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

Protocol Approve Date: 17 August 2020

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 (PPD) 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.

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

Phase 3 Alogliptin Pediatric Study

Sponsor: **Takeda Development Center Americas, Inc**
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Study Number: SYR-322_309

IND Number: 69,707 **EudraCT Number:** 2015-000208-25

Compound: alogliptin

Date: 17 August 2020 **Amendment Number:** 9 IT v1

Amendment History:

Date	Amendment Number	Amendment Type	Region
17 August 2020	Amendment 9 IT v1	Substantial	Italy
13 November 2019	Amendment 8	Substantial	Russia
28 November 2018	Amendment 7	Substantial	Brazil
27 June 2018	Amendment 6	Substantial	Germany
09 February 2018	Amendment 5	Substantial	Germany
17 January 2018	Amendment 4	Substantial	Italy
10 May 2017	Amendment 3	Nonsubstantial	Global
09 November 2016	Amendment 2	Substantial	Global
29 April 2016	Amendment 1	Substantial	Global
28 July 2015	Initial Protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site.

Contact Type/Role	North American Contact	South American Contact	European Contact
Serious adverse event and pregnancy reporting	PPD		
Medical Monitor (medical advice on protocol and compound)			
Responsible Medical Officer (carries overall responsibility for the conduct of the study)			

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B - Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

1.3 Protocol Amendment No. 9 IT v1 Summary of Changes

This section describes the changes in reference to the protocol incorporating Amendment 9 IT v1.

The primary reasons for this amendment are to:

- Describe how to manage study procedures, data collection, investigational product, and statistical analysis during unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic.
- Revise the sample size as per United States (US) Food and Drug Administration (FDA) recommendation and in accordance with the approved European Medicines Agency (EMA) modified Paediatric Investigational Plan (PIP), EMEA-000496-PIP01-08-M08.
- Remove the specific dropout/hyperglycemic rescue rate of 30%, as recommended by the US FDA.
- Update the text to include the recent availability of liraglutide for type 2 diabetes mellitus (T2DM) treatment in children and adolescents.
- Remove pharmacogenomic sampling.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 9 IT v1		
Summary of Changes Since the Last Version of the Approved Protocol for Italy		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Reduced the sample size from 100 subjects per arm to 75 subjects per arm.	To revise the sample size as per US FDA recommendation and in accordance with the approved EMA modified PIP, EMEA-000496-PIP01-08-M08.
Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Removed the specific dropout/hyperglycemic rescue rate of 30%.	To remove the specific dropout/hyperglycemic rescue rate of 30% as recommended by US FDA.
Section 4.1 Background	Updated text to reflect availability of liraglutide for children and adolescents aged 10 to 17 years.	To update text to include current availability of liraglutide for treatment of T2DM in children and adolescents aged 10 to 17 years.

Protocol Amendment 9 IT v1		
Summary of Changes Since the Last Version of the Approved Protocol for Italy		
Sections Affected by Change	**Description of Each Change and Rationale**	
Section 6.1 Study Design Section 7.6 Criteria for Discontinuation or Withdrawal of a Study Drug Section 8.2 Investigational Drug Assignment and Dispensing Procedures Section 9.1.1 Alternative Approaches to Study Procedures and Data Collection Due to Unavoidable Circumstances Section 9.1.9 Procedures for Clinical Laboratory Samples Section 9.3 Schedule of Observations and Procedures Section 13.1 Statistical and Analytical Plans Section 14.2 Protocol Deviations Appendix A Schedule of Study Procedures	Added instructions for managing study procedures, data collection, and investigational product during unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster).	To provide instruction for managing study components impacted by unavoidable circumstances.
Section 9.1.2.1 Pharmacogenomic Informed Consent Procedure Section 9.1.12 Pharmacogenomic Sample Collection Section 9.4 Biological Sample Retention and Destruction Appendix A Schedule of Study Procedures	Discontinued collection of pharmacogenomic sample	As of the date of this amendment, a sufficient number of samples have been collected and no more are needed.
Section 13.1.3 Efficacy Analysis	Added sensitivity analysis for the primary endpoint only that excludes subjects affected by COVID-19.	To add sensitivity analysis to the primary endpoint.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. Takeda Development Centre Europe Ltd. Takeda Development Center Asia Pte. Ltd.	**Compound:** Alogliptin	
Title of 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	**IND No.:** 69,707	**EudraCT No.:** 2015-000208-25
Study Number: SYR-322_309	**Phase:** 3	

Study Design:

This will be a multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alogliptin 25 mg once daily (QD) compared to placebo, in children and adolescents 10 to 17 years, inclusive, at the time of randomization, with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) and who are experiencing inadequate glycemic control. Subjects will enter into a Screening Period of up to 2 weeks. If certain entry criteria are not met, subjects will participate in a Pre-Randomization Stabilization Period. On Study Day 1, eligible subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups, alogliptin 25 mg QD or matching placebo. In addition to receiving double-blind study medication, subjects will be required to maintain their background antidiabetic therapy, at the same dose, throughout the first 26 weeks of the Double-Blind Treatment Period. Subjects who complete the 52-Week Double-Blind Treatment Period 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.

Primary Objective:

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

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 at 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.

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[redacted]

Subject Population: Pediatric subjects aged 10 to 17 years, inclusive, with T2DM.

Number of Subjects:	**Number of Sites:**
150 randomized subjects	Estimated total: 60 sites in 20 countries
Dose Level(s): Alogliptin 25 mg QD Placebo QD	**Route of Administration:** Oral
Duration of Treatment: 52 weeks	**Period of Evaluation:** Approximately 56 weeks plus a variable Pre-Randomization Stabilization Period

Main Criteria for Inclusion:

A confirmed diagnosis of T2DM using American Diabetes Association (ADA) and World Health Organization (WHO) criteria (laboratory determinations of FPG ≥126 mg/dL, random glucose ≥200 mg/dL [≥11.10 mmol/L], HbA1c ≥6.5%, or 2-hour oral glucose tolerance test [OGTT] glucose ≥200 mg/dL), documented in the subjects' medical record.

Main Criteria for Exclusion:

1. The subject has a confirmed diagnosis of type 1 diabetes mellitus or maturity-onset diabetes of the young (MODY).
2. The subject has a hemoglobin level <11.0 g/dL (<110 g/L) for males and <10.0 g/dL (<100 g/L) for females.
3. The subject has a history of any hemoglobinopathy that may affect determination of HbA1c levels.

Additional Criteria That Must Be Met Following Screening and/or Completion of the Pre-Randomization Stabilization Period and Prior to Randomization:

1. The subject will be required to have an HbA1c level of ≥6.5% to <11.0% if the subject is on metformin alone or ≥7.0% to <11.0% if the subject is on insulin alone or in combination with metformin.
2. The subject must not have received any investigational compound within 30 days or 5 half-lives, whichever is longer, prior to randomization.
3. The subject must not have received an antidiabetic agent other than metformin or insulin within the 12 weeks prior to randomization.
4. The subject must not have received oral or parenteral steroids for more than 3 weeks (cumulatively) within the 6 months prior to randomization or have received a course of oral or parenteral steroids within the 2 months prior to randomization.
5. The subject has a systolic blood pressure <160 mmHg and a diastolic pressure <100 mmHg. (Antihypertensive medications will be allowed during the study).
6. The subject has an alanine aminotransferase (ALT) level <3× upper limit of normal (ULN) or an ALT level <5×ULN with a confirmed diagnosis of nonalcoholic fatty liver disease (NAFLD).
7. The subject does not plan to leave the geographic area within 1 calendar year following randomization.
8. Male or female subjects, 10 to 17 years of age, inclusive, at the time of randomization.

For subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin prior to

randomization, the following criteria must also be met:

9. The subject must have a fasting C-peptide concentration ≥0.6 ng/mL (≥0.20 nmol/L) (drawn at least 1 week after treatment for ketosis or acidosis, if applicable).
10. No presence of autoantibodies as documented by glutamic acid decarboxylase [GAD] 65 and islet antigen [IA]-2 antibodies below the upper limit of the normal reference ranges at randomization.
11. The subject must have a BMI >85th percentile, documented at randomization.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is HbA1c change from Baseline at Week 26.

Secondary endpoints for this study are:

Efficacy

HbA1c change from Baseline at Weeks 12, 18, 39, and 52.

Safety:

- 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).
- Change from Baseline in biomarkers of bone turnover (bone-specific alkaline phosphatase and CTX) at Weeks 26 and 52.
- Change from Baseline in CD26 surface antigen levels at Weeks 26 and 52.

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Statistical Considerations:

The primary efficacy analysis will be conducted using a contrast at Week 26 derived from a mixed model for repeated measures (MMRM) with change from Baseline in HbA1c as the response variable, treatment, visit, and visit-by-treatment interaction as fixed categorical effects, and baseline HbA1c and visit-by-baseline HbA1c interaction as continuous covariates.

The secondary efficacy variable will be analyzed using additional contrasts at Weeks 12, 18, 39, and 52 derived from the primary analysis model. Continuous exploratory efficacy variables will be analyzed using models similar to the primary analysis model. Categorical variables and time to hyperglycemic rescue will be analyzed using logistic regression models and a Cox regression model, respectively.

Safety variables will be summarized using descriptive statistics or frequency counts as appropriate.

Sample Size Justification: 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%, and a 2-sided false-rejection rate of 5%.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities document. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
BID	twice daily
BMI	body mass index
CCI	[redacted]
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CTX	C-terminal telopeptide
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
CCI	[redacted]
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
CCI	[redacted]
IA	islet antigen
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee
CCI	[redacted]
INR	international normalized ratio
IRB	institutional review board

ISPAD	International Society for Pediatric and Adolescent Diabetes
IVRS	interactive voice response system
IWRS	interactive web response system
K_2EDTA	potassium ethylenediamine tetraacetic acid
CCI	[redacted]
CCI	[redacted]
MMRM	mixed model for repeated measures
MODY	maturity-onset diabetes of the young
MTD	maximum tolerated dose
NAFLD	nonalcoholic fatty liver disease
NOAEL	no-observed-adverse-effect level
OGTT	oral glucose tolerance test
PD	pharmacodynamic(s)
PI	Principal Investigator
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PPG	postprandial glucose
PPS	per protocol set
PTE	pretreatment event
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization

3.4 Corporate Identification

TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Europe, TDC Americas and/or TDC Asia, as applicable
TDC Asia	Takeda Development Center Asia Pte. Ltd.
Takeda	TDC Europe, TDC Americas and/or TDC Asia as applicable

4.0 INTRODUCTION

4.1 Background

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder of heterogeneous and multifactorial etiology, with a strong hereditary component and genetic predisposition overlaid by social, behavioral, and environmental risk factors [1-9]. Information on the underlying mechanisms, the phases of pathogenesis, clinical presentation and course, risk factors, attendant complications, and treatment is still comparatively sparse for pediatric populations and is being widely debated. Overall, however, the pathophysiology of T2DM in children and adolescents appears to be similar to that in adults [1,6,10-15].

The incidence of T2DM among children and adolescents is on the rise, largely due to the worldwide increase in childhood obesity. In the US, the SEARCH for Diabetes Youth Study reported the prevalence of T2DM among children and adolescents (10-19 years) to be 0.46 cases per 1000 in 2009, which is a 35% increase from that reported in 2001 [16]. Projections from the SEARCH study estimate that the number of children and adolescents with T2DM could quadruple over the next 40 years [17].

The global increase in T2DM in children and adolescents has evolved into an important public health issue [10,18-20]. T2DM is associated with multiple long-term complications leading to morbidity as well as premature mortality, including: accelerated development of cardiovascular diseases; nephropathy and kidney failure; retinopathy and blindness; nervous system disease including peripheral neuropathy; macrovascular complications; high blood pressure; peripheral vascular disease and lower limb amputation; non-alcoholic fatty liver disease, including non-alcoholic steatohepatitis; and increased risk of death from infection such as pneumonia. In children and adolescents, the increased incidence of T2DM and obesity observed globally during the past 2 decades not only places a severe burden on the individual's physical, psychological, emotional, and social well-being, but will also have long-term public health and societal consequences, as these patients are at risk of progressing to the aforementioned chronic complications at a relatively young age and may experience subsequent loss of their productivity as adults [1,10,12,18,21-26]. In addition, the rates of long-term medication use for treatment of the diabetes-related complications, of physician contacts, and of hospitalizations are likely to increase.

