Title: A  Randomized, Open-Label, Single-Dose, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin (25 mg) and Pioglitazone (15 and 30 mg) When Administered as Individual Tablets and as Fixed-Dose Combination Tablets to Healthy Russian Subjects

NCT Number: NCT03501277

Protocol Approve Date: 23 January 2018

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.

**TAKEDA PHARMACEUTICALS**

**PROTOCOL**

# A Randomized, Open-Label, Single-Dose, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin (25 mg) and Pioglitazone (15 and 30 mg) When Administered as Individual Tablets and as Fixed-Dose Combination Tablets to Healthy Russian Subjects

**Bioequivalence Study of Medicinal Product – SYR-322-4833 BL**

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Pharmaceuticals LLC<br>2 bld 1, Usatchyova Str.<br>Moscow 119048<br>Russian Federation | | |
| **Study Number:** | Alogliptin-1002 | | |
| **IND Number:** | Not Applicable | **EudraCT Number:** | Not Applicable |
| **Compound:** | SYR-322-4833 BL | | |
| **Date:** | 23 January 2018 | **Amendment Number:** | 02 |

**Amendment History**:

| Date | Amendment Number | Amendment Type | Region |
|---|---|---|---|
| 25 July 2017 | Initial version | Not applicable | Global |
| 19 October 2017 | 01 | Substantial | Global |
| 23 January 2018 | 02 | Substantial | Global |

# 1.0 ADMINISTRATIVE INFORMATION

## 1.1 Contacts

A separate contact information list will be provided.

| Contact Type / Role | Contact |
|---|---|
| Serious adverse event and pregnancy reporting | PPD |
| Medical Monitor<br>(medical advice on protocol and study drug) | |
| 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 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 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.

Electronic Signatures are provided on the last page of this document.

PPD

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert, 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 Good Clinical Practice: 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 study site agreement.
- Responsibilities of the Investigator (Appendix B).

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 02 Summary of Changes

### Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02.

The primary reason for this amendment is to align with local requirements for clinical supplies.

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

For specific descriptions of text changes and where the changes are located, see Appendix F.

### Changes in Amendment 02

1. Revised descriptions of study drugs to align with local requirements.
2. Corrected inconsistency in length of pregnancy monitoring time after the end of the study.
3. Updated information for shipping label and contact information for the bioanalytical laboratory.

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## LIST OF IN-TEXT FIGURES

## LIST OF APPENDICES

## 2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):<br>Takeda Pharmaceuticals LLC</td><td colspan="2">Compound:<br>SYR-322-4833</td></tr>
<tr><td colspan="2">Title of Protocol: A Randomized, Open-Label, Single-Dose, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin (25 mg) and Pioglitazone (15 and 30 mg) When Administered as Individual Tablets and as Fixed-Dose Combination Tablets to Healthy Russian Subjects</td><td>IND No.:<br>Not applicable</td><td>EudraCT No.:<br>Not applicable</td></tr>
<tr><td colspan="2">Study Number: Alogliptin-1002</td><td colspan="2">Phase: Bioequivalence</td></tr>
<tr><td colspan="4">Study Design:<br>This is a single-center randomized, open-label, 4-sequence, 4-period, single-dose, crossover study to assess the bioequivalence, pharmacokinetics (PK), and safety of alogliptin and pioglitazone administered as individual tablets and as the fixed-dose combination (FDC) tablet product.<br>Subjects will be randomized in the order in which they are enrolled into the study. The 72 eligible subjects will be randomized to 1 of 4 drug intake sequences in a 1:1:1:1 ratio. Due to the large sample size, volunteers may be divided into 2 or 3 cohorts according to space limitations at the site. All cohorts will be dosed sequentially.<br>The study consists of a Screening Period (Days -28 to Day-2) and 4 Drug Intake Periods. A washout interval of 7 days (beginning immediately after dosing on Day 1) will separate the doses of each study period. Subjects will be admitted into the clinic on Day -1 (Day 7 of the preceding period for Periods 2, 3, and 4) and will be dosed on Day 1 of each period. Starting on Day 1 of each period, blood samples for determination of alogliptin and pioglitazone plasma concentrations will be collected predose through 72 hours postdose. The subjects will be discharged from the clinic after the 24-hour blood sample collection on Day 2 of each period and will return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures. Final Visit procedures will be performed on Day 4 of Period 4 and a Follow-up call will be made 14 days ±2 days following the last dose of study drug.</td></tr>
<tr><td colspan="4">Primary Objective:<br>To assess the relative bioavailability and bioequivalence of 2 strengths of the fixed-dose combination tablet product SYR-322-4833 BL compared to the individual alogliptin and pioglitazone tablets in healthy Russian subjects.<br>Additional Objectives:<br>To perform a comparative analysis of adverse event (AE) data after the administration of SYR-322-4833 BL and after coadministration of alogliptin and pioglitazone to healthy volunteers within the scope of the trial.</td></tr>
<tr><td colspan="4">Subject Population: Healthy subjects aged 18 to 55 years, inclusive.</td></tr>
<tr><td colspan="2">Number of Subjects:<br>Approximately 144 subjects will be screened.<br>72 subjects (18 per sequence) will be enrolled.</td><td colspan="2">Number of Sites:<br>1 site in Russia</td></tr>
<tr><td colspan="2">Dose Level(s):<br>A= SYR-322-4833 BL (25 mg + 15 mg) (test regimen)<br>B= alogliptin 25 mg + pioglitazone 15 mg (reference regimen)<br>C= SYR-322-4833 BL (25 mg + 30 mg) (test regimen)<br>D= alogliptin 25 mg + pioglitazone 30 mg (reference regimen)</td><td colspan="2">Route of Administration:<br>Oral</td></tr>
<tr><td colspan="2">Duration of Treatment:<br>4 single doses, 1 dose in each of 4 periods</td><td colspan="2">Period of Evaluation:<br>Total study duration: approximately 66 days (including Screening Period, Drug Intake Period, and Follow-up telephone call).</td></tr>
</table>

**Main Criteria for Inclusion:**

- The subject is a healthy male or female 18 to 55 years of age, inclusive.
- The subject has an estimated glomerular filtration rate (eGFR) ≥ 90 mL/min.
- The subject has a body mass index (BMI) of within 18.5 to 30 kg/m2.

**Main Criteria for Exclusion:**

- Female subjects of childbearing potential who have had unprotected sex with nonsterilized men within 30 days before the investigational medicinal product administration.
- The subject has a history of clinically significant allergic reactions or has a known hypersensitivity to any component of the formulation of alogliptin, pioglitazone or related compounds.
- The subject has a positive alcohol breath test at Screening or Check-in (Day -1).
- The subject has a fasting blood glucose level lower than 3.88 mmol/L.
- The subject experienced acute infectious diseases within 4 weeks prior to Screening.
- The subject has a non-standard diet (eg, vegetarian or vegan) or lifestyle (including nighttime work, extreme physical activity such as weights lifting), which may interfere with the trial.
- The subject has participated in a clinical study within 3 months prior to Day -1 of Period 1.
- The subject has taken medicines with pronounced effects on blood circulation, liver function (barbiturates, omeprazole, cimetidine, etc.) within 2 months prior to Day -1 of Period 1.
- The subject has abnormalities in routine clinical examination, laboratory and/or ECG findings.
- The subject has current or a history of cardiovascular, respiratory, neurological, endocrine, hematopoietic, immune, urinary, genital, gastrointestinal, hepatic, or psychiatric diseases or a history of epilepsy or convulsive seizures.

**Main Criteria for Evaluation and Analyses:**

Primary: The following plasma PK parameters of alogliptin and pioglitazone will be derived on Day 1 of each period:

- Maximum observed concentration ($C_{max}$).
- Area under the concentration-time curve from the time 0 to time 72 hours ($AUC_{72}$).

Exploratory/Additional: PPD

Criteria of Subject Condition Assessment**:** The following variables will be used to characterize the safety and tolerability of SYR-322-4833 BL, alogliptin, and pioglitazone.

- Percentage of subjects who experience at least 1 postdose AE.
- Percentage of subjects who have clinically significant changes in laboratory tests at least once postdose.
- Percentage of subjects who have clinically significant changes in vital sign measurements at least once postdose.
- Percentage of subjects who have clinically significant changes in electrocardiogram (ECG) parameters at least once postdose.
- Percentage of subjects who experience at least 1 postdose event of hypoglycemia.

**Statistical Considerations:**

Descriptive statistics (N, mean, SD, SE, percent coefficient of variation [%CV], median, minimum, and maximum) will be used to summarize the PK parameters of alogliptin and pioglitazone for each regimen. Geometric means will be computed for AUCs and $C_{max}$.

Statistical inference to determine if the test regimens are bioequivalent to the reference regimens will be performed using an analysis of variance (ANOVA) model with effects for regimen, period, sequence, and subjects nested within sequence. The effect due to subject nested within sequence will be considered a random effect in the ANOVA model while all other effects will be treated as fixed. The ANOVA model will be applied to the natural logarithms of $AUC_{72}$ and $C_{max}$ of alogliptin or pioglitazone as dependent variables to compare the test and reference regimens. Within the framework of the ANOVA model for natural logarithms of $AUC_{72}$ and $C_{max}$, the ratios and the 90% confidence intervals (CIs) for the ratios of central values of each test regimen relative to the corresponding reference regimen of alogliptin or pioglitazone will be provided. The ratios will be obtained as the antilog of the difference of the least squares (LS) means on a natural logarithm scale, and the 90% CIs will be obtained by taking the antilog of the 90% CI for the difference between the LS means on the natural logarithmic scale.

