Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Alogliptin Compared With Placebo in Pediatric Subjects With Type 2 Diabetes Mellitus

NCT Number: NCT02856113

SAP Approve Date: 20Apr2021

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: SYR-322_309

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Alogliptin Compared With Placebo in Pediatric Subjects With Type 2 Diabetes Mellitus

Alogliptin Pediatric Study

PHASE 3

Version: 1.0

Date: 20Apr2021

Prepared by:

PPD

Based on:

Protocol Version: Amendment 09

Protocol Date: 11 August 2020

2.0 TABLE OF CONTENTS

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
CCI	[redacted]
COVID-19	Coronavirus disease 2019
CI	confidence interval
CTX	C-terminal telopeptide
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
CCI	[redacted]
HbA1c	glycosylated hemoglobin
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
LLN	lower limit of normal
MAV	markedly abnormal value
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model for repeated measures
MODY	maturity-onset diabetes of the young
OR	odds ratio
PK	pharmacokinetics
PPG	postprandial glucose
PPS	per protocol set
PT	preferred term
PTE	pretreatment event
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	system organ class
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal
WHODrug	world health organization drug dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy of alogliptin 25 mg once daily (QD) compared to placebo when administered as monotherapy, or when added onto a background of metformin alone, insulin alone, or as combination of metformin and insulin, as measured by the glycosylated hemoglobin (HbA1c) change from Baseline at Week 26 in pediatric subjects with type 2 diabetes mellitus (T2DM).

4.2 Secondary Objectives

To evaluate the HbA1c change from Baseline after treatment with alogliptin as compared with placebo at Weeks 12, 18, 39, and 52.

To evaluate the safety of alogliptin compared to placebo by assessing:

- The incidence of hypoglycemic events, treatment emergent adverse events (TEAEs), clinical laboratory parameters, electrocardiogram (ECG) readings, physical examinations, and vital signs for Weeks 26 and 52.
- The effects on biomarkers of bone turnover (bone-specific alkaline phosphatase and C-terminal telopeptide [CTX]) markers at Weeks 26 and 52.
- The effects on CD26 surface antigen levels at Weeks 26 and 52.

CCI

[redacted]

4.4 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study with 52-week double-blind treatment period to evaluate the efficacy and safety of alogliptin 25 mg QD compared to placebo in children and adolescents 12 to 17 years in Russia and 10 to 17 years in all other countries, inclusive, at the time of randomization, with a confirmed diagnosis of T2DM and who are experiencing inadequate glycemic control.

Subjects who have completed all required Screening Procedures, and who meet all entry criteria may proceed to randomization. Subject randomization will be stratified by background antidiabetic regimen. Eligible subjects will be assigned to 1 of 2 Schedules (ie, Schedules A and B), based on the antidiabetic therapy 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.

Subjects who have not met all of the additional randomization criteria listed in protocol Section 7 will be allowed to enter a Pre-Randomization Stabilization Period described in protocol Section 6.2.

If randomized, then, in addition to receiving double-blind study medication, subjects will be required to maintain their background antidiabetic therapy (if applicable), at the same dose at the day of randomization (eg, baseline insulin doses, if applicable), throughout the first 26 weeks of the Double-Blind Treatment Period. Subjects who complete the 52-Week Double-Blind Treatment Period will complete an End-of-Treatment Visit and Follow-Up Visit, 2 weeks after the End-of-Treatment Visit. Subjects who terminate double-blind study drug prematurely will complete an End-of-Treatment Visit and Follow-Up Visit, 2 weeks after the End-of-Treatment Visit, and will continue to be followed for the 52-week duration of the study and complete a projected Week 52 visit.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint of this study is HbA1c change from Baseline to Week 26.

5.2 Secondary Endpoints

5.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are HbA1c changes from Baseline at Weeks 12, 18, 39, and 52.

5.2.2 Safety Endpoints

The safety endpoints of this study are:

- Physical examination findings.
- Vital sign measurements.
- 12-lead ECG abnormalities.
- Adverse events (AEs).
- Incidence of infections (Total and urinary and respiratory tract infections) and hypersensitivity reactions.
- Incidence of hypoglycemia.
- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis).
- Changes from Baseline in biomarkers of bone turnover (bone-specific alkaline phosphatase and CTX) at Weeks 26 and 52.
- Changes from Baseline in CD26 surface antigen levels at Weeks 26 and 52.

