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

CLINICAL STUDIES

BLA/Supplement Number:	125469 / S-051
Drug Name:	Trulicity (Dulaglutide)
Proposed Indications:	As an adjunct to diet and exercise to improve glycemic control in patients 10 years of age and older with type 2 diabetes mellitus
Applicant:	Eli Lilly and Company
Date(s):	Submission Date: 5/17/2022 PDUFA Date: 11/17/2022
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewers:	Roberto Crackel, Ph.D., Mathematical Statistician
Concurring Reviewers:	Yoonhee Kim, Ph.D., Team Leader
Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity
Clinical Team:	Medical Officer: Suchitra Balakrishnan Medical Team Leader: Patrick Archdeacon
Project Manager:	Supendeep Dosanjh
Keywords:	T2DM in pediatrics, Wash-out, Treatment regimen

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1 Executive Summary

Eli Lilly and Company submitted a supplemental BLA 125469 S-051 for Dulaglutide (Trulicity) to expand the indication for the treatment of type 2 diabetes mellitus (T2DM) to pediatric patients aged 10 to less than 18 years old. Study H9X-MC-GBGC was completed to fulfill PREA PMR 2781-1, and to respond to the Trulicity Written Request (WR) issued by the FDA on August 31, 2016, and amended on February 6, 2017, April 3, 2020, and June 2, 2021.

1.1 Brief Overview of Clinical Studies

The submission included the results of study GBGC, a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. A 4-week screening period was followed by the 26-week double-blind period, followed by a 26-week open-label period, and 30 days of safety follow-up. The rationale of the study is to evaluate the superiority of dulaglutide (0.75mg, 1.5mg, and pooled) compared with placebo in pediatric patients with T2DM who have inadequate glycemic control despite diet and exercise, with or without metformin and/or basal insulin.

The primary endpoint was change from baseline to Week 26 in HbA1c. The key secondary endpoints are percentage of patients who achieved HbA1c < 7.0% at Week 26, change from baseline to Week 26 in fasting blood glucose (FBG), and change from baseline to Week 26 in body mass index (BMI). The primary comparison for each endpoint was pooled dulaglutide versus placebo, followed by the individual doses versus placebo. Safety was assessed through the evaluation of hypoglycemia, in this review.

1.2 Statistical Issues

There are no major statistical issues. The amount of missing data for primary endpoint assessments is 7.8%. The sponsor's pre-specified primary analysis appropriately addressed missing data via a multiple imputation, placebo wash-out approach under the treatment-regimen estimand. In addition, a 2-way tipping point analysis was also performed.

There are two minor issues:

1) Against our recommendation in a previous statistical analysis plan (SAP) review, the sponsor removed the pre-specified analysis window from the SAP. Also, due to the COVID-19 impact, visit windows were extended for the clinical study report (CSR). This reviewer performed additional sensitivity analyses using an analysis window of 7 and 14 days from the analysis target date for the primary endpoint. Results are robust regardless of analysis window sizes.

2) The applicant reported a statistically significant treatment-by-sex interaction effect (p-value =0.023). The sponsor utilized a different methodology than considering the average of the interaction p-values (0.77). Shrinkage analyses were performed by this reviewer and alleviates any concerns that different treatment effects between males and females were the result of a random low/high.

1.3 Collective Evidence

The primary efficacy analysis demonstrated statistically significant superiority of pooled dulaglutide against placebo. The least squares(LS) mean difference in HbA1c is -1.35%, with 95% CI (-1.87, -0.84), and p-value < 0.001 (Table 1). The LS mean change in HbA1c for placebo at Week 26 was 0.57%, however, the LS mean change in HbA1c for pooled dulaglutide was -0.78%, which is a clinically meaningful reduction. Further, the individual doses of 0.75mg and 1.5mg demonstrated statistically significant superiority against placebo. Considering HbA1c measurements outside the 1-week window as missing, the treatment effect of pooled dulaglutide relative to placebo is -1.19% (95% CI: -1.75, -0.63). Further, considering measurements outside the 2-week window as missing, the treatment effect of pooled dulaglutide relative to placebo is -1.27% (95% CI: -1.81, -0.73). The robustness of the superiority of pooled dulaglutide is confirmed with respect to missing data assumptions based on the results of a 2-way tipping point analysis (Section 3.2.4, Figure 3). The results of the key secondary endpoints supported the effectiveness of dulaglutide except for body mass index (BMI) (Section 3.2.4). Further, there was no elevated risk of hypoglycemia when considering the incidence rate among the number of patients with at least 1 hypoglycemic episode (Section 3.3).

Subgroup analyses for age, sex, race, region, metformin use, and insulin use favored dulaglutide (pooled and individual doses). In subgroup analyses by sex, the LS mean difference in HbA1c for pooled dulaglutide versus placebo among males is -1.64% (95% CI: -2.96, -0.33), and -1.32% (95% CI: -1.86, -0.78) among females. After shrinkage analysis, the mean difference among males is -1.45% with 95% Credible Interval (-2.32, -0.58), and -1.35% (95% Credible Interval: -1.88, -0.83) among females (see Section 4 and appendix for details).

Table 1: Results for HbA1c (%) at Week 26: Treatment-Regimen Estimand, Wash out analysis

	Dula 1.5 mg (N=52)	**Dula 0.75 mg (N=51)**	**Dula Pooled (N=103)**	**Placebo (N=51)**
Baseline mean (SD)	8.2 (1.39)	7.9 (1.27)	8.0 (1.33)	8.1 (1.12)
Change from baseline				
LS Mean (SE)	-0.94 (0.21)	-0.62 (0.21)	-0.78 (0.15)	0.57 (0.21)
Comparison to Placebo				
LS Mean	-1.51	-1.19	-1.35	
95% C.I.	(-2.10, -0.92)	(-1.78, -0.60)	(-1.87, -0.84)	
P-value[a]	< 0.001	< 0.001	< 0.001	

a P-value (2-sided) for superiority

Source: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) Page 67-69, 184

1.4 Conclusions and Recommendation

Statistical findings in this study demonstrated that dulaglutide (pooled and individual doses) is superior in lowering HbA1c compared to placebo with robust and consistent efficacy evidence. Further there is no unacceptable risk in hypoglycemia. I recommend approval of expanding the indication for the treatment of T2DM to pediatric patients aged 10 to less than 18 years old.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Dulaglutide s.c. (Trulicity) is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist and is approved at 0.75mg, 1.5mg, 3mg, and 4.5mg dosage levels as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, and to reduce the risk of major adverse cardiovascular events in adults with T2DM who have established cardiovascular disease or multiple cardiovascular risk factors. The sponsor is seeking to expand the product label to include patients 10 years of age to less than 18 years old. Pediatric patients will be able to initiate dulaglutide at 0.75mg subcutaneously once weekly and if additional glycemic control is needed, increase to a maximum dose of 1.5mg once weekly after at least 4 weeks on the 0.75mg dose.

2.1.2 History of Drug Development

Dulaglutide was approved in 2014 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In 2020, dulaglutide was approved to reduce the risk of major adverse cardiovascular events in adults with T2DM who have established cardiovascular disease or multiple cardiovascular risk factors.

For this study, discussion of a sample size re-estimation began in the early stages and was tentatively planned, however, was never performed until in late 2019. In 2019, due to concerns that the study was overpowered, the FDA recommended the sponsor perform a variance check. The sponsor performed the blinded variance check, and the standard deviation was estimated to be 1.4. The sponsor also updated the assumed treatment effect size to be -0.8 and confirmed the study was still adequately powered (91%) and no increase or reduction was made to the sample size (N=154).

In version 6 of the SAP (January 24, 2018), the sponsor removed the appendix for the analysis windows, and opted to use the collected visit number to simplify the programming process. FDA responded that an appropriate analysis window and analysis visit number based on the window should be included in the SAP (review entered in DARRTS on December 4, 2019). The advice letter containing this comment was sent to the sponsor on November 25, 2019, however, the sponsor did not follow-up and the final version of the SAP (dated February 18, 2021) does not include a pre-specified analysis window. Database lock occurred on February 7, 2022.

2.1.3 Specific Studies Reviewed

Table 2 below summarizes study GBGC. This review details the statistical methodology and results of the primary and key secondary endpoints, subgroup analyses, and a brief review of safety

endpoints. The first and last patient visit dates are December 29, 2016, and January 12, 2022, respectively. Regarding the COVID-19 pandemic, the sponsor concludes that patient safety and standards were maintained, and the primary and key secondary objectives were all achieved with minimal missing data due to the pandemic, and that the pandemic did not have an impact on efficacy and safety results of the study.

Table 2: Study Synopsis Included in the Submission

Study number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
H9X-MC-GBGC	Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-arm	26 weeks	26-week open-label period followed by a 30-day safety follow-up period	52 on Dula 1.5mg 51 on Dula 0.75mg 51 on Placebo	Pediatrics with T2DM with or without metformin and/or basal insulin

2.2 Data Sources

The datasets (SDTM and ADAM) and final study report were submitted electronically as an eCTD submission. The submission can be accessed through the following link:

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The following documents were used to support this review.

Document
Clinical Study Report
Documentation of Statistical Methods
Protocol/Statistical Analysis Plan
Regulatory Response to Information Request submitted on September 9, 2022

All results presented in this review are based on data derived from the submitted datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are no statistical issues concerning the submission of datasets and files. The quality and integrity met regulatory standards.