Alternative statistical analyses will be used if deemed appropriate.

All subject condition assessments, including AEs, physical examinations, clinical laboratory evaluations, 12-lead ECGs, and vital signs will be presented in the data listings and summarized with descriptive statistics, if appropriate.

**Sample Size Justification:** A sample size of 72 subjects (18 per sequence) will be enrolled in this 4-period, 4-sequence crossover study. The sample size is appropriate to assess the bioavailability of alogliptin and pioglitazone from the FDC relative to the individual tablets and also provide greater than 80% power for $C_{max}$ of pioglitazone establishing bioequivalence between regimens for both strengths (SYR-322-4833 BL 25 mg+15 mg and SYR-322-4833 BL 25 mg+30 mg). This is based on acceptance ranges of 80% to 125%, the intra-subject variability (%CV) of 33% for $C_{max}$ of pioglitazone; the expected ratios of the central values for $C_{max}$ are between 0.95 and 1.05, and drop-out rate of 14%. Since the intra-subject variability for pioglitazone area under the concentration-time curve from time 0 to time t ($AUC_t$), and alogliptin $C_{max}$ and $AUC_t$ is less than 33%, the power for assessing bioequivalence for pioglitazone $AUC_t$ and alogliptin $C_{max}$ and $AUC_t$ are each greater than 80% for both strengths.

# 3.0 STUDY REFERENCE INFORMATION

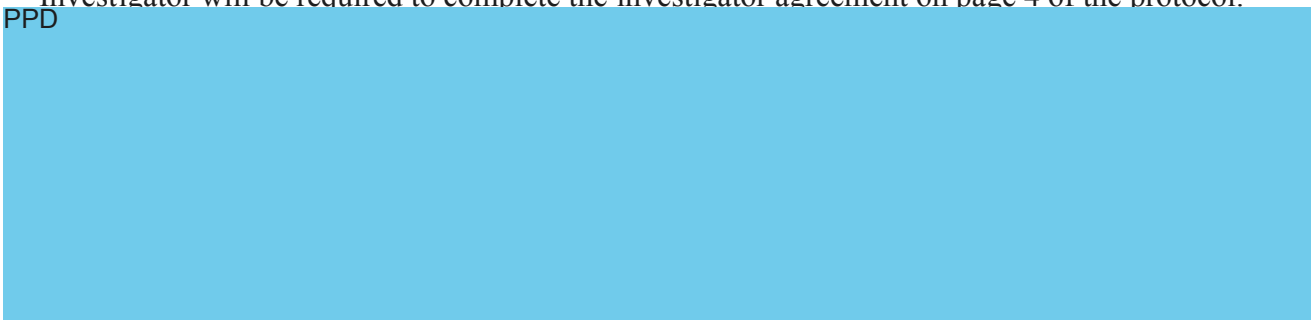
## 3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. 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 Principal Investigator

The Principal Investigator will be confirmed once the study site is selected. The Principal Investigator will be required to complete the investigator agreement on page 4 of the protocol.

PPD



## 3.3 List of Abbreviations

| | |
|---|---|
| $\lambda_z$ | terminal disposition phase rate constant |
| %CV | percent coefficient of variation |
| AE | adverse event |
| AESI | adverse event special interest |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variables |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| CCI | [redacted] |
| $AUC_{72}$ | area under the concentration-time curve time from time 0 to 72 hours |
| $AUC_t$ | area under the concentration-time curve from time 0 to time t |
| BMI | body mass index |
| bpm | beats per minute |
| CI | confidence interval |
| CL/F | apparent clearance after extravascular administration |
| $C_{max}$ | maximum observed concentration |
| CS | clinically significant |
| DPP-4 | dipeptidyl peptidase-4 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| FDC | fixed-dose combination |
| FPG | fasting plasma glucose |
| GCP | Good Clinical Practice |
| HbA1c | glycosylated hemoglobin |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HIV | human immunodeficiency virus |
| GIP | glucose-dependent insulinotropic polypeptide |
| GLP-1 | glucagon-like peptide-1 |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| INR | international normalized ratio |
| IRB | institutional review board |
| $K_2EDTA$ | potassium ethylenediamine tetra-acetic acid |
| LDL | low-density lipoprotein |

| | |
|---|---|
| LFT | liver function test |
| LS | least square |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCS | not clinically significant |
| PK | pharmacokinetic(s) |
| PPAR-γ | peroxisome proliferator-activated receptor-gamma |
| QD | once daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SE | standard error |
| SU | sulfonylurea |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{1/2z}$ | terminal disposition phase half-life |
| T2DM | type 2 diabetes mellitus |
| $t_{max}$ | time of first occurrence of $C_{max}$ |
| TZD | thiazolidinedione |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# 4.0 INTRODUCTION

## 4.1 Background

### 4.1.1 Alogliptin

Alogliptin is an orally available, selective and highly potent inhibitor of dipeptidyl peptidase-4 (DPP-4), the primary enzyme involved in the in vivo degradation of at least 2 incretin hormones released in response to nutrient ingestion: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretin hormones exert important effects on pancreatic islet β-cells to stimulate glucose-dependent insulin secretion and regulate β-cell proliferation and cytoprotection. By preventing the rapid degradation of these hormones, alogliptin enhances the body's ability to control elevated blood glucose by triggering pancreatic insulin secretion and suppressing pancreatic glucagon secretion, resulting in reductions in glycemia.

Alogliptin has been approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). Alogliptin has been commercially available since 2010 and is approved in several major markets including Japan, the United States (US), the European Union (EU), and Russia.

### 4.1.2 Pioglitazone

Pioglitazone is an insulin sensitivity enhancer, which decreases insulin resistance by binding to peroxisome proliferator-activated receptor-gamma (PPAR-γ). Pioglitazone depends on the presence of insulin for its mechanism of action. It decreases insulin resistance in the periphery and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is a potent and highly selective agonist for PPAR-γ. Activation of PPAR-γ leads to increased insulin-mediated glucose uptake in skeletal muscle [1], decreased hepatic glucose production, reduced lipolysis, enhanced adipose differentiation [2], improved fibrinolysis, decreased microalbuminuria [3], and improved inflammatory markers, such as C-reactive protein [4].

Pioglitazone has been commercially available since 1999 and is approved in several major markets including the United States, Japan, and the European Union as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings.

Pioglitazone is a thiazolidinedione (TZD) that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for PPARγ. PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Treatment with pioglitazone as monotherapy or in combination with metformin, a sulfonylurea, or insulin results in improvements in glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG). Pioglitazone also appears to preserve β-cell function, which may explain its

antihyperglycemic durability [5]. Pioglitazone has favorable effects on lipids, including increasing high-density lipoprotein (HDL) cholesterol, decreasing triglycerides, and shifting low-density lipoprotein (LDL) particle size and concentration to a less atherogenic profile [6]. Pioglitazone treatment has also been associated with improvements in several other cardiovascular risk factors, such as markers of vascular effects (eg, reduced blood pressure, reduced smooth muscle proliferation, improved endothelial function, reduced microalbuminuria, and increased nitric oxide levels), anti-inflammatory effects (eg, decreased C-reactive protein levels, decreased interleukin-6 levels), and antithrombotic effects (eg, decreased plasminogen activator inhibitor-1 levels) [7,8].

### 4.1.3 SYR-322-4833 BL

SYR-322-4833 BL is an oral, immediate-release, alogliptin fixed-dose combination (FDC) product with pioglitazone developed by Takeda as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. Alogliptin FDC with pioglitazone has also been approved in several major markets including United States and European Union.

## 4.2 Summary of Relevant Clinical Studies

### 4.2.1 Summary of Clinical Studies With Alogliptin

Alogliptin has been evaluated in 59 completed clinical studies (31 phase 1, 1 phase 2, and 27 phase 3 studies) in both healthy subjects and subjects with T2DM, as part of the alogliptin clinical program. Alogliptin doses ranged from 6.25 to 800 mg in the clinical pharmacology studies, and from 6.25 to 100 mg in the phase 2 efficacy and safety study. Alogliptin doses of 12.5 and 25 mg were used in the pivotal phase 3 studies.

Results from 5 main, pivotal phase 3 double-blinded placebo-controlled studies (monotherapy and add-on to a sulfonylurea, metformin, TZD, and insulin) indicated that subjects with T2DM who were treated with alogliptin 12.5 or 25 mg once daily (QD) for 26 weeks achieved significantly greater least squares (LS) mean reductions in HbA1c levels versus those who received placebo.

Both doses of alogliptin evaluated in the phase 3 clinical program (12.5 and 25 mg QD) had an acceptable safety profile whether administered as monotherapy or in combination to other established antidiabetic therapies. Alogliptin was generally hypoglycemia and weight neutral. The following adverse drug reactions were associated with alogliptin in the clinical program: headache, upper respiratory tract infection, nasopharyngitis, abdominal pain, gastroesophageal reflux disease, pruritus, and rash. In addition, the following post-marketing adverse drug reactions have been spontaneously reported: acute pancreatitis, hepatic dysfunction including hepatic failure, hypersensitivity, and exfoliative skin conditions including Stevens-Johnson syndrome, erythema multiforme, angioedema, and urticaria.