CCI

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The primary efficacy variable will be the change from Baseline in HbA1c at Week 26. The primary analysis set will be the full analysis set (FAS) defined in Section 7.2. For this variable and set, a total of 75 randomized subjects per treatment group will ensure at least 90% power to detect a difference in mean change from Baseline in HbA1c at Week 26 between alogliptin 25 mg QD and placebo assuming a treatment effect of 0.5%, a SD of 0.9%, a 2-sided false-rejection rate of 5%.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

A masked data review of tables, listings, and figures presented with surrogate treatment codes will be conducted prior to unblinding of subjects' treatment assignments. This review will assess the accuracy and completeness of the study database, subject evaluability (including definition of analysis sets), and appropriateness of the planned statistical methods.

All statistical analyses will be conducted using SAS® Version 9.2, or higher.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at the α=0.05 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a population parameter estimate will be presented using the same number of decimal places as the estimate.

Where appropriate, numbers of patients will be summarized by Schedule A or B based on antidiabetic therapy and variables will be summarized by scheduled study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated by treatment group. For continuous variables, the number of subjects with non-missing values (n), mean, median, SD, minimum, and maximum values will be tabulated.

Mixed model for repeated measures (MMRM) will be used for several endpoints and unless otherwise specified the following general practices will be employed when using MMRM analysis. An unstructured covariance matrix will be used to model the correlation among repeated measurements; parameter estimates will be calculated using restricted maximum-likelihood estimation (REML). Degrees of freedom will be estimated using the Kenward-Roger approximation. The Shapiro-Wilk test will be used to test the normality of the residuals from each continuous endpoint that is examined using an MMRM model. If the hypothesis of normality is rejected, the natural logarithm will be applied to the measurements at each timepoint, the model will be re-fit, and model-based quantities will be back-transformed and expressed on the ratio scale.

7.1.1 Definition of Study Days and Baseline

Study Day 1 is defined as the date on which a subject is administered the first dose of the study medication. Other study days are defined relative to the Study Day 1 with Day 2 being the day after Study Day 1 and Day -1 being the day prior to Study Day 1.

For all the endpoints, baseline is defined as the last non-missing measurement prior to first dose of study drug unless otherwise stated.

7.1.2 Definition of Study Visit Windows

All scheduled study visits will be defined relative to Study Day 1. For example, the appropriate day for the scheduled Week 8 visit should be: Day 1 + 56 = Day 57.

A windowing convention will be used to determine the analysis value for a given study visit and will be applicable for all by-visit summaries and analyses. The windowing conventions for all efficacy and safety variables are summarized in Table 1.

Table 1. Visit Windows for Efficacy and Safety Endpoints

Visit ID (Scheduled Study Day)	Window Interval (day) for Efficacy Endpoints	Window Interval (day) for Safety Endpoints
Baseline (Day 1)	1	1
Week 4 (Day 29)	27 –31	2 –57
Week 12 (Day 85)	78 – 92	58 – 106
Week 18 (Day 127)	120 – 134	107 – 155
Week 26 (Day 183)	176 – 190	156 – 204
Week 32 (Day 225)	218 –232	205 –250
Week 39 (Day 274)	267 – 281	251 – 295
Week 45 (Day 316)	309 – 323	296 – 341
Week 52 (Day 365)	358 – 372	342 – 372
Week 54 (Day 378)	376 – 380	373 – 380

For efficacy variables, a 2-day rule will be applied to Week 4 and Week 54 visits, and a 7 day rule will be applied all other scheduled visits; ie, the lower bound of the window will be either 2 or 7 days before the scheduled study day, and the upper bound of the window will be either 2 or 7 days after the scheduled study day, as applicable. For safety variables, visit windows are exhaustive; the bounds of each window are the midpoints between the scheduled days for the current visit and the adjacent visits, with the exception that, for Week 54, the upper bound of the window will be 2 days after the scheduled study day. One or more results for a particular efficacy or safety variable may be obtained in the same visit window. If more than one are obtained, the result with the date closest to the scheduled visit date will be used. In the event that multiple observations are equidistant from the scheduled visit date then the later observation will be used.

7.2 Analysis Sets

The safety set will include all subjects who took at least 1 dose of study medication. In safety summaries, subjects will be analyzed according to the treatment most often received.

