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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 022350, NDA 200678
Supplement #:	S-026, S-028
Drug Name:	Onglyza (saxagliptin), Kombiglyze XR (saxagliptin and metformin HCl extended release) tablets
Indication(s):	[Approved] As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus No new indication was proposed
Applicant:	AstraZeneca
Date(s):	Date Received: December 10, 2023 PDUFA date: October 12, 2024
Review Priority:	Standard
Biometrics Division:	DB II
Statistical Reviewer:	Yoonhee Kim, PhD (Team Lead)[1]
Concurring Reviewers:	Pablo Bonangelino (Supervisory Mathematical Statistician)
Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity
Clinical Team:	Medical Officer: Mari Suzuki Medical Team Leader: Justin Penzenstadler
Project Manager:	Anne (Christine) Wright

Keywords: Type 2 diabetes, pediatric study, DPP4 inhibitor, shared control, second randomization, placebo washout imputation

[1] The primary statistical reviewer, Dr. Roungu Ahmmad, contributed to this submission between January and August 2024.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

AstraZeneca submitted supplemental new drug application (sNDA) 022350 S-026 for ONGLYZA (saxagliptin or saxa) and sNDA 200678 S-028 for KOMBIGLYZE XR (saxa and metformin HCI extended-release). Saxa is currently indicated for treating adults with type 2 diabetes mellitus (T2DM) as adjunct to diet and exercise. In the current submission, the sponsor proposes labeling updates in Section 8.4: Pediatric Use. The label updates of both products were based on a single Phase 3 clinical 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). This study was submitted in compliance with pediatric PMR-3199-1, which applies to all drug products containing saxa, saxa + HCI, and dapagliflozin or dapa. This review focuses on saxa and saxa +HCI products. The statistical review under NDAs 202293 and 205649 is relevant to dapa.

1.1 Brief Overview of Clinical Study

This study D1680C00019 was a 26-week Phase 3b, multicenter, randomized, placebo-controlled, double-blind, parallel-group study intended to evaluate efficacy and safety of saxa 2.5 mg and 5 mg combined vs placebo after 26 weeks treatment in pediatric patients with T2DM. The primary efficacy endpoint was assessed at the end of 26 weeks of double-blind treatment. Total of 164 eligible patients with HbA1c of 6.5% to 10.5% at screening were randomized in 1:1 to receive saxa 2.5 mg, or placebo. Patients were stratified by baseline antidiabetic medication (Metformin, insulin, or a combination of both), sex, and age (10 to 15 years and 15 to 18 years).

At second randomization, all patients with Week 12 HbA1c values < 7% were to remain on low-dose treatment saxa 2.5 mg, or placebo, and patients with Week 12 HbA1c values ≥ 7% were to be randomized in a 1:1 ratio to continue low-dose treatment saxa 2.5 mg or to high-dose treatment of saxa 5 mg or placebo.

1.2 Major Statistical Issues

There were 6.8% (saxagliptin) and 7.9% (placebo) missing data in changes in HbA1c from baseline at Week 26 for primary endpoint assessments. The applicant handled missing data appropriately using multiple imputation based on placebo washout method due to lack of retrieved dropouts. There were no statistical issues with handling missing data.

1.3 Collective Evidence

Table 1 summarizes the primary efficacy results. This study did not demonstrate a significant treatment effect of pooled saxa compared to placebo for the primary endpoint changes in HbA1c from baseline to Week 26 for the pediatric patients (Table 1). The results from sensitivity analyses were similar to the primary efficacy results (Section 3.2.4). The results of secondary

endpoint analyses were consistent with the primary analysis result. Subgroup analyses on the primary efficacy endpoint demonstrated consistent results in subgroup levels defined by age, sex, race, region, ethnicity and background anti-diabetic medications (Section 4). The risk of hypoglycemia was comparable in subjects receiving saxa compared to placebo (Section 3.3).

Table 1. Primary Efficacy Results on HbA1c (%) Change from Baseline at Week 26

Efficacy endpoint statistics	**Pooled Saxagliptin N=88**	**Placebo N=76**
Baseline HbA1c, Mean (SD)	8.02 (1.43)	7.96 (1.63)
Week 26 Missing, n (%)	6 (6.8)	6 (7.9)
Change from baseline to Week 26[1], LS Mean (SE)	0.06 (0.19)	0.50 (0.20)
Difference from Placebo		
LS Mean difference (95% CI)		-0.44 (-0.93, 0.05)
Two-sided P-value		0.078

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

[1] The least square (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: The sponsor's clinical study report (CSR) page 135, and Statistical Reviewer's Analysis, data: adsl.xpt, adeff.xpt

1.4 Conclusion and Recommendations

The study of D1680C00019 did not establish the effectiveness of saxa for the treatment of pediatric patients with T2DM. The applicant only sought to add the study information in Section 8.4: Pediatric Use without an efficacy claim for pediatric patients with T2DM to fulfill the PMR. We recommend approval of updating the Section 8.4.

2 INTRODUCTION

2.1 Overview

Study D1680C00019 was designed to test the efficacy and safety of saxa (DPP4 inhibitor), and dapa (SGLT2 inhibitor) in improving glycemic control in pediatric patients with T2DM aged 10 to 17 years without increasing hypoglycemia risk to fulfill the post marketing requirement. This statistical review focuses on saxa, saxa + HCI under NDA 022350 and NDA 200678, respectively. Refer to a separate review for dapa, dapa + HCI under NDA 202293 and NDA 205649. The study started on October 11, 2017, and was 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. A total of 245 patients were randomized from 94 sites in 21 countries: 81 patients to the dapa group, 88 patients to the saxa group, and 76 patients to the placebo group.

An overview of the study design, and preliminary findings are presented in Table 2.

