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 #:	NDAs 022200 and 209210
Supplement #:	S031 and S017
Drug Name:	Byetta (generic Bydureon / Bydureon BCise)
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Applicant:	AstraZeneca AB
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1 EXECUTIVE SUMMARY

In this supplemental New Drug Application (NDA), AstraZeneca (the applicant) submitted a pediatric study for Bydureon and Bydureon BCise. The supplement is submitted as a part of the Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) that was issued on January 27, 2012 following approval of Bydureon (NDA 22200 and NDA 209210). This supplemental application also serves to fulfill the terms of the written request (WR) for pediatric studies issued under the Best Pharmaceuticals for Children Act. The purpose of this clinical program was to examine the effects of 2 mg exenatide once weekly (EQW) on glycemic control in children and adolescent patients (ages 10 to 17 years old) with Type 2 diabetes (T2DM).

With this submission, AstraZeneca requests a three-year period of marketing exclusivity for Bydureon for the pediatric indication.

The clinical part of this submission consisted of one double-blind, multi-center, phase 3 trial. The study was conducted in pediatric subjects diagnosed with Type 2 diabetes.

Primary analysis results:

The borderline superiority of EQW over placebo was achieved since the upper bound of the 95% confidence interval of the difference between EQW and placebo contains zero (2-sided p-value=0.052).

	EQW N 58	Placebo N=24	Difference (EQW versus Placebo) at Week 24
Estimate	-0.25	0.45	-0.71
95%CI	(-0.66, 0.16)	(-0.11, 1.02)	(-1.42, 0.00]

Statistical issues and findings:

1. **Outdated approach in the prespecified analysis of the primary endpoint.** The study protocol was initiated in 2006. Statistical methodology requirements in effect at that time do not meet current Agency standards.

    a. **Handling of intercurrent events.** The written request (WR) protocol prespecified exclusion of HbA1c measurements after initiation of rescue therapy. Our current standard requires inclusion of all data regardless of treatment discontinuation.
    b. **Primary analysis methodology.** The prespecified statistical methodology did not include multiple imputations for missing data. The applicant utilized the prespecified mixed model repeated measures (MMRM) model. The missing at random (MAR) model assumption considers that the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are

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on-treatment in the same treatment arm. The missing at random assumption made in the MMRM model may not be valid here. The results of the prespecified MMRM analyses showed superiority of EQW over placebo.

2. **Secondary endpoints.** The prespecified secondary endpoints: change in Fasting Plasma glucose (FPG) and change in BMI did not demonstrate superiority of EQW over placebo.

3. **Missing data.** The overall missing HbA1c data rate at week 24 was about 13%. Most missing data were in the EQW arm (15%).

My recommendations:
Although the prespecified MMRM results demonstrated superiority, the statistical superiority of EQW over placebo was borderline when the more appropriate, conservative, and current analysis techniques (washout imputations) were utilized. While the directionality of HbA1c trajectories suggested improved glycemic control in pediatric patients treated with EQW, the confidence intervals for the change in HbA1c were rather large because of the small sample size of the trial. Given the directionality of the treatment effect, low number of severe hypoglycemia side effects, and general logistical difficulties in recruitment and conduct of pediatric trials, I would recommend approval of EQW.
I recommend using HbA1c results based on washout imputations and analysis of covariance model (ANCOVA) in the label, to replace the MMRM results proposed by the applicant.

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2 INTRODUCTION

2.1 Overview

A brief description of the drug indication and history of the submission is presented below.

2.1.1 Indication

Bydureon, a GLP-1 receptor agonist, is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In this new supplement the applicant is seeking approval of Bydureon for adolescents ages 10 to 17 years old diagnosed with T2DM.

2.1.2 History of Drug Development

Since April 28, 2005, Bydureon and Bydureon BCise are approved in the US as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The efficacy and safety of Bydureon and Bydureon BCise in adults have been documented and evaluated in the clinical development program for exenatide.

This supplemental New Drug Application (NDA) is submitted as a part of the Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) that was issued on January 27, 2012 following approval of Bydureon (NDA 22200 and NDA 209210). This supplemental application also serves to fulfill the terms of the written request (WR) for pediatric studies initially issued on March 29, 2006 under the Best Pharmaceuticals for Children Act. The Written Request was subsequently amended seven times: on September 8, 2006, April 18, 2007, March 18, 2008, October 27, 2010, September 16, 2014, August 16, 2018, and the final 8th version was created on July 16, 2020.

Of note, the original primary analysis (MMRM evaluation based on data collected prior to rescue or discontinuation of treatment) was prespecified in the written request agreement. On July 16, 2020, the Agency issued a letter informing the applicant that we do not accept the MMRM-based primary analyses and recommended using placebo-based washout imputations for missing data instead. The Agency also recommended utilizing the tipping point analysis to examine robustness of imputations. In this submission, the applicant provided the requested analyses as a separate post-hoc analyses document. The results provided in the proposed label are based on the prespecified MMRM analysis.

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2.1.3 Specific studies reviewed

Table 1. List of all studies included in analysis

	Phase	Design	# of Subjects per Arm	Study Population
D5551C00002	Phase 3	MC, R, DB, PG, PC trial (24 weeks)	EQW/ N_{EQW}=59 Placebo/ N_p=24	Adolescent patients (10 to <18 years old) with type 2 diabetes mellitus (T2DM) treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin.

Legend: * MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, CO: Crossover, PC: placebo controlled, EQW: exenatide once weekly

2.2 Data Sources

This submission is in electronic common technical document (eCTD) format. The submission is archived at the following link: \\CDSESUB1\evsprod\NDA022200\0573 .
Study datasets were provided as SAS XPORT transport files. The datasets were in good organization. The Define.pdf file was clear enough.
My analyses on the primary and secondary efficacy endpoints provided approximately the same results as those reported in the clinical study report (CSR).

I derived all of the results presented in this review using the submitted datasets. I created all tables and figures in this review unless otherwise noted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submission quality was acceptable.

3.2 Evaluation of Efficacy

This section provides an overview of the trial that I reviewed.