The full analysis set (FAS) will include all randomized subjects in the safety set. For a particular variable, the FAS analysis will consist of all subjects who receive at least one dose of study treatment. In FAS efficacy summaries, subjects will be analyzed as randomized.

The per protocol set (PPS) will include all FAS subjects who had no major protocol violations. Relevant major protocol violations will be finalized prior to database lock, if the final criteria is different from the criteria presented here below. Major protocol deviations criterion for initial consideration include the following: any violations of study inclusion criteria; exclusion criteria 1, 3, 4, 8, 9, 10; drug compliance < 80% or > 120%; receiving incorrect randomized treatment; not completing the Week 26 assessment (including HbA1C value). If a subject has titration (up or down) of the background antidiabetic therapy while on study treatment, this subject will be excluded from the PPS. Final criteria will be documented prior to unblinding if different from the above preliminary criteria.

The pharmacokinetic (PK) set will include all randomized subjects who had at least 1 blood draw taken for pharmacokinetic assessments during the course of this trial.

7.3 Disposition of Subjects

A summary of total number of subjects who failed the screening, and the reason for failure will be provided in the screen failures table.

Subject disposition will be summarized for all randomized subjects. The numbers and percentages of subjects randomized but not treated, subjects who completed study drug, and subjects who prematurely discontinued study drug by "Reason for discontinuation from study drug" will be displayed.

In addition, the numbers and percentages of randomized subjects who completed planned study visits, and who prematurely discontinued the study visits by "reason for discontinuation of study visits" and "reason for discontinuation from study" will be summarized separately.

The number and percentage of subjects with at least 1 significant protocol deviation, and the number and percentage of subjects within each deviation category will be summarized based on all randomized subjects in separate table.

All randomized subjects breakdown by the stratification factor (antidiabetic therapy (Y/N)) will also be summarized.

7.4 Demographic and Other Baseline Characteristics

Summary statistics will be provided for continuous variables (age, height, weight, and body mass index (BMI), BMI Z score, Baseline HbA1c, Baseline Blood Glucose) measured at Baseline. The BMI (in kg/ m^2) is defined as the subject's weight (in kg) divided by the square of their height (in m). BMI Z score calculations use the reference provided by Centers for Disease Control and Prevention 3rd to 97th Percentile growth charts to determine BMI-for-age percentiles (http://www.cdc.gov/growthcharts/clinical_charts.htm#Set2). The reported values will be rounded to 2 decimal places. BMI percentiles will be listed for each subject.

The numbers and percentages of subjects will be presented for the following categorical variables: race, ethnicity, gender, age group (10-13 years, 14-17 years), BMI group (<25 kg/m^2, 25 kg/ m^2 to <30 kg/ m^2, ≥30 kg/ m^2), Tanner Stage Score, and prior antidiabetic therapy (Schedule A or B).

Subjects with non-alcoholic fatty liver disease (NAFLD) will be recorded in the medical history and be summarized as well.

Demographic and other baseline characteristics data will be summarized by treatment group and total based on the FAS.

7.5 Medical History and Concurrent Medical Conditions

Summaries of medical history and concurrent medical conditions will be presented for the safety set. Medical history will consist of any significant conditions or diseases that stopped at or prior to the time of signing the informed consent. Ongoing conditions will be considered concurrent medical conditions. Concurrent medical conditions are significant ongoing conditions or diseases present at time of informed consent through end of study. These include clinically significant laboratory, ECG, or physical examination abnormalities.

Medical history and concurrent medical conditions will be coded using the latest version of Medical Dictionary for Drug Regulatory Activities (MedDRA). The numbers and percentages of subjects with medical history and concurrent medical conditions will be reported by system organ class (SOC) and preferred term (PT) in separate tables.

7.6 Prior, Concomitant, and Post-treatment Medications

Any non-study medication that was stopped prior to the first study drug dose date (Day 1) will be considered prior medication. Any non-study medication with a start date between Day 1 and on or prior to the last study drug dose date, inclusive, or with a start date before Day 1 and an end date after Day 1 or ongoing, will be considered concomitant medication. Any medication with a start date after the last study drug dose date will be considered post-treatment medication. For summary purpose, if the medication's start or stop dates are missing or partially missing and the medication is not checked as ongoing, the following imputation rules will be applied:

- If the year is present but the month and day are missing, then 01JAN will be imputed for the start date and 31DEC for the stop date.
- If the year and month are present but the day is missing, then 01 will be imputed for the start date and the last day of the month for the stop date.
- If the year is missing or the date otherwise cannot be imputed, then the date will be treated as missing and the medication will be treated as a concomitant medication.