See the investigator brochure for detailed information about alogliptin clinical studies.

### 4.2.2 Summary of Clinical Studies With Pioglitazone

The clinical trial database for pioglitazone consists of 47 studies (36 controlled, 11 uncontrolled) in a total of >27,000 treated subjects. These studies include 12 long-term controlled trials, ≥1 year in duration. Across these studies, the efficacy of pioglitazone has been evaluated in terms of glycemic control, lipid metabolism, and cardiovascular effects.

Pioglitazone 7.5 to 45 mg daily has been compared with placebo in several randomized, double blind, parallel-group studies in patients with T2DM. Pioglitazone 15, 30, and 45 mg produced significant improvements in HbA1c (–0.3% to –1.8% and up to –2.6%, respectively) and FPG. Pioglitazone also produced significant decreases in triglycerides and significant increases in high density lipoprotein [9].

In combination trials with metformin, patients poorly controlled with a sulfonylurea (SU) were randomly assigned to metformin or pioglitazone, with comparable improvements seen in both compounds with respect to HbA1c and FPG [9]. In a combination trial, metformin plus pioglitazone 30 mg was compared with metformin plus placebo in patients with poorly controlled T2DM. Treatment with pioglitazone 30 mg plus metformin resulted in significant improvements in HbA1c, FPG, and lipid profiles compared with placebo plus metformin. [9,10]. In 2 active-comparator trials, treatment with metformin and pioglitazone resulted in equal, significant reduction in HbA1c while insulin sensitivity measured by homeostasis model assessment showed significant improvement in the pioglitazone, but not the metformin group at 32 weeks [9].

In comparative/combination trials with SUs, pioglitazone produced comparable reduction in HbA1c and FPG as SU. Pioglitazone produced a slower but more sustained reduction in HbA1c compared with an earlier effect in the SU treated group, and improvements in insulin sensitivity were not seen in the SU treatment group [9]. Similar to results observed in combination trials with metformin, pioglitazone-treated subjects demonstrated significant improvements in glycemic control and lipid profiles compared with treatment with SU [9].

### 4.2.3 Summary of Clinical Studies With Alogliptin in Combination With Pioglitazone

The coadministration of alogliptin and pioglitazone has been studied in subjects with T2DM inadequately controlled on either diet and exercise alone, pioglitazone alone, or pioglitazone in combination with metformin.

There have been no completed clinical efficacy studies conducted with alogliptin/ pioglitazone FDC; however, bioequivalence of alogliptin/ pioglitazone FDC with coadministered alogliptin and pioglitazone tablets was demonstrated, and efficacy of the combination of alogliptin and pioglitazone has been demonstrated in 4 phase 3 efficacy studies.

Results from 4 phase 3 double-blinded placebo or active-controlled clinical safety and efficacy studies ranging from 16 to 52 weeks indicated that subjects with T2DM who were treated with alogliptin (12.5 mg or 25 mg) and pioglitazone (15, 30, or 45 mg) combination therapy achieved significantly greater LS mean reductions in HbA1c compared to placebo and each individual monotherapy.

All dose combinations studied in the alogliptin/pioglitazone FDC program were well tolerated. The majority of subjects completed the studies, and the overall discontinuation rate due to adverse events (AEs) was low. The safety profile of combination treatment was consistent with the known safety profiles of pioglitazone and alogliptin.

The following adverse drug reactions were associated with alogliptin and pioglitazone combination therapy in the clinical program: upper respiratory tract infection, sinusitis, headache, nausea, dyspepsia, abdominal pain, pruritus, myalgia, edema peripheral, and weight increased.

See the investigator brochure for detailed information about alogliptin/pioglitazone combination clinical studies.

### 4.3 Benefit/Risk Profile

Data from the clinical studies have demonstrated that the coadministration of alogliptin and pioglitazone results in improved glycemic control. In these studies, combination therapy with alogliptin with pioglitazone resulted in greater clinically meaningful reductions in HbA1c than with either agent given alone. This greater reduction in HbA1c resulted in a higher percentage of subjects who achieved the HbA1c goal of ≤7%. An additional glycemic benefit of combination therapy was a reduction in FPG levels without a corresponding increase in risk of hypoglycemia, an AE that often restricts use with other antidiabetic agents.

Another goal of T2DM treatment is to reduce cardiovascular risk factors such as dyslipidemia and elevated inflammatory markers, which are common in patients with T2DM. Combination therapy of pioglitazone and alogliptin enhanced the pioglitazone effects of reduced triglycerides, increased HDL, decreased LDL, improved LDL particle size, and decreased C-reactive protein levels.

Some risks that have been identified with the use of pioglitazone or other TZDs are congestive heart failure, edema, bladder cancer, hepatic effects, hematological effects, hypoglycemia (when used with other antihyperglycemic medicinal products), bone fractures, and macular edema. Risks that have been identified with the use of alogliptin or other DPP-4 inhibitors are hypoglycemia (when used with other antihyperglycemic medicinal products), cardiac failure, hypersensitivity reactions, acute pancreatitis, and hepatic effects.

The alogliptin/ pioglitazone FDC will provide flexibility in reaching efficacy goals without compromising safety, thereby allowing prescribers to individualize therapy. In addition, it is generally accepted that the convenience of an FDC product provides significant improvement with respect to compliance and alleviation of pill burden in patients with chronic illnesses such as T2DM [11-13]. Based on the efficacy and safety data, the benefit:risk ratio is favorable for the use of alogliptin/ pioglitazone FDC to improve glycemic control in adults with T2DM.

### 4.4 Rationale for the Proposed Study

Takeda has developed an FDC product with alogliptin and pioglitazone (SYR-322-4833 BL). Alogliptin and pioglitazone potentially have complimentary mechanisms of action and could potentially be prescribed in combination. An FDC product may provide improve convenience for the patient, and therefore, may improve compliance.

The bioequivalence of alogliptin/pioglitazone FDC with co-administration of alogliptin and pioglitazone tablets has been established in the US and EU population. However, this bioequivalence has not been demonstrated specifically in the Russian population. In order to better bridge the alogliptin and pioglitazone combination therapy clinical data to the Russian population and meet local regulatory requirements for further alogliptin/pioglitazone FDC registration in Russia, this study is designed to determine whether peak and total exposures to alogliptin and to pioglitazone are bioequivalent when the 2 agents are administered as an FDC product and as individual tablets in Russian subjects.

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objective

To assess the relative bioavailability and bioequivalence of 2 strengths of the fixed-dose combination tablet product SYR-322-4833 BL compared to the individual alogliptin and pioglitazone tablets in healthy Russian subjects.

### 5.1.2 Additional Objective

To perform a comparative analysis of AE data after the administration of SYR-322-4833 BL and after coadministration of alogliptin and pioglitazone to healthy volunteers within the scope of the trial.

## 5.2 Endpoints

### 5.2.1 Primary Endpoints

The following plasma pharmacokinetic (PK) parameters of alogliptin and pioglitazone will be derived on Day 1 of each period:

- Maximum observed concentration ($C_{max}$).
- Area under the concentration-time curve from the time 0 to time 72 hours ($AUC_{72}$).

### 5.2.2 Additional Endpoints

#### *5.2.2.1 Exploratory*

CCI [redacted]

#### *5.2.2.2 Criteria of Subject Condition Assessment*

- Percentage of subjects who experience at least 1 postdose AE.
- Percentage of subjects who have clinically significant changes in laboratory tests at least once postdose.
- Percentage of subjects who have clinically significant changes in vital sign measurements at least once postdose.
- Percentage of subjects who have clinically significant changes in electrocardiogram (ECG) parameters at least once postdose.
- Percentage of subjects who experience at least 1 postdose event of hypoglycemia.

# 6.0 STUDY DESIGN AND DESCRIPTION

## 6.1 Study Design

This is a single-center, open-label, randomized, 4-sequence, 4-period, single dose crossover study involving 72 healthy adult, male and female subjects between the ages of 18 and 55 years, inclusive.

Subjects will be randomized in the order in which they are enrolled into the study. The 72 eligible subjects will be randomized to 1 of 4 drug intake sequences in a 1:1:1:1 ratio. Due to the large sample size, volunteers may be divided into 2 or 3 cohorts according to space limitations at the site. All cohorts will be dosed sequentially.

The study consists of a Screening Period (Days -28 to Day-2) and 4 Drug Intake Periods. A washout interval of 7 days (beginning immediately after dosing on Day 1) will separate the doses of each study period. Subjects will be admitted into the clinic on Day -1 (Day 7 of the preceding period for Periods 2, 3, and 4) and will be dosed on Day 1 of each period. Starting on Day 1 of each period, blood samples for determination of alogliptin and pioglitazone plasma concentrations will be collected predose through 72 hours postdose. The subjects will be discharged from the clinic after the 24-hour blood sample collection on Day 2 of each period and will return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures. Final Visit procedures will be performed on Day 4 of Period 4 and a Follow-up call will be made 14 days ±2 days following the last dose of study drug.

