U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 021773
Supplement #:	S045
Drug Name:	Byetta (exenatide 5 µg, 10 µg twice daily, EBID)
Indication(s):	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	AstraZeneca
Date(s):	Stamp Date: January 6, 2021
	PDUFA goal date: November 4, 2021
Review Priority:	Standard
Biometrics Division:	DB II
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Keywords:

PMR, Pediatric study, GLP-1, Washout analysis

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1 EXECUTIVE SUMMARY

The applicant, Astra Zeneca, submitted sNDA with a final study report for a study H8O-MC-GWBQ (GWBQ) for BYETTA (exenatide 5 μg, 10 μg twice daily, EBID). GWBQ was conducted for PREA-PMR 1559-1: *Deferred pediatric study under PREA for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10 to 16 years (inclusive)* issued in 2006. The applicant proposed an update to the Pediatric Use in Section 8.4 of the product label to add the study results without requesting an indication change.

GWBQ was a multicenter, phase 3, randomized, double-blind, placebo-controlled study conducted in adolescents (10 to 17 years of age) with T2DM. Due to difficulties of enrollment of qualified subjects, the applicant stopped study GWBQ after agreement with Agency in 2019. Randomized 122 subjects, out of originally planned 195 subjects, were analyzed for the final study report. Due to smaller sample size than planned, two dose groups of EBID (Total EBID) were pooled for a comparison to the placebo group to increase power. The primary endpoint was changes in HbA1c (%) from baseline to Week 28.

Statistical issues and reviewer's approaches to address them are following:

- Analysis set used in the primary analysis (see Section 3.2.2.1)
    - Applicant: Evaluable Analysis Set (EAS) of all randomized subjects who received at least 1 dose of randomized study drug and had a baseline and at least 1 post-baseline HbA1c assessment after excluding data from subjects who used rescue therapy and/or discontinued study.
    - Agency: Full Analysis Set (FAS) of all randomized subjects who received at least 1 dose of randomized study drug including data from post-rescued and/or treatment discontinued subjects
- Statistical method to deal with missing data (see Section 3.2.2.2)
    - Applicant: Mixed-effect model with repeated measures (MMRM) for primary analysis, which is inadequate to deal with high missing data (28%).
    - Agency: Washout analysis method to handle missing data in this review

Statistical findings in GWBQ were not significant for testing superiority of EBID compared to placebo. HbA1c increased at Week 28 in both EBID and placebo arms. Treatment difference estimate indicates a reduction of HbA1c changes with EBID compared to placebo, but it is not statistically significant (Table 1). Findings from the sensitivity, subgroup, and secondary endpoint analyses were consistent with that from the primary analysis (see Section 3.2).

Table 1. Primary Analysis Results for Changes in HbA1c (%) at Week 28 (FAS population)

	Total EBID N=78	***Placebo N=42***	***P-value***
LS mean[1] change at Week 28 (SE)	0.12 (0.25)	0.75 (0.30)	
LS mean[1] difference from placebo (95% CI)	-0.63 (-1.39, 0.13)		0.10

Abbreviations: FAS= full analysis set; CI=confidence interval; LS=least square; SD=standard deviation; SE=standard error [1]LS means are from ANCOVA model with treatment group, baseline values and stratification factor as covariates after multiple imputation using washout for missing data *Source: Reviewer's analysis using adsl.xpt and adlb.xpt*

In conclusion, effectiveness of EBID compared to placebo was not demonstrated in GWBQ. This reviewer agrees with adding descriptive information only about study results in Pediatric Use subsection of labeling.

