurement) had a bone age > 14 years of bone age at baseline suggest most patients had already near completed growth at baseline; therefore, detecting a possible impact of drug on linear growth is challenging. Furthermore, an

analysis of linear growth is unlikely to be meaningful in the small number of patients with unfused epiphyses, particularly considering male and females should be analyzed separately.

In addition, the Applicant's data does not suggest meaningful between-group differences in change from baseline in IGF-1 and bone turnover markers during the controlled assessment period.

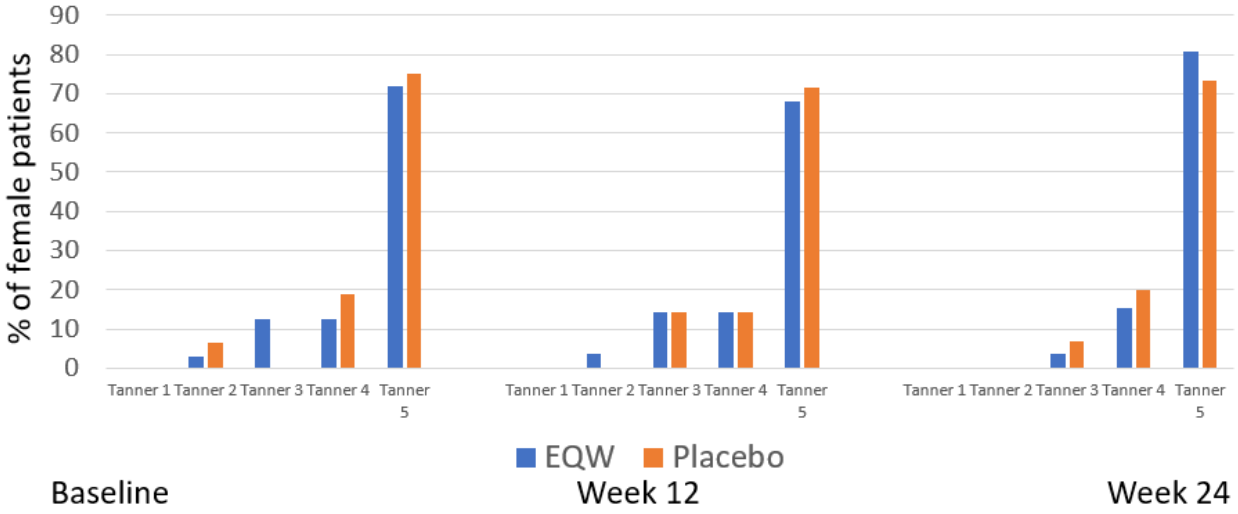
Puberty
Puberty was monitored by Tanner staging at Week 0, 12, 24, 40, 52, and early termination visit. Tanner staging was conducted for breast development in females, for genitalia in males, and for pubic hair development in both males and females. Pubic hair development reflects adrenarche rather than puberty, therefore the most relevant assessments for puberty is the Tanner stage assessment of breast development in females and genitalia development in males.

Per protocol, testicular volume was measured by an orchidometer and correlated to the respective tanner stage; however, no data on testicular volume was captured on the eCRF and therefore not available. Data on menarchal status was also not collected on the eCRF in this study.

Females
Most of the female patients in the EQW and placebo treatment groups were at Tanner stage 4 (4 [12.5%] and 3 [18.8%]) and Tanner stage 5 (23 [71.9%] and 12 [75%]) for breast development at baseline.

No patient in the EQW or placebo group was at Tanner stage 1 for breast development at baseline. 1 (3.1%) and 1 (6.3%) of patients in the EQW and placebo groups respectively were at Tanner stage 2 for breast development at baseline.

Figure 38: Tanner pubertal progression for breast development in females, controlled assessment period, safety population



Graphed from Applicant's data in BCB114 CSR. Percentage is based on the number of any patient who had a Tanner stage assessment at each visit and does not exclude patients with no postbaseline assessment.

