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 022271, NDA 203414 |
| **Supplement #:** | S-015 and S-016 |
| **Drug Name:** | alogliptin (Nesina) and alogliptin and metformin hydrochloride (Kazano) tablets |
| **Indication(s):** | [Approved] An adjunct to diet and exercise to improve glycemic control in adults with T2DM<br>No new indication was proposed |
| **Applicant:** | Takeda |
| **Date(s):** | Receipt date: November 27, 2022<br>Review due date: June 16, 2023<br>PDUFA date: July 28, 2023 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | DB II |
| **Statistical Reviewer:** | Sung Hee Kim, PhD, Mathematical Statistician |
| **Concurring Reviewers:** | Yoonhee Kim, PhD, Team Leader (TL) |
| **Medical Division:** | Division of Diabetes, Lipid Disorders, and Obesity |
| **Clinical Team:** | Kim Shimy, MD / Michelle Carey, MD (TL) |
| **Project Manager:** | Michael Oyewole |
| **Keywords:** | T2DM in pediatrics, Glycemic Control |

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# 1 EXECUTIVE SUMMARY

The applicant, Takeda, submitted a supplemental new drug application (sNDA) 022271 S-015 for NESINA (alogliptin) and sNDA 203414 S-016 for KAZANO (alogliptin and metformin hydrochloride) to propose changes to *Section 8.4: Pediatric Use* in the labels. The proposed changes include additional information on the efficacy and safety of alogliptin for pediatric use. Specifically, alogliptin was not effective among the pediatric population based on the results from pediatric study: SYR-322-309 for alogliptin as treatment for type 2 diabetes mellitus (T2DM) in pediatrics (10 to 17 years old), either as an initial oral therapy (NESINA) or as add-on to metformin (KAZANO). This study was conducted to address the Post Marketing Requirements (PMRs) 2007-2, 2007-3, and 2009-1.

## 1.1 Brief overview of Clinical Study

The submission included the results of study SYR-322-309, a Phase 3, multi-center, randomized, double-blinded, placebo-controlled 52-week study for pediatrics (10 to 17 years old). A up to 2 weeks screening period was followed by the 52-week duration of treatment period and a follow-up visit 2 weeks after the end-of-treatment visit. The rationale of the study is to evaluate the superiority of alogliptin (25 mg once daily (QD)) compared to placebo in pediatrics with T2DM who have inadequate glycemic control despite diet and exercise, with or without metformin and/or insulin.

The primary endpoint was change from baseline at Week 26 in HbA1c. The secondary endpoints are change from baseline at Week 12, 18, 39, and 52 in HbA1c. Safety was assessed through the evaluation of hypoglycemia in this review.

## 1.2 Major Statistical Issues

The study had large missing data (18.7% with alogliptin, 17.1% with placebo) and few retrieved dropouts for primary endpoint assessments. Two statistical review issues were found:

- **Estimand:** The applicant did not specify the definition of Estimands in the protocol, statistical analysis plan (SAP), or clinical study report (CSR). Further, the applicant excluded subjects who received hyperglycemic rescue before Week 26 from the primary analysis implying hypothetical strategy for these intercurrent events.
- **Analysis method to deal with missing data:** The applicant used mixed model for repeated measure (MMRM) as the primary analysis to deal with large missing data. MMRM approach may be inappropriate due to overestimation of the treatment effect under the assumption of missing at random. And there were insufficient number of retrieved dropouts in the study.

To address above issues in this review, the efficacy of alogliptin was evaluated with preferred estimand using treatment policy strategy for intercurrent events. This reviewer used all randomized and treated subjects without excluding subjects who received hyperglycemic rescue before Week 26 in the primary analysis. Due to insufficient number of retrieved dropouts, this reviewer handled missing data using placebo washout multiple imputation to reflect the missing not at random, which is more plausible assumption in this study (Section 3.2.2).

## 1.3 Collective Evidence

The study did not demonstrate efficacy of alogliptin regarding HbA1c reduction when compared to placebo, either as a monotherapy or as an add-on to metformin (Section 3.2.4). The change in HbA1c at Week 26 from baseline in subjects treated with alogliptin (N=75) was 0.02% compared to 0.20% in subjects treated with placebo (N=76), resulting in a difference of -0.18% (95% confidence interval (CI): -0.84, 0.49) in Table 1. Sensitivity analysis and secondary endpoints analyses confirmed non-significant effect of alogliptin. Subgroup analyses on the primary efficacy endpoint demonstrated consistent findings in subgroup levels defined by sex, age, race, ethnicity, geographic region, and schedule of antidiabetic therapy status (Section 4).

Alogliptin did not significantly increase the incidence of hypoglycemic episodes (Section 3.3).

**Table 1: Primary Analysis Results for HbA1c (%) Change from Baseline at Week 26**

| | **Alogliptin 25 mg QD N=75** | **Placebo N=76** |
|---|---|---|
| Baseline, Mean (SD) | 8.16 (1.51) | 8.11 (1.33) |
| Week 26 Missing, n (%) | 14 (18.7) | 13 (17.1) |
| Change from baseline to Week 26, LS Mean (SE) | 0.02 (0.25) | 0.20 (0.23) |
| Comparison to Placebo[1] | | |
| LS Mean difference (95% CI) | | -0.18 (-0.84, 0.49) |
| Two-sided P-value | | 0.60 |

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputation placebo wash-out model.
Source: Statistical Reviewer's Analysis

## 1.4 Conclusion and Recommendations

Since alogliptin did not establish the efficacy in the study of SYR-322-309, the applicant only sought to add the study information in Section 8.4: Pediatric Use without efficacy claim for pediatrics. From a statistical perspective, I recommend approval of updating the pediatric information.

# 2 INTRODUCTION

## 2.1 Overview

### 2.1.1 Class and Indication

Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. The current indication for alogliptin (NESINA®) is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The approved doses for alogliptin are 25 mg, 12.5 mg, or 6.5 mg once daily. Besides, alogliptin is also used to manufacture KAZANO® (a combination of alogliptin and metformin hydrochloride (HCI)). This product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and metformin is appropriate. The dosing should be individualized based on subjects' current regimen, effectiveness, and tolerability, between two recommended daily doses including (12.5 mg alogliptin and 500 mg metformin HCI) and (12.5 mg alogliptin and 1000 mg metformin HCI).

