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 202293, 205649
Supplement #:	S-031, S-022
Drug Name:	Farxiga (dapagliflozin) tablets, Xigduo XR (dapagliflozin and metformin HCl extended release) tablets
Indication(s):	As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus
Applicant:	AstraZeneca
Date(s):	Date Received: December 10, 2023 PDUFA date: June 12, 2024
Review Priority:	Priority
Biometrics Division:	DB II
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Keywords:

Type 2 diabetes, pediatric study, SGLT-2 inhibitor, shared control, second randomization, placebo washout imputation

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1 EXECUTIVE SUMMARY

The applicant, AstraZeneca, submitted NDA 202293 S-031 for Farxiga (dapagliflozin, or dapa) and NDA 205649 S-022 for Xigduo XR (dapagliflozin and metformin HCI extended release, or dapa + HCI), in support of product label updates with respect to the pediatric indication. The label updates of both products were based on a single Phase 3 pediatric trial titled "A 26-Week, Multicentre, Randomised, Placebo-Controlled, Double-Blind, Parallel-Group, Phase III Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus Who Are Between 10 and Below 18 Years of Age" (D1680C00019). The study was conducted to satisfy the pediatric PMR-3199-1, which applies to all drug products containing dapa, dapa + HCI and saxagliptin. This review is focused on dapa and dapa+HCI. For saxagliptin, refer to statistical review under NDAs 022350 and 200678.

The two drug products containing dapa are currently indicated for treatment of adult patients with type 2 diabetes mellitus (T2DM) as adjuncts to diet and exercise. In the current submissions, the applicant proposed to expand the T2DM indication to the pediatric population aged 10 to 17 years for dapa and dapa + HCI.

1.1 Brief overview of Clinical Study

The Study D1680C00019 was a multicentre, placebo-controlled, double-blinded, parallel-group, phase III study intended to evaluate the efficacy and safety of dapa 5 mg and 10 mg vs. placebo after 26 weeks of treatment in children and adolescents with T2DM. A total of 157 subjects were randomized in a 1:1 ratio to one of the two treatment arms: dapa 5 mg or placebo. At Week 14, non-responders [1] underwent a second randomization to either 10 mg or 5 mg (dapa or matching placebo) in a 1:1 ratio. The primary endpoint is HbA1c change from baseline at Week 26.

1.2 Major Statistical Issues

The overall missing rate of primary efficacy endpoint was 7.4% for dapa, and 7.9% for placebo. Missing data were handled appropriately by placebo washout method that was agreed by Agency.

Statistical review issues were identified as follows. Firstly, after the second randomization at Week 14, no dose-response relation was observed among the non-responders to dapa 5 mg. Secondly, for proportions of subjects who achieved HbA1c < 7% at Week 26, the applicant used the subset of population after excluding subjects with baseline HbA1c less than 7% instead of all randomized subjects.

1.3 Collective Evidence

[1] Non-responders to dapa 5 mg refer to subjects who were randomized to dapa 5 mg at Day 1 but failed to achieve HbA1c < 7% assessed at Week 12.

The study demonstrated a statistically significant treatment effect for dapa compared to placebo with respect to the primary endpoint HbA1c change from baseline at Week 26 (Table 1). The results from secondary analyses were consistent with the primary analysis (Section 3.3). For the proportions of subjects who achieved HbA1c < 7%, the analysis with including all randomized subjects showed numerically larger proportion of subjects who achieved HbA1c < 7% with dapa. Results from sensitivity analyses demonstrated robustness of the primary efficacy results to untestable assumptions on missing data. Subgroup analyses on the primary efficacy endpoint found consistent treatment effect of dapa in subgroup levels on age, sex, race, ethnicity, region, and background antidiabetic medications (Section 4). Risk of hypoglycemia was comparable in subjects treated with dapa compared to those treated with placebo (Section 3.4).

Table 1. Primary Efficacy Result on HbA1c Change from Baseline at Week 26

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81	**Placebo N=76**
Baseline, Mean (SD)	8.22 (1.46)	7.96 (1.63)
Week 26 Missing, n (%)	6 (7.4)	6 (7.9)
Change from baseline to Week 26[1], LS Mean (SE)	-0.62 (0.22)	0.41 (0.22)
Comparison to Placebo[1]		
LS Mean difference (95% CI)		-1.03 (-1.57, -0.49)
Two-sided P-value		<0.001

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error, QD = once daily

[1]The LS mean estimate is based on an ANCOVA model adjusted for baseline HbA1c, baseline age stratum (<15 years vs 15 to <18 years), sex, background antidiabetic medication (metformin only vs insulin ± metformin), and treatment after imputing missing endpoint using placebo washout method.

Source: Table 20 of Clinical Study Report (CSR) and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

1.4 Conclusion and Recommendations

Statistical analyses based on the clinical data from study D1680C00019 have demonstrated robust evidence to support the effectiveness of dapagliflozin regarding glycemic control among pediatrics (10 to <18 years) with T2DM. I recommend approval of the proposed label updates for dapagliflozin and dapagliflozin with metformin HCI extended release.

2 INTRODUCTION

2.1 Overview

Dapagliflozin (Farxiga), a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and its fixed dose combination (FDC) with metformin HCI extended release (Xigduo XR) were approved by the FDA in 2014, both as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. In the current NDA supplements, the applicant proposed to expand the indication of both Farxiga and Xigduo XR to pediatric patients (aged 10 to 17 years) with T2DM. The placebo group for dapagliflozin was shared for saxagliptin. This statistical review focuses on dapa, its FDC with dapa + HCI under NDA 202293 and NDA 205649, respectively. Refer to a separate review for saxa, its FDC with saxa + HCI under NDA 022350 and NDA 200678. The proposed label updates were based on the analysis results from the Phase 3 study D1680C00019 conducted among pediatric patients with T2DM aged 10 to 17 years. The study started on October 11, 2017 and completed on February 1, 2023. The FDA agreed with the final statistical analysis plan (SAP) on December 20, 2022 and database lock occurred on March 8, 2023. An overview of the study is presented in Table 2.

Table 2. Overview of Study D1680C00019

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
D1680C00019	MC, R, DB, PG, PC trial (26 weeks)	Dapagliflozin 5mg or 10 mg† (dapa pooled)/ N=81 Placebo (PBO)/ N=76	Primary: Change in HbA1c from baseline at Week 26 Secondary: Change in FPG from baseline and proportion of subjects achieving HbA1c < 7% at Week 26 with different dosing regimens Primary Endpoint Analysis: ANCOVA MI-WO using mITT population adjusted for baseline A1c, treatment, and randomization strata (sex, age group, and background medication)	Superiority of the primary endpoint was achieved for dapa. The PBO-adjusted lsmeans in HbA1c reduction (95% CI): -1.03% (95% CI -1.57, -0.49), p < 0.001

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, FPG: fasting plasma glucose: ANCOVA: analysis of covariance, MI-WO: multiple imputation-washout, mITT: modified intent-to-treat
† Based on a blinded HbA1c assessment at Week 12, patients on active treatment with HbA1c values < 7% remained on low-dose treatment while those with HbA1c values ≥ 7% were randomised 1:1 to continue on low-dose treatment or uptitrate to high-dose treatment (dapagliflozin 10 mg) starting from Week 14

2.2 Data Sources

The Electronic Document Room (EDR) location for the Farxiga submission package is \\CDSESUB1\evsprod\NDA202293\1346. Datasets for the study D1680C00019 (both in ADAM format and SDTM format) and the programming codes for the efficacy analyses can be found under the subdirectory: m5\datasets\d1680c00019. The EDR location for the Xigduo XR submission package is \\CDSESUB1\evsprod\NDA205649\0248.

