Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Comparative Study and a Phase 3, Multicenter, Open-Label, Long-term Study to Evaluate the Efficacy and Safety of SYR-472 When Orally Administered at a Dose of 25 mg Once Weekly in Patients with Type 2 Diabetes Mellitus Complicated by Severe Renal Impairment or End-Stage Renal Failure

NCT Number: NCT02512068

Protocol Approve Date: 12-Sep-2016

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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- 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.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

PROTOCOL

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Comparative Study and a Phase 3, Multicenter, Open-Label, Long-term Study to Evaluate the Efficacy and Safety of SYR-472 When Orally Administered at a Dose of 25 mg Once Weekly in Patients with Type 2 Diabetes Mellitus Complicated by Severe Renal Impairment or End-Stage Renal Failure

A Phase 3, Randomized, Double-Blind, Parallel-Group, Comparative Study and a Phase 3, Multicenter, Open-Label, Long-term Study of SYR-472 (25 mg) in Patients with Type 2 Diabetes Mellitus Complicated by Severe Renal Impairment or End-Stage Renal Failure

Sponsor: Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-chome, Chuo-ku, Osaka

Study Number: SYR-472-3003

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: SYR-472

Date: 12 September 2016 **Amendment Number:** 1

Amendment History:

Date	Amendment Number	Region
1 April 2015	Initial Protocol	All study sites
12 September 2016	Amendment 1	All study sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See Annex 1.

1.2 Principles of Clinical Studies

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

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

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2.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**	
Takeda Pharmaceutical Company Limited	SYR-472	
Title of Protocol:	**IND No.:**	**EudraCT No.:**
A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study and a phase 3, multicenter, open-label, long-term study to evaluate the efficacy and safety of SYR-472 when orally administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure	Not Applicable	Not Applicable
Study Number: SYR-472-3003	**Phase**: 3	

Study Design:

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study (Treatment Period I) and a phase 3, multicenter, open-label, long-term study (Treatment Period II) to evaluate the efficacy and safety of SYR-472 when administered orally at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and with inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug (Table 2.a) in addition to diet and/or exercise therapy (if any).

Table 2.a Concomitant Antidiabetic Drugs Permitted in the Study

Type	Drug Name (Nonproprietary Name or Class)
Rapid-acting insulin secretagogues	Mitiglinide calcium hydrate, repaglinide
α-glucosidase inhibitors	Acarbose, miglitol, voglibose
Insulin preparations	Mixed, intermediate-acting, or long-acting soluble insulin (40 units/day or less*)

*For change in the dosing unit of insulin preparations, see 2 (2) in Section 7.3.

Subjects who enter the screening period after signing informed consent and are considered eligible according to the inclusion and exclusion criteria will be randomly assigned to either of the SYR-472 25 mg group or placebo group. Subjects who are assigned to the SYR-472 25 mg group in Treatment Period I will continue to be treated with SYR-472 25 mg in Treatment Period II, while those assigned to the placebo group will be switched to SYR-472 25 mg in Treatment Period II.

In Treatment Period I, 1 SYR-472 25 mg tablet or placebo tablet will be orally administered once weekly before breakfast. In Treatment Period II, 1 SYR-472 25 mg tablet will be orally administered once weekly before breakfast.

The study period consists of 6 weeks of screening, 52 weeks of treatment, and 2 weeks of follow-up, a total of 60 weeks. The treatment period consists of Treatment Period I (double-blind) from Week 0 to Week 12 and Treatment Period II (open-label) between Week 12 and Week 52. Subjects will visit the site at the start of the screening period (Week -6), Week -2 of the screening period, end of the screening period (Week 0), Week 2 and Week 4 of the treatment period, and at every 4 weeks until Week 52 of the treatment period, and at the end of the follow-up period (Week 54) (total of 18 visits).

The planned sample size is 106 randomized subjects (53 per group).

Objectives:

To evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly using placebo as a control in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug in addition to diet and/or exercise therapy (if any); and to evaluate the long-term safety and efficacy of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure.

Subject Population:

Patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug in addition to diet and/or exercise therapy (if any)

Number of Subjects:	**Number of Sites:**
Randomized: 53 subjects per group, 106 in total (Changed as of 12 September 2016)	Approximately 50 sites

Dose Level:	**Route of Administration:**
<Treatment Period I> One SYR-472 25 mg tablet or placebo tablet will be orally administered once weekly before breakfast. <Treatment Period II> One SYR-472 25 mg tablet will be orally administered once weekly before breakfast.	Oral

Duration of Treatment:	**Period of Evaluation:**
<Treatment Period I> SYR-472 25 mg tablet or placebo tablet: 12 weeks <Treatment Period II> SYR-472 25 mg tablet: 40 weeks	Screening period : 6 weeks Treatment Period I : 12 weeks Treatment Period II: 40 weeks Follow-up period : 2 weeks Total : 60 weeks

Criteria for Inclusion:

1. The subject has a diagnosis of type 2 diabetes mellitus.
2. The subject has a fasting C-peptide value of 0.6 ng/mL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
3. The subject has a hemoglobin value of 10.0 g/dL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
4. The subject has an hemoglobin A1c (HbA1c) value of 7.0% or higher but less than 10.0% at Week -2 of the screening period. However, subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% at Week -2 of the screening period are permitted to be enrolled if they have a glycoalbumin value of 20% or higher.
5. <Subjects with an HbA1c value of 7.0% or higher but less than 10.0% at Week -2 of the screening period>

   The subject has an HbA1c value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the HbA1c value at the start of the screening period (Week -6).

   <Subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% and glycoalbumin value of 20% or higher at Week -2 of the screening period>

   The subject has a glycoalbumin value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the glycoalbumin value at the start of the screening period (Week -6).

   *: rounded to one decimal place
6. The subject has been on a fixed diet and/or exercise therapy (if any) from at least 6 weeks prior to the start of the screening period (Week -6).
7. The subject meets any of the following:
   - The subject has not received any antidiabetic medications (including insulin preparations) from at least 6 weeks prior to the start of the screening period (Week -6).
   - The subject is being treated with 1 oral hypoglycemic drug* starting from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen.

     *: Any of the following medications: mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or

voglibose

- The subject is being treated with 1 insulin preparation** from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen (≤40 units/day).

  **: Any of the following insulin monotherapies: mixed (rapid-acting or ultrarapid-acting insulin containing no more than 30% of volume), intermediate-acting, or long-acting soluble insulin preparations

8. The subject is not undergoing hemodialysis or peritoneal dialysis and has severe renal impairment (creatinine clearance [Ccr] <30 mL/min at the start of the screening period [Week -6]), or the subject is undergoing hemodialysis and has end-stage renal failure.
9. In the opinion of the investigator or sub-investigator, the initiation of hemodialysis or peritoneal dialysis within 12 weeks after initiation of the study drug is not expected. (in cases where the subject is not undergoing hemodialysis or peritoneal dialysis [patients with severe renal impairment])
10. The subject has been undergoing hemodialysis started from at least 6 months prior to informed consent and, in the opinion of the investigator or sub-investigator, the subject is clinically stable. (in cases where the subject is undergoing hemodialysis [patient with end-stage renal failure])
11. The subject is male or female and is aged 20 years or older at the time of informed consent.
12. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use adequate contraception from signing of informed consent until 1 month after the end of the study.
13. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
14. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.

Criteria for Exclusion:

1. The subject has clinically evident hepatic impairment (e.g., AST or ALT >=2.5 times the upper limit of normal or total bilirubin of >=2.0 mg/dL at the start of the screening period [Week -6] or at Week -2 of the screening period).
2. The subject has any serious cardiac diseases, cerebrovascular disorders, or serious pancreatic or hematological diseases (e.g., subjects who require inpatient treatment or had been hospitalized for treatment within 24 weeks prior to the start of the screening period).
3. The subject has severe ketosis, diabetic coma or pre coma, type 1 diabetes, severe infection, or severe external injury, or is immediately before or after surgery.
4. The subject has hemoglobinopathy (sickle cell disease, thalassemia, etc.).
5. The subject experienced hypoglycemia (subjects with a blood glucose value of ≤70 mg/dL or hypoglycemic symptoms) within 6 weeks prior to the start of the screening period or during the screening period (at least twice per week).
6. The subject has inadequately controlled hypertension.
7. For subjects who are being treated with 1 antidiabetic agent, the subject had been treated with at least 2 antidiabetic agents on the day before 6 weeks prior to the start of the screening period (Week -6) (43 days prior to the start of the screening period).
8. The subject has malignancies.
9. The subject has a history of hypersensitivity or allergies to dipeptidyl peptidase-4 (DPP-4) inhibitors.
10. The subject has a history of gastrectomy or small intestinal resection.
11. The subject is a habitual drinker and consumes a daily average of more than 100 mL of alcohol.
12. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse.
13. The subject is required to take excluded medications during the study period.
14. The subject has received SYR-472 in a previous clinical study.
15. The subject received any investigational products (including investigational drugs in a post-marketing clinical study) within 12 weeks prior to the start of the screening period.
16. The subject is participating in other clinical studies at the time of informed consent.

17. If female, the subject is pregnant or lactating or intending to become pregnant from the time of informed consent to within 1 month after the end of the study; or intending to donate ova during such time period.
18. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
19. The subject is hospitalized during the screening period or is deemed as requiring hospitalization during the study period by the investigator or sub-investigator, unless the hospitalization is for short-term evaluations including complete health checkups or for short-term admission for shunt operation (including shunt maintenance).
20. The subject is deemed ineligible for the study for any other reason by the investigator or sub-investigator.

Criteria for Evaluation and Analyses:

1. Primary Endpoints

Efficacy: Change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0)

Safety: Adverse events (AEs)

2. Secondary Endpoints

Efficacy: HbA1c, fasting blood glucose, glycoalbumin

Safety: Vital signs, 12-lead electrocardiogram (ECG), clinical laboratory values

3. Additional Endpoints

Efficacy	: Fasting C-peptide, fasting glucagon, DPP-4 activity, weight
Safety	: Hypoglycemia (only for subjects using insulin preparations)
Pharmacokinetics	: Plasma concentration of unchanged SYR-472 (SYR-472Z)

Statistical Considerations:

1. Efficacy Analysis

<Efficacy endpoint (primary endpoint)>

Change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0)

<Analytical methods (primary analysis)>

The following analyses will be performed in the Full Analysis Set (FAS).

The population mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) will be compared between SYR-472 25 mg group and placebo group based on an analysis of covariance (ANCOVA) model for the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) with factors of treatment group and HbA1c at the end of the screening period (Week 0).

The same ANCOVA model will be used to calculate the least square (LS) mean and the two-sided 95% confidence interval (CI) for each treatment group, as well as the intergroup difference in the LS mean between the treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI.

2. Safety Analysis

<Safety endpoint (primary endpoint)>

AEs

<Analytical methods>

The following analyses will be performed in the Safety Analysis Set.

The following analyses will be performed for TEAEs that occur prior to the start of the study drug for Treatment Period II by treatment group, and for those that occur after the start of SYR-472 25 mg tablet. In the analysis of TEAEs occurring after the start of SYR-472 25 mg tablet, subjects who received SYR-472 25 mg tablet will be included in the analyses.

TEAEs will be coded using MedDRA dictionary. Frequency distributions will be provided using System

Organ Class and Preferred Term for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

Sample Size Justification:

In Study CCT-002, the intergroup difference (two-sided 95% CI) in the mean change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) between the SYR-472 100 mg group and placebo group was -0.56 ([-0.753, -0.367])%. In the same study, the standard deviation of the change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) for each treatment group ranged from 0.523% to 0.628%.

In this study, which will administer SYR-472 at a dose of 25 mg once weekly to patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure, the intergroup difference in the mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) between the SYR-472 25 mg group and placebo group is assumed to be -0.40%, given that the efficacy of SYR-472 25 mg in this study is similar to that of SYR-472 100 mg administered once weekly to patients with type 2 diabetes mellitus not complicated by renal impairment. The common standard deviation in each treatment group is assumed to be 0.80%.

Based on these assumptions, 86 subjects per group will be required to provide a 90% power in a two-sample t-test with a significance level of 5% (two-sided). Therefore, the sample size was set at 90 as randomized subjects per group at the start of the study allowing for the possibility that there exits some subjects whose primary endpoint cannot be evaluated.

However, achievement of the sample size as originally planned at the start of the study was found difficult because there were more than expected numbers of candidate subjects who did not provide consent and who dropped out during screening after providing consent for the study. It was therefore decided to change some of the inclusion and exclusion criteria for this study. After these changes, the ultimate number of subjects randomized and evaluable for the primary endpoints are expected to be around 53 and 51, respectively, per group.

