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

NCT Number: NCT02989649

Protocol Approve Date: 1st April 2016

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

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.

OBSERVATIONAL STUDY PROTOCOL

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

Sponsor:	Takeda Pharmaceutical (China) Co., Ltd.
Study Number:	Alogliptin-5009
Compound:	This is an observational study. Alogliptin or alogliptin fixed-dose combinations with pioglitazone and with metformin will be prescribed per routine clinical practice.
Version of Protocol:	1.1
Date of Protocol:	1st April 2016

CONFIDENTIAL

All financial and non-financial support for this study will be provided by Takeda. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Takeda.

This non-interventional study will be conducted according to Guidelines for Good Pharmacoepidemiology Practices (GPP).

Senior Medical Manager(CVM)

Personal Protected Data

Medical Director, Pharmacovigilance

Personal Protected Data

Table of Contents

List of Tables

Protocol Abstract

This is an observational study and no medication will be provided. Patients enrolled into the study will be patients that are currently being treated by their physician. No intervention or change in the patients' management will be required as a result of this study.

Protocol Number:	Alogliptin-5009
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
Sponsor:	Takeda Pharmaceutical (China) Co., Ltd
Study Sites:	Approximate 40 sites in China and Hong Kong.
Indication:	Type 2 diabetes mellitus
Rationale:	Alogliptin is a potent, highly selective, orally available, quinazolinone-based inhibitor of the serine protease dipeptidyl peptidase-4, which has received marketing approval in over 40 countries worldwide as monotherapy and in over 35 countries worldwide as a fixed-dose combination (FDC) with pioglitazone and with metformin. The safety of alogliptin has been assessed in 28 clinical studies, alone or in combination with other compounds. Adverse reactions reported in ≥4% of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are upper respiratory tract infections, nasopharyngitis, and headache; other common adverse reactions included abdominal pain, gastroesophageal reflux disease, pruritus, and rash. Additional adverse reactions that have been spontaneously reported post-marketing are hypersensitivity reactions including anaphylaxis, angioedema, urticaria, and severe cutaneous reactions including Stevens-Johnson syndrome. In addition, acute pancreatitis and hepatic dysfunction (including fulminant hepatic failure) have also been reported post-marketing. This study is designed to observe alogliptin and alogliptin FDCs in real-life settings in a non-interventional manner. Alogliptin or alogliptin FDCs will be prescribed independent of the inclusion of the patient in the study. All treatment decisions will be based on the prescribing physician's current clinical practice.
Objectives:	**Primary objective**: • To describe the real-world clinical response to treatment with

alogliptin or alogliptin FDCs as assessed by glycated hemoglobin (HbA1c) level change in patients with type 2 diabetes mellitus.

Secondary objectives:

- 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.
  - To describe the real-world clinical response to treatment with alogliptin as assessed by glycated hemoglobin (HbA1c) level reduction to the goal <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.

Exploratory objectives:

Company Confidential Information

Company Confidential Information

Patient Population:	Adult (18 years of age or older) patients with a diagnosis of T2DM who have made the decision, along with their treating physician, to begin treatment with alogliptin or alogliptin FDCs, according to the approved label for China and Hong Kong.
Study Design:	This is an observational, prospective, multicenter study. This is a non-interventional study as defined in the Directive 2001/20/EC and will follow the Good Pharmacoepidemiology Practices guidelines. No investigational product will be administered 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. Patients switching treatment from alogliptin or alogliptin FDCs to another T2DM treatment will be followed until the end of the study.
Estimated Study Duration:	The observation period for each patient will be six months, or up to loss to follow-up or death, whichever occurs first.

Assessments:	Clinical response to treatment with alogliptin or alogliptin FDCs will be evaluated based on HbA1c levels. The HbA1c level goal for the patient will be collected at baseline, when determined as part of standard clinical practice. Response will be defined as (1)HbA1c level change from baseline; (2) HbA1c levels reduction to the goal of <7%; and (3) HbA1c reduction >0.3% with no tolerability findings (hypoglycemic event, or weight gain ≥5%). The HbA1c levels will be obtained from any assessments performed as per standard clinical practice. No study-specific measurements will be performed. If multiple HbA1c levels are available, then the assessment closest to the visit time point will be used. Data on the use of alogliptin or alogliptin FDCs will include start date, dose, and end date. Information will also be collected on any additional T2DM treatment, both added in combination to alogliptin or due to switching treatment from alogliptin or alogliptin FDCs to another T2DM treatment. Incidence of newly diagnosed co-morbidities and complications will be collected. Body weight will be obtained from any assessments performed as per standard clinical practice. No study-specific measurements will be performed. Healthcare resources utilization will be assessed by number of hospitalizations (including length of stay during each hospitalization, reason, and urgency [urgent/not urgent]), emergency room visits, and physician office visits. Safety will be assessed by ADRs, SAEs, and AEs of special interest.
Study Drug:	This is an observational study. Alogliptin or alogliptin FDCs will be prescribed per routine clinical practice.
Sample Size:	Approximate 1199 patients are planned to be enrolled, not less than1027, and no more than 1383.
Statistical Methods:	This study is observational and epidemiological 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. A flow chart according to CONSORT guidelines will capture the

patient enrollment and the analysis sets at each analysis. No formal significance testing will be performed.