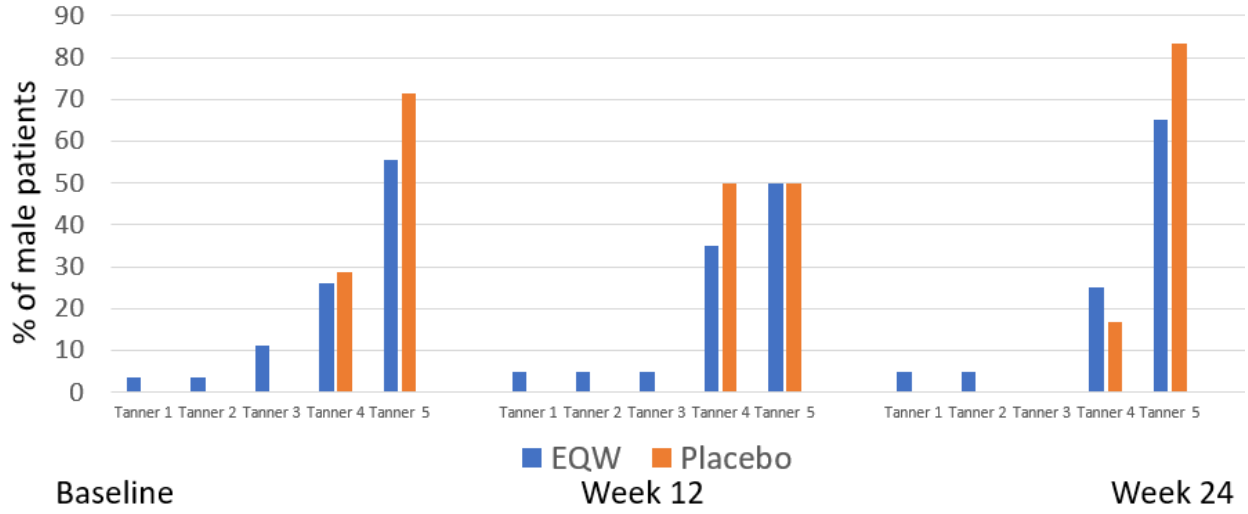
Reviewer Comment: Given that postmenarchal females are not expected to grow significantly, in retrospect, age of menarche and data on menstruation might have been useful. Due to very small number of patients in the lower Tanner stages, interpretation of data is challenging

Males

Most male patients in the EQW and placebo treatment groups (22 [81.4%] and 7 [100%]) were at Tanner stages 4 or 5 for genitalia development at baseline. In the EQW arm, there was 1

(3.7%) patient in each Tanner stage 1 and 2. Due to these small numbers, meaningful conclusions on a possible effect of drug on puberty progression cannot be made.

Figure 39: Tanner pubertal progression for genitalia development in males, controlled assessment period, safety population



Graphed from Applicant's data in BCB114 CSR. Percentage is based on the number of nay patient who had a Tanner stage assessment at each visit and does not exclude patients with no postbaseline assessment.

Reviewer Comment: The trial is unlikely to detect an impact on pubertal development because most of the patients in this study were older (median age 16 years old) and at latter stages of pubertal development at baseline.

There were no meaningful differences between treatment groups in LH, FSH, testosterone (in males) and estradiol (in females). As the assessments of hormones in females were not collected in relation to the individual patient's menstrual cycle, the interpretability of data is limited and meaningful conclusions cannot be made.

The 2007 FDA guidance on growth assessment suggests avoiding enrollment of children near the time of puberty in growth studies because of the rapid increase in growth velocity and normal physiologic acceleration associated with puberty that could occur in a short period. This will minimize the confounding effects of nonlinear growth rates. Given that T2DM pediatric patients in the postmarket setting will likely be children with advanced pubertal status and near completed growth, any potential drug effect on growth may not be clinically significant. Moreover, T2DM in prepubertal children is uncommon. Therefore, conducting a growth study in prepubertal children does not appear necessary at this time.

Some of the patient level data is presented below. While narratives were generally not available, this information was gathered from the submitted data.