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2 INTRODUCTION

2.1 Overview

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist. BYETTA (exenatide 5 μg, 10 μg twice daily) was approved in the United States (US) on 28 April 2005 and in Europe on 20 November 2006 to improve glycemic control in adults with T2DM. BYETTA is administered twice daily (here after: EBID) as a SC injection of 5μg or 10μg. Subsequently, BYDUREON (exenatide once-weekly aqueous suspension) was approved in 2011 and BYDUREON BCise (exenatide once-weekly non-aqueous suspension, extended release) was approved in 2017 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

GWBQ was conducted for PREA-PMR 1559-1: *Deferred pediatric study under PREA for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10 to 16 years (inclusive)* as per Written Request (WR) issued in 2006. The WR was amended several times- September 2006, April 2007, March 2008, October 2010, September 2014, and August 2018. Following the 2018 WR amendment, the applicant wanted to stop the study because recruiting subjects were difficult after other once weekly products were approved. In 2019, Agency advised the applicant may stop the study GWBQ and the applicant committed to analyzing all available data from the 122 randomized patients in the study. The Last Patient, Last Visit occurred on 1 April 2020. Due to smaller sample size than planned, two dose groups of exenatide were pooled (Total EBID) for a comparison to the placebo group to increase power in the amended SAP (dated April 22, 2020) prior to database lock (May 15, 2020).

The applicant submitted the final study report for GWBQ (Table 2) to satisfy PREA requirements with an appropriate update to the pediatric use section of the USPI section 8.4 only (USE IN SPECIFIC POPULATION/Pediatric Use).

Table 2. Study H8O-MC-GWBQ (GWBQ)

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis
H8O-MC-GWBQ Phase III 10 to 17 years of age	Randomized, double-blind, placebo-controlled, multicenter, parallel, 3-arm study (28 weeks) Stratficiation factor: naive, metformin, an SU or SU with metforimn	Total EBID: 80 5 μg: 42* 10 μg: 38 Placebo: 42 Background: naive or metformin with/without an SU **Note: 2 subjects did not receive study drug*	Primary: HbA1c changes at Week 28 *MMRM-Evaluable Analysis Set* Secondary: HbA1c <7%, ≤6.5%, <6.5% at Week 28 *CMH test* Body weight at Week 28 *MMRM*

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Abbreviations EBID exenatide twice daily; HbA1c glycosylated hemoglobin; MMRM mixed-effect model with repeated measures; CMH cochran mantel-haenszel; SU sulfonylurea; Evaluable Analysis Set all randomized subjects who received at least one dose of randomized study medication and had a baseline and at least 1 post-baseline HbA1c assessment.
Source Statistical reviewer

2.2 Data Sources

The applicant submitted materials for this review including clinical study report and datasets (STDM and ADAM) electronically in the electronic common technical document (eCTD) form and archived under the network path location.

\\CDSESUB1\evsprod\NDA021773\0443\m5\53-clin-stud-rep : Clinical study report
\\CDSESUB1\evsprod\NDA021773\0448\m5\datasets\d5550c00002 : GWBQ data sets
\\CDSESUB1\evsprod\NDA021773\0451: Results and programs for post-hoc sensitivity analyses using washout methods and subgroup analyses

This reviewer ran independent coding for the descriptive statistics, plots, and sensitivity analyses using R language and modified the applicant's SAS program.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

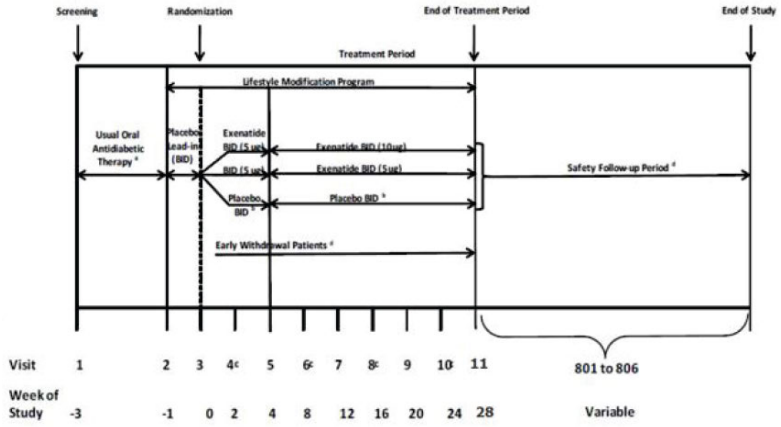
The applicant submitted data of adequate quality and made it possible for the statistical reviewer to reproduce their results of pre-specified primary analysis as well as sensitivity analyses. For data integrity, this reviewer checked derived variables from STDM to ADAM datasets and basic statistics including patient dispositions using descriptive analysis. There was no issue for data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Design features of GWBQ are in Table 2. Study design schematics are shown in Figures 1. For efficacy evaluation, the 28-week treatment period was considered as a study period.