### 2.1.2 History of Drug Development

NESINA® (NDA 022271, IND 069707) and KAZANO® (NDA 203414, IND 101628) were approved in 2013 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Pediatric Research Equity Act (PREA) post marketing requirements (PMRs) were issued in 2013. The following PMRs were included for pediatric subjects between 10 and 17 years of age: NDA 022271 (NESINA®): PMR 2007-1, PMR 2007-2, PMR 2007-3 and NDA 203414 (KAZANO®): PMR 2009-1. After discussion and alignment with the FDA, PREA PMR 2007-2 and PREA PMR 2009-1 and PMR 2007-3 were combined into a single phase 3 study (SYR-322-309) to assess the safety and efficacy of alogliptin in the pediatric population. The protocol (Amendment 9) submitted on August 14, 2020 was reviewed by the statistical reviewer (IND 069707, SDN 892 and SDN 895) and the database was locked on April 15, 2022. All studies related to the PREA PMRs for both NESINA and KAZANO have been submitted to the respective NDAs (NDA 022271 and NDA 203414).

### 2.1.3 Specific Studies Reviewed

Table 2 below summarizes study SYR-322-309. Date first subject signed informed consent form was on October 14, 2016 and date of last subject's las visit was on February 14, 2022.

**Table 2: Summary of Trials to be Assessed in the Statistical Review**

| Trial ID | Phase and Design | Treatment Period | Follow-up Period | # of Subjects per Arm | Study Population |
|---|---|---|---|---|---|
| SYR-322-309 | Phase 3, multicenter, randomized, double-blind, placebo-controlled<br><br>Stratification factors: background antidiabetic regimen | 52 weeks* | 2-week follow-up | 75 on alogliptin 25 mg QD<br><br>77 on Placebo** | Pediatrics aged 10-17 years, inclusive, with T2DM and who were experiencing inadequate glycemic control with or without metformin and/or insulin |

*Primary endpoint assessment at Week 26
** One placebo subject was randomized but was not treated.

## 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 022271 S-015: \\CDSESUB1\evsprod\NDA022271\0237
NDA 203414 S-016: \\CDSESUB1\evsprod\NDA203414\0182

Regulatory response to Information Request (IR) for primary endpoint analysis including subjects who received hyperglycemic rescue before Week 26 and increasing the number of imputed datasets to 100 submitted on November 16, 2022

NDA 022271 S-015: \\CDSESUB1\evsprod\NDA022271\0240
NDA 203414 S-016: \\CDSESUB1\evsprod\NDA203414\0185

Regulatory response to Information Request (IR) for the investigation of numerically increasing treatment difference of changes in HbA1c from baseline at Weeks 39 and 52 submitted on March 10, 2023

NDA 022271 S-015: \\CDSESUB1\evsprod\NDA022271\0245
NDA 203414 S-016: \\CDSESUB1\evsprod\NDA203414\0190

Regulatory response to Information Request (IR) for primary endpoint analysis and subgroup analyses with the updated schedule of antidiabetic therapy status at randomization instead of at screening submitted on March 24, 2023

NDA 022271 S-015: \\CDSESUB1\evsprod\NDA022271\0246
NDA 203414 S-016: \\CDSESUB1\evsprod\NDA203414\0191

The following documents were used to support this review.

| |
|---|
| Clinical Study Report |
| Documentation of Statistical Methods |
| Protocol/Statistical Analysis Plan |
| Regulatory Response to Information Request submitted on November 16, 2022 |
| Regulatory Response to Information Request submitted on March 10, 2023 |
| Regulatory Response to Information Request submitted on March 24, 2023 |

All the datasets (both in ADAM format and STDM format) and the programming codes for the statistical analyses documented the NDA submission can be found under the subdirectory: m5/datasets.

# 3 STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

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

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

**Study Design**

Study SYR-322-309 was a multi-center, randomized, double-blind, placebo-controlled trial 52-week trial, with a 2-week screening period, followed by a 52-week treatment period, and 2-week follow-up (Figure 1). The primary objective was to evaluate the efficacy of 25 mg alogliptin QD compared with placebo when administered as monotherapy, or when added on a background of metformin alone, insulin alone, or a combination of metformin and insulin. The primary efficacy was measured by the glycosylated hemoglobin (HbA1c) change from baseline in Week 26 in pediatric subjects with T2DM. Subjects were randomized in a 1:1 fashion to alogliptin 25 mg or placebo.

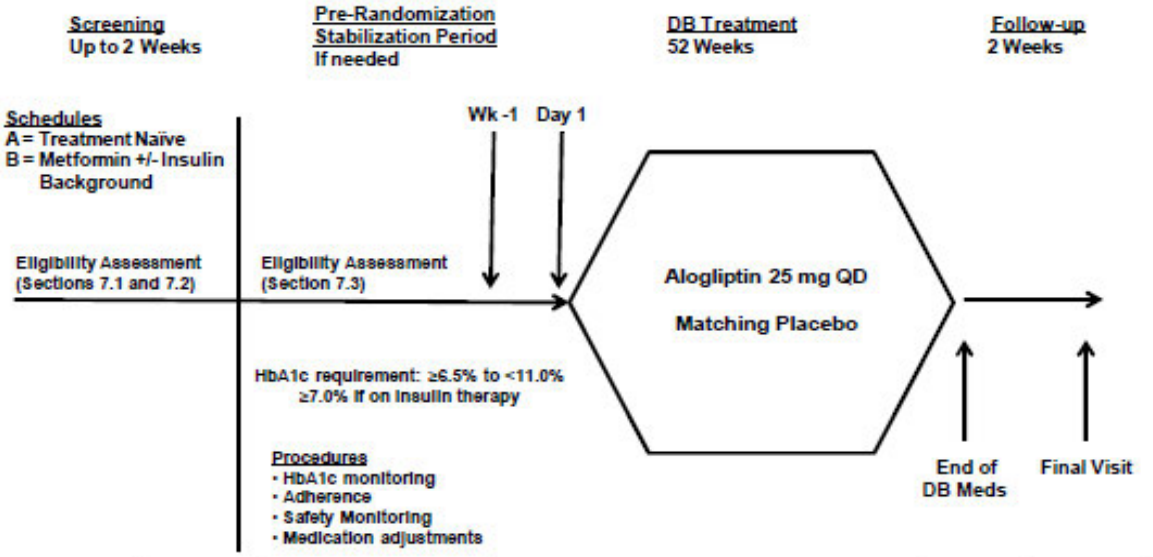
The study population were subjects who were at least 10 years of age and no more than 17 years of age, and who had T2DM as diagnosed by the American Diabetes Association and World Health Organization criteria. Further, subjects were required to have an HbA1c measurement greater than or equal to 6.5% and less than 11% at screening if the subject was treatment-naïve or on metformin alone, or an HbA1c measurement greater than or equal to 7.0% and less than 11% if the subject was on insulin alone or in combination with metformin.