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

**Figure 6.a Schematic of Study Design**

| Predose Period | | | Drug Intake Period (c) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Screening (a) | Check-in (b) | | Period 1 | | Period 2 | | Period 3 | | Period 4 | | |
| Days -28 to -2 | Day -1 | | Day 1 Dosing | Days 2 to at least 7 | Day 1 Dosing | Days 2 to at least 7 | Day 1 Dosing | Days 2 to at least 7 | Day 1 (d) Dosing | Days 2 to 3 | Day 4 Final Visit/ET |
| | | Sequence I (n=18) | A | WO | B | WO | C | WO | D | WO | |
| | | Sequence II (n=18) | B | | C | | D | | A | | |
| | | Sequence III (n=18) | C | | D | | A | | B | | |
| | | Sequence IV (n=18) | D | | A | | B | | C | | |

A=SYR-322-4833 BL (25 mg + 15 mg) (test regimen), B=alogliptin 25 mg + pioglitazone 15 mg (reference regimen), C=SYR-322-4833 BL (25 mg + 30 mg) (test regimen), D=alogliptin 25 mg + pioglitazone 30 mg (reference regimen), ET=Early Termination, WO=Washout of 7 days between dosing.
(a) Screening may consist of 1 or more visits. Subjects will sign an informed consent form at the first visit and return to the clinic in a fasted state for safety laboratory testing at the second visit.
(b) Subjects are admitted into the clinic on Day -1 of each period (~Day 7 of the preceding period for Periods 2, 3, and 4).
(c) Randomization occurs on Day 1 of Period 1. Subjects check out of the unit on Day 2 following the 24-hour blood sample collection but return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures.
(d) Follow-up call will be made 14 days ±2 days following the last dose of study drug.

## 6.2 Justification for Study Design, Dose, and Endpoints

The dose of alogliptin selected for this study (25 mg) is the approved daily dose, which was efficacious and well-tolerated in the monotherapy program. The doses of pioglitazone (15 and 30 mg) chosen for this study are approved therapeutic doses.

A randomization schedule for dose administration assignment will be used to reduce the potential for bias. A crossover design will be used to allow for intrasubject comparisons. To minimize the potential for carryover effect, a 7-day washout interval, which is >5 half-lives of either alogliptin or pioglitazone, will separate the dose administrations.

Single doses will be administered because single doses generally allow for a more sensitive assessment of the release of the drug substance from the drug product into the systemic circulation. Only parent drug released from the dosage form, rather than metabolites, will be measured, because the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite.

The safety endpoints in this study, including AEs, vital signs, 12-lead ECGs, clinical laboratory tests and physical examination data, are standard methods for assessing safety and tolerability in clinical pharmacology studies.

This study is being conducted for the purpose of registration of SYR-322-4833 BL by the Russian Ministry of Health.

## 6.3 Premature Termination or Suspension of Study or Study Site

### 6.3.1 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 drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

### 6.3.2 Criteria for Premature Termination or Suspension of Study 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.

### 6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site

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 a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

# 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization or first dose.

## 7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is a healthy male or female.
4. The subject is aged 18 to 55 years, inclusive, at the time of informed consent and first study drug dose.
5. The subject has an eGFR ≥90 mL/min.
6. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.5 to 30.0 kg/m$^2$, inclusive at Screening.
7. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent throughout the duration of the study and for 35 days after last dose. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use an effective method of contraception* from signing of informed consent and throughout the duration of the study and for 35 days after last dose.

| * Definitions and effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10. |
|---|

## 7.2 Exclusion Criteria

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

1. The subject has received any investigational compound or has participated in a clinical study within 3 months prior to Check-in (Day-1).
2. The subject has received alogliptin or pioglitazone in a previous clinical study or as a therapeutic agent within 90 days prior to Check-in (Day-1).
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

4. The subject has current or a history of cardiovascular, respiratory, neurological, endocrine, hematopoietic, immune, urinary, genital, gastrointestinal, hepatic, or psychiatric diseases, or a history of epilepsy or convulsive seizures.
5. The subject has a fasting blood glucose level lower than 3.88 mmol/L.
6. The subject experienced acute infectious diseases within 4 weeks prior to Screening.
7. The subject has a history of clinically significant allergic reactions or has a known hypersensitivity to any component of the formulation of alogliptin, pioglitazone or related compounds.
8. The subject has a positive urine drug result for super potent substances and drugs of abuse (defined as any illicit drug use) or positive alcohol breath test at Screening or Check-in (Day -1).
9. The subject consumes over 10 drinks weekly (1 drink is equivalent to 0.5 liters of beer, 200 mL of dry wine or 50 mL of ardent spirits) or has a history of alcoholism, drug and/or substance abuse.
10. The subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products table listed in Section 7.3, including intake of medicines with pronounced effects on blood circulation, liver function (barbiturates, omeprazole, cimetidine, etc.) within 2 months prior to Day -1 of Period 1.
11. If female, the subject is pregnant (confirmed by a positive pregnancy test) or lactating or intending to become pregnant before, during, or within 35 days after participating in this study; or intending to donate ova during such time period.
12. Female subjects of childbearing potential who have had unprotected sex with nonsterilized men within 30 days before the investigational medicinal product administration.
13. The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
14. The subject has a non-standard diet (eg, vegetarian or vegan) or lifestyle (including nighttime work, extreme physical activity such as weights lifting), which may interfere with the trial.
15. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1 of Period 1.
16. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody or syphilis at Screening.
17. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days prior to Check-in Day -1. Cotinine test is positive at Screening or Check-in (Day -1).
18. The subject has poor peripheral venous access.

19. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 30 days prior to Day 1 of Period 1.
20. The subject has abnormalities in routine physician examination, laboratory and/or ECG findings.
21. The subject has a systolic blood pressure >130 mm Hg or <100 mm Hg, diastolic blood pressure >90 mm Hg or <70 mm Hg; heart rate <60 beats per minute (bpm) or >80 bpm at Screening (Day -28 to Day -2) or Check-in to Period 1 (Day -1).
22. The subject has consumed caffeine or xanthine-containing food or drinks within 72 hours prior to Check-in (Day -1).
23. The subject has dehydration due to vomiting, diarrhea, or any other reason within 24 hours prior to study start.
24. The subject has drug intolerance.

## 7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

**Table 7.a Prohibited Medications**

| 90 days prior to Check-in (Day -1) | 60 days prior to Check-in (Day -1) | 28 days prior to Check-in (Day -1) | 7 days prior to Check-in (Day -1) | 72 hours prior to Check-in (Day -1) |
|---|---|---|---|---|
| • Alogliptin<br>• Pioglitazone | • Medicines with pronounced effects on blood circulation, liver function (barbiturates, omeprazole, cimetidine, etc.)<br>• **Female subjects:** hormonal contraceptives should have been discontinued 60 days prior to Day-1 | • Prescription medications<br>• Neutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)<br>• Immunization / Vaccines<br>• Nicotine-containing products | • OTC medications<br>• Vitamin supplements<br>• Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats<br>• Alcohol containing products | • Products containing caffeine or xanthine<br>• poppy seeds |

OTC=over-the-counter.

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

## 7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic from Check-in (Day -1) of Dosing Period 1 until the 24-hour blood sample has been collected on Day 2 of Dosing Period 1 and from Day 7 of Dosing Periods 1, 2, and 3 until the 24-hour blood sample has been collected on Day 2 of Dosing Periods 2, 3, and 4, respectively. During confinement, subjects will be given a menu that includes 3 meals and an evening snack, except dosing days when breakfast will not be served. Study drug will be administered with 240 mL of water. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. On Day 1 of each period, all subjects will remain fasted until a standard lunch is served approximately 4 hours postdose (after the 4-hour blood collection). Each meal will contain approximately 30% fat (relative to the total calories). The meals served in each period should be identical. Each meal provided in the study clinic should be completed within 30 minutes. The meal start and stop times and whether or not a meal was consumed will be recorded on the source documentation and the electronic case report form (eCRF) for the Day-1 snack and all meals on Day 1 of each period. The study menu should be

documented and submitted to the study file with a copy provided to the sponsor prior to the start of the study.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal. Subjects will remain upright (seated, standing, or ambulatory) for at least 2 hours following administration of study medication, except as necessitated by the occurrence of an adverse event. Subjects will refrain from strenuous exercise throughout the entire course of the study.

## 7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.14.

1. AE. The subject has experienced an 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 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 in the subject's source documentation.
4. Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   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).
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 9.1.10.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

## 7.6 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 7.5. 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 Early Termination Visit.

# 8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications 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 study material.

## 8.1 Study Drug

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to:

- Alogliptin 25 mg film-coated tablets No. 28 (commercially available on the Russian market) manufactured by Takeda (product released by Takeda Ireland)
- Pioglitazone 15 and 30 mg tablets No. 30 manufactured by Pliva Hrvatska d.o.o., Croatia and sourced as commercial packs from the commercial market of Croatia.
- Alogliptin/Pioglitazone FDC 25/15 mg film-coated tablets No. 28 manufactured by Takeda (product released by Takeda Ireland) and sourced as commercial packs from the commercial market under the name NesinaAct. For this clinical study, NesinaAct will be supplied to the site as commercial packs and labeled as SYR-322-4833 BL 25/15.
- Alogliptin/Pioglitazone FDC 25/30 mg film-coated tablets No. 28 manufactured by Takeda (product released by Takeda Ireland) and sourced as commercial packs from the commercial market under the name Incresync. For this clinical study, Incresync will be supplied to the site as commercial packs and labeled as SYR-322-4833 BL 25/30.