Assuming the number of subjects per group as 51 under these assumptions, the study will provide a 70.6% power in a two-sample t-test with a significance level of 5% (two-sided).

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
Ccr	creatinine clearance
CKD	chronic kidney disease
CRO	contract research organization
DPP-4	dipeptidyl-peptidase-4
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	glucagon like peptide-1
γ-GTP	γ-glutamyl transpeptidase
hCG	human chorionic gonadotropin
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
ICH	International Conference on Harmonisation
INR	international normalized ratio
JAPIC-CTI	Japan Pharmaceutical Information Center- Clinical Trials Information
JDS	The Japan Diabetes Society
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NGSP	national glycohemoglobin standardization program
PGx	pharmacogenomics
PMDA	Pharmaceuticals and Medical Devices Agency
PTE	pretreatment event
QTcF	corrected QT interval by Fridericia formula
SGLT	sodium glucose co- transporter
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Type 2 diabetes mellitus is thought to be mainly caused by a combination of deficient insulin secretion and insulin resistance. Currently used oral medications for type 2 diabetes mellitus (oral hypoglycemic drugs) include sulfonylureas (SUs), rapid-acting insulin secretagogues, and dipeptidyl peptidase-4 (DPP-4) inhibitors, which stimulate insulin secretion; α-glucosidase inhibitors, which delay glucose absorption through the digestive tract; biguanides and thiazolidinediones, which improve insulin resistance: and sodium-glucose co-transporter 2 inhibitors, which exhibit hypoglycemic effects by inhibiting glucose reabsorption in the renal proximal tubules and promoting glucose excretion into the urine.

It has been believed that deficient insulin secretion is mainly associated with the etiology of type 2 diabetes mellitus in Japanese people, and SUs and DPP-4 inhibitors are widely used in the Japanese clinical setting. Compared with other oral hypoglycemic drugs, SUs exhibit more potent hypoglycemic effects, but have longer-lasting insulinotropic effects; therefore, several issues such as hypoglycemic risk and secondary failure resulting from pancreatic beta cell exhaustion associated with long-term treatment have been pointed out.

Meanwhile, DPP-4 inhibitors are oral hypoglycemic drugs that increase the blood concentrations of glucagon-like peptide-1 (GLP-1), and thereby stimulate insulin secretion glucose-dependently. GLP-1 is an incretin hormone that has a crucial role in glucose metabolism, and stimulates insulin secretion glucose-dependently. It is also reported that GLP-1 has a protective effect on pancreatic beta cells and an inhibitory effect on glucagon secretion [1][2].

SYR-472, a DPP-4 inhibitor synthesized by Takeda California, Inc, is expected to stimulate insulin secretion glucose-dependently via an increase of GLP-1 concentration and preserve pancreatic function. SYR-472 is also expected to be useful as a once-weekly oral antidiabetic drug, since prolonged inhibition of DPP-4 activity has been shown in pharmacodynamic assessments.

Of clinical studies conducted in Japan, non-inferiority of SYR-472 100 mg once weekly to alogliptin 25 mg once daily has been assessed in a confirmatory study conducted in Japanese patients with type 2 diabetes mellitus using the once-daily DPP-4 inhibitor alogliptin 25 mg as a comparator (Study CCT-002). In addition, the efficacy and safety of SYR-472 in long-term monotherapy and combination therapy with SYR-472 and other approved oral hypoglycemic drug shaving different mechanisms of action, such as α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, biguanides, and rapid-acting insulin secretagogues have been confirmed (Study-OCT 001, SYR-472 administered 100 mg/week).

Based on these findings, the manufacture and marketing approval of SYR-472 was obtained in March 2015 as a drug for the treatment of type 2 diabetes mellitus administered once weekly.

Currently, a confirmatory and long-term study to evaluate the efficacy and safety of SYR-472 in combination with insulin preparations in patients with type 2 diabetes mellitus (Study CCT-101) is ongoing.

4.2 Rationale for the Proposed Study

The clinical dose of SYR-472 is 100 mg once weekly as a usual dose [3].

Meanwhile, in an overseas clinical pharmacology study in subjects with renal impairment (Study 101; SYR-472 50 mg given as a single dose), the AUC(0-tlqc) of unchanged SYR-472 (SYR-472Z) was 1.56, 2.06, 3.01, and 3.68 times higher in subjects with mild renal impairment (Ccr: >50 to ≤80 mL/min), subjects with moderate renal impairment (Ccr: ≥30 to ≤50 mL/min), subjects with severe renal impairment (Ccr: <30 mL/min, but not performing hemodialysis), and subjects with end-stage renal failure requiring hemodialysis, respectively, as compared with healthy adults (Ccr: >80 mL/min).

Based on this result, there is no need to adjust the SYR-472 dose for patients with mild renal impairment, while half the usual dose (50 mg once weekly) is recommended suitable for patients with moderate renal impairment, and the manufacture and marketing approval of SYR-472 50 mg and 100 mg tablets was obtained. In addition, SYR-472 is contraindicated in patients with severe renal impairment and end-stage renal failure for whom 1-quarter of the usual dose (25 mg once weekly) is considered appropriate [3].

However, since patients with type 2 diabetes mellitus often have renal impairment, it was decided to develop SYR-472 25 mg tablets to contribute to the treatment of diabetes mellitus in patients with severe or more severe renal impairment.
Therefore a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study and a phase 3, multicenter, open-label, long-term study to evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure was planned. Currently, a clinical pharmacology study (Study 1005) to evaluate the bioequivalence of SYR-472 25 mg tablets and 50 mg tablets in healthy adults is ongoing.

Pharmacogenomic (PGx) analysis may be conducted to investigate a possible contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study subjects in PGx sample collection is optional.

As PGx is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research on stored samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly using placebo as a control in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and with inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug in addition to diet and/or exercise therapy (if any); and to evaluate the long-term safety and efficacy of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure.

5.2 Endpoints

5.2.1 Primary Endpoints

Efficacy: Change in Hemoglobin A1c (HbA1c) at the end of Treatment Period I from the end of the screening period (Week 0)

Safety: Adverse Events (AEs)

5.2.2 Secondary Endpoints

Efficacy: HbA1c, fasting blood glucose, glycoalbumin

Safety: Vital signs, 12-lead ECG, clinical laboratory values

5.2.3 Additional Endpoints

Efficacy : Fasting C-peptide, fasting glucagon, DPP-4 activity, weight

Safety : Hypoglycemia (only for subjects using insulin preparations)

Pharmacokinetics : Plasma concentration of SYR-472Z

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study (Treatment Period I) and a phase 3, multicenter, open-label, long-term study (Treatment Period II) using placebo as a control to evaluate the efficacy and safety of SYR-472 when administered orally at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and with inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug (Table 6.a) in addition to diet and/or exercise therapy (if any).

Table 6.a Concomitant Antidiabetic Drugs Permitted in the Study

Type	Drug Name (Nonproprietary Name or Class)
Rapid-acting insulin secretagogues	Mitiglinide calcium hydrate, repaglinide
α-glucosidase inhibitors	Acarbose, miglitol, voglibose
Insulin preparations	Mixed, intermediate-acting, or long-acting soluble insulin (40 units/day or less*)

*: For change in the dosing unit of insulin preparations, see 2 (2) in Section 7.3.

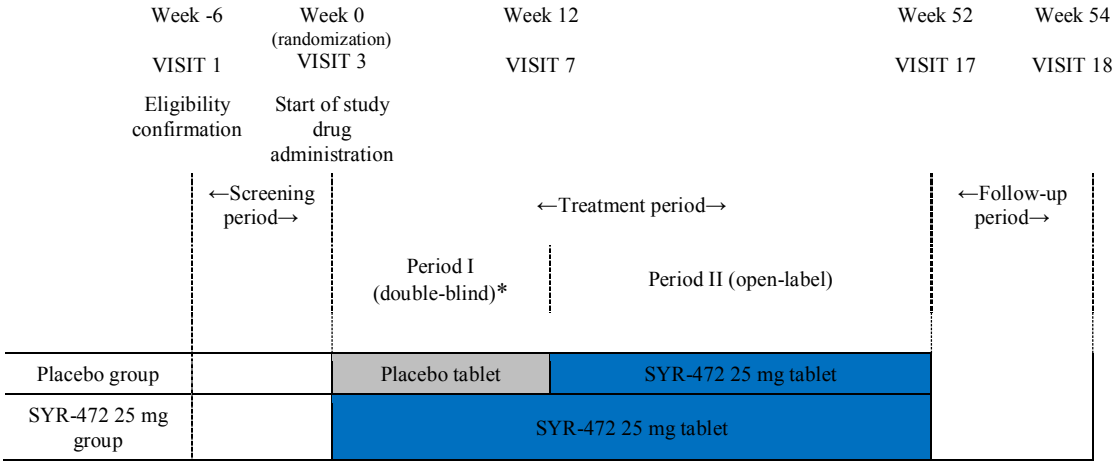
Subjects who enter the screening period after signing informed consent and are considered eligible according to the inclusion and exclusion criteria will be randomly assigned to either of the SYR-472 25 mg group or placebo group. Subjects who are assigned to the SYR-472 25 mg group in Treatment Period I will continue to be treated with SYR-472 25 mg in Treatment Period II, while those assigned to the placebo group will be switched to SYR-472 25 mg in Treatment Period II.

In Treatment Period I, 1 SYR-472 25 mg tablet or placebo tablet will be orally administered once weekly before breakfast. In Treatment Period II, 1 SYR-472 25 mg tablet will be orally administered once weekly before breakfast.

The study period consists of 6 weeks of screening, 52 weeks of treatment, and 2 weeks of follow-up, a total of 60 weeks. The treatment period consists of Treatment Period I (double-blind) between Week 0 and Week 12 and Treatment Period II (open-label) between Week 12 and Week 52. Subjects will visit the site at the start of the screening period (Week -6), Week -2 of the screening period, end of the screening period (Week 0), Week 2 and Week 4 of the treatment period, and at every 4 weeks until Week 52 of the treatment period, and at the end of the follow-up period (Week 54) (total of 18 visits).

The planned sample size is 106 randomized subjects (53 per group).

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



*: The study drug blind in Treatment Period I will be maintained until the end of the study.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

(1) Justification for the study design

This study, which aims to evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure, will be conducted in a double-blind manner until Week 12 of the treatment period (Treatment Period I) to evaluate the efficacy and safety of SYR-472 by comparing the SYR-472 25 mg group and placebo group. Subsequently, it will be conducted in an open-label manner between Week 12 and Week 52 of the treatment period (Treatment Period II) to evaluate the long-term safety of SYR-472.

(2) Justification for the dose and regimen

The usual dose of SYR-472 is 100 mg once weekly; however, since Study 101 showed that the AUC of SYR-472Z in patients with severe renal impairment and end-stage renal failure was 3.01 and 3.68 times higher than that in healthy adults, respectively, 1-quarter of the usual dose is considered appropriate for patients with severe to end-stage renal failure, and a dose of 25 mg once weekly has thus been selected for the study.

(3) Justification for the study period

1) Justification for the Screening Period

The duration of the screening period was set at 6 weeks to select subjects who meet all of the inclusion criteria and none of the exclusion criteria, and to select subjects with a stable HbA1c value in reference to the “the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)” [4].

2) Justification for the treatment period

<Justification for Treatment Period I (double-blind period)>

In Study CCT-002, the change (mean) in HbA1c at Week 8, 12, 16, 20, and 24 of the treatment period following oral administration of SYR-472 at a dose of 100 mg once weekly was -0.39%, -0.40%, -0.38%, -0.34%, and -0.31%, respectively, and the

difference from the placebo group (SYR-472 100 mg group - placebo group) was -0.42%, -0.53%, -0.59%, -0.63%, and -0.52%, respectively. These results suggest that the HbA1c-lowering effect of SYR-472 almost reaches a plateau by Week 12 of treatment. The incidence of AEs including hypoglycemia did not increase depending on the duration of treatment. In addition, the results of Study 101 suggest that administration of 1-quarter (25 mg/week) of the usual dose to patients with severe renal impairment or end-stage renal failure will result in a similar exposure level to that observed in patients with normal renal function. Based on these results, the HbA1c-lowering effect in patients with severe renal impairment or end-stage renal failure will almost reach a plateau by Week 12 when treated at 1-quarter (25 mg/week) of the usual dose, just as observed in patients with normal renal function.

Furthermore, the basic treatment (diet and/or exercise therapy and an antidiabetic drug) of subjects is required to remain fixed from at least 6 weeks prior to the start of the screening period (Week -6) through the end of Treatment Period I in principle, with respect to the possible influence on assessments in the study. However, since strict glycemic control is required especially for patients with type 2 diabetes mellitus complicated by renal impairment, it is considered difficult to continue with fixed fundamental treatment over a long period.