Table 2. Overview of Study D1680C00019

Trial ID	Phase and Design*	Treatment/ Sample Size	Endpoint/ Analysis	Preliminary Findings
D1680C00019	MC, R, DB, PG, PC trial (26 weeks)	Saxa 2.5 mg or 5 mg (saxa pooled)/ N=88 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 HbA1c, treatment, and randomization strata (sex, age, and background medication)	Superiority of the primary endpoint was not demonstrated for Saxa The PBO-adjusted LS-means in HbA1c reduction (95% CI): -0.44% (95% CI: -0.93, 0.05) p = 0.078

Source: The sponsor's clinical study report (CSR) page 135
* 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 randomized 1:1 to continue on low-dose treatment or up titrate to high-dose treatment (saxa 5 mg) starting from Week 14

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:

NDA 022350/S-026 Onglyza (saxagliptin) tablets
\\CDSESUB1\evsprod\NDA022350\0266

NDA 200678/S-028 Kombiglyze XR (saxagliptin and metformin HCl extended release) tablets
\\CDSESUB1\evsprod\NDA200678\0206

The following documents were used to support this review:

- Clinical Study Report (CSR)
- Documentation of Statistical Methods

- Protocol and Statistical Analysis Plan (SAP)
- Regulatory Response to Information Request
  - \\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%.
  - \\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.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submission of datasets and files did not encounter any issues to data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

The study D1680C00019 was a Phase 3b, multicenter, randomized, placebo-controlled, double-blind, parallel-group design to evaluate the efficacy and safety of saxa 2.5 mg and/or 5 mg dosing regimen vs placebo after 26 weeks of treatment period in pediatric patients with T2DM. Figure 1 represents the study design framework. This study consisted of a maximum 6-month screening period, 2-week lead-in period, 26-week short term (ST) treatment period, 26-week long-term (LT) period, 28-day follow-up period, and 104-week post study visit.

First Randomization at Day 1
A total of 164 patients were randomized in a 1:1 ratio to either the placebo arm or the saxa 2.5 mg arm on Day 1 of the ST treatment period. A stratified randomization was conducted on Day 1 based on baseline antidiabetic medication use (metformin, insulin, or a combination of both), sex (male vs female), and age (10 to below 15 years and 15 to below 18 years).

Second Randomization at Week 14
All patients underwent blinded HbA1c assessments at Week 12, and a second randomization took place at Week 14, based on the Week 12 HbA1c values. Patients who achieved HbA1c values < 7% at Week 12 remained on previously assigned saxa 2.5 mg or placebo. Patients who failed to achieve HbA1c value <7%, underwent a second randomization at week 14 in a 1:1 ratio

to either 2.5 mg o 5 mg (saxa or matching placebo) . The primary endpoint HbA1c change from baseline was assessed at the end of the ST treatment period (i.e., Week 26).

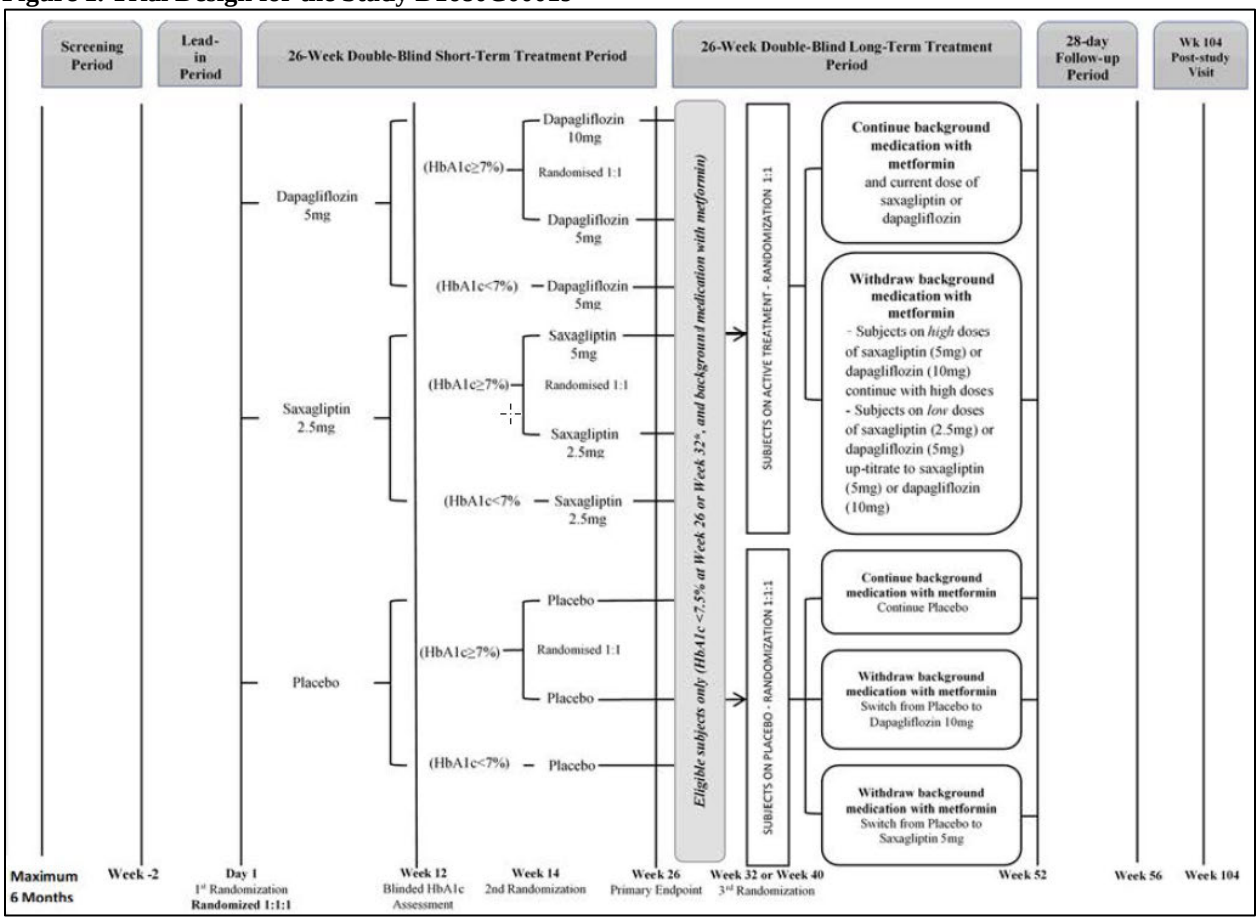
Randomized withdrawal of metformin at Week 32 or Week 40

After the primary endpoint assessment (ST period), 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. Saxa 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 5 mg saxa for subjects previously with high dose (5 mg) and up-titrate to saxa 5 mg for subjects previously with low dose (2.5 mg). Placebo subjects were randomized in a 1:1 ratio to either 1) continue background medication with metformin or 2) withdraw background medication with metformin but switch from placebo to saxa 5 mg.

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 for the Study D1680C00019



Source: The sponsor's clinical study report (CSR) page 42

The primary objective of the study was to determine if there will be a greater mean reduction from baseline at Week 26 in HbA1c of saxa (2.5 mg or 5 mg pooled) compared to placebo in pediatric patients with T2DM.