The applicant's responses to IRs are located:

- \\CDSESUB1\evsprod\NDA202293\1410 : the programming codes for the demographic, patient, disease characteristics tables.
- \\CDSESUB1\evsprod\NDA202293\1413 and \\CDSESUB1\evsprod\NDA202293\1415: 1) additional analyses for the count of level 2 and severe or level 2 hypoglycemia using negative binomial regressions, 2) the analyses for the percentage of patients who achieve an HbA1c level < 7% at Week 26 using the randomized patients data set, but without excluding patients with baseline HbA1c < 7%, and 3) two-way tipping point analysis and the corresponding programming codes.
- \\CDSESUB1\evsprod\NDA202293\1432: 1) the programming codes for the disposition table and the listing of subjects who prematurely discontinued the treatment or the study during the 26-week short-term (ST) period, and 2) FPG analyses using mg/dL units and corresponding programming codes.
- \\CDSESUB1\evsprod\NDA202293\1439 : 1) additional information for the results of change from HbA1c at Week 26 between high-dose and low-dose dapagliflozin for subjects who did not achieve HbA1c < 7% at Week 12, and 2) clarification for the subjects who discontinued treatment, discontinued study, or both during the ST period.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No issues have been identified with respect to data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The Study D1680C00019 was a multi-center, randomized, parallel-group, placebo-controlled study intended to evaluate the efficacy and safety of dapa 5 mg and a dapa dosing regimen vs. placebo after 26 weeks of treatment in children and adolescents with T2DM. The study consisted

of a maximum 6-month screening period, a 2-week lead-in Period, a 26-week short-term (ST) treatment period, a 26-week long-term (LT) treatment period, a 28-day follow-up period, and a Week 104 post-study visit (Figure 1). In the first randomization at Day 1, subjects were randomized 1:1 to receive dapa 5 mg or placebo. Based on a blinded HbA1c assessment at Week 12, subjects with HbA1c < 7% remained on 5 mg while those with HbA1c ≥ 7% were randomized 1:1 to continue on 5 mg or uptitrate to 10 mg (dapa or matching placebo) starting from Week 14 (second randomization). After the efficacy assessment at the end of 26-week ST period, all subjects were to enter the safety 26-week LT treatment period. The eligible subjects for randomized withdrawal of background medication underwent a third randomization at Week 32 or Week 40 to continue or withdraw background therapy with metformin ("randomized metformin withdrawal"). The other not eligible subjects ("not randomized metformin withdrawal") at Week 32 or Week 40, who did not qualify for the third randomization, were treated with the same treatment.

First randomization at Day 1

At Day 1 of the ST treatment period, a total of 157 subjects were randomized in a 1:1 ratio to one of the two treatment arms: dapa 5 mg or placebo. The randomization was stratified by sex (male vs female), age stratum (< 15 years vs 15 to <18 years), and background antidiabetic medication (metformin only vs insulin only vs metformin+insulin).

Second randomization at Week 14

At Week 12, subjects were assessed for their HbA1c levels. Those who failed to achieve HbA1c < 7% (i.e., non-responders) underwent a second randomization at Week 14, during which subjects were randomized to either 5 mg or 10 mg (dapa or matching placebo) in a 1:1 ratio. The primary endpoint HbA1c change from baseline was assessed at the end of the ST treatment period (i.e., Week 26).

Randomized withdrawal of metformin at Week 32 or Week 40

After efficacy assessment at Week 26, the eligible subjects, who had HbA1c < 7.5% at Week 32 or Week 40 and with background medication of metformin only, underwent the third randomization at Week 32 or Week 40. Dapa subjects were randomized in a 1:1 ratio to either 1) continue background medication with metformin or 2) withdraw background medication with metformin and change dosage to continue 10 mg dapa for subjects previously with high dose (10 mg) and up-titrate to dapa 10 mg for subjects previously with low dose (5 mg). Placebo subjects were randomized to either 1) continue background medication with metformin or 2) withdraw background medication with metformin but switch from placebo to dapa 10 mg in a 1:1 ratio. Discontinuation of background metformin occurred in an unblinded manner.

Not eligible subjects for randomized withdrawal of metformin continued to receive their treatment at the beginning of the safety extension LT treatment period followed (Week 26-52).

Safety monitoring continued following the Week 52 end-of-treatment visit until the Week 104 post-treatment visit.

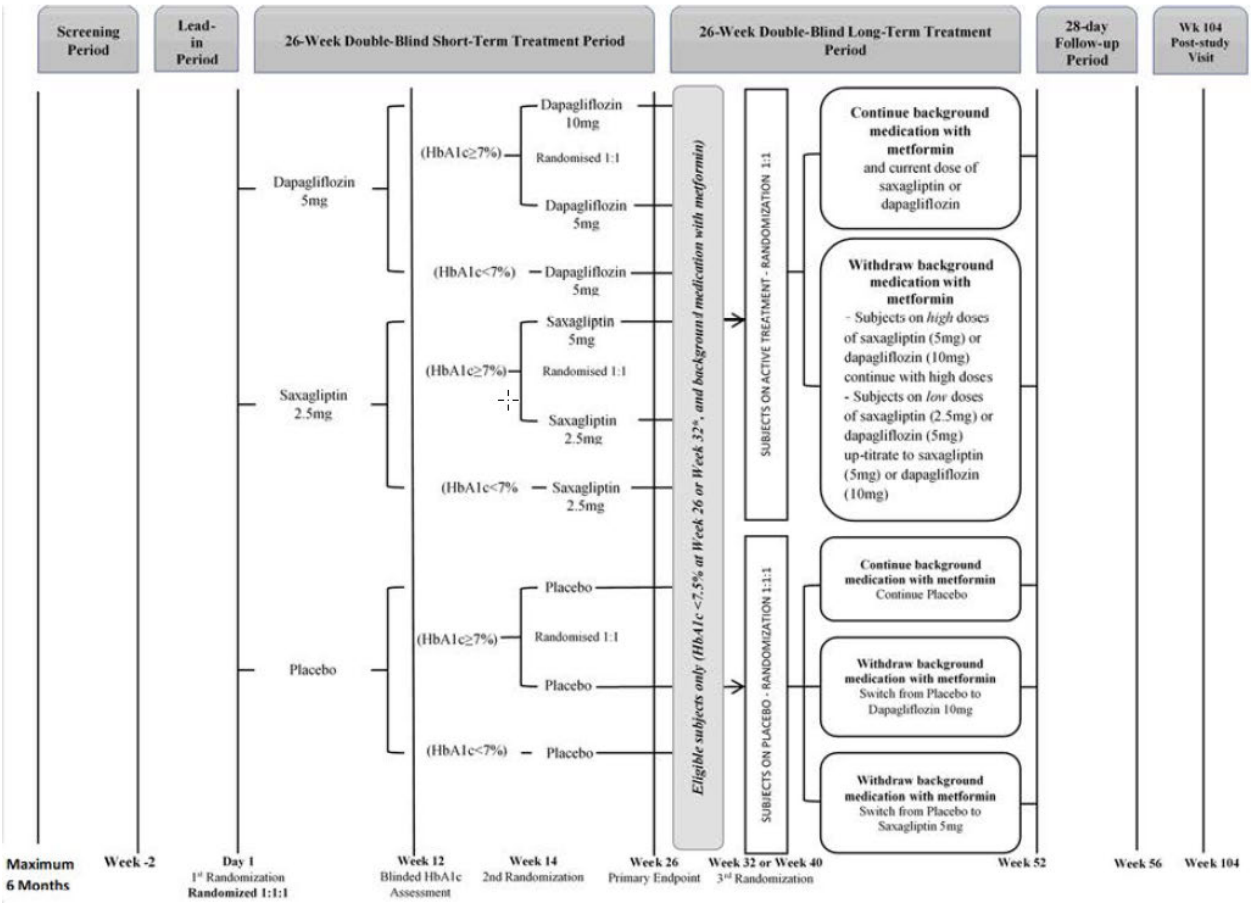

Figure 1. Trial Design
Source: Figure 3 of CSR

The primary objective of the study was to demonstrate the superiority of dapa (5mg or 10 mg pooled) to placebo as assessed by the primary endpoint: HbA1c (%) change from baseline at Week 26.

Sample Size

The determination of the study sample size specified in the SAP is as follows. Assuming a -0.75% treatment effect difference between the active treatment group (dapa) and the placebo group and a 1.7% standard deviation (SD), a sample size of 81 subjects per initial randomized treatment arm (162 subjects in total) would provide 80% power at a two-sided 0.05 level. In the study, 81 subjects on dapa and 76 subjects on placebo were randomized and treated. From study results, the pooled SD for the dapa and the placebo groups was 1.64%, and the estimated treatment effect was -1.03% for dapa after placebo adjustment. The study was adequately powered.

Primary Endpoint

- Change from baseline in HbA1c (%) at Week 26

Secondary Endpoint

- Change from baseline in fasting plasma glucose (FPG) at Week 26

- Incidence of HbA1c < 7.0% at Week 26

3.2.2 Statistical Methodologies

The applicant pre-specified an estimand framework for statistical analyses in the SAP. The key components of an estimand are summarized as follows based on the statistical approaches used for the primary efficacy analysis.

