CLINICAL REVIEW and SUMMARY BASIS FOR REGULATORY ACTION

Application Type	Supplemental NDA
Application Number(s)	NDA 021773
Priority or Standard	Standard
Submit Date(s)	01/06/2021
Received Date(s)	01/06/2021
PDUFA Goal Date	11/04/2021
Division/Office	OCHEN/DDLO
Reviewer Name(s)	Justin Penzenstadler, PharmD
Review Completion Date	Electronic stamp
Established/Proper Name	exenatide for subcutaneous injection
(Proposed) Trade Name	Byetta
Applicant	AstraZeneca
Dosage Form(s)	5 and 10 mcg per dose, multiple use prefilled pen
Applicant Proposed Dosing Regimen(s)	5 or 10 mcg
Applicant Proposed Indication(s)/Population(s)	None being sought – labeling changes only
Recommendation on Regulatory Action	Labeling changes: Approval PMR-1559: Release
Recommended Indication(s)/Population(s)	N/A

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0. Summary Review

Table 1: Materials consulted for this Summary Review

Office of New Drugs (OND) Action Package Material Reviewed/Consulted	Names of Discipline Reviewer(s); Dates of Review in DARRTS or Panorama	Sections Referencing
Office of Pharmaceutical Quality Review	Pallaiah Thammana; September 9, 2021	Section 4.2
Office of Clinical Pharmacology	S. W. Johnny Lau; September 27, 2021	Section 4.5
Office of Biostatistics	Yoonhee Kim; September 20, 2021	Section 4, Section 6 (Review of Relevant Individual Trials Used to Support Efficacy) and Section 7 (Integrated Assessment of Efficacy)
Office of Prescription Drug Promotion memorandum	Samantha Bryant; September 30, 2021	Section 10.1 (Prescription labeling)
Division of Medication Error Prevention and Analysis memorandum	Ariane O. Conrad; September 30, 2021	Section 10.1 (Prescription labeling)
Division of Diabetes, Lipid Disorders, and Obesity Clinical Review Template	Justin Penzenstadler; Electronic stamp date	Review follows
Pediatric Review Committee minutes from the September 14, 2021 meeting	Jacquline Yancy; 9/28/2021	Section 13 (Post marketing Requirements and Commitments)

1. Executive Clinical Summary

This document summarizes clinical and cross-disciplinary review of supplemental New Drug Application (sNDA) 021773/S045 and provides the basis for regulatory action. The subject matter of this review is a single adequate and well controlled (A&WC) safety and efficacy pediatric study, referred to as "GWBQ" throughout this document. The Sponsor initiated GWBQ to fulfill the Pediatric Research Equity Act (PREA) - mandated post-marketing requirement (PMR) 1559-1: Deferred pediatric study under PREA for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive).

Due to interpretability issues GWBQ does not fulfill the PREA PMR 1559-1. However, recently, the Division approved two Glucagon Like Receptor Subtype 1 (GLP-1) Receptor Agonists (GLP1RAs) for treatment of pT2D based on successful pediatric studies. These treatments offer with more convenient dosing schedules (BYDUREON – once weekly, VICTOZA – once daily). Therefore, the review team recommends releasing PMR 1559-1 on the grounds that Byetta does not provide meaningful clinical benefit over existing therapies for this indication.

1.1. Product Introduction

Exenatide (synthetic exendin-4) is a subcutaneously (SC) administered 39 amino acid peptide of the GLP1RA class. Exenatide mimics GLP-1, an endogenous molecule released by intestinal cells in response to a meal. Exenatide potentiates insulin release in response to a meal, directly inhibits inappropriate glucagon release, delays gastric emptying, and has central anorectic effects. Byetta is the first GLP1RA, FDA approved in 2005. Byetta is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Byetta is available in a 250 mcg/mL single patient use prefilled pen with filled with volume sufficient to administer 60 doses at either 5 or 10 mcg per dose and is administered at 5 or 10 mcg doses twice daily (within 60 minutes prior to the two main meals of the day, at least 6 hours apart).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study GWBQ demonstrated a nominal treatment difference (change from baseline in HbA1c at 28 weeks) favoring Byetta over placebo but failed to meet prespecified acceptance criteria (p-value less than 0.05). A post-hoc supplementary analysis, consistent with the intention-to-treat and treatment-policy principle, also failed to meet contemporary acceptance criteria (p ~ 0.08), although suggested a clinically significant treatment effect was more likely than not (point estimate was ~0.6%). Substantial evidence of effectiveness was not demonstrated. The Applicant is NOT requesting to expand the indication for Byetta to pediatric patients.

1.3. Benefit-Risk Assessment

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric type 2 diabetes is rare (affecting ~ 20,000 to 25,000 individuals) and disproportionally affects racial minorities, and those with lower access to clinical care. • Youth with T2D have more rapid decline in pancreatic function, and accelerated development of diabetes complications and comorbidities.	Adolescents with T2D are both difficult to study in a clinical trial, and serious consequences of their disease. Insufficient evidence of disease and treatment response similarity between adolescents and adults prohibits application of a partial efficacy extrapolation approach.
Current Treatment Options	• Metformin • Insulin and insulin analogues • GLP1Ras	There are limited treatment options for pediatric patients with type 2 diabetes mellitus, including only one oral antihyperglycemic agent (metformin). Glycemic response to liraglutide and once weekly exenatide in adults and youth with T2D appeared similar in clinical trials. The other GLP1Ras approved for pediatric type 2 diabetes have a better dosing schedule (once weekly or once daily), statistically persuasive efficacy in pediatrics, and more efficacy than Byetta in adults (via head-to-head comparisons).
Benefit	• Primary endpoint and measure of effect: Placebo-adjusted change from baseline in HbA1c at 28 weeks o The prespecified primary endpoint was not consistent with biostatistical best practices (it represented a hypothetical effect, rather than intention-to-treat, treatment-policy effect). This analysis failed to meet prespecified acceptance criteria ($p < 0.05$).	Overall, the results of GWBQ do not allow robust conclusion of a clinically relevant effect. aIt is not clear if GWBQ failed because Byetta is truly not efficacious, or if the study design and enrollment were inadequate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ The Sponsor and Agency conducted post-hoc analyses on the primary and key secondary endpoints consistent with the preferred "treatment-policy" estimand. With this approach, the sample of 78 Byetta treated subjects was observed to have a 0.63% lower change from baseline in HbA1c at 28 weeks than a sample of 42 placebo treated subjects with a 0.95 2-sided compatibility interval of [-1.39% to 0.13%]. In a Bayesian framework, these data suggest a clinically relevant benefit is much more likely than not, although more data is needed to confirm this to the 0.05 level. • GWBQ was underpowered due to both overly conservative power calculation assumptions and premature enrollment discontinuation. • The primary analysis discarded subjects after treatment discontinuation or glycemic rescue therapy. More subjects in the placebo arm required rescue therapy and were omitted from the primary analysis -omission of these subjects influenced the treatment effect unfavorably. • Secondary endpoints, including fasting plasma glucose, body weight, and proportion of subjects meeting glycemic goals at 28 weeks, did not show a treatment effect	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No deaths occurred • Serious adverse events were infrequent and unlikely related to study treatment • Common adverse reactions were similar to adult studies, including nausea, diarrhea, and upper respiratory infections • The clinical study was not powered to identify rare AEs (i.e., those with a NNH > 10-20)	Byetta appeared to be well tolerated in the pediatric population. Current labeling based on adult data is applicable to pediatric patients. No additional safety labeling is warranted.

1.4. Patient Experience Data

☐	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)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context (Analysis of Condition and Current Treatment Options)

There are important distinctions between adult and pediatric T2D which make it particularly challenging to develop and implement pharmacotherapy for pediatrics. Pediatric T2D patients

are rare and poorly accessible - the SEARCH study initiated in 2000[1], estimates approximately 20,000- 25,000 US adolescents had physician-diagnosed pT2D in 2009. Despite the rarity of pT2D, the prevalence is overall increasing as the incidence increased from 9.0 per 100,000 in 2002-2003 to 13.8 in 2014-2015 in US adolescents. This is in stark contrast to adult populations, where up to 10% (or 34.2M adults[2] have T2D. Adolescents with T2D are disproportionally affected by social and economically challenged with inherent barriers to clinical trial participation, including economic challenges, and difficulties participating in clinical trials[3].

T2D in adults and pediatrics has some similarity in that there is insulin resistance and loss of beta-cell function. However, there is evidence that glycemic control and β-cell function declines more rapidly in adolescents: the rate of loss of glycemic control on either metformin monotherapy or combination therapy with rosiglitazone in the TODAY study appears to be three- to fourfold higher than published rates in adults, via cross-study comparisons with ADOPT and UKPDS[4]. Youth-onset development T2D results in longer duration of disease and thus, increased potential for disease-associated complications. Additionally, youth with T2D also appear to have accelerated development of diabetes complications and co-morbidities, including high prevalence of hyperfiltration (predicting rapid GFR decline), diabetic retinopathy, and echocardiographic changes associated with major cardiovascular risk. Data from the SEARCH study estimate that 72% of youth with type 2 diabetes experience at least one comorbidity or complication by early Adulthood[5]. These differences do not suggest that full extrapolation from adults is supported. Therefore, at least one adequate and well controlled trial in pediatric T2D is needed to demonstrate effectiveness.

Prior to 2019, the only US FDA-approved drugs for the treatment of T2DM in adolescent patients were metformin and insulin. Recently, two members of the same therapeutic class as Byetta: BYDUREON (extended release exenatide) and VICTOZA (liraglutide), were approved for pT2D. Both VICTOZA and BYDUREON have more convenient dosing regimens (administered once daily and once weekly, respectively) and both have demonstrated greater glycemic control than Byetta in adults[6]. Therefore, Byetta would not confer benefit over already approved alternatives.

3. Regulatory Background

[1] Hamman 2014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4237981/
[2] National diabetes statistics report https://www.cdc.gov/diabetes/data/statistics-report/index.html
[3] National diabetes statistics report https://www.cdc.gov/diabetes/data/statistics-report/index.html
[4] Nadeau et al 2016 https://care.diabetesjournals.org/content/39/9/1635
[5] Pyle and Kelsey 2021: https://pubmed.ncbi.nlm.nih.gov/34075436/
[6] LEAD-6 demonstrated superiority of liraglutide 1.8 mg to Byetta 10 mg BID. DURATION-1 and DURATION-5 demonstrated superiority of BYDUREON 2mg QW to Byetta 10 mcg BID.

3.1. U.S. Regulatory Actions and Marketing History

Byetta was approved in the US on April 28, 2005 and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

3.2. Summary of Presubmission/Submission Regulatory Activity

A written request (WR) was issued in March 2006, which included a request for the following studies:

- Study 1: A short-term pharmacokinetics (PK), pharmacodynamics (PD), and tolerability study in children with type 2 diabetes.
- Study 2: A clinical safety and efficacy study of exenatide as monotherapy and as add-on to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea in children with type 2 diabetes.