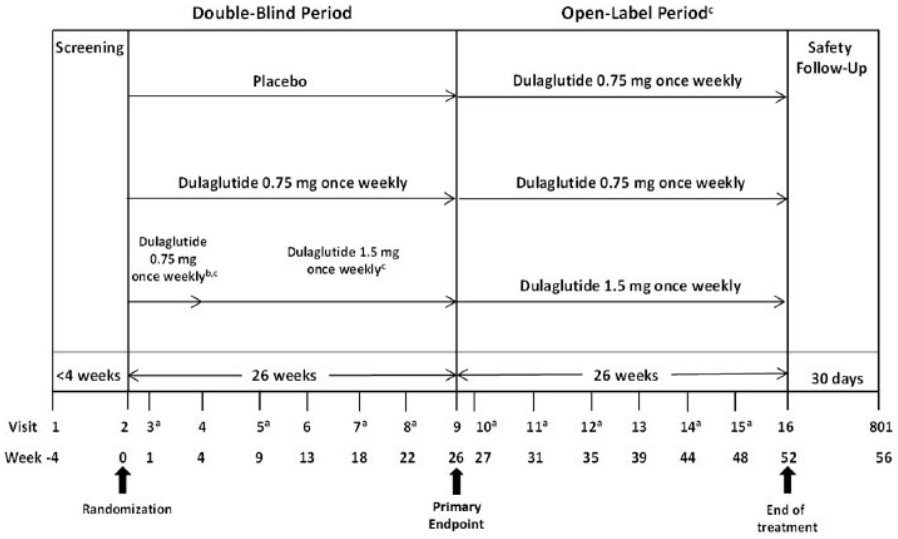
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

Study H9X-MC-GBGC was a multi-center, randomized, double-blind, placebo-controlled, parallel-arm trial, with a 26-week double-blind period, followed by a 26-week open label period 4-weeks of safety follow-up. The primary objective was to test the hypothesis that dulaglutide (pooled 0.75mg and 1.5mg doses, and individual doses) given subcutaneously once a week for 26 weeks to children and adolescents with T2DM who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin is superior to placebo in the treatment of T2DM. Patients were randomized in a 1:1:1 fashion to dulaglutide 1.5mg, 0.75mg, or placebo. At randomization, patients were stratified by background therapy of insulin and metformin usage and screening HbA1c. Patients started on 0.75mg at randomization and if tolerated in the opinion of the investigator increased to 1.5mg at week 4. Figure 1 below illustrates the study design:

Figure 1: Design for Study GBGC



a Phone visits.
b Patients who tolerate the 0.75 mg/week dose in the opinion of the investigator will be changed to dulaglutide 1.5 mg/week at Week 4.
c If patients do not tolerate the higher dose, they will be allowed to go back to the previous dose.

Source: CSR Page 33

The population for the study consisted of male (n=44) and female (n=110) patients who were at least 10 years of age and no more than 17 years of age, and who had T2DM as diagnosed by the Global International Diabetes Foundation/International Society for Pediatric and Adolescent Diabetes criteria. Further, patients were required to have had an HbA1c measurement greater than 6.5% and less than or equal to 11% at screening, unless the patient was newly diagnosed and only

treated with lifestyle measures, in which case their HbA1c was to be greater than 6.5% and less than or equal to 9.0% at screening.

Primary Endpoint

The primary endpoint is change from baseline to week 26 in HbA1c (%-point).

Key Secondary Endpoints

1. Changes from baseline to week 26 in HbA1c (%) for dulaglutide 1.5mg
2. Changes from baseline to week 26 in HbA1c (%) for dulaglutide 0.75mg
3. Percentage of patients with HbA1c < 7.0% at week 26
    - Pooled, 1.5mg, and 0.75mg dulaglutide
4. Change from baseline to week 26 in FBG (mg/dL)
    - Pooled, 1.5mg, and 0.75mg dulaglutide
5. Change from baseline to week 26 in BMI (kg/m^2)
    - Pooled, 1.5mg, and 0.75mg dulaglutide

3.2.2 Statistical Methodologies

Protocol Specified Primary Analysis

- Definitions:
    - Intention to Treat (ITT): All randomized patients who took at least 1 dose of study medication for an assigned treatment arm

- Primary estimand: Treatment regimen estimand
    - Treatment condition: Dulaglutide 1.5mg, Dulaglutide 0.75mg, or Placebo
    - Variable/Endpoint: Change from baseline to week 26 in HbA1c
    - Population: All randomized patients who took at least 1 dose of study medication for an assigned treatment arm
    - Intercurrent events:
        - Initiation of rescue medication
        - Treatment discontinuation

      Handling of data after intercurrent events: All available data, regardless of initiation of rescue medication or treatment discontinuation will be used in the analysis
    - Population level summary measure: Mean difference in change from baseline in HbA1c

- Primary analysis model for the treatment regimen estimand:

Step 1: Patients on dulaglutide 1.5mg or 0.75mg with missing week 26 HbA1c measurements, will have their missing data imputed using only baseline and week 26 data from placebo completers. None of the patients' intermediate measurements will be used.

Step 2: Patients on placebo with missing week 26 HbA1c measurements, will have their missing data imputed using baseline, intermediate, and week 26 measurements from placebo completers. The patients' intermediate measurements will be used.

Step 3: For each patient with missing week 26 data, 1000 measurements will be imputed, thus generating 1000 complete datasets. Each dataset will be analyzed using ANCOVA with treatment, metformin use, and insulin use as fixed effects, and baseline HbA1c as a covariate. Rubin's rule will be applied for inference.

- Additional estimands: The sponsor also considered the efficacy estimand, which excludes post-rescue data, and performed analyses for the following audiences:

    - European Medicines Agency (EMA): Efficacy estimand and excluding patients treated at baseline with diet and exercise only who were metformin naïve from the ITT population
    - All other audiences: Efficacy estimand

This review will focus on results under the treatment regimen estimand as the most appropriate in this study.

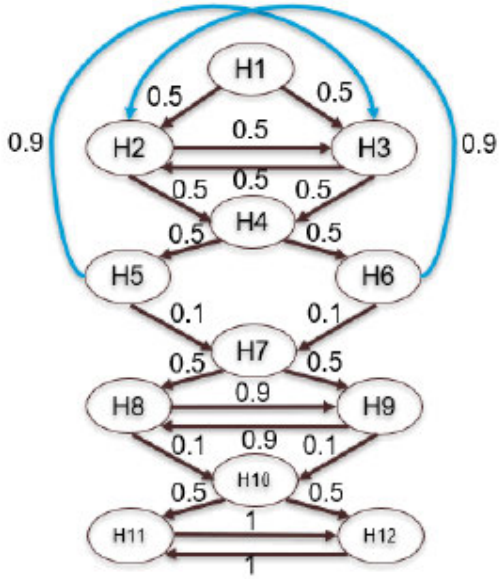
- Reviewer's sensitivity analysis for the primary endpoint:

A 2-way tipping point analysis for the treatment regimen estimand was performed to assess the robustness of the primary analysis with respect to missing data assumptions. The analysis is performed by beginning with the primary analysis described above, followed by adding positive (detrimental) penalties to pooled dulaglutide and negative (beneficial) penalties to placebo, and considering when results tip from superiority of pooled dulaglutide to inconclusive, and then considering the clinical plausibility of such scenarios.

Protocol Specified Control of Type-I Error

A graphical testing scheme was used to control two-sided alpha level = 0.05 in Figure 2 below. From the figure, H1, H4, H7, and H10 test pooled dulaglutide against placebo and is the gatekeeper to the individual doses.

Figure 2: Graphical Testing Scheme for Study GBGC



Source: The sponsor's statistical analysis plan (SAP) Page 23

H_1: Superiority of pooled dulaglutide versus placebo in HbA1c
H_2: Superiority of dulaglutide 1.5mg versus placebo in HbA1c
H_3: Superiority of dulaglutide 0.75mg versus placebo in HbA1c
H_4: Superiority of pooled dulaglutide versus placebo in % of patients achieving HbA1c < 7.0%
H_5: Superiority of dulaglutide 1.5mg versus placebo in % of patients achieving HbA1c < 7.0%
H_6: Superiority of dulaglutide 0.75mg versus placebo in % of patients achieving HbA1c < 7.0%

H_7: Superiority of pooled dulaglutide versus placebo in FBG
H_8: Superiority of dulaglutide 1.5mg versus placebo in FBG
H_9: Superiority of dulaglutide 0.75mg versus placebo in FBG

H_{10}: Superiority of pooled dulaglutide versus placebo in BMI
H_{11}: Superiority of dulaglutide 1.5mg versus placebo in BMI
H_{12}: Superiority of dulaglutide 0.75mg versus placebo in BMI

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics and baseline characteristics are displayed in Table 3 below. The population consisted of 71.4% females, while 61.0% were at least 14 years of age and 54.5% were white. Further, 47.4% were from the United States. Overall, demographics were generally balanced between treatment arms. There were slightly less Whites and African Americans and more Asians on placebo compared to dulaglutide 1.5mg and 0.75mg. Among Region (US vs Non-US), there was a slight imbalance, with more patients on dulaglutide 1.5mg having more patients in the United States than dulaglutide 0.75mg and placebo. Subgroup analyses for Race (White vs Others) and Region (US vs Non-US) were performed to check for differences.