3.2.1 Study Design and Endpoints

Study D5551C00002 is a multicenter, randomized, parallel-group, phase III study in adolescent patients with type 2 diabetes (T2DM) treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin. The study timeline consisted of 5-week screening, 24-week double-blind period comparing EQW with placebo and a 28-week open label extension period with 10-week follow-up. At the end of the screening period, subjects were randomized in a 5:2 ratio to EQW or placebo. Randomization was stratified by screening HbA1c (<9.0% or ≥9.0%). A graphical description of the study is presented in the (Figure 1) below:

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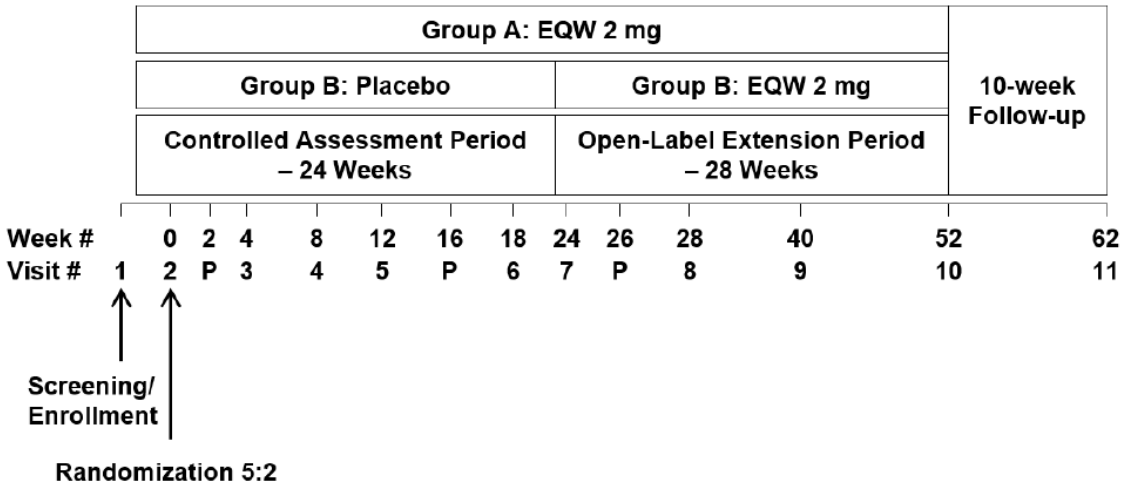
Figure 1. Study schema



All visits scheduled during the controlled assessment period and during the open-label extension period were to occur within ± 2 days of the scheduled date, relative to Visit 2 (Week 0).

Visit 11 was to take place at least 10 weeks and no later than 12 weeks after the last dose of EQW.

The Investigator and/or qualified study-site personnel was to contact patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address any questions related to study medication, and review AEs.

AE Adverse event; EQW Exenatide once weekly; P Phone call.

Sourse: CSR p. 7

Primary objective:

To assess the effect on glycemic control, as measured by glycated hemoglobin A1c (HbA1c), of exenatide once weekly (EQW) following 24 weeks of treatment compared to placebo in children and adolescents with type 2 diabetes mellitus

Secondary objectives:

To compare the effects of EQW following 24 weeks of treatment to those achieved by placebo in children and adolescents with type 2 diabetes mellitus on the following:

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

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3.2.2 Statistical Methodologies

Applicant's approach:
Prespecified analysis method:

A longitudinal repeated measures analysis was used to estimate the change in HbA1c from baseline; the model included change in HbA1c as the dependent variable and treatment group, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects.

Primary analysis population and analysis dataset: The primary analysis population consisted of all randomized subjects that received at least one dose of study medication during the double-blind treatment period. HbA1c data obtained after discontinuation of protocol treatment were excluded from the primary analysis.

Secondary endpoint analyses:
Similar to the primary endpoint, an MMRM model was utilized in analysis of change in FPG and change in body weight.

FDA approach:
Primary analysis: Because all post-discontinuation data points were excluded from the analysis, the sponsor's analysis examines the effect of week 24 HbA1c change under the assumption that the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment arm). I do not believe that in clinical practice none of the subjects for whom the drug is intended will need rescue. Thus, the outcomes based on this assumption might not be realistic. Also, subjects who discontinued treatment would not have the same outcomes as subjects who completed the entire treatment period. Analysis that excludes all post-discontinuation data will not represent all subjects who participated in the study. Therefore, my analysis will include data regardless of adherence, i.e. all available data points collected after rescue or discontinuation will be included in the analysis. In my view, this approach more appropriately describes real world outcomes.

Also, in my analysis, I implemented a multiple imputation approach that imputed data for subjects who did not have HbA1c endpoint at week 24.

Imputation approach (washout imputations, ANCOVA):

1. First, 300 copies of the dataset were generated.

2. Second, for subjects in the placebo group both, non-monotone and monotone missing HbA1c data were imputed using HbA1c data from subjects on placebo who had observations at week 24. The missing data was imputed using the MCMC statement of SAS PROC MI. The imputation model included treatment, region and HbA1c measurements from baseline to Week 24.

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3. For subjects on EQW, the week 24 data were imputed based on data from the completers in the placebo arm only using regression method (SAS PROC MI with statement MONOTONE REG using the same model as specified in step 2). No Intermediate data from either placebo or EQW arm were used in imputation for missing data in EQW arm.

4. For each dataset separately, the change in HbA1c at week 24 was analyzed using ANCOVA model. Each ANCOVA model contained baseline HbA1c, region, and treatment group as covariates.

5. Results from an ANCOVA model fit to the imputed datasets were analyzed and combined using Rubin's method. Treatment effect estimates and limits from the 95% confidence interval (CI) were retained.

Additional analyses:

MMRM analysis

Similar to the applicant, a longitudinal repeated measures analysis was used to estimate the change in HbA1c from baseline until week 24; the model included the categorical fixed effects of treatment, visit, and treatment-by-visit interaction, region as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-visit interaction. In contrast to the applicant's approach, these analyses were performed using all data points obtained prior to and after the rescue/discontinuation.

As it was alluded to in the History of drug development section (2.1.2), the applicant provided the imputations-based analyses (change in HbA1c and 2-way tipping point evaluations) requested by the Agency.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Since the randomization ratio in this trial was 5:2, a much larger number of subjects were randomized to treatment (EQW) i.e. almost 72% of subjects (Table 2). Most of the trial and treatment withdrawals were in the EQW arm (13.6% of the EQW subjects withdrew from the trial).

Table 2. Disposition table

	EQW	Placebo
Randomized	59	24
Treated	58 (98.3%)	24(100%)
Completed Treatment	49(83.1%)	23(95.8%)
Withdrawals from Study:	8(13.6%)	1(4.2%)
Lost to follow-up	2 (3.4%)	1(4.2%)
Withdrawal by subject	6(10.2%)	
Discontinued treatment:	9(15.3%)	1(4.2%)
Lost to follow-up	2 (3.4%)	1(4.2%)
Protocol deviation	1(1.7%)	0
Withdrawal by subject	6(10.2%)	0
Rescued	2(3.4%)*	0
Available HbA1c at week 24†	50(84.7%)	22(91.7%)

*one of the subjects was identified as initiated new antidiabetic medications and met the criteria of rescue. This information was uncovered after the FDA information request (IR) from May 4, 2021 was sent to the applicant. The CSR did not include this information. Also, the response to the same IR, the sponsor disclosed the list of 7 subjects on EQW who also initiated new antidiabetic medication during the trial but did not meet the prespecified rescue criteria.