Figure 1. Study Design for GWBQ



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Source Clinical Study Report Figure 1 (page 5)

Primary endpoint:

- Change in HbA1c (%) from baseline to Week 28

Secondary endpoints:

- Proportions of subjects who achieved HbA1c < 7%, ≤6.5%, <6.5% at Week 28
- Changes from baseline in body weight (kg) at Week 28

No adjustments for multiplicity were made for primary and secondary endpoints.

Sample size

The applicant's original sample size, 195 subjects (65 subjects in each arm), was powered at > 95% power to demonstrate that EBID each dose is superior to placebo assuming treatment difference -0.7 and -0.5 for 10 μg and 5 μg respectively with a common standard deviation (SD) of 1% at 5% significance level.

Because the study stopped, 122 subjects instead of planned 195 subjects were randomized and used for the analysis. Two dose groups of EBID (Total EBID) were pooled for a comparison to the placebo group to increase power. In the amended SAP, the applicant stated that study power is 87% with the assumed combined effect of the total EBID doses compared to placebo as -0.6 with SD of 1% at the 5% significance level and as low as 64% study power with the adjusted combined effect of -0.45 and SD of 1% because of possible dropouts.

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%).

3.2.2 Statistical Methodologies

3.2.2.1 Statistical Analysis Set

The applicant used Intent-to-Treat (ITT) population of all randomized subjects for summarizing disposition of subjects and baseline characteristics.

The applicant assessed the primary efficacy endpoint (change in HbA1c from baseline to Week 28) using EAS of all randomized subjects who received at least 1 dose of randomized study drug and had a baseline and at least 1 post-baseline HbA1c assessment. Also, the applicant excluded data from subjects who used rescue therapy and/or discontinued study in the primary analysis. However, this analysis set is not appropriate for evaluating effectiveness of drug in practice for T2DM population. To evaluate the most likely true treatment efficacy of EBID in a regulatory setting, intent-to-treat principle with "treatment policy" estimand is appropriate for estimating

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potential outcomes that would have been observed under different exposures regardless of use of rescue therapy or discontinuation of study drug.

In this review, Agency used Full Analysis Set of all randomized subjects who received at least 1 dose of study treatment including data from post-rescued and/or treatment discontinued subjects for primary analysis under intent-to-treat principle with "treatment policy" estimand. As per Agency's request, the applicant also performed post-hoc sensitivity analyses using this preferred analysis set.

3.2.2.2 Statistical analysis method to deal with missing data

The applicant analyzed the difference in primary efficacy endpoint (change in HbA1c from baseline to Week 28) between treatment groups (Total EBID versus placebo) using MMRM with baseline HbA1c, background diabetes therapy strata (drug naive, metformin only, SU with or without metformin (combined stratum due to small sample size in SU only)), week of visit, baseline HbA1c by visit interaction and treatment by visit interaction as the fixed effects. The least squares (LS) mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the total EBID and placebo groups at Week 28 were provided as results. MMRM assumes data are missing at random (MAR) and the conclusions from the MMRM analysis may be subject to bias due to violation of the MAR assumption under intent-to-treat principle with "treatment policy" estimand, especially with high percentage of missing data. The applicant conducted several sensitivity analyses including MMRM after including subjects with rescue therapy and treatment discontinuation and MMRM based on pattern mixture model imputation (similar to "washout analysis").