Population & Analysis Set
The primary population for analysis was the modified intent-to-treat (mITT) population, defined as all randomized subjects who received at least one dose of study drug, regardless of treatment adherence or rescue medication.

Handling of Missing Data
Multiple imputation based on placebo washout was applied. Specifically, missing data from the placebo arm were imputed with a sequential linear regression constructed based on observed HbA1c values from the placebo arm, measured at baseline, Week 6, 12, 20 and 26. Missing data from the treatment arm were imputed with a sequential linear regression constructed based on the observed HbA1c values from the placebo arm, measured at baseline and Week 26. 200 imputed datasets were created, and Rubin's Rule was used to combine the analysis results.

Weighting Scheme
The secondary hypotheses intended to explore the question of whether non-responders to dapa 5 mg would benefit from a dose up-titration to dapa 10 mg. Each hypothesis test from the secondary hypotheses was performed based on the same ANCOVA as for the primary hypothesis test, but with the application of the inverse probability weighting (IPW) technique. To explain how IPW works, consider comparing dapa 5 mg (without dose up-titration) vs placebo as an example. At the beginning of the study, a weight variable ω was created for each subject. All subjects started with □ = 1. At Week 14, non-responders (HbA1c at Week 12 ≥ 7.0%) were randomized to either dapa non-responders up-titrated to dapa 10 mg (TITR10) or dapa non-responders continued with dapa 5 mg (TITR5). The dapa non-responders who were up-titrated to dapa 10 mg (TITR10) would have their weights transferred to the dapa non-responders who were randomized to continue with dapa 5 mg (TITR5) (i.e., the TITR5 group had □ = 2, and the TITR10 group had □ = 0). This way, the TITR10 group were represented by the TITR5 group. All other subjects not involved in the second randomization had □ = 1. The diagonal matrix **W** was created accordingly and used in the ANCOVA model as the weight matrix[2]:

$$\boldsymbol{W} = \begin{bmatrix} \boldsymbol{I}_n & \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \boldsymbol{I}_{rn} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & 2 * \boldsymbol{I}_{\frac{(1-r)n}{2}} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} * \boldsymbol{I}_{\frac{(1-r)n}{2}} \end{bmatrix}$$

[2] This was implemented in the SAS procedure PROC MIXED, with the WEIGHT statement specified as the weight matrix.

In the matrix **W**, **I** is an identity matrix, with its dimension specified by the subscript. n is the sample size for each treatment arm, r is the proportion of responders in dapagliflozin arm. $\boldsymbol{I}_n$ indicates $\omega = 1$ for all subjects in the placebo arm; $\boldsymbol{I}_{rn}$ indicates $\omega = 1$ for dapa responders; $2 * \boldsymbol{I}_{\frac{(1-r)n}{2}}$ indicates $\omega = 2$ for dapa non-responders randomized to remain on dapa 5 mg; and $\boldsymbol{0} * \boldsymbol{I}_{\frac{(1-r)n}{2}}$ indicates $\omega = 0$ for dapa non-responders up-titrated to dapa 10 mg.
As similar weighting scheme was applied for the comparison of dapa up-titration to 10 mg vs placebo, where the transfer of weight was from TITR5 to TITR10. Since the two hypothesis tests from the secondary hypothesis share the same subset of dapa responders, the comparisons of TITR5 and TITR10 to placebo are highly correlated.

Multiplicity Adjustment

Hierarchical testing at a 2-sided alpha level of 0.05 of the primary and secondary efficacy endpoints was presented. The primary hypothesis testing is to determine if there will be a greater mean reduction from baseline in HbA1c achieved after 26 weeks of the pooled dapa compared to placebo. After having obtained statistically significant result for the primary hypothesis, secondary hypotheses that compare different dapa regimen groups against placebo were tested formally in the order listed as follows.

- Mean reduction in HbA1c from baseline at Week 26
    - of the low-dose/high-dose treatment regimen (dapa responders or TITR10) vs Placebo
    - of the low-dose treatment regimen (dapa responders or TITR5) vs Placebo
- Mean reduction in FPG from baseline at Week 26
    - of the pooled dapa vs Placebo
    - of the low-dose/high-dose treatment regimen vs Placebo
    - of the low-dose treatment regimen vs Placebo
- Percentage of subjects with HbA1c < 7% at Week 26
    - of the pooled dapa vs Placebo
    - of the high-dose/low-dose treatment regimen vs Placebo
    - of the low-dose treatment regimen vs Placebo
- For the TITR10 vs the TITR5
    - Mean reduction in HbA1c from baseline at Week 26
    - Mean reduction in FPG from baseline at Week 26
    - Percentage of subjects with HbA1c < 7% at Week 26

Primary Efficacy Analyses

The primary hypothesis test was performed based on an ANCOVA, with HbA1c change from baseline at Week 26 as the response variable, and treatment, baseline HbA1c, sex, baseline age stratum (<15 years vs 15 to <18 years), and background antidiabetic medication (metformin only vs insulin ± metformin) as covariates.

Sensitivity Analysis

To check for the robustness of the primary analysis result, return-to-baseline (RTB) approach to handle missing data was performed as a sensitivity analysis. The same ANCOVA model as the primary efficacy analysis was fitted to 200 imputed datasets, and Rubin's Rule was applied to combine the analysis results.

A 2-way tipping point analysis for the treatment policy estimand was also performed to assess the robustness of the primary analysis with respect to missing data assumptions. The analysis is performed by adding positive (detrimental) penalties to dapa and negative (beneficial) penalties to the placebo, and considering when results tip from superiority of dapa to non-superiority.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of subject disposition is presented in Table 3. All randomized subjects received at least one dose of the study drug. At Week 14, 81 subjects initially randomized to the dapa 5mg were still on treatment. 42 (52%) subjects of them were non-responders at Week 12, and underwent a second randomization to either dapa 10 mg (TITR10, N=21) or dapa 5 mg (TITR5, N=21). Of the randomized subjects, 8 (9.4%) in the dapa group and 11 (13.4%) in the placebo group discontinued the study treatment, and 5 (6.2%) in the dapa group and 8 (10.5%) in the placebo group discontinued study drug during the ST period. At Week 26, six subjects (7.4%) from the dapa arm and six subjects (7.9%) from the placebo arm missed their primary endpoint assessments. Two subjects treated with placebo were discontinued from study visit up to Week 26 but were measured for HbA1c value at Week 26.

Table 3. Subject Disposition and Data Capture (HbA1c and FPG at Week 26)

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81	**Placebo N=76**	**Total**
Randomized [n]	81	76	157
Randomized and treated with at least 1 dose [n(%)]	81 (100.0)	76 (100.0)	157 (100.0)
Discontinuation from study treatment up to Week 26 [n(%)]	8 (9.4)	11 (13.4)	19 (12.1)
Lost to follow-up [n]	2	0	2
Withdrawal by subject [n]	3	7	10
Others [n]	3	4	7
Discontinuation from study visits up to Week 26 [n(%)]	5 (6.2)	8 (10.5)	13 (8.3)
Lost to follow-up [n]	2	1	3
Withdrawal by subject [n]	3	7	10
Completed 26-week HbA1c [n(%)]	75 (92.6)	70 (92.1)	145 (92.4)
On Treatment [n]	73	66	139
Off Treatment (Retrieved Drop-outs) [n]	2	4	6
Missing in 26-week HbA1c [n(%)]	6 (7.4)	6 (7.9)	12 (7.6)
On Treatment [n]	0	0	0
Off Treatment [n]	6	6	12
Completed 26-week FPG [n(%)]	75 (92.6)	68 (91.9)	143 (92.3)
On Treatment [n]	73	65	138
Off Treatment (Retrieved Drop-outs) [n]	2	3	5
Missing in 26-week FPG [n(%)]	6 (7.4)	6 (8.1)	12 (7.7)
On Treatment [n]	0	0	0

Off Treatment [n]	6	6	12
Discontinuation from study treatment up to Week 52 [n(%)]	10 (12.3)	20 (26.3)	30 (19.1)
Lost to follow-up [n]	2	1	3
Withdrawal by subject [n]	4	9	13
Others [n]	4	10	14
Discontinuation from study visits up to Week 52 [n(%)]	7 (8.6)	17 (22.4)	24 (15.3)
Lost to follow-up [n]	1	3	4
Withdrawal by subject [n]	5	12	17
Others [n]	1	2	3
Affected by Covid-19 pandemic [n(%)]	14 (17.3)	18 (23.7)	32 (20.4)

Abbreviations: QD = once daily
Source: Figure 4, 6 of CSR and Statistical Reviewer's Analysis

After 26-week short term treatment period, 13 subjects treated with dapa and 8 subjects treated with placebo underwent randomized withdrawal of background medication at Week 32 or Week 40 if HbA1c < 7.5% at Week 32 or Week 40 and with background medication of metformin only. 68 subjects with dapa and 68 subjects with placebo were not eligible for randomized withdrawal of background medication. Of note, efficacy assessment is based on only 26-week short term treatment period.

