Title: A Prospective, Non-Interventional Study of the Use of Alogliptin and Alogliptin Fixed-Dose Combinations With Pioglitazone and With Metformin in Standard Clinical Practice

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Takeda Pharmaceuticals Greater China

A Prospective, Non-Interventional Study of the Use of Alogliptin and Alogliptin Fixed-Dose Combinations With Pioglitazone and With Metformin in Standard Clinical Practice

Alogliptin-5009

Statistical Analysis Plan

Version: 1.0

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ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
CFR	Code of Federal Regulations
CI	confidence interval
eCRF	electronic case report form
FDC	fixed-dose combination
GPP	Good Pharmacoepidemiology Practices
HbA1c	glycated hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
SAE	serious adverse event
T2DM	type 2 diabetes mellitus

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses and methods for Protocol Alogliptin-5009 (Version 1.1, released on 1-Apr-2016).

All decisions regarding final analysis, as defined in this SAP document, have been made prior to Database Lock (DBL) of the study data.

2. STUDY OBJECTIVE (S)

2.1. Primary Objective

The primary objective of this study is to describe the real-world clinical response to treatment with alogliptin or alogliptin FDCs as assessed by glycated hemoglobin (HbA1c) level change in patients who have been diagnosed with T2DM and initiated alogliptin or alogliptin FDCs therapy during the observational period.

2.2. Secondary Objective

The secondary objectives of this study are:

- To describe real-world clinical response to treatment with alogliptin or alogliptin FDCs in patients who have been diagnosed with T2DM and initiated alogliptin or alogliptin FDCs therapy during the observational period, as assessed by:
  - Change from baseline in HbA1c level on alogliptin or its FDCs therapy in subgroups with different clinical characteristics;
  - HbA1c levels reduction to the goal of <7.0%;
  - HbA1c reduction >0.3% with no tolerability findings (hypoglycemic event, or weight gain ≥5%);
  - To evaluate fasting blood glucose dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3);
  - To evaluate the effect of alogliptin or alogliptin FDCs on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 (V3) in dependence on clinical characteristics;
  - Safety (as assessed by adverse drug reactions [ADRs], serious AEs [SAEs], and AEs of special interest [AESI]) to treatment with alogliptin or alogliptin FDCs in standard clinical practice;

- To describe utilization pattern information of alogliptin and alogliptin FDCs (as assessed by percentage of patients who remain on treatment, and time to alogliptin or alogliptin FDCs dose escalation or dose reduction) during the observation period in patients who have been diagnosed with T2DM and initiated alogliptin or alogliptin FDCs therapy during the observational period.

2.3. Exploratory Objective

3. STUDY DESIGN

This is an observational, prospective, multicenter study in adult patients with T2DM diagnosis who have made the decision, along with their treating physician, to begin treatment with alogliptin or alogliptin FDCs.

The purpose of this study is to observe alogliptin and alogliptin FDCs utilization patterns, as well as clinical response to treatment with alogliptin or alogliptin FDCs, in standard clinical practice. No investigational product will be administered in this study.

The observational study will include approximate 1142 patients with T2DM treated with alogliptin or alogliptin FDCs in approximately 40 sites.

The planned maximum duration of this study per patient will be 6 months or up to loss to follow-up or death, whichever occurs first. In this study, Patients will attend a baseline visit followed by visits approximately at Month 3 and 6. Patients will not be asked to travel to the site only for the purpose of this study; the study visits will be performed during regular doctor's appointments.

4. ENDPOINTS

4.1. Primary Endpoint

- The primary endpoint is Change from baseline in HbA1c level on alogliptin or its FDCs therapy (V3).