All non-study medication will be coded by Anatomical Therapeutic Chemical (ATC) code and PT using the latest version of World Health Organization Drug Dictionary (WHODrug). All the medication history, concomitant medications, and post-treatment medications will be summarized for the safety set in frequency tabulations (subject counts and percentages) and by ATC first level and PT in separate tables.

A listing of non-study medication will also be provided, to include dose, unit, frequency, route of administration, start and end dates, and reason for use.

7.7 Study Drug Exposure and Compliance

A subject's drug exposure, measured in days, will be defined as (date of last dose - date of first dose+1). Drug exposure in weeks will be calculated by dividing the exposure in days by 7, and be summarized as a continuous variable. The numbers and percentages of subjects within exposure categories (<12 weeks, 12 to <26 weeks, ≥26 weeks) will also be presented.

If the date of last dose is missing and a subject has discontinued from the study, then, for summary purposes, the last dose date will be estimated using the earliest of the following after the last available drug dispensation: date of death, date of last contact (recorded on eCRF).

A subject's study drug compliance (%) will be calculated as {(number of tablets dispensed - number of tablets returned)/ (number of tablets dispensed)}*100%. This compliance will be summarized with descriptive statistics and subject counts within compliance categories (<80%, 80 to <90%, ≥90%). If the number of returned capsules and/or the return date are missing, then 100% compliance will be assigned for each day up to the number of capsules dispensed, the date of return, or the date of last dose, whichever is earliest.

Summaries of study drug exposure and compliance will be based on the safety set.

7.8 Efficacy Analysis

The primary analysis set for all the efficacy analyses will be the FAS. Supportive analyses will be conducted with the PPS for the primary and secondary efficacy endpoints. Efficacy values collected >1 day after the last dose of double-blind study drug (>7 days for HbA1c) will be considered post-treatment values and will be listed but not analyzed. If maturity-onset diabetes of the young (MODY) has been observed in the study from adverse event reports,

a. a description of the results will be provided separately for each individual subject with MODY, and

b. the mixed modeling for the primary and secondary efficacy endpoints will be repeated, excluding the MODY subjects.

If subjects have been observed to down-titrate background antidiabetic therapy while continuing study treatment, a sensitivity analysis will be conducted for primary and secondary endpoints by excluding data collected after the down-titration based on PPS.

7.8.1 Primary Efficacy Endpoint

The primary endpoint is HbA1c change from Baseline at Week 26. In the primary efficacy analysis, the corresponding 2-sided hypotheses tested are:

- H_0: $\mu_{(alogliptin)} = \mu_{(Placebo)}$

versus

- H_1: $\mu_{(alogliptin)} \neq \mu_{(Placebo)}$

where $\mu_{(treatment)}$ is the population mean HbA1c change from Baseline at Week 26 of the corresponding treatment. The primary analysis will be conducted using the FAS. A contrast at Week 26 derived from the MMRM analysis will be used for the statistical inference. Any significant p-value (< 0.05) from the contrast of the model (alogliptin minus placebo), and corresponding 95% confidence interval (CI), with upper confidence limit below 0, will permit concluding better treatment effect of alogliptin 25 mg QD compared to placebo.

In this MMRM model, change from Baseline in HbA1c will be the response variable; randomized treatment, scheduled visit (Weeks 12, 18, 26, 39, and 52), antidiabetic therapy (Y/N also known as Schedule B/A), and visit-by-treatment interaction will be fixed categorical effects; and baseline HbA1c and visit-by-baseline HbA1c interaction will be continuous covariates. An unstructured covariance matrix will be used to model the correlation among repeated measurements; parameter estimates will be calculated using restricted maximum-likelihood estimation (REML). Degrees of freedom will be estimated using the Kenward-Roger approximation. Data collected following discontinuation of double-blind study medication or hyperglycemic rescue will not be included in the analysis.