A summary of patient demographics and baseline characteristics is presented in Table 4. Based on the summary, demographics and baseline characteristics are well balanced between the dapa and placebo groups.

Table 4. Demographics and Baseline Characteristics

	Dapagliflozin Pooled [5 mg and 10 mg] QD N=81	**Placebo N=76**	**Total N=157**
Sex, n (%)			
Female	49 (60.5)	44 (57.9)	93 (59.2)
Male	32 (39.5)	32 (42.1)	64 (40.8)
Age, years			
Mean (SD)	14.4 (2.00)	14.7 (1.64)	14.5 (1.83)
Median	15.0	15.0	15.0
IQR	13.0, 16.0	14.0, 16.0	13.0, 16.0
Min, Max	10.0, 17.0	11.0, 17.0	10.0, 17.0
Age categories, n (%)			
>=10 and <15	38 (46.9)	35 (46.1)	73 (46.5)
>=15 and <18	43 (53.1)	41 (53.9)	84 (53.5)
Race, n (%)			
American Indian or Alaska Native	11 (13.6)	12 (15.8)	23 (14.6)
Asian	18 (22.2)	24 (31.6)	42 (26.8)
Black or African American	7 (8.6)	3 (3.9)	10 (6.4)
Native Hawaiian or Other Pacific Islander	0	3 (3.9)	3 (1.9)
Other	3 (3.7)	2 (2.6)	5 (3.2)
White	42 (51.9)	32 (42.1)	74 (47.1)
Ethnicity, n (%)			
Hispanic or Latino	45 (55.6)	34 (44.7)	79 (50.3)
Not Hispanic or Latino	36 (44.4)	42 (55.3)	78 (49.7)

	Dapagliflozin Pooled [5 mg and 10 mg] QD N=81	Placebo N=76	Total N=157
Geographic Region 1, n (%)			
Asia/Pacific	19 (23.5)	23 (30.3)	42 (26.8)
Europe	11 (13.6)	17 (22.4)	28 (17.8)
Latin America	39 (48.1)	23 (30.3)	62 (39.5)
North America	12 (14.8)	13 (17.1)	25 (15.9)
Baseline BMI Z-score			
Mean (SD)	1.7 (0.72)	1.5 (0.83)	1.6 (0.79)
Median	1.8	1.6	1.7
IQR	1.5, 2.2	1.0, 2.1	1.2, 2.1
Min, Max	-1.8, 2.9	-1.7, 3.0	-1.8, 3.0
HbA1c at Baseline (%)			
Mean (SD)	8.2 (1.46)	8.0 (1.63)	8.1 (1.54)
Median	8.4	7.7	7.9
IQR	7.1, 9.3	6.6, 9.1	6.8, 9.2
Min, Max	5.1, 11.1	5.2, 12.0	5.1, 12.0
Background Diabetes Medication, n (%)			
Insulin	10 (12.3)	8 (10.5)	18 (11.5)
Metformin	42 (51.9)	39 (51.3)	81 (51.6)
Metformin and Insulin	29 (35.8)	29 (38.2)	58 (36.9)

Abbreviations: IQR = interquartile range, SD = standard deviation, QD = once daily
No information was collected for "Other" category in race.
The geographic region 1 category "North America" indicates US.
Source: Statistical Reviewer's Analysis; adsl.xpt

3.2.4 Results and Conclusions

Primary Endpoint

As demonstrated in Table 5, the LSMean difference (95% CI) in HbA1c change from baseline at Week 26 is -1.03 (-1.57, -0.49) for dapa pooled vs placebo, with a two-sided p-value less than 0.001. The study has successfully demonstrated superiority of dapa to placebo with respect to glycemic control.

Table 5. HbA1c Change from Baseline at Week 26, Primary Hypothesis

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81	Placebo N=76
Baseline, Mean (SD)	8.22 (1.46)	7.96 (1.63)
Week 26 Missing, n (%)	6 (7.4)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	-0.62 (0.22)	0.41 (0.22)
Comparison to Placebo[1]		
LS Mean difference (95% CI)		-1.03 (-1.57, -0.49)
Two-sided P-value		<0.001

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error, QD = once daily
Primary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: Table 20 of CSR and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

For sensitivity analysis, missing primary endpoint was multiply imputed based on the return-to-baseline approach. The same ANCOVA model as the primary efficacy analysis was fitted on 200 imputed datasets, and Rubin's Rule was applied to combine the analysis results. As shown in Table 6, the placebo-adjusted treatment effect was -1.06 with a 95% CI (-1.61, -0.52). This has confirmed the conclusion based on the primary analysis.

Table 6. HbA1c Change from Baseline at Week 26, Sensitivity Analysis

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81	**Placebo N=76**
Baseline, Mean (SD)	8.22 (1.46)	7.96 (1.63)
Change from baseline to Week 26, LS Mean (SE)	-0.69 (0.22)	0.38 (0.22)
Comparison to Placebo LS Mean difference (95% CI)		-1.06 (-1.61, -0.52)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error, QD = once daily
Primary efficacy analysis is based on multiple imputations using return-to-baseline model. 200 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, sex, age group (10-14/15-<18), background antidiabetes medication (metformin only/insulin±metformin), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis

A 2-way tipping point analysis was also performed to assess the robustness of the primary analysis results with respect to missing data assumptions. Positive penalties were added to dapa, and negative penalties were added to placebo. The heatmap is shown in Figure 2 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 imputed values for dapa. Each unit is worth 0.5 penalty. For example, the point (-1,0) means a penalty (benefit) of -0.5 is added to placebo and no penalty added to dapa. Likewise, the point (-8, 8) means a penalty (benefit) of -4 is added to placebo and a penalty of 4 is added to dapa.

From the primary analysis, the average change from baseline for the 6 subjects with missing data on dapa is 0.69%, and the average change from baseline for the 6 subjects with missing data on placebo is 0.25%. Let us consider the following scenarios where the results would tip the conclusion of superiority, and the clinical plausibility:

i. When the penalty on dapa is 0, the penalty (benefit) on placebo needed is ~ -10*0.5 = -5.0%, so that the average decrease is 0.25% - 5.0% = -4.75%. This is clearly not possible. Likewise, when the penalty on placebo is 0, the penalty on dapa needed is >5.0%, so that the average increase is > 0.69 + 5.0% = 5.69%, which is clearly not possible.
ii. Let us consider a penalty of 5*0.5 = 2.5% for dapa. The 6 subjects on dapa then have an average increase is 0.69% + 2.5% = 3.19% (unlikely). To tip the results, the imputed change for the 6 subjects on placebo is -6*0.5 = -3.0%, so that the average decrease is 0.25% - 3.0% = -2.75% (unlikely). This scenario is clearly not plausible.

Clearly, anywhere on the graph where results will tip requires a clinically impossible scenario. Thus, the robustness of the primary analysis with respect to missing data assumptions under the treatment policy estimand is confirmed.