In this review, Agency performed "washout analysis" method to handle missing data. The preferred method for addressing missing data under "treatment policy" estimand would be to model patients with missing data after retrieved dropouts by assumption of missing data would have been like retrieved dropouts if they were assessed. However, in GWBQ, the applicant did not follow up enough patients who discontinued treatments to measure Week 28 endpoints. Because there were too few retrieved dropouts and GWBQ was a placebo-controlled trial, this reviewer performed "washout" analysis instead of retrieved drop-out analysis.

The missing HbA1c data at Week 28 were imputed by washout the effect of treatment using placebo completers. Measurements for subjects on the placebo arm without observed Week 28 data were imputed using a monotone regression model based on observed HbA1c data of completers on the placebo arm. For patients on Total EBID arm who had missing Week 28 data, the imputation model with only baseline HbA1c and background therapy stratification factor was used.

One hundred data sets were generated and an ANCOVA with the baseline HbA1c and stratification factor was run on each data set and the results were combined to yield a multiple imputation point estimate and standard error.

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Upon request by the agency, the applicant also performed post-hoc sensitivity analysis in light of "washout" analysis. The applicant imputed changes in HbA1c at Week 28 from baseline instead of values at Week 28 and used mnar option for placebo group in SAS programming, while this reviewer imputed HbA1c values at Week 28 instead of changes and used monotone regression in the placebo group in SAS programming with obsmargins option.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 122 subjects were randomized but 2 subjects were not treated with study drug, so a total of 120 subjects (40 subjects in 5 µg EBID, 38 subjects in 10 µg EBID and 42 subjects in placebo) were used as FAS for the efficacy analyses (Table 3). All subjects who were randomized and treated with at least one dose of study drug had baseline HbA1c and at least one post-baseline HbA1c value. Thus, FAS and EAS were same number of subjects. Total of 81 subjects (66%) completed the 28-week treatment period.

Of those within the randomized set, 39 (33%) subjects prematurely discontinued study drug prior to Week 28. In the placebo group, more subjects discontinued treatment due to loss of glycemic control (24% with placebo vs 3% with Total EBID) and withdrawals from the study (10% with placebo vs 5% with Total EBID). The sponsor did not follow up enough patients who have discontinued study drug but assessed HbA1c endpoint (i.e. retrieved dropouts) during a visit window (from 169 days from treatment starting date to follow up date) of Week 28 visit. Retrieved dropouts were only 5 subjects (4%) in total. Thus, HbA1c measurements at Week 28 were missing for 20 (26%) subjects in Total EBID arm and 14 (33%) subjects in the placebo arm.

After the 28 -week treatment periods, total of 19 subjects (12 subjects (15%) in Total EBID and 7 subjects (17%) in placebo) entered safety follow-up period without treatment. Among those, 16 subjects completed the study.

Table 3. Subjects Disposition in GWBQ and Reasons for Treatment Discontinuation-ITT population

	Total EBID N=80 n (%)	***Placebo N=42 n (%)***	***Total N=122 n (%)***
Randomized	80 (100)	42 (100)	122(100)
Randomized & Treated study drug (FAS[1])	**78 (97.5)**	**42 (100)**	**120 (98.4)**
Completed the study (including the 28-week treatment period and the safety follow-up (SFU) period)	9 (12)	7 (17)	16 (13)
Subjects who did not enter the SFU period	66 (85)	35 (83)	101 (84)
Subjects who entered the SFU period	12 (15)	7 (17)	19 (16)
Subjects who discontinued the SFU period	3 (4)	0	3 (2)
Completed the 28-week treatment	56 (72)	25 (60)	81 (66)
Initiated rescue medication prior to Week 28	*5 (6)*	*3 (7)*	*8 (7)*
Discontinued the 28-week treatment	22 (28)	17 (41)	39 (33)