Although a diverse range of oral antidiabetic agents are available, few of these have been evaluated in children and adolescents. Until recently, only metformin and insulin were approved in the US and Europe for treatment of T2DM in pediatric patients. Liraglutide, an injectable glucagon-like peptide-1 receptor agonist (GLP-1 RA), has become available for children and adolescents aged 10 to 17 years with T2DM. According to treatment guidelines set forth by the AAP (American Academy of Pediatrics) and the IDF/ISPAD (International Diabetes Federation/International Society for Pediatric and Adolescent Diabetes), initial care may require insulin until diagnostic classification of T2DM has been confirmed and the patient is metabolically stable [27,28]. Once metabolically stable, metformin is the initial pharmacologic treatment of choice for children and adolescents with T2DM. However, both metformin and insulin have disadvantages. Metformin must be administered twice daily (BID), and is commonly associated

with unpleasant gastrointestinal side effects. Furthermore, most children do not maintain adequate glycemic control with metformin alone for the long term. This was recently demonstrated in the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study that evaluated metformin and rosiglitazone vs dietary modifications and exercise alone in approximately 700 pediatric patients with T2DM [29]. The primary outcome of this study was loss of glycemic control, defined as a glycated hemoglobin level of at least 8% for 6 months or sustained metabolic decompensation requiring insulin. Results of this study showed that metformin alone was effective in maintaining durable glycemic control in only one-half of the study participants. This suggests that a majority of youth with T2DM may require combination treatment or insulin therapy within just a few years after diagnosis [29].

Treatment with insulin is not ideal for the pediatric population as it has several limitations such as weight gain and hypoglycemia, and requires multiple daily injections that can lead to poor compliance [30]. Therefore, there is a need to investigate alternative oral therapies available for children. Having a once daily oral antidiabetic agent available as an alternative or as add-on to metformin or insulin may provide benefit to the patient, potentially for newly diagnosed patients as well as for those who cannot tolerate metformin or whose diabetes is not controlled on metformin and/or insulin.

As part of the pediatric program, 2 studies have been conducted to assess potential alogliptin toxicity in the juvenile rat. A 4-week toxicity study was conducted in male and female rats that were 4 weeks of age at initiation of dosing. Because the pivotal toxicity studies were conducted using rats that were 8 weeks of age at study initiation, this 4-week study was conducted to provide alogliptin toxicity information in the young rodent through the age of the rats at initiation of dosing in the pivotal repeat-dose toxicity studies (SYR-322-00610). To ensure no effect on the developing reproductive organs of the juvenile male, a second toxicity study was conducted in 4-week old male rats administered alogliptin for 8 consecutive weeks (SYR-322-18040). Doses selected for this study were the same as those used in the pivotal 4-week toxicity study in which rats were 8 weeks of age at dose initiation. The NOAEL (no-observed-adverse-effect level) in that study was 300 mg/kg/day and produced exposure margins (based on area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) that were 53- to 58-fold the AUC_{24} measured in adult men and women, respectively, at the clinical dose of 25 mg/day.

No toxicologically meaningful effects were noted in juvenile rats (4-weeks of age at dose initiation) administered alogliptin daily for 4 consecutive weeks. Similarly, the 8-week repeat-dose toxicity study in male juvenile rats (4 weeks of age at dose initiation) did not show any alogliptin-related effects on the developing male reproductive organs. Toxicokinetic data in the juvenile rats were similar to those obtained in adult rats.

With regard to reproductive toxicity, alogliptin administered to pregnant rabbits and rats was not teratogenic at doses of up to 200 and 500 mg/kg, or 149 and 180 times, respectively, the mean exposure in adults at the 25 mg dose. Additionally, doses of alogliptin up to 250 mg/kg (~ 95 times the mean exposure in adults at the 25 mg dose) administered to pregnant rats did not harm the developing embryo or adversely affect growth and development of offspring.

Alogliptin has been shown to be safe and effective in the treatment of adults with T2DM in a comprehensive clinical program that included 55 clinical studies and involved approximately 1000 healthy adult subjects and more than 12,000 adult subjects with T2DM. This includes phases 1, 2, and 3 controlled and uncontrolled studies (including those conducted in Japan and China).

A total of 30 phase 1 and 2 clinical pharmacology studies were conducted using single and multiple doses of alogliptin 6.25 to 800 mg, in healthy adults, adults with T2DM, adults with renal impairment, and adults with hepatic impairment.

4.2 Rationale for the Proposed Study

As discussed above, there is a need for new antidiabetic therapies, in addition to metformin and insulin, for treatment of T2DM in children.

In accordance with the US FDA Pediatric Research Equity Act and the EMA PIP requirements, a phase 3 study is being conducted to investigate the safety and efficacy of alogliptin in a pediatric population with T2DM aged 10 to 17 years, inclusive. The choice of the age group is supported by epidemiologic data that indicates that T2DM in children and adolescents is most commonly diagnosed at the time of puberty, between approximately 12 and 14 years, inclusive.

A phase 1, pediatric, pharmacokinetic (PK)/pharmacodynamic (PD) study of alogliptin (SYR-322_104) was completed. This study was conducted to determine the PK and PD profiles, safety, and tolerability of a single dose of alogliptin 12.5 mg and 25 mg in subjects with T2DM between 10 to 17 years old and adult subjects with T2DM. This phase 3 study will evaluate alogliptin 25 mg since it was determined to be the appropriate dose for pediatric subjects based on the results of the phase 1 study (see Section 6.3 for dose selection rationale).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 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

5.2 Endpoints

5.2.1 Primary Endpoint

HbA1c change from Baseline to Week 26.

5.2.2 Secondary Endpoints

Efficacy

HbA1c change from Baseline at Weeks 12, 18, 39, and 52.

Safety:

- 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).
- Change from Baseline in biomarkers of bone turnover (bone-specific alkaline phosphatase and CTX) at Weeks 26 and 52.
- Change from Baseline in CD26 surface antigen levels at Weeks 26 and 52.

CCI

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This will be a multicenter, randomized, double-blind, placebo-controlled 52-week study evaluating the efficacy and safety of alogliptin 25 mg QD compared to placebo, in children and adolescents 10 to 17 years of age, inclusive, at the time of randomization, with a confirmed diagnosis of T2DM and who are experiencing inadequate glycemic control. Subjects who are recruited for this study should be on a background of metformin alone, insulin alone, or on a combination of metformin and insulin.

Subjects will enter into a Screening Period of up to 2 weeks. During the Screening Period investigators should:

- Assess the subjects' and their respective guardians' suitability for the study, in terms of study-procedure compliance and long-term commitment.
- Educate subjects on diet and exercise consistent with standard of care for T2DM.
- Educate subjects on compliance with protocol procedures.

Subjects who have completed all required Screening Procedures, and who meet all entry criteria may proceed to Randomization/Day 1. Eligible subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups, alogliptin 25 mg QD or matching placebo.

Subjects who have not met all of the additional randomization criteria listed in 7.3, will be allowed to enter a Pre-Randomization Stabilization Period (see Section 6.2).

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 Day 1 (eg, baseline insulin doses, if applicable), throughout the first 26 weeks of the Double-Blind Treatment Period.

Subjects will receive diabetes education and home glucose monitoring training during the Pre-Randomization Stabilization Period (if applicable) and during the first 26 weeks of the Double-Blind Treatment Period. Subjects will maintain blood glucose diaries which will be reviewed at each study visit throughout the study.

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.

Subjects who are not eligible for randomization will be referred back to their primary care physician for resumption of their care.

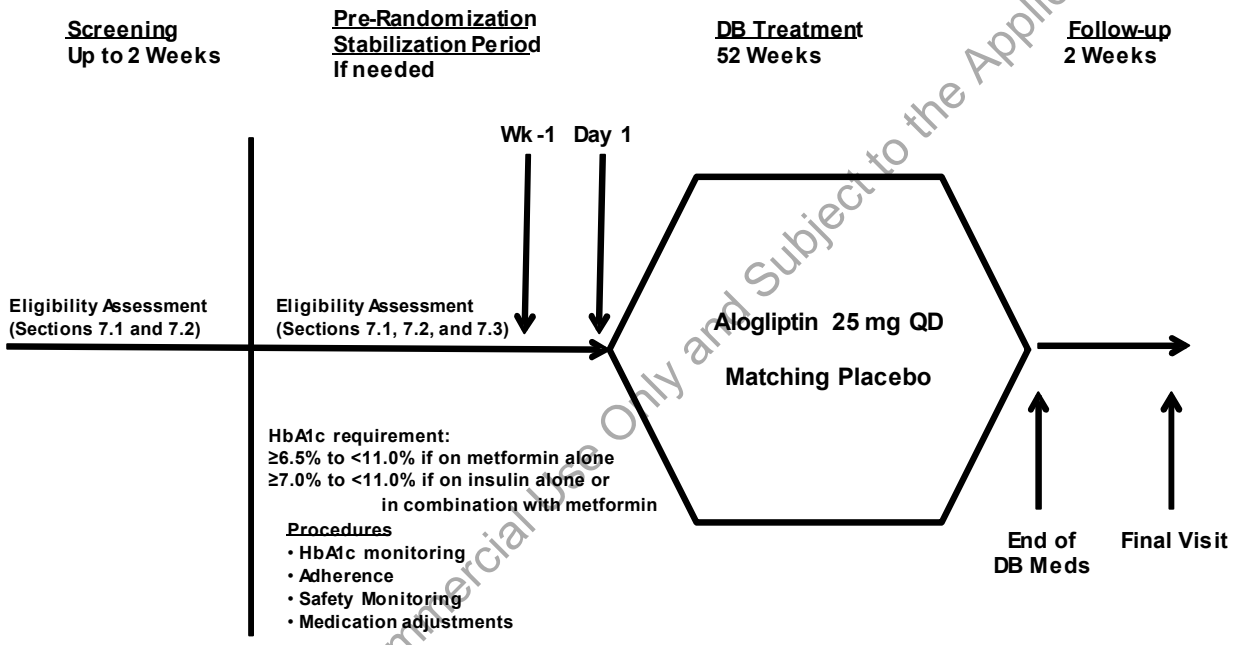
This study will be conducted at approximately 60 sites in 20 countries.

Sites will employ all efforts to see subjects in the clinic for assessments. In unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural

disaster), exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor. Such instances will be documented in the study records. Data collected with alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

A schematic of the study design is shown in Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



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

(a) 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.
(b) The Screening Visit will be scheduled within 2 weeks prior to Day 1 or the start of the Pre-Randomization Stabilization Period. During the Pre-Randomization Stabilization Period, subjects will visit the study center at regular intervals according to the investigator's discretion but at least every 3 months and at Week -1 prior to randomization.
(c) The Week 4, 32, 45, and 54 visits will be conducted only via telephone call to the subject.
(d) The Sponsor or its designee will decide whether the Week 18 Visit will be conducted as an in-clinic visit, or optionally, as a home health visit.

6.2 Pre-Randomization Stabilization Period (if needed)

Subjects who meet all inclusion and exclusion criteria listed in Sections 7.1 and 7.2, respectively, AND who are anticipated to meet the additional entry criteria listed in Section 7.3 following medical oversight (ie, washout of prior medications, adjustment to their metformin or insulin doses, adjustment to antihypertensive regimen) by the investigator will be allowed entry into the Pre-Randomization Stabilization Period.

The Pre-Randomization Stabilization Period is intended to meet the following objectives:

- Allow a period of wash-out of prior medications and adjustment of anti-hypertensive treatment;
- Evaluate underlying etiology and persistence of elevated alanine aminotransferase (ALT) levels;
- Allow subjects who are on metformin to reach their maximum tolerated dose (MTD) of metformin and maintain that dose for a minimum of 2 months;
- Allow for subjects to be monitored for deterioration of glycemic control and potential study qualification;
- If considered appropriate, initiate insulin therapy in subjects with HbA1c levels ≥11.0% on MTD of metformin alone;
- Allow establishment of a stable insulin regimen for participants entering the Pre-Randomization Stabilization Period on insulin;
- Allow investigators to intensify or wean insulin therapy as appropriate for the management of each individual subject;
- Subjects treated on insulin should be carefully monitored with a goal to discontinue insulin therapy [31]. If the subject is unable to discontinue insulin therapy, the dose of insulin must be stable and maintained for 2 months prior to randomization and their HbA1c must be ≥7% to be eligible to proceed to randomization.

Regardless of participation in the Pre-Randomization Stabilization Period, investigators should ensure the following for all subjects:

- The study site staff adequate time to assess the subjects' and their respective guardians' suitability for the study, in terms of study-procedure compliance and long-term commitment;
- Subjects are encouraged to intensify dietary and exercise regimen;
- Subjects are encouraged to be compliant with all aspects of the treatment regimen.

Subjects will return to the clinic for assessments at regular intervals during the Pre-Randomization Stabilization Period at the investigator's discretion, but at least every 3 months. The duration of participation in the Pre-Randomization Stabilization Period will vary for each subject based on his/her status.

During the Pre-Randomization Stabilization Period, subjects receiving metformin will continue to receive metformin with a treatment goal of at least 1000 mg BID or their documented MTD without treatment-related side effects nor symptoms of ketosis. Subjects who are already receiving metformin 1000 mg BID or their MTD will not need to adjust their dose unless side effects associated with metformin, such as gastrointestinal symptoms or other symptoms associated with metformin, require a decrease in dose.

In subjects already receiving insulin alone or insulin in combination with MTD of metformin, insulin doses can be reduced, and insulin can be discontinued in patients who are able to maintain HbA1c levels <8.0%.

Subjects with HbA1c levels ≥11% on MTD of metformin alone will be allowed to initiate insulin therapy at the discretion of the investigator.