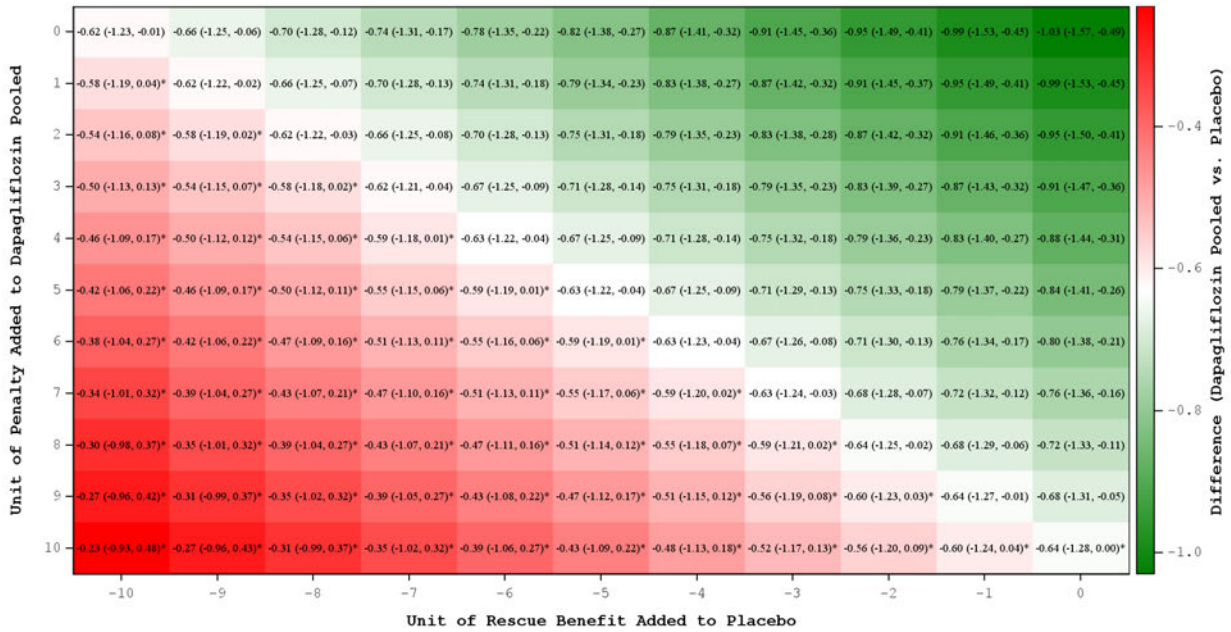

Figure 2. HbA2c - Two-Way Tipping Point Analysis (Heatmap) for the Primary Endpoint
Each unit = 0.5
Each cell contains the mean difference and 95% CI between dapa and placebo. The x-axis represents the penalties added to the imputed values for placebo, and y-axis represents the penalties added to the imputed values for pooled dapagliflozin. The asterisk indicates that the superiority was not demonstrated.
Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Low-dose/High-dose Regimen

The analysis results for the secondary hypotheses were presented in Tables 7 and 8. The low-dose/high-dose treatment regimen group included 39 dapa responders (including the subjects who discontinued study drug/study before Week 14 [n=4] and the subject on study drug but missed Week 14 visit [n=1] and 34 responders) and 21 dapa non-responders second-randomized to TITR10, and low-dose treatment regimen group included 39 dapa responders and 21 dapa non-responders second-randomized to TITR5. The placebo-adjusted treatment effect (95% CI) was -0.86 (-1.44, -0.27) for the subjects with the low-dose/high-dose treatment regimen, and -1.19 (-1.76, -0.62) for the subjects with the low-dose treatment regimen. A reversed dose response was observed for dapa 10mg and dapa 5mg in this second randomization regimen.

Table 7. HbA1c (%) Change from Baseline at Week 26, TITR10 vs Placebo

	TITR10 + Responders N=60	**Placebo N=76**
Baseline, Mean (SD)	7.94 (1.52)	7.96 (1.63)
Week 26 Missing, n (%)	6 (10)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	-0.42 (0.21)	0.43 (0.21)
Comparison to Placebo LS Mean difference (95% CI)		-0.86 (-1.44, -0.27)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, with the application of inverse probability weighting, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c. The analysis was performed in the mITT using all observed data.
Source: Table 20 of CSR and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Table 8. HbA1c (%) Change from Baseline at Week 26, TITR5 vs Placebo

	TITR5 + Responders N=60	Placebo N=76
Baseline, Mean (SD)	8.03 (1.47)	7.96 (1.63)
Week 26 Missing, n (%)	4 (6.7)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	-0.79 (0.20)	0.43 (0.21)
Comparison to Placebo LS Mean difference (95% CI)		-1.19 (-1.76, -0.62)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, with the application of inverse probability weighting, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c. The analysis was performed in the mITT using all observed data.
Source: Table 20 of CSR and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

To further investigate this reversed trend in dose response, an ANCOVA without the application of IPW was applied to compare the treatment effect of TITR10 vs TITR5. The ANCOVA was based on data from dapa non-responders only, with the response variable HbA1c change from baseline at Week 26. As presented in Table 9, a dose response was observed numerically but the difference was minuscule, suggesting that the reversed dose response may be by chance. As shown in Table 10, the effect of TITR10 compared to TITR5 from Week 12 (at second randomization) at Week 26 was not observed.

Table 9. HbA1c (%) Change from Baseline at Week 26, Dapa Non-responders Only

	TITR10 N=21	TITR5 N=21
Baseline, Mean (SD)	8.74 (1.33)	9.00 (0.90)
Week 26 Missing, n (%)	2 (9.5)	0
Change from baseline to Week 26, LS Mean (SE)	-0.78 (0.34)	-0.76 (0.32)
LS Mean difference (95% CI)		-0.03 (-1.00, 0.94)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Table 10. HbA1c (%) Change from Week 12 at Week 26, Dapa Non-responders Only

	TITR10 N=21	TITR5 N=20
Week 12, Mean (SD)	8.40 (1.17)	7.73 (0.73)
Week 26 Missing, n (%)	2 (9.5)	0
Change from Week 12 to Week 26, LS Mean (SE)	0.11 (0.31)	-0.03(0.31)
LS Mean difference (95% CI)		0.14 (-0.78, 1.06)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), HbA1c at Week 12. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

As displayed in Table 11, it is worth noting that the non-responder group, by definition, consisted of subjects who failed to meet the glycemic target when treated with dapa 5mg. The mean HbA1c change from baseline at Week 12 were -1.25% for the responders, as opposed to -0.75% for the non-responders. Hence, while dapa 5mg appears generally effective among the full study population, its efficacy seems limited among the non-responder group. When compared to the responder group, the non-responder group on average had a higher HbA1c at baseline, a

higher percentage of subjects with HbA1c ≥ 8.5% at baseline, and a higher percentage of subjects on a more aggressive background treatment regimen (i.e., metformin + insulin). All these facts suggested that at the first randomization, the non-responders tend to have had more advanced T2DM than the responders, which may explain the lack of responsiveness to the dapa treatment observed in the dapa non-responder group.

Table 11. Dapa Non-Responders vs Responders

Baseline characteristics	**Dapa non-responders N=42**	**Dapa responders N=34**
Baseline HbA1c (%), mean (SD)	8.87 (1.13)	7.52 (1.51)
Baseline HbA1c ≥ 8.5%, n (%)	29 (69.1%)	10 (29.4%)
On Background metformin and insulin, n (%)	17 (40.5%)	12 (35.3%)
HbA1c Change from Baseline at Week 12, mean (SD)	-0.75 (1.57)	-1.25 (1.25)

Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Secondary Endpoints

Besides the primary endpoint, analysis results for the secondary endpoints FPG change from baseline at Week 26, and the proportion of subjects with HbA1c < 7.0% (responders) at Week 26 in the population after excluding subjects with baseline HbA1c < 7% were presented in Tables 12 and 13, respectively. A significant difference was found between the dapa pooled group and the placebo group with respect to FPG change from baseline. The proportions of subjects with baseline HbA1c ≥ 7.0% and achieved HbA1c < 7.0% at Week 26 were listed in Table 13. On the other hand, the proportions of responders at Week 26 with baseline HbA1c < 7% were 64.7% (# of baseline responders=17, # of responders at Week 26=11) for dapa pooled group and 53.9% (# of baseline responders=26, # of responders at Week 26=14) for the placebo group. For the proportions of responders at Week 26, we recommended the analysis with including all randomized subjects (Table 14) instead of subset of population. The proportion of responders was numerically higher on the dapa pooled group compared to the placebo group, however, the difference is not significantly higher since the 95% confidence intervals include 1.