The Sponsor submitted the clinical study report to fulfill WR study 1 on September 28, 2007. The protocol for the study intended to fulfill study 2 of the WR was submitted on February 8, 2008. In October 2009, Byetta was approved as monotherapy and the following post-marketing requirement (PMR) was issued at that time:

- PMR 1559-1: Deferred pediatric study under PREA for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-16 years (study report due December 31, 2010). PMR 1559-1 was also intended to address Study 2 of the WR.

Deferral extensions for both the WR and PMR 1559-1 were granted three times since the PMR was issued in 2009, including 2013, 2014, and in June 2018, due to enrollment difficulties. The Sponsor requested to use (b) (4) (February 2014) and (b) (4) for GWBQ (2015), however, the Agency declined both requests.

In January 2019, the Division denied a Type C meeting request to discuss continued delays in GWBQ, as the Sponsor was recently granted a deferral extension in August 2018. Per further email communications with AZ regarding this PMR, on March 13, 2019, the Division issued informal advice regarding the January 2019 meeting request, requesting the Sponsor to submit a justification memo to the IND providing information on why the GWBQ study should be closed. AZ submitted this to IND (b) (4) on April 11, 2019. The FDA team reviewed this and issued a statistics advice/IR letter on April 29, 2019. AZ provided an informal response to this letter via email on May 15, 2019 and requested feedback. DMEP emailed feedback on June 27, 2019, and AZ provided a response to it via email on July 5, 2019.

In July 2019, the Division held a teleconference. The Sponsor noted their intention to stop the study regardless of meeting the requirements for the written request. The Division acknowledged the difficulty in GWBQ recruitment and stated that, the Agency would discuss internally to release the PMR on the grounds of no clinically meaningful benefit over existing

therapies (since the recent approval of VICTOZA for pediatric type 2 diabetes). The Division also requested that the Sponsor submit the full study report (which is the subject matter of this review) to determine if the PMR is fulfilled or could be released.

After consulting the PeRC for concurrence (July 24, 2019 meeting minutes), the Agency issued a General Advice Letter dated 30 July 2019, stating the Sponsor may stop GWBQ. Based on this agreement, the Sponsor committed to analyzing all available data from the study.

An FDA-requested teleconference was held in June 2020 to discuss the Sponsor's request to amend the WR that was submitted to the FDA on April 20, 2020. The outcome of this discussion was that Sponsor agreed to withdraw the request to amend the WR and to submit a revised WR amendment in which Study 2 (GWBQ) would be replaced with the pediatric study of exenatide once weekly (BYDUREON study BCB-114) because of the difficulties in interpreting the results of study GWBQ. The revised WR amendment was submitted to the FDA on July 3, 2020.

In June 2020, a final Deferral Extension Granted Letter was granted for PMR 1559-1, with a final report submission date of January 31, 2021.

3.3. Foreign Regulatory Actions and Marketing History

Byetta was approved by the European Medical Agency (EMA) in November 2006 for adults who have not achieved adequate glycemic control on maximally tolerated doses of oral therapies or as an adjunct treatment with insulin glargine. EMA labeling (most recently updated August 24, 2021) includes a brief description of GWBQ and the results. (b) (4) .

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

4.1. Office of Scientific Investigations (OSI)

OSI inspection or audit of individual case report forms were not requested because (a) GWBQ results will not be labeled in detail, (b) the failure of the study is due to design elements and enrollment issues rather than trial conduct (refer to section 7 for details), and (c) Dr. Yoonhee Kim, biostatistics reviewer and the clinical reviewer did not identify any data quality or integrity issues.

4.2. Product Quality

There are no new data regarding chemistry, manufacturing, and controls (CMC), sterility, or biopharmaceutics in the submission. The annotated Package Insert for Byetta was submitted which did not contain any CMC related changes to review.

The draft carton labeling was reviewed and found to be adequate from the CMC review perspective. OPQ concluded the overall efficacy supplement is adequate from the CMC review perspective.

4.3. Clinical Microbiology

There are no new data regarding microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

There are no new data regarding non-clinical pharmacology or toxicology in the submission.

4.5. Clinical Pharmacology

Study GWBQ did not include any evaluable pharmacokinetics information. No pharmacodynamic endpoints that were not also secondary endpoints were studied. Previously, a dedicated PK study of Byetta in adolescents was conducted to partially fulfill the WR. This study (2993-124; "A Randomized, Single-Blind, Dose-Rising, Placebo-Controlled, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Tolerability of Exenatide in Adolescent Subjects with Type 2 Diabetes Mellitus.") was submitted and reviewed. The Office of Clinical Pharmacology (OCP) concluded the pediatric exenatide Cmax and AUC0-inf data are consistent with the adult exenatide Cmax and AUC0-inf data, although noted 2993-124 had a small sample size (See Dr. Manoj Khurana's Clinical Pharmacology review for Study 2993-124 dated July 17, 2008 in DARRTS). The clinical reviewer concurs with their conclusions.

The Office of Clinical pharmacology deferred to Clinical and Statistical reviewers for adequacy of the submitted data to support approval.

4.6. Devices and Companion Diagnostic Issue

N/A

4.7. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

This is a PMR-related submission, which includes the final report for clinical study H8O-MC-GWBQ (referred to as GWBQ throughout this document), with NCT identifier 00658021. Study GWBQ was initiated to fulfill PMR-1559.

Study GWBQ is a randomized, double blind, placebo control safety and efficacy study of pediatric subjects. 122 pediatric subjects (ages 10 to 17, inclusive) were enrolled in 8 countries: Brazil (4 centers), India (3 centers), South Korea (1 center), Mexico (8 centers), the Philippines (1 center), Russia (3 centers), the United States (33 centers), and South Africa (4 centers).

5.2. Review Strategy

The clinical reviewer followed these steps:

(1) Examined and scrutinized the protocol for GWBQ, focusing on study design, endpoint ascertainment, and analysis plan and how such elements pertain to interpretation of study results
(2) Exploration of raw safety data as it pertains to adverse event data listings and clinical laboratory values, and reading of individual patient narratives for all serious adverse events
(3) Review of the Applicant's clinical study report to ensure concordance in results and conclusions.

The statistical reviewer confirmed and supplemented the Applicants' analyses; therefore, this document reviews and comments on the efficacy results presented in the statistical review. Refer to the statistical review (Section 0) for in-depth review of the raw efficacy datasets.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. H8O-MC-GWBQ

6.1.1. Study Design

Overview and Objective

The study was designed to serve as an adequate and well controlled investigation to determine safety and efficacy. The primary objective of GWBQ is to test for superiority in glycemic control (as measured by change from baseline in HbA1c) of Byetta 5 mcg, 10 mcg, or both, against placebo at 28 weeks in adolescent subjects with T2D.

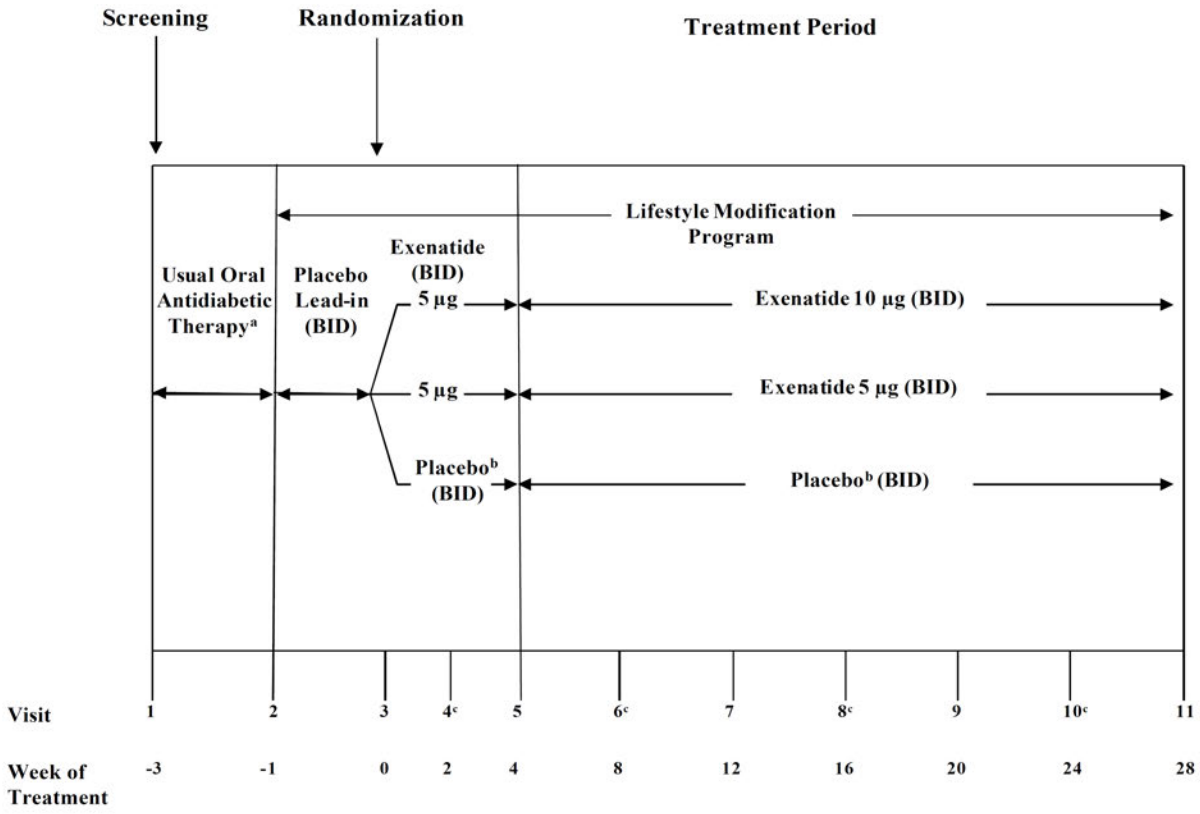
Trial Design

GWBQ is a multi-national, multi-center, placebo controlled, randomized, double-blind, parallel arm study in in adolescents 195 patients were to be enrolled, and first undergo a 1-week, single-blind, injectable placebo lead-in period before assigned active treatment.

Randomization via interactive voice response system will occur at 2:2:1:1 (5 mcg BID, 10 mcg BID, volume matched placebo to 5 mcg BID, volume matched placebo to 10 mcg BID). Subjects assigned to 10 mcg BID would first undergo a 4-week titration period with 5 mcg, as per adult

labeling. Study drug will be administered within 60 minutes before morning and evening meals (or the 2 main meals of the day, 6 hours or more apart) for 28 weeks. Randomization will be stratified by screening HbA1c values (<= 8% and >8%) as well as background diabetes therapy. All patients were expected to participate in a lifestyle modification program throughout this study, include both dietary education (visits with a dietician or certified diabetes educator at clinic visits) and physical activity components. The Sponsor will be blinded to post-baseline HbA1c and anti-exenatide antibodies. If investigator, patient, or other personnel were unblinded, the patient was discontinued from the study.

Figure 1: Design for GWBQ



Source: Sponsor's figure

Reviewer's comments: The study design of GWBQ meets the statutory requirements[7] to be considered adequate and well controlled. This study is similar in design to the studies used to support a pediatric indication for metformin, BYDUREON, and liraglutide.