Investigators may intensify or wean insulin therapy as appropriate for the management of each individual subject. These subjects should be adequately monitored for potential hypo- or hyperglycemia.

Subjects will receive insulin with the goal of achieving a stable dose required for glycemic control before proceeding to randomization. A stable dose of insulin is defined as a period of at least 1 month during which an insulin dose change is not required to prevent hypoglycemia or symptomatic hyperglycemia.

Once subjects meet the objectives of the Pre-Randomization Stabilization Period, they will return to the clinic (Week -1) to confirm qualification for all inclusion and exclusion criteria specified in Section 7.3.

6.3 Justification for Study Design, Dose, and Endpoints

The selection of the alogliptin 25 mg dose for the proposed phase 3 pediatric study is based on the results of the phase 1 PK/PD study (Study SYR-322_104). Following single oral administration of alogliptin 12.5 or 25 mg tablets to children, adolescents and adults with T2DM in Study SYR-322_104, the PK and PD of alogliptin appeared to be generally similar between the 2 age groups of pediatric subjects (10-13 and 14-17 years of age, respectively), with dose-proportional increases in the mean maximum observed plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity (AUC_{∞}) values of alogliptin and higher mean E_{max} (maximum drug-induced effect) and $AUEC_{24}$ (area under the effect curve from 0 to 24 hours) values for dipeptidyl peptidase-4 (DPP-4) inhibition with the 25 mg dose, relative to 12.5 mg.

Compared to adult subjects receiving 25 mg alogliptin, the mean C_{max} and AUC_{∞} values of alogliptin were 54% to 68% lower in pediatric subjects following a 12.5 mg dose and 23% to 29% lower at the 25 mg dose.

Model-based simulations of steady state exposures following dosing of alogliptin 12.5 mg and 25 mg in pediatric and adult subjects (n=75 each) were performed, assuming similar distribution of body weights between pediatric and adult subjects with T2DM. Based on the PK and PD data and model simulations, pediatric subjects with T2DM require the 25 mg dose of alogliptin to best approach alogliptin exposures and DPP-4 inhibition similar to those in adults with T2DM.

Therefore, the 25 mg dose is proposed for evaluation in the pediatric phase 3 program. The results of these studies are deemed to be adequate to support the safe and effective use of alogliptin in a pediatric population whose disease is not adequately controlled with diet and exercise alone or with metformin, insulin, or a combination of metformin and insulin. Targeting this patient population is clinically important because this strategy focuses on the medical need to improve glycemic control regardless of current therapy and is consistent with current pediatric diabetes practice of aggressively treating hyperglycemia.

6.4 Premature Termination or Suspension of Study or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- The independent Data Monitoring Committee (DMC) recommends that the study should be suspended or terminated.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria in Sections 7.1 and 7.2 will need to be confirmed as part of Screening procedures; additional criteria will need to be met prior to randomization (refer to Section 7.3).

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. A confirmed diagnosis of T2DM using American Diabetes Association (ADA) and World Health Organization (WHO) criteria (laboratory determinations of FPG ≥126 mg/dL, random glucose ≥200 mg/dL [≥11.10 mmol/L], HbA1c ≥6.5%, or 2-hour oral glucose tolerance test [OGTT] glucose ≥200 mg/dL), documented in the subjects' medical record.

Note: Previous inclusion criteria numbers 2 through 5 were moved to Section 7.3.

6. The subject is thought to be able to swallow the tablet containing the study medication.
7. A male subject who is sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study.
8. A female subject of childbearing potential* who is sexually active with a male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study.

> *Female subjects of childbearing potential are defined as reaching Tanner Stage 3. Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

9. The subject and his/her legal representative (ie, parents or legal guardians) are able and willing to provide written informed consent/assent.
10. The subject and his/her legal representative (ie, parents or legal guardians) are capable of understanding and complying with the protocol requirements, including scheduled clinic appointments.
11. The subject and his/her legal representative (ie, parents or legal guardians) are able and willing to monitor their own blood glucose concentrations with a home glucose monitor and complete subject diaries.

For subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin at Screening, additional criteria will need to be met prior to randomization (refer to Section 7.3).

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject is treatment-naïve.
2. The subject has a history of hypersensitivity or allergy to alogliptin, other DPP-4 inhibitors, metformin, insulin, or related compounds.
3. The subject has a confirmed diagnosis of type 1 diabetes mellitus or maturity-onset diabetes of the young (MODY).

4. The subject has a hemoglobin level <11.0 g/dL (<110 g/L) for males and <10.0 g/dL (<100 g/L) for females.
5. The subject has a history of any hemoglobinopathy that may affect determination of HbA1c levels.
6. The subject has a history of bariatric surgery.
7. The subject has a history of proliferative diabetic retinopathy within the 6 months prior to Screening.
8. The subject has had an episode of diabetic ketoacidosis (DKA) at any time after diagnosis of T2DM.
9. The subject has a history of pancreatitis.
10. Serum creatinine ≥1.5 mg/dL for male subjects or ≥1.4 mg/dL for female subjects, or creatinine clearance <60 mL/min based on calculation by central lab using the Schwartz formula [32] for estimated glomerular filtration rate (eGFR) at the Screening Visit.
11. The subject has a documented history of infection with human immunodeficiency virus or chronic active viral hepatitis.
12. The subject has any unstable endocrine, psychiatric or severe rheumatic disorder, or major illness or debility that, in the Investigator's opinion, prohibits the subject from being a suitable candidate for and/or completing the study, or may affect the interpretability of his/her efficacy or safety data.
13. Female subjects who are pregnant, planning to become pregnant, or who admit to sexual activity without appropriate contraception.
14. The subject and/or his/her legal representative (ie, parents or legal guardians) is unable to understand verbal or written English, or any other language for which a certified translation of the approved informed consent/assent is available.
15. The subject and/or his/her legal representative (ie, parents or legal guardians) is an immediate family member (ie, child or sibling) of a study site employee who is involved in the conduct of this study.

7.3 Additional Randomization Criteria That Must Be Met Following Screening and/or Completion of the Pre-Randomization Stabilization Period

Subjects must meet the following criteria in order to qualify for randomization:

1. The subject will be required to have an HbA1c level of ≥6.5% to <11.0% if the subject is on metformin alone or ≥7.0% to <11.0% if the subject is on insulin alone or in combination with metformin.
2. The subject must not have received any investigational compound within 30 days or 5 half-lives, whichever is longer, prior to randomization.

3. The subject must not have received an antidiabetic agent other than metformin or insulin within the 12 weeks prior to randomization.
4. The subject must not have received oral or parenteral steroids for more than 3 weeks (cumulatively) within the 6 months prior to randomization or have received a course of oral or parenteral steroids within the 2 months prior to randomization.
5. The subject has a systolic blood pressure <160 mmHg and a diastolic pressure <100 mmHg. (Antihypertensive medications will be allowed during the study).
6. The subject has an ALT level <3× upper limit of normal (ULN) or an ALT level <5×ULN with a confirmed diagnosis of nonalcoholic fatty liver disease (NAFLD). (See Appendix G for diagnostics leading to confirmation of NAFLD.)
7. The subject does not plan to leave the geographic area within 1 calendar year following randomization.
8. Male or female subjects, 10 to 17 years of age, inclusive, at the time of randomization.

For subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin prior to randomization, the following criteria must also be met:

9. The subject must have a fasting C-peptide concentration ≥0.6 ng/mL (≥0.20 nmol/L) (drawn at least 1 week after treatment for ketosis or acidosis, if applicable).
10. No presence of autoantibodies as documented by glutamic acid decarboxylase [GAD] 65 and islet antigen [IA]-2 antibodies below the upper limit of the normal reference ranges at randomization.
11. The subject must have a BMI >85th percentile, documented at randomization.

7.4 Excluded Medications

During this study, any medications deemed necessary for the management of any AEs may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that the details regarding the medication are recorded in full in the electronic case report form (eCRF).

Treatment with antidiabetic agents (including DPP-4 inhibitors or GLP-1 RA analogues) other than study drug, metformin and insulin is not allowed within 12 weeks prior to Screening and through the completion of Week 52/End-of-Treatment Visit, with the exception of those subjects who require hyperglycemic rescue medications.

Treatment with any investigational medication is not allowed from 30 days or 5 half-lives prior to randomization through the completion of the End-of-Treatment procedures. Chronic treatment with inhaled steroids >1000 mcg QD (or Flovent equivalent) should be avoided from 30 days prior to randomization through the completion of the End-of-Treatment procedures. Chronic treatment with oral or parenteral steroids should be avoided within 2 months prior to randomization and through the completion of the End-of-Treatment procedures. It is anticipated that the acute use of steroids may be required during the double-blind treatment period of the study; this will be allowed,

if required for the medical management of subjects. If a subject requires chronic use of steroids during the study, such cases should be discussed with the Medical Monitor prior to consideration of study drug withdrawal. The chronic use of steroids, however, is discouraged.

Initiation of treatment with an atypical antipsychotic medication following Screening and throughout the first 26 weeks of the Double-Blind Treatment Period is not allowed unless discussed prior to initiation with the sponsor or designee.

7.5 Diet, Fluid, Activity Control

Subjects will be instructed on proper nutrition and exercise, how to recognize signs and symptoms of hypoglycemia, and the use of a glucometer. Each study center should provide nutritional guidance in accordance with its standard of care for subjects with diabetes [33].

CCI

[redacted]

7.6 Criteria for Discontinuation or Withdrawal of a Study Drug

A subject's study medication may be temporarily suspended or permanently ceased at any time at the discretion of the Investigator. Subjects are free to stop taking study medication at any time without prejudice to further treatment. If a subject refuses to return to the clinic for study visits, specific study visit procedures per Section 7.7, should be collected via telephone contact reports. If the subject refuses telephone contact, follow options as per Section 7.7.

The primary reason for permanent discontinuation of the subject from study medication should be recorded in the eCRF using the following categories. For screen failure or Pre-Randomization Stabilization failure subjects, refer to Section 9.1.15.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE or AE.
2. Significant protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost-to-follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF. If a subject chooses to withdraw from study participation due to personal concerns

related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal in the eCRF.

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.
7. Principal Investigator (PI) discretion. Investigator has determined that the subject should be withdrawn from the study for reasons other than the above reasons (1-7).
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF, including unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster).

Also see Sections 7.8 for liver safety withdrawal criteria, 7.9 for renal safety withdrawal criteria, and 7.10 for pancreatitis withdrawal criteria.

In consultation with the Medical Monitor, the Investigator may cease providing study drug to a subject at any time during the study when either (1) the subject meets the study drug termination criteria described above, or (2) the Investigator determines discontinuation of study drug is in the subject's best interest.

Note: The subject will remain in the study to collect information regarding all assessments of study endpoints, unless the subject has explicitly withdrawn consent, as recorded in the source documents.

7.7 Criteria for Discontinuation or Withdrawal from Study Participation

7.7.1 Voluntary Withdrawal

The subject (or subject's legally acceptable representative) may discontinue his or her participation without giving a reason at any time during the study.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

The following options should be offered to the subject regarding continued participation:

1. Subject discontinues study medication, but continues to participate in study site visits and procedures following the protocol specified visit schedule.
2. Subject discontinues study medication and study procedures, however, continues telephone (or other communication) contact following the protocol-specified visit schedule. The Projected Week 52 Visit should be at the clinic, if at all possible. Concomitant medications, update

contact information, and serious adverse event (SAE) assessments should be collected at each telephone visit (or other communication), at a minimum.

3. Indirect Method: Subject is not willing to have the PI or staff contact them. However, the subject will allow the site to contact their Primary Care Physician/Designated Contact, preferably every 2 months and at a minimum at the Projected Week 52 Visit to ensure their safety.
4. No further contact/withdrawal of consent, preferably in writing-- Subject revokes consent to contact them directly or their Primary Care Physician/Designated Contact. Vital status will be checked using appropriate available information sources such as public records.

The subject's continued level of participation should be clearly documented and updated in the subject's source documents. Should a subject no longer wish any further contact, the primary criterion for termination must be recorded as well. In addition, efforts should be made to perform all procedures scheduled for the End-of-Treatment Visit, Telephone Follow-up Visit, and Projected Week 52 Visit.

Discontinued or withdrawn subjects will not be replaced.

7.7.2 Lost-to-Follow-up

Every effort will be made to ensure that the subject continues to return to the clinic for study visits and to avoid "Lost-to-Follow-up" during the conduct of the study. The study staff should make diligent attempts to contact subjects who fail to return for study visits by using public information websites, institutional databases, subjects' health professionals, and any other means that comply with country, state, and local laws and regulations. At a minimum, after the first missed visit, subjects who are considered temporarily Lost-to-Follow-up will have at least 2 documented telephone contact attempts and 1 certified letter in an effort to contact subjects. Thereafter, every 2 months, and at the end of the study, attempts will be made to determine the health status of temporarily Lost-to-Follow-up subjects.