All medication sourced by the Sponsor as follows:

- Commercial alogliptin 25 mg tablets, sourced locally from the Russian market.
- Commercial pioglitazone 15 and 30 mg tablets sourced locally from the Croatian market.
- Commercial alogliptin/pioglitazone FDC 25/15 mg tablets and 25/30 mg tablets in commercial packs sourced from Takeda and labeled as SYR-322-4833 BL 25/15 and SYR-322-4833 BL 25/30, respectively.

Each commercial pack supplied will be labeled with a single panel open computer- generated label containing the required information including information “For clinical trial only”

#### *8.1.1.1 Study Drug*

Alogliptin/Pioglitazone FDC 25/15 mg and 25/30 mg tablets are manufactured by Takeda Ireland.

Pioglitazone tablets are manufactured and packed by Pliva Hrvatska d.o.o., Croatia.

Alogliptin tablets are manufactured and packaged by Takeda Pharmaceuticals. These will be supplied to the site as commercial packs sourced from the Russian market and labelled with “for clinical trials use only.”

These will be supplied to the site as commercial packs with a Takeda clinical label that will contain, but will not be limited to, the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, medication identification number, caution statement, directions for use, and storage conditions.

#### *8.1.1.2 Sponsor-Supplied Drug*

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

- Alogliptin, 25 mg.
- Pioglitazone, 15 and 30 mg.
- SYR-322-4833 BL 25/15 mg and SYR-322-4833 BL 25/30 mg (Alogliptin/Pioglitazone FDC, 25/15 mg and 25/30 mg.)

### 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, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Drug supplies must be stored, as defined on the commercial packs provided, in a secure location until dispensed to study subjects or returned to Takeda. Temperature excursions must be reported to the sponsor. In order to protect drug supply from moisture, the container should be kept tightly closed (bottle) or stored in the original package (blister). Do not take a tablet out of the blister foil until the subject is ready to take it.

### 8.1.3 Dose and Regimen

On Day 1 of each period, study medication will be administered at 08:00 (±1) hour with 240 mL of water following a minimum 8-hour fast. On Day 1 of each period, all subjects will remain fasted until a standard lunch is served approximately 4 hours postdose (after the 4-hour blood collection). The sequence of drug intake administration for each subject as described in Table 8.a will follow the randomization schedule. The investigator or investigator's designee will instruct the subject on dosing procedures.

Following administration of study drug, hand-and-mouth checks will be performed to ensure that the dose was swallowed and will be recorded on the source document. Although timing of events requires that each subject receive the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. The actual date and time of administration of the dose of study medication will be recorded on the source documents and the appropriate eCRF.

**Table 8.a Dose and Regimen**

| Group | Dose | Drug Description | | | | |
|---|---|---|---|---|---|---|
| | | Alogliptin/ Pioglitazone FDC 25/15 mg Tablet | Alogliptin/ Pioglitazone FDC 25/30 mg Tablet | Alogliptin 25 mg Tablet | Pioglitazone 15 mg Tablet | Pioglitazone 30 mg Tablet |
| A | SYR-322-4833 BL (25 mg + 15 mg) | 1 Tablet | N/A | N/A | N/A | N/A |
| B | Alogliptin 25 mg + pioglitazone 15 mg | N/A | N/A | 1 Tablet | 1 Tablet | N/A |
| C | SYR-322-4833 BL (25 mg + 30 mg) | N/A | 1 Tablet | N/A | N/A | N/A |
| D | Alogliptin 25 mg + pioglitazone 30 mg | N/A | N/A | 1 Tablet | N/A | 1 Tablet |

### 8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study 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 CRF(s) according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

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

## 8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive a 4-digit medication identification number. The number will be assigned by the clinic site personnel in sequential order beginning with 1001 and ending with 1072. This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

## 8.3 Randomization Code Creation and Storage

The randomization schedule will be generated prior to the start of the study, and will be provided to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

## 8.4 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 signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda 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:

- Continuously monitoring expiration dates if expiration date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- 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 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, expiry/retest date, date and amount dispensed, including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, 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.

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.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

# 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 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

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 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race as described by the subject, height, weight, caffeine consumption, xanthine consumption, alcohol use, reproductive status (including last menstrual period) and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

### 9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study 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.

Any abnormal finding on a predose physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a predose event or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7. Any abnormal findings at Screening or prior to first dose, will exclude the subject from participating.

On subsequent examinations, any abnormal change or new diagnosis as a result of the abnormal change, compared to physical examination prior to first dose, as determined by the investigator, will be recorded as an AE in source documentation and on the AE eCRF described in Section 10.0.

### 9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = weight\ (kg)/height\ (m)^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.56818\ kg/m^2$.

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 $kg/m^2$. If the BMI is used as an entry criterion based on the 18.5 to 30.0 $kg/m^2$ cut-off point, then this determination must be made after rounding.

### 9.1.5 Vital Sign Procedure

Vital signs will include body temperature oral measurement, respiratory rate, sitting blood pressure (resting at least 5 minutes), and pulse (bpm).

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.

### 9.1.6 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. Administration of any concomitant medications will result in exclusion of the subject from the trial. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

### 9.1.7 Documentation of Concurrent Medical Conditions

Any abnormal medical conditions, abnormalities in laboratory, ECG or physical examination findings found at Screening will exclude the subject from participating in this clinical trial.

### 9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Table 9.a lists the tests that will be obtained for each laboratory specimen.

## Table 9.a Clinical Laboratory Tests

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| RBC<br>WBC with differential (Neutrophils, Eosinophils, basophils, Lymphocytes, Monocytes)<br>Hemoglobin<br>Hematocrit<br>Platelets<br>ESR | ALT<br>Albumin<br>Alkaline phosphatase<br>AST<br>Total bilirubin<br>Direct bilirubin (a)<br>Total protein<br>Creatinine<br>Blood urea nitrogen<br>Creatine kinase<br>γ-Glutamyl transferase<br>Potassium<br>Sodium<br>Glucose | pH<br>Specific gravity<br>Protein<br>Glucose<br>Blood<br>Ketones<br>Urine color<br>Presence of bile pigments<br>Microscopic Analysis:<br>RBC/high power field<br>WBC/high power field<br>Epithelial cells, casts, etc |

Diagnostic Screening:

| Serum | Urine (b) |
|---|---|
| HIV test, syphilis test<br>Hepatitis panel, including HBsAg and anti-HCV | Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates and cotinine. |
| **Female Subjects only:** | **Female Subjects only:** |
| FSH (c) | hCG (for pregnancy) for female subjects of child bearing potential |

ALT=alanine aminotransferase, AST= aspartate aminotransferase, ESR=erythrocyte sedimentation rate, FSH=follicle-stimulating hormone, hCG=human chorionic gonadotropin, RBC=red blood cell, WBC=white blood cell.
(a) Direct bilirubin will be measured only if total bilirubin is elevated.
(b) Urine screen for the presence of drugs of abuse will also be conducted on Day-1 and Days 3 and 4 of each study period (alcohol will be measured by administering an alcohol breath test at these time-points).
(c) At Screening, if menopause is suspected (defined as at least 12 months since last regular menses) and subject is not surgically sterile. FSH must be >40 IU/L to confirm menopausal status.

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

If subjects experience ALT or AST >3 ×upper limit of normal (ULN), follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and international normalized ratio [INR]) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible

alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All laboratory abnormalities must be recorded as an AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

### 9.1.9 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 35 days after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use an effective or highly effective method of contraception from the list below.

In addition, they must be advised not to donate ova during this period.

*The following definitions apply for contraception and pregnancy avoidance procedures.*

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than a 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are excluded, highly effective methods of contraception are:

**Non-Hormonal Methods**

- Copper T PLUS condom or spermicide.
- Bilateral Tubal Occlusion.

- Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.

Genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drugs. Therefore, an effective method of contraception where there may be a higher than 1% failure rate can be used. An effective method of contraception is:

**Barrier methods:**

- Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).

Female subjects must discontinue any use of hormonal contraceptives (if applicable), at least 2 months before the start (Day-1) of the trial.

Subjects will be provided with information on effective and highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative urine hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at Check-in (Day-1 of each Period) prior to receiving any dose of study medication.

### 9.1.10 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 35 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, or within 35 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.

If the subject and/or female partner of a male subject agree to the primary care physician being informed, the investigator should notify the primary care physician that the subject or female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the dose that the subject received.

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

### 9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded.

### 9.1.12 PK Sample Collection

#### *9.1.12.1 Collection of Blood for PK Sampling*

Blood samples (one 6-mL sample per scheduled time) for the determination of alogliptin, pioglitazone, and potential pioglitazone M-IV metabolite plasma concentrations will be collected into chilled vacutainers containing anticoagulant potassium ethylenediamine tetra-acetic acid ($K_2$EDTA) according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in Appendix E.

Serial blood samples for determination of alogliptin and pioglitazone will be collected according to Table 9.b.