Major Inclusion/Exclusion criteria

[7] 21 CFR 314.126 (b) accessahttps://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.126

GWBQ included males and females aged 10 to 17 years (inclusive) with T2DM with a documented and confirmed history of T2D consistent with the ADA diagnostic criteria[8] with additional criteria (absence of islet autoimmune antibodies and C-peptide greater than 0.6 nmol/L) to prevent inclusion of subjects with type 1 diabetes. Subjects must have a screening HbA1c between 6.5% and 10.5% (inclusive). Subjects must be either (a) naïve to antidiabetic agents, (b) receiving oral treatment with metformin, (c) a sulfonylurea (SU), or (d) a combination of metformin and an SU at the time of enrollment.

Major exclusions:

- DRUGS: have recently[9] used an alpha-glucosidase inhibitor, meglitinide, pramlintide, inhaled corticosteroids (at doses >= 1000 mcg FLOVENT daily), oral steroids, thiazolidinedione, any weight loss medications, anabolic (e.g., illicit) steroids
- insulin use for more than 10 weeks during the 3 months prior to screening
- pregnant, planning to become pregnant, or lactating
- history of kidney disease or a serum creatinine (SCr) greater than 1.6 mg/dL (males) or greater than 1.4 mg/dL (females)
- transaminitis (> 3 x ULN for Alanine transaminase (ALT) or Aspartate transaminase (AST))

Reviewer's Comments: The inclusion criteria encompass a large majority of the population who would be treated with a GLP1RA outside of a clinical study.

The prior drug use exclusion criteria broadly fit into three categories: (a) unapproved (for pediatric use) antidiabetics, which is reasonable given current pT2D guidelines dissuade their use, (b) corticosteroids, which affect glucose homeostasis, making efficacy readouts less easily interpretable, and (c) recent, prolonged, insulin use.

Regarding insulin use, a significant portion of newly diagnosed pediatric T2D patients require insulin at time of diagnosis[10], perhaps up to 30%[11] based on the presence of patients presenting with ketosis/ketoacidosis at diagnosis. Additionally, in the TODAY study, approximately 50% of subjects required insulin by 2 years of diagnosis. This exclusion criteria may have prevented a significant portion of patients, perhaps those with the most severe disease, with pediatric T2D from enrolling.

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[8] One or more of the following: FBG > 126 mg/dL, random BG > 200 mg/dL, 2h-OGTT glucose > 200 mg/dL; negative for both GAD65 and ICA512; and fasting C-peptide >0.6 ng/mL

[9] Washout period and treatment duration and were different between certain drug classes, detailed descriptions excluded for brevity

[10] Pinhas-Hamiel et. al. 2007, PMID: 17531891

[11] Rosenbloom et. al., 2008; PMID: 18694453

The kidney and liver function exclusion criteria are also broad and strike a reasonable balance between allowing study of individuals with common comorbidities (e.g., microvascular, fatty liver disease), but preventing higher-risk subjects from participating in an investigational study.

Overall, exclusion criteria do not limit the external validity of the study. I believe the inclusion/exclusion criteria are sufficiently broad enough to apply the safety and efficacy findings from this study to the general US adolescent population who are not currently using insulin. (b) (4)

Study Endpoints

All efficacy endpoints are calculated as change in parameter from baseline to week 28. The objectives and endpoints reflect the change to comparison between a pooled group of 5 mcg and 10 mcg twice daily exenatide (referred to as EBID for the remainder of this document) and placebo, compared with the separate comparisons between placebo and both 5 mcg and 10 mcg twice daily exenatide (Table 2).

Table 2: GWBQ Endpoints

Primary Efficacy	The change in HbA1c from baseline to week 28 (superiority hypothesis test)
Secondary Efficacy	Proportion of patient achieving HbA1c goals of <7%, ≤6.5%, and <6.5% Change in body weight from baseline Change in fasting serum glucose from baseline Change from baseline in SMBG measurements before and 2 hours after the 2 main meals of the day on 3 days during the week before Change in in fasting serum insulin from baseline Change in HOMA-B and HOMA-S as measured by homeostasis model assessment from baseline Proportions of patients discontinuing the study, due to failure to maintain glycemic
Secondary Safety	Adverse events (serious and nonserious) Incidence and frequency of hypoglycemic events Laboratory measurements (including clinical chemistry, calcitonin, CEA, hematology and urinalysis) Antibodies to exenatide Electrocardiograms Vital signs Pubertal assessment Height

Reviewer Generated. Exploratory endpoints excluded for brevity

Statistical Analysis Plan

This review only discusses statistical elements which are important in interpreting the study findings. For a detailed summary and impression of the statistical analysis plan, refer to Dr. Yoonhee Kim's review (DARRTs; September 20, 2021)

No adjustments for multiplicity (including hierarchical testing) were made for the primary, secondary, and exploratory variables. SAP was agreed upon and finalized before unblinding.

Primary analysis method and estimand framework

The primary analysis encompasses randomized subjects received at least one dose of study medication (i.e., mITT) and had at least one baseline and post-baseline HbA1c measurement. HbA1c observations after an intercurrent event (n.b., received rescue therapy, discontinued treatment early) were omitted from this analysis, representing a hypothetical treatment effect for a population if no rescue therapy or premature treatment discontinuation occurred. The chosen model, MMRM, implicitly assumes data are missing randomly (i.e., the probability of HbA1c measurement being missing is not related to the true, unobserved value itself).

The model-based estimate will be adjusted for baseline HbA1c and background diabetes therapy strata (drug naïve, metformin, an SU, and a combination of metformin and an SU).

Sample size/power calculation

The study was originally designed to enroll 195 subjects. The original aim of the study was to separately assess EBID doses of 5 mcg and 10 mcg versus placebo. However, because of ongoing clinical pediatric studies using other more conveniently administered therapies (e.g., once daily oral, or once weekly injection) at that time, recruitment to study GWBQ was difficult and slow despite extensive efforts by the Sponsor. The planned number of patients would have taken an unreasonably extended period to recruit so a decision was made with agreement by the European Medicines Agency and the US FDA to stop recruitment and to pool patients' data from both exenatide dose groups (referred to as Total EBID) for comparison with placebo.

Modifications to the SAP were made in attempt to preserve power given the decrease in sample size due to difficulties recruiting patients. Dr. Yoonhee Kim stated that given these assumptions (N=122, 2:1 randomization, ES of -0.45%, SD of 1%), the study power was 64%.

Patient level residual SD estimated from the actual study results was 1.7%, which was larger than the assumed SD of 1.0% in the sample size calculation. Reassessed power with study results indicated that this study is underpowered (e.g., treatment effect of -0.6 and SD 1.7% using washout analysis with sample size 120 (2:1) reassessed study power of 45%).

Reviewer's Comments: Recruitment issues are a common in pT2D drug development. Some experts[12]suggest only 2% (500-600) subjects are eligible for pT2D trials at any given time. Because GWBQ is underpowered, there is over a 50% chance that a truly efficacious drug would fail to "win" under the current study design. Thus, negative results could be due to the study design itself, making them uninterpretable.

The primary analysis model, MMRM, assumes data are missing at random, and the primary analysis data set excludes data following intercurrent events (treatment rescue or discontinuation of therapy). This is significant – effect estimates from this population represent an answer to a hypothetical situation: what would have been seen (contrary to fact), had NO subjects been given rescue medication or discontinued the treatment to which they were randomized to receive.

For population benefit-risk calculations, this estimate is not consistent with current best practice. Instead, the de facto (i.e., intention to treat, treatment policy principle) estimand is preferred: it tells us what happens to the outcome variable, on average, if you randomize a patient to one arm versus the other, including the effects of all the various things that might happen (e.g., rescue medication, treatment discontinuation, etc.). The Agency provided advice to analyze the data according to this principle (see section 3.2) following database lock, so the appropriate analysis, according to the treatment policy principle, might be considered exploratory. Dr. Yoonhee Kim conducted post-hoc, supplementary analyses using preferred methods, which the clinical reviewer agrees with.

Dose Selection/Study Treatments:

5 mcg and 10 mcg BID are the approved doses in adults. Additionally, a PK study in adolescents (refer to section 4.5) demonstrated single doses of exenatide 2.5 and 5 mcg had similar exposures to adults.

Intercurrent Events and Glycemic Rescue Criteria:

Importantly, the protocol does not explicitly differentiate treatment discontinuations and study discontinuation. The Protocol does not urge follow up of patients regardless of treatment continuation. Patients were to be discontinued from the study in any of the following circumstances:

- if the patient experiences a loss of glycemic control (discussed below)
- pregnancy
- if the patient misses more than 10 consecutive days of study treatment or background oral antidiabetic therapy
- if a patient uses excluded concomitant medications

[12] Nadeau, 2016; https://care.diabetesjournals.org/content/39/9/1635

- any other discretionary measures by the investigator, sponsor, or patient

Specific glycemic rescue criteria are as follows:

- increase in HbA1c >= 0.5% from baseline at 2 consecutive visits at least 1 month apart
- FPG >250 mg/dL or random glucose >300 mg/dL for 4 days in a 7-day period via SMBG (must be confirmed in clinic)

Investigators will be instructed to maintain patients on stable doses of metformin and an SU so that treatment arm differences can be attributed to study treatment rather than other agents. For patients using an SU, the SU dose may be reduced if hypoglycemic episodes occur, and eventually stopped, if hypoglycemia continues. Treatment with insulin may be given for emergency reasons during the treatment period. If the period of insulin use exceeds 10 days during a 3-month period, or if any additional anti-diabetic treatment was initiated, HbA1c observations following that period were to be omitted from the primary efficacy analysis, but subjects were permitted to stay on study.

Treatment Compliance

No specific study data were collected for analysis of treatment compliance.

Protocol Amendments

There was a total of 5 protocol amendments, and 4 protocol addendums. The only remarkable change was the addition of a long-term safety follow up and additional safety assessments, including CEA, calcitonin, and Tanner staging, in May 2012, (b) (4). No protocol amendments were identified which would change the interpretation of the study results relevant to an application of this scope.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant affirms (page 1 of CSR) that the studies were conducted in accordance with good clinical practice (GCP) standards and considerations for the ethical treatment of human participants.

Financial Disclosure

The Agency requested financial disclosure forms as part of an information request dated February 18, 2021. In their response[13], AstraZeneca disclosed commercial interests of

[13] \\CDSESUB1\evsprod\NDA021773\0452

investigators. Three investigators participated in financial arrangements or hold financial interest that are required to be disclosed (i.e., filed a form 3455). One of the three investigators randomized patents (n=(b) (6).

Reviewer's comments: Overall, the investigator financial disclosures do not raise questions about the data integrity because (a) (b) (6) patients were randomized under an investigator requiring a disclosure, (b) the study was double blinded and (c) the primary endpoint was an objective laboratory measurement.

Patient Disposition

240 subjects were screened, 110 were screen failures, 122 were randomized, and 120 received study treatment. Table 3 describes the outcomes of patients after randomization and receiving at least one dose.