The Investigator must attempt to document assessments of study endpoints and occurrence of events through the Projected Week 52 Visit. At randomization, all subjects will be asked to provide all (within local legal limits) contact details, which may include, but is not limited to, acceptable representative(s), address(es), phone number(s), email address(es), government issued identification, health insurance provider, relatives, other contacts, such as primary care physician, or other health care provider to ensure final follow-up. At each study visit, subjects should be asked about any updates to their contact details.

If unknown, the subject's status should be obtained from a reliable contact at approximately 6 months after subject discontinued drug (if applicable) and at the Projected Week 52 Visit, either by speaking with the subject or someone who has knowledge of the subject's vital status or by documented source (eg, lab reports, medical visit records).

In regions where allowed by local law, subject locator services may be used to help ascertain the health status of subjects believed to be Lost-to-Follow-up. If contact is made with the subject at any step in this process, the subject's preferred method of continued participation in the trial

should be determined and documented in the subject's source and updated in electronic data capture, as appropriate.

Only just prior to the end of the study, and after the above attempts have been exhausted, will a subject be considered officially Lost-to-Follow-Up. If subject vital status is known at the end of the study, the subject will not be considered Lost-to-Follow-up.

7.8 Liver Safety Monitoring and Withdrawal Criteria

7.8.1 Liver Function Test Monitoring

Liver function will be carefully monitored throughout the study. Additional monitoring may be necessary and is recommended for subjects with abnormal liver function tests.

If subjects with normal baseline ALT or aspartate aminotransferase (AST) levels experience ALT or AST >3× ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), and international normalized ratio [INR]) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

If subjects with elevated baseline ALT or AST levels experience ALT or AST >5× ULN and 2-fold increases above baseline, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

If subjects with either a normal or elevated baseline ALT or AST levels experience ALT or AST >8× ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be repeated within a maximum of 48 hours after the abnormality was found.

7.8.2 Considerations for Temporary Discontinuation of Study Drug

If the ALT or AST levels remain elevated >3× ULN in subjects with normal baseline ALT or AST levels **OR** if the ALT or AST levels remain elevated >5× ULN and a 2-fold increase above baseline occurs in subjects with elevated baseline ALT or AST levels on 2 consecutive occasions, the investigator must contact the Medical Monitor to discuss additional testing, recommended monitoring, possible temporary discontinuation of study medication, and possible alternative etiologies.

The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

7.8.3 Permanent Discontinuation of Study Drug

If the following circumstances occur at any time during treatment, the study medication should be permanently discontinued:

Subject Baseline Aminotransferases	Criteria for Discontinuation of Study Medication
Normal or Elevated ALT or AST (all subjects)	• ALT or AST >8 × ULN
Normal ALT and AST	• ALT or AST >5 × ULN and persists for more than 2 weeks • ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN **or** INR >1.5 • ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
Elevated ALT or AST	• ALT or AST >5 × ULN **AND** 2-fold increases above baseline values and persists for more than 2 weeks • ALT or AST >5× ULN **AND** 2-fold increases above baseline values in conjunction with elevated total bilirubin >2 ULN or INR >1.5 • ALT or AST >5 × ULN **AND** 2-fold increases above baseline values with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

In each of these instances, appropriate clinical follow-up should be instituted (including repeat laboratory tests) until a satisfactory conclusion (ie, until the AE resolves, the laboratory value returns to Baseline, or the condition becomes stable).

If a subject meets the liver safety criteria and must be discontinued from study medication, the subject will continue to be followed per the protocol schedule until the study is completed. If the subject refuses to return for the study visits, telephone visits may be conducted; however, this is not preferred nor recommended. The reason for discontinuation of study medication should be listed as an AE.

If any of the above circumstances occur at any time during the study, the abnormality should be documented as an AE, and a Liver Function Test Increase form completed.

The Investigator must complete the AE/SAE eCRF page. If the event meets serious criteria, the SAE eCRF page must be completed and an SAE Fax Notification form must be sent to the sponsor or sponsor's designee within 1 working day of the repeat laboratory test.

7.8.4 Re-initiation of Study Drug

If the study medication is discontinued due to any of the scenarios provided above, study medication must not be re-initiated without consultation with the Medical Monitor.

7.9 Renal Safety Withdrawal Criteria

If a subject does not have renal impairment at Screening or randomization, but later develops renal impairment that is confirmed by a repeat test within a maximum of 7 days by the central laboratory AND a creatinine clearance <60 mL/min (utilizing the Schwartz formula, and based on a calculation by the central laboratory), the subject will discontinue study medication after consultation with the Medical Monitor. The central laboratory will calculate these values at the same visits where a full laboratory panel is performed. If a subject's calculated creatinine clearance indicates moderate or severe renal impairment, a laboratory alert will occur to notify the site to discontinue the double-blind study medication.

If a subject discontinues double-blind study medication according to the Renal Safety Withdrawal Criteria, the event should be recorded as an AE and the reasons for study drug discontinuation must be recorded as an AE. The subject will be required to return for protocol study visits and procedures.

7.10 Pancreatitis Monitoring and Withdrawal Criteria

All subjects will be carefully monitored for pancreatitis during the study. Investigators will urge subjects to immediately call the study staff if the subject experiences persistent nausea and/or vomiting for ≥3 days, with or without abdominal pain.

Blood samples for analysis of serum amylase and lipase by a central laboratory should be obtained at the visit, and other additional investigations should be performed in order to establish diagnosis.

Study drug should be interrupted immediately if any of the following circumstances occur at any time during treatment:

- If pancreatitis is suspected, or
- Serum amylase ≥2 × ULN, or
- Serum lipase ≥2 × ULN.

The pancreatic enzyme tests should be repeated within 7 days after the first sample (with both samples analyzed by the central laboratory), and appropriate imaging tests (as per standard of care) should be performed to establish diagnosis. The results of these tests should be recorded in the source documents.

All subjects with elevated pancreatic enzymes that meet the above criteria should be kept under observation with multiple serum amylase and lipase tests to be followed-up until resolution.

If pancreatitis is confirmed, the study drug should not be restarted.

If any of the circumstances described above occur during the study, the event should be recorded as an AE. A Pancreatic AE of Special Interest Form must be completed. If the event meets the SAE criteria, an SAE Fax Notification form must be sent to the sponsor or sponsor's representative within 1 working day of the repeat laboratory test.

If a subject discontinues double-blind study medication according to the Pancreatitis Monitoring and Withdrawal Criteria, the event should be recorded as an AE and the reason for withdrawal

should be documented as an AE. The subject will be required to return for protocol study visits and procedures.

7.11 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the End-of-Treatment Visit. Withdrawn subjects will continue to the Week 52/End-of-Treatment assessments followed by the Week 54/Follow-up telephone call. The Week 54/Follow-Up Visit assessments will be completed 2 weeks following the Week 52/End-of-Treatment Visit assessments.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below:

Alogliptin benzoate 25 mg tablet or matching placebo.

Subjects should be instructed to take one tablet daily at the same time with or without food.

8.1.1.1 Investigational Drug

Alogliptin benzoate or matching placebo tablets

Alogliptin benzoate tablets are manufactured by Takeda Pharmaceuticals and are composed of 25 mg alogliptin drug substance and excipients; the matching placebo tablets consist of excipients only. Alogliptin or placebo tablets will be provided in 35 count high-density polyethylene bottles with a child resistance cap. Tablets are oval biconvex light red, film coated with no markings. Bottles will bear a blinded single panel or booklet label containing medication ID, pertinent protocol information and required caution statements.

8.1.1.2 Companion Medication

Metformin HCl and/or insulin will be prescribed to subjects on background antidiabetic therapy during the double-blind period of the study.

Insulin: Subjects will continue to receive insulin with the goal of achieving a stable dose required for glycemic control dependent on the subject's requirements, at the Investigator's discretion.

Metformin: Subjects will receive metformin with the goal of being treated with at least 1000 mg BID or their documented MTD.

8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

Alogliptin benzoate and matching placebo tablets.

8.1.1.4 Rescue Medications

Subjects who meet protocol-defined hyperglycemia rescue criteria will be rescued with an antidiabetic regimen at the Investigator's discretion as per Section 9.1.17.3: Criteria for Hyperglycemia Rescue.

8.1.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label (25°C [77°F] excursions permitted to 15°C to 30°C [59°F to 86°F]), and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
		Active	Placebo
A	placebo QD	0 active tablets	1 placebo for 25 mg tablet
B	alogliptin 25 mg QD	1 alogliptin 25 mg tablet	0 placebo tablets

Dose interruptions are acceptable based on medical need. The sponsor or designee must be notified and consulted for any dose interruptions longer than 14 continuous days.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

The SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

The Investigator or Investigator's designee will access the interactive voice response system/ interactive web response system (IVRS/IWRS) at Screening to obtain the subject study number. The Investigator or the Investigator's designee will utilize the IVRS/IWRS to randomize the subject into the study. During this contact, the Investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication ID number of the investigational drug to be dispensed will then be provided by the IVRS/IWRS. If sponsor-supplied drug (alogliptin 25 mg or matching placebo) is lost or damaged, the site can request a replacement from IVRS/IWRS. (Refer to the IVRS/IWRS manual provided separately.) At subsequent drug-dispensing visits, the Investigator or designee will again contact the IVRS/IWRS to request additional investigational drug for a subject.

Subjects will be dispensed blinded study drug at Day 1, and Weeks 12, 26, and 39. Subjects will be dispensed sufficient bottles for the visit interval. Subjects will be instructed to take their blinded study drug QD with or without food and to return their study drug bottles whether empty or full at each visit.

On occasion in unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), additional drug supply may be provided to subjects (either at an in-person visit or delivered to the subject's residence) to cover extended periods between onsite visits. Any additional resupply must be reviewed and approved in advance by the sponsor or designee.

8.3 Randomization Code Creation and Storage

On Study Day 1, qualified subjects will be randomized to 1 of the 2 treatment groups using the IVRS/IWRS.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IVRS/IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the Investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the Investigator, by accessing the IVRS/IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately, and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The Investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the Investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, Investigator or designee should acknowledge the receipt of the shipment by recording in IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda or designee must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file.

The Investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IVRS/IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The Investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of Investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The Investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Alternative Approaches to Study Procedures and Data Collection Due to Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Appendix A), contingency measures may be implemented. In acknowledgement of study site, hospital, local, state, and national restrictions established in response to unavoidable circumstances, the following measures are being taken for the current study:

- For subjects active in the study, all attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
  - Sites impacted by unavoidable circumstances must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection.
  - Sites may seek approval from the sponsor or designee to continue subjects in the study despite departures from the Schedule of Study Procedures. The principal investigator is expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.
  - Other than the End-of-Treatment Visit, alternative methods for conducting subject visits (eg, video conferencing, telephone visits, or in-home study visits conducted by

study site personnel or designated medical personnel, contingent upon local regulations) may be used per approval by the sponsor or designee:

- Under these circumstances, collection of certain study assessments may be omitted and visit windows may be extended.
- When approval is given for a subject to miss an in-person study visit, a study site physician or other qualified site personnel will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
- The study site physician or other qualified site personnel should conduct the following assessments within specified-visit window timeframes: AE assessments, documentation of concomitant medication, review of diaries and glucometer readings, and drug accountability and an assessment of clinical symptoms.
- Home nurses or other qualified clinical personnel may be deployed at the request of the site, when appropriate. Advance approval from the sponsor or designee should be obtained.
- Other study assessments may be collected using an alternative method as feasible, and may involve audio or video recording where allowed by local regulation. This will be documented in the study records.
- In some instances, sites may need to split visits or sites may only be able to perform a few procedures on site and some procedures may need to be performed remotely. Sites should inform sponsor or designee when this occurs.
- Sites may seek approval to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window or within the visit window granted by the sponsor or designee will be considered missing data and such departures will be recorded in the study records.

– Study site personnel may dispense additional IP to subjects at a visit to allow for potentially longer intervals between visits than originally planned per protocol, or IP may be supplied to subjects via delivery by site personnel or by courier.
– The End-of-Treatment Visit should be performed in person. When it is not possible for the subject to come to the study site and the protocol-specified visit window cannot be extended further, the preferred alternative for the visit is for qualified study site personnel or designated clinical personnel to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at a subject's residence should comply with applicable local regulations. If neither option is available with sponsor or designee approval, sites may conduct end-of-treatment procedures remotely as is feasible.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Study Procedures) due to unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) must be documented in the study records. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the SAP.

9.1.2 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2. Informed consent from the subject's legal representative (ie, parents or legal guardians) and assent, as appropriate, must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2.1 Pharmacogenomic Informed Consent Procedure

As of the date of this amendment, a sufficient number of samples have been collected and no more are needed; therefore, pharmacogenomic samples no longer need be taken.

Under previous versions of this protocol, the participation of study subjects and study sites in the collection of pharmacogenomic sample(s) was optional and only to be performed in selected countries/sites where approved. A separate informed consent/assent form pertaining to storage of the sample(s) must have been obtained prior to collecting a blood and/or saliva sample for Pharmacogenomic Research for this study. The provision of consent/assent to collect and analyze the pharmacogenomic sample is independent of consent to the other aspects of the study.