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Withdrawal criteria	*2 (3)*	*0*	*2 (2)*
Adverse events	*4 (5)*	*0*	*4 (3)*
Withdrawal by subject/parent/guardian	*4 (5)*	*4 (10)*	*8 (7)*
Loss of glucose control	*2 (3)*	*10 (24)*	*12 (10)*
Protocol violation	*2 (3)*	*1 (2)*	*3(3)*
Physician decision	*3 (4)*	*1 (2)*	*4 (3)*
Other (unknown)	*5 (6)*	*1 (2)*	*6 (5)*
HbA1c values missing for Week 28	20 (26)	14 (33)	34 (28)
Retrieved dropouts	2 (3)	3 (7)	5 (4)

[1]*FAS full analysis set;* [2]*EAS evaluable analysis set; Source: extracted from CSR Table 9 and confimred by reviewer's analysis (adsl.xpt)*

Major baseline characteristics by treatment arm are summarized in Table 4. Eight percent (8%) of population was of age > 16 years at baseline. More girls (67%) were enrolled in this trial than boys (33%), and the boy to girl ratio was similar between treatment arms. For race, 46% of subjects were categorized in Hispanic (from Latin America or US). More whites (31% vs 15%) were in the placebo group and more African Americans (28% vs 17%) in Total EBID group. The collection of race data was not of high quality.

Table 4. Demographics and Baseline Characteristics- ITT population

		Total EBID N=80	***Placebo N=42***	***Total N=122***
Age*				
	Mean (SD)	13.9 (1.9)	14.4 (1.8)	14 (1.9)
	Median (Min, Max)	14 (10, 17)	15 (10, 17)	14 (10, 17)
	≤ 16 years (%)	73 (91)	39 (93)	112 (92)
	>16 years (%)	7 (9)	3 (7)	10 (8)
Sex, n (%)				
	Female	53 (66)	29 (69)	82 (67)
	Male	27 (34)	13 (31)	40 (33)
Race, n (%)				
	White	12 (15)	13 (31)	25 (21)
	African American	22 (28)	7 (17)	29 (24)
	Asian	5 (6)	5 (12)	10 (8)
	American Indian or Alaska Native	1 (1)	0	1 (1)
	Hispanic (Latin American)	40 (50)	17 (41)	57 (46)
Region, n (%)				
	USA	53 (66)	30 (71)	83 (68)
	Rest of the world	27 (34)	12 (29)	39 (32)
Background therapy, n(%)				
	Naïve	20 (25)	10 (24)	30 (25)
	Metformin	52 (65)	25 (60)	77 (63)
	SU	0	2 (5)	2 (2)
	Metformin + SU	8 (10)	5 (12)	13 (11)
Duration of diabetes (years)				
	Mean (SD)	1.63 (1.6)	1.75 (1.8)	1.67 (1.7)
	Median (Min, Max)	0.96 (0.1, 7.0)	1 (0.1, 7.0)	1 (0.1, 7.0)

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HbA1c (%)			
Mean (SD)	7.6 (1.3)	7.7 (1.1)	7.6 (1.2)
Median (Min, Max)	7.2 (6, 11.9)	7.3 (6.1, 10.3)	7.2 (6, 11.9)
Body mass index (BMI) (kg/m^2)			
Mean (SD)	34. 3 (9.6)	34.1 (9.8)	34.2 (9.6)
Median (Min, Max)	32 (15, 75)	31 (21, 59)	32 (15, 75)

** Age=the date of informed consent - birth date. Source: extracted from clinical study report Tables 13, 14, 15 (pages 81~ 85)*

3.2.4 Results and Conclusions

Primary endpoint: Change from Baseline to Week 28 in HbA1c (%)

Mean HbA1c (%) increased from baseline to Week 28 both in the Total EBID arm and in the placebo arm (Table 5). Treatment difference between Total EBID and placebo in mean change of HbA1c from baseline to Week 28 was estimated as -0.28 with 95% CI as (-1.01, 0.45) by the applicant's pre-specified primary analysis, MMRM (p-value= 0.44). Because the upper limit of 95% CI of treatment difference is above 0, the GWBQ study failed to show superiority of EBID compared to placebo. The results using MMRM including all subjects who initiated rescue therapy and discontinued treatment also showed similar results.