Based on the above considerations, the duration of Treatment Period I was set at 12 weeks as a period during which the efficacy and safety of SYR-472 25 mg can be evaluated in patients with severe renal impairment or end-stage renal failure and with respect to the safety of the subjects.

<Justification for Treatment Period II (open-label period)>

Treatment Period II was set as an open-label period and the total duration of Treatment Periods I and II was set at 1 year (52 weeks) in reference to the “The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions” [5] and “the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)” [4].

<Justification for Follow-up Period>

In Study 101, the elimination half-life (mean) of unchanged SYR-472 following the administration of SYR-472 50 mg under fasted conditions (without breakfast) to patients with severe renal impairment and end-stage renal failure was 88.45 and 107.97 hours, respectively, which were longer than those in matched healthy adults (56.43 and 56.75 hours). Based on these results, the time of assessment at the end of the follow-up period was set at Week 54 by reference to 5 times the elimination half-life (18.4 and 22.5 days, or longer) from the last administration of SYR-472 25 mg tablets (Week 51).

(4) Justification for the primary endpoints

According to “the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)” [4], HbA1c should be used as an efficacy endpoint in phase 3 studies in principle. In addition, the safety of the study drug should be used as the primary endpoint in long-term studies. Therefore, HbA1c at the end of Treatment Period I will be evaluated as the efficacy endpoint and AEs throughout the treatment period will be evaluated as the safety endpoint.

(5) Justification for the secondary endpoints

In reference to "the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)" [4] and based on the results of clinical studies of SYR-472 conducted so far, HbA1c, fasting blood glucose, and glycoalbumin were set as efficacy endpoints, and vital signs, 12-lead ECG, and clinical laboratory test values were set as safety endpoints to evaluate the efficacy and safety of SYR-472 25 mg.

(6) Justification for the inclusion criteria

See Section 7.1.

(7) Justification for the exclusion criteria

See Section 7.2.

(8) Justification for the excluded medications and other exclusions

See Section 7.3.

(9) Justification for the sample size

See Section 13.3.

6.3 Premature Termination or Suspension of Study or Investigational 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 medication 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 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 Investigational Sites

A study site may be terminated prematurely or suspended if the study 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 Investigational Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

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

1. The subject has a diagnosis of type 2 diabetes mellitus.
2. The subject has a fasting C-peptide value of 0.6 ng/mL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
3. The subject has a hemoglobin value of 10.0 g/dL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
4. The subject has an HbA1c value of 7.0% or higher but less than 10.0% at Week -2 of the screening period. However, subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% at Week -2 of the screening period are permitted to be enrolled if they have a glycoalbumin value of 20% or higher.
5. <Subjects with a HbA1c value of 7.0% or higher but less than 10.0% at Week -2 of the screening period>

   The subject has an HbA1c value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the HbA1c value at the start of the screening period (Week -6).

   <Subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% and glycoalbumin value of 20% or higher at Week -2 of the screening period>

   The subject has a glycoalbumin value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the glycoalbumin value at the start of the screening period (Week -6).

   *: rounded to one decimal place
6. The subject has been on a fixed diet and/or exercise therapy (if any) from at least 6 weeks prior to the start of the screening period (Week -6).
7. The subject meets any of the following:

   - The subject has not received any antidiabetic medications (including insulin preparations) from at least 6 weeks prior to the start of the screening period (Week -6).
   - The subject is being treated with 1 oral hypoglycemic drug* starting from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen.

     *: Any of the following medications: mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or voglibose

- The subject is being treated with 1 insulin preparation** from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen (≤40 units/day).

  **: Any of the following insulin monotherapies: mixed (rapid-acting or ultrarapid-acting insulin containing no more than 30% of volume), intermediate-acting, or long-acting soluble insulin preparations

8. The subject is not undergoing hemodialysis or peritoneal dialysis and has severe renal impairment (Ccr <30 mL/min at the start of the screening period [Week -6]), or the subject is undergoing hemodialysis and has end-stage renal failure.
9. In the opinion of the investigator or sub-investigator, the initiation of hemodialysis or peritoneal dialysis within 12 weeks after the initiation of the study drug is not expected. (in cases where the subject is not undergoing hemodialysis or peritoneal dialysis [patients with severe renal impairment])
10. The subject has been undergoing hemodialysis started from at least 6 months prior to informed consent and, in the opinion of the investigator or sub-investigator, the subject is clinically stable. (in cases where the subject is undergoing hemodialysis [patient with end-stage renal failure])
11. The subject is male or female and is aged 20 years or older at the time of informed consent.
12. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use adequate contraception from signing of informed consent until 1 month after the end of the study.

Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

13. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
14. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.

<Justification of Inclusion Criteria>

1. The criterion was set as the target disease of the study.
2. In order to select subjects who maintain capacity for secreting intrinsic insulin, the lower limit of the fasting C-peptide value was set at 0.6 ng/mL based on Training Guidebook for Board Certified Diabetologists (the revised 6th edition)[6].
3. The criterion was set to require a blood hemoglobin value of 10.0 g/dL or higher in reference to the therapeutic target for renal anemia provided in the "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" [7] and "Evidence-based Clinical Practice Guideline for CKD 2013" [8] because a low blood hemoglobin level may affect HbA1c, which is defined as an efficacy endpoint.

4. The criterion was set to define a lower limit of 7.0% because The Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 [9] recommends that the target value of HbA1c should be less than 7.0% from the perspective of prevention of complications. However, since subjects on hemodialysis (patients with end-stage renal failure) may have a low HbA1c level because of factors such as increased immature erythrocytes and shorter erythrocyte lifespan [8], it was decided to take glycoalbumin value additionally into consideration in evaluating subjects with the lower limit of HbA1c level of less than 7.0%. The acceptable glycoalbumin level for such subjects was set at 20% or higher in reference to Best Practice for Diabetic Patients on Hemodialysis 2012 [10]. In addition, the upper limit of HbA1c level was set at 10.0% to exclude subjects with very poor glycemic control with respect to the safety of the subjects.

5. The criterion was set to select subjects with stable glycemic control.

6. The Evidence-based Practice Guideline for the Treatment of Diabetes 2013 [9] recommends to change treatment for patients who cannot achieve the target glucose level despite continuous diet and exercise therapy for 2 to 3 months; therefore, patients who have been on a fixed diet and/or exercise therapy (if any) from at least 6 weeks prior to the start of the screening period (Week -6), i.e., at least 12 weeks prior to the start of Treatment Period I, will be included in this study.

7. The Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)" [4] stipulates that subjects for phase 3 confirmatory and long-term studies should be "adults patients with type 2 diabetes mellitus who are stable and are not treated with any hypoglycemic drugs," while subjects for long-term combination therapy studies should be "adult patients with type 2 diabetes mellitus refractory to 1 of commercially available hypoglycemic drugs treated over a certain period." Therefore, patients who are not using antidiabetic drugs (including insulin preparations) from at least 6 weeks prior to the start of the screening period (Week -6) (i.e., at least 12 weeks prior to the start of Treatment Period I) or those who are using 1 antidiabetic drug (including insulin preparations) at a fixed dose and regimen will be included in this study.
With respect to the safety of the subjects, the antidiabetic drug should be any 1 of mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, voglibose, or insulin preparations, which can be used for patients with severe renal impairment or end-stage renal failure according to the package insert. Similar DPP-4 inhibitors and GLP-1 receptor agonists are excluded with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety.

8. The criterion was set to exclude patients with moderate or milder renal impairment in reference to the "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" [7]. In addition, hemodialysis was set as the only dialysis method permitted for patients with

end-stage renal failure with respect to the possible influence on the evaluation of efficacy and safety in the study.

9. The criterion was set to select subjects who are not receiving hemodialysis and do not have the possibility of starting hemodialysis during Treatment Period I with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety in the study.

10. The criterion was set to select subjects showing stable effects of hemodialysis with respect to the possible influence on the evaluation of efficacy and safety in the study.

11 The criterion was set to define a minimum of 20 years of age at which subjects can voluntarily consent to participation in the study. An upper limit of age was not set in order to collect results in elderly patients as much as possible.

12. to 14. These criteria were set as basic matters to conduct clinical studies.

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 clinically evident hepatic impairment (e.g., AST or ALT >=2.5 times the upper limit of normal or total bilirubin of >=2.0 mg/dL at the start of the screening period [Week -6] or at Week -2 of the screening period).
2. The subject has any serious cardiac diseases, cerebrovascular disorders, or serious pancreatic or hematological diseases (e.g., subjects who require inpatient treatment or had been hospitalized for treatment within 24 weeks prior to the start of the screening period).
3. The subject has severe ketosis, diabetic coma or pre coma, type 1 diabetes, severe infection, or severe external injury, or immediately before or after surgery.
4. The subject has hemoglobinopathy (sickle cell disease, thalassemia, etc.).
5. The subject experienced hypoglycemia (subjects with a blood glucose value of ≤70 mg/dL or hypoglycemic symptoms) within 6 weeks prior to the start of the screening period or during the screening period (at least twice per week).
6. The subject has inadequately controlled hypertension.
7. For subjects who are being treated with 1 antidiabetic agent, the subject had been treated with at least 2 antidiabetic agentss on the day before 6 weeks prior to the start of the screening period (Week -6) (43 days prior to the start of the screening period).
8. The subject has malignancies.
9. The subject has a history of hypersensitivity or allergies to dipeptidyl peptidase-4 (DPP-4) inhibitors.
10. The subject has a history of gastrectomy or small intestinal resection.
11. The subject is a habitual drinker and consumes a daily average of more than 100 mL of alcohol.

12. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse.
13. The subject is required to take excluded medications during the study period.
14. The subject has received SYR-472 in a previous clinical study.
15. The subject received any investigational products (including investigational drugs in a post-marketing clinical study) within 12 weeks prior to the start of the screening period.
16. The subject is participating in other clinical studies at the time of informed consent.
17. If female, the subject is pregnant or lactating or intending to become pregnant from the time of informed consent to within 1 month after the end of the study; or intending to donate ova during such time period.
18. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
19. The subject is hospitalized during the screening period or is deemed as requiring hospitalization during the study period by the investigator or sub-investigator, unless the hospitalization is for short-term evaluations including complete health checkups or for short-term admission for shunt operation (including shunt maintenance).
20. The subject is deemed ineligible for the study for any other reason by the investigator or sub-investigator.

Reference) Alcohol Conversion Chart

Type	Type	Alcohol Content	Volume Equivalent to 100 mL of Alcohol
Brewages	Sake	15%	670 mL (approximately 3 gou)
	Beer	5%	2000 mL (approximately 3 beer bottles in large size)
	Low-malt beer	5%	2000 mL
	Wine	12%	830 mL
	Shaoxing rice wine	18%	560 mL
Distilled liquors	Distilled spirit (Kou-type shouchu)	35%	290 mL
	Distilled spirit (Otsu-type shouchu)	25%	400 mL
	Whiskey	40%	250 mL (approximately 3 double shots)
	Brandy	40%	250 mL (approximately 3 double shots)
	Vodka	40%	250 mL (approximately 3 double shots)
Mixed liquors	Plum wine	13%	770 mL
	Synthetic sake	16%	630 mL

<Justification of Exclusion Criteria>

1., 2., 6., 8., and 9.

These criteria were set with respect to the safety of the subjects.

3. The criterion was set with respect to the safety of the subjects and possible influence on the evaluation of efficacy in the study.

4., 10. to 12., and 14.
These criteria were set because they could influence the evaluation of efficacy and safety in the study.

5. The criterion was set with respect to the safety of the subjects and possible influence on the evaluation of safety in the study.

7. The criterion was set because if excluded antidiabetic drugs are discontinued in order to participate in the study under informed consent, the discontinuation of 2 or more drugs may jeopardize the safety of the subject.

13. The criterion was set with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety in the study.

15. to 18. and 20.
These criteria were set as basic requirements to conduct clinical studies.

19. The criterion was set because intervention in lifestyles due to hospitalization is likely to influence the glucose metabolism of subjects.