The HbA1c outcomes (change of HbA1c from baseline to different follow-up period, and HbA1c clinical response rates) will be summarized as descriptive statistics and incidence rates. Secondary study outcome - change from baseline in glycosylated hemoglobin level on alogliptin or its FDCs therapy in subgroups with different clinical characteristics, is proposed to use multifactorial regression model to determine factors related to effect of alogliptin or its FDCs.

Overall and center-specific proportion of participants remaining on alogliptin at the end of the follow-up period will be summarized as frequency and percentages. Treatment patterns will be summarized at each follow-up time and overall at 6 months as descriptive statistics and incidence rates. Alternatively, Kaplan-Meier curves may be used. Receipt of another T2DM treatment will be summarized at each time period and overall at 6 months as incidence rates. Similar analyses will be performed for other time to event endpoints.

Other endpoints (rates of comorbidities and complications, changes in body weight, number of hospitalizations and healthcare resources utilization, and length of hospitalization) will be summarized by descriptive statistics and incidence rates at each time period and for the overall duration.

All safety endpoints (ADRs, SAEs, and AESIs) will be summarized.

Date of Protocol: 1st April 2016

List of Abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
CFR	Code of Federal Regulations
CI	confidence interval
CRO	contract research organization
DPP-4	dipeptidyl peptidase-4
eCRF	electronic case report form
FDC	fixed-dose combination
GPP	Good Pharmacoepidemiology Practices
HbA1c	glycated hemoglobin
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
SAE	serious adverse event
T2DM	type 2 diabetes mellitus

1 Introduction

Over the past 30 years, the prevalence of diabetes has increased dramatically throughout the world due to population growth, aging, urbanization, increasing obesity, and physical inactivity (Zimmet et al 2001; Wild et al 2004). Globally, the prevalence of diabetes was 8.3% in 2014 and was estimated to increase to 10.1% in 2035 (International Diabetes Federation [IDF] 2014). The total number of people with diabetes worldwide was projected to rise from 387 million in 2014 to 592 million in 2035 (IDF 2014). Type 2 diabetes mellitus (T2DM) accounts for approximately 90% to 95% of all diagnosed cases of diabetes (Centers for Disease Control and Prevention [CDC] 2014). Major risk factors for T2DM include race/ethnicity, age (elderly), obesity, family history of diabetes, history of gestational diabetes, and physical inactivity (CDC 2014). Over the coming years, a marked increase in the number of adults with T2DM is expected to place an ever increasing burden on families and the healthcare system (Hogan et al 2003; Wild et al 2004).

Alogliptin is a potent, highly selective, orally available, quinazolinone-based inhibitor of the serine protease dipeptidyl peptidase-4 (DPP-4) developed to treat adult patients with T2DM. Alogliptin has received marketing approval in over 40 countries worldwide, including Australia, China, Europe, Japan, Mexico, South Korea, and the United States. Alogliptin has also received marketing approval as a fixed-dose combination (FDC) with pioglitazone and with metformin in over 35 countries worldwide.

The safety of alogliptin has been assessed in 14 randomized, controlled clinical trials: 2 placebo-controlled monotherapy trials; 4 placebo-controlled add-on combination therapy trials with metformin, with a sulfonylurea, with a thiazolidine, and with insulin; 4 placebo-controlled trials and 1 active-controlled trial in combination with metformin, with pioglitazone, and with pioglitazone added to background metformin therapy; and 3 active-controlled trials in patients treated with pioglitazone and metformin, in combination with metformin, and as monotherapy compared to glipizide.

Adverse reactions reported in ≥4% of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are upper respiratory tract infections, nasopharyngitis, and headache; other common adverse reactions included abdominal pain, gastroesophageal reflux disease, pruritus, and rash. Additional adverse reactions that have been spontaneously reported post-marketing are hypersensitivity reactions including

anaphylaxis, angioedema, urticaria, and severe cutaneous reactions including Stevens-Johnson syndrome. In addition, acute pancreatitis and hepatic dysfunction (including fulminant hepatic failure) have also been reported post-marketing.

The EXAMINE study was conducted in 5380 patients (2679 receiving placebo and 2701 receiving alogliptin) to assess potentially elevated cardiovascular risk related to alogliptin through a composite primary endpoint including death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke (White et al 2013). The results of this study showed that the composite primary endpoint occurred at similar rates in both treatment groups after a median exposure of 18 months (alogliptin: 11.3%; placebo: 11.8%; hazard ratio: 0.96; upper boundary of the 1-sided repeated confidence interval [CI]: 1.16; $p<0.001$ for non-inferiority; $p=0.32$ for superiority).

This study is designed to observe alogliptin and alogliptin with pioglitazone and with metformin (alogliptin FDCs) (depends on the different drugs available in China and Hong Kong) in real-life settings a non-interventional manner. Patients will be enrolled after they and their healthcare provider make the decision to employ alogliptin or alogliptin FDCs for the treatment of T2DM. Therefore, alogliptin or alogliptin FDCs will be prescribed independent of the inclusion of the patient in the study. All treatment decisions will be based on the prescribing physician's current clinical practice.

2 Study Objectives

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 Objectives

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 Objectives

Company Confidential Information

3 Investigational Plan

3.1 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.

This is a non-interventional study as defined in the Directive 2001/20/EC (The European Parliament and the Council of the European Union 2001) and will follow the Good Pharmacoepidemiology Practices (GPP) guidelines (Epstein 2005). This means that:

- The assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the patients.
- Epidemiological methods shall be used for the analysis of collected data.
- The prescription of alogliptin or alogliptin FDCs is clearly separated from the decision to include the patient in the study.