In Washout analysis, a preferred multiple imputation method with high (28% in Table 3) missing data, the size of treatment difference increased but still the treatment difference was not statistically significant (p-value= 0.10). The Agency's washout analysis to impute the missing values at Week 28 with obsmargins option in the SAS programming showed treatment effect, -0.63 with 95% CI as (-1.39, 0.13). As exploratory analyses, comparison to placebo for each dose of EBID showed consistent results (5 ug EBID vs Placebo: -0.68 (-1.54, 0.17); 10 ug EBID vs Placebo: -0.58 (-1.51, 0.36)).

All sensitivity analyses by the applicant showed similar results (data not shown) and did not alter the conclusion of the primary analysis.

Table 5. Primary Analysis Results for Changes 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*

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Secondary endpoints

Results for key secondary endpoints (i.e., proportion of patients achieving HbA1c < 7 %, ≤ 6.5%, and <6.5%, changes in Body weight and changes in FSG from baseline at Week 28) are shown for descriptive purposes (Table 6). Proportions of subjects who achieved the goal were calculated, subjects with missing data were considered as non-responders who did not achieve the goal. Nominal p-values from CMH test for were 0.51, 0.42 and 0.13, respectively.

The applicant's pre-specified MMRM analysis after excluding measurements after initiation of rescue therapy or treatment discontinuation and the Agency's washout analysis using FAS population showed similar results for body weight and FSG. None of the results support the efficacy of EBID compared to placebo.

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*

Efficacy Conclusion

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.

3.3 Evaluation of Safety

An evaluation of safety refers to clinical review by Dr. Justin Penzenstadler.

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses using the primary efficacy analysis (i.e., washout analysis for change in HbA1c (%) from baseline to Week 28 in FAS population) were performed. Due to small sample size in race and region subgroups, race other than White and region other than US were collapsed into one group. Subgroups are defined by sex (Female vs. Male), race (White vs. Others) and region (US vs. non-US) in this review. There were no geriatric (> 65 years old) population in GWBQ. Interaction between subgroup and treatment arm was tested.

Shrinkage methods- Bayesian hierarchical model

In the above-mentioned traditional subgroup analyses, there were some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimates of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. With a shrinkage method, sample estimate is "shrunk" towards the overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage).

The Bayesian hierarchical model was used in this review as a shrinkage method with sample estimates from the traditional subgroup analysis with the same flat prior to derive shrinkage estimates for all subgroups and assumptions as followings:

Y_i: the observed sample estimate of treatment effect in a subgroup level i (i=1,2, … , total number of subgroups), assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$ with $\mu \sim N(0, (4*1.7)^2)$, $1/\tau^2 \sim$ Gamma (0.001, 0.001) (noted as "shrinkage", 1.7 from patient-level standard deviation

Shrunken estimates and 95% credible interval (equivalent to confidence interval of sample estimate) are calculated.

4.1 Gender, Race, and Geographic Region

No interaction terms between subgroup and treatment group were significant (interaction p-values > 0.10). The sample and shrinkage estimate of treatment effect in subgroups, are presented in Table 7. Subgroup analysis using Bayesian shrinkage estimate exhibits narrower credible interval (equivalent to confidence interval of sample estimates), and the shrinkage subgroup estimate is toward the overall mean.

The subgroup treatment effects (BHM-shrinkage estimates) are consistent across subgroups (numerically favoring to EBID, but not statistically significant difference compared to placebo).