**Table 9.b Collection of Blood Samples for PK Analysis**

| Analyte | Matrix | Dosing Day | Scheduled Time (hours) |
|---|---|---|---|
| Alogliptin | Plasma | 1 | Predose (within 15 minutes prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose |
| Pioglitazone and (potential) pioglitazone M-IV metabolite | Plasma | 1 | Predose (within 15 minutes prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose |

The actual time of sample collection will be recorded on the source document and eCRF.

Note that bioanalytical data for pioglitazone M-IV metabolite will be collected and stored for possible future use but that plasma concentrations will not be calculated or reported at this time.

#### *9.1.12.2 Bioanalytical Methods*

Plasma concentrations of alogliptin will be measured using a validated high-performance liquid chromatography with tandem mass spectrometry method. Plasma concentrations of pioglitazone will be measured using a validated high-performance liquid chromatography with tandem mass spectrometry method.

### 9.1.13 PK Parameters

The PK parameters of alogliptin and pioglitazone will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated for plasma concentration values of alogliptin and pioglitazone:

| Symbol/Term | Definition |
|---|---|
| **Plasma** | |
| $AUC_{72}$ | Area under the concentration-time curve from the time 0 to time 72 hours. |
| $AUC_t$ | Area under the concentration-time curve from time 0 to time t. |
| CCI | [redacted] |
| $C_{max}$ | Maximum observed concentration. |
| CL/F | Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration. |
| $\lambda_z$ | Terminal disposition phase rate constant. |
| $t_{1/2z}$ | Terminal disposition phase half-life. |
| $t_{max}$ | Time of first occurrence of $C_{max}$. |

### 9.1.14 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If a subject is withdrawn at the screening visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

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

Subject identification numbers assigned to subjects who fail screening should not be reused.

### 9.1.15 Documentation of Randomization

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

## 9.2 Monitoring Subject Dosing Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study drug, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study drug supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

## 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).

### 9.3.1 Screening

Subjects will be screened within 28 days prior to randomization. Screening may consist of 1 or more visits. Subjects will sign an informed consent form at the first visit and return to the clinic in a fasted state for safety laboratory testing at the second visit. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. A screen failure rate of approximately 50% is anticipated. Therefore, an estimated 144 subjects will be screened in order to enroll 72 subjects. See Section 9.1.14 for procedures for documenting screening failures.

### 9.3.2 Study Randomization

Study randomization will take place on Day 1 of Period 1.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized as described in Section 8.2. Subjects will be administered the first dose of test or reference drug in the unit under the supervision of the investigator or designee, as described in Section 8.2. The procedure for documenting Screening failures is provided in Section 9.1.14.

### 9.3.3 Drug Intake/Washout Period

Subjects will be confined to the clinic from Check-in (Day -1) of Dosing Period 1 until the 24-hour blood sample has been collected on Day 2 of Dosing Period 1 and from Day 7 of Dosing Periods 1,

2, and 3 until the 24-hour blood sample has been collected on Day 2 of Dosing Periods 2, 3, and 4, respectively. Subjects will be discharged or released from the unit unless deemed inappropriate by the investigator because of safety concerns. Subjects will return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures.

There is a 7-day washout interval between the dose in each period.

The study consists of a Screening Period (Days -28 to Day-2) and 4 Drug Intake Periods. A washout interval of 7 days (beginning immediately after dosing on Day 1 of Period 1) will separate the doses of each study period. Subjects will be admitted into the clinic on Day -1 (at least 10 hours prior to study drug administration), will be dosed on Day 1 and discharged from the clinic after the 24-hour blood sample has been collected on Day 2 of each period. Blood samples for determination of alogliptin and pioglitazone plasma concentrations will be collected prior to dosing on Day 1 through 72 hours postdose.

### 9.3.4 Final Visit/ Early Termination

If a subject discontinues, the reason for discontinuation must be documented in the source document and eCRF. The PK sample collection should be collected at the Early Termination Visit, if possible and relatively close to a protocol-specified time point. The site may seek guidance. For example, collect samples if early withdrawal is due to an AE, and/or if several hours elapsed since last blood draw.

Final Visit procedures will be performed on Day 4 of Period 4.

For all subjects receiving study drug, the investigator must complete the End of Study eCRF page.

### 9.3.5 Follow-Up Visit/Telephone Call

At 14 days ±2 days following the last dose of study drug a Follow-up telephone call will be made by the site to inquire for any ongoing AEs or SAEs, new AEs or SAEs, and concomitant medications taken since final dose of study medication. Subject who withdrew consent should still be contacted for a safety Follow-up telephone call, but the contact should only be recorded in the medical records and not in the eCRF, according to data protection regulations.

## 9.4 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c

**Table 9.c Approximate Blood Volume**

| Sample Type | Sample Volume (mL) | Number of Samples | | | | | Total Volume (mL) |
|---|---|---|---|---|---|---|---|
| | | Screening | Period 1 | Period 2 | Period 3 | Period 4 | |
| Clinical laboratory test samples | 10 (a) | 1 | 1 | 0 | 0 | 1 | 33 |
| PK samples alogliptin and pioglitazone | 6 | - | 16 | 16 | 16 | 16 | 384 (b) |
| | | | **Total Approximate Blood Sampling Volume** | | | | 417 |

(a) The sample volume at Screening will be 13 mL.
(b) Additionally, up to 52 mL of blood will be discarded at time points when blood is drawn using a catheter.

The approximate total volume of blood collected from one subject for the study is 469 mL.

Blood samples for PK analysis will be collected via venous catheter through the 24-hour postdose PK sample in each period. With use of a peripheral venous catheter, the catheter will be irrigated with 0.5 mL heparinized saline solution (500 ME per 100 mL of 0.9% NaCl) after each blood sampling or after the catheter is inserted, in order to avoid catheter thrombosis. In addition, prior to taking each PK blood sample from the catheter, 1 mL blood will be drawn and discarded, in order to take into account the holdup volume (approximately 0.1 mL) within the catheter. Blood samples will be collected via venipuncture in cases of catheter thrombosis and for outpatient blood sampling at 36, 48, and 72 hours postdose.

# 10.0 PREDOSE EVENTS AND ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Predose AEs

A predose AE 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. Any AE, including abnormalities in laboratory, ECG, vital signs, or physical examination, will exclude the subject from participating in this clinical study.

### 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 dosing.

An AE can therefore be any unfavorable and unintended sign (eg, abnormal laboratory value), 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 AEs

An untoward finding generally may:

- Indicate a new diagnosis.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an 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 an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are considered to be AEs. Repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is allowed.
- 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 an AE.

Pre-existing conditions:

- Subjects with pre-existing medical conditions will not be enrolled to this study.

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE, 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 intensity of AEs:

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

Elective surgeries or procedures:

- Elective surgeries or procedures are not permitted during the trial; should they be required, the subject will be withdrawn.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered 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 |
| | Spontaneous abortion / stillbirth and fetal death |

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

Predose events 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 AEs of Special Interest

An AE of special interest (AESI), 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. Pancreatitis, hypersensitivity, and hepatic events are considered AESIs and full details of the event should be recorded using the relevant AESI forms.

### 10.1.6 Intensity of 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 Relationship of AEs to Study Drug(s)

The relationship (causality) of each AE to study drug(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 medications 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 medications and concurrent treatments. |

### 10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all 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 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 is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

### 10.1.11 Frequency

Episodic AEs (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 Drug

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

### 10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.

- Recovering/resolving – the intensity is lowered by 1 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 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 state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE 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 AE Collection Period*

Collection of AEs will commence from the time the subject signs the informed consent to participate in the study and continue until 14±2 days after Study Exit Visit or the last dose of study medication.

#### *10.2.1.2 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.

All subjects experiencing AEs, whether considered associated with the use of the study drug 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 AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the study drug. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.

4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

#### *10.2.1.3 AEs of Special Interest*

If an AESI, including but not limited to hypersensitivity, pancreatitis, hepatic disorders, occurs during the drug intake period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in a targeted form or an SAE Form. The form should be completed and reported to the SAE email address within 24 hours.

AESI criteria include:

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

The AESIs 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 drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

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

### 10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, a liver function test (LFT) Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

## 10.3 Follow-up of SAEs

If information is 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 European Medicines Agency (EMA), investigators and IRBs or IECs, 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 the study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

## 11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

## 12.0 DATA HANDLING AND RECORDKEEPING

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

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 to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. 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 informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), 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 study site agreement between the investigator and sponsor.

Refer to the 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 statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

### 13.1.1 Analysis Sets

The safety set will include all randomized subjects who receive at least 1 dose of study medication, including subjects who do not complete the study. Subjects in this set will be used for demographic and baseline characteristics as well as safety summaries.

The PK set will consist of all subjects in the safety set who have sufficient plasma concentration data to facilitate the derivation of at least 1 PK parameter. Details regarding how to handle missing data will be predefined in the statistical analysis plan.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Set by sequence and overall. Summary statistics [number of non-missing values (N), mean, standard deviation (SD), median, minimum, and maximum] will be presented for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, ethnicity, race). Individual subject demographic and baseline characteristics data will be listed.