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 1199 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. China Guideline For Type 2 Diabetes recommends HbA1c as the gold standard for blood glucose monitoring. The guideline recommends HbA1c should be tested every 3 months when new treatment regimen is initiated, and when HbA1c is in the treatment target, HbA1c test can be followed every 6 months. In this study, since the treatment of all the patients recruited are with alogliptin initiated, according to the guideline and the standard clinical practice, HbA1c is normally tested every 3 months before HbA1c hits the treatment target and keep stable. So 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.

The data collected for this study are detailed in Section 6, and the Data Collection Schedule is provided in Table 12-1.

3.1.1 Rationale of Study Design

This study is intended to describe the real-world clinical response as assessed by HbA1c level change from baseline in a real world setting. An observational design is adequate to fulfill the primary objective of this study, as it will not interfere with the prevailing standard of care for patients with T2DM.

The proposed data collection schedule has been designed to have a negligible impact on the site standard clinical practice for the treatment of patients with T2DM, and thus to ensure the validity of the study results. Although the patients included in this study will be treated as per standard clinical practice and will not receive any direct benefit from the study, the study will provide an opportunity to gain a better understanding on what type of patients are being treated with alogliptin or alogliptin FDCs, and what type of patients benefit the most from treatment with alogliptin or alogliptin FDCs in a real-world setting as this is different from the clinical trial setting. This will allow providing real-life data to prescribers to best serve patients, and will contribute to increase scientific knowledge about alogliptin and alogliptin FDCs.

The primary endpoint of HbA1c level, as well as the additional secondary endpoints related to HbA1c levels reduction to the goal <7.0%, will be achieved by collection of available HbA1c levels, a well-documented biomarker of disease control in T2DM. To preserve the observational nature of the study, this information will be obtained from any assessments performed as per standard clinical practice, and no study-specific measurements will be performed.

The proposed number of patients (approximate 1199 enrolled patients) and the planned duration of the study (6 months or up to loss to follow-up or death, whichever occurs first) are considered to be sufficient to achieve a satisfactory degree of precision and to provide valuable data on the study objectives, as described in Section 7.5.

3.1.2 Patient selection and procedure for avoiding of selection bias

In order to reduce selection bias, each patient who is planned to treat diabetes by alogliptin or its FDCs has to be documented in an anonymous patient log file (independent of prescribed treatment and signing of the Informed Consent Form) in a consecutive manner at each site.

Eligible patients who receive alogliptin or its FDCs must be enrolled consecutively into the study and documented in the case report form. No eligible patient must be skipped. In case a patient is not eligible (e.g. no informed consent signed), the reason for non-eligibility must be documented in the patient log file. Additionally, for each informed consent signed, there will be CRFs recorded with the patient data.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed and written informed consent, and agrees to comply with protocol requirements. In case the patient is blind or unable to read, informed consent will also be witnessed.
2. Is 18 years of age or older.
3. Has a diagnosis of T2DM.
4. Has made the decision, along with his/her treating physician, to begin treatment with alogliptin or alogliptin FDCs.
5. Has an HbA1c value recorded at most 3 months before initiation of treatment with alogliptin or alogliptin FDCs.
6. Alogliptin or alogliptin FDCs is prescribed according to the approved label for China and Hong Kong.

Alogliptin or alogliptin FDCs will be prescribed independent of the inclusion of the patient in the study and as per standard clinical practice.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Has gestational diabetes or type 1 diabetes mellitus.
2. Patients who has used Dipeptidyl peptidase-4 inhibitors (DPP-IV inhibitors) or Glucagon like peptide-1 agonists (aGLP-1) within the 3 months prior to the start of alogliptin or alogliptin FDCs treatment.
3. The patients is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling).

4. Is currently participating in a clinical trial. Participation in non-interventional registries is permitted.
5. Is being treated with any investigational drug.
6. In the opinion of the physician, the patient has any reasons of medical and non-medical in character, which should prevent patient participation in the study.

4.2 Withdrawal of Patients From the Study

The duration of the study is defined for each patient as the date signed written informed consent is provided through to the last study visit. Patients may withdraw their consent at any time and for any reason without prejudice to their future medical care by the investigator or at the study site.

Patients switching treatment from alogliptin or alogliptin FDCs to another T2DM treatment will be followed until the end of the study.

4.2.1 Reasons for Withdrawal

This study does not require administration of any investigational product and therefore does not require any stopping criteria.

The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

1. The patient does not meet the protocol inclusion/exclusion criteria.
2. The patient withdraws consent or the investigator or Takeda decides to discontinue the patient's participation in the study.

The investigator will also withdraw a patient if Takeda terminates the study.

4.2.2 Handling of Withdrawals

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.

5 Study Treatments

This is an observational study in patients with T2DM. No study medications will be administered in this study. Patients enrolled in the study will have been under the care and treatment of their physician and will be treated according to their physician criteria and as per standard clinical practice. Alogliptin or alogliptin FDCs will have been prescribed as part of the patients' T2DM treatment program, independent of participation in this study. Alogliptin or alogliptin FDCs will be prescribed as determined by the physician and standard clinical practice. No intervention or change in the patients' T2DM management will be required as a result of this study.

6 Study Assessments and Collection of Data

Before collecting any data, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator will also sign the ICF. Refer to Section 8.3 for additional details on patient's consent.