- Patient (b) (6) a 12-year-old Indian male with good diabetes control and no significant past medical history randomized to EQW remained at Tanner stage 2 for genital development with a bone age increase from 12.2 to 13 over 52 weeks. This apparent slow pubertal progression appeared inconsistent with his growth data, which indicated a possible growth spurt (increase in height by about 10 cm over 52 weeks). Additional information such as midparental target height information and pre-trial growth pattern is needed to assess whether the height increase or the lack of progression in pubertal staging is within a normal range for the patient.

- Patient (b) (6) a 13-year-old White male on EQW progressed from Tanner stage 3 to 4 for genital development s with a 3-year advancement in bone age (from 14 to 17 years) over 52 weeks. Despite rapid advancement in bone age, height increased by only X cm over 52 weeks, with a height of X cm at the conclusion of the study. Additional information such as midparental target height or prior growth pattern was not available to help understand if the pattern of linear growth is normal for the patient and no conclusion can be made as to whether the rapid advancement in bone age is within the normal range for this patient.

- (b) (6) 13/F/X with well-controlled T2DM and no other significant past medical history was judged as Tanner stage 3 for breast development throughout 52 weeks while the measured bone age increased from 14.5 at baseline to 16 years at Week 52 and linear growth was minimal (1.2 cm over 52 weeks). The reported Tanner stage is inconsistent with the bone age and height data, which would suggest that she had nearly completed puberty at baseline (and would be expected to be Tanner stage 5). Additional information such as midparental target height, prior growth pattern, and whether the patient was postmenarchal at baseline was unavailable.

- (b) (6): 12-year old male on EQW progressed from Tanner stage 3 to 4 for genital development over 52 weeks along with a change in bone age from 14 to 16 but height only increased by 1 inch and half during the study which is inconsistent with the progression in bone age and pubertal status.

Reviewer Comment: Overall interpretation of data to assess a possible drug effect on progression of puberty based on small number of patients at lower tanner stages is challenging. Additional information on expected adult height or expected target height, midparental height target, and pre-trial growth pattern is required to assess growth patterns in pediatric patients. One must also account for factors that may influence linear growth and pubertal timing such as obesity and T2DM, and a variation in timing of peak height velocity as it relates to pubertal

stage, variations in normal pubertal development, different growth patterns and timing in puberty based on race and ethnicity.

8.4.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This section was evaluated as part of the original NDA review. There are no unique considerations for pediatrics that warrant discussion.

8.5. Safety in the Postmarket Setting

8.5.1. Safety Concerns Identified Through Postmarket Experience

The Applicant states the cumulative global post-marketing adult patient exposure to EQW since launch to March 31, 2020, has been estimated to be approximately 2128373 patient-years. The cumulative global post-marketing patient exposure to EQWS (autoinjector) in adults with T2DM since launch to March 31, 2020, has been estimated to be approximately 149,964 patient-years. No new safety concerns have been identified in the adult population with T2DM by the Applicant that are not already described in the product label for EQW.

8.5.2. Expectations on Safety in the Postmarket Setting

The safety of EQW in the postmarketing setting is expected to be no worse than observed in the BCB114 trial, or from what is currently labeled.

8.5.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.6. Integrated Assessment of Safety

The overall safety profile for EQW in study BCB114 is generally similar to the known and labeled risks in adults with T2DM and no new safety issues were identified in the study that warrant Contraindications or Warnings and Precautions beyond what are already in the label. In general, the incidence of treatment-emergent serious adverse events (SAE) in study BCB114 was low; during the controlled assessment period 2 (3.4%) patients on EQW compared to 1 (4.3%) patient on placebo experienced a SAE which were unlikely drug-related. In the controlled assessment period, the most frequent adverse reactions were related to gastrointestinal events, hypoglycemia, and injection site reactions). During the controlled assessment period 1 (1.7%) patient on EQW experienced severe hypoglycemia (requiring assistance) versus 0 on placebo. Consistent with the label, most of the patients (6 [21.4%]) who experienced an event of hypoglycemia were treated at baseline with insulin compared to 2 (6.5%) patients who were not treated with insulin at baseline.