†Based on the submitted data file. In the submitted document (table in post-hoc analyses of efficacy, table p.2), the applicant did not include one additional missing subject on placebo.

Demographics and baseline characteristics of all randomized subjects are presented in Table 3 and

Table 4. Most study participants were female (54.2% in the treatment group and 71% on placebo). Half of the subjects on placebo and 41% of subjects on treatment were white. Almost 64% of subjects came from the United States (61% on treatment and 71% on placebo). Most subjects in both groups had BMI>=97 percentile (78% on EQW and 71% on placebo).

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Table 3. Demographic characteristics

		EQW N=59 n(%)	Placebo N=24 n(%)
Sex	Female	32 (54.2)	17 (70.8)
	Male	27(45.8)	7 (29.2)
Race	American Indian Or Alaska Native	4(6.8)	1(4.2)
	Asian	2(3.4)	1(4.2)
	Black or African American	17(28.8)	8(33.3)
	Other	12(20.3)	2(8.3)
	White	24(40.7)	12(50.0)
Region	Europe	8(13.6)	4(16.7)
	Middle East	2(3.4)	1(4.2)
	North America	36(61.0)	17(70.8)
	South America	13(22.0)	2(8.3)
Country	Bulgaria	1(1.7)	
	Hungary	3(5.1)	1(4.2)
	Israel	4(6.8)	3(12.5)
	Kuwait	2(3.4)	1(4.2)
	Mexico	13(22.0)	2(8.3)
	USA	36(61.0)	17(70.8)
Baseline BMI percentile	missing	1(1.7)	
	>=3 to <85	4(6.9)	
	>=85 to <97	9(15.5)	7(29.2)
	>=97	45(77.6)	17(70.8)
Insulin use	No	32(54.2)	13(54.2)
	Yes	27(45.8)	11(45.8)

Source: reviewer. Baseline characteristics provided by the applicant in CSR p.97-98

Overall, age and baseline diabetes characteristics of subjects in each arm were relatively balanced. On average, subjects on placebo were slightly older (15 years old on EQW and 15.6 on placebo), although baseline BMI was slightly lower among subjects on placebo (36.9 vs 35.1). The average FPG of subjects on placebo was 5 mg/dL higher than of subjects on EQW. Aligned with their age, the duration of diabetes was slightly longer for the subjects on placebo (2.2 vs 2.5 years). The percentage of insulin users between treatment groups was similar (45.8% of subjects in each arm).

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Table 4. Patient and disease characteristics

		EQW N=58	Placebo N=24
Age (yrs)	Mean (std)	15(1.9)	15.6(1.7)
	Median	15	16
	Range	(11, 17)	(12,17)
Baseline Body Mass Index (kg/m2)	Mean (std)	36.9(9.3)	35.1(6.6)
	Median	36.7	33.2
	Range	(18.5, 71.2)	(25.4, 50.3)
HbA1c at Baseline (%)	Mean (std)	8.1(1.2)	8.3(1.5)
	Median	8	7.6
	Range	(6.3, 11.2)	(6.6, 11.2)
Baseline Fasting Plasma Glucose (mg/dL)	Mean (std)	165(59.3)	170.5(60.3)
	Median	147	144
	Range	(71,342)	(90, 301)
Duration of Diabetes (yrs)	Mean (std)	2.2(2.2)	2.5(2)
	Median	1.4	2
	Range	(0,10.4)	(0.2, 9.6)

Source: reviewer. Baseline characteristics provided by the applicant in CSR p.99-102

Missing data

Most missing HbA1c evaluations were observed in the EQW arm (Table 2).

Based on the submitted file, 9 of 59 (15.3%) of subjects randomized to EQW did not have an observation at week 24. One subject was randomized but not treated and 8 (13.6%) discontinued. Of note, there was a discrepancy between missing HbA1c data in subjects on placebo at week 24. According to the post-hoc-analyses-of-efficacy-tables-and-figures.pdf submitted by the applicant, the table on page 2, indicates that there was only one subject on placebo who had HbA1c at week 24 missing. According to the datafile and all other tables in the document listed above, the number of subjects on placebo was listed as 22, i.e. 2 subjects (8.3%) on placebo did not have an endpoint observation. The timing of the last recorded HbA1c in the treatment period is presented in the dot plot below (Figure 2). According to the graph, most subjects who discontinued EQW did it in the beginning of the trial. According to the CSR, p.89, 3 subjects were lost to follow-up (2 on EQW and 1 on placebo), six subjects on EQW withdrew from the study. No patients were withdrawn due to adverse events (AEs) during the study. All discontinuations were observed among US subjects (Figure 8 in appendix).

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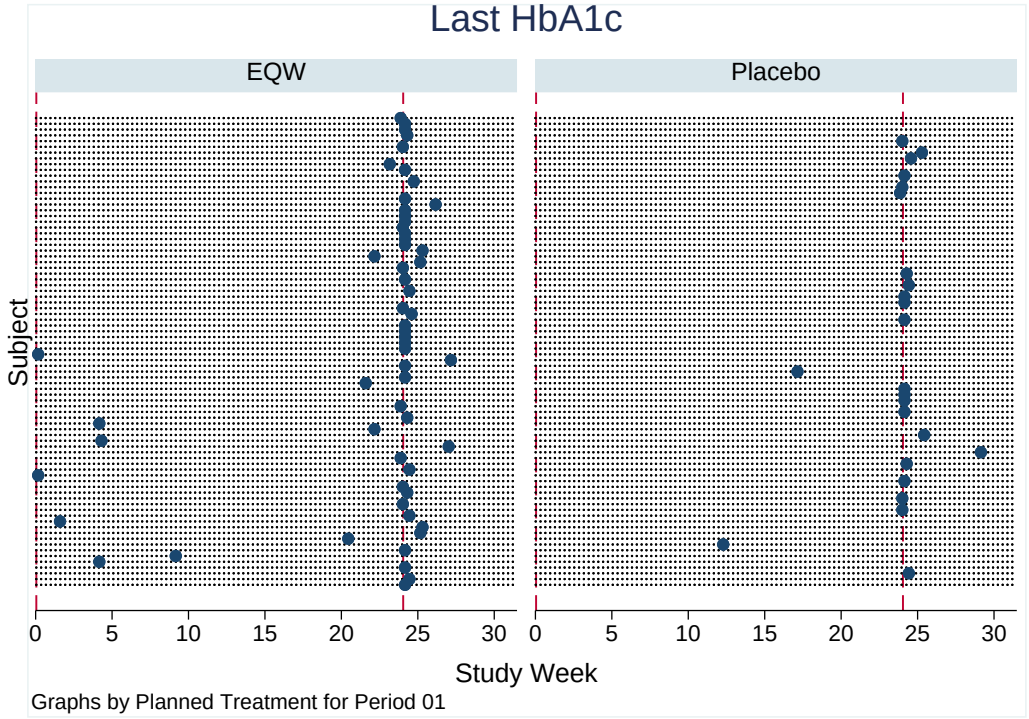
Figure 2. Treatment discontinuation patterns by treatment group