Study assessments will be performed as outlined in this section and in the approximate time points indicated in the Data Collection Schedule (Table 12-1). The time points reflect the standard clinical practice, and patients will not be asked to travel to the site only for the purpose of this study (see Section 3.1).

6.1 Study Assessments

6.1.1 Indication and Prescribing Physician-Related Data

The following information related to the drug indication and treating physician will be collected as shown in the Data Collection Schedule (Table 12-1):

- **Indication information:** alogliptin and alogliptin FDCs market status, T2DM standard of care
- **Prescribing physician-relevant information:** general/specialized practitioner

6.1.2 Demographic Data and Medical History

Patient demographic data will include date of birth (if allowed by local regulations), sex, race, ethnicity, height, and body weight.

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).

Demographic data and medical history will be obtained from medical records and as shown in the Data Collection Schedule (Table 12-1).

6.1.3 Prior and Concomitant Medications

All prior and concomitant medications, including but not limited to T2DM treatments, will be collected and recorded in the eCRF as shown in the Data Collection Schedule (Table 12-1). Changes in all medication will also be collected.

For each prior and concomitant medication, the following information will be collected: medication name, start date, dose, and end date.

6.1.4 Clinical Response to Treatment With Alogliptin or Alogliptin Fixed-Dose Combinations

6.1.4.1 HbA1c

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 HbA1c level goal for the patient will be collected at baseline, when determined as part of standard clinical practice.

Clinical response to treatment with alogliptin or alogliptin FDCs will be evaluated based on HbA1c levels, as per the following endpoints:

- Change from baseline in HbA1c levels.
- Change in HbA1c levels over time
- Clinical response rates: incidence rates of responders. The following definitions of response will be used:
  - HbA1c level reduction to the goals of <7.0%.
  - HbA1c reduction >0.3% with no tolerability findings (hypoglycemic event, or weight gain ≥5%) (Mathieu et al 2013).

The HbA1c levels will be recorded in the eCRF as shown in the Data Collection Schedule (Table 12-1). The HbA1c levels will be obtained from any assessments performed as per standard clinical practice. No study-specific measurements will be performed. If multiple HbA1c levels are available, then the assessment closest to the visit time point will be used.

6.1.4.2 Other Assessments Related to Clinical Response

Data for other assessment related to clinical response will be collected as shown in the Data Collection Schedule (Table 12-1) and will include the following:

- 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)
- Incidence of newly diagnosed co-morbidities and complications.
- Body weight: this information will be obtained from any assessments performed as per standard clinical practice. No study-specific measurements will be performed.
- Healthcare resources utilization: number of hospitalizations (including length of stay during each hospitalization, reason, and urgency [urgent/not urgent]), emergency room visits, and physician office visits.

6.1.5 Utilization of Alogliptin, Alogliptin Fixed-Dose Combinations, and Other Type 2 Diabetes Mellitus Therapies

Data on the use of alogliptin and alogliptin FDCs will include start date, dose, and end date. Information will also be collected on any additional T2DM treatment, both added in combination to alogliptin or due to switching treatment from alogliptin or alogliptin FDCs to another T2DM treatment. Additional T2DM treatment may include glucagon-like peptide-1 agonists, other oral glucose lowering agents, injectable insulin, other insulins, and other injectable glucose lowering agents.

Information on alogliptin, alogliptin FDCs, and other T2DM treatments will be collected as shown in the Data Collection Schedule (Table 12-1).

6.2 Safety Assessments

The investigator or site staff will be responsible for eliciting, documenting, and reporting events that meet the definition of ADR, AESI, or SAE, as described in Sections 6.2.1 to 6.2.5. Any AE volunteered by the patient will also be recorded.

6.2.1 Definitions of 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 6-1).

Table 6-1 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.

6.2.2 Eliciting and Documenting Adverse Events

Adverse drug reactions, AESIs, and SAEs will be assessed from the time the patient signs the ICF until the end of study participation. Any AE volunteered by the patient will also be recorded.

The investigator is responsible for following SAEs and AESIs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.2.3 Reporting Adverse Events

All ADRs, AESIs, and SAEs reported or observed during the study, as well as any AE volunteered by the patient, will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified

assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse drug reactions, AESIs, and SAEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at baseline but does not deteriorate should not be reported as ADRs, AESIs, or SAEs. However, if it deteriorates at any time during the study, it should be recorded as an ADR, AESI, or SAE.

Any AE that meets SAE criteria (Section 6.2.1) must be reported to Takeda immediately (i.e., within 24 hours) after the time site personnel first learn about the event. Any ADR or AESI must be reported to Takeda within 1 business day after the time site personnel first learn about the event. Adverse events of special interest will be followed up with specific target forms provided by Takeda. The (S)AEs will be reported by telephone and faxing the appropriate forms to Takeda. After office hours, the emergency telephone number is the one of Takeda as mentioned in the appropriate (S)AE forms.

6.2.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	An event usually transient in nature and generally not interfering with normal activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal activities.
Severe:	An AE that is incapacitating and prevents normal activities.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of alogliptin or alogliptin FDCs in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.3 Vital Sign Measurements

Vital sign data will include systolic and diastolic blood pressure.

Vital sign measurements will be recorded in the eCRF as shown in the Data Collection Schedule (Table 12-1). Vital sign data will be obtained from any assessments performed as

per standard clinical practice. No study-specific measurements will be performed. If multiple vital sign data are available, then the assessment closest to the visit time point will be used.