Table 3: Patient Disposition

	Exenatide	Placebo
N	78	42
Completer	56 (72)	25 (59)
Adverse event	4 (5.1)	0 (0.0)
Development of study-specific withdrawal criteria	2 (2.6)	0 (0.0)
Loss of glucose control	2 (2.6)	10 (23.8)
Physician decision	3 (3.8)	1 (2.4)
Protocol violation	2 (2.6)	1 (2.4)
Withdrawal by parent/guardian	2 (2.6)	1 (2.4)
Withdrawal by subject	2 (2.6)	3 (7.1)

Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio. Emphasis is the Reviewer's

*Reviewer's Comments: Although the inclusion and exclusion criteria appeared at least adequate to apply to the larger population (discussed in section 6.1), the screen failure rate is high (46%), which would raise concerns about the external validity of findings. This failure rate is in-line with other pediatric programs such as liraglutide (ELLIPSE) with a 56% screen failure rate, and sitagliptin (P083, P170, and P289) with 39.5 to 70% screen failure rates. Reasons for screen failures were **not** provided, however, I strongly suspect the requirement of no recent insulin, and 6.5% HbA1c lower threshold is responsible.*

Protocol Violations/Deviations

56 "important" protocol deviations were recorded in 34 patients. (27.9% of the mITT population). The Sponsor reports 14 patients were treated with systemic corticosteroid (CCS)

therapy for >= 5 days, and 13 patients (10.7%) had a major protocol deviation of receiving no (or incorrect) study medication during the 28-week treatment period; this included 2 patients who received no study treatment, 1 patient who did not take study treatment for 2 days, and 10 patients with 1 occasion where they took an incorrect dose of study treatment. An additional 3 patients were randomized according to an incorrect stratification block (e.g., were miscategorized by the investigator when prompting the IVRS).

Reviewer's Comments: The most common protocol deviation was receiving "systemic" CCS therapy. In my review of the individual listings, it appeared that most of the suspect drugs were inhaled, topical, or nasal CCS moieties. I am not concerned regarding these agents since the systemic bioavailability is exceptionally low.

The second most common protocol deviation was missing or taking the wrong dose. This is common in actual practice and is not a concern when interested in a treatment policy estimand. All other protocol violations were both isolated (i.e., one or two subjects) and at a minimal risk to impart study bias (wrong stratification factor used, change in background therapy).

Demographics

The demographics of GWBQ are described in

Table 4.

Table 4: Demographic Characteristics of GWBQ

	Overall	**EBID**	**Placebo**
N	120	78	42
Age (years)	14.05 (1.92)	13.87 (1.96)	14.38 (1.82)
Sex, Number of Males (%)	40 (33.3)	27 (34.6)	13 (31.0)
Diabetes duration (years)	1.63 (1.68)	1.57 (1.61)	1.75 (1.82)
Fasting plasma glucose (mg/dL)	140.55 (53.18)	135.72 (52.72)	149.52 (53.50)
BMI	34.15 (9.69)	34.18 (9.71)	34.10 (9.79)
Hba1c at screening (%)	7.77 (1.13)	7.75 (1.12)	7.80 (1.15)
HbA1c at baseline (%)	7.59 (1.22)	7.57 (1.27)	7.65 (1.14)
eGFR (MDRD, ml/min)	144.50 (13.07)	145.93 (13.34)	141.84 (12.27)
Height (cm)	162.97 (9.02)	162.00 (8.42)	164.78 (9.89)
Race			
Other	1 (0.8)	1 (1.3)	0 (0.0)
Asian	10 (8.3)	5 (6.4)	5 (11.9)
Black	27 (22.5)	20 (25.6)	7 (16.7)
Hispanic	57 (47.5)	40 (51.3)	17 (40.5)

White	25 (20.8)	12 (15.4)	13 (31.0)
Prior treatment			
MET	75 (62.5)	50 (64.1)	25 (59.5)
MET+SU	13 (10.8)	8 (10.3)	5 (11.9)
Naïve	30 (25.0)	20 (25.6)	10 (23.8)
SU	2 (1.7)	0 (0.0)	2 (4.8)
COUNTRY (%)			
Brazil	2 (1.7)	1 (1.3)	1 (2.4)
India	6 (5.0)	3 (3.8)	3 (7.1)
Korea	1 (0.8)	1 (1.3)	0 (0.0)
Mexico	27 (22.5)	20 (25.6)	7 (16.7)
Russia	2 (1.7)	1 (1.3)	1 (2.4)
United States	81 (67.5)	51 (65.4)	30 (71.4)
South Africa	1 (0.8)	1 (1.3)	0 (0.0)

Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio.

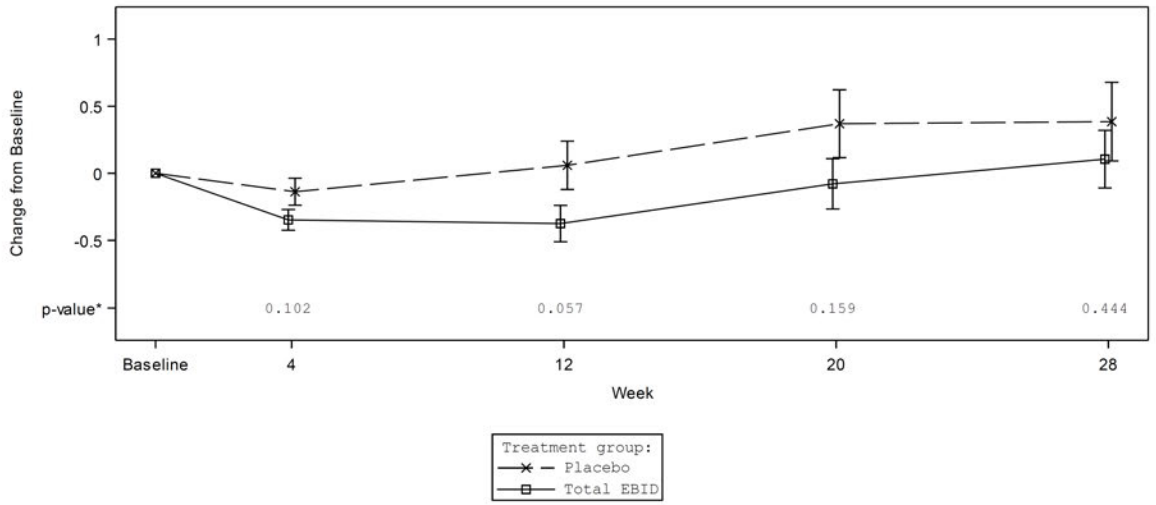
The average subject in GWBQ is 14 years old with a history of diabetes spanning 1.6 years, HbA1c of 7.6%, and comorbid obesity (average BMI is 34). Most subjects are derived from the US (67.5%) and concurrently treated with metformin (62.5%).

Reviewer's comments: I did not identify any concerning imbalances between treatment and control arms which may influence the efficacy outcome (p-values not shown, since the statistical significance of such differences would be due to chance alone). The average subject in GWBQ is 14 years old with a history of diabetes spanning 1.6 years, HbA1c of 7.6%, and comorbid obesity (average BMI is 34). Most subjects are derived from the US (67.5%) and concurrently treated with metformin (62.5%). The characteristics of GWBQ participants are broadly congruent with the to-be-marketed U.S. population.

Efficacy Results – Primary Endpoint

The primary efficacy population excluded patients after treatment discontinuation or rescue therapy (i.e., a "per protocol" population). The primary analysis included 53 subjects treated with EBID (68% of randomized) and 26 subjects treated with placebo (62% of randomized) at 28 weeks. This model estimated a placebo-adjusted change from baseline of -0.28%, which was not statistically significant (p=0.444).

Figure 2: Change in HbA1c (%) at Scheduled Visits, Evaluable Analysis Set



Source: CSR figure 6. Point estimates and confidence intervals are derived from MMRM model including treatment, baseline HbA1c, background diabetes therapy, visit, HbA1c by visit interaction, and treatment by visit interaction as fixed effects and an unstructured covariate matrix.

There are several issues with the Sponsor's analysis methods which are described in detail in Dr. Yoonhee Kim's review (DARRTs, September 20, 2021) and the statistical analysis plan section of this review (Section 6.1.1: Statistical Analysis Plan). Briefly, the Sponsor ignored intercurrent events (i.e., omitted data after initiation of rescue therapy or treatment discontinuation) and used an MMRM model which assumes data were missing at random. "Per-protocol" analysis set (i.e., omitting data after initiation of rescue therapy or treatment discontinuation) used by the Sponsor is not appropriate for evaluating benefit, since rescue therapy and treatment nonadherence are expected (i.e., in the real world) and contribute meaningfully to true, population-level benefit. Additionally, the MMRM model implicitly assumes that missing data are missing randomly, which is particularly troublesome when there is both a high percentage of missing data, and missingness of an observation confers information about the value itself. In the case of GWBQ, both criteria are met: a disproportionately high percentage of placebo patients dropped out due to loss of glycemic control (24%). In removing these subjects from analysis, one is comparing those treated with Byetta to only those who did "good" on placebo.

For these reasons, the Agency requested the Sponsor to conduct analyses which do not require data to be missing at random, and Dr. Yoonhee Kim performed sensitivity analyses herself. Dr. Kim performed a "washout analysis" which is the preferred method for dealing with data which are not missing at random under "treatment policy" principles. This approach assumes treated subjects who drop out of the study to behave like placebo. The results of the Sponsor's analysis and Dr. Kim's analysis are presented below.

Table 5: Primary Analysis Results for Change in HbA1c (%) at Week 28 – FAS population

Changes in HbA1c from baseline at Week 28	*Total EBID N=78 LS mean§ (SE)*	*Placebo N=42 LS mean§ (SE)*	*LS mean§ Difference from placebo at Week 28 (95% CI)*
MMRM- excluding[1]	0.11 (0.22)	0.38 (0.29)	-0.28 (-1.01, 0.45)
MMRM[2]	0.24 (0.23)	0.66 (0.31)	-0.41 (-1.18, 0.35)
The applicant's Washout Analysis[3]	-0.10 (0.42)	0.57 (0.42)	-0.67 (-1.44, 0.10)
Agency's Washout Analysis[4]	**0.12 (0.25)**	**0.75 (0.30)**	**-0.63 (-1.39, 0.13)**

§ LS means are from ANCOVA model with treatment group, baseline values and stratification factor as covariates after missing data imputation; [1]*Excluding measurements after initiation of rescue therapy or treatment discontinuation;* [2]*Including measurements after initiation of rescue therapy or treatment discontinuation;* [3] *Washout analysis: monotone imputation with intermediate values in the placebo group; monotone imputation with baseline values only using placebo completers in the Total EBID group using the applicant's code (imputing changes);* [4] *Washout analysis using agency's code (imputing HbA1c value (aval), monotone regression in the placebo group, obsmargins option used in PROC MIXED)*
**Sources: CSR Table 17 (page 91), Table 14.2.1.3 (page 333), and reviewer's analysis using adlb.xpt and adsl.xpt*

Source: Dr. Yoonhee Kim's statistical review, Table 5

The preferred washout analyses did not reach contemporary significance thresholds and are exploratory. Overall, Dr. Kim concludes "Statistical findings in GWBQ did not show effectiveness of EBID compared to placebo in reduction of HbA1c (%) and key secondary endpoints. The study results did not support efficacy of EBID compared to placebo in adolescents with T2DM population." The review team agrees with her assessment.