At randomization, subjects were stratified by background antidiabetic regimen (Schedules A and B) and they have been receiving for the 12 weeks prior to the screening period as follows:

- Schedule A: Subjects who are naïve to antidiabetic therapy
- Schedule B: Subjects who are receiving metformin and/or insulin

***Reviewer's note:*** *Given the fact that schedule (A vs. B) of antidiabetic therapy status was assigned initially at screening instead of at randomization, the agency requested the applicant to perform additional exploratory analysis using the updated schedule variable at randomization on March 24, 2023. I validated the consistency of efficacy conclusion when using the updated schedule variable at randomization.*

**Figure 1: Design for Study SYR-322-309**




| | Screening | Pre-Randomization Stabilization Period (if needed) | | DB Treatment Period Weeks 1- 52 After Randomization [a] | | | | | | | End-of-Treatment Visit | Follow-Up Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Assessment | Screening Visit [b] | Every 3 Months [b] | Week -1 | Baseline Visit (Day 1) | 4[c] | 12 | 18 [d] | 26 | 32 [c] | 39 | 45 [c] | 52 | 54 [c] |
| Visit windows (days) | (Up to 14 Days) | | | | ±2 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±2 |

DB: double-blind; HbA1c: glycosylated hemoglobin; QD: once daily; Wk: week.
Section numbers refer to the relevant section of the protocol.
[a] Subjects who terminated double-blind study treatment prematurely were to complete an end-of-treatment visit and a follow-up visit 2 weeks after the end-of-treatment visit, and were to continue to be followed for the 52-week duration of the study and complete a projected Week 52 visit.
[b] The screening visit was to be scheduled within 2 weeks before Day 1 or the start of the pre-randomization stabilization period. During the pre-randomization stabilization period, subjects were to visit the study center at regular intervals according to the investigator's discretion but at least every 3 months and at Week -1 before randomization.
[c] The Week 4, 32, 45, and 54 visits were to be conducted only via a telephone call to the subject.
[d] The sponsor or its designee were to decide whether the Week 18 visit would be conducted as an in-clinic visit, or optionally, as a home health visit.

**Source: Clinical Study Report (CSR) Page 22**

## Primary Endpoint

HbA1c change from baseline at Week 26 (%-point)

## Secondary Endpoints

HbA1c change from baseline at Weeks 12, 18, 39, and 52

## Other Secondary Endpoints

- Incidences of HbA1c ≤6.5%, ≤7.0%, and ≤7.5% at Weeks 26 and 52
- Incidences of HbA1c decrease from Baseline ≥ 0.5% and ≥ 1.0% at Weeks 26 and 52

- Changes from baseline in 2-hr postprandial glucose (PPG) at Weeks 26 and 52
- Incidence of and time to hyperglycemic rescue events
- Changes from Baseline in fasting plasma glucose (FPG) at Weeks 12, 26, and 52
- Changes from Baseline in lipids, including total cholesterol, HDL-C, LDL-C, and triglycerides at Weeks 12, 26, and 52
- Changes from Baseline in body weight, height, body mass index (BMI) Z-scores, Tanner Stage Score findings, microalbuminuria, insulin-like growth factor-1, and IGF-binding protein 3 at Weeks 26 and 52

**Sample Size**

The determination of the study sample size, as initially specified in the SAP, is as follows. Assuming -0.50% treatment effect difference between the active treatment group (alogliptin) and the placebo group and a 0.9% standard deviation (SD), a sample size of 75 subjects per initial randomized treatment arm (150 subjects in total) would provide 93% power at a two-sided 0.05 level.

In the study, 152 subjects (75 in alogliptin and 77 in placebo) were randomized (Section 3.2.3). Since one placebo subject was not treated, the statistical analysis set includes 151 subjects (75 in alogliptin and 76 in placebo). The observed patient level residual standard deviation from the primary endpoint analysis was 1.9%, and the estimated treatment effect difference was -0.18 (Section 3.2.4). The study was underpowered for comparing alogliptin vs. placebo with a smaller effect size and a larger SD than the assumptions used in the sample size determination.

### 3.2.2 Statistical Methodologies

**Estimand**

The applicant did not pre-specify an estimand framework in the protocol or statistical analysis plan so this reviewer defined preferred estimand using treatment policy strategies for all intercurrent events.

- Primary estimand:
  - Treatment condition: alogliptin 25 mg QD or Placebo
  - Endpoint: Change (%) in HbA1c from baseline to Week 26
  - Population: The modified ITT (mITT) population, defined as all randomized and treated T2DM pediatric subjects who received at least 1 dose of study medication
  - Intercurrent events:
    - Treatment discontinuation
    - Initiation of rescue therapy

    Handling of data after intercurrent events: Under treatment policy strategies, all available data, regardless of initiation of rescue medication or treatment discontinuation will be used in the analysis
  - Population level summary: Difference in mean changes in HbA1c from baseline

**Primary analysis model to handle the missing data**

The applicant used a mixed model for repeated measure (MMRM) based on the mITT population excluding subjects who received hyperglycemic rescue before Week 26 as primary endpoint analysis. This is considered insufficient from a regulatory perspective, as an MMRM assumes data are missing at random, which is an unlikely scenario for most missing data in clinical trials. Agency recommended multiple imputation method instead of MMRM during IND communications. However, the applicant did not change the primary analysis method, but performed placebo washout imputation as a sensitivity analysis.

In this review, missing primary endpoints were multiply imputed based on the placebo washout approach and the primary endpoint was modeled with the ANCOVA adjusting for treatment, schedule (A/B), and baseline HbA1c based on the mITT population without excluding subjects who received hyperglycemic rescue before Week 26.

In the IR letter issued on November 16, 2022, we requested the applicant to perform primary endpoint analysis using the placebo washout imputation that includes subjects who received hyperglycemic rescue before Week 26 and increases the number of imputed datasets to 100. We validated the applicant's program codes and found that the data manipulation and imputation steps were technically different from Agency's recommendation as below:

Applicant's placebo washout imputation

The applicant imputed multiple times for missing week 26 HbA1c measurement using a modified placebo-based pattern mixture model (PMM).

Step 1: For each patient with missing Week 26 data, 100 measurements will be imputed, thus generating 100 complete datasets as follows:

- Subjects on alogliptin 25 mg with missing week 26 HbA1c measurement**:** A *multiple imputation regression* is used with sex, schedule (A/B) at screening, baseline and Week 26 data from placebo completers. None of the subjects' intermediate measurements will be used.