Legend: Each horizontal dotted line represents one study participant. The large blue circles show time of last HbA1c observation measured during the double-blind period. A red dashed vertical line delineates the 24 weeks of the double-blind period.
Source: reviewer

3.2.4 Results and Conclusions

3.2.4.1 Graphical exploration

According to a simple unadjusted waterfall plot of changes in HbA1c, a larger percentage of subjects experienced lowering of HbA1c during the trial (Figure 3). A maximum HbA1c increase of more than 4 was observed in subjects on placebo. At the same time, the maximum increase on EQW was only above 2. Also, the maximum HbA1c reduction was larger among subjects on EQW than the reduction in subjects on placebo.

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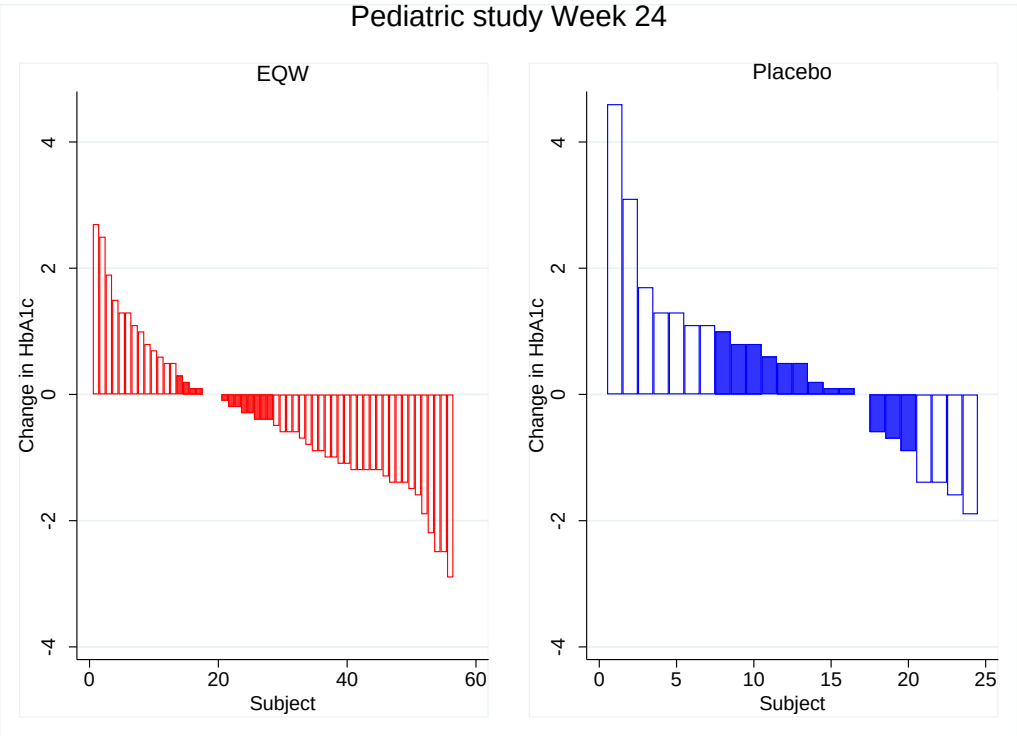
Figure 3. Waterfall plots showing change from baseline



Legend: Each waterfall plot shows individual unadjusted changes in HbA1c. Each vertical bar represents an individual study participant. Values above zero represent an individual's increase in HbA1c during 24-week treatment. Values below zero represent an individual's reduction of HbA1c during treatment period.
Source: reviewer

3.2.4.2 Primary analysis

Although the waterfall plots show a larger improvement for subjects on EQW, the ANCOVA results based on data with washout imputations demonstrated only a borderline result (Table 5). According to the analysis, a borderline superiority of EQW over placebo was achieved (the upper confidence limit is equal to zero). The applicant conducted a 2-way tipping point analysis using a base model with a placebo washout imputation approach. According to their findings, a change of -0.2% HbA1c units for EQW (while leaving imputed placebo values the same) led to a p-value of 0.041 (change from a p value of 0.052 in the primary analysis) for the placebo washout analysis with an LS mean of -0.74% . The applicant's results of the 2-way tipping point analyses are presented in Table 11 and Table 12 of the Appendix.

Table 5. Primary analysis outcomes (ANCOVA with washout imputations)

Change in HbA1c	EQW N 58	Placebo N=24	Difference (EQW versus Placebo) at Week 24
Estimate	-0.25	0.45	-0.71
95%CI	(-0.66, 0.16)	(-0.11, 1.02)	(-1.42, 0.00]

The results based on MMRM analyses suggest superiority (Table 6).

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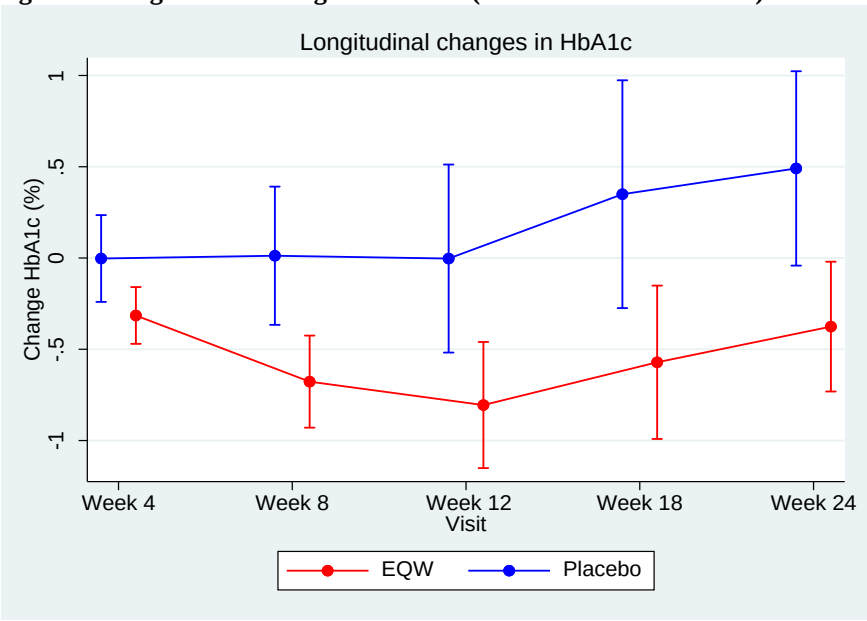
Table 6. MMRM analysis results

Change in HbA1c	EQW N 58	Placebo N=24	Difference (EQW versus Placebo) at Week 24
Estimate	-0.38	0.49	-0.87
95%CI	(-0.73, -0.02)	(-0.04, 1.02)	(-1.51, -0.23)

A graphical exploration of longitudinal changes with HbA1c adjusted for baseline HbA1c and country without imputations for missing data suggests that the estimates of HbA1c changes in subjects on EQW were larger, but the 95% confidence intervals (CIs) were overlapping (Figure 4).