7.3 Excluded Medications and Treatments

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

1. Excluded Medications

Use of the following medications is prohibited in each period:

(1) Screening Period and Treatment Period I

- New antidiabetic drugs*
- Other DPP-4 inhibitors and GLP-1 receptor agonists
- Sulfonylureas, biguanides, thiazolidinediones, nateglinide, and SGLT-2 inhibitors

*: Except for antidiabetic drugs that are being used at the start of the screening period (Week -6) and will be concomitantly used during the study period

(2) Treatment Period II and Follow-up Period

- New insulin preparations*
- Other DPP-4 inhibitors and GLP-1 receptor agonists
- Sulfonylureas, biguanides, thiazolidinediones, nateglinide, and SGLT-2 inhibitors

*: Except for insulin preparations that are being used at the start of the screening period (Week -6) and will be concomitantly used during the study period

<Justification for Excluded Medications>

In the screening period and Treatment Period I, changes in the basic treatment are prohibited with respect to the possible influence on the efficacy and safety evaluation of SYR-472. However, the addition of new insulin preparations is only prohibited in Treatment Period II and thereafter with respect to the safety of the subjects. In addition, the use of antidiabetic drugs that are contraindicated in patients with serious renal impairment and SGLT-2 inhibitors that cannot be used over a long period as of the start of the study is prohibited with respect to the safety of the subjects. Furthermore, the use of similar DPP-4 inhibitors and GLP-1 receptor agonists is prohibited with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety.

2. Restricted Medications

(1) Oral Hypoglycemic Agents

1) Screening Period and Treatment Period I

Changes in the dose/regimen or discontinuations/interruptions of oral hypoglycemic drugs that are being used at the start of the screening period (Week -6) and will be concomitantly used in the study period are prohibited.

2) Treatment Period II and Follow-up Period

- Changes in the dose/regimen or discontinuations/interruptions of oral hypoglycemic drugs that are being used at the start of the screening period (Week -6) and will be concomitantly used in the study period are allowed.
- For subjects who are not using any other antidiabetic drug in Treatment Period I (those who are only treated with the study drug), the use of 1 new oral hypoglycemic drug* is allowed at Week 16 of the treatment period and thereafter.

  *: Any 1 of the following medications: mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or voglibose

(2) Insulin Preparations

For subjects who are receiving insulin preparations at the start of the screening period (Week -6) and continue to receive in the study period, insulin preparations should be administered as specified below.

- Type of Insulin Preparation

Any 1 of the mixed (rapid-acting or ultrarapid insulin containing no more than 30% of volume), intermediate-acting, or long-acting soluble insulin preparations should be used alone, and should not be changed throughout the study period.

- Daily Dose (Unit) of Insulin Preparation

1) Screening Period

The daily dose (unit) of insulin preparation should be 40 units/day or less at the start of the screening period (Week -6), and the dose and regimen should not be changed during the screening period (for subjects on hemodialysis who receive different daily doses [unit] of insulin preparation on days of hemodialysis and on other days, each dose and regimen of insulin preparation should not be changed).

2) Treatment Period I

The dose and regimen of insulin preparations at the start of the screening period (Week -6) should be maintained and no changes will allowed, in principle.

However, the investigator or sub-investigator should consider reduction or increase in the daily dose (unit) of insulin preparation if the criteria described below are met. After dose reduction or increase, the unit after reduction or increase should be continued.

Even if reduction in the daily dose (unit) of insulin preparation results in the discontinuation of insulin use, the study may be continued. If increase in the daily dose (unit) of insulin preparation results in a dose exceeding 40 units/day on a continuing basis, the investigator or sub-investigator should determine whether the study should be continued or discontinued, with respect to the safety of the subject.

Criteria for dose reduction: If either criterion (i) or (ii) described below is met, the daily dose (unit) of insulin preparation may be reduced from the unit administered at the start of the screening period (Week -6) by up to 4 units (regardless of the number of changes).

If it is necessary to reduce the dose from the unit administered at the start of the screening period (Week -6) by more than 4 units/day, the study should be discontinued and appropriate measures should be taken.

i) A subject shows hypoglycemic symptoms, and the investigator or sub-investigator considers that the dose reduction of insulin preparation is necessary in view of the safety of the subjects.

ii) Hypoglycemia is suspected since a subject has had 2 or more consecutive self-monitoring blood glucose values of ≤70 mg/dL, and the investigator or sub-investigator considers that the risk of developing hypoglycemia is high.

Criteria for dose increase: If a subject has had 2 or more consecutive self-monitoring blood glucose values of >240 mg/dL and the investigator or sub-investigator considers that the increase of insulin preparation is necessary in view of the safety of the subjects, the daily dose (units) of insulin preparation at the start of the screening period (Week -6) can be increased by up to 4 units (regardless of the number of dose changes).

If dose increase greater than 4 units/day from the unit administered at the start of the screening period (Week -6) is required, the subject will be withdrawn from the study and receive appropriate treatment.

3) Treatment Period II and Follow-up Period

The investigator or sub-investigator should consider reduction or increase in the daily dose (unit) of insulin preparation if the criteria described below are met. After dose reduction or increase, the unit after reduction or increase should be continued.

Even if reduction in the daily dose (unit) of insulin preparation results in the discontinuation of insulin use, the study may be continued. If increase in the daily dose (unit) of insulin preparation results in a dose exceeding 40 units/day on a continuing basis, the investigator or sub-investigator should determine whether the study should be continued or discontinued, with respect to the safety of the subject.

Criteria for dose reduction: If either criterion (i) or (ii) described below is met, reduction in the daily dose (unit) of insulin preparation should be considered.

i) A subject shows hypoglycemic symptoms, and the investigator or sub-investigator considers that the dose reduction of insulin preparation is necessary in view of the safety of the subjects.

ii) Hypoglycemia is suspected since the subject has had 2 or more consecutive self-monitoring blood glucose values of ≤70 mg/dL, and the investigator or sub-investigator considers that the risk of developing hypoglycemia is high.

Criteria for dose increase: If a subject has had 2 or more consecutive self-monitoring blood glucose values of >200 mg/dL and the investigator or sub-investigator considers that the increase of insulin preparation is necessary in view of the safety of the subjects, whether or not to increase the daily dose (units) of insulin preparation should be considered.

<Justification of Restricted Medications>

For oral hypoglycemic drugs, changes in the basic treatment are prohibited in the screening period and Treatment Period I with respect to the possible influence on the efficacy and safety evaluation of SYR-472. In Treatment Period II and the follow-up period, changes in the dose or regimen as well as discontinuations and interruptions are allowed due to ethical considerations on the state of glycemic control for patients with type 2 diabetes mellitus complicated by renal impairment during the 54-week study period. In addition, for subjects who do not receive any other antidiabetic drug in Treatment Period I and still show inadequate glycemic control after 4 weeks following entry into Treatment Period II (Week 16 of the treatment period or thereafter), 1 oral hypoglycemic drug only may be additionally administered at the discretion of the investigator and sub-investigator.

For insulin preparations, changes in the daily dose (unit) are permitted according to the fixed criteria for dose reduction or increase, if the investigator or sub-investigator considers it necessary from the perspective of the safety of the subject.

3. Other medications

For medications other than those specified in 1 and 2 above, the daily dose administered at the start of the screening period (Week -6) should not be changed in Treatment Period I, in principle. However, if deemed necessary for treatment by the investigators due to the occurrence of an AE or other reasons, changes in the daily dose and administration of a new medication are permitted. It should be confirmed that the medication can administered to individuals with renal impairment. Caution should be exercised for medications that require careful use with the study drug and/or antidiabetic drug that is used at the start of the screening period (Week -6) and continued during the study period as recommended in the package insert.

<Justification for Medications Other Than Excluded Medications and Restricted Medications>

The use of other medications is permitted because they are unlikely to influence the evaluation of drug effects unless the daily dose is changed. The daily dose of such medications should not be changed in principle; however, changes in the daily dose and administration of a new medication due to the onset of an AE or other reasons are permitted for ethical considerations.

4. Other prohibitions

Hospitalization is prohibited during the study period, excluding short-term hospitalization for medical evaluations including complete health checkups or for short-term admission for shunt operation (including shunt maintenance).

<Justification for Other prohibitions>

Hospitalization during the study period is prohibited because intervention in lifestyle due to hospitalization is likely to influence glucose metabolism (for example, continued hospitalization for 1 week or longer), possibly affecting the evaluation of drug effects.

7.4 Diet, Fluid, Activity Control

The investigator, sub-investigator, and study coordinator will pay attention to the following requirements and provide necessary instructions to subjects:

1. For diet and/or exercise therapy (if any), the investigator or sub-investigator should provide fixed instructions on diet and/or exercise therapy throughout the study period. In addition, subjects should be instructed to follow instructions on diet and/or exercise therapy.
2. Subjects are required to comply with the prescribed dose and regimen of the study drug. Subjects are required to bring study drug sheet to the study site at each visit.

   Study drug administration should be started after all procedures scheduled for the end of the screening period (Week 0) are completed (the day when study drug administration is started is defined as the first day of dosing). The SYR-472 25 mg or placebo tablets should be taken once weekly (on the same day of the week as the day of the first dose). If a dose is missed, just 1 tablet for the last missed dose should be taken immediately after the subject notices it. Subjects should not take more than 1 SYR-472 25 mg or placebo tablet for several missed doses prior to the next scheduled dosing day.
3. Subjects should be instructed to ingest glucose or sucrose (sugar) in case any hypoglycemic symptom (e.g., unusual hunger, weakness, finger tremor, cold sweat, or palpitations) appears, and to visit the study site immediately if the symptom does not improve despite glucose or sucrose ingestion.
4. For subjects using insulin preparations, the investigator or sub-investigator should provide explanations and instructions about the method and timing of self-monitoring of blood glucose at the end of the screening period (Week 0). Subjects should also be instructed to report the results of self-monitoring of blood glucose to the investigator or sub-investigator at each visit. In particular, they should be instructed to report to the investigator or sub-investigator whether or not they have experienced a blood glucose value exceeding 240 mg/dL (Treatment Period I) or 200 mg/dL (Treatment Period II and follow-up period), or a blood glucose value of 70 mg/dL or less as measured by self-monitoring, and whether or not they have experienced any hypoglycemic symptoms.

   For the time points of self-monitoring of blood glucose, refer to Section 9.1.21.
5. If a subject plans to use any drugs (including over-the-counter [OCT] drugs) other than those prescribed by the investigator or sub-investigator, he/she should consult

with the investigator or sub-investigator in advance, whenever possible. In case these drugs have already been used, immediate notification is required.

6. If a subject plans to visit another physician, prior notification to the investigator or sub-investigator is required. If a subject has already been treated by another physician, immediate notification is required.
7. Subjects are required to be punctual for visit appointments and undergo physical examinations and prescribed tests as scheduled. If a subject cannot visit the study site on the scheduled day, immediate contact to the study site is required.
8. Subjects should be instructed to avoid excessive drinking and eating, extreme changes in diet (e.g. ingestion of a high-fat diet), or excessive exercises and live as usual on the days before the study visit.
9. On the day of the visit, subjects should visit the site under fasted conditions (at least 10 hours of fasting). Subjects using oral hypoglycemic drugs or insulin preparations should visit the site without taking them on the day of the visit.
10. Subjects are required to undergo routine ophthalmologic examination and pay attention to complications including diabetic retinopathy.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.25.

1. **Pretreatment event (PTE) or AE**
   The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   Liver Function Test (LFT) Abnormalities

   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status [value at immediately after the inforned consent for PTEs and at immediately before the initiation of the study drug for AEs], see Section 9.1.9), if the following circumstances occur at any time during study drug treatment:

   – alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
   – ALT or AST >5 × ULN and persists for more than 2 weeks, or
   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

- Renal Function Test Abnormalities

  For subjects not on hemodialysis at the start of the screening period (Week -6) (patients with severe renal impairment), the study drug should be discontinued with

appropriate clinical follow-up until a subject's laboratory profile has returned to normal/baseline status for subjects not on hemodialysis at the start of the screening period (Week -6) (patients with severe renal impairment) if the subject shows worsening of renal function that may necessitate hemodialysis in Treatment Period I and is considered inappropriate to continue the study in the opinion of the investigator or sub-investigator, or if the subject shows rapid worsening of Ccr (e.g., reduction of 30% or more) on 2 consecutive post dose measurements, as compared with the value at the end of the screening period (Week 0), and is considered inappropriate to continue the study in the opinion of the investigator or sub-investigator.

- Serious hypoglycemia

  A serious hypoglycemic symptom (coma, depressed consciousness, etc.; severe enough to require active sugar or glucagon administration or other resuscitation by other people) appears. For reporting in the event of serious hypoglycemia, refer to Section 10.2.1.3 and Section 10.2.2.

- Serious hyperglycemia

  A serious hyperglycemic symptom (coma, ketosis, ketoacidosis, etc.; severe enough to require assistance by other people) appears. For reporting in the event of serious hyperglycemia, refer to Section 10.2.2.

- Acute pancreatitis

  Acute pancreatitis is conclusively diagnosed. For reporting in the event of acute pancreatitis, refer to Section 10.2.1.3.