4.2. Secondary Endpoint

The secondary endpoints related to real-world clinical response to alogliptin or alogliptin FDCs are the following:

- Clinical response rates: incidence rates of responders. The following definitions of response will be used as secondary endpoints:
  - Change from baseline in HbA1c level on alogliptin or its FDCs therapy in subgroups with different clinical characteristics (V3).
  - HbA1c levels reduction to the goals of <7.0% (V3).
  - HbA1c reduction >0.3% with no tolerability findings (hypoglycemic event, or weight gain ≥5%) (V3).
  - To evaluate the effect of alogliptin and its FDCs on fasting blood glucose dynamics in patients with diabetes mellitus type 2 over time (V1-V2-V3).
- To evaluate the effect of alogliptin or alogliptin FDCs on glycosylated hemoglobin (HbA1c) level dynamics in patients with diabetes mellitus type 2 in dependence on clinical characteristics (V1-V2-V3).
- ADRs, SAEs, and AESIs.

The secondary endpoints related to alogliptin or alogliptin FDCs utilization patterns are the following:

- Percentage of patients who remain on treatment with alogliptin or alogliptin FDCs (V2-V3).
- Time to alogliptin or alogliptin FDCs dose escalation or dose reduction (V2-V3).

4.3. Exploratory Endpoint

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- Time to add-on therapy (V2-V3).
- Time to T2DM treatment switching/discontinuation.
- Reasons for alogliptin or alogliptin FDCs discontinuation.
- Number of hospitalizations, emergency room visits, and physician office visit.
- Length of hospital stay.

5. STATISTICAL HYPOTHESIS

NA.

6. SAMPLE SIZE CONSIDERATION

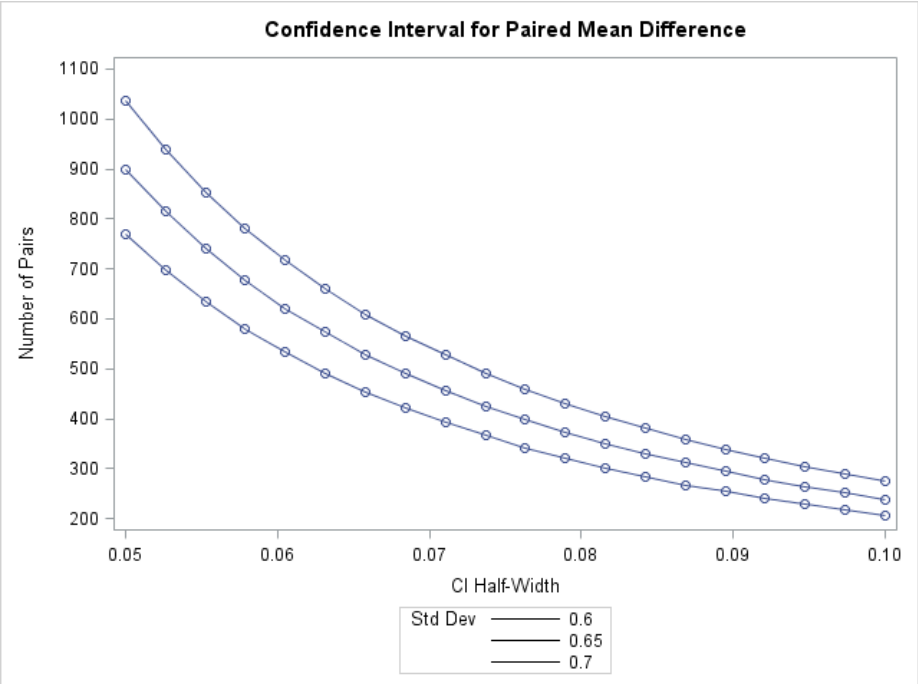
Sample size was calculated for the primary endpoint of the study: to evaluate the effect of Alogliptin or its FDCs on glycosylated hemoglobin (HbA1c) level in patients with diabetes mellitus type 2 (V3). Sample size was calculated using SAS 9.3 proc power procedure (power for Confidence Interval for Paired Mean Difference as for accuracy of parameter estimation) for following parameters (fixed scenario elements):