Sample Size

The sample size determination of the study was pre-specified in SAP. Assuming a treatment effect of -0.75 for the active treatment arm vs. placebo and a 1.7% standard deviation (SD) after a blinded interim check for the SD as recommended by the Agency, a sample of 81 subjects per initial randomized treatment arm (162 subjects in total) would provide 80% power at a two-sided alpha of 0.05. In the study, total of 164 patients (88 patients on saxa and 76 patients on placebo) were randomized and treated. The pooled SD for the saxa and placebo groups was 1.54% and estimated treatment effect was -0.44% for saxa after placebo adjustment. The study was adequately powered.

Primary Endpoint

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

Secondary Endpoints

- Change from baseline in fasting plasma glucose (FPG) (mg/dL) at Week 26
- Incidence of HbA1c < 7.0% at Week 26

3.2.2 Statistical Methodologies

The sponsor pre-specified an estimand framework for statistical analyses in the SAP. Following are the key components of estimand for the primary efficacy analysis.

Population and 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. There were 200 imputed datasets generated, and Rubin's Rule was used to combine the results of the analysis.

Weighting Scheme

Secondary hypotheses explored whether dose-titration to saxa 5 mg would benefit non-responders with HbA1c >7% compared to saxa 2.5 mg. Each hypothesis test from the secondary

hypotheses were 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 saxa 2.5 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 $\omega = 1$. At Week 14, HbA1c ≥7.0% (non-responder) were randomized to either up titrate to 5 mg (TITR5) or continued with 2.5 mg (TITR2.5). The saxa non-responders who were up titrated to saxa 5 mg would have their weights transferred to the saxa non-responders where randomized to continue with saxa 2.5 mg (i.e., the TITR2.5 group had $\omega = 2$, and the TITR5 group had $\omega = 0$). This way, the TITR5 group were represented by the TITR2.5 group. All other subjects not involved in the second randomization had $\omega = 1$. The diagonal matrix W was created accordingly and used in the ANCOVA model as the weight matrix.[2]

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

In the weight matrix W, I is an identical matrix with its dimension specified by the subscript. n is the sample size for each treatment arm, r is the proportion of the subjects in the saxa arm. I_n indicates $\omega = 1$ for all subjects in the placebo arm, I_{rn} indicates $\omega = 1$ for saxa responders; $2 * \boldsymbol{I}_{\frac{(1-r)n}{2}}$ indicates $\omega = 2$ for saxa non-responders randomized to remain on saxa 2.5 mg and $\mathbf{0} * \boldsymbol{I}_{\frac{(1-r)n}{2}}$ indicates $\omega = 0$ for saxa non-responders up titrated to saxa 5 mg. As similar weighting scheme was applied for the comparison of saxa up-titration to 5 mg vs placebo, where the transfer of weight was from low dose to high dose. Since the two hypothesis tests from the secondary hypothesis share the same subset of saxa responders, the comparisons of low dose and high dose to placebo are highly correlated.

Multiplicity Adjustment

The primary and secondary efficacy endpoints were analyzed using hierarchical testing at a 2-sided alpha level of 0.05. 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 saxa compared to placebo. After having obtained statistically significant result for the primary hypothesis, secondary hypotheses that compare different saxa regimen groups against placebo were to be 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 (saxa responders or TITR5) vs Placebo

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

    - of the low-dose treatment regimen (saxa responders or TITR2.5) vs Placebo
- Mean reduction in FPG from baseline at Week 26
    - of the pooled saxa 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 saxa vs placebo
    - of the low-dose/high-dose treatment regimen vs placebo
    - of the low-dose treatment regimen vs placebo
- For the high dose vs low dose regimen
    - 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

An ANCOVA was used to test the primary hypothesis, with HbA1c change from baseline at Week 26 as the response variable, and treatment, baseline HbA1c, sex (male vs female), baseline age stratum (<15 years vs 15 to <18 years), and background antidiabetic medication (metformin only vs insulin + metformin) as covariates.

Sensitivity Analysis

The return-to-baseline (RTB) method was used as a sensitivity analysis to check the robustness of the primary analysis result. 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.

3.2.3 Patients disposition, demographic and baseline characteristics

Table 3 represents a summary of patient's disposition and data capture for this study. All randomized subjects received at least one dose of the study drug. At Week 14, 88 subjects initially randomized to the saxa 2.5 mg were still on treatment. 52 (59.1%) subjects were HbA1c ≥7.0% (non-responders) at Week 12 and underwent a second randomization to either saxa 5 mg (high-dose, n=26) or saxa 2.5 mg (low-dose, n=26). There were 82 (93.2%) patients in the saxa group and 66 (86.2%) patients in the placebo group who remained on study drugs throughout the 26-week ST treatment period. Of the randomized subjects, 6 (96.8%) in the saxa group and 11 (13.4%) in the placebo group discontinued the study treatment, and 5 (6.2%) in the saxa group and 8 (10.5%) in the placebo group discontinued study during the ST treatment period. At Week 26, six subjects (6.8%) from the saxa 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 (short term period) and Data Capture (HbA1c at Week 26)

Treatment Arm (# of randomized subjects)	Saxagliptin pooled 2.5 mg and 5 mg QD N=88	placebo N=76	Total N=164
Randomized [n]	88	76	164
Randomized and treated with at least 1 dose [n (%)]	88 (100)	76 (100)	164 (100)
Discontinuation from study treatment up to Week 26 [n (%)]	6 (6.8)	11 (13.4)	17 (10.4)
Lost to follow-up [n]	1	0	1
Withdrawal by subject [n]	4	7	11
Others [n]	1	4	5
Discontinuation from study up to Week 26 [n (%)]	5 (5.7)	8 (10.5)	13 (7.9)
Lost to follow-up [n]	4	1	5
Withdrawal by subjects [n]	1	7	8
Completed 26-week HbA1c [n (%)]	83 (94.2)	70 (92.1)	153 (92.7)
On Treatment [n]	82	66	148
Off Treatment (Retrieved Dropouts) [n]	1	4	5
Missing in 26-week HbA1c [n (%)]	6 (6.8)	6 (7.9)	12 (7.3)
On Treatment [n]	0	0	0
Off Treatment [n]	6	6	12

Abbreviations: QD = once daily
Source: Figure 5, 6 of CSR and Statistical Reviewer's Analysis

Table 4 shows the summary of the patient's demographics and baseline characteristics. The population consisted of 60.2% females, while 48.9% were ≥ 10 and < 15 years of age and 56.8% were white. There were slightly higher Whites and Hispanic population on pooled saxa arm compared with placebo. Based on the summary, demographics and baseline characteristics were well balanced between the saxa and the placebo groups.