Table 12. Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 26

Endpoint	**Dapagliflozin pooled [5 mg and 10 mg] QD N=81**	**Placebo N=76**
FPG at Week 26		
Baseline, Mean (SD)	162.24 (64.54)	152.01 (57.18)
Week 26 Missing, n (%)	6 (7.4)	8 (10.5)
Change from baseline to Week 26, LS Mean (SE)	-10.27 (6.73)	9.23 (6.91)
Comparison to Placebo LS Mean difference (95% CI)		 -19.49 (-36.42, -2.56)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error, QD = once daily
Other secondary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline FPG as covariates. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Table 13. Proportion of Subjects who achieved HbA1c < 7.0% at Week 26 in the subset of population with baseline HbA1c ≥ 7.0%

	Dapagliflozin pooled [5 mg and 10 mg] QD N=64	Placebo N=50
# known responders (HbA1c < 7.0%) at Week 26, n (%)	17 (26.6)	5 (10.0)
Average # of responders across imputed datasets, n (%)	18.5 (37.0)	5.12 (8.0)
Comparison to Placebo Adjusted Odds Ratio (95% CI)		3.82 (1.24, 11.70)

Abbreviations: CI = confidence interval, QD = once daily
Secondary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with logistic regression, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c. The analysis was performed in the mITT using all observed data.
Source: Table 20 of CSR and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Table 14. Proportion of Subjects who achieved HbA1c < 7.0% at Week 26 in all randomized population

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81	Placebo N=76
Subjects with HbA1c < 7.0% at baseline, n (%)	17 (21.0)	26 (34.2)
# known responders (HbA1c < 7.0%) at Week 26, n (%)	28 (34.6)	19 (25.0)
Average # of responders across imputed datasets, n (%)	29.6 (36.6)	20.1 (26.5)
Comparison to Placebo Adjusted Odds Ratio (95% CI)		2.16 (0.98, 4.73)

Abbreviations: CI = confidence interval, QD = once daily
Secondary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with logistic regression, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c. The analysis was performed in the mITT using all observed data.
Source: IR responses and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

3.3 Evaluation of Safety

Hypoglycemic events were evaluated among the safety set, defined as all subjects who received at least one dose of the treatment. Subjects were analyzed according to their assigned treatments: dapa pooled, vs placebo, from baseline to Week 26. There were 24.7% (59 episodes) of dapa subjects and 26.3% (81 episodes) of placebo subjects, who had ≥ 1 episode of any type of hypoglycemia. The results for hypoglycemia events with plasma glucose (PG) < 54 mg/dL (level 2) and for hypoglycemia events with severe (level 3) or PG < 54 mg/dL are presented in Table 15. Ten subjects with dapa pooled experienced at least one episode and ten subjects with placebo experienced at least one episode. There was one subject with placebo who experienced 2 episodes and one subject with placebo who experienced 3 episodes. All other subjects experienced singular episode.

Table 15. Summary of Hypoglycemic Episodes during the ST Treatment Period

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81		Placebo N=76	
Hypoglycemia	Subjects with ≥ 1 episode (%)	# Episodes	Subjects with ≥ 1 episode (%)	# Episodes
Documented hypoglycemia (level 3)	3 (3.7)	3	4 (5.3)	4
Documented hypoglycemia (level 2)	7 (8.6)	7	6 (7.9)	9

Documented hypoglycemia (level 2 or level 3)	10 (12.3)	10	10 (13.2)	13

Abbreviations: QD = once daily
Source: Statistical Reviewer's Analysis; adsl.xpt, adhypo.xpt

Table 16 below summarize the analysis results for the rate of documented hypoglycemia with level 2 and for the rate of documented hypoglycemia with level 2 or level 3, respectively. The 95% confidence interval for dapa pooled relative to placebo includes 1. Therefore, we conclude that dapa does not significantly increase the incidence of hypoglycemia episodes.

Table 16. Rate Ratios of Hypoglycemia during the ST Treatment Period

Hypoglycemia	**Rate Ratio 95% CI Dapagliflozin pooled [5 mg and 10 mg] QD/Placebo**
Hypoglycemia (level 2)	0.73 (0.23, 2.29)
Hypoglycemia (level 2 or level 3)	0.68 (0.28, 1.66)

Abbreviations: CI = confidence interval, QD = once daily
Rate ratio estimated from a negative binomial model using log link, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetes medication (metformin only/insulin±metformin), and log (exposure in days/365.25) as an offset variable. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis; adsl.xpt, adhypo.xpt

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses on HbA1c (%) change from baseline at Week 26 were conducted with respect to the baseline characteristics: sex (male vs female), age (<15 years vs 15 to <18 years), race (Whites vs Asians vs Others), region (Asia vs Europe vs Latin America vs North America), ethnicity (Hispanic or Latino vs. not Hispanic or Latino) and background antidiabetic medication (metformin only vs insulin ± metformin). Each analysis modeled the primary endpoint with an ANCOVA adjusted for treatment, baseline HbA1c, sex (except for the subgroup analysis on sex), baseline age stratum (except for the subgroup analysis on age stratum), and background antidiabetic medication (except for the subgroup analysis on background antidiabetic medication). Similar to the primary efficacy analysis, missing data were multiply imputed based on placebo washout and the analysis results were combined via Rubin's Rule.

Additionally, Bayesian hierarchical modeling produces shrinkage estimates of the treatment effects in each subgroup. Treatment effects are assumed to be exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals.
For a given baseline characteristic with *k* subgroups, let Y_i (i = 1, ... k) be the observed sample estimate of the treatment effect in subgroup *i*. The shrinkage analysis in this review assumes the following:

- $Y_i \sim N(\mu_i, \sigma_i^2)$, where μ_i is the expected treatment effect for subgroup *i*, and σ_i^2 is the within-subgroup variance
- σ_i^2 is set to the variance for the sample estimate
- $\mu_i \sim N(\mu, \tau^2)$, where $\mu \sim N(0, 16*(1.64)^2)$, and $1/\tau^2 \sim$ 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 1.64 based on the primary analysis results, thus, the variance of the prior distribution of the treatment effect is $16*1.64^2$.

4.1 Sex, Age, Race, Ethnicity, Region, and Background Antidiabetes Medication

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

- Sex (Male vs Female)
- Age (<15 vs 15 to <18)
- Race (White vs Asian vs Others)
- Ethnicity (Hispanic or Latino vs Not Hispanic or Latino)
- Region (Asia vs Europe vs Latin America vs North America)
- Background Antidiabetic Medication (metformin only vs insulin $\pm$ metformin)

The sample estimates and the shrinkage estimates of the treatment difference with respect to HbA1c change from baseline at Week 26 are presented in Figure 3 and Figure 4. The plots include the corresponding 95% confidence and credible intervals for the sample and shrinkage estimates, respectively. Compared to the sample estimate, the shrinkage estimate had less variability and a magnitude closer to the overall estimate. When performing the subgroup analysis on race, the race categories Black or African American (n=10), Native Hawaiian or other Pacific Islander (n=3), and other races (n=5), were combined into the race category "Others", due to insufficient sample sizes. For descriptive purpose, Table 17 displays the treatment effect for each subject from the "Others" category.

Subgroup analyses are consistent with primary analysis results which shows homogeneous treatment effects of dapa across different subpopulations. No significant interactions were found between subgroups and treatment.