6.4 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure patient safety, each pregnancy must be reported to Takeda within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the patient has completed the study, and considered by the investigator as possibly related to alogliptin or alogliptin FDCs, must be promptly reported to Takeda.

6.5 Laboratory Analyses

The following biochemistry parameters will be collected, if available: creatinine, liver enzymes, lipid profile, and urinary albumin.

No laboratory analyses will be performed as part of this study. Any laboratory information (ie, HbA1c and biochemistry parameters) will be obtained from any assessments performed as per standard clinical practice.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements) (including those that worsen from baseline), obtained as part of standard clinical practice and considered to be clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are **not** to be reported as AEs or SAEs.

7 Statistical and Analytical Plan

A complete description of the statistical analyses and methods will be provided in the statistical analysis plan, which will be finalized before the database is locked.

7.1 Primary Endpoint

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

7.2 Secondary Endpoints

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

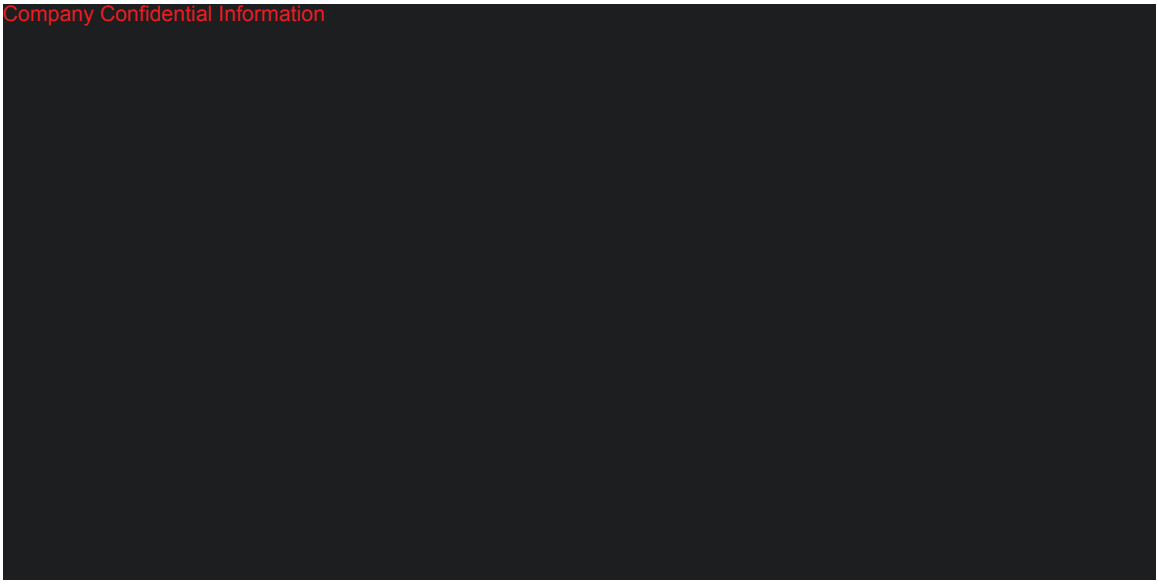
- Clinical response rates: incidence rates of responders. The following definitions of response will be used as secondary endpoints:
  - Change from baseline in HbA1c level on alogliptin or its FDCs therapy in subgroups with different clinical characteristics(V3).
  - HbA1c levels reduction to the goals 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).

7.3 Exploratory Endpoints

Company Confidential Information



7.4 Baseline Covariates

The following baseline covariates will be used:

- 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

7.5 Sample Size Calculations

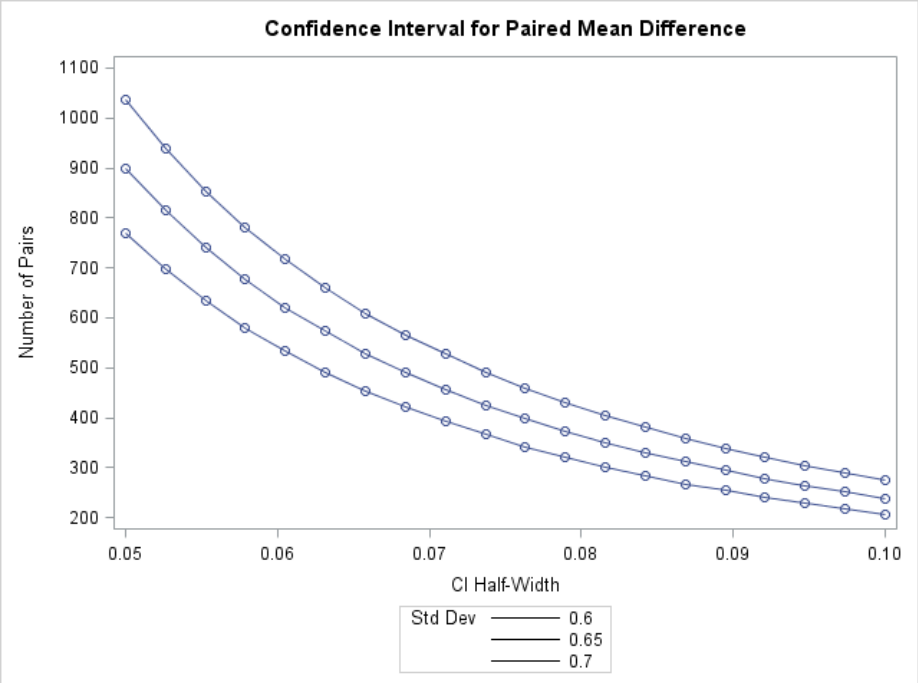
Sample size was calculated for the primary endpoint of the study: to evaluate the effect of Alogliptin or its FDCs on glycosylated hemoglobin (HbA1c) level in patients with diabetes mellitus type 2 (V3). Sample size was calculated using SAS 9.3 proc power procedure (power for Confidence Interval for 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.