Antibodies to exenatide were observed in most of the patients (93%) in the EQW group over 52 weeks and up to 10-week follow-up period during the study; most patients (63.2%) developed high antibody titers (≥ 625) compared to 29.8% who developed low antibody titers (< 625). Acknowledging the limitations of cross-comparing immunogenicity assessments across programs, the overall immune response to exenatide appears higher in pediatric patients compared to adults with T2DM and antibody titers in ADA positive pediatric patients appear to be higher than in ADA positive adult patients. Consistent with labeled information, pediatric patients with high titer antibody to EQW showed a lower reduction in mean HbA1c from baseline (0.07%) compared to those with low titer antibody (-0.73%). The attenuation of HbA1c in patients with high titer antibodies suggest an interference of anti-drug antibody (ADA) with drug effect. This may include a possible cross-reaction with endogenous GLP-1 that neutralizes its function too. The Applicant has not assessed cross-reactivity or neutralizing antibodies in study BCB114 but has evaluated cross-reaction to GLP-1 and glucagon in the samples from adult trials. Due to the possible difference in the overall immune response between adult and pediatric patients, the cross-reactivity results in the T2DM adult patients may not be applicable to the pediatric patients. However, an assessment of cross-reactivity to GLP-1/glucagon in the pediatric patients may not be needed at this time as no serious safety concern with clinical consequence was observed in the study.

The incidence of injection site reactions during the controlled assessment period was low and generally balanced between the treatment arms. None were serious or led to study drug discontinuation. In the controlled assessment period, all the injection site reactions (except 1 event of injection site pruritus) in the EQW arm occurred in patients who at any point during the study developed high titer ADA. Due to small number of events and high rate of high titer ADA positivity in study BCB114 conclusions on a possible relationship between ADA and injection site reactions in study BCB114 is limited.

Over 70% of randomized patients were in the later stages of puberty and had nearly completed linear growth at baseline therefore an evaluation of a possible drug effect on pubertal progression and growth is limited. Residual uncertainties include a possible long-term effect on growth and development (e.g., through a possible effect on pathways such as the hypothalamic-pituitary-adrenal axis as generally described in the literature for GLP-1 receptor agonists[17]). Given that patients in the postmarket setting treated with EQW will likely include pediatric patients with advanced pubertal status and near completed growth, a potential effect on growth may not be clinically significant.

[17] Am J Physiol Endocrinol Metab. 2013 May 15;304(10):E1105-17; Clin Endocrinol Metab 104: 202–208, 2019.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this supplement.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing information is being addressed in internal labeling meetings and labeling negotiations with the Applicant.

I agree with the clinical pharmacology reviewer that the data from BCB114 can be added to the EQWS label because the submitted population PK and exposure-response analysis demonstrate the exenatide plasma concentrations and HbA1c measurements at steady state following administration of EQW were both comparable in adolescent and adults with T2DM (who had anti-drug antibody [ADA] titer ≤ 625). Because the previous population PK analysis[18] showed similarity between EQW and EQWS in adults, the PK behavior of EQWS in adolescent patients with T2DM is expected to be similar to that of EQW. This suggests that the effect of EQWS on HbA1c is expected not to be different from the observed effect of EQW on HbA1c in study BCB114.

10.2. Nonprescription Drug Labeling

This section is not appliable to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

There is no REMS recommended.

12. Postmarketing Requirements and Commitments

The Applicant has not completed human factors (HF) validation testing in pediatric patients to support the proposed pediatric indication for EQWS. Therefore, to address human

[18] Clinical Pharmacology review of NDA 209210 dated December 4, 2018 DARRTS Reference ID: 4358137.

factor/medication error prevention with the use of the autoinjector, an HF study is needed to support the successful self-administration of the product in pediatric patients aged 10 to 17 years, both inclusive. As there is an unmet need for therapies in pediatric patients with T2DM and the possible risk of medication errors could be addressed through labeling, the Division and DMEPA have concluded the HF study could be conducted as a Postmarketing Commitment. The Applicant was notified of the following PMC on June 25,2021:

> *"Conduct a simulated use Human Factors validation study to demonstrate that the user interface has been designed to support that pediatric patients aged 10 years old to < less than 18 years old can safely and effectively use Bydureon BCise for intended uses in the intended use environments."*

Refer to Section 4.6 of this review for details.