- Subjects on placebo with missing non-monotone week 26 HbA1c measurements**:** A *single chain MCMC method* is used with sex, schedule (A/B) at screening, baseline, intermediate, and Week 26 measurements from placebo completers. The subjects' intermediate measurements will be used.

- Subjects on placebo with missing monotone Week 26 HbA1c measurements: A *multiple imputation regression* is used with sex, schedule (A/B) at screening, baseline, intermediate, and Week 26 measurements from placebo completers. The subjects' intermediate measurements will be used.

Step 2: Each complete dataset after imputation will be analyzed using ANCOVA with treatment, schedule (A/B), and baseline HbA1c as covariates. Rubin's rule will be applied for inference.

Statistical Reviewer's placebo washout imputation

Step 1: Generate the monotone data including 100 measurements for each patient using sex, schedule (A/B) at screening, baseline and intermediate, and Week 26 measurements.

Step 2: For each patient with missing Week 26 data, 100 measurements will be imputed, thus generating 100 complete datasets as follows:

- Subjects on alogliptin 25 mg with missing Week 26 HbA1c measurement: A *multiple imputation regression* is used with sex, schedule (A/B) at screening, baseline and Week 26 data from placebo completers. None of the subjects' intermediate measurements will be used.

- Subjects on placebo with missing Week 26 HbA1c measurements: A *multiple imputation regression* is used with sex, schedule (A/B) at screening, baseline, intermediate, and Week 26 measurements from placebo completers. The subjects' intermediate measurements will be used.

Step 3: Each dataset will be analyzed using ANCOVA with treatment, schedule (A/B), and baseline HbA1c as covariates. Rubin's rule will be applied for inference.

In this review, subsequent analyses were performed using statistical reviewer's placebo washout imputation method.

**Statistical Reviewer's Sensitivity Analysis for the Primary Endpoint**

To check the robustness of primary endpoint analysis using placebo washout approach, missing primary endpoint was multiply imputed based on the return-to-baseline approach.

**Protocol Specified Control of Type I Error**

Since there were no key secondary endpoints, no multiplicity adjustment was specified.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics and baseline characteristics are displayed in Table 3 below. The population consisted of 68.9% females, 33.8% subjects at least less than 14 years of age, 58.3% white, and 48% from the United States. Overall, demographics were generally balanced between treatment arms. Ethnicity had large missing rate (52%).

**Table 3: Demographics and Baseline Characteristics**

| | Alogliptin 25 mg QD N=75 | Placebo N=76 | Total N=151 |
|---|---|---|---|
| Sex, n (%) | | | |
| Female | 53 (70.7) | 51 (67.1) | 104 (68.9) |
| Male | 22 (29.3) | 25 (32.9) | 47 (31.1) |
| Age, years | | | |
| Mean (SD) | 14.2 (1.92) | 14.3 (2.21) | 14.2 (2.06) |
| Median | 14.0 | 14.0 | 14.0 |
| IQR | 13.0, 16.0 | 12.0, 16.0 | 13.0, 16.0 |
| Min, Max | 10.0, 17.0 | 10.0, 17.0 | 10.0, 17.0 |
| Age categories, n (%) | | | |
| <14 Years | 23 (30.7) | 28 (36.8) | 51 (33.8) |
| >=14 Year | 52 (69.3) | 48 (63.2) | 100 (66.2) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 11 (14.7) | 14 (18.4) | 25 (16.6) |
| Asian | 0 | 1 (1.3) | 1 (<1) |
| Black or African American | 16 (21.3) | 16 (21.1) | 32 (21.2) |
| Multiple | 4 (5.3) | 1 (1.3) | 5 (3.3) |
| White | 44 (58.7) | 44 (57.9) | 88 (58.3) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 9 (12.0) | 6 (7.9) | 15 (9.9) |
| Not Hispanic or Latino | 26 (34.7) | 31 (40.8) | 57 (37.7) |
| Missing | 40 (53.3) | 39 (51.3) | 79 (52.3) |
| Antidiabetic therapy status, n (%) | | | |
| Schedule A | 13 (17.3) | 14 (18.4) | 27 (17.9) |
| Schedule B | 62 (82.7) | 62 (81.6) | 124 (82.1) |
| Region, n (%) | | | |
| US | 35 (46.7) | 37 (48.7) | 72 (47.7) |
| Others* | 40 (53.3) | 39 (51.3) | 79 (52.3) |
| Body mass index (BMI)(kg/m2) | | | |
| Mean (SD) | 33.7 (8.66) | 33.6 (7.86) | 33.7 (8.24) |
| Median | 32.4 | 31.2 | 31.7 |
| IQR | 27.0, 37.9 | 27.8, 38.9 | 27.7, 38.7 |
| Min, Max | 18.8, 68.1 | 20.6, 56.3 | 18.8, 68.1 |
| HbA1C Baseline Value | | | |
| Mean (SD) | 8.2 (1.51) | 8.1 (1.33) | 8.1 (1.42) |
| Median | 7.7 | 7.7 | 7.7 |
| IQR | 6.8, 9.3 | 7.0, 9.1 | 6.9, 9.2 |
| Min, Max | 6.3, 11.5 | 5.7, 11.3 | 5.7, 11.5 |

Abbreviations: QD = once daily, IQR = interquartile range, SD = standard deviation
*Others include the following countries: Brazil, Israel, Italy, Mexico, Russian Federation
Source: Statistical Reviewer's Analysis and CSR Table 11.c

The patient disposition is displayed in Table 4 below. The proportion of subjects on alogliptin arm who completed the 26-week treatment period was 81%, while the proportion of subjects on placebo who completed the 26-week treatment period was 83%. Lost to follow-up and voluntary withdrawal were the primary reasons for study or treatment discontinuation on both arms. The percent of overall missing data for the primary endpoint is 17.9%. There were 14 subjects from alogliptin and 13 subjects from placebo who discontinued the study before Week 26. Due to the limited sample size of the retrieved dropouts (6 for alogliptin, 7 for placebo), missing data cannot be imputed based on the retrieved dropout group. Regarding the COVID-19 pandemic, the applicant stated that patient safety and standards were maintained, and the primary and key

secondary objectives were all achieved with minimal impact due to the pandemic, and that the pandemic did not have an impact on efficacy and safety results of the study confirmed by supplemental analyses[1].