Table 3: Demographics and Baseline Characteristics

	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Placebo (N=51)	Total (N=154)
Sex [n(%)]				
Male	18 (34.6)	16 (31.4)	10 (19.6)	44 (28.6)
Female	34 (65.4)	35 (68.6)	41 (80.4)	110 (71.4)
Age (years)				
Mean (SD)	14.7 (1.8)	14.7 (2.2)	14.2 (2.1)	14.5 (2.0)
Age Group [n(%)]				
< 14	19 (36.5)	16 (31.4)	25 (49.0)	60 (39.0)
≥ 14	33 (63.5)	35 (68.6)	26 (51.0)	94 (61.0)
Race [n(%)]				
American Indian or Alaska Native	4 (7.7)	6 (11.8)	6 (11.8)	16 (10.4)
Asian	4 (7.7)	4 (7.8)	11 (21.6)	19 (12.3)
Black or African American	9 (17.3)	9 (17.6)	5 (9.8)	23 (14.9)
Native Hawaiian or other Pacific Islander	0	0	1 (2.0)	1 (0.6)
White	30 (57.7)	29 (56.9)	25 (49.0)	84 (54.5)
Multiple	3 (5.8)	1 (2.0)	3 (5.9)	7 (4.5)
Missing	2 (3.8)	2 (3.9)	0	4 (2.6)
Region [n(%)]				
US	29 (55.8)	22 (43.1)	22 (43.1)	73 (47.4)
Non-US	23 (44.2)	29 (56.9)	29 (56.9)	81 (52.6)
Metformin [n(%)]				
Yes	46 (88.5)	44 (86.3)	46 (90.2)	136 (88.3)
No	6 (11.5)	7 (13.7)	5 (9.8)	18 (11.7)
Insulin [n(%)]				
Yes	15 (28.8)	13 (25.5)	15 (29.4)	43 (27.9)
No	37 (71.2)	38 (74.5)	36 (70.6)	111 (72.1)
HbA1c (%)				
Mean (SD)	8.16 (1.39)	7.92 (1.27)	8.14 (1.12)	8.08 (1.26)
Min, max	(6.3, 12.5)	(5.4, 11.4)	(6.5, 10.7)	(5.4, 12.5)
HbA1c category [n(%)]				
< 8.0%	25 (48.1)	25 (49.0)	20 (39.2)	70 (45.5)
≥ 8.0%	27 (51.9)	26 (51.0)	31 (60.8)	84 (54.5)
Duration of diabetes (years)				
Mean (SD)	2.1 (1.6)	1.8 (1.8)	2.0 (1.8)	2.0 (1.7)
Min, max	(0, 6)	(0, 7)	(0, 9)	(0, 9)

Source: Statistical Reviewer's Analysis and CSR Page 55

The patient disposition is displayed in Table 4 below. The proportion of patients on both dulaglutide arms who completed the 26-week treatment period were ~96%, while the proportion of patients on placebo who completed the 26-week treatment period was ~92%. Adverse events were the primary reason for treatment discontinuation on both arms. Further, 139 (90.3%) patients completed the final Week 52 endpoint visit.

Table 4: Patient Disposition

	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Placebo (N=51)	Total (N=154)
Randomized and treated with at least 1 dose [n(%)]	**52 (100.0)**	**51 (100.0)**	**51 (100.0)**	**154 (100.0)**
Completed 26-week treatment period [n(%)]	**50 (96.2)**	**49 (96.1)**	**47 (92.2)**	**146 (94.8)**
On study drug	50	48	47	145
Off study drug	0	1	0	1
Study discontinuation before 26 weeks [n(%)]	**2 (3.8)**	**2 (3.9)**	**4 (7.8)**	**8 (5.2)**
Adverse Event [n(%)]	1	0	1	2
Physician Decision [n(%)]	0	0	1	1
Protocol Deviation [n(%)]	0	0	1	1
Withdrawal by subject [n(%)]	0	1	1	2
Withdrawal by parent [n(%)]	1	0	0	1
Lost to follow-up [n(%)]	0	1	0	1

Source: CSR Page 48-49

3.2.4 Results and Conclusions

Data capture for the primary endpoint

Table 5 below summarize the amount of observed week 26 measurements for the primary endpoint. The percent of overall missing data is 7.8%.

Table 5: Summary of Data Capture at Week 26

	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Placebo (N=51)	Total (N=154)
Randomized and took at least one dose [n (%)]	52 (100.0)	51 (100.0)	51 (100.0)	154 (100.0)
Observed week 26 data [n (%)]	47 (90.4)	48 (94.1)	47 (92.2)	142 (92.2)
On treatment [n]	47	47	47	141
Off treatment [n] (Retrieved Drop-outs)	0	1	0	1
Missing week 26 data [n (%)]	5 (9.6)	3 (5.9)	4 (7.8)	12 (7.8)
Study discontinuation [n]	2	2	4	8
Missed week 26 but on treatment and in study [n]	3	1	0	4

Source: Statistical Reviewer's Analysis

Results of the Protocol Specified Analysis of the Primary Endpoint

Table 6 below display the results for the protocol specified analysis for the primary endpoint of HbA1c. Change from baseline in HbA1c at week 26 for pooled dulaglutide is -0.78% and 0.57% for placebo. The treatment effect of pooled dulaglutide relative to placebo is -1.35% with 95% CI: (-1.87, -0.84) and p-value < 0.001, therefore pooled dulaglutide is superior to placebo in reducing HbA1c. Further, the treatment effect of dulaglutide 1.5mg relative to placebo is -1.51% with 95% CI: (-2.10, -0.92), and likewise, the treatment effect of dulaglutide 0.75mg relative to placebo is -1.19% with 95% CI: (-1.78, -0.60). Thus, the individual doses are superior to placebo in reducing HbA1c.

Table 6: Results for HbA1c (%) at week 26

	Dula 1.5 mg (N=52)	**Dula 0.75 mg (N=51)**	**Dula Pooled (N=103)**	**Placebo (N=51)**
Baseline mean (SD)	8.2 (1.39)	7.9 (1.27)	8.0 (1.33)	8.1 (1.12)
Change from baseline				
LS Mean (SE)	-0.94 (0.21)	-0.62 (0.21)	-0.78 (0.15)	0.57 (0.21)
Comparison to Placebo				
LS Mean	-1.51	-1.19	-1.35	
95% C.I.	(-2.10, -0.92)	(-1.78, -0.60)	(-1.87, -0.84)	
P-value	< 0.001	< 0.001	< 0.001	

Protocol specified analysis is based on multiple imputation placebo wash-out model. 1000 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, insulin use, and metformin use as fixed effects and baseline HbA1c as a covariate. The analysis was performed in the ITT using all observed data. Source: Statistical Reviewer's Analysis and CSR Page 67-69, 184

2-Way Tipping Point Analysis

A 2-way tipping point analysis was performed to assess the robustness of the primary analysis with respect to missing data assumptions. The 2-way tipping point analysis is with respect to the primary analysis as described in steps 1-3 in Section 3.2.2. Positive (detrimental) penalties were added to pooled dulaglutide, and negative (beneficial) penalties were added to placebo. The results are shown in Figure 3 below. The point (0, 0) represents the results of the primary analysis (upper right hand in the figure). The x-axis represents the penalties added to the imputed values for placebo, and the y-axis represents the penalties added to the imputed values for pooled dulaglutide. Each unit is worth 0.9 penalty. For example, the point (-1, 0) means a penalty of -0.9 was added to placebo and no penalty added to pooled dulaglutide. Likewise, the point (-6, 7) means a penalty of -5.4 was added to placebo and a penalty of 6.3 was added to pooled dulaglutide.

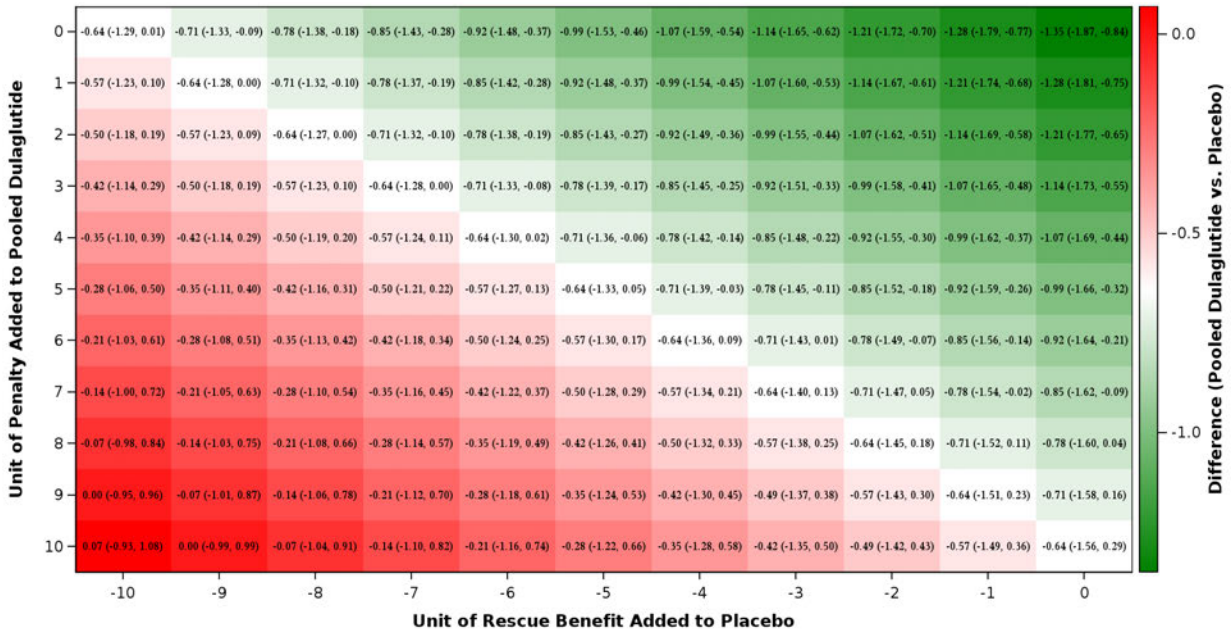
From the primary analysis, the average imputed change for the 8 patients with missing data on dulaglutide is 0.48%, and the average imputed change for the 4 patients with missing data on placebo is 1.20%. Let us consider the following scenarios where the results would tip the conclusion, and the clinical plausibility:

i. When the penalty on dulaglutide is 0, the penalty on placebo needed is ~ -9.0%. This is clearly not possible. Likewise, when the penalty on placebo is 0, the penalty on dulaglutide needed is ~ 7.2%, which is clearly not possible.

ii. The 8 patients on dulaglutide experience a penalty of 0.9%, so that the average increase is 1.38%, almost triple from what was observed. To tip results, the average imputed change for the 4 patients on placebo is ~ -8.1%. This is clearly not possible

Thus, the robustness of the primary analysis with respect to missing data assumptions under the treatment regimen estimand is confirmed.