Fixed Scenario Elements	
Distribution	Normal
Method	Exact
Correlation	0.35
Nominal Prob(Width)	0.9
Number of Sides	2
Alpha	0.05
Prob Type	Conditional

Standard deviation was assessed based on S. Del Prato et al study and was considered to be at most 0.70% (for glycosylated hemoglobin level dynamics). To determine required number of patients values from 0.60% to 0.70% were taken. Desired half-wide for parameter estimation was set as range between 0.05 – 0.1. Following required number of pairs were calculated:

Computed N Pairs				
Index	**Half-Width**	**Std Dev**	**Actual Prob(Width)**	**N Pairs**
1	0.05	0.60	0.904	770
2	0.05	0.65	0.904	899

3	0.05	0.70	0.900	1037
4	0.06	0.60	0.904	542
5	0.06	0.65	0.903	632
6	0.06	0.70	0.903	729
7	0.07	0.60	0.906	404
8	0.07	0.65	0.902	470
9	0.07	0.70	0.904	542
10	0.08	0.60	0.902	313
11	0.08	0.65	0.907	365
12	0.08	0.70	0.905	420
13	0.09	0.60	0.905	251
14	0.09	0.65	0.906	292
15	0.09	0.70	0.907	336
16	0.10	0.60	0.904	206
17	0.10	0.65	0.902	239
18	0.10	0.70	0.904	275



For the worst-case scenario of half-width as 0.05, if Std Dev is 0.65, the required number of pairs is 899. Taking into account a possible dropout of 25%, to reach study objectives in regard to this endpoint, it is recommended to enroll at least 1199. If taking Std Dev as 0.60 or 0.70, the required number of pairs is from 770 or 1037. Taking into account a possible dropout of 25%, it is recommended to enroll at least 1027 or 1383 patients into the study.

7. ANALYSIS POPULATION

7.1. Analysis Sets

The analysis will be performed on the complete set of patients enrolled in the study. Subgroup analyses will be carried out on the subgroups defined in Section 4.3.

7.2. Description of Subgroups to be Analyzed

Subgroup analysis may be performed using any relevant baseline covariates listed as below:

- Age, sex, race, ethnicity, vital signs, body weight, height, and body mass index
- T2DM history: time from date of first diagnosis to first alogliptin use, number of different previous diabetic treatments, percentage of patients with each previous diabetic treatment (eg, metformin, sulfonylurea, thiazolidinediones)
- Medical history: medications, co-morbidities, hospitalizations
- Laboratory evaluations, including HbA1c, fasting blood glucose
- Geographical region/country

8. STATISTICAL METHODS

8.1. General Statistical Considerations

This study is observational and longitudinal statistical methods will be employed for data analyses.

Statistical analysis will be performed using SAS® software (SAS Institute, Inc., Cary, North Carolina) Version 9.2 or later. Continuous variables will be summarized using the mean, the standard deviation, median, 25th percentile, 75th percentile, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

No formal significance testing will be performed.

8.2. Data Handling Conventions

8.2.1. Premature Withdrawal and Missing Data

When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Patients lost to follow-up will be contacted by the site in an attempt to determine the reason for study withdrawal. A maximum of 3 telephone call attempts should be documented on different days. Patients who withdraw from the study will not be replaced.

No imputation will be used for Missing data.

8.2.2. Definition of Baseline and Change from Baseline

In this study, patients will attend a baseline visit followed by visits approximately at Month 3 and 6. Data collected at the baseline visit will be regarded as baseline. For HbA1c assessment, the latest HbA1c value available before the starts of alogliptin or alogliptin FDC (but within 3 months before the first dosage) will be considered the baseline value.

The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

8.3. Study Subjects

8.3.1. Disposition of Subjects

The number and percentage of subjects who were enrolled, complete study, and who prematurely withdraw from the study will be summarized. In addition, the number and percentage of subjects who withdraw from the study will be summarized by primary reason. In addition, individual reasons for discontinuation will be listed.