9.1.3 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (US only) and race as described by the subject of the subject at Screening. Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 12 weeks prior to signing of informed consent.

9.1.4 Physical Examination Procedure

A baseline, complete physical examination (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to the first dose examination. The brief physical exam will consist of the

following body systems: (1) respiratory system; (2) cardiovascular system; (3) nervous system (4) dermatologic system; and (5) gastrointestinal system. The brief and complete physical exams will be performed as indicated in Appendix A.

Assessment of pubertal development in boys and in girls will be conducted at the Day 1, Week 26, and Week 52 Visits. Tanner Stage scoring [34,35] will be assessed at the visits as per Appendix A. An examination to assess Tanner Stage scoring is preferred, but subject-reported scoring (using diagrams) is acceptable.

Tanner stage for breast development in girls, genital development in boys and pubic hair for both sexes should be evaluated. Sites should enter the numerical stage for each of the 2 categories on the eCRF for either boys or girls.

For girls, age of onset of menarche will be collected at the Day 1 visit and if menarche had not yet occurred, this will be verified at each study visit.

9.1.5 Weight, Height and BMI

The subject should have weight and height measured using a stadiometer (or equivalent) and scale while wearing indoor clothing and with shoes off.

BMI will be calculated by the site prior to randomization using the following formula and 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).

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

The values should be reported to 2 decimal places by rounding. The BMI at all other visits and BMI Z-scores will be calculated by the Sponsor or designee.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature (oral or tympanic measurement), respiratory rate, blood pressure (resting more than 5 minutes), and pulse (beats per minute).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination. The condition (ie, diagnosis) should be described.

9.1.8.1 Annual Ophthalmologic Examination

Annual dilated and comprehensive eye examinations are recommended for all subjects [36].

Results of the annual ophthalmologic examination prior to participation and during the course of the study should be reviewed by the Investigator. Any relevant medical history and AEs resulting from the annual exam should be reported on the eCRF.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 24.5 mL, and the approximate total volume of blood for the study is 102 mL. Please refer to Table 9.a and Appendix A on timing of collection for clinical laboratory testing.

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis (a)**
White blood cell count with autodifferential	Albumin	Qualitative:
Platelet count	Alkaline phosphatase	Appearance
Hemoglobin	Alanine aminotransferase	Color
Hematocrit	Aspartate aminotransferase	pH
Red blood cell count	Blood urea nitrogen	Specific gravity
Mean corpuscular volume	Bicarbonate	Ketones
Mean corpuscular hemoglobin	Calcium	Protein (albumin)
Mean corpuscular hemoglobin concentration	Magnesium	Glucose
Other	Chloride	Nitrite
HbA1c	Creatinine	Urobilinogen
CD26 surface antigen	Lactate dehydrogenase	Blood
Bone specific alkaline phosphatase	Phosphorus	Quantitative: (e)
CTX	Potassium	Albumin
CCI	Sodium	Creatinine
	Total bilirubin	Albumin/creatinine ratio
	Direct bilirubin (only if Total bilirubin is elevated)	
	Total protein	
	Uric acid	
	GGT	
	Lipid panel (total cholesterol, high-density lipoproteins, low-density lipoproteins (direct), and triglycerides) (c)	
	Serum amylase (d)	
	Serum lipase (d)	
	Glucose	

Diagnostic Screening:	
Serum	**Urine**
C-peptide (f)	hCG
hCG	(female subjects) (g)
(female subjects) (g)	
eGFR (h)	
2-hour postprandial glucose (i)	
CCI	
CCI	
GAD 65 (f)	
IA-2 (f)	

hCG=human chorionic gonadotropin.

(a) It is recommended that a follow-up urine culture be obtained within 7 days of clinical recovery from all urinary tract infections.

(b) Collected only from those subjects who arrive at the clinic in a fasted state. Always drawn in a separate tube for this study.

(c) Collect only at the visits specified in Appendix A.

(d) Serum amylase and serum lipase to be performed at Day 1 (Baseline Visit) for all subjects and at an Unscheduled Visit for any subject who experiences persistent nausea and/or vomiting for ≥3 days with or without abdominal pain.

Table 9.a Clinical Laboratory Tests

(e) The Week 26 urinalysis will only include quantitative assessments.
(f) Collected once prior to randomization only in subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin.
(g) To be completed on all female subjects. If a urine pregnancy test yields a positive result, a serum pregnancy test must also be collected at the same visit and submitted to the central laboratory for confirmation of results.
(h) Calculated at Screening and Baseline and at Weeks 26 and 52 by the central laboratory using the Schwartz formula.
(i) Select sites only. See section 9.1.9.1 for additional information.
(j) Collected at Baseline and at Weeks 26 and 52.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalyses. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results.

In unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), sites may elect to use local laboratories per approval by the sponsor or designee.

CCI

[redacted]

CCI

9.1.10 Contraception and Pregnancy Avoidance Procedure

This protocol does not condone or endorse under-age sexual activity. Female participants will be asked to use contraception if they are going to be sexually active. Age appropriate contraceptive pill or condom plus spermicide are advised. It is noted that Investigators will neither prescribe contraceptives, nor provide contraceptive advice beyond the protocol requirements; subjects must take responsibility for obtaining advice from the appropriate family doctor or family planning provider and preferably after discussion with their parents/legal guardians. Contraception use must be practiced if sexually active, from the date of the Screening Visit until the last dose of study medication intake. Parents/legal guardians and the subject will be advised of this during the informed consent and assent process, and subjects will be asked to sign an informed assent form or consent form (as appropriate) stating that they understand the requirements for avoidance of pregnancy during the course of the study.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed for all female subjects (Appendix A). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative serum hCG pregnancy test prior to receiving of study medication.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the Investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the Investigator.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the Investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 Pharmacogenomic Sample Collection

As of the date of this amendment, a sufficient number of samples have been collected and no more are needed; therefore, pharmacogenomic samples no longer need be taken.

Under previous versions of this protocol, subjects had the option to sign the pharmacogenomic sample collection informed consent form (ICF). For those who provided consent to participate in the pharmacogenomic sub-study, a 1 mL whole blood sample for DNA isolation, a 2.5 mL blood sample for RNA isolation, as well as a saliva sample were to be collected before dosing on Day 1. An additional 2.5 mL blood sample was to be collected at the Week 12 Visit. If the baseline RNA blood sample collection was missed, the Visit 12 blood draw should not have been done.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. RNA has multiple vital roles in the coding, decoding, regulation, expression of genes, and sensing and communicating responses to cellular signals. Both DNA and RNA samples may be evaluated for the genetic and transcriptional contribution on how the drug is broken down, or how the drug affects the body. This is called a "Pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to alogliptin.
- Finding out more information about how alogliptin works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to alogliptin.
- Identifying variations in genes related to the biological target of alogliptin.

This information may be used, for example, to develop a better understanding of the safety and efficacy of alogliptin and other study medications, and for improving the efficiency, design, and study methods of future research studies.

Samples taken will be stored for no longer than 15 years after completion of the SYR-322_309 study. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. "Stored samples" are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drugs.

9.1.13 ECG Procedure

A standard 12-lead ECG will be recorded. The Investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. A copy of the ECG tracing should be kept with the subject's notes.

CCI

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9.1.15 Documentation of Screen Failure or Pre-Randomization Stabilization Failures

Investigators must account for all subjects from whom informed consent/assent has been obtained.

If the subject is found to be not eligible during the Screening and Pre-Randomization Stabilization Period, the Investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of screen failure or Pre-Randomization Stabilization failure.

The primary reason for Screen failure/Pre-Randomization Stabilization failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost-to-follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail Screening/Pre-Randomization Stabilization should not be reused.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the Investigator should record the primary reason for failure on the applicable eCRF.

9.1.17 Blood Glucose Education and Management

Subjects will meet with a diabetes educator or appropriately trained site personnel at Screening, at the Pre-Randomization Stabilization Visits, and at specified Visits through Week 26, who will instruct them on how and when to test their blood glucose levels using their glucometer, how to recognize the signs and symptoms of hypoglycemia, and how to use supplemental treatment with oral glucose, if necessary. Investigators should individualize recommendations for capillary blood glucose measurements based on the subjects' level and stability of glycemic control, initiation of or change in therapy, intercurrent illness, and risk of hypoglycemia associated with the type and intensity of therapy. Timing of glucose measurements should be based on local guidance on the management of T2DM in youths. For recommendations, see Appendix H.

The glucometer will be returned by the subject and reviewed by site personnel at every subsequent visit.

9.1.17.1 Education on Hypoglycemia

The diabetes educator will instruct subjects on the signs and symptoms of hypoglycemia and on the use of supplemental treatment with oral glucose, if its use is necessary during the study.

Any time a subject experiences signs and symptoms of hypoglycemia, they will be instructed to measure their blood glucose level with the glucometer and record the value, along with their signs and symptoms in the subject diary. Hypoglycemic events must be recorded in the diary any time a subject experiences either of the following:

- Signs and symptoms of hypoglycemia (regardless of blood glucose value by finger stick); and
- Blood glucose value by finger stick ≤70 mg/dL (3.9 mmol/L) (regardless of symptoms).

For these hypoglycemic events, subjects must record the following information in the diary:

- Date and time of hypoglycemic event;
- Symptoms;
- Blood glucose value by finger stick and time of finger stick.

Subjects who experience symptoms of hypoglycemia, such as hunger, irritation, sweating, etc., will be instructed to ingest fast-absorbing carbohydrates such as orange juice. If symptoms persist, or if the severity worsens, subjects will be instructed to immediately seek emergency medical attention.

9.1.17.2 Definitions of Hypoglycemia

Subjects will be instructed to test their blood glucose, using their glucometer, on a daily basis and at any time they experience signs and symptoms of hypoglycemia, to confirm that it is a hypoglycemic episode, as defined below.

The following definitions for severity apply:

Mild to Moderate Hypoglycemia Criteria:

Blood glucose <60 mg/dL (3.33 mmol/L) in the presence of symptoms, or

Blood glucose <50 mg/dL (2.78 mmol/L) with or without symptoms.

Severe Hypoglycemia Criterion:

Any episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, associated with a documented blood glucose <60 mg/dL (3.33 mmol/L) (unless the clinical situation makes obtaining a blood glucose difficult [eg, it involves coma or seizure]).

If a subject experiences a severe hypoglycemic event, the subject and/or his/her legal representative (ie, parent or legal guardian) should be instructed to notify the study site.

Information regarding any episodes of hypoglycemia should be documented in the eCRF.

Subjects will be discontinued from study medication if they experience severe and/or frequent hypoglycemia episodes, defined as ≥1 major or severe episode or recurrent non-major episodes in the event where the possibility of down-titration of contributing concomitant medication(s) (other than the double-blind study medication) and/or other contributing factors has been evaluated and corrected.

Non-major recurrent hypoglycemia is defined as any recurrent hypoglycemia episodes, as determined by the Investigator, not meeting the definition of severe hypoglycemia. It is the Investigator's clinical assessment whether the subjects who experience hypoglycemia episodes should be discontinued from study medication.

9.1.17.3 Criteria for Hyperglycemia Rescue

Subjects will be required to maintain their background antidiabetic therapy, (if applicable) at the same dose, throughout the first 26 weeks of the Double-Blind Treatment Period.

Subjects may be rescued either on the basis of their finger stick measurements or their HbA1c measurements as detailed below.

Subjects will be recommended to test their blood glucose levels via glucometer measurements at the time points recommended in Appendix H. If the subject's glucose level (based on measurements at any of the specified time points, either fasting or non-fasting) is determined to have remained at ≥300 mg/dL (≥16.6 mmol/L) for a period of more than 2 consecutive days, the subject should be instructed to contact the site as soon as possible. The subject should also be instructed to contact the site immediately if there are symptoms suggestive of decompensation such as vomiting, dehydration, lethargy, etc. Upon contact by the subject/subject's parent or guardian, the investigator (or appropriately-trained study coordinator) should assess for signs of illness and, if appropriate and warranted, schedule a visit to the site for further assessment of the hyperglycemia as well as possible metabolic decompensation, including measurement of ketones.

Any subject who meets any of the following criteria, will be rescued with antihyperglycemic agents:

- Subjects with HbA1c values <7.0% at the Baseline Visit will be rescued if their HbA1c remains at ≥8.0% confirmed by a second sample drawn at the next scheduled visit and analyzed by the central laboratory.
- Subjects with HbA1c values ≥ 7.0% at the Baseline Visit will be rescued if their HbA1c values increase by >1.0% as determined by the central laboratory AND confirmed by a second sample drawn at the next scheduled visit and analyzed by the central laboratory.

Upon determining that a subject meets the predefined hyperglycemic criteria, rescue therapy can be added and modified as needed to achieve and maintain adequate glycemic control. Subjects who meet the criteria for rescue will continue double-blind study medication, and will continue participation in the study in order to be evaluated for safety up to 52 weeks.