A table of descriptive statistics (n, mean, SD, median, and range) will be provided for the observed HbA1c as well as the change form baseline for each of the above scheduled visits. Similar presentation will be provided by subgroups, e.g. Schedule (A or B), gender (M/F), race (White/Black/Other), age group (10-13 years, 14-17 years), and BMI group (<25 kg/m^2, 25 kg/ m^2 to <30 kg/ m^2, ≥30 kg/ m^2).

7.8.1.1 Sensitivity Analysis of Handling of Dropouts or Missing Data by Washout Imputation

In washout-imputation, the missing data in an endpoint from both arms will be imputed using observed endpoint data from the placebo. When the missing values in the Alogliptin arm are imputed, no intermediate endpoint values will be used and only baseline data and covariates will be included in the model. When missing values in the placebo arm are imputed, baseline data, intermediate endpoint values, and covariates will be included in the model. This imputation method will only impute the time point at Week 26 using multiple imputation regression with gender, background antidiabetic therapy (ie. Schedule A or B) and baseline HbA1c as the covariates. Sensitivity analysis for HbA1c at other time points will be conducted if the week 26 analysis indicates lack of robustness in the primary analysis.

Twenty imputed datasets will be generated by the aforementioned Washout imputation. ANCOVA will be used as the analytical method for each imputed dataset. Estimates obtained from multiple imputed datasets will be combined based on Rubin's combination rules (Little R., Rubin D.B. 2002).

7.8.1.2 Tipping Point Analysis

Conditional of statistically significant results for the primary analysis, a tipping point analysis will be performed to investigate the robustness of the primary analysis. The tipping point is defined as the difference in the average glycosylated hemoglobin (HbA1c) change between a treatment arm and placebo at which the study conclusion changes from statistical significance to

non-significance. To find this tipping point, a systematic shift will be applied to the imputed values in both treatment arms for weeks missing HbA1c measurements. The multiple imputation process (ie, missing not at random adjustments in the multiple imputation process) will be performed with each shift applied until the values result in a change of the significance of the primary hypothesis test, the tipping point.

Twenty imputed datasets will be generated for each of the shift parameters. MMRM will be used as the analytical method for each imputed dataset. Estimates obtained from multiple imputed datasets will be combined based on Rubin's combination rules. The tipping point can be identified when the result is no longer statistically significant.

7.8.1.3 Supplemental Analysis of COVID-19

A supplemental analysis that excludes subjects affected by COVID-19 will be performed on the primary endpoint. Information concerning a subject being impacted due to COVID-19 before or on week 26 visit for sensitivity analysis for primary endpoint will be collected as protocol deviation, including but not limited to site closure, missingness, self-withdrawal, adverse event, concomitant medications, etc. Prior to unblinding data, meeting will be held to identify those subjects who will be classified as "impacted by COVID-19".

7.8.2 Secondary Efficacy Endpoints

Each secondary efficacy endpoint will be analyzed using the MMRM analysis specified for the primary efficacy endpoint, stated in Section 7.8.1.