8.3.2. Demographic and Baseline Characteristics

Descriptive statistics (e.g., number of participants, mean, standard deviation, median, 25th percentile, 75th percentile, minimum value, and maximum value) will be generated for continuous demographic variables and baseline characteristics variables (age, height, body weight and BMI). The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (sex, ethnicity and race) will be tabulated. Individual subject demographic and baseline characteristics data will be listed.

8.3.3. Medical History

Medical history will include general medical history (including medications, co-morbidities, and hospitalizations), as well as specific T2DM history (including date of diagnosis and previous treatments received). They will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized. All medical history will be listed.

8.3.4. Prior and Concomitant Medications

Prior and Concomitant Medications, including but not limited to T2DM treatments, will be summarized and listed.

8.4. Efficacy Analyses

8.4.1. Primary Efficacy Analyses

Change from baseline in HbA1c level on alogliptin or its FDCs therapy will be summarized as descriptive statistics.

8.4.2. Secondary Efficacy Analyses

The secondary HbA1c or fasting blood glucose outcomes (HbA1c clinical response rates) will be summarized by treatment as descriptive statistics and incidence rates.

If multiple HbA1c levels are available, then the assessment closest to the visit time point will be used. Clinical response rates: incidence rates of responders. The following definitions of response will be used: (1) HbA1c level reduction to the goals of <7.0%. (2) HbA1c reduction >0.3% with no tolerability findings (hypoglycemic event, or weight gain ≥5%).

- HbA1c level change from baseline in subgroups with different clinical characteristics. It is proposed to use multifactorial regression model to determine factors related to effect of alogliptin and its FDCs on HbA1c level dynamics. Change from baseline in HbA1c level on alogliptin or its FDCs therapy (V3) in subgroups with different clinical characteristics will be summarized using relevant descriptive statistics and analyzed using Multiple Linear Regression with following predictors: prior therapy of DM, sex, age, cardiovascular risk group, therapy type (monotherapy or combined therapy), baseline BMI, initial glycemic control.

In addition, change from baseline in HbA1c level will be assessed and evaluated using mixed model repeated measures (MMRM) methodology. The multiple visits for each patient will be incorporated as repeated measures within each patient. Visit will be treated as a categorical predictor and baseline HbA1c level will be included as a covariate. An appropriate covariance structure will be selected to provide estimates (Least Square Means) of change from Baseline and to perform statistical analysis at Visit 3. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by compound symmetry will be used. The dose-response trend hypothesis test will be conducted using the appropriate contrast statement for a linear (ordinal dose) trend. In addition, Least Squares Means, the associated standard errors and 95% confidence intervals will be displayed by each individual dose group.

- Proportion (%) of patients with diabetes mellitus type 2 whose HbA1c<7.0% will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Proportion (%) of patients with diabetes mellitus type 2 who decrease in HbA1c > 0.3% with no tolerability findings (hypoglycemic event, or weight gain ≥5%) over time will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
- Change from baseline in fasting plasma glucose level on alogliptin or its FDCs therapy over time (V1-V2-V3) will be summarized using relevant descriptive statistics and analyzed with mixed model with repeated measures using clinical characteristics as independent factors;
- Change from baseline in HbA1c level on alogliptin or its FDCs therapy over time (V1-V2-V3) will be summarized using relevant descriptive statistics and analyzed with mixed model with repeated measures using clinical characteristics as independent factors;
- Proportion (%) of patients who remain on Alogliptin or its FDCs treatment (V2-V3) and information of dose escalation or reduction (V2-V3) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals.

8.4.3. Exploratory Analyses

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8.5. Safety Analyses

All safety assessments, including adverse event, clinical laboratory and vital sign data will be summarized with descriptive statistics, where appropriate, and presented in the data listings.