### 13.1.3 PK Analysis

Descriptive statistics (eg, N, mean, SD, median, minimum, and maximum) will be used to summarize the plasma concentrations of alogliptin and pioglitazone by regimen and scheduled sampling time point. Individual plasma concentration data for alogliptin and pioglitazone will be presented in the data listings.

Descriptive statistics (N, mean, SD, SE, percent coefficient of variation [%CV], median, minimum, and maximum) will be used to summarize the PK parameters of alogliptin and pioglitazone for each regimen. Geometric means will be computed for AUCs and $C_{max}$.

Statistical inference to determine if the FDC tablet is bioequivalent to alogliptin and pioglitazone administered as individual tablets will be performed using an analysis of variance (ANOVA) model with effects for regimen, period, sequence, and subjects nested within sequence. The effect due to subject nested within sequence will be considered a random effect in the ANOVA model while all other effects will be treated as fixed. The ANOVA model will be applied to the natural logarithms of $AUC_{72}$ and $C_{max}$ of alogliptin or pioglitazone as dependent variables to compare the test and reference regimens.

Within the framework of ANOVA model for natural logarithms of $AUC_{72}$ and $C_{max}$, the ratios and the 90% confidence intervals (CIs) for the ratios of central values of the test regimen relative to the

reference regimen will be provided. The ratios will be obtained as the antilog of the difference of the LS means on a natural logarithm scale, and the 90% CIs will be obtained by taking the antilog of the 90% CI for the difference between the LS means on the natural logarithmic scale. Bioequivalence between administration of alogliptin and pioglitazone as an FDC tablet and as individual tablets will be concluded if the 90% CIs are within the range of (0.80, 1.25) for $C_{max}$ and $AUC_{72}$.

Alternative statistical analyses will be used if deemed appropriate.

### 13.1.4 Subject Condition Assessments

Subject condition assessments will be performed using the Safety Set. All subject condition assessments, including AEs, clinical laboratory evaluations, 12-lead ECG results, and vital signs will be summarized with descriptive statistics, where appropriate, and presented in the data listings.

All AEs will be coded using MedDRA and presented in the data listings.

A postdose AE is defined as an AE that occurs after the subject receives the first dose of study medication and within 30 days after the last dose of study medication is received. Summary of AEs will include numbers and percentages of subjects experiencing AEs by system organ class and preferred term. AEs will also be summarized based on their intensity and relationship to study medication by system organ class and preferred term. If a subject has more than 1 AE that codes to the same preferred term, the subject will be counted only once for that preferred term within regimen. Similarly, if a subject has more than 1 AE within a system organ class category, the subject will be counted only once in the system organ class category within the regimen. In the intensity summary, a subject will be counted only in the highest intensity category for each preferred term and each organ class. In the relationship to study medication summary, a subject will be counted only in the highest relationship category for each preferred term and each system organ class. Each summary table will include incidences of adverse events for each regimen and overall.

All AE summary tables will be listed in the SAP.

AEs will be summarized using preferred term and primary system organ class.

Individual results for clinical hematology and serum chemistry laboratory tests that are outside of normal range and results that meet Takeda predefined criteria for markedly abnormal values will be considered as clinically significant and identified in summary tables, if applicable. Observed values and change from Baseline will be summarized by regimen. All laboratory values will be presented in the data listings.

Individual vital sign values that meet the Takeda predefined markedly abnormal criteria will be considered as clinically significant and identified in a summary table. The vital sign measurements at predefined time points and change from Baseline will be summarized by regimen. All vital signs data will be presented in the data listing.

Individual ECG measurements that meet the Takeda predefined markedly abnormal criteria will be considered as clinically significant and flagged and summarized in a table. Observed values will be summarized by regimens. All ECG data will be listed in the data listings.

## 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

## 13.3 Determination of Sample Size

A sample size of 72 subjects (18 per sequence) will be enrolled in this 4-period, 4-sequence crossover study. The sample size is appropriate to assess the bioavailability of alogliptin and pioglitazone from the FDC relative to the individual tablets and also provide greater than 80% power for $C_{max}$ of pioglitazone establishing bioequivalence between regimens for both strengths (SYR-322-4833 BL 25 mg+15 mg and SYR-322-4833 BL 25 mg+30 mg). This is based on acceptance ranges of 80% to 125%, the intra-subject variability (%CV) of 33% for $C_{max}$ of pioglitazone; the expected ratios of the central values for $C_{max}$ are between 0.95 and 1.05, and drop-out rate of 14%. Since the intra-subject variability for pioglitazone $AUC_t$, and alogliptin $C_{max}$ and $AUC_t$ is less than 33%, the power for assessing bioequivalence for pioglitazone $AUC_t$ and alogliptin $C_{max}$ and $AUC_t$ are each greater than 80% for both strengths.

# 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 study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), 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 unexpected circumstances arise 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 should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol. Significant protocol violations are entered on the eCRF.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

**Table 14.a Windows for PK Blood Sample Collection**

| Minutes | Nominal Sampling Time |
|---|---|
| no more than 30 minutes predose | 0 hour |
| ±5 | immediately postdose to ≤6 hours |
| ±10 | >6 hours to ≤12 hours postdose |
| ±15 | >12 hours to ≤24 hours |
| ±30 | >24 hours |

## 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. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site 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.

This study will also be conducted in accordance to the following local regulations:

- The Constitution of the Russian Federation.
- Federal Law of the Russian Federation dated 21 November 2011 N 323-FZ "Basic Principles of health protection in the Russian Federation."
- Federal Law of the Russian Federation of 12 April 2010 No. 61-FZ "On Circulation of Medicines" (in up-to-date edition of the Federal Law).
- Government Decree of the Russian Federation of 13 September 2010 No. 714 "Regulations on compulsory life and health insurance of the patient participating in the clinical studies of the drug" (with changes from 18 May 2011).
- National Standard GOST R 52379-2005 RF "Good Clinical Practice."
- Guidelines on Expertise of Drugs edited by A.N. Mironov, Federal State Budgetary Institution Scientific Center of Expertise of Medicinal Drugs, volume I. 2013, Chapter 7.
- Rules for conduction of bioequivalence studies of medicines of the Eurasian Economic Union, version 2.0 dated 20 February 2015.
- Eurasian Economic Union Council, Decision. No. 85, 03 November 2016, on Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Eurasian Economic Union.
- Order of the Ministry of Health of the Russian Federation No. 200n from 01 April 2016 "On approval of the rules of Good Clinical Practice."

### 15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable 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.

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 informed consent form, 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, informed consent form) reviewed; and state the approval date. The sponsor will notify 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.

Study 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 informed consent form, 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 informed consent form, 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 informed consent form 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 informed consent form 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 informed consent form and if applicable, the subject authorization form. The informed consent form, 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 informed consent form, 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 informed consent form, 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.

The subject 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 determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subjects 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 informed consent form 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 informed consent form, 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 informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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 informed consent form.

## 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 trial database or documentation via a subject identification 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 identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, Ministry of Health of Russian Federation, Food and Drug Administration, 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 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 study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

### 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 all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/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 America), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study 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 the sponsor providing this information to callers must provide the sponsor 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 study subjects. Refer to the 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.

Subjects will be provided with their individual insurance policy. Takeda has insured subjects with the following insurance company:

«INGOSSTRAKH» Insurance Company (Pyatnitskaya Street 12, bld.2, Moscow, 117997, Russia)

## 16.0 REFERENCES

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## Appendix A Schedule of Study Procedures

| | | Drug Intake Periods 1 through 4 (a) | | | | | Study Exit (Day 4 of Period 4)/ Early Termination Visit | Follow-up Phone Call (d) |
|---|---|---|---|---|---|---|---|---|
| **Study Day:** | **Days -28 to -2 (b)** | **Day -1 (Check-in)** | **Day 1 (c)** | **Day 2** | **Day 3** | **Day 4 (Periods 1, 2, and 3)** | | |
| Informed consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demographics and medical history | X | | | | | | | |
| Medication history | X | | | | | | | |
| Physical examination | X | X | | | | | X | |
| Vital signs (e) | X | X | X | | | X | X | |
| Height, weight and BMI | X | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X |
| 12-lead ECG (f) | X | X | | | | | X | |
| Clinical laboratory evaluations (g) | X | | X (h) | | | | X | |
| Urine drug, cotinine, and alcohol breath screen | X | X | | | X | X | X | |
| Urine pregnancy test (hCG) (i) | X | X | | | | | X | |
| HBsAg, Anti-HCV, HIV, and syphilis (i) | X | | | | | | | |
| Confinement | | X | X (j) | X (j) | | | | |
| Study drug dosing (k) | | | X | | | | | |
| PK blood collection (l) | | | X | X | X | X | X | |
| Predose/AE assessment (m) | X | X | X | X | X | X | X | X |

Footnotes are on the following page.