Please Note: Subjects who require hyperglycemic rescue medications for reasons other than efficacy (ie, metabolic decompensation or change in clinical status [eg, DKA]) should be rescued at the Investigator's discretion at any time point during the study. If glucose control worsens unacceptably in the judgment of the investigator and requires further intensive investigation and/or management, the subject may be scheduled for an early termination visit and withdrawn from the study. The circumstances surrounding the decompensation, along with the use and timing of all related medications will be documented in the eCRF.

Insulin (or increased doses of insulin) may be administered to treat acute metabolic decompensation, which is most commonly due to an intercurrent illness or non-compliance to medical treatment. However, if the supplemental use of insulin extends beyond 2 weeks, the subject will be considered to have met the hyperglycemic rescue criteria.

9.1.18 Biomarkers of Bone Turnover

In order to evaluate the effects of alogliptin on bone turnover, biochemical biomarkers will be measured during the study.

Serum concentrations of bone-specific alkaline phosphatase, which is associated with changes in bone formation, will be measured.

Serum concentrations of CTX, which is associated with changes in bone resorption, will be measured.

Blood samples for the determination of biochemical biomarkers of bone turnover will be collected at the Baseline, Week 26, and the End-of-Treatment Visits. The samples will be collected at the same time the safety laboratory specimens (ie, chemistry and hematology) are drawn.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers/unused medications to the next site visit. If a subject is persistently noncompliant with the study medication (<70% or >125%) of the allocated medication for 2 consecutive visits after randomization), it may be appropriate to

withdraw the subject from the study after consultation with the Medical Monitor. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

For sites not able to conduct onsite visits due to unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), acceptable alternatives to assess subject safety and overall clinical status may include, but are not limited to, visits as per protocol schedule conducted by delegated site staff speaking directly with the subject by telephone or other medium (eg, a computer-based video communication), or sites may send site staff to subjects to conduct study assessments, contingent upon local regulations.

The End-of-Treatment Visit should be performed in person. Alternative methods of data collection may be considered for this visit when it is not possible for the subject to come to the study site. Under such circumstances, a preferred alternative would be for site staff to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at subjects' residence should comply with applicable local regulations.

During contact with the subject by an alternative method, the study site physician or other qualified site staff should also, at minimum, conduct the following assessments within specified-visit window timeframes: AE assessments, documentation of concomitant medication, review of diaries and glucometer readings, drug accountability, and assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such departures will be recorded in the study records. Alternatively, sites may seek approval to extend the visit window up to 3 times the protocol-specified window (Appendix A) in order to conduct an onsite visit.

The interval between successive visits when clinical laboratory tests and vital sign measurements are performed may not be longer than 8 weeks.

9.3.1 Screening

Subjects will be screened within 14 days prior to randomization/Day 1 or the Pre-Randomization Stabilization Period (if applicable) as indicated in Appendix A. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Sections 7.1 and 7.2. See Section 9.1.15 for procedures for documenting Screening failures. Subjects must also meet all criteria specified in Section 7.3 to proceed directly to the Day 1 visit (ie, not enter the Pre-Randomization Stabilization Period).

9.3.2 Pre-Randomization Stabilization Period

Subjects will participate in the Pre-Randomization Stabilization Period until entry criteria and the objectives of the Pre-Randomization Stabilization Period have been met (Please refer to Section 6.2 for additional information). Subjects will return to the clinic for assessments at regular intervals during the Pre-Randomization Stabilization Period at the investigator's discretion, but at least every 3 months, as shown in Appendix A.

Subjects will be informed how to recognize signs and symptoms of hypoglycemia and will measure their fasted blood glucose at least once a day.

See Section 9.1.15 for procedures for documenting Pre-Randomization Stabilization failures.

9.3.3 Week -1

Subjects who participate in the Pre-Randomization Stabilization Period, regardless of the duration, will return to the clinic at Week -1 to confirm qualification for all inclusion and exclusion criteria specified in Section 7.3.

9.3.4 Randomization

If the subject has satisfied all of the inclusion criteria (including the additional randomization criteria that must be met following Screening and/or completion of the Pre-Randomization Stabilization Period) and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS on Day 1, as described in Section 8.2. Subjects will be instructed on when to take the first dose of investigational drug as described in Section 6.1. The procedure for documenting Screening and/or Pre-Randomization Stabilization failures is provided in Section 9.1.15.

9.3.5 Double-Blind Treatment Period

In addition to receiving double-blind study medication, subjects will be required to maintain their background antidiabetic therapy, at the same dose, throughout the first 26 weeks of the Double-Blind Treatment Period.

Subjects who meet protocol-defined hyperglycemia rescue criteria (ie, for efficacy reasons) should be rescued with antidiabetic medications, at the Investigator's discretion. (Refer to Section 9.1.17.3). Subjects who are administered hyperglycemic rescue therapy prior to Week 26 will continue double-blind study medication, and will continue participation in the study in order to be evaluated for safety up to 52 weeks.

Subjects who terminate double-blind study drug prematurely will continue to be followed at their regularly scheduled study visits time points for the 52-week duration of the study. Subjects will complete an End-of-Treatment Visit and Follow-Up Visit, 2 weeks after the last dose of study drug, and a Projected Week 52 Visit.

Some subjects may require temporary suspension of study medication and the use of insulin (or increased doses of insulin). If the acute event resolves and insulin is withdrawn or returned to the maintenance level within 2 weeks, the subject can continue in the study. If the supplemental use of

insulin extends beyond 2 weeks, the subject will be considered to have met the hyperglycemic rescue criteria.

A schedule of assessments is listed in Appendix A.

9.3.6 Unscheduled Visit (As Applicable)

Subjects may return to the study center for unscheduled visits as needed. Unscheduled study visits can be performed when the subject has a study related issue in between regular study visits or as needed to ensure subject safety.

The following procedures should be performed during this visit:

- Concomitant medications review.
- Other protocol procedures, including collection of blood and urine samples, as deemed appropriate by the Investigator.
- AE assessment.
- Blood glucose and HbA1c concentration laboratory samples will be collected as directed in section 9.1.17.

9.3.7 End-of-Treatment Visit

The End-of-Treatment Visit will be performed at Week 52 or after the last dose of study drug.

For all subjects receiving study medication, the investigator must complete the End-of-Treatment eCRF page. A schedule of assessments performed at the end of treatment visit is listed in Appendix A.

9.3.8 Follow-up Visit

A follow-up visit will be conducted via telephone with the subject 2 weeks after the End-of-Treatment Visit. A schedule of assessments performed at the follow-up visit is listed in Appendix A.

9.3.9 Projected Week 52 Visit

Subjects who prematurely discontinue study drug and continue telephone (or other communication) contact will follow the protocol-specified visit schedule for the remainder of the 52-week treatment period. The Projected Week 52 Visit should be conducted at the clinic, if at all possible.

9.3.10 Post Study Care

The study medication will not be provided by the sponsor upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies should be initiated, as required. Subjects will be offered clinical follow-up examinations as considered appropriate per the treating physician.

9.4 Biological Sample Retention and Destruction

As of the date of this amendment, a sufficient number of samples have been collected and no more are needed; therefore, pharmacogenomic samples no longer need be taken.

Under previous versions of this protocol, specimens for genome/gene analysis were to be collected as described in Section 9.1.12. After extraction and purification, the genetic material was to be preserved and retained for up to, but not longer than, 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples were to be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The samples were to be stored initially at PPD Laboratory and then sent to Covance Laboratories for long-term storage. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample was to be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and/or RNA analysis could withdraw their consent and request disposal of a stored sample at any time. The sponsor should be notified of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The Investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is 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:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
Neuroleptic malignant syndrome/malignant hyperthermia	COVID-19-related-disease
Spontaneous abortion/stillbirth and fetal death	COVID-19 pneumonia

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

A special interest AE (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the Investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for Investigators as to how and when they should be reported to Takeda.

The site is required to actively obtain additional clinical information on the following adverse event of special interests (AESIs): Serious hepatic abnormalities, pancreatitis, infections (including urinary tract infections), and severe 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 AEs source documents.

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as related if the Investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as not related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or Investigator.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose interrupted – the dose was interrupted due to the particular AE.

Some subjects may require temporary suspension of study medication and the use of insulin.

10.1.13 Outcome

- Recovered/resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/resolving – the intensity is lowered by one or more stages; the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until Screen/Stabilization failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the Follow-up Visit.

10.2.1.2 PTE and AE Reporting

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

10.2.1.3 Special Interest AE Reporting

If a special interest AE occurs during the treatment period or the follow-up period, and is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (described in the separate contact information list) immediately or within 1 business day of first onset or subject's notification of the event. A special interest AE name form or an SAE form should be completed, signed, and/or sealed by the PI, and reported to appropriate personnel in the separate contact information list within 10 business days.

- Laboratory value threshold if applicable.
- Premature termination for the special interest AE, if applicable.
- Any other specific criteria.

The special interest AEs have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have elevated ALT or AST levels >3 ×ULN please see Section 7.8 for instructions for reporting and managing the subject.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA, Investigators and IRBs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious

events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent Data Monitoring Committee

An independent DMC will be established to periodically review study safety data. Details of the DMC membership and responsibilities will be detailed in a DMC Charter. The outcome of data reviews by the DMC will be communicated to the local IRBs/ECs, where appropriate, as per local regulations.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the MedDRA (Medical Dictionary for Regulatory Activities). Drugs will be coded using the WHODRUG (World Health Organization Drug Dictionary).

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, ID of the person making the correction, the date the correction was made, and the reason for change.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered onto the eCRF.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any

form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The Investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP will be prepared and finalized prior to unblinding of subjects' treatment assignments. This document will provide further details regarding the definitions of analysis variables and analysis methodology to address all study objectives. The SAP will address the characterization of study subjects potentially impacted by COVID-19 and supportive analyses to assist in the interpretation of the overall study results.

A blinded data review will be conducted prior to unblinding of subjects' treatment assignments. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 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 have a baseline assessment and at least

1 postbaseline assessment for the variable. 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. Major protocol violations will be defined prior to database lock.

CCI [redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Subject disposition will be summarized (frequency, percentage) by treatment group for each subject sample, incidence of discontinuation, reason for discontinuation, and incidence of rescue. The summary of all randomized subjects will include a breakdown by the stratification factors for schedule.

Baseline and demographic information will be listed and summarized by treatment group and overall. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

13.1.3 Efficacy Analysis

The primary efficacy variable will be the change from Baseline in HbA1c at Week 26. The primary analysis set will be the FAS. Supportive analyses will be conducted with the PPS. A sensitivity analysis that excludes subjects affected by COVID-19 will be performed on the primary endpoint. The definition of "affected by COVID-19" will be provided in the SAP.

The primary analysis will be conducted using a contrast at Week 26 derived from a mixed model for repeated measures (MMRM) with change from Baseline in HbA1c as the response variable, treatment, visit, and visit-by-treatment interaction as fixed categorical effects, and baseline HbA1c and visit-by-baseline HbA1c interaction as continuous covariates. An unstructured variance-covariance matrix will be used; parameter estimates will be calculated using restricted maximum-likelihood estimation. Degrees of freedom will be estimated using the Kenward-Roger approximation. Data collected following discontinuation of double-blind study medication or hyperglycemic rescue will be censored.

The secondary efficacy variable will be analyzed using additional contrasts at Weeks 12, 18, 39, and 52 derived from the primary analysis model. Continuous exploratory efficacy variables will be analyzed using models similar to the primary analysis model. Categorical variables and time to hyperglycemic rescue will be analyzed using logistic regression models and a Cox regression model, respectively. An appropriate normalizing transformation (eg, natural log) will be applied in the event that an exploratory variable is not normally distributed.

If a subject is diagnosed with MODY during the study, a description of the results will be provided separately for each individual subject with MODY, and additional analyses will be performed that exclude MODY subjects.