- Abnormal QT/QTc interval

  Serious arrhythmia or significant QT interval prolongation (e.g., an absolute QTcF interval of >500 msec or a change of >60 msec from the end of the screening period [Week 0]) is observed, and the investigator or sub-investigator considers it inappropriate for the subject to continue the study. For reporting in the event of abnormal QT/QTc interval, refer to Section 10.2.1.3.

2. **Significant protocol deviation.**
   The discovery postrandomization 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 study site and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

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 (i.e., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

5. **Study termination.**
   The sponsor, IRB, or regulatory agency terminates the study.

6. **Pregnancy**.
   The subject is found to be pregnant.

   NOTE: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. **Lack of efficacy.**
   The investigator or sub-investigator has determined that the subject is not benefiting from the study drug treatment; and, continued participation would pose an unacceptable risk to the subject.

8. **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 or sub-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 or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

8.1 Study Drug

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study drug

The study drug refers to SYR-472DB tablets (SYR-472 25 mg tablets or placebo tablets) for Treatment Period I and SYR-472 25 mg tablets for Treatment Period II.

1. Dosage Form

(i) SYR-472DB tablets (for Treatment Period I)

Genetic name: Trelagliptin Succinate (JAN)

Chemical name: 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)-4-fluorobenzonitrile monosuccinate

Dose:

- SYR-472 25 mg tablets: 1 tablet contains 25 mg of SYR-472 (as free base).
- SYR-472 placebo tablets: the placebo tablet does not contain SYR-472.

Dosage form: Yellow-red film-coated tablets

The appearance of SYR-472 25 mg tablets and SYR-472 placebo tablets is mutually indistinguishable.

(ii) SYR-472 25 mg tablets (for Treatment Period II)

Genetic name: Trelagliptin Succinate (JAN)

Chemical name: 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)-4-fluorobenzonitrile monosuccinate

Dose:

- SYR-472 25 mg tablets: 1 tablet contains 25 mg of SYR-472 (as free base).

Dosage form: Yellow-red film-coated tablets

2. Manufacturing

SYR-472 25 mg and placebo tablets were manufactured by Takeda Pharmaceutical Company Limited.

3. Packaging and Labeling

For Treatment Period I, 2 AL-AL blister sheets each containing 8 tablets (12 tablets for 12 weeks and 4 spare tablets for 4 weeks) are packed in a carton for 1 subject. For Treatment Period II, 16 AL-AL blister sheets each containing 8 tablets (128 tablets) are packed in a carton. The study drug for Treatment Period II can be used in common among all subjects in each study site.

The outer carton is labeled with a statement that it is for clinical study use, and with information such as the name of the study drug, quantity, sponsor's name and address, manufacturing number, and storage conditions.

8.1.2 Storage

The study drug will be stored at room temperature (1 to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All drugs provided by the sponsor 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.

8.1.3 Dose and Regimen

In Treatment Period I, 1 tablet of SYR-472 25 mg or placebo will be orally administered once weekly before breakfast. In Treatment Period II, 1 tablet of SYR-472 25 mg tablet will be orally administered once weekly before breakfast.

Subjects will start study drug administration after all procedures scheduled for the end of the screening period (Week 0) are completed. At subsequent visits when the study drug is administered, all specified procedures should be performed prior to study drug administration.

Table 8.a describes the dose and regimen that will be provided to each group in Treatment Period I.

Table 8.a Dose and Regimen (Treatment Period I)

Treatment Group	Dose	Treatment Description	
		SYR-472 25 mg tablet	SYR-472 placebo tablet
SYR-472 25 mg group	SYR-472 25 mg tablet once weekly	×1	×0
Placebo group	SYR-472 placebo tablet once weekly	×0	×1

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. AEs associated with an overdose will be documented on AE CRFs according to Section 10.0, PRETREATMENT EVENTS AND ADVERSE EVENTS.

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

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

8.2 Study drug Assignment and Dispensing Procedures

After judging and confirming eligibility of a subject, the investigator or sub-investigator will assign the subject to receive the study drugs for Treatment Period I which have been allocated to each study site (SYR-472DB tablets) in consecutive order of medication ID number. The investigator or investigator's designee will record the medication ID number in the eCRF.

In Treatment Period II, the investigator or sub-investigator will start administration of the study drug for Treatment Period II (SYR-472 25 mg tablet) after performing all physical examinations/examinations/assessments scheduled for Week 12 in the treatment period.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

Emergency Key Code Administration Center will maintain the subject's study drug blind information until emergency key code breaking or data lock of all subjects.

Since the measured values of study drug concentration and DPP-4 may hinder study drug blind maintenance in this study, the central laboratory institute should retain the final results of these parameters until the key code breaking without disclosing them externally; the final results will be reported to the investigator via the sponsor after the code breaking.

The study blind in Treatment Period I will be maintained until the end of the study.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator or sub-investigator unless information concerning the study drug is necessary for the medical treatment of the subject.

For unblinding a subject, the study drug blind can be obtained by contacting the Emergency Key Code Administration Center (Annex 1).

If the study drug blind is broken, the date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and submitted to the sponsor. The same information (except the time) must be recorded on the eCRF.

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

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and

collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

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 sub-investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

If a subject undergoing hemodialysis (patients with end-stage renal failure) receive hemodialysis on the day of study site visit, all procedures should be performed before hemodialysis.

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.

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

PGx Informed Consent Procedure

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting a blood sample for PGx Research for this study. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, height, weight, body mass index (BMI), alcohol use, smoking status, onset time of type 2 diabetes, presence or absence of hemodialysis and diet and/or exercise therapy.

The BMI will be calculated by the sponsor using the formula provided below:

Metric: BMI = weight (kg)/[height (m)]^2

Height should be measured in centimeters without decimal places (rounding off the first decimal place). For measurement of weight, refer to Section 9.1.5.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes drug name, route of administration, daily dose, and end date of any antidiabetic drug stopped between 24 weeks prior to the end of the screening period (Week 0) and the start of the screening period (Week -6).

9.1.3 Antidiabetic Drugs Administered During the Study

1. Screening Period

For antidiabetic drugs administered at the start of the screening period (Week -6) and concomitantly used during the study period, the drug name, type (for insulin preparations), and daily dose of antidiabetic drugs used at the start of the screening period (Week -6) and concomitantly used during the study will be recorded in the eCRF.

2. Treatment Period I

For antidiabetic drugs administered at the start of the screening period (Week -6) and concomitantly used during the study period, the drug name, type (for insulin preparations), and daily dose of antidiabetic drugs used at the start of the screening period (Week -6) and concomitantly used during the study period will be recorded in the eCRF.

In case concomitant use of other antidiabetic drugs in addition to an antidiabetic drug used at the start of the screening period (Week -6) is judged to be appropriate, the investigator or sub-investigator should record the reason for the judgment in the eCRF according to the following categories:

- Combination therapy is expected to be more effective.
- Development of AEs due to dose increase is concerned.
- The maximum dose has already been administered.
- Others

3. Treatment Period II

For subjects who do not receive 1 antidiabetic drug other than the study drug in Treatment Period I and start the administration of 1 new oral hypoglycemic drug from Week 16 of the Treatment Period II (or thereafter), the drug name, daily dose, date of the start and end of administration, will be recorded in the eCRF.

9.1.4 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.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to the first dose examination.

9.1.5 Weight

Weight should be measured in kilograms to one decimal place (rounding off the second decimal place) under fasting conditions (at least 10 hours of fasting) to avoid the effect of meal. For subjects receiving hemodialysis (patients with end-stage renal failure), dry weight should be used.

9.1.6 Vital Sign Procedure

Vital signs will include sitting or supine blood pressure (resting more than 5 minutes) (systolic and diastolic) and pulse.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug and antidiabetic drugs. 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 drug (including vitamin supplements, over-the-counter medications, and herbal preparations) used from the start of the screening period (Week -6) through the end of the study, and the drug name, route of administration, dates of the start and end of administration, and purpose of use must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

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

9.1.9 Procedures for Clinical Laboratory Samples

Clinical laboratory tests that will be performed in this study are shown in Table 9.a.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 27 mL, and the approximate total volume of blood for the study is 322 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry
Red blood cells	Alanine aminotransferase
Reticulocytes	Aspartate aminotransferase
White blood cells	γ-Glutamyl transferase
Hemoglobin	Alkaline phosphatase
Hematocrit	Total bilirubin
Platelets	Total protein
White blood cells with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Albumin
	Creatinine
	Amylase
Erythrocyte indices (MCV, MCH, MCHC)	Lipase
	Blood urea nitrogen
	Uric acid
	Creatine kinase
	Lactate dehydrogenase
	Total cholesterol
	Triglyceride (fasting)
	Low-density lipoprotein (LDL) cholesterol (direct measurement)
	High-density lipoprotein (HDL) cholesterol
	high-sensitivity CRP
	Potassium
	Sodium
	Calcium
	Chloride
	Phosphate
	Ferrum
Other:	
Pregnancy test (serum or urine human chorionic gonadotropin [hCG]) (female subjects of childbearing potential)	

The central laboratory (Annex 1) will perform laboratory tests listed above except for the pregnancy test. Creatinine clearance (Ccr) will be calculated by the sponsor using the Cockcroft-Gault equation.

Cockcroft-Gault equation
Male: Ccr = {(140 - age) × weight (kg)} / {72 × serum creatinine (mg/dL)}
Female: Ccr = 0.85 × {(140 - age) × weight (kg)} / {72 × serum creatinine (mg/dL)}

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3)

The results of laboratory tests will be returned to the investigator or sub-investigator, who is responsible for reviewing and filing these results. The investigator will also maintain a copy of the reference ranges including their amendment for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent and throughout the duration of the study and for 1 month after the end of the study, female subjects of childbearing potential (i.e.,

nonsterilized, premenopausal female subjects) who are sexually active must use acceptable methods of contraception. Such subjects will be provided with information on acceptable 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 during the course of the study. During the course of the study, regular serum/urine hCG pregnancy tests will be performed, and subjects will receive continued guidance with respect to avoiding pregnancy as part of the study procedures (Appendix A).

In addition to a negative serum/urine hCG pregnancy test at the start of the screening period (Week -6), subjects also must have a negative serum/urine hCG pregnancy test immediately before randomization. Subjects must also have a negative serum or urine hCG pregnancy test at Week 24 and Week 52 of the treatment period or early termination.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during the study period or within 1 month after the end of the study, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Annex 1.

Should the pregnancy occur during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator or sub-investigator. Subjects randomized to placebo who discontinued in Treatment Period I without proceeding to Treatment Period II need not be followed.

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

All reported pregnancies will be followed up to final outcome under the agreement from the female subject, 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.

9.1.12 ECG Procedure

A standard 12-lead ECG will be recorded after a rest of at least 5 minutes. The investigator or sub-investigator will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval.

9.1.13 Fasting C-peptide

Fasting C-peptide will be measured in the central laboratory. Blood samples will be collected under fasting condition (after at least 10-hour fasting).

9.1.14 HbA1c (NGSP Value)

HbA1c will be measured in the central laboratory.

9.1.15 Fasting Blood Glucose, Fasting Glucagon

Fasting blood glucose and fasting glucagon will be measured in the central laboratory. Blood samples will be collected under fasting condition (after at least 10-hour fasting).

9.1.16 Glycoalbumin

Glycoalbumin will be measured in the central laboratory.

9.1.17 DPP-4 Activity

DPP-4 activity will be measured in the central laboratory. For study drug blind maintenance, refer to Section 8.4.

9.1.18 Blood Transfusion

Whether or not the subject has received a blood transfusion from the start of the screening period (Week -6) through the end of the study (if yes, the date and type of blood transfusion [whole blood, red blood cells, plasma, or platelets]) will be recorded in the eCRF.

9.1.19 Introduction of Hemodialysis

For subjects not receiving hemodialysis (patients with severe renal impairment), whether or not hemodialysis has been introduced between the start of the study drug administration (Day 1 of administration of the study drug for Period I) through the end of the study (if yes, the date of introduction) will be recorded in the eCRF.

9.1.20 Presence or Absence of Changes and Compliance of Diet and/or Exercise Therapy

Presence or absence of changes in diet and/or exercise therapy should be recorded in the eCRFs. If any instruction for diet and/or exercise therapy has to be changed, the date, contents, and reason for the change should be recorded in the source document.

Instructions for diet and/or exercise therapy (if any) given to subjects by the investigator or sub-investigator should be consistent throughout the study.