Efficacy Results – Secondary and other relevant endpoints

Findings from secondary endpoints do not merit extended discussion because (a) the primary endpoint failed to show nominal significance despite using all reasonable analysis methods, (b) secondary endpoints were not controlled for type 1 error, and (c) such endpoints will not be used to make a claim in labeling. Nonetheless, the Sponsor's MMRM (*de jure* estimate of effect, also referred to as "hypothetical") and Dr. Kim's washout (*de facto* estimate of effect, also referred to as "intention to treat, treatment-policy" estimate of effect) analyses of key secondary endpoints were considered (Table 6).

Table 6: Analysis Results for Key Secondary Endpoints- FAS population

	Total EBID N=78	*Placebo N=42*	*Difference from placebo at Week 28*
HbA1c < 7%, n[1] (%)	28 (36%)	13 (31%)	5%
HbA1c ≤ 6.5%, n[1] (%)	20 (26%)	8 (19%)	7%
HbA1c < 6.5%, n[1] (%)	20 (26%)	6 (14%)	12%
Body weight changes (kg), LS Mean§ (SE)			
The applicant's MMRM[2]	-0.81 (0.63)	-0.36 (0.86)	-0.44 (95% CI: -2.56, 1.68)
Agency's Washout anlaysis[3]	-0.55 (0.59)	-0.09 (0.79)	-0.47 (95% CI: -2.39, 1.47)
Fasting Serum Glucose (mmol/L), LS Mean§ (SE)			
The applicant's MMRM[2]	0.79 (0.40)	1.07 (0.55)	-0.28 (95% CI: -1.61, 1.05)
Agency's Washout anlaysis[3]	0.85 (0.37)	1.27 (0.51)	-0.43 (95% CI: -1.68, 0.82)

n: proportions of subjects who achieved the goal at Week 28; SE=standard error.
§ LS means are from ANCOVA model with treatment group, baseline values and stratification factor as covariates after missing data imputation [1] *missing data was considered as subjects who did not achieve the goal;* [2]*Excluding measurements after initiation of rescue therapy or treatment discontinuation*[3] *Washout analysis using agency's code (imputing HbA1c value (aval), monotone regression in the placebo group) including measurements after initiation of rescue therapy or treatment discontinuation*
**Sources: CSR Table 20 (page 103), Table 21 (page 104), and reviewer's analysis using adlb.xpt and adsl.xpt*

Source: Dr. Yoonhee Kim's statistical review, Table 6

Proportions of subjects who achieved the prespecified HbA1c goals were calculated, subjects with missing data were considered as non-responders who did not achieve the goal. Nominal p-values from Cochran–Mantel–Haenszel test for were 0.51, 0.42 and 0.13, respectively. Dr. Kim concluded that none of the results support the efficacy of EBID compared to placebo. The results do, however, trend in the direction that would be expected if Byetta were conferring benefits, i.e. numerically greater reduction in body weight and fasting serum glucose.

Reviewer's Comments: I agree with Dr. Kim's assessment. The results of proportions of subjects meeting prespecified HbA1c goals considers subjects who did poorly (i.e., dropped out due to loss of glycemic control) as non-responders, in contrast to the Sponsor's primary analysis where subjects who did poorly were ignored. Given the loss of glycemic control dropouts were imbalanced favoring placebo, this estimate is a less conservative measure of efficacy. Thus, negative, or clinically insignificant findings are particularly persuasive.

Even if the treatment effect (i.e., point estimate) of this endpoint was the truth, the benefit of the drug would be quite small (NNT to meet glycemic goals would be 8 for reaching less than 6.5% HbA1c and 20 for reaching HbA1c < 7%). Using a similar line of thinking, the beneficial effects on fasting serum glucose (-7.75 mg/dL) and body weight (1 lbs.) would not be particularly meaningful.

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7. Integrated Review of Effectiveness

Since there was only one failed study submitted for review, subsections not applicable to this submission[14] have been deleted.

7.3. Integrated Assessment of Effectiveness

GWBQ included clinical trial elements that ensure an unbiased efficacy readout (i.e., intrinsic validity), including placebo concurrent control, double blinding, and an objective clinical endpoint. The inclusion and exclusion criteria were sufficiently broad and representative of the population who would use this product (i.e., external validity). The trial conduct and reporting seem adequate - protocol violations were mild and thoroughly reported, and no concerning data quality issues were identified. For these reasons, data derived from this study are considered trustworthy, unbiased, and applicable to the external patient population.

However, the study size and subject disposition were concerning. GWBQ was underpowered a priori (i.e., underpowered at the design stage) due to overly conservative assumptions on

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[14] 7.1 Assessment of efficacy across trials, 7.1.1 primary endpoints, 7.1.2 secondary endpoints, 7.1.3. subpopulations, 7.1.4 dose and dose-response, 7.1.5 Onset, duration, and durability of efficacy effects, 7.2 Additional Efficacy Considerations, 7.2.1 Considerations on Benefit in the post market Setting, 7.2.2 Other Relevant Benefits

endpoint variability (Refer to Section 6.1.1: Statistical Analysis Plan for details). Exacerbating the issue, the Sponsor encountered enrollment challenges, randomizing only 122 subjects – fewer than the original target of 195. Based on the actual study size and observed treatment variability, the power to identify even a modest effect (-0.455% difference in HbA1c at 28 weeks) was estimated to be less than 50%. This power calculation did not robustly consider the rate of dropouts, which was quite high (34%). For this reason, a negative read out should not be interpreted as evidence of absence of treatment effect.

Although the randomized subjects were balanced between treatment arms in demographics, the disposition of study subjects was different. Dropouts were more prevalent in placebo (41% dropped out of placebo, 28% dropped out of EBID). Furthermore, the difference in dropout rate was driven by more placebo subjects losing glycemic control (2.6% of subjects in EBID, versus 23.8% of subjects in placebo). Because GWBQ's primary endpoint was a de jure estimate of treatment effect (observations following rescue therapy or treatment discontinuation were excluded), excluding data following glycemic rescue would bias the treatment effect towards the null. This is because more placebo subjects, who did disproportionally poorly in GWBQ, were omitted from the analysis. Considering the sample size and informative censoring, it is not surprising that GWBQ failed to meet its primary endpoint.

To determine a treatment effect consistent with the intention to treat – treatment policy approach, the Sponsor and the Agency conducted post-hoc supplementary analyses using a "washout" approach. In this approach, subjects who dropped out of the study in both treatment arms were assumed to immediately follow the trajectory of those in placebo. However, the study was not designed to continue to observe subjects following intercurrent events, and a large majority (>90%) of the data following intercurrent events required imputation. The washout approach conducted by both the Sponsor did not meet traditional statistical acceptance criteria for the comparison between EBID and placebo (95% CI of placebo adjusted, 28-week change from baseline in HbA1c was -1.39 to +0.13).

One might argue that given the compelling efficacy data in adults, difficulty in studying pediatric patients, and unmet need in these populations, the Agency should be more flexible in interpreting the narrowly missed efficacy readout in the washout analysis. However, this analysis was post-hoc and used an exceptionally large degree of imputation (30-40% of subjects discontinued before the primary endpoint) in a context of informative censoring which introduces intolerable uncertainties implicit with the washout imputation. Furthermore, secondary "responder" analyses, which are less subject to missing data bias, failed to corroborate a clinically significant treatment effect.

8. Review of Safety

8.1. Safety Review Approach

The clinical reviewer inspected all detailed reports, regardless of timing of occurrence, for deaths, serious adverse events (AEs), and AEs leading to withdrawal. For all other adverse events, the Applicant's adverse event dataset (adae.xpt) was interrogated and results were compared to the Clinical Trial Report. Non-serious adverse event listings in the primary 28-week trial period only were considered because (a) the 52-week safety follow up did not include treatment, (b) very few randomized subjects participated (n=19, 16%). Both exenatide arms were pooled to enhance the ability to detect an association between assigned treatment and adverse event occurrence.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Discussed in following section.

8.2.2. Relevant characteristics of the safety population:

The safety population included all randomized subjects who received at least 1 dose of study medication (i.e., modified intention to treat). This is the same population as the full analysis set (FAS) and evaluable analysis set (EAS) which is used for the efficacy analysis (refer to

Table 4 for subject characteristics). The treatment exposure between study arms is displayed in tabular format (

Table 7), and graphical format (Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio.

Figure 3Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio.

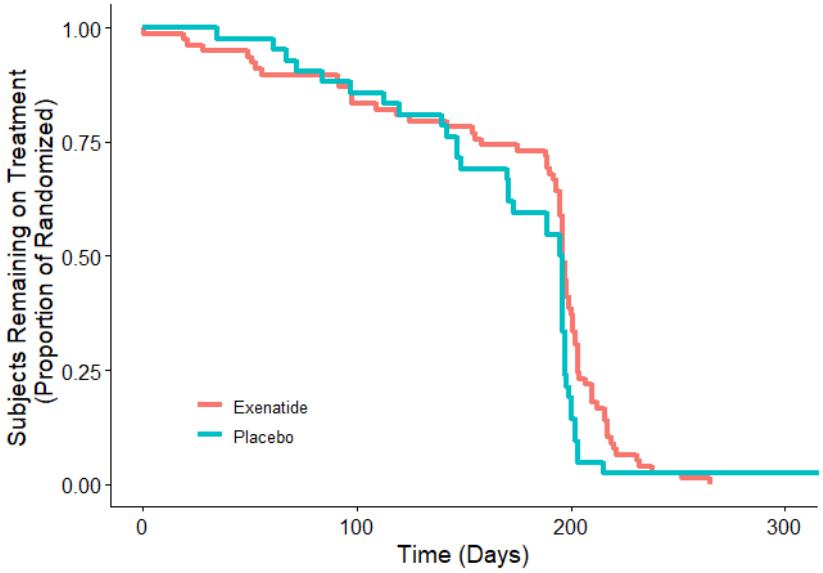
Figure 3).

Table 7: Extent of Exposure to Study Medication (Safety Analysis Set)

	Exenatide BID N=78	Placebo BID N=42
Average Days Treated	174	170
Total Exposure (Patient-Years)	(b) (4)	(b) (4)
Treated for at least		
1-35 days	95%	98%
36 to 70 days	90%	93%
71 to 140 days	79%	79%
28 Weeks or Greater	49%	33%

Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio.

Figure 3: Treatment Exposure to Study Treatment Versus Time (Safety Analysis Set)



Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio.

Most subjects were exposed to study treatment for at least 70 days (92%) and 140 days (79%). There are differences between arms in drop out patterns, with a maximum difference of around 20% around 180 days. EBID subjects tended to drop out earlier (e.g., within 100 days of randomization) but towards the end of the study, placebo subjects dropped more abruptly, overtaking EBID subjects. This is not surprising given more placebo subjects had failure to maintain glycemic control (22 vs 2%) which would manifest towards the end of the study, whereas more EBID subjects (4 vs 0) dropped out early due to adverse events.