(a) There will be at least 7 days between the dose in 1 period and the dose in a subsequent period.
(b) Screening may consist of 1 or more visits. Subjects will sign an informed consent form at the first visit and return to the clinic in a fasted state for safety laboratory testing at the second visit. Screening procedures must be performed within 28 days prior to administration of investigational product.
(c) Day 1 of each drug intake period.
(d) Follow-up phone call will be made 14 ± 2 days after study exit to inquire about any AE or SAEs, and concomitant medications taken since final dose. Any AE/SAE spontaneously reported within 30 days postdose will be included within the database as AEs.
(e) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute). Vital signs will be measured just prior to dosing on Day 1 of periods 1 through 4. 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.
(f) ECG performed at Screening, Check-in (Day -1 of Period 1), and Study Exit Day 4 of Period 4, or if a subject terminates early from the study.
(g) Hematology, serum chemistries, and urinalysis tests will be done at a local laboratory.
(h) Predose hematology, serum chemistries, and urinalysis tests will be done for Period 1 only.
(i) A urine pregnancy test and HBsAg, Anti-HCV, HIV, and syphilis tests will be done locally.
(j) Following the 24-hour blood sample collection on Day 2 of each period, subjects will be discharged from the clinic and will return to the clinic for the 36-hour blood sample collection on Day 2 and on Days 3 and 4 of each period to complete study procedures.
(k) Study drug will be administered on Day 1 of each period at 08:00 (±1) hours, following an 8- hour fast. Dosing may be staggered to help facilitate logistics at the site.
(l) Blood samples for PK obtained predose (within 15 minutes prior to dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. The PK sample should not be collected at the Early Termination Visit if a PK collection is not scheduled.
(m) Predose AEs will be captured immediately following the signing of the informed consent at Screening until dosing on Day 1 of Period 1. The routine collection of AEs will continue through to the follow-up phone call.

## 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. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments, are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. 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 informed consent form 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 informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. 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 informed consent form, the subject 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 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. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form 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 drug(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.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening and throughout the duration of the study, and for 35 days after the last dose of study drug. 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 drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. 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, United States, 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 drug.
- 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, Storage, and Shipment of PK Samples

### Instructions for Processing of Plasma Samples for PK Analysis of Alogliptin and Pioglitazone

1. Collect 6 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All alogliptin and pioglitazone blood samples should be collected into vacutainers containing $K_2$EDTA.
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 (RCF) at room temperature. 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 4 aliquots. A minimum of 0.5 mL needs to be obtained for each sample. Labeling may include protocol number (Alogliptin-1002), sample matrix (ie, plasma), analyte (alogliptin or pioglitazone), randomization sequence number, period, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample). Note: the "SET 1" samples should be transferred first and then the "SET 2" tubes transferred.
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

### Shipping of Plasma Samples Alogliptin and Pioglitazone

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Biological samples (plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order 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.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
5. Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma), number of samples, and "SET 1" on each self-sealing bag.
6. 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 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

7. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study medication (alogliptin, pioglitazone), protocol number (Alogliptin-1002), investigator's name, sample type (ie, plasma) analyte (alogliptin, pioglitazone), subject randomization sequence number, period, 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 self-sealing 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.
8. 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.
9. Place the inventory paperwork (in a large self-sealing 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.
10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
11. Affix an address label to each shipping carton. Complete the address label with the following information:

    Plasma samples for alogliptin and pioglitazone
    PPD

    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, please contact the bioanalytical laboratory.

    For alogliptin and pioglitazone plasma samples, please contact:

PPD

15. 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 Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 02 are indicated. The corresponding text has been revised throughout the protocol.

**Change 1**: Revised descriptions of study drugs to align with local requirements.

The primary change occurs in Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling.

| | |
|---|---|
| Initial wording: | In this protocol, the term study medication refers to:<br>• Alogliptin 25 mg tablets (commercially available on the Russian market).<br>• Pioglitazone 15 and 30 mg tablets manufactured by Takeda, Japan and sourced as commercial packs from the commercial market.<br>• Alogliptin/Pioglitazone FDC 25/15 mg and 25/30 mg tablets manufactured by Takeda, Japan and sourced as commercial packs from the commercial market.<br>All medication sourced by the Sponsor as defined below.<br>• Commercial alogliptin 25 mg tablets, locally available on the Russian market.<br>• Commercial pioglitazone 15 and 30 mg tablets (in commercial packs).<br>• Commercial alogliptin/pioglitazone FDC 25/15 mg tablets and 25/30 mg tablets (in commercial packs).<br>Each commercial pack supplied will be labeled with a single panel open computer-generated label containing the required information. |
| Amended or new wording: | In this protocol, the term study medication refers to:<br>• Alogliptin 25 mg **film-coated** tablets **No. 28** (commercially available on the Russian market) **manufactured by Takeda (product released by Takeda Ireland)**.<br>• Pioglitazone 15 and 30 mg tablets **No. 30** manufactured by **Pliva Hrvatska d.o.o., Croatia** ~~Takeda, Japan~~ and sourced as commercial packs from the commercial market **of Croatia**.<br>• Alogliptin/Pioglitazone FDC 25/15 mg **film-coated** ~~and 25/30 mg~~ tablets **No. 28** manufactured by Takeda~~, Japan~~ **(product released by Takeda Ireland)**, ~~Japan~~ and sourced as commercial packs from the commercial market **under the name NesinaAct. For this clinical study, NesinaAct will be supplied to the site as commercial packs and labeled as SYR-322-4833 BL 25/15**.<br>• **Alogliptin/Pioglitazone FDC 25/30 mg film-coated tablets No. 28 manufactured by Takeda (product released by Takeda Ireland) and sourced as commercial packs from the commercial market under the name** |

**Incresync. For this clinical study, Incresync will be supplied to the site as commercial packs and labeled as SYR-322-4833 BL 25/30.**

All medication sourced by the Sponsor as **follows:** ~~defined below.~~

- Commercial alogliptin 25 mg tablets~~,~~ **sourced** locally ~~available on~~ **from** the Russian market.
- Commercial pioglitazone 15 and 30 mg tablets **sourced locally from the Croatian market** ~~(in commercial packs)~~.
- Commercial alogliptin/pioglitazone FDC 25/15 mg tablets and 25/30 mg tablets ~~(~~in commercial packs~~)~~ **sourced from Takeda and labeled as SYR-322-4833 BL 25/15 and SYR-322-4833 BL 25/30, respectively**.

Each commercial pack supplied will be labeled with a single panel open computer-generated label containing the required information **including information "For clinical trial only"**.

The following sections also contain this change:

- Section 8.1.1.1 Study Drug.
- Section 8.1.1.2 Sponsor-Supplied Drug.

**Change 2:** Corrected inconsistency in length of pregnancy monitoring time after the end of the study.

The primary change occurs in Section 7.2 Exclusion Criteria.

| | |
|---|---|
| Initial wording: | 11. If female, the subject is pregnant (confirmed by a positive pregnancy test) or lactating or intending to become pregnant before, during, or within 30 days after participating in this study; or intending to donate ova during such time period. |
| Amended or new wording: | 11. If female, the subject is pregnant (confirmed by a positive pregnancy test) or lactating or intending to become pregnant before, during, or within ~~30~~ **35** days after participating in this study; or intending to donate ova during such time period. |

**Rationale for Change:**

Corrected inconsistency in length of pregnancy monitoring time after the end of the study.

The following section also contain this change:

- Appendix C Elements of the Subject Informed Consent (item 24).

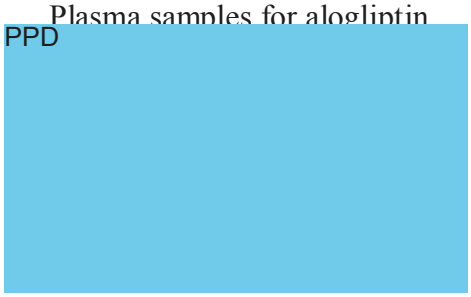
**Change 3:** Updated information for shipping label and contact information for the bioanalytical laboratory.

The primary change occurs in Appendix E Collection, Storage, and Shipment of PK Samples.

| | |
|---|---|
| Initial | 11. Affix an address label to each shipping carton. Complete the address label with the |

wording: following information:

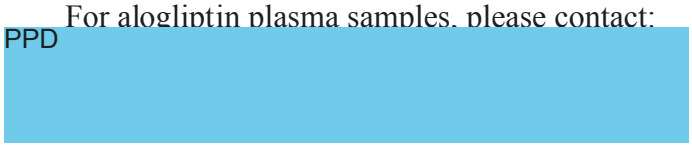
Plasma samples for alogliptin




Plasma samples for pioglitazone


14. After shipping of the samples, please contact the bioanalytical laboratory.

For alogliptin plasma samples, please contact:




For pioglitazone plasma samples, please contact;


Amended or new wording:

11. Affix an address label to each shipping carton. Complete the address label with the following information:

~~Plasma samples for alogliptin~~


Plasma samples for **alogliptin and** pioglitazone

PPD

14. After shipping of the samples, please contact the bioanalytical laboratory.

~~For alogliptin plasma samples, please contact:~~

PPD

For **alogliptin and** pioglitazone plasma samples, please contact:

PPD

**Rationale for Change:**

Updated shipping address label and contact information for the bioanalytical laboratory.

Amendment 02 to A Randomized, Open-Label, Single-Dose, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin (25 mg) and Pioglitazone (15 and 30 mg) When Administered as Individual Tablets and as Fixed-Dose Combination Tablets to Healthy Russian Subjects

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| PPD | Clinical Approval | 06-Mar-2018 18:55 UTC |
| | Biostatistics Approval | 06-Mar-2018 19:41 UTC |
| | Clinical Pharmacology Approval | 09-Mar-2018 13:40 UTC |