Compliance with diet and/or exercise therapy (if any) will be monitored and rated on the 4-grade scale shown below:

1. Fully complied (90% or more)
2. Almost complied (70% or more)
3. Occasionally complied (50% or more)

4. Rarely complied (less than 50%)

9.1.21 Self-Monitoring of Blood Glucose

For subjects using insulin preparations, the investigator or sub-investigator should explain the method of self-monitoring of blood glucose to subjects at the end of the screening period (Week 0), and instruct them to perform self-monitoring of blood glucose using a finger-stick sampling method in the following occasions:

(1) At scheduled monitoring

i) 57

ii) From the end of the screening period (Week 0) to Day 7 of administration of the study drug for Treatment Period II, self-monitoring of blood glucose should be performed every day before breakfast prior to administration of the study drug and insulin preparation.

iii) From Day 8 of administration of the study drug for Treatment Period II to the end of the follow-up period, self-monitoring of blood glucose should be performed at least once weekly before breakfast prior to administration of the study drug and insulin preparation.

(2) In case any hypoglycemic symptom occurs

If case any hypoglycemic symptom (e.g., unusual hunger, weakness, finger tremor, cold sweat, or palpitations) occurs, self-monitoring of blood glucose should be performed at the time of its development (prior to treatment for hypoglycemia, if any) and disappearance.

If the blood glucose in self-monitoring is 70 mg/dL or less, presence or absence of hypoglycemic symptoms should be confirmed and recorded in the eCRF along with the blood glucose value (refer to Section 9.1.22).

The investigator or sub-investigator will record all applicable blood glucose values in the eCRFs, and report whether the case is significant hypoglycemia or not. If the case is significant hypoglycemia and treatment is required, the contents of treatment should be recorded in the eCRF.

CCI [redacted] (provided by PPD [redacted]) should be used as the self-monitoring of blood glucose kit [11][12][13][14].

9.1.22 Hypoglycemia

For subjects using insulin preparations, the investigator or sub-investigator will confirm the presence or absence of hypoglycemic symptoms that have occurred since the previous visit, at each visit in the study period. If the blood glucose in self-monitoring is 70 mg/dL or less, presence or absence of hypoglycemic symptoms should be confirmed and recorded in the eCRF along with the blood glucose value.

If any hypoglycemic symptoms are observed, values of self-monitoring of blood glucose at the time of development and disappearance of the symptom and whether the case is significant hypoglycemia or not should be recorded in the eCRF. If the case is significant

hypoglycemia and treatment is required, the contents of treatment should also be recorded in the eCRF (refer to Section 9.1.21).

If any hypoglycemic symptoms are observed and no blood glucose values have been obtained at appropriate time points, whether or not the symptoms was caused by decreased blood glucose (≤ 70 mg/dL) should be assessed and recorded in the eCRF.

Hypoglycemia will be classified according to the following definitions in reference to the "The Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised draft)" [4].

- Significant hypoglycemia: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- Symptomatic hypoglycemia: an event accompanied by typical symptoms of hypoglycemia with a measured plasma glucose concentration of ≤70 mg/dL (including self-monitoring of blood glucose values).
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration of ≤70 mg/dL (including sself-monitoring of blood glucose values).
- Probable symptomatic hypoglycemia: an event accompanied by symptoms of hypoglycemia without a plasma glucose determination but that was presumably caused by a plasma glucose concentration of ≤70 mg/dL (including self-monitoring of blood glucose values).
- Relative hypoglycemia: an event accompanied by the typical symptoms of hypoglycemia observed in patients with diabetes mellitus is assumed, but with a measured plasma glucose concentration >70 mg/dL (including self-monitoring of blood glucose values).

9.1.23 PGx Sample Collection

One 5-mL whole blood sample for PGx should be collected at the end of the screening period (Week 0) from the subject who signed PGx informed consent after the study drug was assigned for possible exploratory investigation of markers enabling the prediction of drug response.

PGx sample should not be collected from any subject who has received bone marrow transplant or whole blood transfusion within 6 months of any sample collection.

See the separately created procedure for directions on collecting, handling, and storage of PGx samples.

9.1.24 Pharmacokinetic Sample Collection and Analysis

9.1.24.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (5 mL/sample) for pharmacokinetic analysis of SYR-472Z will be collected in blood sampling tubes containing anticoagulant according to the schedule shown in Appendix A, and plasma will be taken.

Instructions for sample processing and shipment are provided in the separately prepared Procedures for Handling of Biological Samples for Drug Concentration Measurement.

The time of blood sample collection for SYR-472Z measurement, and the date and time of the latest study drug administration will be recorded in the source document and eCRF.

9.1.24.2 Bioanalytical Methods

Plasma concentration of SYR-472Z will be determined by high-performance liquid chromatography with tandem mass spectrometry at PPD (Annex 1).

Measurement will not be performed for samples collected from subjects assigned to the placebo group. In addition, measurement results will be handed as data that will not be recorded in the eCRF, and stored at the laboratory until the breaking of the study drug blind without disclosing externally. After notification of the breaking from randomization personnel, these results will be reported to the investigator through the sponsor. If measurement results are disclosed before breaking the study drug blind, these results can be reported to the sponsor through the randomization personnel after laboratory personnel makes the measurement results blind, such as re-numbering of the drug number, such that the sponsor cannot identify subjects (refer to Section 8.4).

The investigator will confirm these measurement results.

9.1.25 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

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

- PTE/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.
- Pregnancy.
- Other <specify reason>.

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

9.1.26 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment period. If the subject is found to be not eligible for randomization, the investigator or sub-investigator should record the primary reason for failure on the eCRF.

9.1.27 Hospitalization

If a subject is hospitalized for 1 week or longer during the study period due to a SAE or other reasons, the investigator or sub-investigator will record the hospitalization in the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring unused study drugs and antidiabetic drugs (if any) to the study site at each visit.

For the SYR-472DB tablets (for use in Treatment Period I) and the SYR-472 25 mg tablets (for use in Treatment Period II), the date of dosing will be recorded in the eCRFs.

For antidiabetic drugs (if any), treatment compliance during the study will be assessed and rated on the 4-point scale shown below at each visit:

1. Fully Complied (90% or more)
2. Almost complied (70% or more)
3. Occasionally complied (50% or more)
4. Rarely complied (less than 50%)

If a subject is persistently noncompliant with the study drug (e.g., 70% of the allocated medication for the period since the last visit), it may be appropriate to withdraw the subject from the study. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening (Week -6 to Week 0)

At the start of the screening period (Week -6), subjects will be screened within 49 to 35 days prior to study drug administration.

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

Subjects will be randomized at the end of the screening period (Week 0).

See Section 9.1.25 for procedures for documenting screening failures.

9.3.2 Randomization

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 instructed on when to take the first dose of study drug as described in Section 6.1.

9.3.3 Treatment Period

All specified procedures will be performed at each visit.

9.3.4 Week 52 in the Treatment Period or Early Termination

All procedures scheduled for the final visit will be performed at Week 52 of the treatment period.

For subjects prematurely withdrawn from the study during the treatment period, all procedures scheduled for Week 52 will be performed within 7 days after the final dose of the study drug (reckoned from the day after the final dose) whenever possible.

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

9.3.5 Follow-up

All procedures scheduled for the end of the follow-up period will be performed at the 21st day after the final dose of the study drug (reckoned from the day after the final dose).

For subjects who discontinued study treatment, all procedures scheduled for the end of the follow-up period should be performed wherever possible.

9.3.6 Post Study Care

The study drug will not be available upon completion of the subject's participation in the study.

9.4 Biological Sample Retention and Destruction

Samples of 5-mL whole blood collected for PGx will be stored frozen at the storage site for PGx samples (Annex 1).

The collected samples will be retained for 20 years from the day when a first PGx sample was collected during the study.

When subjects request disposal of a stored sample during the retention period, the site will ask the storage site for PGx samples (Annex 1) to destroy the sample via the sponsor according to the procedure. The storage site for PGx samples (Annex 1) will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents (including medical records) have been destroyed which could identify the subject and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when PGx investigation has been conducted, the remaining samples will be destroyed and the results of PGx investigation of anonymized subject will be retained by the sponsor.

The sponsor will build a management system required for protection of the subject's personal information, define standards for collecting store and destruction of samples, and prepare appropriate procedures.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, any abnormal finding related to study procedures (e.g., bruise after blood draw) should be recorded as a PTE. If the subject experiences a worsening or complication of a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators or sub-investigator should ensure that the event term recorded captures the change in the condition from baseline (e.g., "worsening of hypertension").

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

Worsening of PTEs or AEs:

If the subject experiences a worsening or complication of a PTE after starting administration of the study drug, the worsening or complication should be recorded appropriately as an AE. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in intensity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING*
   * The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to 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

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

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

10.1.5 Adverse Events of Special Interest

An AE of Special Interest (AESI) (serious or non-serious) is 1 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 the sponsor (refer to Section 10.2.1.3).

- AESIs: hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs

<Hypoglycemia-related AEs>

Hypoglycemia-related AEs are defined as AESIs since special attention is generally paid to these events in patients with diabetes mellitus using antidiabetic drugs and severe hypoglycemia has been reported in combination therapy with other DPP-4 inhibitors and insulin preparations.

<Intestinal obstruction-related AEs>

Intestinal obstruction-related AEs are defined as AESIs since adverse reaction reports on intestinal obstruction with the use of incretin-related drugs (GLP-1 receptor agonists and other DPP-4 inhibitors) in the same class as SYR-472 have been accumulated.

<Acute pancreatitis-related AEs>

Acute pancreatitis-related AEs are defined as AESIs since adverse reaction reports on acute pancreatitis with the use of incretin-related drugs in the same class as SYR-472 have been accumulated.

<QT/QTc interval prolongation-related AEs>

In thorough QT/QTc study (Study CPH-005), QT/QTc interval prolongation was reported in the SYR-472 800 mg group, although it was not reported in the SYR-472

200 mg group; therefore, QT/QTc interval prolongation-related AEs are defined as AESIs.

10.1.6 Intensity of PTEs and AEs

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

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

10.1.7 Causality of AEs

The relationship of each AE to study drugs will be assessed using the following categories:

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

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs. The relationship should be assessed as Related if the investigator or sub-investigator considers that there is a 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 AEs/PTEs is determined based on the following criteria:

AE/PTE	Start Date
Signs, symptoms, and diseases (diagnosis)	Date when the subject and/or the investigator or sub-investigator first notices the sign or symptom of the AE.
Asymptomatic disease	Date when a definite diagnosis is determined based on the results of diagnostic testing: Even if obsolete findings are indicated based on the test findings or the approximate time of onset can be estimated, the date when a definite diagnosis is made should be recorded.
Worsening of concurrent medical conditions or PTE	Date when the subject or the investigator or sub-investigator first notices worsening of the disease or symptom.
Normal in the initial assessment after signing informed consent but abnormal in the subsequent assessment (for PTEs) Abnormal in the assessment after the start of study drug (for AEs)	Date when the test is performed in which a clinically significant abnormal test value is observed.

Abnormal in the initial assessment after signing informed consent and has worsened at the subsequent assessment (in case of PTEs) Abnormal in the assessment at the start of study drug and has worsened in the subsequent assessment (in case of AEs)	Date when the test is performed in which a medically significant elevation, reduction, increase, or decrease in clinical test values is observed.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The event not has resolved at the end of the study will be assessed as ongoing.

10.1.11 Frequency

Episodic AEs/PTEs (e.g., constipation, diarrhea, or 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

Action taken for the study drug is classified and defined as follows:

Drug withdrawn	A study drug is stopped due to the particular AE (including withdrawal at the discretion of subjects).
Dose not changed	The dose is not changed even after the occurrence of the particular AE. This shall apply in case the study drug is stopped or the dose is reduced or increased due to another AE. This shall also apply, for example, in case the study drug is stopped or the dose is reduced for any reason other than intervention for the particular AE, such as the subject's negligence.
Unknown	For example, attempts to contact the subject are unsuccessful and the course of the particular AE after the start day cannot be followed.
Not Applicable	For example, the study drug has already been completed or stopped before the onset of the particular AE.
Dose interrupted	The study drug is stopped (suspended) due to the particular AE and resumed afterwards (including temporary withdrawal at the discretion of subjects).

10.1.13 Outcome

The outcome of AEs/PTEs is classified as follows:

Classification	Assessment criteria
Recovered/resolved	•The diagnosis or signs/symptoms has disappeared or resolved. •The abnormal laboratory value has improved to the normal range or the value at baseline (AEs), or at the first assessment after signing of informed consent (PTEs). •The event was recorded as another AE in the eCRF due to increased intensity.