Figure 3: HbA1c – Two-Way Tipping Point Analysis (Heatmap) for the Primary Endpoint



Each unit = 0.9.
Each cell contains the mean difference and 95% CI between pooled dulaglutide and placebo.
The x-axis represents the penalties added to the imputed values for placebo, and the y-axis represents the penalties added to the imputed values for pooled dulaglutide.
Source: Statistical Reviewer's Analysis.

Patient level residual standard deviation and power calculations

Prior to the blinded variance check, the power calculations were:

- N=154, Δ = -0.65, SD=1.0%, Power=97%

After the blinded variance check, the power calculations were:

- N=154, Δ = -0.80, SD=1.4%, Power=91%

The observed patient level residual standard deviation from the sponsor's pre-specified analysis is 1.48%, which is approximate to the newly assumed standard deviation from the blinded variance check for 91% study power. Since the observed treatment effect for pooled dulaglutide is -1.35 with SD of 1.48%, we conclude that the study was adequately powered with a larger treatment effect and similar SD to the assumptions in the study power calculation.

HbA1c (%) measurements out of visit window

The final version of the SAP did not include a pre-specified analysis window. If we consider +/- 7-days from Day 182 for the Week 26 visit, the resulting window is [175, 189]. Of the available 142 HbA1c measurements, 118 (83.1%) are within the window. If we consider +/- 14-days from Day 182, the window is [168, 196]. Here, 134 measurements (94.4%) are within the window. The primary analysis of change from baseline to Week 26 in HbA1c include the earliest analysis day as Day 165 and the latest analysis day as Day 218. Given the stability of glucose control as measured by HbA1c, a 2-week window of assessments (e.g., Week 24 to Week 28 for Week 26 visit) has been commonly used in diabetes trials.

To address this issue, sensitivity analyses were performed considering the observed data outside the window as missing under two different window sizes. After considering the 24 measurements outside the 1-week window as missing, the treatment effect of pooled dulaglutide relative to placebo is -1.19% with 95% CI: (-1.75, -0.63). After considering the 8 measurements outside the 2-week window as missing, the treatment effect of pooled dulaglutide relative to placebo is -1.27% with 95% CI: (-1.81, -0.73). Hence, given the potent effect of dulaglutide, the impact of measurements outside a reasonable visit window does not change the conclusion that dulaglutide is superior to placebo in reducing HbA1c.

Key Secondary and Other Secondary Endpoints

Results for Key Secondary Endpoints

Since the primary endpoint for pooled dulaglutide and individual doses are significant in HbA1c, formal testing moves forward to the proportion of patients with HbA1c < 7.0% at week 26.

- **Proportion of patients with HbA1c < 7.0% at week 26**

Table 7 below summarize the results for the proportion of patients with HbA1c < 7.0% (i.e. responders) at week 26, after considering patients with missing week 26 measurements as non-responders. There are 53 (51.5%) responders on pooled dulaglutide compared to 7 (13.7%) on placebo. The odds ratio comparing pooled dulaglutide to placebo is 8.08 with 95% CI: (3.10, 21.06), and p-value < 0.001, therefore pooled dulaglutide is superior to placebo in helping patients achieve the target goal of HbA1c < 7.0% (p-value <0.001). Likewise, the individual doses of 1.5mg and 0.75mg are superior to placebo in helping patients achieve the target goal of HbA1c < 7.0% at week 26 (p-value's <0.001).

Table 7: Results for % of patients with HbA1c < 7.0% at week 26

	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Dula Pooled (N=103)	Placebo (N=51)
Number of responders at week 26 (%)	25 (48.1)	28 (54.9)	53 (51.5)	7 (13.7)
Odds Ratio	7.43	8.80	8.08	
95% C.I.	(2.60, 21.25)	(3.07, 25.18)	(3.10, 21.06)	
P-value	< 0.001	< 0.001	< 0.001	

Protocol specified analysis is a logistic regression with treatment, insulin use, and metformin use as fixed effects and baseline HbA1c as a covariate. The analysis was performed in the ITT using all observed data. Patients with missing week 26 measurements were considered non-responders.
Source: Statistical Reviewer's Analysis and CSR Page 67-69, 194

Additionally, considering the average number of responders, after imputing missing week 26 measurements in the primary analysis across the 1000 imputations, we have:

- Dula 1.5mg: 25.657 / 52 = 49.34%
- Dula 0.75mg: 28.694 / 51 = 56.26%
- Pooled Dula: 54.351 / 103 = 52.77%
- Placebo: 7.074 / 51 = 13.87%

We see that the average proportion of responders across imputations are similar to the proportion of responders when considering patients with missing week 26 measurements as non-responders.

- **Fasting Blood Glucose (mg/dL)**

Since the primary endpoint for pooled dulaglutide and individual doses are significant in the proportion of patients with HbA1c < 7.0% at week 26, formal testing moves forward to FBG. Table 8 below display the results for the protocol specified analysis for fasting blood glucose (FBG). The treatment effect of pooled dulaglutide relative to placebo is -35.92 with 95% CI: (-54.19, -17.64), and p-value < 0.001, therefore pooled dulaglutide is superior to placebo in reducing FBG. Further, the individual doses are superior to placebo in reducing FBG (p-value's <0.001).

Table 8: Results for Fasting Blood Glucose (mg/dL) at week 26

	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Dula Pooled (N=103)	Placebo (N=51)
N	52	51	103	51
Baseline mean (SD)	162.7 (61.65)	149.3 (60.26)	156.0 (61.04)	159.4 (59.36)
Change from baseline				
LS Mean (SE)	-24.90 (7.45)	-12.84 (7.29)	-18.87 (5.21)	17.05 (7.69)
Comparison to Placebo				
LS Mean	-41.95	-29.88	-35.92	
95% C.I.	(-63.00, -20.89)	(-50.70, -9.07)	(-54.19, -17.64)	
P-value	< 0.001	0.005	< 0.001	

Protocol specified analysis is based on multiple imputation placebo wash-out model. 1000 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, insulin use, metformin use, and baseline HbA1c group as fixed effects and baseline FBG as a covariate. The analysis was performed in the ITT using all observed data.
Source: Statistical Reviewer's Analysis and CSR Page 67-69, 197

- **Body Mass Index (kg/m^2)**

Since the primary endpoint for pooled dulaglutide and individual doses are significant in FBG, formal testing moves forward to BMI. Table 9 below display the results for the protocol specified analysis for body mass index (BMI). The treatment effect for pooled dulaglutide relative to placebo is -0.14, with 95% CI: (-0.62, 0.33), and p-value = 0.553, therefore pooled dulaglutide is not superior to placebo in reducing BMI. Since pooled dulaglutide is a gatekeeper to the individual doses, formal testing stops. We see that the nominal p-values comparing the individual doses to placebo are greater than 0.05.

Table 9: Results for BMI (kg/m^2) at week 26

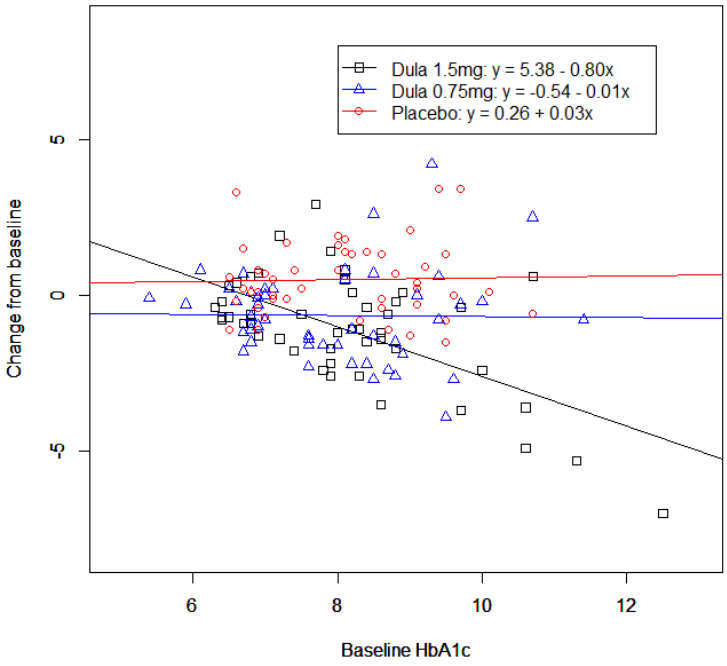
	Dula 1.5 mg (N=52)	Dula 0.75 mg (N=51)	Dula Pooled (N=103)	Placebo (N=51)
N	52	51	103	51
Baseline mean (SD)	34.3 (6.98)	33.6 (9.04)	34.0 (8.03)	34.3 (10.22)
Change from baseline				
LS Mean (SE)	-0.08 (0.19)	-0.18 (0.20)	-0.13 (0.14)	0.01 (0.20)
Comparison to Placebo				
LS Mean	-0.10	-0.19	-0.14	
95% C.I.	(-0.64, 0.45)	(-0.74, 0.35)	(-0.62, 0.33)	
P-value	0.732	0.492	0.553	