Table 4. Demographics and Baseline Characteristics

	Pooled saxagliptin (N = 88)	Placebo (N = 76)	Total, (N = 164)
Age (in Years)			
Mean (SD)	14.5 (1.75)	14.7 (1.64)	14.6 (1.7)
Median	15.0	15.0	15.0
IQR	12.0, 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 group (years) n (%)			
≥ 10 and < 15	43 (48.9)	35 (46.1)	78 (48.0)
≥ 15 and < 18	45 (51.1)	41 (53.9)	86 (52.0)
Sex, n (%)			
Male	35 (39.8)	32 (42.1)	67 (40.9)
Female	53 (60.2)	44 (57.9)	97(59.2)
Race n (%)			
White	50 (56.8)	32 (42.1)	82 (50)
Black or African American	4 (4.5)	3 (3.9)	7 (4)
Asian	23 (26.1)	24 (31.6)	47 (29)
Native Hawaiian or Other Pacific Islander	0 (0.0)	3 (3.9)	3 (2.0)
American Indian or Alaska Native	7 (8.0)	12 (15.8)	19 (11.0)
Other	4 (4.5)	2 (2.6)	6 (4.0)

Ethnic group n (%)			
Hispanic or Latino	43 (48.9)	34 (44.7)	77 (47)
Not Hispanic or Latino	45 (51.1)	42 (55.3)	87 (53)
Geographic region n (%)			
Asia/Pacific	26 (29.5)	23 (30.3)	49 (29.8)
Europe	15 (17.0)	17 (22.4)	32 (19.5)
Latin America	25 (39.8)	23 (30.3)	48 (39.3)
North America	12 (13.6)	13 (17.1)	25 (15.2)
Baseline BMI Z-score			
Mean (SD)	1.8 (0.69)	1.5 (0.8)	1.6 (0.8)
Median	1.9	1.6	1.7
IQR	1.4, 2.3	0.9, 2.1	1.2, 2.2
Min, Max	-0.6, 2.9	-1.7, 3.0	-1.7, 3.0
Baseline HbA1c (%)			
Mean (SD)	8.0 (1.4)	7.9 (1.6)	7.9 (1.5)
Median	7.7	7.6	7.7
IQR	6.9, 9.2	6.6, 9.1	6.8, 9.2
Min, Max	5.5, 12.2	5.2,12.0	5.2, 12.2
Background Diabetes Medication, n (%)			
Insulin	12 (13.6)	9 (11.8)	21 (12.8)
Metformin	45 (51.1)	40 (52.6)	85 (51.8)
Metformin and Insulin	31 (35.2)	27 (35.5)	58 (35.4)

Source: Statistical Reviewer's Analysis and the sponsor's CSR Table 15.

3.2.4 Results and Conclusions

Primary Endpoint: HbA1c (%) Change from baseline at Week 26

Table 5 displays the results for pooled saxa vs placebo regarding effect on HbA1c change from baseline at Week 26 (primary efficacy analysis). The mean difference from baseline at Week 26 for pooled saxa is 0.06% and 0.50% for placebo. The treatment effect (LS-mean difference) of pooled saxa to placebo with 95% confidence interval (CI) is -0.44% (-0.93, 0.05). The results were not statistically significant (p-value=0.078). The formal hypothesis testing is stopped due to non-significance of the primary endpoint and further analysis results in this review are all exploratory purpose.

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

Efficacy endpoint statistic	**Saxagliptin pooled l2.5 mg and 10 mg] QD N=88**	**Placebo N=76**
Baseline, Mean (SD)	8.02 (1.43)	7.96 (1.63)
Week 26 Missing, n (%)	6 (6.8)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	0.06 (0.19)	0.50 (0.20)
Difference from Placebo[1]		
LS Mean difference (95% CI)		-0.44 (-0.93, 0.05)
Two-sided P-value		0.078

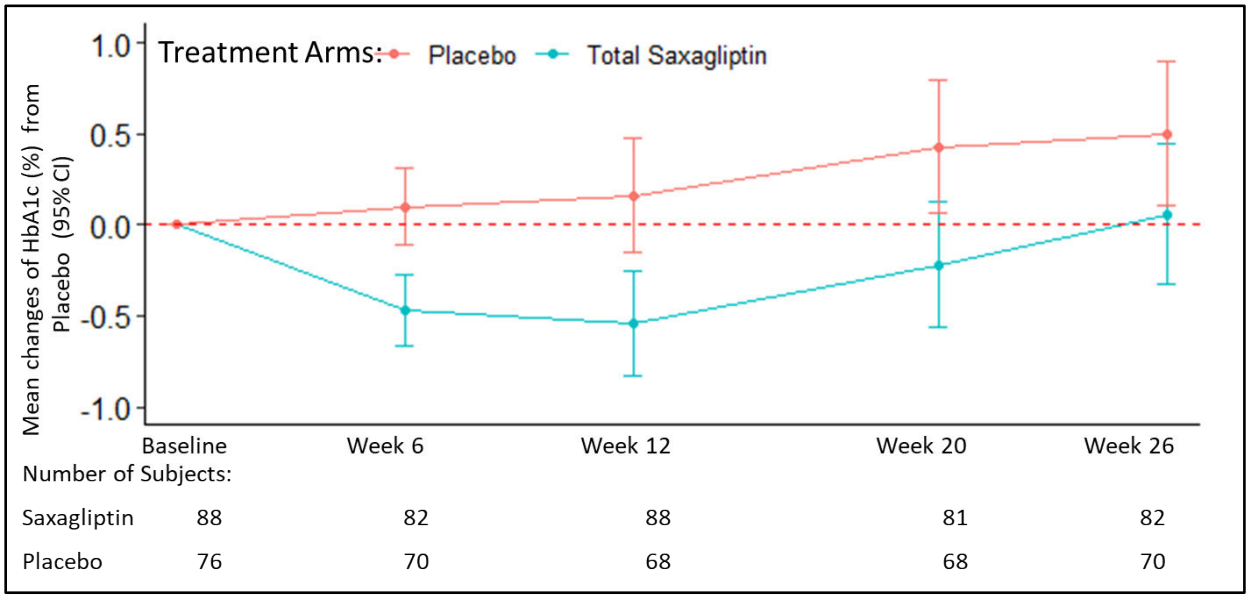
Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error

[1]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: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) page 131

To explore the reason of the negative primary results, Figures 2 illustrates the treatment effects at Weeks 6, 12, 20 and 26 among treatment groups. This figure shows that there were numerical difference in mean change in HbA1c from baseline between pooled saxa and placebo at Weeks 6, 12, and 20 but not at Week 26. Of note, a high number of rescue events were recorded in this study among patients with T2DM due to the rapid progression of their disease. A similar number of patients were rescued and continued in the study at Week 20 for the saxa and placebo groups (5/88 [5.7%] and 5/76 [6.6%] respectively). On the other hand, the placebo group rescued more than twice as many patients at Week 26 as the saxa group (4/88, 4.5% in saxa and 10/76, 13.2%, in the placebo group). It may partly explain why the saxa effect lost significance against placebo at Week 26 after remaining nominally significant in Weeks 6 through 20 (Figure 2) owing to this imbalance in patients receiving rescue medication. Note that there was a mean change of approximately 0.0% for the saxa group at Week 26, indicating the absence of a meaningful change from baseline despite the rescue medication.