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[redacted]

13.1.5 Safety Analysis

Safety parameters will be summarized using descriptive statistics or frequency counts as appropriate. Separate summaries using (1) data collected prior to discontinuation of double-blind study medication or hyperglycemic rescue (if applicable) and (2) all data will be conducted.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 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 FAS. 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%, and a 2-sided false-rejection rate of 5%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution guarantee access to source documents by the sponsor or its designee contract research organization and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unavoidable circumstances arise (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) that will require

deviation from protocol-specified procedures, the Investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form/eCRF should be completed by the site and electronically signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of

the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor or designee will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed

appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICF must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The Investigator is obliged to provide the sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with Investigator's city, state (for Americas Investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting trial information. Once subjects receive Investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any Investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject

compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Assessment	Screening	Pre-Randomization Stabilization Period (if needed)		Double-Blind Treatment Period Weeks 1- 52 After Randomization (a)								End-of-Treatment Visit	Follow-Up Visit
	Screening Visit (b)	At Least Every 3 Months (b)	Week -1	Baseline Visit (Day 1)	4 (b)	12	18 (c)	26	32 (b)	39	45 (b)	52 (a)	54 (a,b)
Visit windows (days)	**(Up to 14 Days)**				**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±2**
Informed consent and assent	X												
Inclusion/exclusion	X	X (d)	X (d)										
Demographics; medical history (including medication history and concurrent conditions)	X												
8-hour fast (e)	X		X	X				X				X	
Diabetes education (f)	X	X		X	X	X		X					
Randomization				X									
Complete physical examination	X			X				X				X	
Brief physical examination (g)						X				X			
Vital signs	X	X	X	X		X		X		X		X	
Temperature	X			X								X	
Body weight and height	X			X				X				X	
12-lead ECG	X			X				X				X	
Issue subject diary and glucometer		X (h)		X									
Review diaries and glucometer readings		X	X	X		X		X		X		X	
Review concomitant medications and PTE/AEs	X (i)	X	X	X	X	X		X	X	X	X	X	X(i)
Hematology, serum chemistry	X		X	X		X		X				X	
CCI [redacted]													
Lipid panel	X			X		X		X				X	
Amylase/lipase (k)				X									
Urinalysis	X			X				X (l)				X	
CCI [redacted]													
C-peptide (n)	X		X										

	Screening	Pre-Randomization Stabilization Period (if needed)		Double-Blind Treatment Period Weeks 1- 52 After Randomization (a)								End-of-Treatment Visit	Follow-Up Visit
Assessment	**Screening Visit (b)**	**At Least Every 3 Months (b)**	**Week -1**	**Baseline Visit (Day 1)**	**4 (b)**	**12**	**18 (c)**	**26**	**32 (b)**	**39**	**45 (b)**	**52 (a)**	**54 (a,b)**
Visit windows (days)	**(Up to 14 Days)**				**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±2**
eGFR (o)	X			X				X				X	
HbA1c	X	X	X (p)	X		X	X	X		X		X	
Tanner Stage scoring				X				X				X	
Serum pregnancy test (q)	X			X		X		X				X	
Urine (dipstick) pregnancy test (q)		X	X							X			
CCI													
In-clinic dosing				X		X		X		X (s)		X (t)	
Access IVRS/IWRS	X			X		X		X		X		X	
Dispense blinded study drug (u)				X		X		X		X			
Document drug accountability						X		X		X		X	
CD26 surface antigen				X				X				X	
Biomarker labs (v)				X				X				X	
GAD 65 and/or IA-2 (w)	X		X										
CCI													

(a) 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 last dose of study drug. Subjects who terminate study drug prematurely will complete an End-of-Treatment Visit and a Follow-Up Visit 2 weeks later and will continue to be followed for the 52-Week duration of the study and complete a Projected Week 52 Visit. The same procedures should be conducted at the Projected Week 52 Visit as the End-of-Treatment Visit for subjects who prematurely discontinue the study. For sites not able to conduct onsite visits due to unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), acceptable alternatives to assess subject safety and overall clinical status may include, but are not limited to, visits as per protocol schedule conducted by delegated site staff speaking directly with the subject by telephone or other medium (eg, a computer-based video communication), or sites may send site staff to subjects to conduct study assessments, contingent upon local regulations.

The End-of-Treatment Visit should be performed in person. Alternative methods of data collection may be considered for this visit when it is not possible for the subject to come to the study site. Under such circumstances, a preferred alternative for the visit would be for site staff to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at subjects' residence should comply with applicable local regulations. If neither option is available with sponsor or designee approval, sites may conduct end-of-treatment procedures remotely as is feasible.

During contact with the subject by an alternative method, the study site physician or other qualified site staff should also, at minimum, conduct the following assessments within the visit: AE assessments, documentation of concomitant medication, drug accountability, and assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such departures will be recorded in the study records. Alternatively, sites may seek approval to extend the visit window up to 3 times the protocol-specified window in order to conduct an onsite visit. The interval between successive visits when clinical laboratory tests and vital sign measurements are performed may not be longer than 8 weeks.

(b) The Screening Visit will be scheduled within 2 weeks prior to Day 1 or prior to the start of the Pre-Randomization Stabilization Period. During the Pre-Randomization Stabilization period, subjects will visit the study center at regular intervals according to the

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

investigator's discretion but at least every 3 months and at Week -1 prior to randomization. The Week 4, 32, 45, and 54 visits will be conducted only via telephone call to the subject. A follow-up visit will be conducted via telephone with the subject 2 weeks after the End-of-Treatment Visit.

(c) The Sponsor or its designee will decide whether the Week 18 Visit will be conducted as an in-clinic visit, or optionally, as a home health visit.

(d) The randomization criteria listed in Section 7.3 will be assessed at the visits before Week -1 and all inclusion and exclusion criteria will be assessed at Week -1 prior to randomization.

(e) Subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin at the time of randomization will be required to fast for at least 8 hours prior to the Screening or Week -1 visit for the assessment of fasting c-peptide. Subjects who are participating in postprandial glucose testing (refer to section 9.1.9.1) will be required to fast for at least 8 hours prior to the visits indicated in the Schedule of Procedures.

(f) Subjects will be instructed on proper nutrition and exercise, how to recognize signs and symptoms of hypoglycemia, and the use of the glucometer.

(g) The brief physical exam will consist of the following body systems: (1) respiratory system; (2) cardiovascular system; (3) nervous system (4) dermatologic system; and (5) gastrointestinal system.

(h) During the Pre-Randomization Stabilization Period, the site will supply a glucometer to subjects who do not have one or cannot obtain access to one. Subjects who do not enter the Pre-Randomization Stabilization Period should receive their glucometer (if needed) and diary at the Day 1 Visit.

(i) At the Screening visit, review only concomitant medications. At the Follow-up Visit, review only AEs.

(j) Collected only from those subjects who arrive at the clinic in a fasted state.

(k) Serum amylase and serum lipase to be performed at Day 1 (Baseline Visit) for all subjects, and at an Unscheduled Visit for any subject who experiences persistent nausea and/or vomiting for ≥3 days with or without abdominal pain.

(l) The Week 26 urinalysis will only include quantitative assessments.

(m) CCI [redacted]

(n) Required prior to randomization only for subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin.

(o) Calculated by the central laboratory.

(p) HbA1c concentration should be ≥6.5% to <11.0% or ≥7.0% to <11.0% if the subject is on insulin. If this criterion is not met, the assessment may be repeated every 3 months.

(q) To be completed on all female subjects. If a urine pregnancy test yields a positive result, a serum pregnancy test must also be collected at the same visit and submitted to the central laboratory for confirmation of results.

CCI [redacted]

(s) Subjects may be dosed in the clinic if dose was not self-administered at home.

(t) CCI [redacted]

(u) Subjects who meet the criteria for rescue will continue double-blind study medication, and continue to participate in the duration of the study.

(v) The following labs will be collected at Baseline and at Weeks 26 and Week 52/End-of-Treatment: Bone specific alkaline phosphatase and C-terminal telopeptide.

(w) Collected once prior to randomization for subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin at time of randomization.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the Investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the Investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of Investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting Investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Shipment, and Storage of Pharmacokinetic Samples

Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis of Alogliptin (SYR-322)

1. Collect 3 mL of venous blood into a chilled Becton-Dickinson vacutainer. For all alogliptin samples, blood samples should be collected into vacutainers containing potassium ethylenediamine tetraacetic acid (K_2EDTA).
2. Gently invert the vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the vacutainers for 10 minutes at approximately 1100 to 1300 (relative centrifugal force) at approximately 4°C in a refrigerated centrifuge. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 0.6 mL needs to be obtained for each sample. Labeling may include protocol number (SYR322_309), matrix (ie, plasma), analyte (alogliptin), subject number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower. No more than 45 minutes will elapse between blood collection and freezing the plasma sample.
6. Keep samples frozen at approximately -20°C or lower until shipment to PPD central laboratory. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.

Instructions for Shipping of Samples for Pharmacokinetic Analyses

Site may adhere to the site's Standard Operating Procedures on shipping samples if the Standard Operating Procedure differs from the sample instructions provided.

Biological samples should be shipped on dry ice to prevent thawing during transit. Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.

1. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
2. Separate the duplicate SET 2 samples from the SET 1 samples.

3. Place SET 1 samples for each subject into zipper lock bag containing additional absorbent material.
4. Using a permanent marker, write the randomization number, sample matrix (ie, plasma), analyte, number of samples, and "SET 1" on each zipper lock bag.
5. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3-6 above when preparing duplicate samples for shipment, except zipper lock bags should be marked "SET 2."
6. An inventory of individual samples should accompany each shipment and should include the sponsor's name (Takeda), study drug (alogliptin), protocol number (SYR-322_309), Investigator's name, sample type (ie, plasma, subject's randomization number, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large zipper lock bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
7. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
8. Place the inventory paperwork (in a large zipper lock bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
9. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
10. Affix an address label to each shipping carton by send the samples to PPD central laboratory.
11. Affix a carbon dioxide label on each carton, specifically:

    Carbon Dioxide Solid UN-1845
    Class 9 PKG GR III
    Quantity _____
    (fill in weight to nearest lb/kg and specify unit of measure used)
12. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark KEEP FROZEN on each carton. Specify a return address and contact person on the carton.
13. Obtain the airway bill number and a receipt of shipment from the carrier.

14. After shipping of the samples, contact PPD central laboratory for all samples to notify them of next day delivery. When calling, provide the following information:

    Name of courier or transport company
    Time and date the shipment left the clinical site
    Airway bill number

Appendix F Collection, Shipment, and Storage of Pharmacogenomic Samples

Collect 1 mL whole blood for DNA isolation before dosing on Day 1 into plastic potassium ethylenediamine tetraacetic acid (K_2EDTA) spray-coated tubes from each subject which signs the optional pharmacogenomic sample collection ICF.

Collect 2.5 mL whole blood for RNA isolation at predose on Day 1 and Week 12 into a PaxGene TM tube.

A saliva sample will also be obtained from the subject at Day 1.

For detailed instructions on sample collection and storage follow the laboratory manual provided by the central laboratory.

Sample Shipment

Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday. The laboratory must confirm arrival of the shipped samples.

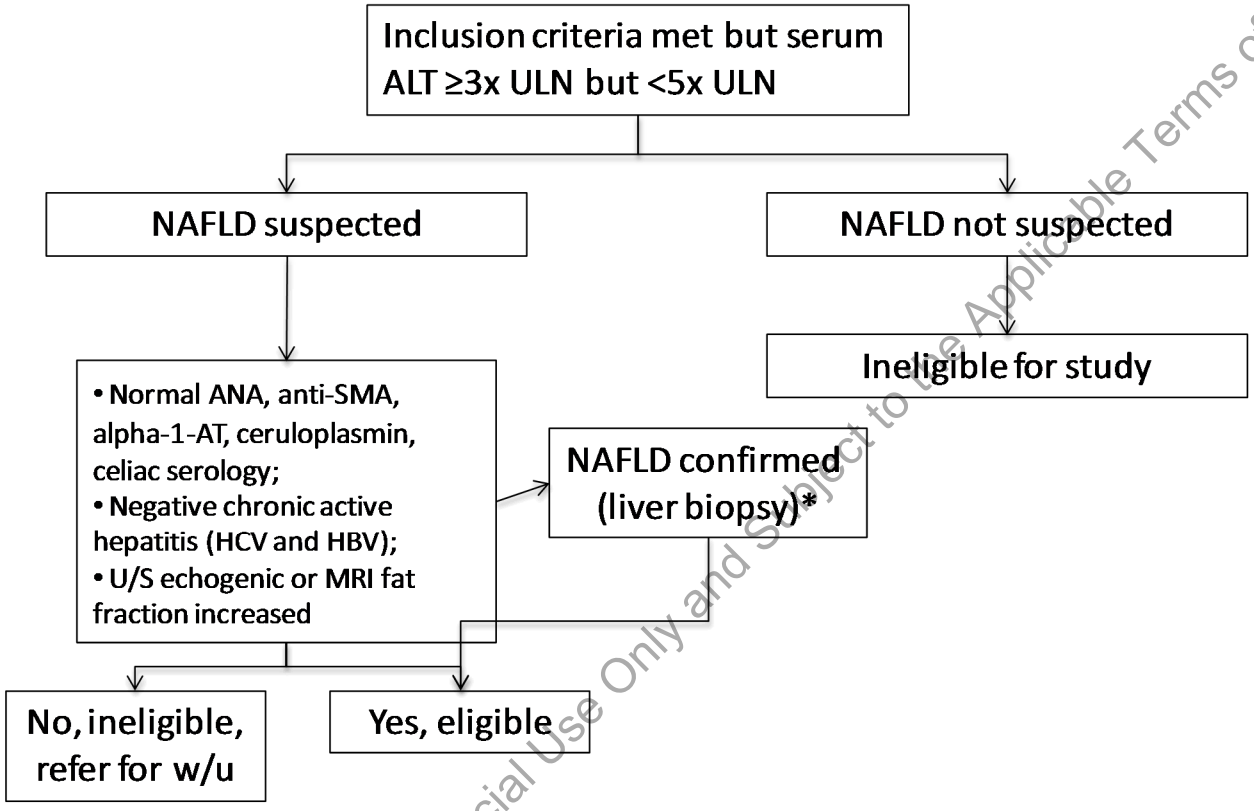
For instructions on shipping and packing follow the laboratory manual and shipping instructions provided by the central laboratory.