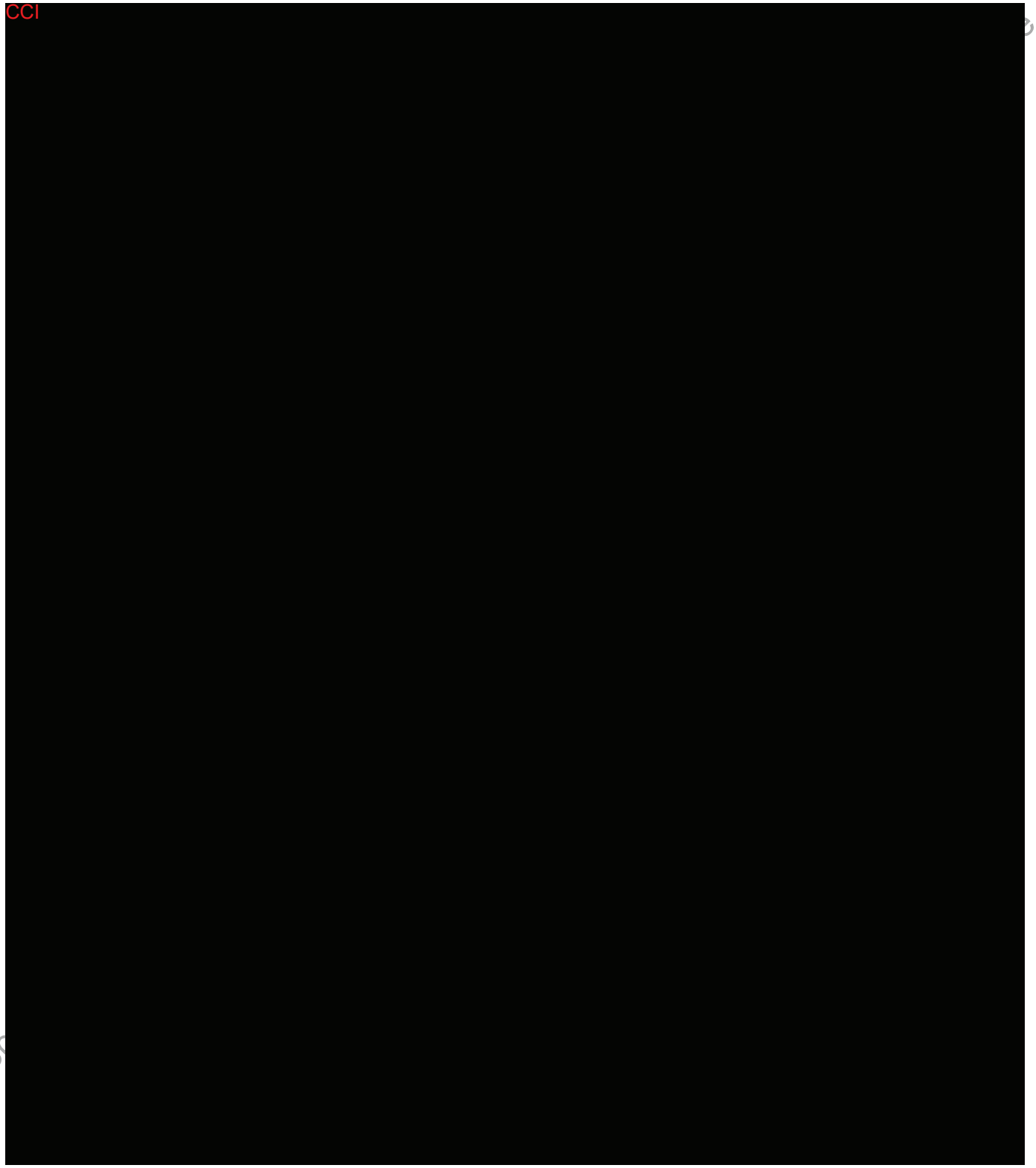
Summary statistics of observed values at each visit will be presented, and the corresponding estimate, standard error (SE), 95% CI, and p-value of the contrast from the mixed model will be reported on the table. Figures, i.e. a plot of point estimate with SE error bars, of HbA1c over time will be presented by treatment group for both the LS means estimates and changes from baseline.

Descriptive statistics will be provided, including subgroups, as provided for the primary endpoint.

CCI

CCI

[redacted]



CCI

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Safety Analysis

All safety summary tables will be presented for all subjects in the safety set, unless otherwise stated. Separate summaries using (1) data collected from baseline through the date of last dose + 7 days for labs (+ 14 days for AEs) or date of hyperglycemic rescue (if applicable), whichever is earlier and (2) all data collected at or after baseline throughout the study will be conducted. No statistical tests will be performed for the safety analyses, unless otherwise stated.

7.10.1 Pre-treatment Events and Adverse Events

A pretreatment event (PTE) is defined as any untoward medical occurrence prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation. An adverse event (AE) is defined as any untoward medical occurrence on or after the first administration date of the study medication, it does not necessarily have to have a causal relationship with this treatment. Adverse event verbatim reported terms will be coded by system organ class (SOC) and preferred term (PT) using the latest version of MedDRA.