Figure 2. Primary efficacy results on HbA1c change at Week 6, Week 12, Week 20, and Week 26 among pooled saxagliptin and placebo arm with corresponding the number of available subjects



Source: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) Figure 12.

Table 6 shows the sensitivity analysis using return-to-baseline (RTB) for the primary endpoint anlaysis. As shown in Table 6, the treatment effect of pooled saxa relative to placebo was -0.46% with 95% CI is (-0.88, 0.04). This sensitivity analysis confirms the conclusions of the primary analysis.

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

Efficacy endpoint statistic	**Saxagliptin pooled 2.5 mg and 10 mg] QD N=88**	**Placebo N=76**
Baseline, Mean (SD)	8.02 (1.43)	7.96 (1.63)
Change from baseline to Week 26, LS Mean (SE)	-0.01 (0.19)	0.45 (0.21)
Comparison to Placebo[1]		

LS Mean difference (95% CI)	-0.46 (-0.95, 0.03)
Two-sided nominal P-value	0.064

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
[1] 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 antidiabetic 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

Low-dose/High-dose Regimen and Placebo

Table 7 and 8 represent the analysis results for the secondary hypothesis. The low-dose/ high-dose treatment regimen group included 36 saxa responders (including the subjects who discontinued study drug/study before Week 14 [n=1] and 35 responders) and 26 saxa non-responders second-randomized to TITR5, and low-dose treatment regimen group included 36 saxa responders and 26 saxa non-responders second-randomized to TITR2.5. There were 4 (6.5%) subjects missing inTITR10 + Responders and 6 (7.9%) subjects missing in the placebo arm. The placebo-adjusted treatment effect (95% CI) was -0.51 (-1.05, 0.04) for low-dose/high-dose treatment regimen (Table 7) and -0.39 (-0.92, 0.14) for the subjects with the low-dose treatment regimen (Table 8).

Table 7. Change in HbA1c from baseline at Week 26 between the low-dose/high-dose treatment regimen and placebo.

Efficacy endpoint statistic	**TITR10 + Responders N=62**	**Placebo N=76**
Baseline, Mean (SD)	7.78 (1.38)	7.96 (1.63)
Week 26 Missing, n (%)	4 (6.45)	6 (7.89)
Change from baseline to Week 26, LS Mean (SE)	-0.04 (0.19)	0.47 (0.20)
Comparison to Placebo LS Mean difference (95% CI)		-0.51 (-1.05, 0.04)

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: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) table 30

Table 8. Change in HbA1c from baseline at Week 26 between the low-dose treatment regimen and placebo.

Efficacy endpoint statistic	**Saxagliptin (Low dose) N=62**	**Placebo N=76**
Baseline, Mean (SD)	7.78 (1.38)	7.96 (1.63)
	5 (8.06)	6 (7.89)
Change from baseline to Week 26, LS Mean (SE)	0.07 (0.19)	0.47 (0.19)
Comparison to Placebo LS Mean difference (95% CI)		-0.39 (-0.92, 0.14)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
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: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) table 30

Secondary Endpoint Analysis:

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 9 and 10, respectively. There was no difference between the pooled saxa and placebo arms with respect to FPG change from baseline (Table 9). The proportions of subjects with baseline HbA1c ≥ 7.0% and achieved HbA1c < 7.0% at Week 26 were presented in the Table 10. There were 61 subjects in the treatment arm who had the baseline HbA1c ≥ 7%, and 50 subjects in the placebo arm. The proportion of patients with baseline HbA1c ≥ 7% who achieved an HbA1c level < 7% at Week 26 was numerically higher in the pooled saxa group (21.3% vs 10.0%) than placebo group (Table 10). For the proportions of responders at Week 26, we recommended the analysis with including all randomized subjects (Table 11) instead of subset of population. The proportion of responders was numerically lower on the pooled saxa group compared to the placebo group (30.7% vs. 26.5%).

Table 9. **Change in FPG (mg/dL) from baseline at Week 26 between the pooled saxa and placebo.**

Efficacy endpoint statistic	**Pooled Saxagliptin N=88**	**Placebo N=76**
FPG at Week 26		
Baseline, Mean (SD)	172.25 (154.09)	152.02 (57.18)
Week 26 Missing, n (%)	8 (9.1)	8 (10.5)
Change from baseline to Week 26, LS Mean (SE)	-1.16 (7.13)	2.65 (7.56)
Comparison to Placebo		
LS Mean difference (95% CI)		-3.81 (-22.19, 14.58)

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 and the sponsor's clinical study report (CSR)

Table 10. Proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c < 7% at Week 26 between pooled saxa and placebo.

Efficacy endpoint statistic	**Pooled Saxagliptin N=88**	**Placebo N=76**
Number of subjects with baseline HbA1c >= 7%	61	50
Number (%) of subjects with baseline HbA1c >= 7% who achieve HbA1c < 7% at Week 26, n (%)	13 (21.3)	5 (10.0)

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated,
Source: Statistical Reviewer's Analysis and the sponsor's clinical study report (CSR) Table 30.

Table 11. Proportion of Subjects who achieved HbA1c < 7.0% at Week 26 in all randomized population.

Efficacy endpoint statistic	**Pooled Saxagliptin N=88**	**Placebo N=76**
Subjects with HbA1c < 7.0% at baseline, n (%)	27 (30.7)	26 (34.2)
Average # of responders across imputed datasets, n (%)	27.0 (30.7)	20.1 (26.5)

Secondary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated. The analysis was performed in the mITT using all observed data.
Source: IR responses and Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

Efficacy Conclusion:

This study failed to demonstrate significant difference between pooled saxa and placebo with respect to glycemic control in pediatric patietns with T2DM. The benefit of saxagliptin in treating T2DM in pediatric patients (10 to 17 years old) was not established in this study D1680C00019.