Classification	Assessment criteria
Recovering/resolving	•The intensity is lowered by 1 or more stages. •The diagnosis or sign/symptom has almost disappeared. •The abnormal laboratory value improved, but has not returned to the normal range or to baseline (AEs) or to the first assessment after signing of informed consent (PTEs). •The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (in this case, no need to record the date of death).
Not recovered/not resolved	•There is no change in the diagnosis or signs/symptoms, or laboratory values. •The intensity of the diagnosis or signs/symptoms, or laboratory value on the last day of the observed study period has got worse than when it started. •An irreversible congenital anomaly. •The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" (in this case, no need to record the date of death).
Resolved with sequelae	•Dysfunction that interferes with the subject's daily life is observed.
Fatal	•There is a direct relationship between the death and the AE/PTE. A "direct relationship" means that the AE/PTE caused or apparently contributed to the death. •The outcome of another AE/PTE reported in the same subject that is not determined (considered or estimated) to cause the death is not assessed as "fatal." •If the outcome is "fatal," the date of death should be recorded.
Unknown	•The course the AE/PTE after the start day cannot be followed up as specified in the protocol due to hospital change or residence change.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Visit 3). For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Visit 3). Routine collection of AEs will continue until Visit 18.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent or irreversible PTEs). Non-serious

PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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 (permanent or irreversible AEs). All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator or sub-investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date.
- Frequency.
- Intensity.
- Causal relationship between the event and administration of study drug(s) (related or not related).
- Action concerning study drug.
- Outcome of event.
- Causal relationship to study procedure(s) (if related, include the details of the suspected procedure).
- Seriousness.

AEs and serious PTEs should be followed up until the AEs/PTEs have resolved or follow-up is no longer necessary in the opinion of the investigator or sub-investigator.

10.2.1.3 AESI Reporting

If any AESI, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (Annex 1) immediately or within 1 business day of first onset or subject's notification of the event. In addition, AESI Form should be completed by the investigator, and reported to the Safety Information Emergency Call Center (Annex 1) within 10 business days.

The original AESI Form should be submitted to the sponsor.

The criteria for AESIs (hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs) are as described below. If any AE considered to be related to these condition occurs, whether or not to handle it as an AESI should be considered.

<Hypoglycemia-related AEs>

AEs related to hypoglycemia

<Intestinal obstruction-related AEs>

Intestinal obstruction, ileus, subileus, gastrointestinal obstruction, gastrointestinal motility disorder, impaired gastric emptying, and AEs related to these conditions

<Acute pancreatitis-related AEs>

AEs related to pancreatitis or acute pancreatitis

<QT/QTc interval prolongation-related AEs>

Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, disturbance of consciousness, convulsion, ECG QT prolonged, and AEs related to these conditions.

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. Any PTE which meets the SAE criteria described in Section 10.1.4 should be reported in the same manner as SAEs:

An SAE should be reported to the sponsor (Annex 1) within 1 business day of first onset or subject's notification of the event. The investigator should submit the completed SAE form within 10 calendar days.

The information to be reported within 1 business day 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 or sub-investigator's name.
- Name of the study drug(s)
- Causality assessment.

Any SAE spontaneously reported to the investigator or sub-investigator's following the AE collection period should be reported to the sponsor.

10.2.3 Reporting of Abnormal Liver Function Tests

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 or sub-investigator must contact sponsor, and investigate the details of the subject and possible alternative etiologies immediately, 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 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the detailed report becomes available at a later date, the investigator or sub-investigator should complete a follow-up SAE form or provide other written documentation and submit it to the sponsor (Annex 1) immediately. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested by the sponsor or IRB.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, 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, investigators and IRBs/the head of the study site, 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 (contract research organization [CRO]), 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. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug or that would be sufficient to consider changes in the study 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.

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, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs

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

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

The investigator or sub-investigator should complete assessments scheduled for Treatment Period I prior to starting study drug administration in Treatment Period II; the schedule of assessments should not be changed unless there is an appropriate reason.

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

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

The following data will not be recorded directly into the eCRFs:

- Laboratory parameters measured in the central clinical laboratory

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator or sub-investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed (e)CRFs 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 and the head of the institution agree to keep the records stipulated in Section 12.1 and documents include the study-specific documents, identification log of all participating subjects, medical records, source worksheets, all original signed and dated 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. The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

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

13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS), and safety analysis set. The FAS, the main analysis set used for efficacy analysis, is defined as all subjects who were randomized and received at least 1 dose of the study drug. The safety analysis set, is defined as all subjects who received at least 1 dose of the study drug. The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data and supplement descriptions about handling of the unspecified issues, consulting a medical expert as needed. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Key demographics and other baseline characteristics will be summarized for each treatment group and for overall treatment groups using the all randomized subjects.

13.1.3 Efficacy Analysis

(1) Primary endpoint and analytical methods

[Primary endpoint]

Change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0)

[Primary analysis]

The following analyses will be performed in the FAS.

The population mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) will be compared between SYR-472 25 mg group and placebo group based on an analysis of covariance (ANCOVA) model for the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) with factors of treatment group and HbA1c at the end of the screening period (Week 0).

The same ANCOVA model will be used to calculate the least square (LS) mean and the two-sided 95% confidence interval (CI) for each treatment group, as well as the intergroup difference in the LS mean between the treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI.

[Secondary analysis]

For the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0), summary statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and two-sided 95% CI for the mean will be calculated for each treatment group, as well as the intergroup difference in the mean between treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI.

In addition, the same analyses as the primary analysis and the secondary analysis described above will be performed using the PPS to evaluate the robustness of the results in terms of a sensitivity analysis.

[Adjustment for covariates]

The following analyses will be performed in the FAS.

The treatment effect of SYR-472 25 mg will be assessed in consideration of the effects of baseline characteristics based on the ANCOVA model for the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) with factors of treatment group, HbA1c at the end of the screening period (Week 0) and baseline characteristics that may affect the primary endpoint at the blind data review.

(2) Secondary Endpoints and Analysis Methods

[Secondary endpoints]

HbA1c, fasting blood glucose, glycoalbumin

[Analytical methods]

The following analyses will be performed in the FAS.

For each endpoint, summary statistics and two-sided 95% CI for the mean will be calculated for each treatment group at each time point. In addition, summary statistics for the change from the end of the screening period (Week 0) and two-sided 95% CI for the mean will be calculated for each treatment group at each time point, and the intergroup difference in the mean between treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI will be calculated at each time point in Treatment Period I.

For the proportions of subjects who achieved an HbA1c less than 6.0%, 7.0%, or 8.0% at the end of Treatment Period I and Treatment Period II, the proportions and the two-sided 95% CIs will be calculated for each treatment group, and the intergroup difference in the proportions between treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CIs will be calculated at the end of Treatment Period I. In the analysis of each proportion, subjects who did not achieve the relevant target HbA1c at the end of the screening period (Week 0) will be included in the analysis.

(3) Additional efficacy endpoints

See Section 5.2.

(4) Method of data conversion and handling of missing data

Details will be specified separately in the Handling Rules for Analysis Data and the SAP.

(5) Significance level and confidence coefficient

- Significance level: 5% (two-sided tests)
- Confidence coefficient: 95% (two-sided)

13.1.4 Safety Analysis

The following analyses will be performed in the Safety Analysis Set.

(1) Primary endpoint and analytical methods

[Primary endpoint]

AEs

[Analytical methods]

A treatment-emergent adverse event (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug administration.

The following analyses will be performed for each treatment group for TEAEs that occur before the start of the study drug for Treatment Period II, and for those that occur after the start of SYR-472 25 mg tablet. In the analysis of TEAEs occurring after the start of SYR-472 25 mg tablet, subjects who received SYR-472 25 mg tablet will be included in the analyses.

TEAEs will be coded using MedDRA dictionary. Frequency distributions will be provided using System Organ Class and Preferred Term for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

(2) Secondary endpoints and analytical methods

[Secondary endpoints]

Vital signs, 12-lead ECGs, clinical laboratory tests

[Analytical methods]

For continuous variables, the observed values and change from the end of the screening period (Week 0) will be summarized using descriptive statistics for each treatment group at each time point. In addition, case plots over time for observed values will be presented for each treatment group.

For 12-lead ECG findings and laboratory tests classified as "Low", "Normal" or "High" based on the normal reference ranges, shift tables showing the number of subjects in each

category at the end of the screening period (Week 0) and each post-baseline time point will be presented for each treatment group.

(3) Additional endpoint and analysis methods

[Additional endpoint]

Hypoglycemia

[Analytical methods]

The following analyses will be performed for hypoglycemia that occur prior to the start of the study drug for Treatment Period II by treatment group, and for those occurring after the start of SYR-472 25 mg tablet. Subjects who concomitantly receive insulin preparation will be included in these analyses of hypoglycemia, while subjects who concomitantly receive insulin preparation and SYR-472 25 mg tablet will be included in the analysis of hypoglycemia occurring after the start of SYR-472 25 mg tablet.

- Severe hypoglycemia
- Documented symptomatic hypoglycemia
- Asymptomatic hypoglycemia
- Probable symptomatic hypoglycemia
- Relative hypoglycemia

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Randomized subjects: 53 subject per group, 106 in total

(Changed as of 12 September 2016)

<Justification of sample size>

In Study CCT-002, the intergroup difference (two-sided 95% CI) in the mean change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) between the SYR-472 100 mg group and placebo group was -0.56 ([-0.753, -0.367])%. In the same study, the standard deviation of the change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) for each treatment group ranged from 0.523% to 0.628%.

In this study, which will administer SYR-472 at a dose of 25 mg once weekly to patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure, the intergroup difference in the mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) between the SYR-472 25 mg group and placebo group is assumed to be -0.40%, given that the efficacy of SYR-472 25 mg in this study is similar to that of SYR-472 100 mg administered once weekly to patients with type 2 diabetes mellitus not complicated by renal impairment. The common standard deviation in each treatment group is assumed to be 0.80%.

Based on these assumptions, 86 subjects per group will be required to provide a 90% power in a two-sample t-test with a significance level of 5% (two-sided). Therefore, the sample size was set at 90 as randomized subjects per group at the start of the study allowing for the possibility that there exit some subjects whose primary endpoint cannot be evaluated.

However, achievement of the sample size as originally planned at the start of the study was found difficult because there were more than expected numbers of candidate subjects who did not provide consent and who dropped out during screening after providing consent for the study. It was therefore decided to change some of the inclusion and exclusion criteria for this study. After these changes, the ultimate number of subjects randomized and evaluable for the primary endpoints are expected to be around 53 and 51, respectively, per group.

Assuming the number of subjects per group as 51 under these assumptions, the study will provide a 70.6% power in a two-sample t-test with a significance level of 5% (two-sided).

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 the head of the institution guarantee access to source documents by the sponsor or its designee and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator or sub-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 or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., 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 regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable 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. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from reviewing and voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB 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 for approval. The IRB'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 (i.e., before conclusion of study contract). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., 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. Until the site receives notification, no protocol activities, including the informed consent procedure, may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB 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 and sponsor.

Regarding PGx investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for PGx investigations and a research protocol will require prior approval of the company IRB in Japan.

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 describes 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 further explains the nature of the study, its objectives, and potential risks and benefits. 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 approval of the informed consent form. The informed consent form must be approved by the IRB prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

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 must be signed or signed and sealed, and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal name, not nickname, using blue or black ballpoint ink. The investigator or sub-investigator must also sign or sign and seal and date the informed consent form at the time of consent and prior to the subject entering into the study.

Once signed or signed and sealed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs or signs and seals the informed consent in the subject's medical record. Copies of the signed or signed and sealed informed consent form 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.

The informed consent form for PGx research in the clinical study of SYR-472 will be used to explain the PGx research to subjects after the study itself is explained with the informed consent form for the study. PGx samples will be collected from subjects who have consented to both the study and the PGx research.

If a subject requests disposal of stored sample, the procedures described in Section 9.4 should be followed.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited

subject attributes, such as sex, age, or date of birth 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 its monitor or designee's monitor, representatives from any regulatory authority (e.g., Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs 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 (i.e., 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 the study, only the sponsor may make study information available to other study investigators, sub-investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results 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.

The investigator or sub-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 interventional clinical trials it sponsors anywhere in the world on the publicly accessible website (ClinicalTrials.gov and Japan Pharmaceutical Information Center-Clinical Trials Information) before start of study, as defined in Takeda Policy/Standard.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator or sub-investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-57.

[2] Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153-65.

[3] Takeda Pharmaceutical Company Limited. Package Insert for Zafatek® Tablets 100 and 50. March 2015 (Version 1)

[4] "The Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)" [Internet]. 2014 [cited 2014 Dec]; [30 p.]. Available from: http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495140050

[5] The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (PMSB/ELD Notification No. 592 dated 24 May 1995)

[6] The Japan Diabetes Society. Training Guidebook for Board Certified Diabetologists revised 6th Edition. Shindan to Chiryo Sha. Inc. 2014.