Overall, less than 10% of the randomized population discontinued during the early phase of treatment where the majority of known adverse events would occur. Therefore, at least for adverse events which tend to occur acutely relative to treatment initiation, the total randomized subjects are a reasonable denominator. There were (b) (4) patient-years of exposure in the treatment arm, and (b) (4) patient-years of exposure in the placebo arm.

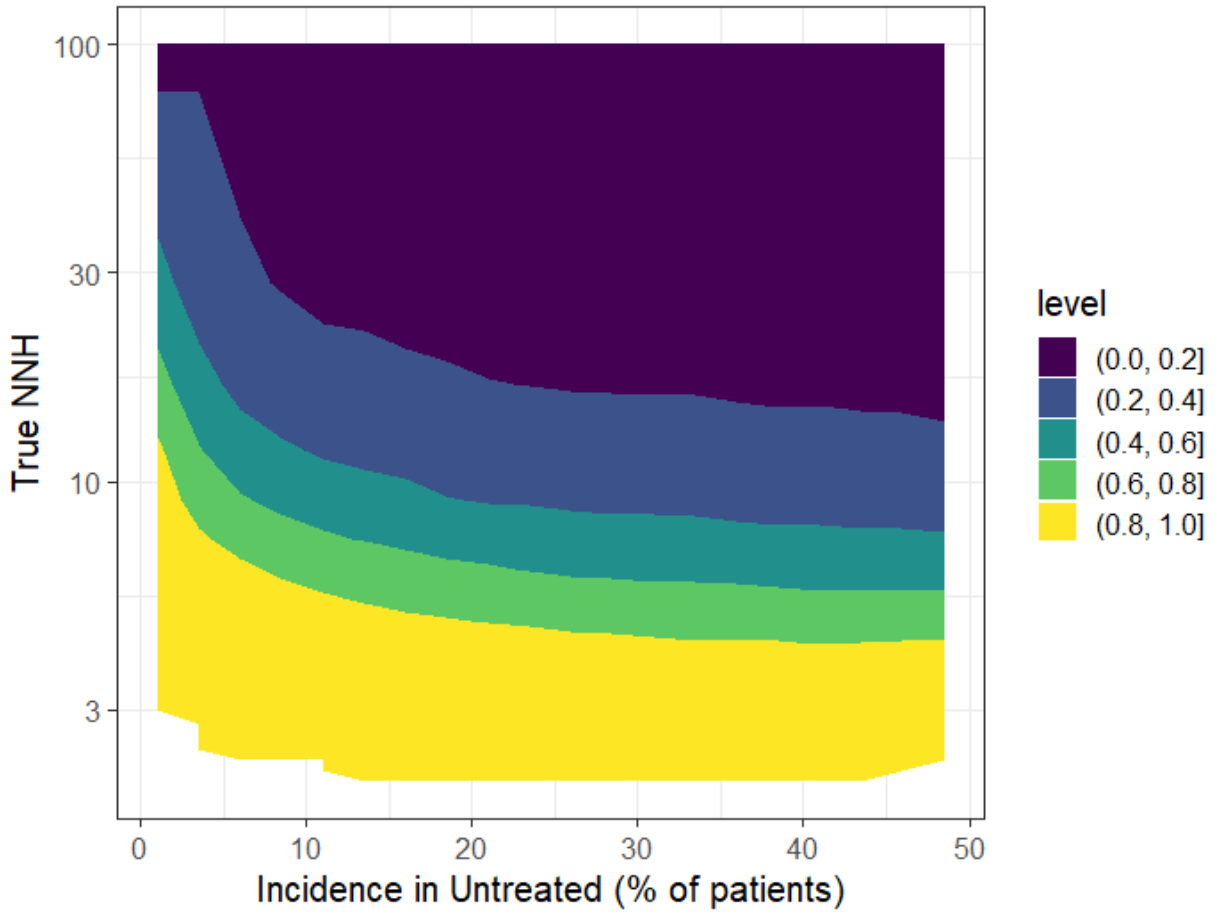
Reviewer's Comments: I agree with the Applicant's definition of the safety population and pooling approach.

There were (b) (4) patient-years of exposure in the treatment arm, and (b) (4) patient-years of exposure in the placebo arm. Less than 10% of the randomized population discontinued during the early phase of treatment. The completeness of the data during this period is reassuring that incidence rates, derived from total randomized subjects as a denominator, will be reliable and unbiased. Fortunately, the common adverse events observed in adult studies also occur during this period. In other words, I do not believe exposure-adjusting or more complicated methods of adverse event analysis are warranted.

8.2.3. Adequacy of the safety database:

Safety databases for other pT2D programs studies include sitagliptin (N=400, (b) (4) patient-years), BYDUREON (N=80, (b) (4) patient-years), and VICTOZA (N=134, (b) (4) patient-years). The clinical reviewers for those applications concluded the clinical trial databases were adequate. Byetta included 122 patients and (b) (4) PYE. For GWBQ, the power to detect a nominal (at the p=0.1 level) risk difference for various levels of background adverse event rates and risk differences is shown below (Figure 4).

Figure 4: Power To Detect Treatment Differences (As Risk Difference) In GWBQ, For Differing NNH and Placebo Rates



Source: Clinical Reviewer, using R 3.4, RStudio. For each data point (true background rate, true NNH pair) 10000 clinical trials identical to GWBQ were simulated assuming adverse event occurrences were binomially distributed. Power was calculated using parametric assumptions for simulated risk difference, and calculating the proportion of simulated trials meeting p-value threshold criteria (alpha = 0.1, N = 78 EBID, 40 placebo)

Reviewer Comment: Byetta's safety profile has been previously evaluated in adults. The size of the safety database (number of subjects) is broadly consistent with the other three pediatric clinical programs. Regardless, these studies are only powered to detect common AEs to any reasonable precision. I consider the safety database for Byetta adequate to corroborate known common adverse events seen in adults. This safety database would not support establishment of a causative relationship of rare or isolated adverse events (e.g., serious).

8.1. Adequacy of Applicant's Clinical Safety Assessments

8.1.1. Issues Regarding Data Integrity and Submission Quality

The dataset included preferred term (PT) and system organ class (SOC) but did not include higher level term groupings. Accordingly, the Applicant provided tabulations of PTs most frequently occurring by SOC. These tables were replicated without issue.

The lack of higher-level term coding inhibited my ability to group similar adverse events together, which opened a risk of underestimating, or missing all together, adverse event signals (e.g., safety signals can easily be obscured by "splitting" similar preferred terms, with identical meanings, into multiple categories). For this reason, the clinical reviewer manually inspected verbatim to PT coding, and manually grouped similar PTs in an exploratory fashion. The clinical reviewer determined the adverse event coding was reasonable.

8.1.2. Categorization of Adverse Events

Reported AE terms were coded according to MedDRA version 23. The definitions for AEs, TEAEs, SAEs were present in the protocol and consistent with best practices. *A priori* AEs of special interest were malignancies (n.b., thyroid and pancreas), and pancreatitis. AEs were solicited at week 2 (via telephone), week 4, and every 4 weeks thereafter via in-person visit.

Reviewer's Comments: The severity/intensity of the event was not defined in the protocol and study report. There were not explicitly stated procedures for the ascertainment of adverse events. Thus, severity and intensity information should be considered with caution.

8.1.3. Routine Clinical Tests

All planned laboratory assessments were to be taken in the fasting state. Pregnancy tests were done locally, and confirmed centrally, for subjects of childbearing potential.

Hematology, chemistry, fasting glucose, HbA1c, UA, calcitonin, and CEA were collected at baseline, early discontinuation visits, or at week 28. Investigators were not asked to record their impression of clinical significance of any laboratory values.

A 12-lead ECG was performed at screening and week 28. Vitals (body weight, blood pressure, and heart rate) were collected at every in-person visit (baseline, weeks 4, 8, 12, 16, 20, 24, and 28).

8.2. Safety Results

8.2.1. Deaths, SAEs, Dropouts due to AEs[15]

Overall occurrence of adverse events is summarized below (Table 8)

Table 8: Deaths, Serious Adverse Events, and Dropouts due to Adverse events in GWBQ (Full Safety Analysis Set)

Adverse Event Category	Total EBID (N = 78)	Placebo (N = 42)
Any TEAE	63 (80.8)	29 (69.0)
Deaths	0	0
SAEs	4	1
TEAEs leading to study dropout	3	0
Severe TEAEs	3	2

Source: Adapted from Table 29 in CSR

[15] Combined clinical review template sections 8.2.1 Deaths, 8.2.2 Serious Adverse Events, 8.2.3 Dropouts and/or Discontinuations Due to Adverse Effects, and 8.2.4 Significant Adverse Events for brevity

Five patients (4 EBID, 1 placebo) reported serious events. Summary narratives are as follows:

- 15/F/5 mcg EBID - experienced cellulitis 80 days after randomization, and staphylococcal abscess 195 days after randomization. These events were "moderate" in intensity and resolved by the end of the study. The location was not associated with EBID injection.

- 15/F/5 mcg EBID - experienced a mild, but serious event of intentional self-injury 36 days after randomization. The patient had an ongoing history of major depression at screening, and this event was coded as non-treatment emergent by the Sponsor.

- 16/F/5 mcg EBID - experienced acute gastroenteritis (day of onset: day 157), which was mild in intensity and resolved by the end of the study.

- 16/F/10 mcg EBID - became pregnant 168 days after randomization. The patient ended study treatment on day 199. The patient had gestational hypertension 385 days after treatment, which was considered serious and severe in intensity. The patient delivered 407 days after randomization (33 weeks gestation, via C-section weighing 6 lbs. 11 oz), and spent 4 days in the NICU with no fetal abnormalities noted.

- 15/F/placebo - experienced serious events of gastroenteritis (days 49 and 86), which were both considered severe in intensity and had resolved by the end of the study.

Reviewer Comments: All reported acute events were observed longer than 30 days after starting treatment and eventually resolved. In review of the patient narratives, the Sponsor's assessment that the serious events (except for gastritis) were unlikely to be related to study treatment because (a) they are not consistent with the adult safety profile (b) not consistent with the drug mechanism, (c) not temporally related to starting/titration events and (d) occur relatively frequently in this population, is reasonable.

Three patients in the EBID group and no patients in the placebo group experienced TEAEs leading to discontinuation from study treatment and had resolved by the end of the study. There were no serious events leading to discontinuation from the study.

- 17/F/5 mcg EBID-- experienced severe intensity vomiting on day 2.

- 10/M/10 mcg EBID – experienced moderate intensity vomiting on day 49.

- Patient (b) (6), a 14-year-old female in the 5 mcg EBID group, experienced "diabetes mellitus inadequate control." This patient had a baseline HbA1c of 10.1, which increased to 13.6 on day 86, and 13.7 on day 96 (day of adverse event coding).