3.3 Evaluation of Safety

Hypoglycemia was evaluated in the safety set, which included all subjects who had received at least one dose of study treatments. From baseline to Week 26, subjects were analyzed for safety evaluation according to their assigned treatments: pooled saxa vs. placebo. A total of 25.0% (71 episodes) of subjects in the treatment arm and 26.3% (81 episodes) of those in the placebo arm experienced any hypoglycemia. Table 11 shows the results for those subjects who experienced more than one episode of hypoglycemia, including hypoglycemia events with plasma glucose (PG) < 54 mg/dL (level 2), as well as hypoglycemia events with severe (level 3) or PG < 54 mg/dL. Approximately equal numbers of hypoglycemia (levels 2,3) were observed in the saxa and placebo arms.

Table 12. Summary of Hypoglycemic Episodes during the ST Treatment Period

	Pooled Saxagliptin. N=88		Placebo, N = 76	
Hypoglycemia	Subjects with ≥ 1 episode (%)	# Episodes	Subjects with ≥ 1 episode (%)	# Episodes
Documented hypoglycemia (level 3)	2 (2.3)	6	4 (5.3)	4
Documented hypoglycemia (level 2)	8 (9.1)	18	6 (7.9)	9
Total documented Hypo (Level 2, 3)	10 (11.3)	24	10 (13.2)	13

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

Table 12 summarizes the safety analysis results for the rate of documented hypoglycemia with level 2 and the rate of documented hypoglycemic with level 2 or level 3 respectively. The 95% confidence interval for pooled saxa relative to placebo includes 1. Therefore, we conclude that saxa did not significantly increase the incidence of hypoglycemia episodes in this study.

Table 13. Rate Ratios of Hypoglycemia during the ST Treatment Period

Hypoglycemia	Rate Ratio (95% CI) Pooled Saxa (2.5 mg and 5 mg) vs Placebo
Hypoglycemia (level 2)	1.66 (0.57, 4.80)
Hypoglycemia (level 2 or level 3)	1.33 (0.51, 3.45)

Abbreviations: CI = confidence interval, QD = once daily, Incidence Rate Ratio estimated from a negative binomial model using log link and includes treatment and baseline HbA1c as fixed effects, and log (exposure in days/365.25) as an offset variable. The analysis was performed in the treated subject's data set using all observed data. A negative binomial regression model adjusting for treatment, sex, age group, and background antidiabetic medication with an offset for log [exposure time (years)] in the ST period.
Source: Statistical Reviewer's Analysis; adsl.xpt, adhypo.xpt, and IR response page 3 and 5

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were conducted based on the following baseline characteristics: sex (male vs female), age (<15 years vs 15 to 18 years), race (White vs Asian vs American Indian or Alaska Native vs Other), region (North America vs Asia vs Europe vs Latin America), ethnicity (Hispanic or Latino vs. Not Hispanic or Latino), background anti-diabetic medications (metformin only vs insulin and metformin) , and background anti-diabetic medications (metformin with/without vs Others). An ANCOVA was used to model the primary endpoint in each analysis, adjusting for treatment, baseline HbA1c, sex (except for the subgroup analysis based on sex), baseline age strata (except for the subgroup analysis based on age strata), and background antidiabetic medication (except for the subgroup analysis based on background antidiabetic medication). Similar to the primary efficacy analysis, missing data were imputed multiple times based on placebo washout and the results were combined using Rubin's Rule.

A Bayesian hierarchical model was used to estimate the shrinkage estimates for the individual study treatment effects. The effect of a treatment was assumed to be exchangeable, which allows them to be different but related at the same time. In general, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals for the point estimation.

For a given baseline characteristic with *k* subgroups, let, Y_i ($i = 1,2, ..., k$) be the observed sample estimate of the treatment effect in the 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 a set to the variance for the sample estimate.
- $\mu_i \sim N(\mu, \tau^2)$, where $\mu_i \sim \mathrm{N}(0, 16 * 1.54^2)$ and $1/\tau^2 \sim \mathrm{Gamma}\ (0.001, 0.001)$,

Before seeing the data, we assumed the treatment effect is 0 based on patient on each treatment arms. The patient level residual standard deviation was estimated of 1.54 based on the primary analysis results. Therefore, the variance of the prior distribution of the treatment effect would be $16 * 1.54^2$.

4.1 Subgroup analysis for Age, Sex, Race, and Region

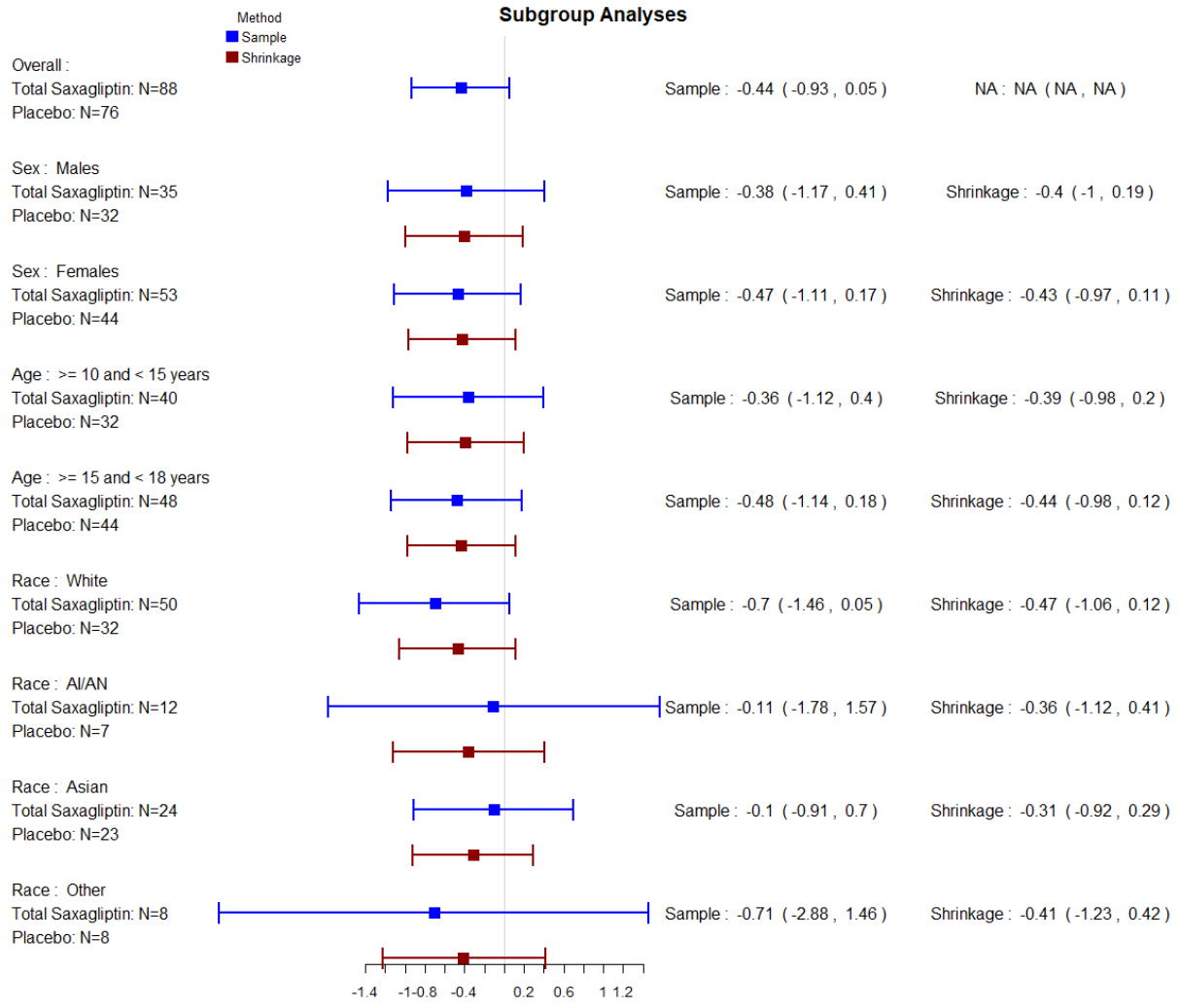
In this section, subgroup analyses are presented to summarize the results of the primary endpoint within each subgroup population. The following subgroups and levels were examined:

- Sex (Male vs Female)
- Age (<15 years vs 15 to 18 years)
- Race (White vs Asian vs American Indian or Alaska Native vs Other)

Figure 3 illustrate the sample estimates and shrinkage estimates of the treatment difference with respect to HbA1c change from baseline at Week 26. Plots of the sample and shrinkage estimates were provided with 95% confidence intervals and credible intervals, respectively. The shrinkage

estimate had less variability than the sample estimate and was narrower confidence/credible interval of the point estimate. When performing the subgroup analysis on race, the race categories Black or African American (n=10, in saxa group 7, and in placebo group 3), Native Hawaiian or other Pacific Islander (n=3, in saxa group 0, in placebo 3), and other races (n=5, saxa group 3, placebo 2), were combined into the race category "Others", due to insufficient samples. Table 17 represents a descriptive statistics of mean HbA1c at baseline and changes from baseline at week 26. The treatment effect for each subject in the "Others" category represent in the forest plots. Subgroup analyses were consistent with primary analysis results. No interactions were found between subgroups and treatment.

Figure 3. Forest plot of subgroup analyses for Age, Sex, and Race: placebo-adjusted HbA1c change from baseline at Week 26



Abbreviations: AI/AN = American Indian or Alaska Native
Values on the negative side favor saxa, values on the positive side favor placebo.
Source: Statistical Reviewer's Analysis and CSR; adls.xpt, adeff.xpt

Table 14. Mean baseline HbA1c and mean change from baseline at Week 26, A breakdown of the race category "Others" considered in the subgroup analysis

Race group: Others	Pooled Saxagliptin	Placebo
Black or African American	**N = 7**	**N = 3**
Mean baseline HbA1c	7.82	8.43
Mean Change from baseline to Week 26	-0.39	-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	7.92	6.50
Mean Change from baseline to Week 26	-0.27	-0.30