Protocol specified analysis is based on multiple imputation placebo wash-out model. 1000 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, insulin use, metformin use, and baseline HbA1c group as fixed effects and baseline BMI as a covariate. The analysis was performed in the ITT using all observed data.
Source: Statistical Reviewer's Analysis and CSR Page 67-69, 207

Baseline HbA1c as an effect modifier

It is well known that baseline HbA1c is an effect modifier, (i.e., the treatment effect on HbA1c change will depend on a patients' baseline HbA1c measurement). Figure 4 below is a scatter plot and regression lines based off the completers from dulaglutide 1.5mg, dulaglutide 0.75mg and placebo. Regression lines were computed and superimposed over the scatter points. Here, the difference in slopes between dulaglutide 1.5mg and placebo is -0.83%, which means that for every 1% increase in baseline HbA1c, the difference in change from baseline ($\Delta_{Dula1.5}$ - $\Delta_{Placebo}$) decreases by 0.83% (i.e., the effect of dulaglutide decreases by 0.83). As an illustration, when baseline HbA1c is 7%, the average change from baseline for dulaglutide 1.5mg and placebo are -0.22% and 0.47%, respectively, which amounts to a difference of -0.69%. However, when baseline HbA1c is 8%, the average change from baseline for dulaglutide 1.5mg and placebo are -1.02% and 0.5%, which amounts to a difference of -1.52%. Hence, the higher the baseline HbA1c, the larger the treatment effect. In the primary analysis, baseline HbA1c was included in the ANCOVA model to adjust for this modification effect. Comparing dulaglutide 0.75mg and placebo, the slopes are almost parallel, so that the treatment effect of dulaglutide 0.75mg relative to placebo changes very little as baseline HbA1c increases. The p-value for a test for no difference in slopes between dulaglutide 1.5mg and placebo is less than 0.001, while the p-value for a test for no difference in slopes between dulaglutide 0.75mg and placebo is 0.85. So, baseline HbA1c modified the treatment effect in the high dose (1.5mg) but not the low dose (0.75 mg).

Figure 4: Scatter Plot and Regression Lines Based off Completers



Source: Statistical Reviewer's Analysis

3.3 Evaluation of Safety

- **Hypoglycemia**

Table 10 below displays the number of patients with at least 1 hypoglycemic episode and the total number of episodes by category, during the 26-week treatment period. All tables and discussion in this section are based off the use of all observed data, including post-rescue records. There were no severe hypoglycemic episodes in the study.

Table 10: Summary of Hypoglycemic Episodes During 26-Week Treatment Period

	Dula 1.5mg (N=52)		**Dula 0.75mg (N=51)**		**Pooled Dula (N=103)**		**Placebo (N=51)**	
Hypoglycemic category	Patients with ≥ 1 episode	# episodes	Patients with ≥ 1 episode	# episodes	Patients with ≥ 1 episode	# episodes	Patients with ≥ 1 episode	# episodes
Severe	0	0	0	0	0	0	0	0
Documented symptomatic hypoglycemia with PG < 54 mg/dL	1	1	1	14	2	15	1	1
All confirmed PG < 54 mg/dL	2	2	2	27	4	29	1	1

Source: Statistical Reviewer's Analysis

For documented symptomatic hypoglycemia with PG < 54mg/dL, each arm had 1 patient who experienced at least 1 episode. For the patient on dulaglutide 1.5mg and the patient on placebo, each only had 1 episode, however, the patient on dulaglutide 0.75mg had 14 episodes. For all confirmed PG < 54mg/dL, there were 2 patients on each of dulaglutide 1.5mg and dulaglutide 0.75mg who experienced at least 1 episode, while there was 1 patient on placebo who experienced at least 1 episode. Each of the 2 patients on dulaglutide 1.5mg had 1 episode, and the patient on placebo had 1 episode, however, the 2 patients on dulaglutide 0.75mg accounted for a total of 27 episodes.

Table 11 below summarize the analyses results for the rate of documented symptomatic hypoglycemia with PG < 54mg/dL and all confirmed PG < 54mg/dL. The 95% confidence interval for dulaglutide 0.75mg relative to placebo for documented symptomatic hypoglycemia with PG < 54mg/dL and for pooled dulaglutide relative to placebo for all confirmed PG < 54mg/dL exclude 1. However, since many episodes on dulaglutide 0.75mg were experienced among only a small number of patients, caution should be taken when interpreting results.

Table 11: Rate Ratios of Hypoglycemia During 26-Week Treatment Period

Hypoglycemic category	Rate Ratio 95% CI Dula 1.5mg/Placebo	Rate Ratio 95% CI Dula 0.75mg/Placebo	Rate Ratio 95% CI Pooled Dula/Placebo
Documented symptomatic hypoglycemia with PG < 54 mg/dL	0.99 (0.08, 13.02)	17.49 (1.20, 255.14)	9.58 (0.84, 109.22)
All confirmed PG < 54 mg/dL	4.46 (0.40, 50.17)	15.10 (0.77, 296.81)	12.98 (1.31, 128.50)

Rate ratio estimated from a negative binomial model using log link and includes treatment, insulin use, metformin use, and baseline HbA1c group as fixed effects, and log (exposure in days/365.25) as an offset variable. The analysis was performed in the ITT using all observed data.
Source: Statistical Reviewer's Analysis and Response to Information Request dated (9/9/22) Page 18, 20, 23-24

Table 12 below summarize the analysis results for the number of patients with at least 1 episode of documented symptomatic hypoglycemia with PG < 54mg/dL and all confirmed PG < 54mg/dL. For documented symptomatic hypoglycemia with PG < 54mg/dL, the odds ratios are between 0.99 and 1.3 for all comparisons, and the 95% confidence intervals include 1. For all confirmed PG < 54mg/dL, the odds ratios are between 1.94 and 2.61 for all comparisons, and the 95% confidence intervals include 1. Therefore, we conclude that dulaglutide does not significantly increase the incidence rate of patients who experience at least 1 episode.

Table 12: Incidence Rates of Hypoglycemia During 26-Week Treatment Period

Hypoglycemic category	Odds Ratio 95% CI Dula 1.5mg/Placebo	Odds Ratio 95% CI Dula 0.75mg/Placebo	Odds Ratio 95% CI Pooled Dula/Placebo
Documented symptomatic hypoglycemia with PG < 54 mg/dL	0.99 (0.06, 15.62)	1.30 (0.07, 24.33)	1.13 (0.09, 13.47)
All confirmed PG < 54 mg/dL	1.94 (0.16, 24.03)	2.61 (0.19, 35.17)	2.23 (0.22, 22.46)

Odds ratio estimated from a binomial model using logit link and includes treatment, insulin use, metformin use, and baseline HbA1c group as fixed effects. The analysis was performed in the ITT using all observed data.
Source: Statistical Reviewer's Analysis

In conclusion, 96.2% of patients on dulaglutide 1.5mg, 96.1% of patients on dulaglutide 0.75mg, and 98% of patients on placebo did not experience a confirmed PG < 54mg/dL. There were 2 patients on dulaglutide 0.75mg who experienced many episodes, and the patient on each of dulaglutide 1.5mg and placebo who did have an episode, only experienced the singular episode. Among the 5 patients who experienced a confirmed PG < 54mg/dL, 4 had an increase in HbA1c (Table 13 in the appendix). Given that most patients did not experience a hypoglycemic episode on dulaglutide, and there were no reported cases of severe hypoglycemia, and that there is potential to receive a large benefit in reduction in HbA1c, we conclude that the benefit of dulaglutide outweighs the risk.

4 Findings in Special/Subgroup Populations

4.1 Sex, Age, and Race

This section summarizes results from the analysis of the primary endpoint within subgroups. The subgroups and levels explored are:

- Age (≤ 14; > 14)
- Sex (Male; Female)
- Race (White; Other races)
- Region (USA; Outside of USA)
- Metformin use (Yes; No)
- Insulin use (Yes; No)