**Table 4: Patient Disposition**

| | Alogliptin 25 mg QD | Placebo | Total |
|---|---|---|---|
| Randomized [n] | 75 | 77* | 152 |
| Randomized and treated with at least 1 dose [n(%)] | 75 (100.0) | 76 (100.0) | 151 (100.0) |
| Discontinuation from study treatment up to Week 52 [n(%)] | 13 (17.3) | 12 (15.8) | 25 (16.6) |
| Pretreatment event/adverse event [n] | 2 | 2 | 4 |
| Significant protocol deviation [n] | 0 | 1 | 1 |
| Lost to follow-up [n] | 4 | 3 | 7 |
| Voluntary withdrawal [n] | 5 | 4 | 9 |
| Pregnancy [n] | 1 | 0 | 1 |
| Principal investigator discretion [n] | 1 | 2 | 3 |
| Discontinuation from study visits up to Week 52 [n(%)] | 12 (16.0) | 10 (13.2) | 22 (14.6) |
| Pretreatment event/adverse event [n] | 0 | 1 | 1 |
| Significant protocol deviation [n] | 0 | 1 | 1 |
| Lost to follow-up [n] | 5 | 3 | 8 |
| Voluntary withdrawal [n] | 5 | 3 | 8 |
| Pregnancy [n] | 1 | 0 | 1 |
| Principal investigator discretion [n] | 1 | 2 | 3 |
| Completed 26-week treatment period [n(%)] | 61 (81.3) | 63 (82.9) | 124 (82.1) |
| On Treatment [n] | 55 | 56 | 111 |
| Off Treatment (Retrieved Drop-outs) [n] | 6 | 7 | 13 |
| Missing in 26 weeks HbA1c [n(%)] | 14 (18.7) | 13 (17.1) | 27 (17.9) |
| Affected by Covid-19 pandemic [n(%)] | 15 (20.0) | 7 (9.2) | 22 (14.6) |

*One subject randomized to placebo was not treated, and not included in the primary analysis set.
Source: CSR Table 10.b and Statistical Reviewer's Analysis

### 3.2.4 Results and Conclusions

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

Table 5 below displays the results for the primary efficacy analysis. Change in HbA1c from baseline at Week 26 for alogliptin is 0.02% and 0.20% for placebo. Based on the statistical reviewer's placebo washout imputation, the treatment effect of alogliptin relative to placebo is estimated to be -0.18% with 95% CI: (-0.84, 0.49). As the CI contains zero, the study failed to demonstrate superiority of alogliptin to placebo for the primary endpoint. The result of the primary endpoint by applicant's placebo washout imputation (change from baseline to Week 26 LS mean for alogliptin was 0.03% and for placebo was 0.15%) was similar and consistent.

[1] Among 129 subjects not affected by COVID-19, the LS mean (SE) of alogliptin relative to placebo was 0.21 (0.41) (95% CI: -0.62, 1.04) at CSR section 11.4.1.1.2 and Table 15.2.1.6.

**Table 5: Primary Efficacy Results on HbA1c (%) Change from Baseline at Week 26**

| | **Alogliptin 25 mg QD N=75** | **Placebo N=76** |
|---|---|---|
| Baseline, Mean (SD) | 8.16 (1.51) | 8.11 (1.33) |
| Week 26 Missing, n (%) | 14 (18.7) | 13 (17.1) |
| Change from baseline to Week 26, LS Mean (SE) | 0.02 (0.25) | 0.20 (0.23) |
| Comparison to Placebo[1] | | |
| LS Mean difference (95% CI) | | -0.18 (-0.84, 0.49) |
| Two-sided P-value | | 0.60 |
| Comparison to Placebo[2] | | |
| LS Mean difference (95% CI) | | -0.12 (-0.75, 0.51) |
| Two-sided P-value | | 0.70 |

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputation placebo wash-out model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: [1]Statistical Reviewer's Analysis and [2]Applicant's IR response dated November 30, 2022. On November 16, 2022, we requested that the applicant should include subjects who received hyperglycemic rescue before Week 26 and increase the number of imputed datasets to 100.

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 to 100 imputed datasets, and Rubin's Rule was applied to combine the inference results. As shown in Table 6, the treatment effect of alogliptin relative to placebo was -0.16% with 95% CI: (-0.82, 0.50). The estimates based on different imputation methods generated similar results, which confirmed the robustness of the primary analysis result.

**Table 6: HbA1c Change from Baseline at Week 26, Sensitivity Analysis to Primary Endpoint**

| | **Alogliptin 25 mg QD N=75** | **Placebo N=76** |
|---|---|---|
| Baseline, Mean (SD) | 8.16 (1.51) | 8.11 (1.33) |
| Change from baseline to Week 26, LS Mean (SE) | -0.00 (0.24) | 0.16 (0.23) |
| Comparison to Placebo | | |
| LS Mean difference (95% CI) | | -0.16 (-0.82, 0.50) |
| Nominal two-sided P-value | | 0.63 |

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Primary efficacy analysis is based on multiple imputation return-to-baseline model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis

## Secondary Endpoints: HbA1c (%) Change from baseline at week 12, 18, 39, and 52

Secondary endpoints which are the HbA1c (%) change from baseline at Weeks 12, 18, 39, and 52 were analyzed for descriptive purpose in Table 7. The reviewer noted numerical increasing treatment difference of HbA1c changes at Week 39 and 52. The mean HbA1c increased in both treatment arms, this numerical difference of HbA1c changes was driven mainly by larger increase in HbA1c in the placebo arm.

**Table 7: Results for HbA1c (%) Change from Baseline at Week 12, 18, 39, and 52**

| Endpoint | | Alogliptin 25 mg QD N=75 | Placebo N=76 |
|---|---|---|---|
| **At Week 12** | Change from baseline to Week 12, LS Mean (SE) | -0.19 (0.19) | -0.12 (0.19) |
| | Comparison to Placebo<br>LS Mean difference (95% CI)<br>Nominal two-sided P-value | | <br>-0.07 (-0.57, 0.43)<br>0.78 |
| **At Week 18** | Change from baseline to Week 18, LS Mean (SE) | 0.00 (0.23) | -0.05 (0.22) |
| | Comparison to Placebo<br>LS Mean difference (95% CI)<br>Nominal two-sided P-value | | <br>0.05 (-0.57, 0.68)<br>0.86 |
| **At Week 39** | Change from baseline to Week 39, LS Mean (SE) | 0.26 (0.24) | 0.68 (0.23) |
| | Comparison to Placebo<br>LS Mean difference (95% CI)<br>Nominal two-sided P-value | | <br>-0.42 (-1.07, 0.24)<br>0.21 |
| **At Week 52** | Change from baseline to Week 52, LS Mean (SE) | 0.47 (0.29) | 1.03 (0.27) |
| | Comparison to Placebo<br>LS Mean difference (95% CI)<br>Nominal two-sided P-value | | <br>-0.56 (-1.35, 0.22)<br>0.16 |