Before shipping, ensure the sample tubes are tightly sealed.

Sample Storage

The DNA and RNA samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on alogliptin continues for up to but not longer than 15 years or as required by applicable law.

Appendix G Determination of Eligibility in Subjects With Elevated ALT Levels



*Liver biopsies are not required, however, may be recommended by the investigator to confirm NAFLD and thereby, render the subject eligible for the study.

Appendix H Recommendations for Home Glucose Monitoring

Subjects should be advised to check their blood glucose levels on a daily basis, at the following time points, at a minimum:

- Two times per day.
  - In the morning upon awakening (fasting).
  - One additional time (for example, before dinner, or 2 hours after dinner).
- Additional testing of blood glucose levels is recommended during periods of illness, or when signs or symptoms of hypoglycemia are thought to be experienced.
- Additional testing of blood glucose levels is also recommended during the study, such as when rescue medications are required and/or when rescue medications are being down-titrated.

Appendix I Protocol History

Date	Amendment Number	Amendment Type	Region
17 August 2020	Amendment 9 IT v 1	Substantial	Italy
13 November 2019	Amendment 8	Substantial	Russia
28 November 2018	Amendment 7	Substantial	Brazil
27 June 2018	Amendment 6	Substantial	Germany
09 February 2018	Amendment 5	Substantial	Germany
17 January 2018	Amendment 4	Substantial	Italy
10 May 2017	Amendment 3	Nonsubstantial	Global
09 November 2016	Amendment 2	Substantial	Global
29 April 2016	Amendment 1	Substantial	Global
28 July 2015	Initial Protocol	Not applicable	Global

Protocol Amendments 5 through 8:

Protocol Amendments 5 through 8 were local amendments applicable to single countries other than Italy; therefore, details of these amendments are not included in this local protocol amendment for Italy.

Protocol Amendment 4 Italy Summary and Rationale

The primary purpose of this country-specific amendment for Italy was to incorporate suggested changes made by the central ethics committee (CEC) and the local regulatory authority in Italy.

In a letter dated 23 October 2017, the CEC stated the need to clarify the risk for treatment-naïve subjects in the event of assignment to the placebo group. In a letter dated 30 October 2017 ("A Denial of Authorisation" issued by the Agenzia Italiana del Farmaco [AIFA] for the Clinical Trial Application for Study SYR-322_309), AIFA provided feedback on exclusion criterion 7 ("The subject has had more than 1 episode of diabetic ketoacidosis at any time after diagnosis of T2DM") and exclusion criterion 8 ("The subject has a history of more than 1 episode of pancreatitis").

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4 Italy		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.a Schematic of Study Design Section 7.2 Exclusion Criteria Section 7.3 Additional Randomization Criteria That Must Be	Excluded treatment-naïve subjects.	The CEC raised objection to including naïve subjects ("The Committee does not consider the clarifications provided to be thorough and reiterates the need to clarify the risk for naïve patients in the event they are assigned to the

Protocol Amendment 4 Italy		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Met Following Screening and/or Completion of the Pre-Randomization Stabilization Period Section 13.1.3 Efficacy Analysis		placebo group"). In order to be compliant with CEC requests, treatment-naïve subjects were excluded in this local amendment for Italian subjects.
Section 7.2 Exclusion Criteria Section 8.3 Randomization Code Creation and Storage	Excluded subjects with a history of diabetic ketoacidosis (DKA).	Because this is a clinical trial involving a pediatric population and DKA is a serious clinical disease, the benefit-risk ratio cannot be considered favorable in subjects with a history of DKA. This change ensures that the inclusion of subjects at risk for DKA will be minimized.
Section 7.2 Exclusion Criteria	Excluded subjects with a history of pancreatitis.	Because this is a clinical trial involving a pediatric population and pancreatitis is a serious clinical disease for which, in the vast majority of the cases, it is impossible to identify a cause in the target age group, the benefit-risk ratio cannot be considered favorable in subjects with a history of pancreatitis. This change ensures that the inclusion of subjects at risk for pancreatitis will be minimized.

Protocol Amendment 3 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary purpose of this amendment was to provide updated contact information. A number of editorial changes were made throughout the protocol to provide clarity. The following is a summary of the changes made in the amendment.

Protocol Amendment 3		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.1 Contacts	Updated contact information.	To reflect personnel changes.
Section 1.2 Approval	Updated list of protocol approvers.	To reflect personnel changes.
8.1.1.2 Companion Medication	Removed the provision of pharmacy cards for companion medications by	The use of pharmacy cards was removed to allow more flexibility

Protocol Amendment 3		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
	deleting Section 8.1.1.5 Pharmacy Card Supplied Drugs.	on how companion medications can be obtained.
Section 8.1.1.3 Rescue Medication Section 8.1.1.6 Rescue Medications	Combined text for rescue medications.	To consolidate text in 2 different sections for rescue medications.

Protocol Amendment 2 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary purpose of this amendment is to enhance clarity, provide additional guidance, and remove unnecessary procedures. A number of editorial and administrative changes were made throughout the protocol to provide clarity. The following is a summary of the changes made in the amendment.

Protocol Amendment 2		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.1 Contacts	Updated contact information.	To reflect personnel changes.
Section 1.2 Approval	Updated list of protocol approvers.	To reflect personnel changes.
Section 5.2.2 Secondary Endpoints Section 2.0 Study Summary	Added respiratory tract infections and hypersensitivity reactions, in addition to total and urinary tract infections, to the "incidence of infections" in the safety endpoints.	To align with adverse events of special interest.
Section 5.2.2 Secondary Endpoints Section 5.1.2 Secondary Objectives Section 9.1 Study Procedures Section 13.1.1 Analysis Sets Appendix A Schedule of Study Procedures	Removed dual-energy x-ray absorptiometry scans.	These scans are not needed as DPP-4 inhibitors have not shown an impact on bone density in clinical studies.
Section 5.2.3 Exploratory Endpoints Section 2.0 Study Summary Table 9.a Clinical Laboratory Tests Appendix A Schedule of Study Procedures	CCI [redacted]	To align with planned analyses.
Section 6.2 Pre-Randomization Stabilization Period (if needed)	Modified the length of time for the maintenance of stable anti-hyperglycemic therapy from 1 month to 2 months.	To allow more time for stabilization.

Protocol Amendment 2		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 6.2 Pre-Randomization Stabilization Period (if needed)	Added recommendations regarding managing insulin therapy.	To provide more guidance to the investigator.
Section 7.1 Inclusion Criteria and 7.3 Additional Randomization Criteria That Must Be Met Following Screening and/or Completion of the Pre-Randomization Stabilization Period Section 2.0 Study Summary Table 9.a Clinical Laboratory Tests Appendix A Schedule of Study Procedures	Clarified that inclusion criteria regarding C-peptide, autoantibodies, age, and BMI apply at randomization and that C-peptide, autoantibodies, and BMI criteria apply to subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin.	Applied criteria to the pediatric diabetic population to those most at risk for misdiagnosis of type 1 diabetes and to align with clinical practice guidelines. Also, clarified that these criteria are to be met prior to randomization.
Section 7.2 Exclusion Criteria Section 7.9 Renal Safety Withdrawal Criteria Table 9.a Clinical Laboratory Tests Section 16.0 References	Changed eGFR calculations to be based on the Schwartz formula rather than Cockcroft-Gault.	The Schwartz formula is a more appropriate formula than the Cockcroft-Gault formula for the estimation of GFR in the pediatric population.
Section 7.2 Exclusion Criteria	Modified wording of exclusion criteria regarding sexual activity to align with Section 9.1.9.	Clarified wording to align with Section 9.1.9.
Section 7.3 Additional Randomization Criteria That Must Be Met Following Screening and/or Completion of the Pre-Randomization Stabilization Period Section 2.0 Study Summary Figure 6.a Schematic of Study Design Section 6.2 Pre-Randomization Stabilization Period (if needed) Appendix A Schedule of Study Procedures	Added a randomization criterion for subjects on insulin to require and HbA1c level of ≥7.0%.	This criterion threshold was raised for subjects on insulin to allow for additional therapy before they reach their treatment goal and to minimize the risk of hypoglycemia.

Protocol Amendment 2		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.3 Additional Randomization Criteria That Must Be Met Following Screening and/or Completion of the Pre-Randomization Stabilization Period Section 2.0 Study Summary Table 9.a Clinical Laboratory Tests Appendix A Schedule of Study Procedures	Updated laboratory testing terminology from ICA 512 antibody to IA-2 antibody.	To match the terminology used by the laboratory.
Section 7.4 Excluded Medications	Added clarification regarding the use of oral or parenteral steroids during the treatment period.	Chronic steroid use impacts glucose levels and therefore, may affect measurements of HbA1c, which is primary endpoint. For this reason, the chronic use of steroids should be avoided if possible.
Section 7.9 Renal Safety Withdrawal Criteria	Added wording to the renal safety withdrawal criteria to clarify that the confirmation by a repeat laboratory test is to be conducted within a maximum of 7 days.	Clarified that repeat testing should occur within a specified period of time.
Section 9.1.3 Physical Examination Procedure	Added details regarding assessment of pubertal development.	Added menarche and clarification of Tanner stage categories.
Section 9.1.4 Weight, Height and BMI	Added clarification regarding BMI measurements.	Clarified the process for BMI measurements.
Section 9.1.7 Documentation of Concurrent Medical Conditions	Added a recommendation for annual ophthalmologic examinations.	To monitor the subjects for retinopathy, one of the known complications of T2DM.
Section 9.1.8 Procedures for Clinical Laboratory Samples	Adjusted the volume of blood collected for clinical laboratory samples.	Blood volume was adjusted based on updated laboratory tests.
Table 9.a Clinical Laboratory Tests Section 9.1.8.1 2-Hour Postprandial Glucose Test Table 9.b [redacted] Appendix A Schedule of Study Procedures	Removed insulin and proinsulin measurements and clarified that C-peptide will only be measured once prior to randomization.	These measurements were removed as they were expected to produce inconclusive results in pediatric patients treated with diet and exercise, insulin, and/or metformin.
Table 9.a Clinical Laboratory Tests Appendix A Schedule of Study Procedures	Clarified that GAD and IA-2 antibody testing may be performed by the central laboratory.	These tests may be performed by the central laboratory.

Protocol Amendment 2		
Summary of Changes Since the Last Global Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.1.8.1 2-Hour Postprandial Glucose Test	Added clarification regarding postprandial glucose testing.	Approval of the meal is not required. Also, oral glucose tolerance testing was added as an option for measuring postprandial glucose at sites who to do not have the ability to perform standardized meal tests.
Section 12.1 CRFs (Electronic)	Made a correction to the eCRF process regarding data changes after database lock.	These statements were removed to reflect the data handling process.
Section 16.0 References	Added recent literature references.	To provide additional information.
Appendix A Schedule of Study Procedures	Added hematology and serum chemistry testing at the Week -1 Visit.	To specify time point.
Appendix A Schedule of Study Procedures	CCI [redacted]	CCI [redacted]
Appendix A Schedule of Study Procedures Table 9.a Clinical Laboratory Tests	Added eGFR measurements at Baseline and at Weeks 26 and 52.	To monitor for renal safety.
Appendix A Schedule of Study Procedures	Added clarification regarding inclusion/exclusion criteria assessments and in-clinic dosing to the schedule of assessment.	Footnotes were added for clarification.

Rationale for Amendment 1

The primary purpose of this amendment was to enhance clarity and simplify the study design to more closely align with standard of care practices and reduce the overall burden on subjects and caretakers throughout the duration of the study. A number of editorial and administrative changes were made throughout the protocol to provide clarity.

Changes in Amendment 1

1. Study entry criteria were modified, including broadening glycosylated hemoglobin (HbA1c) criteria and hepatic enzyme criteria, in order to better reflect the study population and allow subjects with non-alcoholic fatty liver disease (NAFLD) into the study.
2. The number of schedules was reduced in order to simplify the study design.

3. A Pre-Randomization Stabilization Period was added for those subjects who are not yet stabilized on their current antidiabetic therapy or who have not yet met certain entry criteria.
4. The guidance for hepatic safety monitoring and withdrawal criteria was revised to reflect the potential inclusion of subjects with NAFLD.
5. The assessment of retinopathy by fundus photography was removed as this microvascular complication is very unlikely to have manifested at this early stage in the natural history of T2DM in this population to warrant evaluation.
6. Home glucose management and hyperglycemic rescue language were clarified to allow investigators to individualize glucose management based on the needs of the subject and according to local guidance.
7. The schedule of assessments was adjusted to decrease the number of clinic visits, allow for telephone visits, and minimize fasting requirements in order to reduce the burden on subjects.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	01-Jun-2022 21:45 UTC
	Clinical Science Approval	02-Jun-2022 20:53 UTC