Figure 4. Longitudinal changes in HbA1c (LS means with 95% CIs)



Source: reviewer; results based on observed data without imputations for missing data.

Of note, the applicant provided graphs showing longitudinal changes in HbA1c (CSR p. 111) where instead of means and 95%CIs, the applicant presented means with standard errors, thus creating an illusion of a larger difference in treatment effect. Similar plots were provided for the secondary endpoints, FPG (CSR p. 115) and body weight (CSR p. 117).

3.2.4.3 Analysis of secondary endpoints

A graphical exploration of the changes in FPG during the double-blind period is presented below (Figure 5). Although the estimates of the change in FPG had a larger magnitude in subjects on EQW, the 95%CIs had a large overlap starting at week 8.

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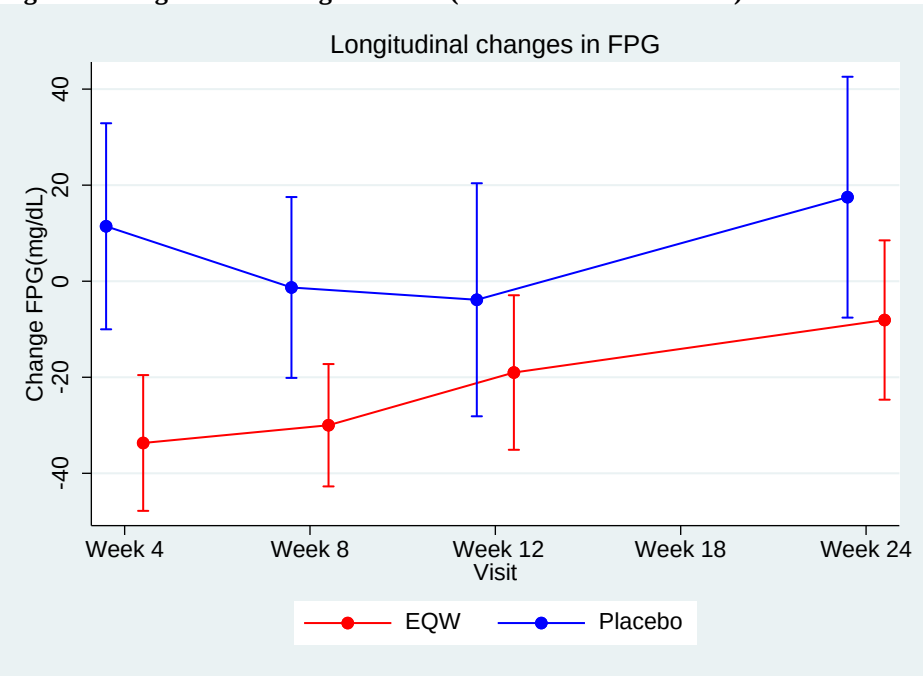
Figure 5. Longitudinal changes in FPG (LS means with 95% CIs)



Source: reviewer; results based on observed data without imputations for missing data.

The numerical results for change in FPG adjusted for baseline FPG, treatment, geographic region, baseline – and treatment-by-visit interactions do not demonstrate superiority of EQW over placebo (Table 7).

Table 7. Outcomes of FPG analysis (MMRM)

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

source: reviewer

Subjects on EQW experienced some reductions in body weight while subjects on placebo did not experience weight changes. Similar to the FPG results, the treatment effect estimates for subjects on EQW were larger, and the 95% CIs overlapped at each visit.

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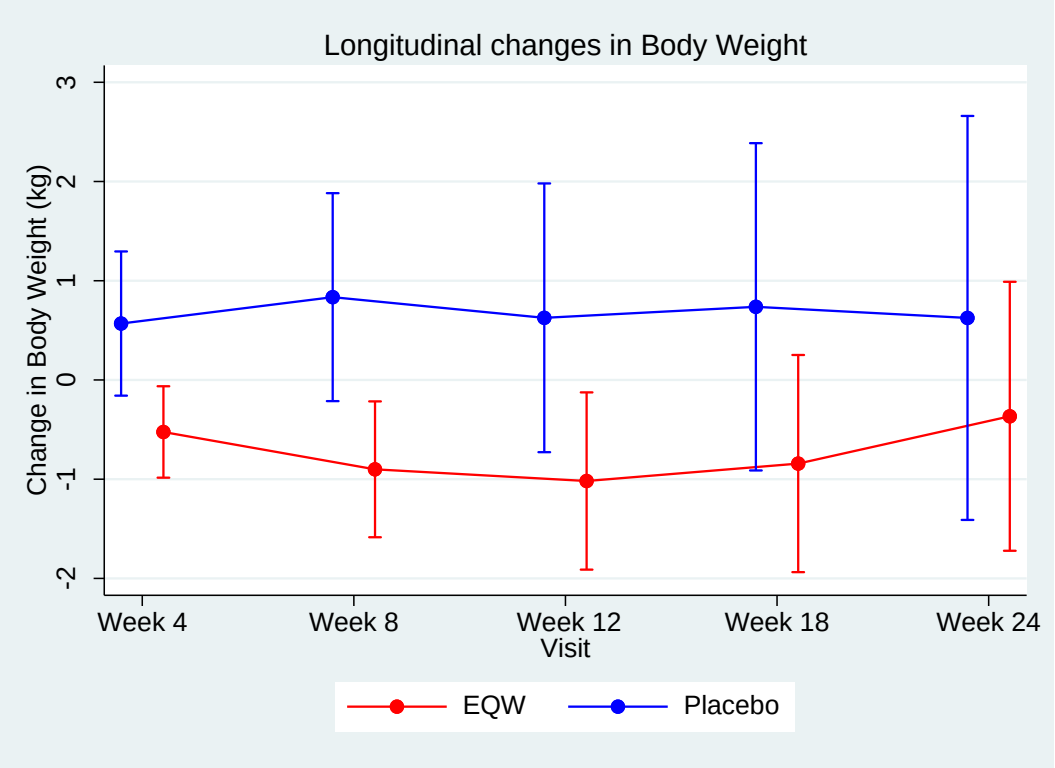
Figure 6. Longitudinal changes in Body Weight (LS means with 95% CIs)



Source: reviewer; results based on observed data without imputations for missing data.