Reviewer's Comment: This subject was recorded as a withdrawal due to AE, rather than a withdrawal due to loss of glycemic control. At screening, the patient met HbA1c threshold (< 10.5%) but had fasting SMBG in the 300-400 mg/dL range and was severely glycosuric (3+ glucose in the urine, hyperfiltrating eGFR > 150 ml/min). HbA1cs of 13.6 and 13.7 were recorded 10 days apart, however, the patient had neither recorded SMBG nor had HbA1c values 1-month apart to allow for treatment discontinuation criteria to be algorithmically met.

If a more scrutinous analysis was warranted (e.g., the primary endpoint involving time to glycemic failure), one might argue that this subject could be re-coded. However, this is outside the scope of the current review.

5 patients experienced a "significant" severe adverse event (3 EBID, 2 Placebo). However, these events are discussed elsewhere (led to study withdrawal, were coded as serious), or could not be attributed to therapy (infection of first digit, ear pain). Thus, they are not described in detail.

8.2.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, a higher proportion of patients in the Total EBID group had TEAEs compared with the placebo group (80.8% and 69.0%, respectively). Total number of events was similar between Total EBID group and placebo (3.4 events/patient and 3.2 events/patient, respectively). The proportion of patients with severe TEAEs was low and similar between the Total EBID and placebo groups (3.8% and 4.8%, respectively). At the PT level, none of the severe events were reported by more than 1 patient in either group. Common treatment emergent adverse events are reported in Table 9.

Table 9: Treatment Emergent Adverse Events Reported in Greater than 5% of Subjects or with a Risk Excess of 2.5% By SOC and PT (Safety Analysis Set – 28 Weeks Only)

Adverse event (Preferred term, SOC, or grouping)	Exenatide BID N=78	Placebo BID N=42	Risk Difference (95% CI)
Infections and infestations	37 (47.4%)	16 (38.1%)	9.3 [-12 - 30]
*ENT Infection**	28 (35.9%)	12 (28.6%)	7.3 [-13 - 27]
Influenza	3 (3.8%)	0 (0%)	3.8 [-2 - 9.6]
Skin/soft tissue infection@	8 (10.3%)	3 (7.1%)	3.2 [-8.8 - 15]
GI inflammation or infection#	4 (5.1%)	2 (4.8%)	0.3 [-9 - 9.6]
Musculoskeletal and connective tissue disorders	10 (12.8%)	3 (7.1%)	5.7 [-7 - 18]
Arthralgia	3 (3.8%)	0 (0%)	3.8 [-2 - 9.6]
Muscle spasms	2 (2.6%)	0 (0%)	2.6 [-2.2 - 7.4]
Gastrointestinal disorders	27 (34.6%)	15 (35.7%)	-1.1 [-22 - 19]
Nausea	15 (19.2%)	7 (16.7%)	2.5 [-14 - 19]

GI discomfort, pain$	8 (10.3%)	4 (9.5%)	0.8 [-12 - 14]
Diarrhea	5 (6.4%)	5 (11.9%)	-5.5 [-18 - 6.8]
Vomiting	10 (12.8%)	3 (7.1%)	5.7 [-7 - 18]
Nervous system disorders	21 (26.9%)	12 (28.6%)	-1.7 [-21 - 17]
Dizziness	4 (5.1%)	2 (4.8%)	0.3 [-9 - 9.6]
Headache	18 (23.1%)	11 (26.2%)	-3.1 [-22 - 15]
Reproductive system and breast disorders	6 (7.7%)	4 (9.5%)	-1.8 [-14 - 10]
Dysmenorrhea	5 (6.4%)	4 (9.5%)	-3.1 [-15 - 8.5]
General disorders/administration site conditions	10 (12.8%)	7 (16.7%)	-3.9 [-19 - 11]
Pyrexia	3 (3.8%)	3 (7.1%)	-3.3 [-13 - 6.4]
Ear and labyrinth disorders	4 (5.1%)	3 (7.1%)	-2 [-12 - 8.2]
Ear pain	4 (5.1%)	3 (7.1%)	-2 [-12 - 8.2]

Source: Clinical Reviewer, generated from ADAE.XPT using R 3.4, RStudio.
* includes preferred terms 'Nasopharyngitis', 'Pharyngitis', 'Ear infection', 'Pharyngitis streptococcal', 'Sinusitis', 'Viral rhinitis', 'Pharyngotonsillitis', 'Otitis media', 'Upper respiratory tract infection'
@ includes preferred terms "Furuncle", "Staphylococcal abscess", 'Abscess limb', 'Staphylococcal abscess', 'Localized infection', 'Paronychia', 'Fungal skin infection', 'Abscess', 'Vulvovaginitis', 'Cellulitis', 'Subcutaneous abscess', 'Fungal infection', 'Soft tissue infection'
# includes preferred terms 'Colitis', 'Food poisoning', 'Gastroenteritis', 'Gastroenteritis viral'
$ includes preferred terms 'Abdominal discomfort', 'Gastrointestinal tract irritation', 'Abdominal pain upper', 'Dyspepsia', 'Abdominal pain', 'Gastroesophageal reflux disease'

Reviewer's Comments: No PT or groupings reached statistical significance, which is related to study power.

The treatment difference between adverse events related to the infections and infestations SOC is unusual and unexpected. This difference is primarily driven by ENT infections (such as pharyngitis, sinusitis, rhinitis, or upper respiratory tract infection). A similar treatment difference was observed in the BYDUREON pediatric study (BCB114). Nonetheless, it is unknown if this is a true treatment difference. It is not supported by the safety profile observed in adults.

Based on point estimates, the adverse event profile is broadly like labeled risks in adults.

8.2.6. Laboratory Findings

Hematology and chemistry investigations include hematocrit, red blood cell count, hemoglobin, white blood cell count, platelet count, mean corpuscle hemoglobin, mean corpuscle hemoglobin content, mean cell volume, red blood cell distribution width, AST, ALT, and creatinine. Importantly, bilirubin was not routinely collected per protocol to identify potential cases of Hy's law.

Urinalysis investigations include qualitative investigations on protein, urobilirubin, ketones, and red blood cells. Specific gravity and pH were quantified.

The Sponsor examined laboratory data in three ways:

(1) descriptive statistics of changes in values over time
(2) shift tables of counts of changes in individual patient categories over time,
(3) as needed - and individual clinically important abnormalities.

The clinical reviewer reproduced the Sponsor's aggregate analyses without issue. In addition, the clinical reviewer inspected the 28-week percent change from baseline (median, IQR, and p value for between-group differences[16]), and inspected the proportion of subjects shifting within, above, or below the reference range at 28 weeks.[17] If a 28-week laboratory finding was not collected, the most recent on treatment value was used instead (i.e., using last observation carried forward). Uniquely for GFR, the Sponsor provided an MMRM analysis using a "hypothetical" estimate (i.e., subjects were counted as missing after treatment discontinuation or rescue), therefore, the clinical reviewer generated a table according to the treatment-policy principle using LOCF (Table 10).

Table 10: Estimated GFR (via MDRD) At Baseline and Week 28 By Treatment Group (Safety Analysis Set)

	EBID n=68	Placebo n=38	p-value
Baseline eGFR (ml/min)	152 [133, 172]	152 [135, 167]	0.984
Week 28 eGFR (ml/min)	143 [131, 158]	147 [134, 159]	0.614
Change from Baseline (ml/min)	-3.00 [-16.00, 7.00]	-5.50 [-21.25, 5.00]	0.846
% Change from Baseline	-2.46 [-10.84, 4.17]	-3.57 [-11.55, 3.72]	0.961

Source: Clinical Reviewer, generated from ADLB.XPT using R 3.4, RStudio.

The following laboratory observations were notable:

- One EBID patient (13/M/5 mcg BID) had a > 60% decrease from baseline in leukocyte count, from $13.2x10^9$ to $3.6x10^9$. No concurrent AEs were reported.
- One EBID patient (11/M/10 mcg BID) – AST increased from 2.2 X ULN at baseline to 152 IU/L (3.4X ULN) at Week 28. No concurrent AEs were reported.

[16] Man-Whitney U non-parametric test
[17] Chi-squared test

- There was a trend (nominal p-value 0.032 – 0.163) towards decreased hematocrit, hemoglobin, and red blood cells in the 28-week change from baseline not favoring EBID, and the absolute difference was quite small (treatment difference in change from baseline was 1.8-2.2%). The change from baseline in RDW was 1.45% higher in the EBID group (p=0.169).

Reviewer's Comments: Neither I nor the Sponsor identified safety signals of concern.

(1) Leukopenia - I am not concerned about the occurrence of leukopenia given the isolation of the event, lack of associated clinical sequelae, and lack of effect identified for exenatide or the GLP1RA class in much more robust adult datasets.

(2) Anemia - The RDW, HCT, RBC, and HGB findings are small in magnitude, and likely a chance finding.

(3) Transaminitis/Potential Hy's law cases: Only one EBID treated subjects experienced treatment emergent AST and ALT elevations >3x ULN. Transaminases were elevated at baseline, and week 28 elevations were mild (<5 x ULN). Bilirubin was not reported. Aggregate values did not suggest a concerning trend.

8.2.7. Vital Signs

GLP-1 receptor agonists, including Byetta, have shown to lower blood pressure while increasing heart rate. This effect is labeled in BYDUREON and VICTOZA for adults. The consequence to the patient (e.g., cardiovascular outcomes) is thought to be at least neutral. There were no notable differences between the EBID and placebo groups in change over time in blood pressure or heart rate.

8.2.8. Electrocardiograms (ECGs)

ECGs were performed at baseline and week 28. ECG findings were categorized by the investigator as either: normal; abnormal, not clinically significant; or as abnormal, clinically significant. Overall, 89 subjects had normal ECG recordings at baseline. 6 of these subjects shifted to an abnormality during treatment, and only one was deemed clinically significant. 15 subjects had abnormal ECGs at baseline, 7 of which reverted to normal during treatment.

Reviewer's Comments: There was insufficient data to draw any meaningful conclusions.

8.2.1. QT

Thorough QT studies were conducted at the time of the original NDA review. There were no QT studies performed as part of the evaluation in pediatric T2DM population.

8.2.2. Immunogenicity

Pertinent information regarding the immunogenicity of Byetta (in adults) is described in labeling as follows:

(a) Mean antibody titer peaked at week 6 and reduced by 55% by week 30
(b) 38% of patients in one study (n=360) had low titer antibodies (<1/625) at 30 weeks
(c) 28% of patients on another study (n=40) had low titer antibodies at 24 weeks
(d) 1-6% of patients had higher tier antibodies at 24-30 weeks, of which, about half had an attenuated glycemic response to Byetta.

Pertinent information regarding the immunogenicity of BYDUREON (in adults) is as follows:

(a) In the Bydureon pediatric T2D study (referred to as BCB114), reviewed by Dr. Mahtab Niyyati (Clinical review for NDA022200/S031) 41% (n=20) and 55% (n=27) of subjects had high and low titer antibodies, respectively.
(b) In the adult BYDUREON T2DM program (in 5 comparator-controlled studies; n=918), 405 (45%) had low titer ADA and 107 (12%) EQW-treated patients had high titer antibodies at study endpoint (24-30 weeks).
(c) Dr. Niyyati observed that the rates of immunogenicity appear higher (while acknowledging the limitations of cross-study comparisons) in BCB114.
(d) Dr. Niyyati conducted exploratory safety analyses and concluded that "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."