7.6 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 7.4.

7.7 Description of Subgroups to be Analyzed

Subgroup analysis may be performed using any relevant baseline covariates listed in Section 7.4.

7.8 Statistical Analysis Methodology

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. A flow chart according to CONSORT guidelines will capture the patient enrollment and the analysis sets at each analysis.

Index date or date of study entry will be the patient's first day on alogliptin. Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan.

No formal significance testing will be performed.

7.8.1 Primary Analysis

HbA1c level change from baseline

Change of HbA1c levels will be summarized as descriptive statistics.

7.8.2 Secondary Analyses

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

- 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 glycosylated hemoglobin (HbA1c) level dynamics. Change from baseline in glycosylated hemoglobin (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 glycosylated hemoglobin (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 glycosylated hemoglobin (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. 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% (V3) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;

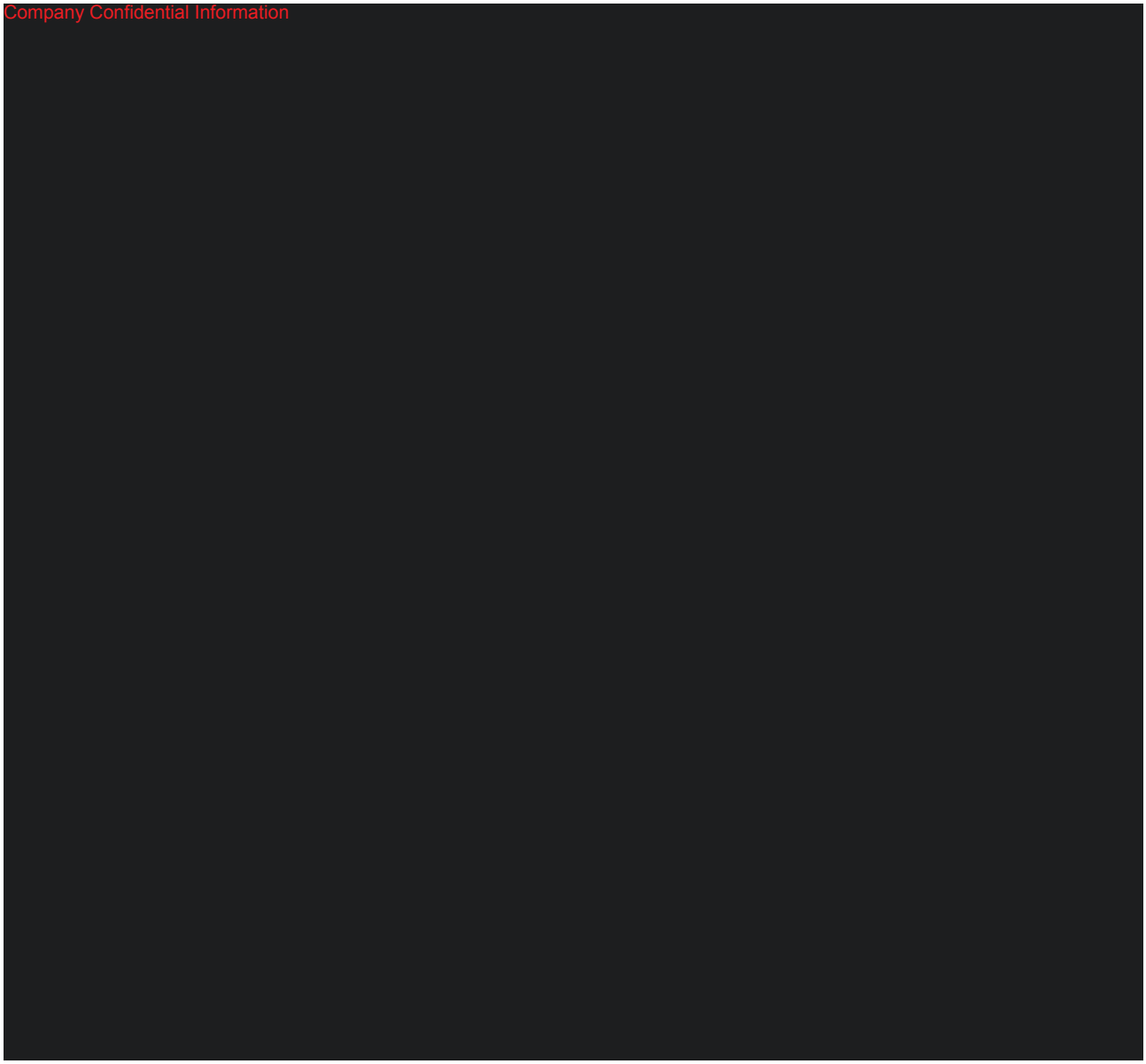
- Proportion (%) of patients with diabetes mellitus type 2 who decrease in HbA1c ≥ 0.3% over time (V3) will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;