AE summary tables will include numbers and percentages of subjects experiencing at least one AE by SOC and PT. Unless otherwise specified AEs will be sorted by relative frequency (highest to lowest) in the alogliptin arm, unless where the AE summary is two-tiered the AE will be sorted alphabetically at the first tier (eg. SOC) and relative frequency at the second tier (eg. PT). The following AE summary tables will be generated:

- Overview of AE
- AEs by SOC, PT and SOC and PT
- Serious AE (SAE) by SOC and PT
- Relationship of AEs to Study Drug by SOC and PT
- Relationship of AEs to Study Procedure by SOC and PT
- Drug-Related AEs by SOC and PT
- Procedure-Related AEs by SOC and PT
- Drug-Related SAE by SOC and PT
- Procedure-Related SAE by SOC and PT
- Most Frequent AEs (excluding SAEs) by PT
- Intensity of AEs by SOC and PT
- Severe AEs by SOC and PT
- Intensity of Drug-Related AEs by SOC and PT
- Intensity of Procedure -Related AEs by SOC and PT
- AE with Action of Dose Interrupted by SOC and PT
- AE with Action of Drug Withdrawn SOC and PT
- Adverse events of special interest, including serious hepatic abnormalities, pancreatitis, infections (including urinary tract infections), and severe hypersensitivity reactions including angioedema, anaphylaxis, and Stevens-Johnson Syndrome

Other AE/SAE summary tables may be added as appropriate.

A subject with 2 or more different adverse events within the same level of the MedDRA term will be counted only once in that level using the most extreme incident (most intense for the intensity tables, and related for the relationship to study drug tables). For the AE with missing relationship to drug/procedure will be imputed as related.

Most Frequent AEs are defined as the adverse events occurring in at least 5% of the safety set. If no AEs satisfy the 5% criteria then 3% or 2% maybe be used.

For summary table purposes, it is assumed that AEs with missing/incomplete start dates have occurred during the treatment period if there is not enough information to determine that the AEs occurred prior to the first dose date. Specifically, the missing/incomplete onset dates will be imputed as follows:

1. If the onset date is completely missing, then impute the date as the first dose date.
2. If the onset date is partially missing, the following scenarios will be considered:
    1) If the year is the year of the first dose, and month and day are missing, then impute month and day as the month and day of the first dose date.
    2) If month and year are present and day is missing:
        i) If month is equal to the month of first dose date then set day to the day of first dose date;
        ii) If month is before the month of first dose date then set day to the last day of the month of AE start date;
        iii) If month is after the month of first dose date then set day to the first day of the month of AE start date.
    3) If year and day are present and month is missing:
        i) If day is on or after the first dose date, then set month to the same month of first dose date;
        ii) If day is before the first dose date, then set month to the next month of first dose date.

After imputation, if the imputed AE start date is after the available AE end date, death date or last visit date, that imputed date will be re-set as the earliest of AE end date, death date and last visit date. Partial dates will be presented as they are in the listings.

PTEs, AEs, SAEs, AEs leading to study drug withdrawn, AEs leading to study discontinuation, and AEs resulting in death will be listed separately.

7.10.2 Clinical Laboratory Evaluations

Clinical safety laboratory evaluations include clinical hematology, serum chemistry, and urinalysis.

These evaluations will be summarized for baseline, post-dosing, and change from baseline at each visit. Only the scheduled measurements will be included in the summaries.

Individual results for hematology and serum chemistry laboratory evaluations will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix A) using the result and criteria in SI units. The number and percentage of subjects with at least one postdose MAV will also be summarized. All postdose clinical lab results, including scheduled and unscheduled measurements, will be included in the MAV summaries.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

7.10.3 Vital Signs

Vital sign measurements include body temperature (oral or tympanic measurement), respiratory rate, blood pressures (resting more than 5 minutes), and pulse

These measurements will be summarized for baseline, post-dosing, and change from baseline at each visit. Only the vital signs collected at the scheduled visits or time points will be included in the summary.

All individual vital signs that meet Takeda's predefined corresponding MAV criteria (Appendix B) will be listed. The number and percentage of subjects with at least one post first dose of study drug markedly abnormal vital sign measurement will be summarized. All postdose vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

7.10.4 Physical Examination

Complete physical examinations will be performed at Baseline, Week 26 and Week 52. Brief physical examinations will be performed at Week 12 and Week 39. The body system will be assessed as normal, abnormal, or not examined at each scheduled visit, and the percentage of subjects with abnormal physical examination findings at each time point will be summarized by body system and by treatment arm.

7.10.5 12-Lead ECGs

Interpreted ECGs will be recorded in the database using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Shift tables will be provided to summarize interpretation status changes from baseline to each scheduled post-baseline measurement. Interpreted ECG will also be listed by visit.

7.10.6 Other Observations Related to Safety

7.10.6.1 Incidence of infections and hypersensitivity reactions

Numbers and percentages of subjects experiencing at least one infection/ hypersensitivity reaction, and numbers of infections/ hypersensitivity reactions at each post-dose visit, will be summarized.