4.1.1 Shrinkage Analyses

Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. Below is the model used in the analysis for age, sex, race, region, metformin use, and insulin use:

$$Y_i \sim N(\mu_i, \sigma_i^2), i = 1, 2$$

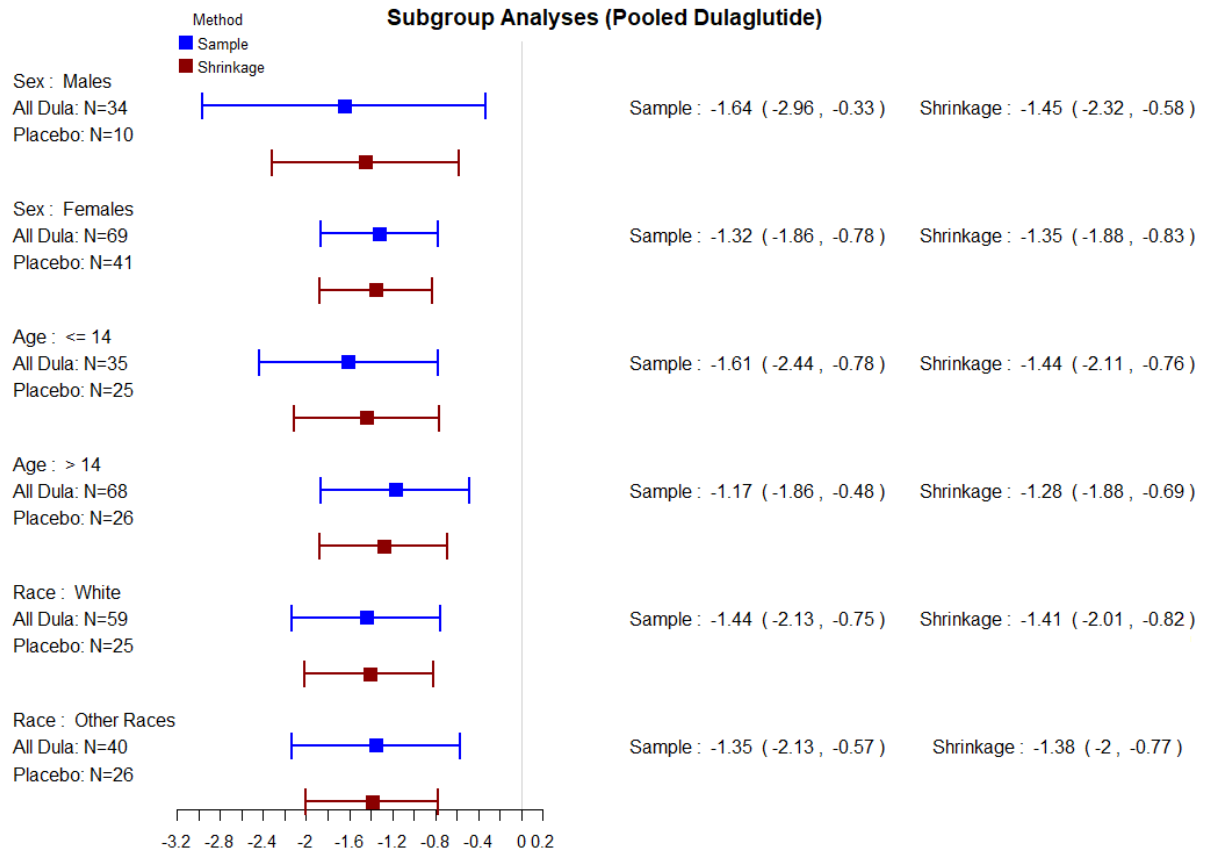
$$\mu_i \sim N(\mu, \tau^2), i = 1, 2$$

$$\mu \sim \mathrm{N}(0, 35), \quad \tau^{-2} \sim Gamma(0.001, 0.001)$$

We assume that before seeing data, the treatment effect is 0 based on one-eighth of a patient on each treatment arm. The patient level residual standard deviation was estimated to be 1.48, thus, the variance of the prior distribution of the treatment effect is $16*1.48^2 \approx 35$.

Figure 5 below is a forest plot which display the results of the subgroup analyses for age, sex, and race, and Figure 6 is a forest plot which display the results for region, metformin use, and insulin use, based off the primary analysis. The plots include point estimates and 95% confidence and credible intervals for the sample and shrinkage estimates, respectively. As expected, the estimates for the treatment effects for levels within each subgroup pull toward each other.

Figure 5: Forest Plot of Subgroup Analyses: Pooled Dulaglutide for Sex, Age, and Race

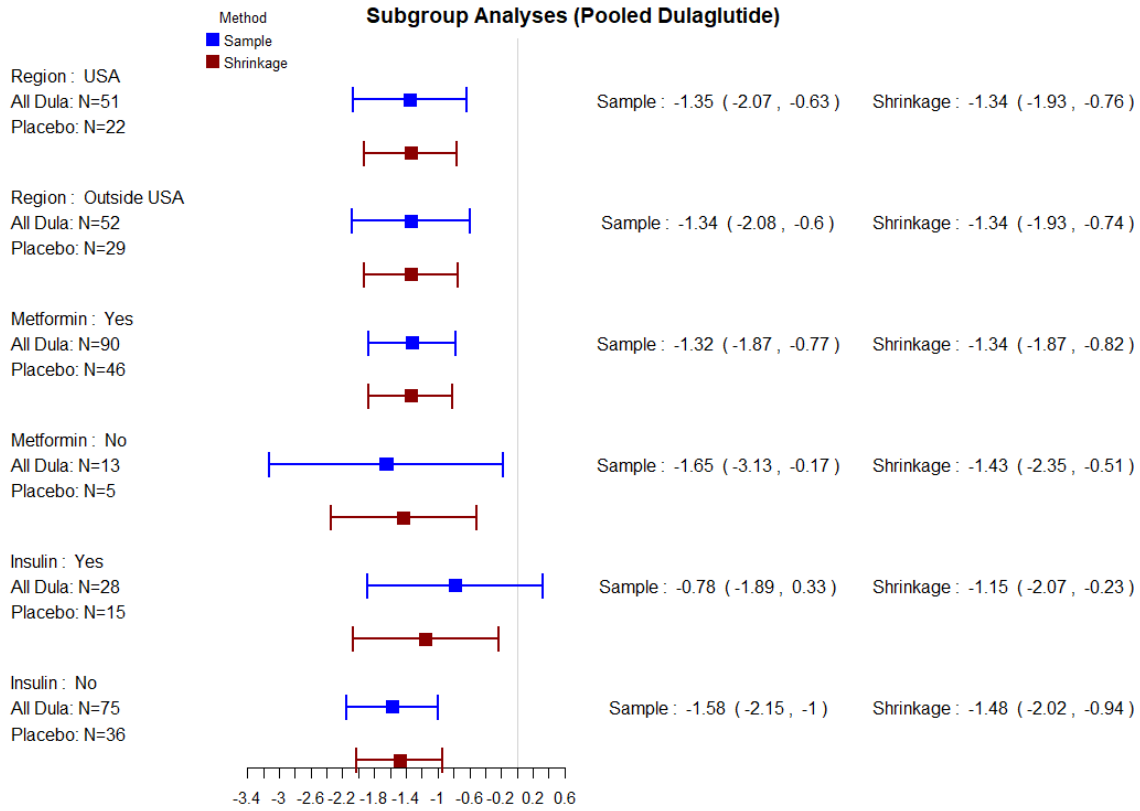


Values less than 0 favor Pooled Dulaglutide
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

Regarding the subgroup of Sex, the small sample size among males explains the wide confidence interval and may partially explain the sponsor's reported interaction p-value (0.023), based on adjusted F-statistics from the error term after merging all imputed datasets[1,2]. However, the average of the interaction p-values over the imputed datasets is 0.77. Similarly, the confidence intervals for males are wide when considering the individual doses of 1.5mg (Figure 7) and 0.75mg (Figure 9). Since the sample size among males is small, caution should be taken when interpreting results. Before shrinkage analysis, the LS mean difference in HbA1c for pooled dulaglutide versus placebo among males is -1.64% (95% CI: -2.96, -0.33), and -1.32% (95% CI: -1.86, -0.78) among females. After shrinkage analysis, the mean difference among males is -1.45% with 95% Credible Interval (-2.32, -0.58), and -1.35% (95% Credible Interval: -1.88, -0.83) among females. After performing the shrinkage analyses, the treatment effects among males and females are more similar, and results are consistent to the primary analysis.

[1] Raghunathan, Trivellore, and Qi Dong. "Analysis of variance from multiply imputed data sets." Ann Arbor: University of Michigan (2011).
[2] van Ginkel, Joost R., and Pieter M. Kroonenberg. "Analysis of variance of multiply imputed data." Multivariate behavioral research 49.1 (2014): 78-91.

Figure 6: Forest Plot of Subgroup Analyses: Pooled Dulaglutide for Region, Metformin use, and Insulin use



Values less than 0 favor Pooled Dulaglutide
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

Results from the subgroup analyses based on Race (White vs Others) and Region (US vs Non-US) showed that treatment effects are consistent and homogenous despite these subgroups having a slight imbalance in patient disposition across arms.

All subgroup levels prior to the shrinkage analyses were nominally significant, except for patients who were on insulin. After the shrinkage analyses, the treatment effect for patients on insulin flipped from non-significant to nominally significant. In conclusion, subgroup results are homogeneous to the primary results for superiority of pooled dulaglutide compared to placebo. Shrinkage analyses results for individual doses are included in the appendix.

5 Summary and Conclusions

5.1 Statistical Issues

There are no major statistical issues, as the amount of missing data is 7.8%, and the sponsor's pre-specified analysis for addressing missing data via a multiple imputation, wash-out analysis, based on placebo completers, under the treatment regimen estimand is appropriate.

The two minor issues and resolution are summarized as follows:

1) Against our recommendation, the sponsor removed the pre-specified analysis window from the SAP. Also, due to the COVID-19 impact, visit windows were extended. Additional sensitivity analyses for the primary endpoint were performed using a window of 7 and 14 days from the analysis target date, and results are robust and supportive for the primary analysis.

2) The applicant reported a statistically significant treatment-by-sex interaction effect (p-value =0.023) using merged F-statistics of error terms across imputed datasets compared to the Agency's analysis (p-value=0.77) computed using the average p-values of the interaction terms across imputed data sets. Shrinkage analyses were performed and alleviates any concerns that the difference in treatment effects between females and males were due to a random low/high. The consistent and homogeneous treatment effects for both females and males support the superiority of dulaglutide compared to placebo in pediatric patients with T2DM.