Similar to FPG, the numerical results for change in body weight adjusted for baseline weight, treatment, geographic region, baseline – and treatment-by-visit interactions do not demonstrate superiority of EQW over placebo (Table 8).

Table 8. Outcomes of body weight analysis (MMRM)

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

Source: reviewer

3.3 Evaluation of Safety

My safety review only provides a high-level summary of potential safety issues. Safety events were also reviewed by Dr. Mahtab Niyyati from Medical Division of Diabetes, Lipid Disorders, and Obesity. For more detailed safety events review, readers are referred to Dr. Niyyati's review for this section.

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An overall summary of adverse events suggests that treatment-related adverse events were relatively balanced (25% on EQW and 22% on placebo). The percentage of any AEs was larger for subjects on placebo (74% on placebo and 61% on EQW).

Table 9. An overall summary of adverse events

	Number (%) of Patients[a]			
	Controlled Assessment Period		Extension Period	
Patients with AE category	**EQW (N = 59)**	**Placebo (N = 23)**	**EQW (N = 50)**	**Placebo → EQW (N = 22)**
Any AE	36 (61.0)	17 (73.9)	27 (54.0)	11 (50.0)
Any AE with outcome of death	0	0	0	0
Any SAE including events with outcome of death	2 (3.4)	1 (4.3)	3 (6.0)	1 (4.5)
Any AE leading to discontinuation of treatment	0	0	0	0
Any SAE leading to discontinuation of treatment	0	0	0	0
Any AE leading to discontinuation from study	0	0	0	0
Any SAE leading to discontinuation from study	0	0	0	0
Any AE related to treatment[b]	15 (25.4)	5 (21.7)	5 (10.0)	2 (9.1)

Sourse: CSR, p. 150

In terms of hypoglycemia events, a larger percent of subjects on EQW experienced hypoglycemia (14% on EQW vs 4% on placebo). No hypoglycemia event was major. Most hypoglycemia events did not meet the criteria for a major or a minor event (
Table **10**).
Major hypoglycemia was defined as loss of consciousness, seizure, or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) or an event that required third party assistance and was associated with a plasma or capillary glucose concentration of < 54 mg/dL;
Minor hypoglycemia was defined as event non-major hypoglycemia event that had symptoms consistent with hypoglycemia and a glucose value of < 54 mg/dL prior to treating the episode.

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Table 10. Hypoglycemia events

Hypoglycemia Intensity	EQW (N=59)		Placebo (N=23)	
	Number (%) of patients[a]	Number of events[b]	Number (%) of patients[a]	Number of events[b]
Patients with any hypoglycemia	8 (13.6)	13	1 (4.3)	7
Any hypoglycemia[c]				
Major	0	0	0	0
Minor	1 (1.7)	1	1 (4.3)	1
Other	8 (13.6)	12	1 (4.3)	6

Sourse: CSR, p. 163

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The sample estimates of treatment effect in change in HbA1c among all of the subgroups including age, gender, and race, were obtained by using the same ANCOVA model as for the primary analysis. Since most subjects were from the US while other countries had only a few subjects each, the subgroup analysis by region included only two categories: US and outside of US. The detailed numeric information on subgroup outcomes is presented in the Appendix (Table 13).

Additionally, shrinkage estimates of subgroup treatment effects were derived 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 estimate 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. The analysis utilized the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For $i = 1, 2\ldots,$ Y_i represents the observed sample estimate of treatment effect in subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 50)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups are presented in (Figure 7).

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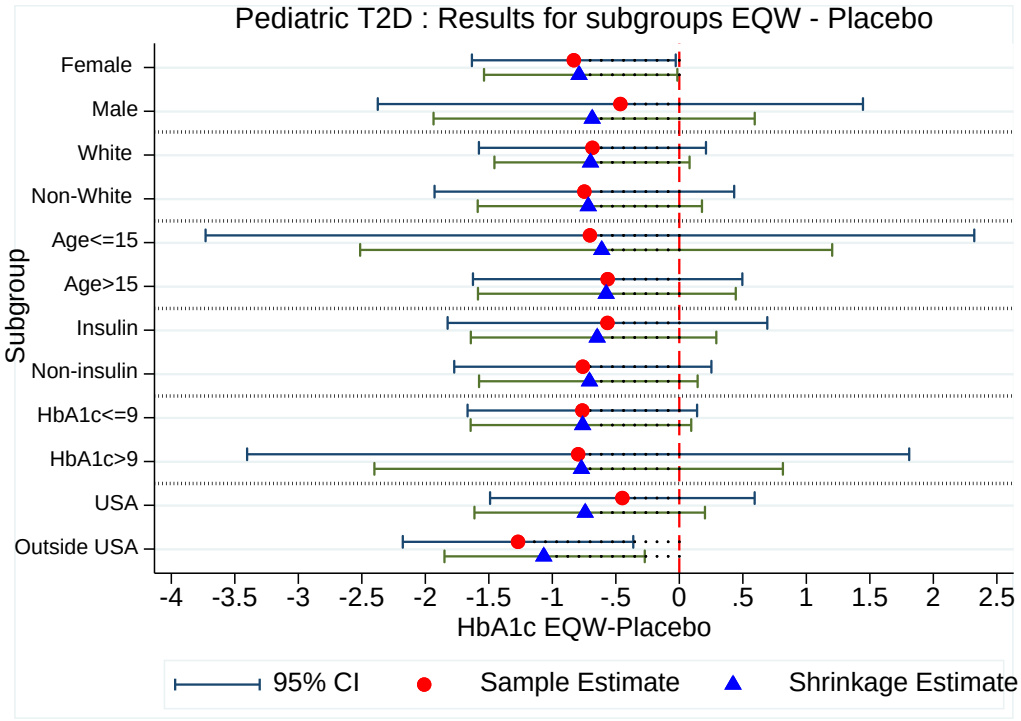
Although given the small sample size for each subgroup, the subgroup results are underpowered and therefore might not be reliable, from the sample and shrinkage estimates, it is shown that the subgroups results are consistent with what was observed for the overall population.