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Secondary efficacy analysis is based on multiple imputation placebo wash-out model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis

***Reviewer's note:*** *Per clinical's request, we did exploratory analyses by investigating potential contributors for the numerical difference of HbA1c change at Week 39 and 52. The reviewer did not find any significant contributors. Instead, we observed that the numerical difference of HbA1c change at Week 39 and 52 was mainly derived by the cohort with schedule B. And the agency requested the applicant to provide the rationale for the numerical difference of changes from baseline at weeks 39 and 52 submitted on March 10, 2023. On March 31, 2023, the responses from the applicant were received and they concluded the consistent finding with the reviewer and confirmed that very few subjects required hyperglycemic rescue and HbA1c for the majority of subjects remained stable throughout the study. Therefore, it is reasonable to conclude that this numerical difference of HbA1c changes is most likely spurious.*

## Other Secondary Endpoints

Table 8 below displays the results for the statistical reviewer's analysis for FPG and Body Mass Index Z-score as descriptive purpose. All secondary endpoints analysis results showed the consistent conclusion of no treatment effect for alogliptin.

**Table 8: Results for Fasting Plasma Glucose (mg/dL) and Body Mass Index Z-score at Week 26**

| Endpoint | Alogliptin 25 mg QD N=75 | Placebo N=76 |
|---|---|---|
| **FPG at Week 26** | | |
| Baseline, Mean (SD) | 158.30 (63.35) | 147.59 (54.65) |
| Change from baseline to Week 26 LS Mean (SE) | 7.56 (8.99) | 11.09 (8.52) |
| Comparison to Placebo LS Mean difference (95% CI) Nominal two-sided P-value | | -3.52 (-26.94, 19.90) 0.77 |
| **BMI Z-score at Week 26** | | |
| Baseline, Mean (SD) | 2.04 (0.60) | 2.08 (0.57) |
| Change from baseline to Week 26 LS Mean (SE) | 0.0007 (0.02) | -0.0042 (0.02) |
| Comparison to Placebo LS Mean difference (95% CI) Nominal two-sided P-value | | 0.005 (-0.05, 0.06) 0.87 |

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
Other secondary efficacy analysis is based on multiple imputation placebo wash-out model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis

## Efficacy Conclusion

The primary efficacy analysis failed to demonstrate a statistically significant difference between alogliptin 25mg and placebo with respect to glycemic control. Consistent with the primary analysis, the sensitivity analysis using return-to-baseline approach also showed that superior efficacy of alogliptin were not established.

Besides the primary efficacy analysis and sensitivity analysis, secondary analyses including the analysis on FBG change from baseline and the analysis on BMI Z-score change from baseline demonstrated the same conclusion of the non-significant efficacy of alogliptin compared to placebo.

In conclusion, the benefit of alogliptin in treating T2DM pediatrics (10 to 17 years old) was not established in the study SYR-322-309.

## 3.3 Evaluation of Safety

Hypoglycemic event counts 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: alogliptin 25mg, vs. placebo, from Week 0 to Week 52.

Table 9 below displays the number of subjects with at least 1 hypoglycemic episode and the total number of episodes, while on treatment (52 weeks). As per clinical reviewer's request, we used documented hypoglycemia with plasma glucose (PG) < 50 mg/dL instead of < 54 mg/dL in this review. Four subjects with alogliptin experienced at least one episode and three subjects with

placebo experienced at least one episode. There was one subject with alogliptin 25mg who experienced 12 episodes and one subject with placebo who experienced 4 episodes. All other subjects experienced singular episode.

**Table 9: Summary of Hypoglycemic Episodes while on Treatment**

| | **Alogliptin 25mg QD (N=75)** | | **Placebo (N=76)** | |
|---|---|---|---|---|
| **Hypoglycemia** | Number of Subjects with ≥ 1 episode | Number of Episodes | Number of Subjects with ≥ 1 episode | Number of Episodes |
| Documented hypoglycemia with PG < 50 mg/dL with or without symptoms | 4 | 15 | 3 | 6 |

Source: Statistical Reviewer's Analysis and CSR Table 15.3.4.7.1

Table 10 below summarize the analysis results for the rate of documented hypoglycemia with PG < 50 mg/dL with or without symptoms. The 95% confidence interval for algoliptin 25mg relative to placebo includes 1. Therefore, we conclude that alogliptin does not significantly increase the incidence of hypoglycemic episodes. Also, since many episodes on alogliptin 25mg were experienced among only one patient, caution should be taken when interpreting results.

**Table 10: Rate Ratios of Hypoglycemia while on Treatment**

| **Hypoglycemia** | **Rate Ratio 95% CI Alogliptin 25 mg QD /Placebo** | **P-value** |
|---|---|---|
| Hypoglycemia with PG < 50 mg/dL with or without symptoms | 3.22 (0.41, 25.02) | 0.26 |

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 mITT using all observed data.
Source: Statistical Reviewer's Analysis

# 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, age (<14 years vs. 14 to 17 years), race (Whites vs. Others), region (US vs outside of US), ethnicity (Hispanic, not Hispanic or missing) and schedule (A vs B) of antidiabetic therapy status. In addition, the subgroup analysis was performed by COVID-19 (Affected vs. not Affected). Each analysis modeled the primary endpoint with an ANCOVA adjusted for treatment arm, baseline HbA1c, and schedule (except for the subgroup analysis on schedule). 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 individual study treatment effects. 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 $\mu_i$ is the expected treatment effect for subgroup *i*, and $\sigma_i^2$ is the within-subgroup variance
- $\sigma_i^2$ is set to the variance for the sample estimate
- $\mu_i \sim N(\mu, \tau^2)$, where $\mu \sim N(0, 16*(1.91)^2)$, and $1/\tau^2 \sim$ Gamma (0.001, 0.001)