5.2 Collective Evidence

Pooled dulaglutide is superior in reducing HbA1c compared to placebo, and the estimated treatment effect is -1.35% (95% CI: -1.87, -0.84). Patients on pooled dulaglutide experienced an average reduction of ~0.78% compared to an average increase of ~0.57% for patients on placebo (Table 6). The individual doses of 1.5mg and 0.75mg are also superior in reducing HbA1c compared to placebo. In addition, a 2-way tipping point analysis confirmed the robustness of the conclusion that pooled dulaglutide is superior to placebo in reducing HbA1c with respect to missing data assumptions. Further, subgroup analyses demonstrated that results are homogeneous to the primary results for superiority of pooled dulaglutide compared to placebo (Figure 5 and Figure 6).

The key secondary endpoints of the proportion of patients achieving HbA1c less than 7.0% at week 26 (Table 7) and fasting blood glucose (Table 8) for pooled dulaglutide and the individual doses are significant. However, BMI was not statistically significant, although patients on pooled dulaglutide and the individual doses did numerically experience a reduction in BMI, on average, compared to patients on placebo (Table 9).

The safety profile is considered acceptable (Table 10, Table 11, and Table 12). There were no reported cases of severe hypoglycemic episodes during the study and 96% of patients on both dulaglutide arms did not have a confirmed PG < 54mg/dL. The proportion of patients with at least

1 episode are similar between dulaglutide and placebo. No notable increase of risk of dulaglutide was identified in this study.

5.3 Conclusions and Recommendations

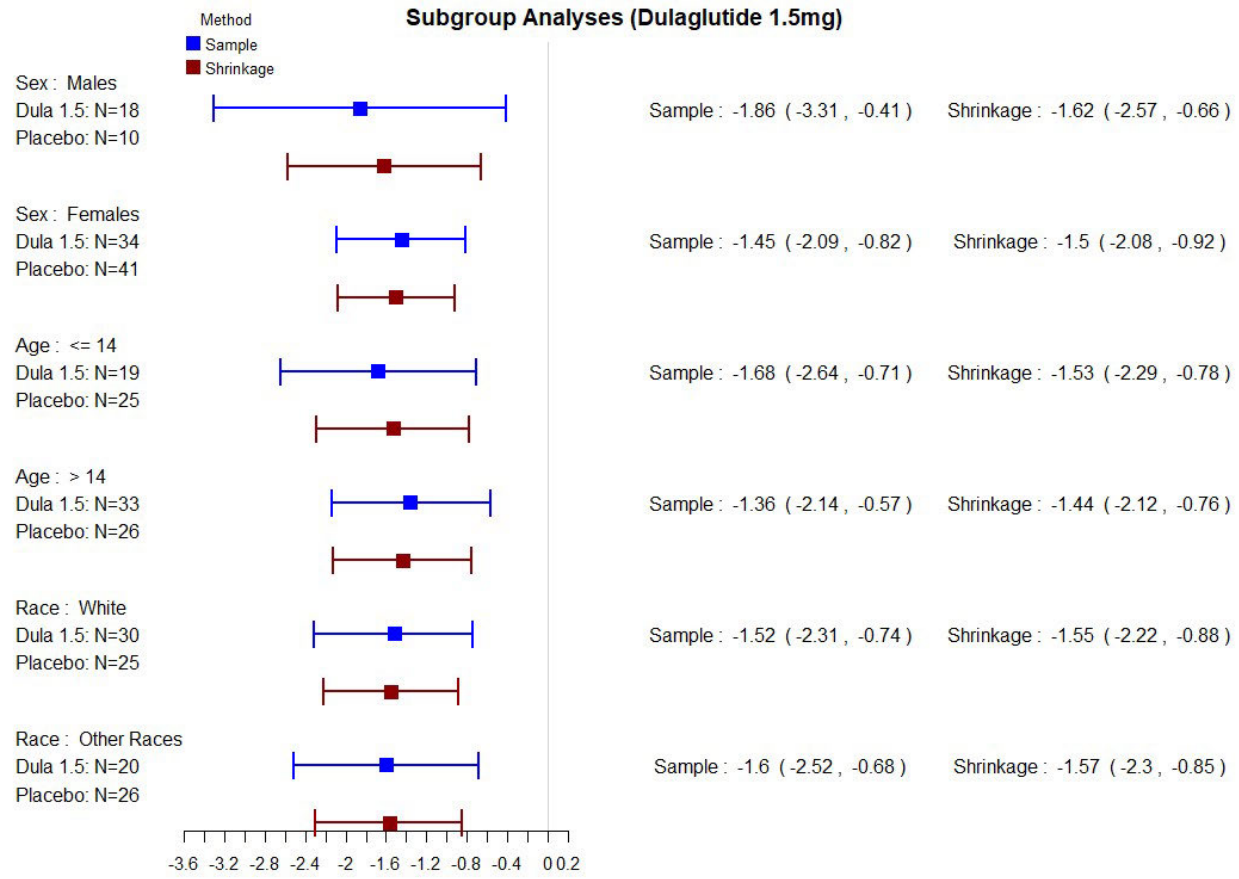
Dulaglutide (1.5 mg, 0.75 mg, and pooled) is superior in reducing HbA1c compared to placebo in pediatric patients (between 10 and less than 18 years of age) with T2DM. Considering the comparable safety profile, the benefit of pediatrics initiating dulaglutide outweighs the risk. Therefore, I recommend approval of updating the indication, dosage, administration, and clinical studies section to allow pediatric patients to initiate dulaglutide.

5.4 Labeling Recommendations

The sponsor proposed adding the study GBGC results with a result table including changes in HbA1c, percentage of subjects achieving HbA1c <7.0%, and FBG to appear in the product label in Section 14 CLINICAL STUDIES. Labeling negotiation is under way and this reviewer suggested adding information of missing data percentages and more details of the analysis model in the footnotes.

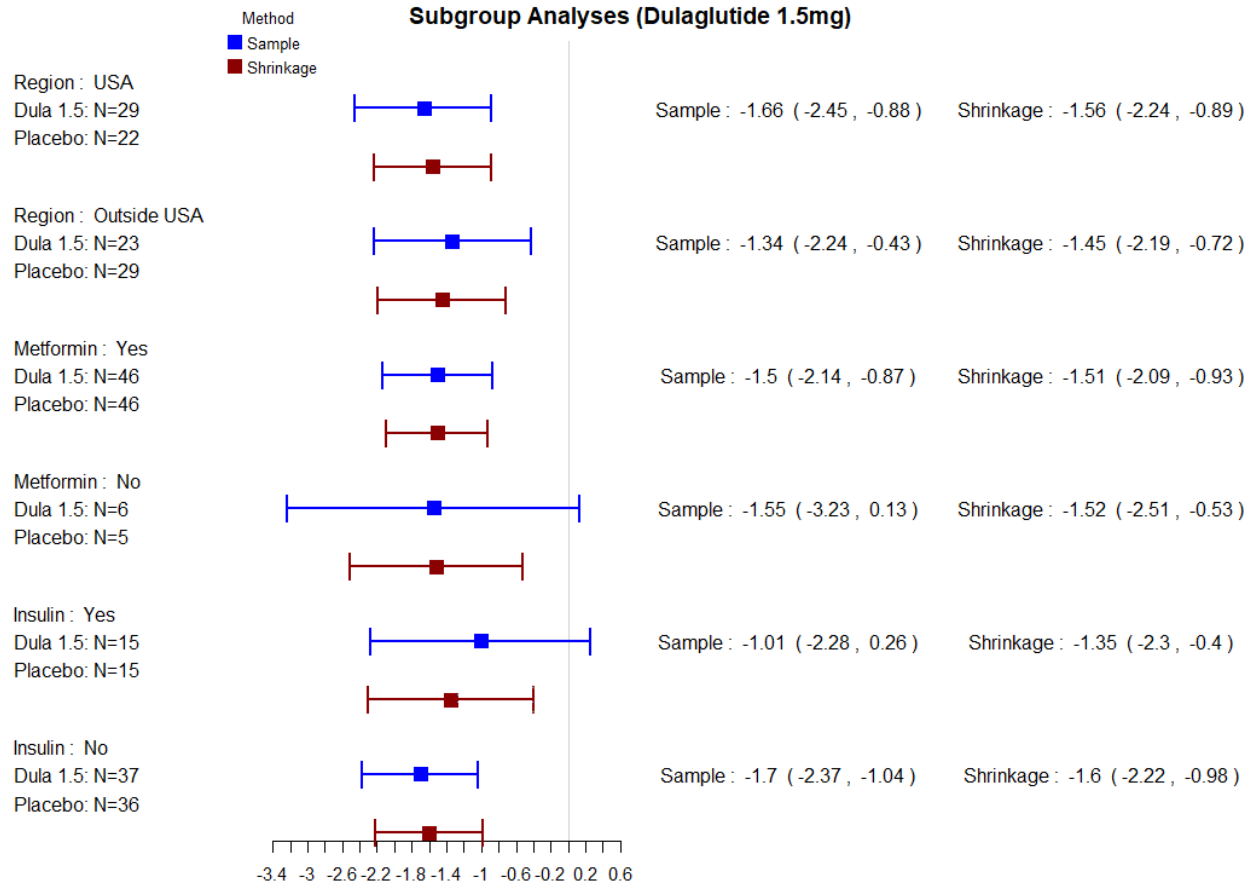
6 Appendix

Figure 7: Forest Plot of Subgroup Analyses: Dulaglutide 1.5mg for Sex, Age, and Race