- 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 glycosylated hemoglobin (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;
- All safety data will be analysed on the safety population. Prior to analysis, adverse drug reactions will be coded using MedDRA.
    - Incidence and characteristic of adverse drug reactions will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;
    - Evaluation of AEs, including the AEs, will consist of the determination of total number of AEs, total number of patients with AEs and the number of AEs requiring discontinuation of the study treatment. The incidence and severity of all AEs will be summarized by body system. Treatment discontinuation due to AEs will be tabulated
    - AEs reported in the study as well as AEs reported directly to authorities and to Takeda International Drug Safety and not captured in the study database will be extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR).
- Proportion (%) of patients who remain on Alogliptin or its FDCs treatment (V2-V3) and information of dose escalation or reduction will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals

7.8.3 Exploratory Analyses

Company Confidential Information

Company Confidential Information



7.8.4 Safety Analyses

All safety endpoints (ADRs, SAEs, SADR and AESIs) will be summarized.

7.8.5 Other Analyses

Summary statistical analyses will be provided for demographics, medical history, and prior medications at baseline.

Summary statistical analyses will also be provided for country and prescribing physician-related data (see Section 6.1.1) at baseline.

7.9 Data Quality Control

The handling of data, including data quality assurance, will comply with regulatory guidelines (eg, GPP) and applicable Takeda standards.

The study will be monitored by the contract research organization (CRO) on a regular basis throughout the study period and will include an electronic data collection that has a set of automatic data checks with data queries for programmed data collection.

7.9.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients with regard to from whom data are collected under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation (which may include, but is not limited to, the patient's clinic and/or office chart, hospital chart, ICFs, treatment notes, laboratory reports, radiographs, or and any other records maintained to conduct and evaluate this observational study) as part of the case histories.

Study site personnel will enter patient data into the Medidata system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable Takeda standards and data cleaning procedures to ensure the integrity of the data, as outlined in the data management plan.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Independent ethics committee (IEC)/institutional review board (IRB) must be constituted according to the applicable local law and requirements, and only when required. Each site will require documentation noting all names and titles of members who comprise the respective IEC. If any member of the IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

When IEC/IRB are required according to the applicable local law and requirements, the protocol, informed consent, advertisements to be used for the recruitment of study patients (if permitted), and any other written information regarding this study to be provided to the patient must be approved by the IEC/IRB before study onset. Documentation of all IEC/IRB approvals will be maintained by the site and will be available for review by Takeda or its designee.

All IEC/IRB approvals should be signed by the IEC/IRB chairman or designee and must identify the IEC/IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

Sites must adhere to the requirements stipulated by their respective IEC/IRB. This may include notification to the IEC/IRB regarding any amendments or updates to the documents initially submitted, materials intended for viewing by subjects, local safety reporting requirements and reports, and updates regarding the ongoing review of the investigator.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, GPP guidelines, and all applicable local regulations.

8.3 Patient Information and Consent

A written informed consent in compliance with local regulatory authority regulations and US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study. An informed consent template may be provided by Takeda to study sites. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IEC/IRB but will not result in protocol amendments.

9.1 Confidentiality

Patient data will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by Takeda, its designee, or regulatory authorities.

The investigator and all employees and co-workers involved with this observational study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Takeda or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Takeda to submit the complete and accurate certification or disclosure statements required under 21 CFR 54 (Food and Drug Administration, 2014). In addition, the investigator must provide to Takeda a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither Takeda nor the CRO is financially responsible for further testing or treatment of any medical condition that may be detected at baseline. In addition, in the absence of specific arrangements, neither Takeda nor the CRO is financially responsible for further treatment of the patient's disease.

9.3 Investigator Documentation

Prior to beginning this observational study, the investigator will be asked to provide the following documents:

- IEC/IRB approval, as required by country-specific regulations, as detailed in Section 8.1

- Authority approval, as required by country-specific regulations
- Original investigator-signed investigator agreement page of the protocol
- Curriculum vitae for the investigator
- Financial disclosure information
- IEC/IRB-approved informed consent and samples of site advertisements for recruitment for this study (if permitted by local regulations)
- Laboratory certifications and normal ranges for any local laboratories used by the site
- Local insurance certificate, if applicable
- Written agreement between Takeda and study site

9.4 Study Conduct and Adherence to Protocol

The investigator agrees that the study will be conducted in accordance with the protocol, the principles of the declaration of Helsinki and GPP guidelines, and all national, state, and local laws or regulations.

9.5 Adverse Events and Study Report Requirements

By participating in this observational study, the investigator agrees to submit reports of AEs according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit reports to the study site IEC/IRB as stipulated by his or her respective IEC/IRB.

9.6 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IEC/IRB with a summary of the study's outcome and Takeda and regulatory authorities with any reports required.

9.7 Records Retention

Essential documents should be retained until at least 2 years after the end of study. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Takeda. It is the responsibility of Takeda to inform the investigator/institution as to when these documents no longer need to be retained.

9.8 Publications

After completion of this observational study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal.

Data are the property of Takeda and cannot be published without prior authorization from Takeda, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 External Data Monitoring Committee

As this is an observational study, no external data monitoring committee has been planned.

10.1.2 Monitoring of the Study

The clinical monitor, as a representative of Takeda, has the obligation to follow the study closely. This study will be monitored by the CRO. Also, the monitor may visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact.

All aspects of the study will be monitored, by Takeda or its designee, for compliance with applicable government regulation with respect to current GPP guidelines and current standard operating procedures.