8.5.1. Extent of Exposure

Below by-subject listing will be provided:

- Initial study treatment dosing, including initial treatment, dosage, frequency, time of administration, and ongoing etc. information.
- Study treatment adjustment, including adjustment start/end date, type, action taken, dosage, frequency, unit, primary reason for action taken, AE/ADR name (if available).

8.5.2. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to treatment.

An ADR is defined as any response to a medicinal product that is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of diseases or for the restoration, correction, or modification of physiological function. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses, or abuse).

An SAE is defined as any untoward medical occurrence that, at any dose:

1. Results in DEATH.
2. Is immediately LIFE THREATENING? The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    a. May require intervention to prevent items 1 through 5 above.
    b. May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    c. Includes any event or synonym described in the Takeda Medically Significant AE List (Table 8-1).

Table 8-1 Takeda Medically Significant AE List

Term	
Acute respiratory failure/Acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsade de pointes/Ventricular fibrillation/Ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anaemia	Pulmonary fibrosis
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome/Malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death
	Confirmed or suspected transmission of infection agent by a medicinal product
	Confirmed or suspected endotoxin shock

The following AEs will be considered AESIs: pancreatitis, hepatic disorders, and hypersensitivity reactions (including angioedema, anaphylaxis, and Stevens-Johnson syndrome). Targeted follow-up forms have been developed to further guide the collection of data of AESIs and the forms need to be submitted to the sponsor as part of the AE source documents.

Summaries of below adverse events will be provided by System Organ Class (SOC) and preferred term by treatment using the Medical Dictionary for Regulatory Activities (MedDRA) using absolute frequencies and percentages as well as 95% confidence intervals:

- Overview of all adverse events: consist of total number of AEs, total number of patients with AEs and the number of AEs reguiring discontinuation.
- The incidence and severity of all adverse events will be summarized by body system.
- Adverse events leading to treatment discontinuation.
- Adverse drug reactions
- SAEs
- Serious adverse drug reactions
- AESIs

The summary tables will be displayed alphabetically within system organ class. If a subject reports more than one condition that is coded to the same system organ class or preferred term, the subject will be counted only once at that level.

The following listings will also be generated: a listing of all adverse events with severity and causality information, listing of leading to study drug discontinuation, a listing of adverse drug reactions, a listing of serious adverse events, a listing of serious adverse drug reactions and a listing of adverse event of special interest.

8.5.3. Clinical Laboratory Evaluations

A by-subject listing of baseline values, the values at each visit, and changes from baseline values in the clinical laboratory measurements will be provided. The clinical significance of laboratory abnormalities based on investigator's judgment will be flagged.

8.5.4. Vital Signs

Vital sign data will include systolic and diastolic blood pressure. If multiple vital sign data are available, then the assessment closest to the visit time point will be used.

Vital sign data (including baseline, absolute and change from baseline values) will be summarized by treatment using descriptive statistics. A by-subject listing of baseline values, the values at each visit, and changes from baseline values in the vital signs measurements will be provided.

8.6. Other Analyses

8.6.1. Country Related Analyses

Indication information (alogliptin and alogliptin FDCs market status, T2DM standard of care) will be summarized with categorical statistics, and presented in the data listing.

8.6.2. Physician Related Analyses

Prescribing physician-relevant information (general/specialized practitioner) will be summarized with categorical statistics, and presented in the data listing.

9. Impact on Analysis Due to Study Termination

Due to Takeda's decision, Alogliptin 5009 study need to be early-terminated. The impact will include below three aspects:

9.1. Actual Sample Size

By the study early-termination, the actual sample size enrolled is far less than planned, which can not reach to the worst-case scenario of half-width 0.05. If the sample primary endpoint

standard deviation is the same as expected one (0.65), the actual sample size will lead to the reduction of analysis precision and the broadening of half-width.

9.2. Impact on Analyses

For the analyses results, study termination will have no impact on the point estimation, but the confidence interval range will be broadend.

9.3. Impact of Limited Visit

The study termination will lead to missing visit of V2 or V3, and efficacy results might not be obvious.

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