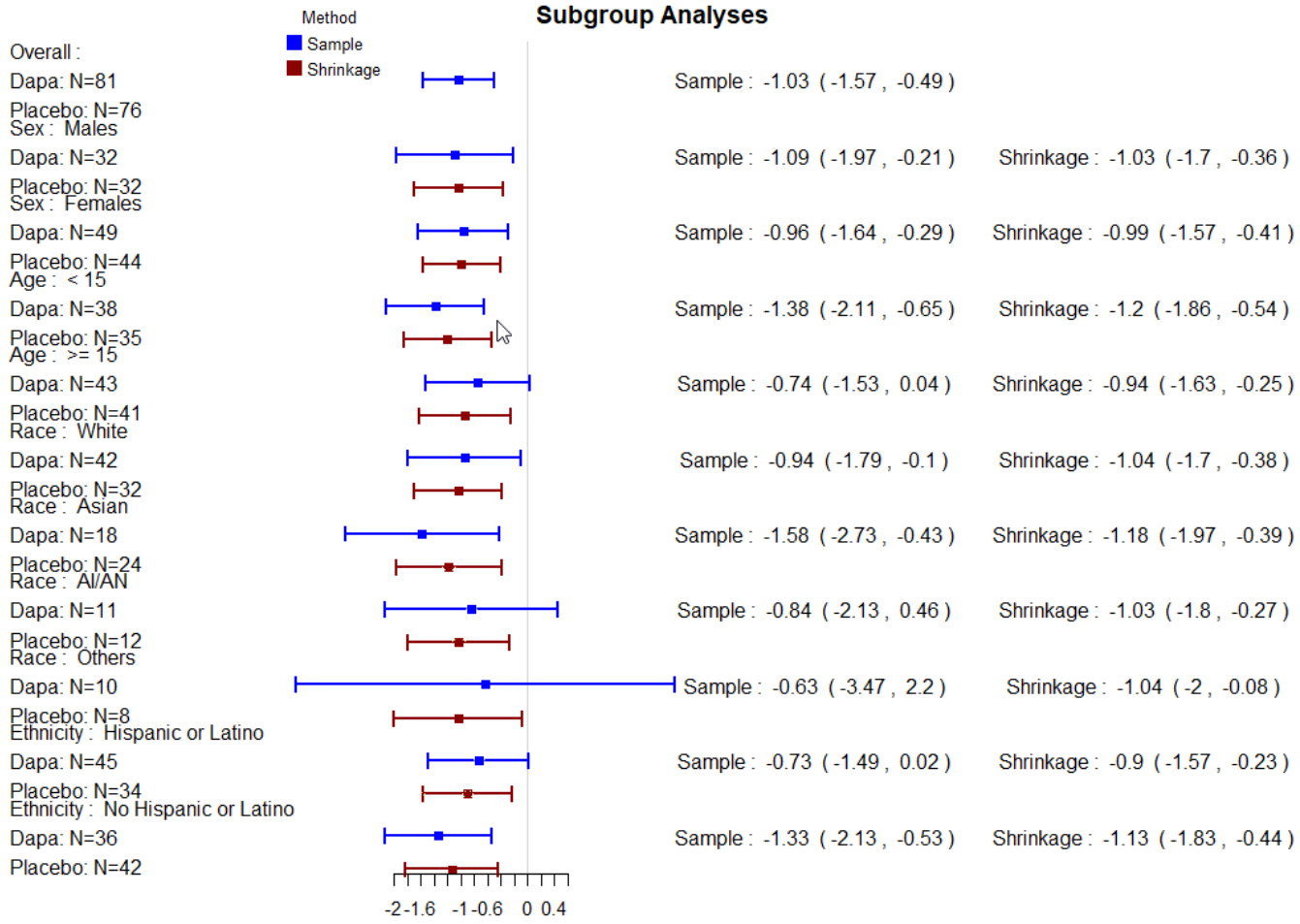

Figure 3. Forest Plot of Subgroup Analyses for Sex, Age, Race, and Ethnicity: Placebo-Adjusted HbA1c (%) Change from Baseline at Week 26

Abbreviations: AI/AN = American Indian or Alaska Native

Values on the negative side favor dapagliflozin, values on the positive side favor placebo.

Source: Statistical Reviewer's Analysis; adls.xpt, adeff.xpt

Table 17. Mean Baseline HbA1c and Mean Change from Baseline at Week 26, A Breakdown of the Race Category "Other"

RACE: Others	Dapagliflozin pooled [5 mg and 10 mg] QD	Placebo
Black or African American	**N=7**	**N=3**
Mean Baseline HbA1c	7.39	8.43
Mean Change from baseline to Week 26	0.10	-0.57
Native Hawaiian or other Pacific Islander	**N=0**	**N=3**
Mean Baseline HbA1c	NA	7.30
Mean Change from baseline to Week 26	NA	2.85
Other races	**N=3**	**N=2**
Mean Baseline HbA1c	8.67	6.50
Mean Change from baseline to Week 26	-1.73	-0.30

Abbreviations: QD = once daily

Source: Statistical Reviewer's Analysis; adls.xpt, adeff.xpt

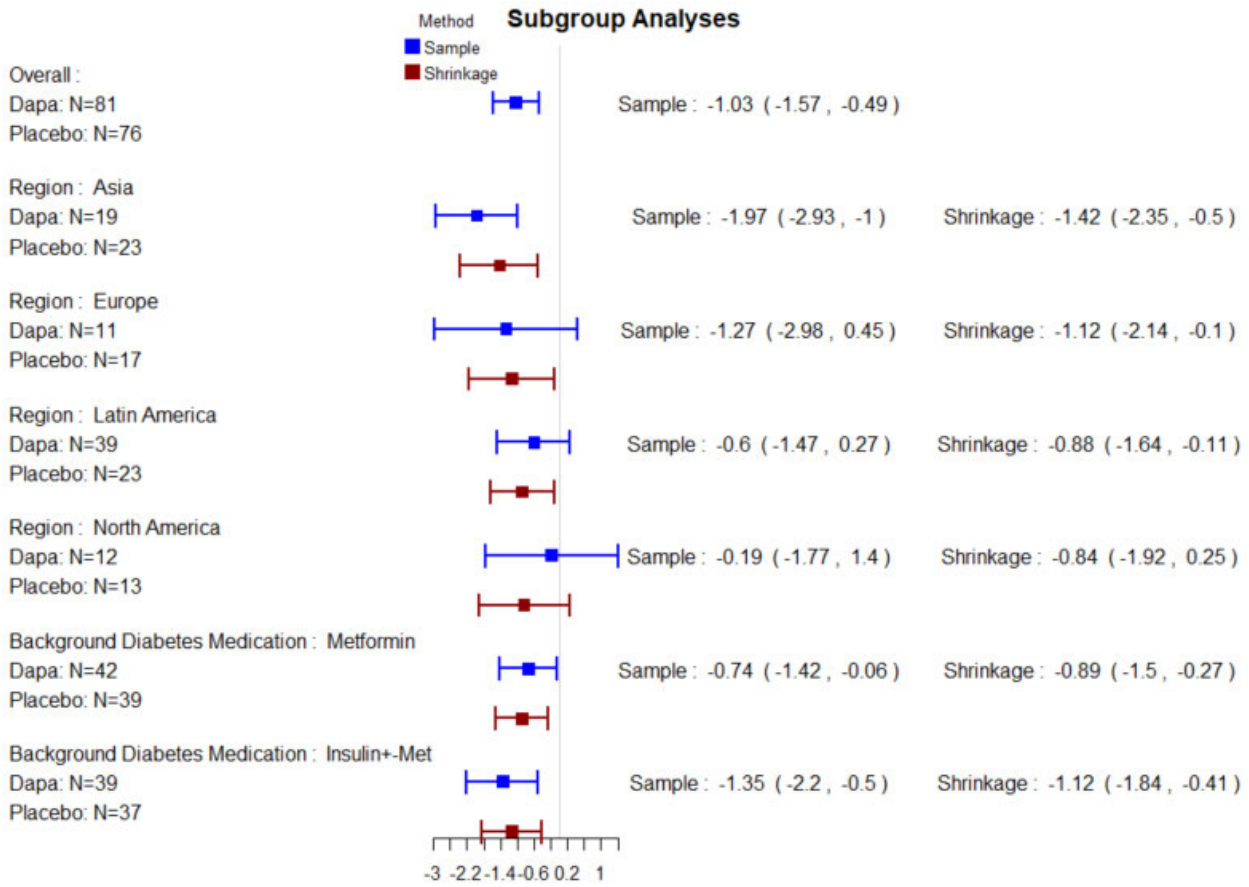

Figure 4. Forest Plot of Subgroup Analyses for Region and Background Antidiabetes Medication: Placebo-adjusted HbA1c (%) Change from Baseline at Week 26

Values on the negative side favor dapagliflozin, values on the positive side favor placebo. North America indicates US.
Background diabetes medication group of Insulin ± Metformin include Insulin only (n=18) or Insulin with Metformin (n=58). For the Insulin only group, the mean baseline HbA1c was 7.84 and 7.46 for dapa (n=10) and placebo (n=8) arms, respectively. The mean change from baseline to Week 26 in HbA1c was -0.88 and 1.07 for dapa and placebo arms, respectively. For the Insulin with Metformin group, the mean baseline HbA1c was 8.79 and 8.48 for dapa (n=29) and placebo (n=29) arms, respectively. The mean change from baseline to Week 26 in HbA1c was -1.23 and 0.57 for dapa and placebo arms, respectively.
Source: Statistical Reviewer's Analysis; adls.xpt, adeff.xpt

4.2 Other Special/Subgroup Populations

Subgroup Analyses Based on Background Antidiabetic Medication

Subgroup analysis on background antidiabetic medications was performed to examine the treatment effect of dapa in combination with metformin. A total of 139 subjects (71 dapa pooled and 68 placebo subjects) were treated by metformin ± insulin in the cohort. We confirmed that the estimated treatment effect was consistent with the overall population and the placebo-adjusted treatment effect for dapa with respect to HbA1c change from baseline at Week 26 was -1.01% with a 95% confidence interval (-1.57, -0.45).