Figure 7 . Results of subgroup analyses



Source: reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and findings

1. **Outdated approach in the prespecified analysis of the primary endpoint.** The study protocol was initiated in 2006. Statistical methodology requirements in effect at that time do not meet current Agency standards.

    a. **Handling of intercurrent events.** The written request (WR) protocol prespecified exclusion of HbA1c measurements after initiation of rescue therapy. Our current standard requires inclusion of all data regardless of treatment discontinuation.

    b. **Primary analysis methodology.** The prespecified statistical methodology did not include multiple imputations for missing data. The applicant utilized the prespecified mixed model repeated measures (MMRM) model. The missing at random (MAR) model assumption considers that the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are

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on-treatment in the same treatment arm. The missing at random assumption made in the MMRM model may not be valid here. The results of the prespecified MMRM analyses showed superiority of EQW over placebo.

2. **Secondary endpoints.** The prespecified secondary endpoints: change in Fasting Plasma glucose (FPG) and change in BMI did not demonstrate superiority of EQW over placebo.

3. **Missing data.** The overall missing HbA1c data rate at week 24 was about 13%. The rate in the EQW arm was 15%.

5.2 Collective Evidence

The collective evidence from the prespecified (MMRM) and more conservative (washout imputations) analysis of the primary endpoint supports effectiveness of EQW in pediatric population.

5.3 Conclusions and Recommendations

Although the prespecified MMRM results demonstrated superiority, the statistical superiority of EQW over placebo was borderline when the most appropriate, conservative, and current analysis techniques (washout imputations) were utilized. While the directionality of HbA1c trajectories suggested an improved glycemic control in pediatric patients treated with EQW, the confidence intervals for the change in HbA1c were rather large because of the small sample size of the trial. Given the directionality of the treatment effect, low number of severe hypoglycemia side effects, and general logistical difficulties in recruitment and conduct of pediatric trials, I would recommend approval of EQW.

5.4 Labeling Recommendations (as applicable)

I recommend using HbA1c results based on washout imputations and analysis of covariance model (ANCOVA) in the label, to replace the MMRM results proposed by the applicant.

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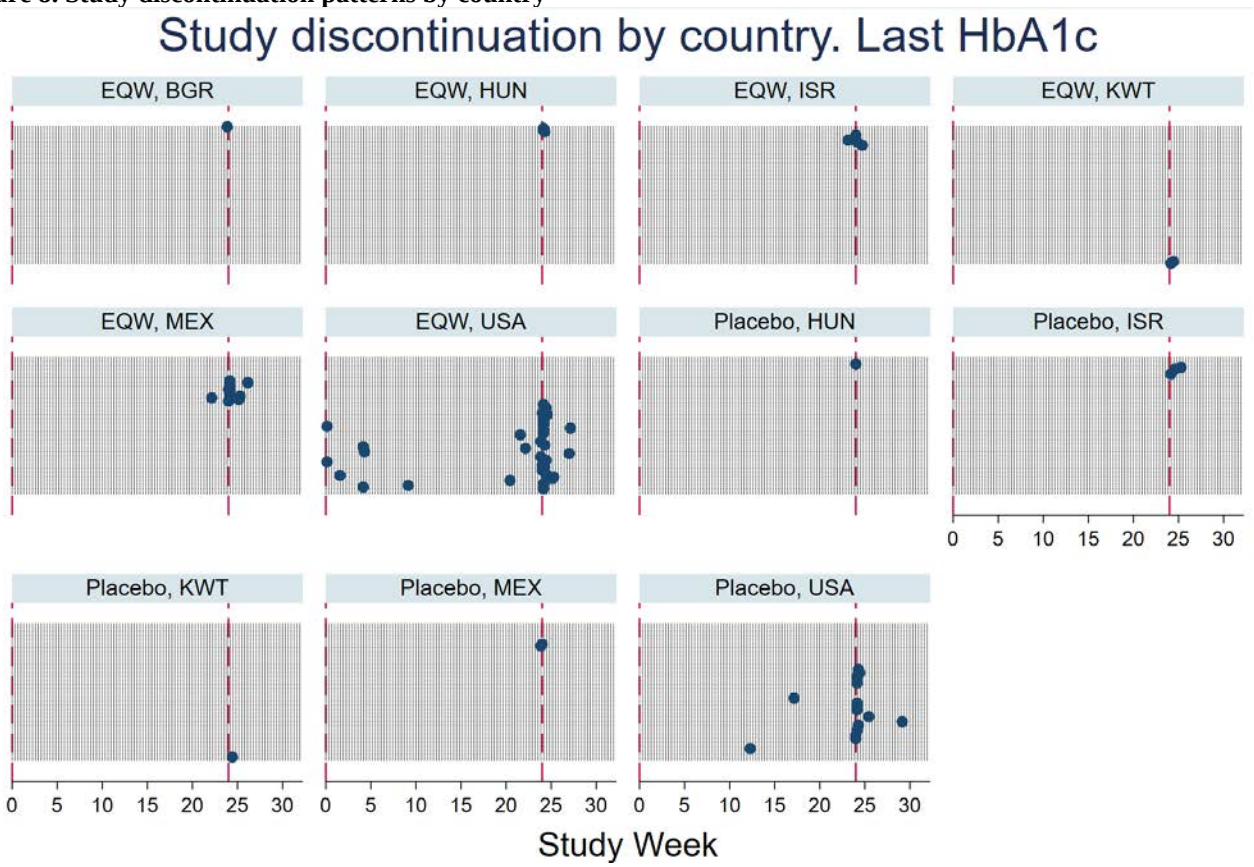
APPENDICES

Figure 8. Study discontinuation patterns by country



Legend: Each horizontal dotted line represents one study participant. The large blue circles show time of last HbA1c observation measured during the double-blind period. A red dashed vertical line delineates the 24 weeks of the double-blind period.