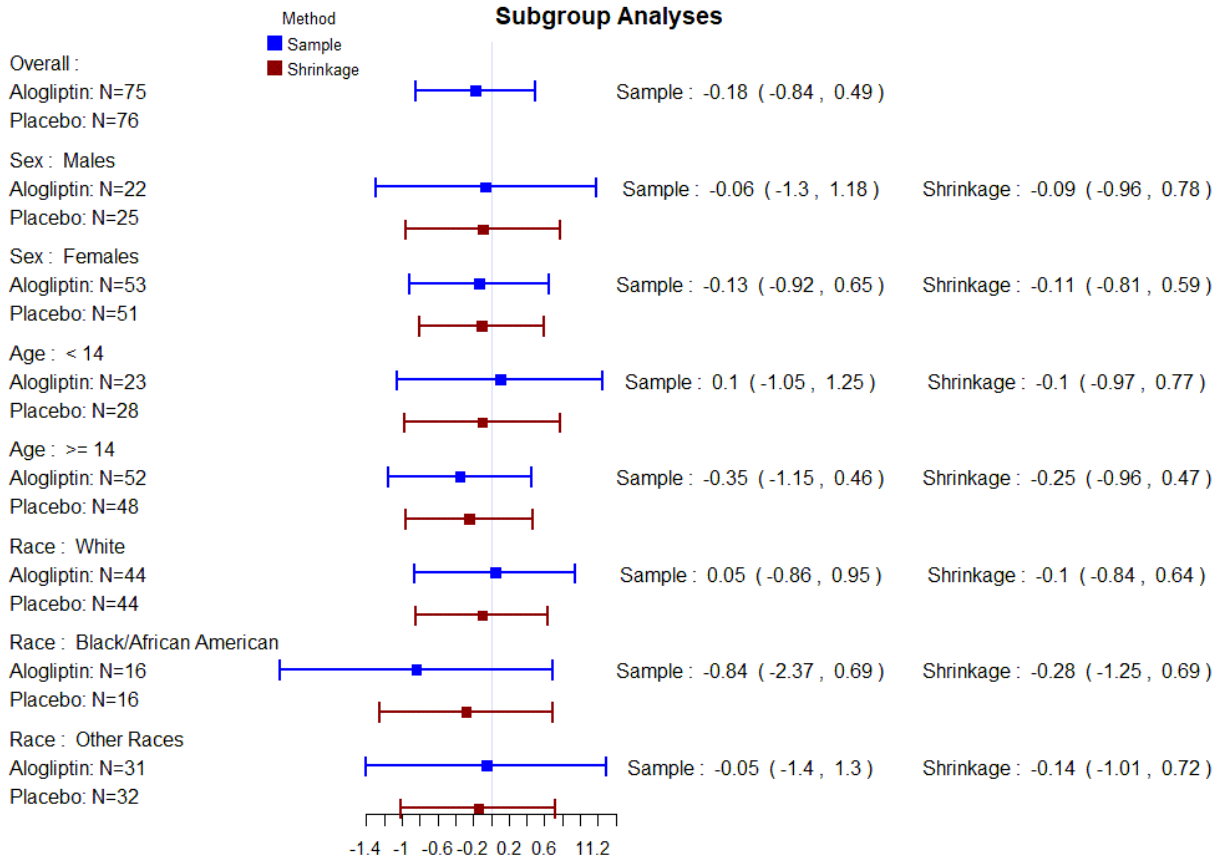
We assume that before seeing data, the treatment effect is 0 based on one-eighth of a patient on each treatment arm. The patient level residual standard deviation was estimated to be 1.91 based on the primary analysis results, thus, the variance of the prior distribution of the treatment effect is $16*1.91^2$.

## 4.1 Sex, Age, Race, Geographic Region, Ethnicity and Schedule of Antidiabetic Therapy Status

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 2 and Figure 3. The plots include the corresponding 95% confidence and credible intervals for the sample and shrinkage estimates, respectively. As expected, the estimates for the treatment effects for levels within each subgroup pull toward each other.

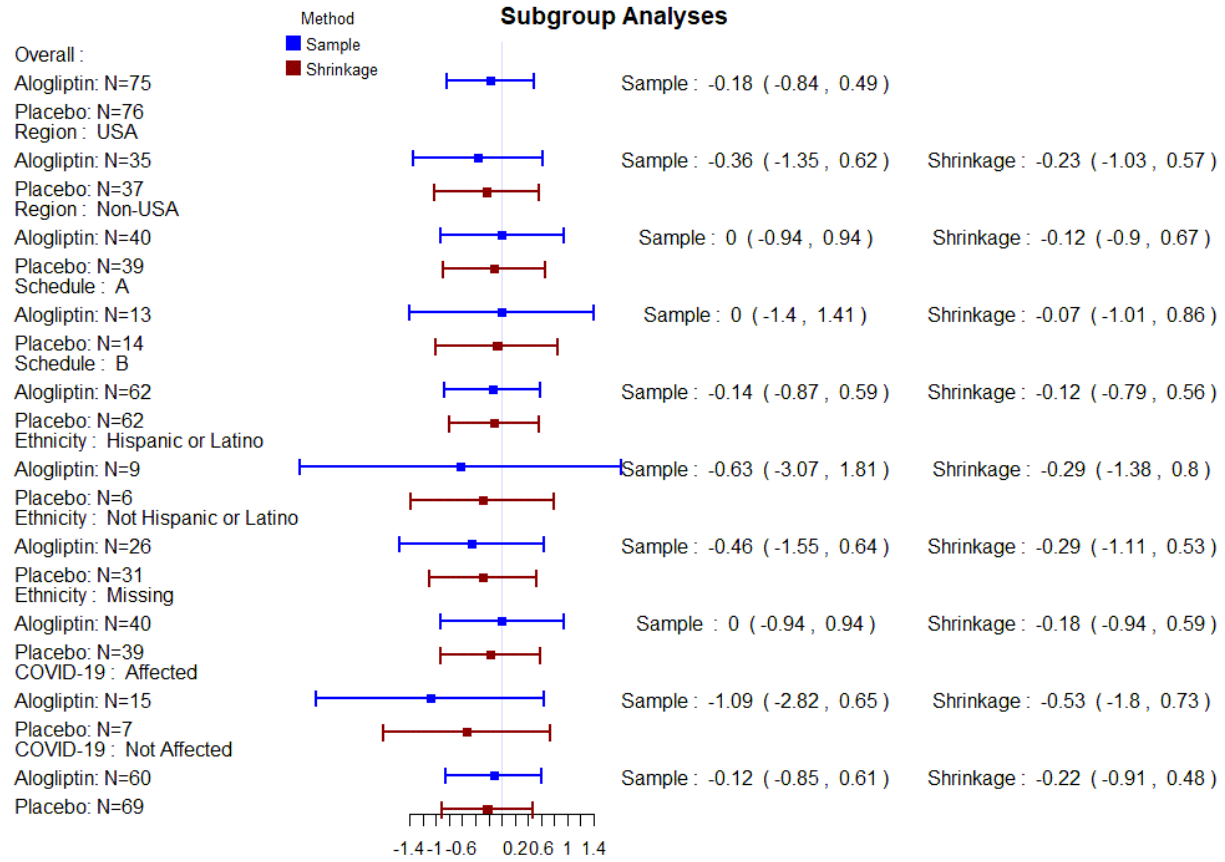
Subgroup analyses are consistent with primary analysis results which shows no benefit of alogliptin in reducing HbA1c compared to placebo.