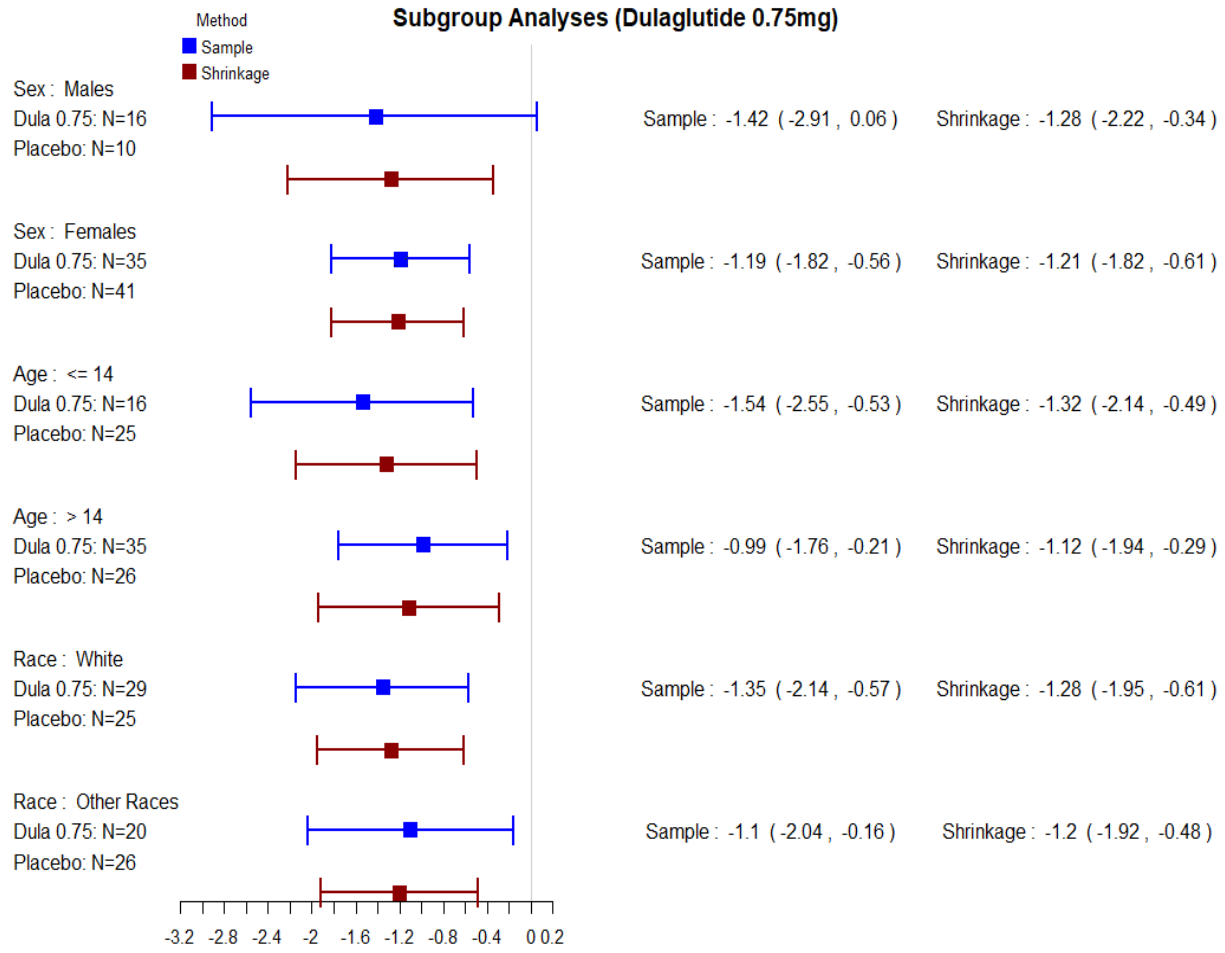
Treatment effects are measured by difference in least squares means
Values less than 0 favor Dulaglutide 1.5mg
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

Figure 8: Forest Plot of Subgroup Analyses: Dulaglutide 1.5mg for Region, Metformin use, and Insulin use



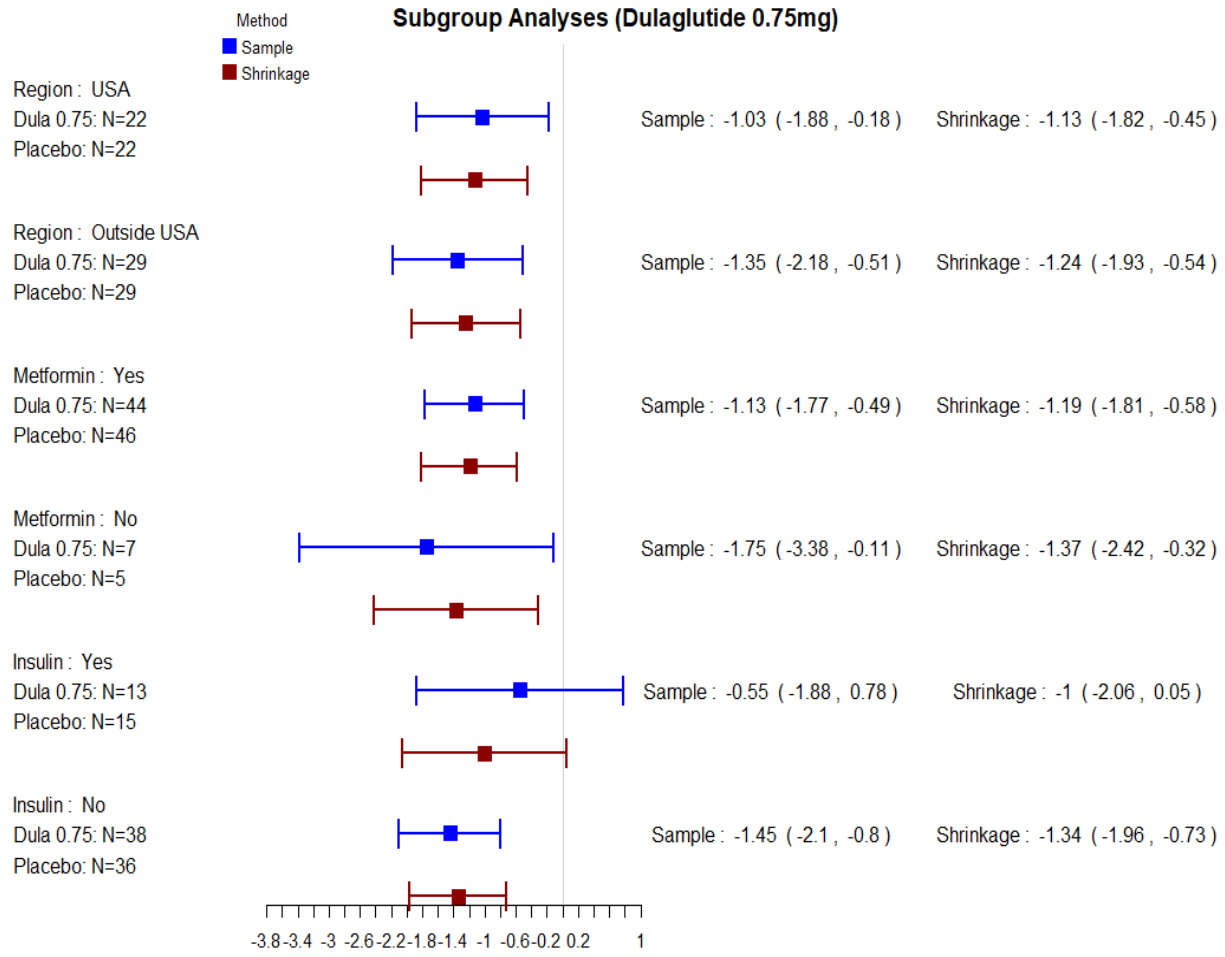
Treatment effects are measured by difference in least squares means
Values less than 0 favor Dulaglutide 1.5mg
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

Figure 9: Forest Plot of Subgroup Analyses: Dulaglutide 0.75mg for Sex, Age, and Race



Treatment effects are measured by difference in least squares means
Values less than 0 favor Dulaglutide 0.75mg
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

Figure 10: Forest Plot of Subgroup Analyses: Dulaglutide 0.75mg for Region, Metformin use, and Insulin use



Treatment effects are measured by difference in least squares means
Values less than 0 favor Dulaglutide 0.75mg
Parentheses indicate 95% Confidence/Credible intervals for sample and shrinkage estimates, respectively
Source: Statistical Reviewer's Analysis

Table 13: Profile for Patients with at least 1 episode During 26-Week treatment Period

Documented symptomatic hypoglycemia with PG < 54 mg/dL

Patient	Arm	# Episodes	Baseline HbA1c	Week 26 HbA1c	Change in HbA1c
(b) (6)	Dula 0.75	14	8.5	11.1	2.6
	Dula 1.5	1	7.2	5.8	-1.4
	Placebo	1	8.1	9.9	1.8

All confirmed PG < 54 mg/dL

Patient	Arm	# Episodes	Baseline HbA1c	Week 26 HbA1c	Change in HbA1c
(b) (6)	Dula 0.75	14	8.5	11.1	2.6
	Dula 0.75	13	6.1	6.9	0.8
	Dula 1.5	1	7.2	5.8	-1.4
	Dula 1.5	1	6.5	6.8	0.3
	Placebo	1	8.1	9.9	1.8

Source: Statistical Reviewer's Analysis

Table 13 displays the patient profile for those who experienced at least 1 episode of documented symptomatic hypoglycemia with PG < 54mg/dL and all confirmed PG < 54mg/dL. We see that the patient on dulaglutide 0.75mg who experienced 14 episodes, had a change in HbA1c of 2.6, and the patient on dulaglutide 1.5mg who experienced 13 episodes for all confirmed PG < 54mg/dL, had a change in HbA1c of 0.8. Of the 5 patients in the table, only 1 had a decrease in HbA1c.

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