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

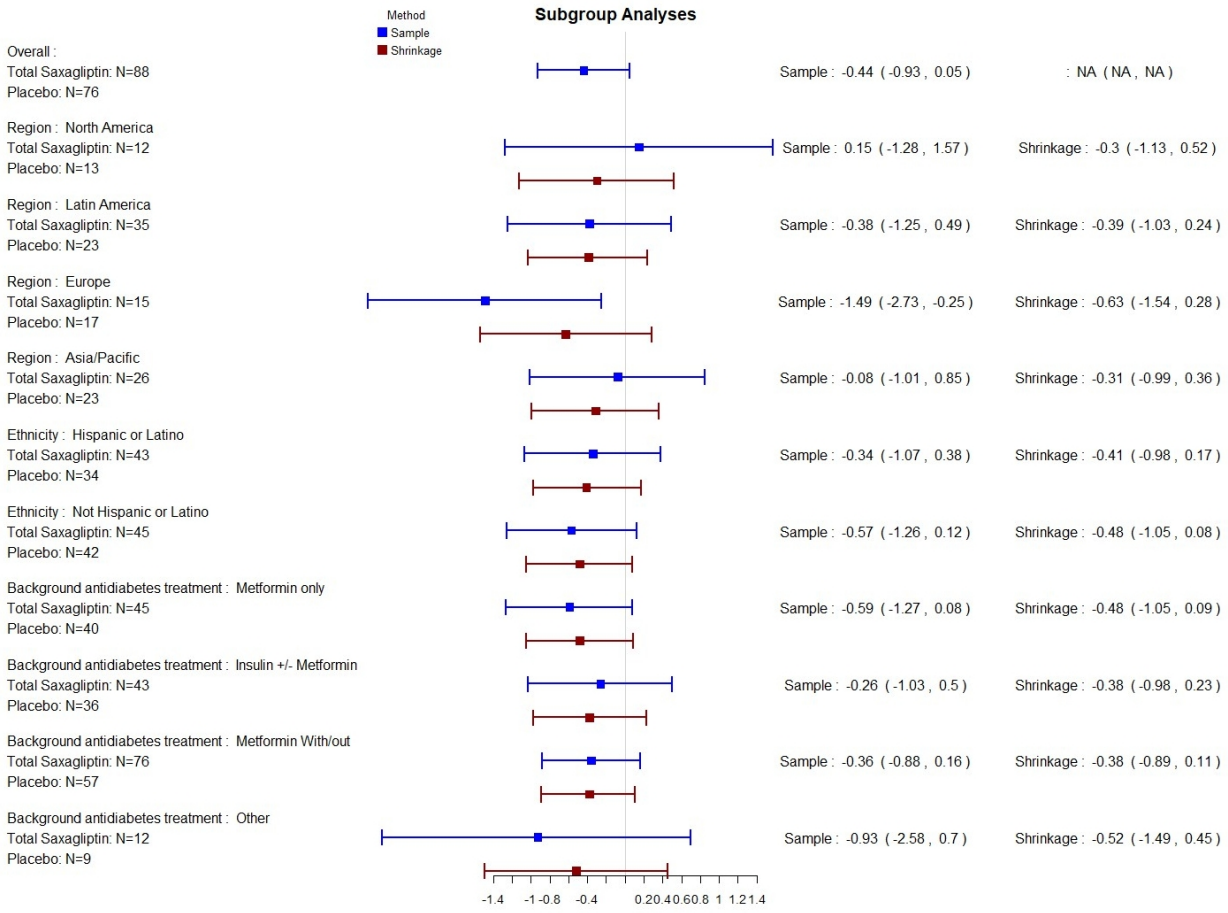
4.2 Other Special/Subgroup Populations

The following subgroups and levels were examined in this section to summarize the results of the primary endpoint within each subgroup population:

- Region (North America vs Asia vs Europe vs Latin America)
- Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino)
- Background anti-diabetic medications (metformin only vs insulin and metformin)
- Background anti-diabetic medications (metformin with/without vs Others)

Figure 4 shows the additional subgroup analysis for background antidiabetics medication, region, and ethnicity. The subgroup analysis was performed on background antidiabetic medication metformin only vs metformin and insulin, and metformin with or without insulin vs other (only insulin). Among 88 patients in the saxa arm, 45 patients were treated metformin only and 43 patients were metformin plus insulin. In addition, 76 patients received saxa regardless of whether they were receiving metformin background medication, while 12 patients received insulin only. Subgroup analyses were consistent with primary analysis results for these subgroup populations. No significant interactions were found between subgroups and treatment.

Figure 4. Forest plot of subgroup analyses for Region, Ethnicity, and Background Antidiabetic Medication: placebo adjusted HbA1c change from baseline at Week 26

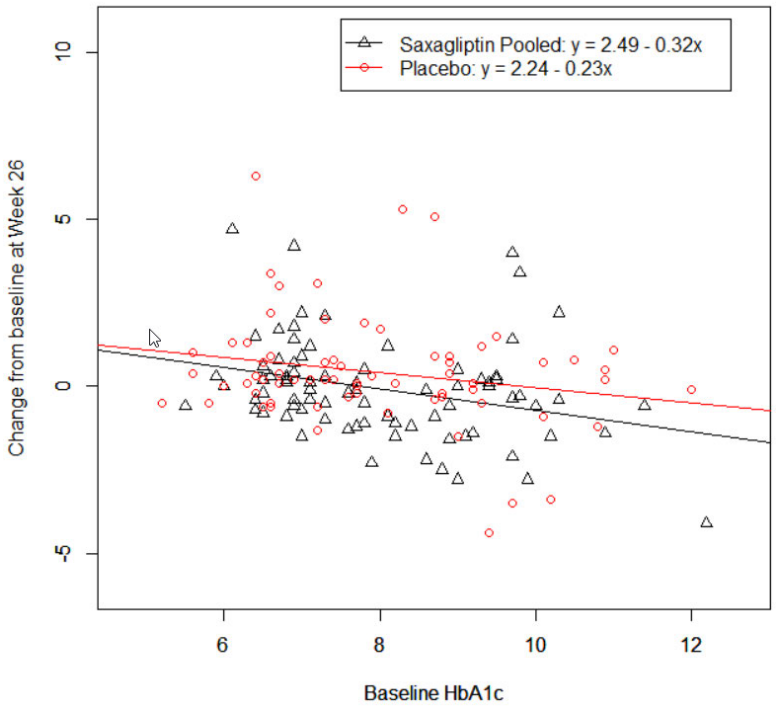


Values on the negative side favor saxa, values on the positive side favor placebo. North America indicates US.
Source: Statistical Reviewer's Analysis and CSR; adls.xpt, adeff.xpt

Baseline HbA1c as an effect modifier

The baseline HbA1c level is well known to be an effect modifier (i.e., the effect of treatment on the baseline HbA1c level will depend on the baseline measurement of HbA1c). A scatter plot of the HbA1c change from baseline at Week 26 compared to baseline HbA1c is shown in Figure 5. The points are color-coded according to the treatment arm. Plots of the pooled saxa and placebo, as well as parallel regression lines, indicate that there is no difference between the two treatment groups. Regression lines were computed and superimposed over the scatter points. Comparing pooled saxa and placebo, the slopes are almost parallel. This means that the treatment effect of pooled saxa relative to placebo changes very little as baseline HbA1c increases. Therefore, the treatment effect of saxa is not modified by baseline HbA1c.

Figure 5. Scatterplot of Change from Baseline vs Baseline HbA1c at Week 26



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

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The D1680C00019 study failed to demonstrate superiority of saxa over placebo in treating T2DM pediatric patients. There was a 6.8% missing rate for saxa and a 7.9% missing rate for placebo for the primary endpoint measurement. Missing data was handled by multiple imputation using placebo washout method.

5.2 Collective Evidence

The placebo-adjusted treatment effect for pooled saxa with respect to HbA1c change from baseline at Week 26 was -0.44, with a 95% CI (-0.94, 0.05). Of note, there was a mean change of approximately 0.0% for the saxa group at Week 26, indicating the absence of a clinically meaningful change from baseline. Sensitivity analyses using return-to-baseline approach that inspected the impact of missing data assumptions demonstrated similar findings to the primary analysis results. Secondary endpoints analyses and subgroup analyses demonstrated consistent conclusions with the primary analysis. For safety, saxa did not significantly increase the incidence of hypoglycemia episodes compared to placebo in this study.

5.3 Conclusions and Recommendations

There was no statistical evidence that saxagliptin is effective compared to placebo in treating T2DM pediatric patients in the study D1680C00019 regarding glycemic control. As the applicant only sought to add the study information to Section 8.4 of the product label without an efficacy claim for saxagliptin use among pediatric patients (10 to 17 years) with T2DM, we recommend approval of updating the label.

5.4 Labeling Recommendations

In Section 8.4, following sentences will be used for updating the label.

"*The safety and effectiveness of ONGLYZA as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus have not been established in pediatric patients.*"

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YOONHEE KIM
08/26/2024 01:02:53 PM
The primary statistical reviewer, Dr. Roungu Ahmmad, contributed to this submission between January and August 2024.

PABLO E BONANGELINO
08/26/2024 03:55:56 PM