10.1.3 Inspection of Records

Takeda may audit the study site to evaluate study conduct and compliance with protocols, standard operating procedures, GPP guidelines, and applicable regulatory requirements. The Takeda quality assurance unit, independent of the Clinical Research Department, is responsible for determining the need for (and timing of) a study site audit. Each investigator must accept that regulatory authorities and Takeda representatives may conduct inspections to verify compliance of the study with GPP guidelines.

Investigators and their relevant personnel must be available during the monitoring visits and possible audits or inspections and sufficient time must be devoted to the process.

10.2 Management of Protocol Amendments

10.2.1 Modification of the Protocol

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when the change involves only logistics or administration. Amendments must be reviewed and approved by Takeda or its designee.

10.3 Study Termination

Although Takeda has every intention of completing the study, Takeda reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of this observational study is defined as the date on which the last patient completes the last visit or loss of contact or death, whichever occurs first.

11 Reference List

American Diabetes Association. Standards of Medical Care in Diabetes—2015. Diabetes Care. 2015;38(Suppl 1):S1-94.

Centers for Disease Control and Prevention (CDC). Basics about diabetes. [updated 21 October 2014] [cited 12 January 2015]. Available from: http://www.cdc.gov/diabetes/consumer/learn.htm.

Epstein M; for International Society of Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2005;14(8):589-95.

Food and Drug Administration. Code of Federal Regulations Title 21, Part 54 Financial Disclosure by Clinical Investigators. [revised 01 April 2014] [cited 28 January 2015]. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54&showFR=1.

Hogan P, Dall T, Nikolov P; and American Diabetes Association. Economic costs of diabetes in the US in 2002. Diabetes Care. 2003;26(3):917-32.

International Diabetes Federation (IDF). Diabetes Atlas Sixth edition. Brussels, 2014. [cited 12 January 2015]. Available from: http://www.idf.org/diabetesatlas.

International Diabetes Federation (IDF). Global Guideline for Type 2 Diabetes. Brussels, 2012. [cited 07 Apr 2015]. Available from: http://www.idf.org/global-guideline-type-2-diabetes-2012.

Mathieu C, Barnett AH, Brath H, et al. Effectiveness and tolerability of second-line therapy with vildagliptin vs. other oral agents in type 2 diabetes: a real-life worldwide observational study (EDGE). Int J Clin Pract. 2013;67(10):947-56.

Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of

Diabetes (EASD). Eur Heart J. 2013;34(39):3035-87; erratum in Eur Heart J. 2014;35(27):1824.

The European Parliament and the Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 04 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Off J Eur Communities. 2001;L121:34-44.

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327-35.

Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-53.

Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414(6865):782-7.

12 Appendices

12.1 Appendix: Data Collection Schedule

Patients will not be asked to travel to the site only for the purpose of this study; the study visits will be performed during the regular doctor's appointments.

Table 12-1 Data Collection Schedule

Procedure	Baseline[1]	Month 3[1]	Month 6[1]
Country-relevant information: alogliptin or alogliptin FDCs market status, T2DM standard of care	X		
Prescribing physician-relevant information: general/specialized practitioner	X		
Patient Data			
Informed consent	X		
Inclusion/exclusion criteria	X		
Demographic data[2,3]	X		
General medical history and prior medications[2]	X		
T2DM diagnosis and previous T2DM treatments[2]	X		
Alogliptin or alogliptin FDCs status: start date[4]	X		
Concomitant medications[2]	X	X	X
Alogliptin or alogliptin FDCs status: dose, end date (if applicable)[4]	X	X	X
Other T2DM treatment[4,5]	X	X	X
HbA1c and fasting blood glucose levels[6,7]	X[2]	X	X
Biochemistry parameters[6,7]	X	X	X
Health status (general and T2DM related)[6]	X[2]	X	X
Body weight [6]	X[2]	X	X
Vital sign measurements[6,9]	X[2]	X	X
Healthcare resources utilization: number of hospitalizations (including length of stay during each hospitalization, reason, and urgency [urgent/not urgent]), ER visits, and physician office visits[4]		X	X
SAFETY REPORT(ADR/SAE/SADR/AESI) [4]		X	X

Abbreviations: ER, emergency room; FDC, fixed-dose combination; HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus. ADR, adverse drug reaction; SAE, serious adverse events; SADR, serious adverse drug reaction; AESI, adverse event of special interest

1. 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.
2. Obtained from medical records.
3. Including date of birth (if allowed by local regulations), sex and height.
4. May be collected from medical records since previous visit.
5. Including glucagon-like peptide-1 agonists, other oral glucose lowering agents, injectable insulin, other insulins, and other injectable glucose lowering agents.
6. Obtained from any assessments performed as per standard clinical practice. No study-specific measurements will be performed.
7. The latest HbA1c or fasting blood glucose 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 fasting blood glucose can be either a blood test or SMBG of the patient.
8. Including creatinine, liver enzymes, lipid profile, and urinary albumin.
9. Systolic and diastolic blood pressure.

12.2 Appendix: Signature Pages

Protocol Approval – Sponsor Signatory

Study 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
Protocol Number	Alogliptin-5009
Protocol Version	1.1
Protocol Date	1 April 2016

Protocol accepted and approved by:

Senior Medical Manager(CVM)

Personal Protected Data

Signature Date

Medical Director, Pharmacovigilance

Personal Protected Data

Signature Date