13. Appendices

13.1. References

When applicable, references are provided as footnotes throughout the review.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BCB114

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: ~140		
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) 0		
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)): N/A 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: _____ 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: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Appendix 1

Table 32: Applicant's prespecified Preferred Terms for potentially immune-related adverse events

Allergic bronchitis	Immediate post-injection reaction	Rash
Allergic colitis	Injection site dermatitis	Rash erythematous
Allergic cough	Injection site eczema	Rash follicular
Allergic cystitis	Injection site erythema	Rash macular
Allergic keratitis	Injection site hypersensitivity	Rash maculo-papular
Allergic oedema	Injection site induration	Rash maculovesicular
Allergic otitis media	Injection site inflammation	Rash papular
Allergic pharyngitis	Injection site macule	Rash pruritic
Allergic respiratory symptom	Injection site nodule	Rash pustular
Hypersensitivity pneumonitis	Injection site oedema	Rash vesicular
Anaphylactic reaction	Injection site papule	Reaction to excipient
Anaphylactic shock	Injection site photosensitivity reaction	Reaction to preservatives
Anaphylactoid reaction	Injection site pruritus	Reversible airways obstruction
Anaphylactoid shock	Injection site pustule	Scleral oedema
Angioedema	Injection site rash	Scleritis allergic
Arthralgia	Injection site reaction	Skin oedema

Arthritis	Injection site recall reaction	Intestinal angioedema
Arthritis allergic	Injection site streaking	Stevens-Johnson syndrome
Asthma	Injection site swelling	Stridor
Auricular swelling	Injection site urticaria	Suffocation feeling
Bronchial hyperreactivity	Injection site vesicles	Swelling face
Bronchial oedema	Joint effusion	Swollen tongue
Bronchospasm	Joint swelling	Throat tightness
Circumoral oedema	Laryngeal obstruction	Tongue oedema
Conjunctival oedema	Laryngeal oedema	Tongue pruritus
Corneal oedema	Laryngitis allergic	Toxic epidermal necrolysis
Dermatitis	Laryngotracheal oedema	Toxic skin eruption
Dermatitis allergic	Lip oedema	Tracheal obstruction
Diffuse cutaneous mastocytosis	Swelling	Tracheal oedema
Drug eruption	Local swelling	Type I hypersensitivity
Drug hypersensitivity	Localised oedema	Type II hypersensitivity
Drug reaction with eosinophilia and systemic symptoms	Mechanical urticaria	Type III immune complex mediated reaction
Encephalopathy allergic	Nasal oedema	Type IV hypersensitivity reaction
Eosinophilia	Nephritis allergic	Urticaria
Eosinophilic oesophagitis	Oculorespiratory syndrome	Urticaria cholinergic
Epiglottic oedema	Oedema mouth	Urticaria chronic
Erythema multiforme	Oedema mucosal	Urticaria contact
Erythema nodosum	Oesophageal oedema	Urticaria papular
Eye oedema	Orbital oedema	Urticaria physical
Eye swelling	Oropharyngeal swelling	Urticaria pigmentosa
Eyelid oedema	Palatal oedema	Urticaria pressure
Face oedema	Periarthritis	Urticaria thermal
Gastrointestinal oedema	Periorbital oedema	Urticaria vesiculosa
Gingival oedema	Pharyngeal oedema	Urticaria vibratory
Gingival swelling	Photosensitivity reaction	Visceral oedema
Haemorrhagic urticaria	Pruritus	Wheezing
Hereditary angioedema	Pruritus allergic	
Hypersensitivity		
Idiopathic urticaria		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAHTAB NIYYATI
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LISA B YANOFF
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