Source: reviewer

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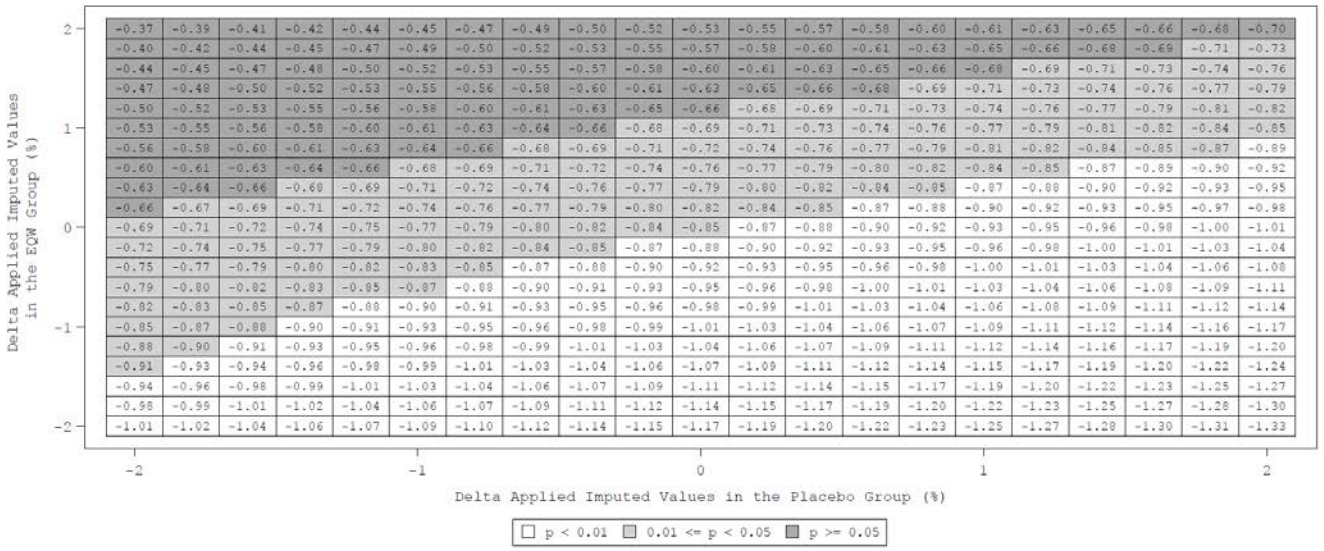
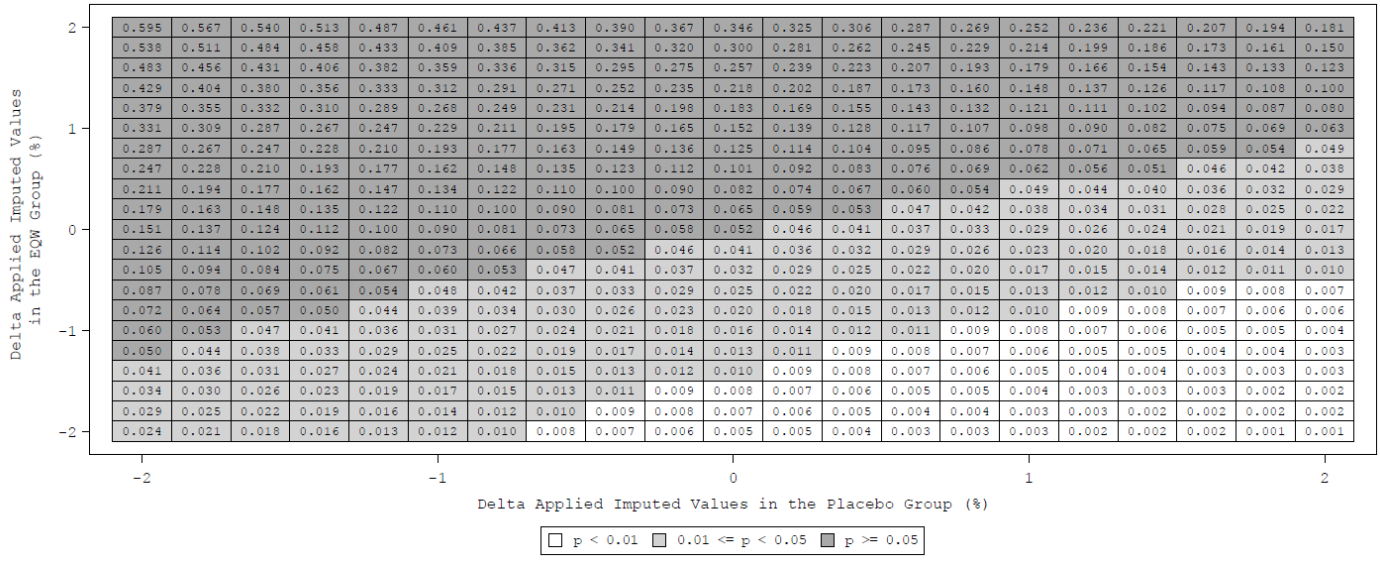
Table 11. Tipping point analysis based on ANCOVA with washout imputations (LS mean treatment differences)



ANCOVA Analysis of Covariance; EQW Exenatide 2mg once weekly; HbA1c Glycated hemoglobin A1c; LS mean Least squares mean; MI Multiple imputation. Change from baseline at Week 24 is modeled using an ANCOVA on imputed data including treatment group, region, and baseline HbA1c value (continuous) as fixed effects. The sequential regression method of MI is used for the sensitivity analyses.
Missing data at Week 24 are imputed based on the missing at random assumption. The imputation model includes treatment, region and HbA1c measurements from baseline to values obtained prior to Week 24. 200 imputations were produced. The seed number used for imputing is 88281. Deltas ranging from -2% to 2% with increments of 0.2% have been applied to the imputed data. LS mean treatment difference (EQW versus Placebo) is presented for each combination of deltas.
Baseline is defined as the last non-missing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication. Data collected after initiation of rescue medication and after discontinuation of study medication are included.

Source: post-hoc analyses p.9

Table 12. Tipping point analysis based on ANCOVA with washout imputations (p-value)



Source: post-hoc analyses p.8

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Table 13. Numerical results of the subgroup analyses

Subgroup	level	Type	Estimate	95%CI
Gender	Female	Sample	-0.83	(-1.633, -0.028)
		Shrink	-0.79	(-1.538, -0.016)
	Male	Sample	-0.46	(-2.374, 1.446)
		Shrink	-0.69	(-1.935, 0.594)
Race	White	Sample	-0.68	(-1.578, 0.210)
		Shrink	-0.70	(-1.456, 0.081)
	Non-White	Sample	-0.75	(-1.927, 0.432)
		Shrink	-0.72	(-1.588, 0.178)
Age	Age≤15 yrs	Sample	-0.70	(-3.730, 2.322)
		Shrink	-0.61	(-2.513, 1.204)
	Age>15 yrs	Sample	-0.56	(-1.625, 0.496)
		Shrink	-0.58	(-1.586, 0.444)
Use of insulin	Yes	Sample	-0.57	(-1.824, 0.692)
		Shrink	-0.65	(-1.642, 0.291)
	No	Sample	-0.76	(-1.772, 0.253)
		Shrink	-0.71	(-1.577, 0.144)
Baseline HbA1c	HbA1c≤ 9%	Sample	-0.57	(-1.824, 0.692)
		Shrink	-0.65	(-1.642, 0.291)
	HbA1c>9%	Sample	-0.76	(-1.772, 0.253)
		Shrink	-0.71	(-1.577, 0.144)
Region	USA	Sample	-0.45	(-1.490, 0.593)
		Shrink	-0.74	(-1.613, 0.202)
	Outside of USA	Sample	-1.27	(-2.177, -0.363)
		Shrink	-1.07	(-1.849, -0.272)

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