In GWBQ, 48% (n=30) of subjects had low titer antibodies and 4.8% (n=3) of subjects had high titer antibodies. 15% (n=12) of subjects had a high titer at any point in the study. The Sponsor did not conduct safety analyses by antibody status. The clinical reviewer conducted a post-hoc analysis by SOC and did notice an imbalance in SOCs related to flu-like symptoms (Nervous system disorders, General disorders, musculoskeletal disorders) that had a 13-19% risk difference (First panel, Table 11). The clinical reviewer then conducted a PT-level analysis focused on PTs that could be related to immune response and the SOC signals above (Second panel, Table 11).

Table 11: Selected Treatment Emergent Adverse Events Reported in EBID treated Subjects (Safety Analysis Set – 28 Weeks Only)

By SOC

	No immunogenicity (n=31)	Low Titer (n=39)	High Titer (n=12)
Nervous system disorders	29%	18%	42%
General disorders and administration site conditions	6%	13%	25%

Musculoskeletal and connective tissue disorders	10%	10%	25%

By Preferred Term or Grouping

	No immunogenicity (n=31)	Low Titer (n=39)	High Titer (n=12)
Constitutional Flu-like Sx#	32%	26%	50%
Ear infection	0%	2.6%	17%
Dizziness	3.2%	2.6%	17%
Upper respiratory tract infection	6.4%	10%	17%
Dysmenorrhea	6.4%	2.6%	17%
Runny, Stuffy Nose + Sore Throat	29%	33%	17%

Source: Clinical Reviewer, generated from ADSL.XPT using R 3.4, RStudio.
#Includes PTs of "Myalgia ", "Headache ", "Pyrexia ", "Pain ", "Arthralgia ", "Back pain ", "Musculoskeletal pain "

8.3. Analysis of Submission-Specific Safety Issues

8.3.1. Hypoglycemia

Hypoglycemia with concomitant insulin or insulin secretagogues (e.g., sulfonylureas) are a labeled risk for adults for GLP1RAs. The 30-week excess risk[18] ranges from a NNH of approximately 25 (monotherapy) to 3 (adjunct to metformin and sulfonylurea), although severe events were rare. Subjects were provided diaries and instructed to record the glucose meter reading, associated symptoms, and treatment in the study diary. The Sponsor defined hypoglycemia as follows:

- confirmed minor hypoglycemic episodes - having a sign or symptom associated with hypoglycemia + a concurrent fingerstick blood glucose < 54 mg/dL

- confirmed major hypoglycemic episodes – symptoms consistent with hypoglycemia resulting in loss of consciousness or seizure OR documented hypoglycemia requiring third party assistance

Signs and symptoms of hypoglycemia not confirmed with SMBG were recorded as "unconfirmed." These definitions are broadly consistent with the ADA definitions of level 2, and level 3 hypoglycemia. Results from GWBQ are presented in Table 12.

Table 12: Incidence of Minor Hypoglycemia (Safety analysis set)

	Total EBID (N = 78)	Placebo (N = 42)

[18] Derived from table 1 in Byetta drug labeling (SUPPL-44, 6/17/2021)

	Number (%) of Patients [Number of Events]	Event Rate (per 100 pt years)	Number (%) of Patients [Number of Events]	Event Rate (per 100 pt years)
Overall	8 (10.3) [22]	59.12	3 (7.1) [4]	20.47
Confirmed	4 (5.1) [4]	10.75	1 (2.4) [2]	10.23
Unconfirmed	5 (6.4) [19]	48.37	2 (4.8) [2]	10.23

Source: Adapted from Table 34 in CSR

No serious or severe hypoglycemia episodes occurred in the study. Overall, more patients reported hypoglycemic episodes in the EBID arm (10.3% versus 7.1%). More overall events occurred in the EBID arm (59 events per patient-year versus 20 events per patient-year), however, this was driven by a single subject treated with 10 mcg BID who had 15 events that occurred over a 7-day period. Of the 11 patients reporting hypoglycemia episodes, 4 occurred in those using sulfonylureas at baseline (3/8 in EBID arm, 1/7 in placebo).

8.3.2. Thyroid cancers

GLP1RAs have been associated with the development of thyroid C-cell tumors after lifetime exposure in rodents. This safety concern resulted in a black box warning for long acting GLP1 analogues, and a PMR requirement for an active surveillance program[19, 20]. Calcitonin concentrations <10 pg/mL are considered to be evidence of absence of MTC. Conversely, serum concentrations >100 pg/mL are highly predictive of medullary thyroid cancer[21]. Carcinoembryonic antigen (CEA) is also a helpful diagnostic agent for some cancers, including MTC.

Calcitonin and CEA measurements were added following implementation of Protocol Amendment b (February 2011) and was therefore not determined for all patients. There were no notable changes in mean values in calcitonin and CEA from baseline to week 28 for serum calcitonin within the treatment groups. In the Safety Follow-up Analysis Set (comprising 12 total EBID and 7 placebo patients), there were no notable changes in mean values from baseline at the start of the treatment period to the end of the Safety Follow-up Period for serum calcitonin and CEA within the treatment groups. No patient had a calcitonin level of > 100 ng/mL

Table 13: Observed and Change from Baseline to Week 28 in Serum Calcitonin (pmol/L)

	EBID		Placebo	
	N	Mean (SD)	N	Mean (SD)
Baseline	38	0.65	21	0.61

[19] https://pubmed.ncbi.nlm.nih.gov/20164475/
[20] https://clinicaltrials.gov/ct2/show/NCT01511393
[21] https://pubmed.ncbi.nlm.nih.gov/17119000/

(c) There are no labeled drug-demographic interactions for any exenatide product (Byetta or BYDUREON), and
(d) drug-demographic interactions for adverse events were deemed small, not clinically relevant, or both, in the original NDA medical reviews[22] [23].

8.5. Specific Safety Studies/Clinical Trials

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[22] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000MedR.pdf
[23] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021773_Byetta_medr.PDF

N/A

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

N/A

8.6.2. Human Reproduction and Pregnancy

N/A

8.6.3. Pediatrics and Assessment of Effects on Growth

Regulatory issues related to this PMR are discussed in section 12. Safety issues uniquely related to pediatric patients are discussed in section 8.3.

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

N/A

8.7. Safety in the Post market Setting

8.7.1. Safety Concerns Identified Through Post Market Experience

N/A

8.7.2. Expectations on Safety in the post market Setting

This section is not relevant since a pediatric indication is not being granted.

8.7.3. Additional Safety Issues from Other Disciplines

None.

8.8. Integrated Assessment of Safety

The mean duration of exposure was similar between the Total EBID and placebo groups with more than 90% of subjects exposed for at least 70 days, and a total of 58 patient-years of exposure. GWBQ, based on number of randomized subjects, could not be expected to identify unique risks to pediatric patients beyond those commonly occurring.

Objective laboratory, urinalysis, and vitals data did not show any clinically meaningful trends in laboratory parameters over time and between treatment groups. The incidence of TEAEs overall was higher in the Total EBID group compared with the placebo group (80.8% and 69.0%, respectively). A higher proportion of patients in the Total EBID group had TEAEs related to ear nose and throat infections (35.9% vs 28.6%) and vomiting (12.8% versus 7.1%).

Vomiting is a known risk, occurring early in treatment, and is a reversable nuisance adverse reaction rather than a dangerous one. The unfavorable treatment difference in ENT infections was small, of unknown statistical significance (i.e., could be due to chance) and is likewise a nonsevere, self-limited nuisance event.

Serious or severe adverse events were balanced; however, it was noted that two patients receiving EBID were hospitalized for gastritis which could be attributed to treatment. While concerning, the clinical diagnosis is based on histopathology, and often used broadly to describe GI-related symptoms. Gastrointestinal adverse events are adequately described in current labeling. For these reasons, additional labeling to describe these events is not warranted.

A total of 61.5% of patients who received EBID had treatment-emergent ADAs, which is similar in magnitude to other exenatide products in adults. No severe hypoglycemic events occurred in the study. The proportion of patients with confirmed or unconfirmed minor (similar to level 2 hypoglycemia per ADA) hypoglycemic events was slightly higher in the Total EBID group (10.3%) compared with the placebo group (7.1%). Development and growth assessed by height and Tanner staging resulted in comparable results for patients treated with exenatide and placebo.

Overall, exenatide was well-tolerated. The clinical reviewer did not identify new safety concerns. If GWBQ demonstrated substantial evidence of efficacy, the safety findings observed in this study would not raise considerations that would bear significantly on the benefit-risk assessment of the drug.

9. Advisory Committee Meeting and Other External Consultations

N/A

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The labeling has been updated as follows: section 8.4: Pediatric Use

> The safety and effectiveness of Byetta have not been established in pediatric patients. Effectiveness of Byetta was not demonstrated in a randomized, double-blind, placebo-controlled study conducted in 120 pediatric patients (78 received Byetta and 42 received placebo) aged 10 to 17 years with type 2 diabetes mellitus.

OPDP was consulted on January 8, 2021. Dr. Samantha Bryant from OPDP reviewed the revised (including the substantiative edits proposed above) proposed product labeling, carton, and container labeling. Dr. Bryant did not have any further comments.

DDLO requested DMEPA review on August 11, 2021, to determine if labeling components are acceptable from a medication error perspective. Dr. Ariane Conrad from DMEPA performed a risk assessment of the revised (including the substantiative edits proposed above) labels and labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement. The DMEPA review determined that the revisions to the 5 mcg and 10 mcg cartons are acceptable from a medication error perspective. DMEPA did identify the following areas of improvement on the carton and container labeling:

(1) Consider revising the statement "5 mcg (or 10 mcg)" in the color bands to read "5 mcg (or 10 mcg) per dose" to increase clarity.
(2) On the PDP, we recommend that you consider revising the statement "each prefilled pen will deliver 60 subcutaneous doses, 5 mcg per dose (or 10 mcg per dose)" to read "each prefilled pen will deliver 60 doses of 5 mcg (or 10 mcg) each" to increase clarity.
(3) For the back panel, we recommend that you consider removing the statement "each prefilled pen will deliver 60 subcutaneous doses, 10 mcg per dose" because this information is considered duplicative considering the other dosing statements on the PDP.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A

12. Post marketing Requirements and Commitments

This application is in response to a PREA PMR 1559-1. GWBQ did not support efficacy of Byetta in pediatric patients 10 to 17 years of age with T2DM. Since the approval of Victoza and Bydureon for pediatric patients, Byetta is no longer expected to provide a meaningful benefit over available therapy. For these reasons, the Division met with PeRC and recommended the PMR be released. The PeRC agreed (PeRC Meeting Minutes, September 9, 2021).

13. Appendices

13.1. References

Cited in line with text as footnotes

13.2. Financial Disclosure

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: >200		
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): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/

JUSTIN A PENZENSTADLER
11/02/2021 11:10:50 AM

LISA B YANOFF
11/02/2021 11:17:00 AM
I contributed to the editing of this document and agree with its conclusions.