**Figure 2: Forest Plot of Subgroup Analyses for Sex, Age, and Race: Placebo-Adjusted HbA1c (%) change from Baseline at Week 26**




Values on the negative side favor alogliptin, values on the positive side favor placebo.
Other races include American Indian or Alaska Native (n=32), Asian (n=1), or multiple races (n=5). For the American Indian or Alaska Native race, the mean baseline HbA1c was 7.89 and 8.40 for alogliptin (n=16) and placebo (n=16) arms, respectively. The mean change from baseline to Week 26 in HbA1c was 0.35 and -0.07 for alogliptin and placebo arms, respectively. For the multiple races, the mean baseline HbA1c was 7.98 and 7.50 for alogliptin (n=4) and placebo (n=1) arms, respectively. The mean change from baseline to Week 26 in HbA1c was 1.30 and 2.9 for alogliptin and placebo arms, respectively.
Source: Statistical Reviewer's Analysis

**Figure 3: Forest Plot of Subgroup Analyses for Geographic Region, Schedule of Antidiabetic Therapy Status, Ethnicity, and COVID-19: Placebo-Adjusted HbA1c (%) change from Baseline at Week 26**




Values on the negative side favor alogliptin, values on the positive side favor placebo.
Source: Statistical Reviewer's Analysis

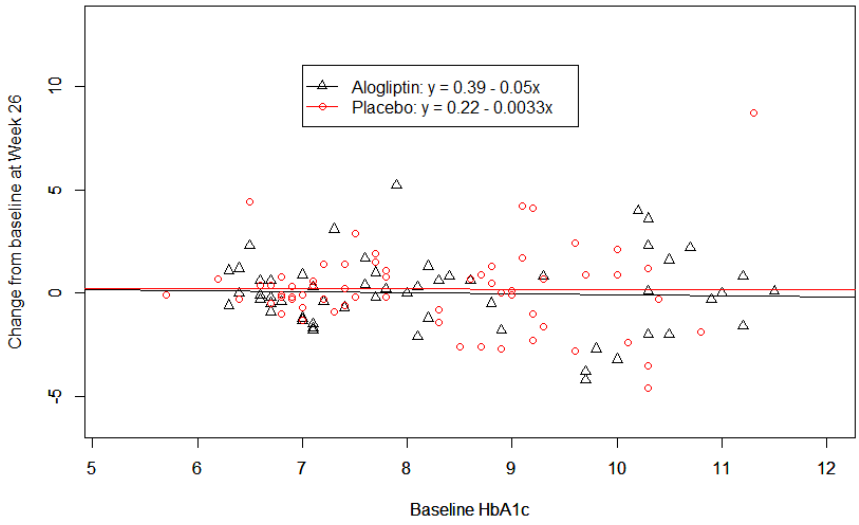
## Baseline HbA1c as an effect modifier

It is well known that baseline HbA1c is an effect modifier, (i.e., the treatment effect on HbA1c change will depend on a subjects' baseline HbA1c measurement). A scatter plot, which is random due to no difference between alogliptin and placebo, including parallel regression lines based off the completers from alogliptin 25 mg and placebo is in Figure 4

.

Regression lines were computed and superimposed over the scatter points. Comparing alogliptin 25mg and placebo, the slopes are almost parallel, so that the treatment effect of alogliptin 25mg relative to placebo changes very little as baseline HbA1c increases. The p-value for a test for no difference in slopes between alogliptin 25mg and placebo is 0.86. So, baseline HbA1c does not modify the treatment effect of alogliptin compared to placebo.

**Figure 4: Scatter Plot and Regression Lines Based off Completers**




Source: Statistical Reviewer's Analysis

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

Superiority of alogliptin 25mg compared to placebo was not established in SYR-322-309 study. The study observed a smaller effect size and a larger SD than assumptions used in the sample size calculation. Large missing data for primary endpoint was observed. Statistical issues were found concerning estimands and statistical method to deal with missing data.

To evaluate the efficacy of alogliptin, these issues were addressed by preferred estimand using treatment policy strategies for all intercurrent events and multiple imputation methods using placebo-washout approach to deal with missing data (Section 3.2).

## 5.2 Collective Evidence

The placebo-adjusted treatment effect for alogliptin with respect to HbA1c change from baseline at Week 26 was -0.18, with a 95% CI (-0.84, 0.49). Sensitivity analyses using return-to-baseline approach that inspected the impact of missing data assumptions demonstrated similar findings to the primary analysis result. Secondary endpoints analyses including HbA1c change from baseline at Week 12, 18, 39, and 52 demonstrated consistent non-significant treatment effect of alogliptin compared to placebo. In addition to the primary efficacy analysis, subgroup analyses on the primary efficacy endpoint found consistent results for alogliptin vs. placebo in subgroup levels defined by sex, age, race, ethnicity, region, and schedule of antidiabetic therapy status.

A greater number of hypoglycemia episodes were observed for subjects receiving alogliptin (15 episodes) than for those receiving placebo (6 episodes) but those were from only few subjects.

## 5.3 Conclusions and Recommendations

Treatment efficacy was not established for alogliptin 25 mg compared to placebo regarding glycemic control for T2DM pediatrics in the study SYR-322-309. As the applicant only sought to add the study information to Section 8.4 of the product label without an efficacy claim for alogliptin use among pediatric subjects (10 to 17 years), we recommend approval of the proposed label updates in Section 8.4 and releasing PMRs for alogliptin.

## 5.4 Labeling Recommendations

The applicant proposed (b) (4) (b) (4) Section 8.4 Pediatric Use of the labels for NESINA (alogliptin). However, Agency disagrees (b) (4) where the effectiveness has not been established due to concerns of off-label use.

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/s/

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SUNG HEE KIM
06/05/2023 05:24:56 PM

YOONHEE KIM
06/05/2023 05:33:03 PM
I concur.