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There was no notable heterogeneity of treatment difference across subgroups to primary analysis results using all subjects. Of note, the collection of race was not of high quality.

Table 7. Subgroup Analysis Results for Changes in HbA1c (%) from Baseline at Week 28

	LS mean[§] (SE) *N*[1] *(miss_n)*[2]		LS mean[§] Difference (95% CI) from placebo	
	Total EBID	**Placebo**	**Sample estimates**	**BHM-Shrinkage**
Overall population	0.12 (0.25) *78 (20)*	0.75 (0.30) *42 (14)*	-0.63 (-1.39, 0.13)	
Sex				
Male	-0.03 (0.54) *27 (7)*	0.18 (0.91) *13 (6)*	-0.21 (-2.24, 1.82)	-0.61 (-1.92, 0.71)
Female	0.16 (0.28) *51 (13)*	1.03 (0.35) *29 (8)*	-0.86 (-1.75, 0.02)	-0.79 (-1.62, 0.05)
Race				
White	0.29 (1.53) *12 (0)*	-1.63 (5.16) *13 (6)*	1.92 (-9.19, 13.04)	-0.12 (-4.48, 4.24)
Others	0.14 (0.29) *66 (20)*	0.62 (0.37) *29 (8)*	-0.47 (-1.42, 0.48)	-0.46 (-1.41, 0.49)
Country				
USA	-0.02 (0.29) *51 (16)*	0.85 (0.32) *30 (12)*	-0.87 (-1.70, -0.03)	-0.74 (-1.53, 0.04)
Others	0.30 (0.49) *27 (4)*	0.25 (0.73) *12 (2)*	0.05 (-1.66, 1.76)	-0.45 (-1.70, 0.80)

N: number of subjects in each subgroup, miss_n: number of missing data in each subgroup to be imputed using washout analysis; SE=standard error. [§] LS means are from ANCOVA model with treatment group, baseline values and stratification factor as covariates after missing data imputation

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The applicant performed MMRM for primary analysis that is inadequate to deal with high missing data (28%, Table 3) and the applicant used EAS excluding data from subjects who used rescue therapy and/or discontinued study that was not acceptable analysis set under treatment policy estimand in T2DM population.

Statistical issues regarding analysis method to handle missing data and analysis set were addressed with reviewer's approaches. This reviewer performed washout analysis to impute missing data under treatment policy estimand using FAS including data from post-rescued and/or treatment discontinued subjects (Tables 1 and 5).

Reference ID: 4859410

5.2 Collective Evidence

Statistical findings in GWBQ do not support superiority of EBID compared to placebo in the efficacy evaluation for adolescents with T2DM. HbA1c increased from baseline to Week 28 in both EBID and placebo arms. Treatment difference estimate was shown as reduction of HbA1c changes with EBID compared to placebo, but it is not statistically significant (Tables 1 and 5). Secondary endpoints also did not support superiority of EBID compared to placebo (Table 6). Sensitivity and subgroup analyses (Table 7) did not alter the efficacy conclusion.

5.3 Conclusions and Recommendations

The collective evidence from GWBQ study results demonstrated that EBID did not show superiority of efficacy compared to placebo in adolescents with T2DM. Because of marketed convenient administration options (once-weekly compared to twice daily), this reviewer concludes that EBID had no additional benefit for adolescents with T2DM. This reviewer agrees with updating Pediatric Use Section only in the label without adding a new indication.

5.4 Labeling Recommendations

Because GWBQ did not demonstrate the effectiveness of BYETTA, study should be briefly described in Pediatric Use subsection only to inform that effectiveness of EBID compared to placebo has not been established in GWBQ in adolescents (10 to 17 year of age) with T2DM. According to the *"FDA Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling,"* the recommended language in the labeling section 8.4 should be as follows: 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.

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/

YOONHEE KIM
09/20/2021 08:45:14 AM

YUN WANG
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