7.10.6.2 Incidence of hypoglycemia

Hypoglycemia is defined in the protocol Section 9.1.16.2. Hypoglycemic events will be summarized, including tabulating numbers and percentages of subjects experiencing at least one hypoglycemic event, the number of hypoglycemic events per day, and the numbers and percentages of days having ≥1 events between each pair of consecutive post-screening visits (e.g., between Day 1 and Week 4, between Week 4 and Week 12, etc). Total number and percentage of days having ≥1 events throughout the treatment phase will also be summarized.

Listings will also be provided to include additional information such as Blood Glucose Value, and Symptoms.

7.10.6.3 Change from Baseline in biomarkers of bone turnover (bone-specific alkaline phosphatase and CTX at Weeks 26 and 52

Biomarkers of bone turnover will be summarized for baseline, post-dosing, and change from baseline at each visit for each parameter. If data permit an MMRM model of the same form as the model specified for the primary endpoint in Section 7.8.1 will be fit to each parameter, and similar quantities will be extracted.

7.10.6.4 Change from Baseline in CD26 surface antigen levels at Weeks 26 and 52.

CD26 surface antigen levels will be summarized for baseline, post-dosing, and change from baseline at each visit for each parameter. If data permit an MMRM model of the same form as the model specified for the primary endpoint in Section 7.8.1 will be fit to each parameter, and similar quantities will be extracted.

7.11 Interim Analysis

Not applicable.

7.12 Changes in the Statistical Analysis Plan

In general, the analyses described in the statistical analysis plan do not differ from the plan specified in the protocol; an exception is given below.

1. In the protocol, we defined “FAS analysis will consist of all subjects who have a baseline assessment and at least 1 postbaseline assessment for the variable.” In this updated SAP, we defined “FAS analysis will consist of all subjects who receive at least one dose of study treatment”

8.0 REFERENCES

1. Protocol: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Alogliptin Compared With Placebo in Pediatric Subjects With Type 2 Diabetes Mellitus. Amendment number 02, 09 November 2016.
2. Little, R. J. A., & Rubin, D. B. (2002). Statistical Analysis with Missing Data. Hoboken, NJ: John Wiley & Sons.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

This appendix provides lists of values for selected laboratory parameters that will be used to identify markedly abnormal values (MAV). The final MAVs used in the statistical presentations may deviate from these predefined lists. However final MAVs will be documented in the statistical presentations and where applicable justifications will be provided in the clinical study report.

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/µL	>600 x 10^3/µL
	SI	<75 x 10^9/L	>600 x 10^9/L
Mean Corpuscular Volume	Both	<70 fL	>100 fL

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	≥3x ULN
AST	Both	--	≥3x ULN
GGT	Both	--	≥3x ULN
Alkaline phosphatase	Both	--	≥3x ULN
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 µmol/L
Direct bilirubin	Both	--	≥2x ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 µmol/L
Blood urea nitrogen	Conventional	--	>30 mg/dL

Parameter	Unit	Low Abnormal	High Abnormal
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
CPK	Both	--	≥5x ULN
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	
	SI	<8.0 mmol/L	
Uric Acid	Conventional	--	>13.0 mg/dL
	SI	--	>773 µmol/L
Magnesium	Conventional	<1.2 mg/dL	>3.0 mg/dL
	SI	<0.5 mmol/L	>1.2 mmol/L
Phosphorus	Conventional	<1.6 mg/dL	>6.2 mg/dL
	SI	<0.52 mmol/L	>2.00 mmol/L
Total Cholesterol	Conventional	--	>300 mg/dL
	SI	--	>7.72 mmol/L
Triglycerides	Both	--	>2.5x ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

This appendix provides a list of values for selected vital signs parameters that will be used to identify markedly abnormal values (MAV). The final MAVs used in the statistical presentations may deviate from this predefined list. However final MAVs will be documented in the statistical presentations and where applicable justifications will be provided in the clinical study report.

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	Bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>150
Diastolic blood pressure	mm Hg	<40	>95
Body temperature	^{o}C	< 35.6	>37.7
	^{o}F	<96.1	>99.9

Appendix C Reference code in SAS

CCI

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	04-May-2021 18:16 UTC