HbA1c Change from Baseline at Week 52

As demonstrated in Table 18, the exploratory analysis during the short-term (ST) + long-term (LT) period supported the main efficacy results and showed a benefit of dapa compared with placebo on glycemic control. However, we need to interpret this exploratory analysis results with caution since some subjects, especially 1) whom were treated initially as placebo at the first randomization and were randomized to withdraw background medication with metformin and switch to active treatment with dapa 10 mg during the third randomization (n=3) and 2) whom were treated initially as dapa from the first randomization and were randomized to withdraw background medication with metformin and up-titrated to 10 mg (n=7), could reduce the overall treatment effect of dapa. Therefore, this result cannot be interpreted as pure overall benefit of dapa.

Table 18. HbA1c Change from Baseline at Week 52, Exploratory Analysis

	Dapagliflozin pooled [5 mg and 10 mg] QD N=81	**Placebo N=76**
Baseline, Mean (SD)	8.22 (1.46)	7.96 (1.63)
Week 52 Missing, n (%)	10 (12.3)	15 (19.7)
Change from baseline to Week 52, LS Mean (SE)	-0.20 (0.32)	0.94 (0.32)
Comparison to Placebo LS Mean difference (95% CI)		-1.13 (-1.90, -0.36)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Exploratory efficacy analysis is based on multiple imputations using placebo washout. 200 datasets were generated, and each dataset was analyzed with ANCOVA, adjusted for treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin±metformin), baseline HbA1c. The analysis was performed in the mITT using all observed data.
Source: Table 14.2.5.1.1.a of CSR and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

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 subject's baseline HbA1c measurement). Figure 5 below is a scatter plot of HbA1c change from baseline at Week 26 vs baseline HbA1c. The scatter points are color-coded by treatment arms. Two regression lines based on completers from dapa pooled and placebo are superimposed over the scatter points. The regression line is $y = 5.06 – 0.71x$ for dapa pooled, and $y=2.24 – 0.23x$ for placebo. The difference in slopes is 0.48, which implies that for every 1% increase in baseline HbA1c, the placebo-adjusted treatment effect measured by HbA1c change from baseline increases by 0.48%. 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. Some of subjects (left hollow from blue vertical dashed line) with baseline HbA1c < 7.0% did not achieve HbA1c < 7.0% at Week 26.

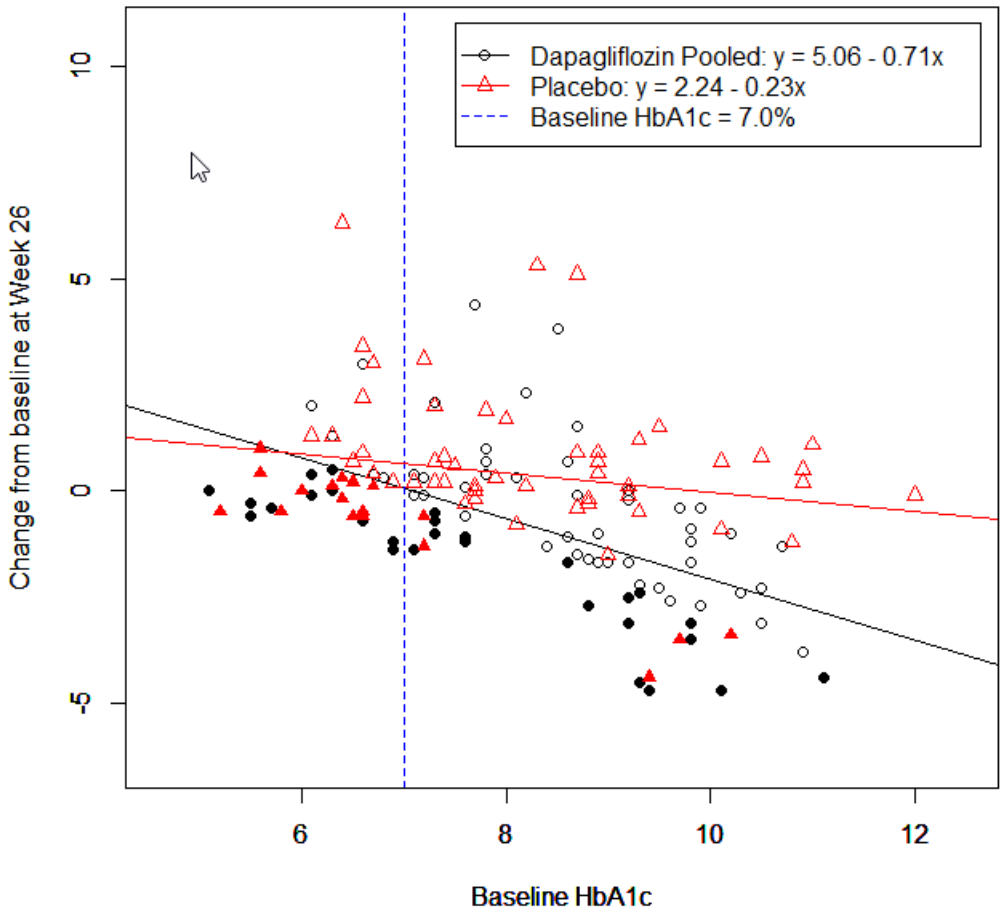

Figure 5. Scatterplot of Baseline HbA1c vs Change from Baseline at Week 26
Solid indicates the subjects who achieved HbA1c < 7.0% at Week 26
Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Statistical issues and resolution for this review are:

1. The missing rate for the primary endpoint measurements was 7.4% for dapa, and 7.9% for placebo. Missing data were handled adequately by placebo washout method that was agreed by Agency.
2. After the second randomization at Week 14, no dose-response relationship was observed among the non-responders to dapa 5 mg. However, it appears non-responders are less responsive due to more advanced disease at baseline.
3. For proportions of subjects who achieved HbA1c < 7% at Week 26, the applicant used the subset of population after excluding subjects with baseline HbA1c less than 7%. We requested the applicant to use all randomized subjects instead.

5.2 Collective Evidence

For the primary efficacy analysis, the placebo-adjusted treatment effect for dapa with respect to HbA1c change from baseline at Week 26 was statistically significant with treatment difference of -1.03% with a 95% confidence interval (-1.57, -0.49). The placebo-adjusted treatment effect (95% CI) was -0.86 (-1.44, -0.27) for the subjects with the low-dose/high-dose treatment regimen, and -1.19 (-1.76, -0.62) for the subjects with the low-dose treatment regimen. Sensitivity analyses using return-to-baseline approach that inspected the impact of missing data assumptions demonstrated similar findings to the primary analysis result. Additionally, the results from two-way tipping point analyses confirmed robustness of the primary efficacy results. Subgroup analyses on the primary efficacy endpoint found consistent treatment effect of dapa in subgroup levels defined by sex, age, race, ethnicity, region, as well as background medications.

Less number of hypoglycemia (level 2 or 3) episodes were observed for subjects receiving dapa (12.3% subjects with $\geq$ 1 episode) than for those receiving placebo (13.2% subjects with $\geq$ 1 episode) and comparable hypoglycemia number was found in subjects treated with dapa compared to those treated with placebo.

5.3 Conclusions and Recommendations

Statistical analyses based on the clinical data from the Phase 3 pediatric study D1680C00019 have demonstrated robust evidence to support the effectiveness of dapa regarding glycemic control among pediatric subjects (11 to <18 years) with T2DM. The statistical team recommend approval of the proposed label updates for Farxiga and Xigduo XR.

5.4 Labeling Recommendations (as applicable)

The applicant proposed to update Section 8.4 *Pediatric Use* with the expansion of T2DM indication to the pediatric population aged 10 to 17 years for Farxiga (dapa) and Xigduo XR (dapa + HCI). In support of this pediatric indication, a new section on pediatric clinical studies (*Section 14.2 Glycemic Control in Pediatric Patients Aged 10 years and Older with Type 2 Diabetes Mellitus*) was proposed to Section 14 of the product label. For the Xigduo XR label, the applicant proposed to include the consistent treatment benefit with dapa in the subgroup of patients with metformin with or without insulin as background therapy in Section 14.2 and we validated the result using the subgroup analysis. During the recent labeling meeting, we recommended the update of the Table 13 in Section 14.2 to replace (b) (4)

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/s/

SUNG HEE KIM
05/17/2024 01:54:30 PM

YOONHEE KIM
05/17/2024 03:04:45 PM
I concur