[7] Japanese Society of Nephrology. Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. Tokyo-igakusha. 2012.

[8] Japanese Society of Nephrology. Evidence-based Clinical Practice Guideline for CKD 2013. Tokyo-igakusha. 2013.

[9] The Japan Diabetes Society. Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013. Nankodo. 2013.

[10] The Japanese Society for Dialysis Therapy. Best Practice for Diabetic Patients on Hemodialysis 2012. Journal of Japanese Society for Dialysis Therapy. 2013;46(3):311-57.

[11] CCI

[12]

[13]

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PROTOCOL

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Comparative Study and a Phase 3, Multicenter, Open-Label, Long-term Study to Evaluate the Efficacy and Safety of SYR-472 When Orally Administered at a Dose of 25 mg Once Weekly in Patients with Type 2 Diabetes Mellitus Complicated by Severe Renal Impairment or End-Stage Renal Failure

A Phase 3, Randomized, Double-Blind, Parallel-Group, Comparative Study and a Phase 3, Multicenter, Open-Label, Long-term Study of SYR-472 (25 mg) in Patients with Type 2 Diabetes Mellitus Complicated by Severe Renal Impairment or End-Stage Renal Failure

Sponsor: Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-chome, Chuo-ku, Osaka

Study Number: SYR-472-3003

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: SYR-472

Date: 12 September 2016 **Amendment Number:** 1

Amendment History:

Date	Amendment Number	Region
1 April 2015	Initial Protocol	All study sites
12 September 2016	Amendment 1	All study sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See Annex 1.

1.2 Principles of Clinical Studies

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

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

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2.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**	
Takeda Pharmaceutical Company Limited	SYR-472	
Title of Protocol:	**IND No.:**	**EudraCT No.:**
A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study and a phase 3, multicenter, open-label, long-term study to evaluate the efficacy and safety of SYR-472 when orally administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure	Not Applicable	Not Applicable
Study Number: SYR-472-3003	**Phase**: 3	

Study Design:

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study (Treatment Period I) and a phase 3, multicenter, open-label, long-term study (Treatment Period II) to evaluate the efficacy and safety of SYR-472 when administered orally at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and with inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug (Table 2.a) in addition to diet and/or exercise therapy (if any).

Table 2.a Concomitant Antidiabetic Drugs Permitted in the Study

Type	Drug Name (Nonproprietary Name or Class)
Rapid-acting insulin secretagogues	Mitiglinide calcium hydrate, repaglinide
α-glucosidase inhibitors	Acarbose, miglitol, voglibose
Insulin preparations	Mixed, intermediate-acting, or long-acting soluble insulin (40 units/day or less*)

*For change in the dosing unit of insulin preparations, see 2 (2) in Section 7.3.

Subjects who enter the screening period after signing informed consent and are considered eligible according to the inclusion and exclusion criteria will be randomly assigned to either of the SYR-472 25 mg group or placebo group. Subjects who are assigned to the SYR-472 25 mg group in Treatment Period I will continue to be treated with SYR-472 25 mg in Treatment Period II, while those assigned to the placebo group will be switched to SYR-472 25 mg in Treatment Period II.

In Treatment Period I, 1 SYR-472 25 mg tablet or placebo tablet will be orally administered once weekly before breakfast. In Treatment Period II, 1 SYR-472 25 mg tablet will be orally administered once weekly before breakfast.

The study period consists of 6 weeks of screening, 52 weeks of treatment, and 2 weeks of follow-up, a total of 60 weeks. The treatment period consists of Treatment Period I (double-blind) from Week 0 to Week 12 and Treatment Period II (open-label) between Week 12 and Week 52. Subjects will visit the site at the start of the screening period (Week -6), Week -2 of the screening period, end of the screening period (Week 0), Week 2 and Week 4 of the treatment period, and at every 4 weeks until Week 52 of the treatment period, and at the end of the follow-up period (Week 54) (total of 18 visits).

The planned sample size is 106 randomized subjects (53 per group).

Objectives:

To evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly using placebo as a control in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug in addition to diet and/or exercise therapy (if any); and to evaluate the long-term safety and efficacy of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure.

Subject Population:

Patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug in addition to diet and/or exercise therapy (if any)

Number of Subjects:	**Number of Sites:**
Randomized: 53 subjects per group, 106 in total (Changed as of 12 September 2016)	Approximately 50 sites

Dose Level:	**Route of Administration:**
<Treatment Period I> One SYR-472 25 mg tablet or placebo tablet will be orally administered once weekly before breakfast. <Treatment Period II> One SYR-472 25 mg tablet will be orally administered once weekly before breakfast.	Oral

Duration of Treatment:	**Period of Evaluation:**
<Treatment Period I> SYR-472 25 mg tablet or placebo tablet: 12 weeks <Treatment Period II> SYR-472 25 mg tablet: 40 weeks	Screening period : 6 weeks Treatment Period I : 12 weeks Treatment Period II: 40 weeks Follow-up period : 2 weeks Total : 60 weeks

Criteria for Inclusion:

1. The subject has a diagnosis of type 2 diabetes mellitus.
2. The subject has a fasting C-peptide value of 0.6 ng/mL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
3. The subject has a hemoglobin value of 10.0 g/dL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
4. The subject has an hemoglobin A1c (HbA1c) value of 7.0% or higher but less than 10.0% at Week -2 of the screening period. However, subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% at Week -2 of the screening period are permitted to be enrolled if they have a glycoalbumin value of 20% or higher.
5. <Subjects with an HbA1c value of 7.0% or higher but less than 10.0% at Week -2 of the screening period>

   The subject has an HbA1c value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the HbA1c value at the start of the screening period (Week -6).

   <Subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% and glycoalbumin value of 20% or higher at Week -2 of the screening period>

   The subject has a glycoalbumin value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the glycoalbumin value at the start of the screening period (Week -6).

   *: rounded to one decimal place
6. The subject has been on a fixed diet and/or exercise therapy (if any) from at least 6 weeks prior to the start of the screening period (Week -6).
7. The subject meets any of the following:
   - The subject has not received any antidiabetic medications (including insulin preparations) from at least 6 weeks prior to the start of the screening period (Week -6).
   - The subject is being treated with 1 oral hypoglycemic drug* starting from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen.

     *: Any of the following medications: mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or

voglibose

- The subject is being treated with 1 insulin preparation** from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen (≤40 units/day).

  **: Any of the following insulin monotherapies: mixed (rapid-acting or ultrarapid-acting insulin containing no more than 30% of volume), intermediate-acting, or long-acting soluble insulin preparations

8. The subject is not undergoing hemodialysis or peritoneal dialysis and has severe renal impairment (creatinine clearance [Ccr] <30 mL/min at the start of the screening period [Week -6]), or the subject is undergoing hemodialysis and has end-stage renal failure.
9. In the opinion of the investigator or sub-investigator, the initiation of hemodialysis or peritoneal dialysis within 12 weeks after initiation of the study drug is not expected. (in cases where the subject is not undergoing hemodialysis or peritoneal dialysis [patients with severe renal impairment])
10. The subject has been undergoing hemodialysis started from at least 6 months prior to informed consent and, in the opinion of the investigator or sub-investigator, the subject is clinically stable. (in cases where the subject is undergoing hemodialysis [patient with end-stage renal failure])
11. The subject is male or female and is aged 20 years or older at the time of informed consent.
12. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use adequate contraception from signing of informed consent until 1 month after the end of the study.
13. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
14. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.

Criteria for Exclusion:

1. The subject has clinically evident hepatic impairment (e.g., AST or ALT >=2.5 times the upper limit of normal or total bilirubin of >=2.0 mg/dL at the start of the screening period [Week -6] or at Week -2 of the screening period).
2. The subject has any serious cardiac diseases, cerebrovascular disorders, or serious pancreatic or hematological diseases (e.g., subjects who require inpatient treatment or had been hospitalized for treatment within 24 weeks prior to the start of the screening period).
3. The subject has severe ketosis, diabetic coma or pre coma, type 1 diabetes, severe infection, or severe external injury, or is immediately before or after surgery.
4. The subject has hemoglobinopathy (sickle cell disease, thalassemia, etc.).
5. The subject experienced hypoglycemia (subjects with a blood glucose value of ≤70 mg/dL or hypoglycemic symptoms) within 6 weeks prior to the start of the screening period or during the screening period (at least twice per week).
6. The subject has inadequately controlled hypertension.
7. For subjects who are being treated with 1 antidiabetic agent, the subject had been treated with at least 2 antidiabetic agents on the day before 6 weeks prior to the start of the screening period (Week -6) (43 days prior to the start of the screening period).
8. The subject has malignancies.
9. The subject has a history of hypersensitivity or allergies to dipeptidyl peptidase-4 (DPP-4) inhibitors.
10. The subject has a history of gastrectomy or small intestinal resection.
11. The subject is a habitual drinker and consumes a daily average of more than 100 mL of alcohol.
12. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse.
13. The subject is required to take excluded medications during the study period.
14. The subject has received SYR-472 in a previous clinical study.
15. The subject received any investigational products (including investigational drugs in a post-marketing clinical study) within 12 weeks prior to the start of the screening period.
16. The subject is participating in other clinical studies at the time of informed consent.

17. If female, the subject is pregnant or lactating or intending to become pregnant from the time of informed consent to within 1 month after the end of the study; or intending to donate ova during such time period.
18. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
19. The subject is hospitalized during the screening period or is deemed as requiring hospitalization during the study period by the investigator or sub-investigator, unless the hospitalization is for short-term evaluations including complete health checkups or for short-term admission for shunt operation (including shunt maintenance).
20. The subject is deemed ineligible for the study for any other reason by the investigator or sub-investigator.

Criteria for Evaluation and Analyses:

1. Primary Endpoints

Efficacy: Change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0)

Safety: Adverse events (AEs)

2. Secondary Endpoints

Efficacy: HbA1c, fasting blood glucose, glycoalbumin

Safety: Vital signs, 12-lead electrocardiogram (ECG), clinical laboratory values

3. Additional Endpoints

Efficacy	: Fasting C-peptide, fasting glucagon, DPP-4 activity, weight
Safety	: Hypoglycemia (only for subjects using insulin preparations)
Pharmacokinetics	: Plasma concentration of unchanged SYR-472 (SYR-472Z)

Statistical Considerations:

1. Efficacy Analysis

<Efficacy endpoint (primary endpoint)>

Change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0)

<Analytical methods (primary analysis)>

The following analyses will be performed in the Full Analysis Set (FAS).

The population mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) will be compared between SYR-472 25 mg group and placebo group based on an analysis of covariance (ANCOVA) model for the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) with factors of treatment group and HbA1c at the end of the screening period (Week 0).

The same ANCOVA model will be used to calculate the least square (LS) mean and the two-sided 95% confidence interval (CI) for each treatment group, as well as the intergroup difference in the LS mean between the treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI.

2. Safety Analysis

<Safety endpoint (primary endpoint)>

AEs

<Analytical methods>

The following analyses will be performed in the Safety Analysis Set.

The following analyses will be performed for TEAEs that occur prior to the start of the study drug for Treatment Period II by treatment group, and for those that occur after the start of SYR-472 25 mg tablet. In the analysis of TEAEs occurring after the start of SYR-472 25 mg tablet, subjects who received SYR-472 25 mg tablet will be included in the analyses.

TEAEs will be coded using MedDRA dictionary. Frequency distributions will be provided using System

Organ Class and Preferred Term for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

Sample Size Justification:

In Study CCT-002, the intergroup difference (two-sided 95% CI) in the mean change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) between the SYR-472 100 mg group and placebo group was -0.56 ([-0.753, -0.367])%. In the same study, the standard deviation of the change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) for each treatment group ranged from 0.523% to 0.628%.

In this study, which will administer SYR-472 at a dose of 25 mg once weekly to patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure, the intergroup difference in the mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) between the SYR-472 25 mg group and placebo group is assumed to be -0.40%, given that the efficacy of SYR-472 25 mg in this study is similar to that of SYR-472 100 mg administered once weekly to patients with type 2 diabetes mellitus not complicated by renal impairment. The common standard deviation in each treatment group is assumed to be 0.80%.

Based on these assumptions, 86 subjects per group will be required to provide a 90% power in a two-sample t-test with a significance level of 5% (two-sided). Therefore, the sample size was set at 90 as randomized subjects per group at the start of the study allowing for the possibility that there exits some subjects whose primary endpoint cannot be evaluated.

However, achievement of the sample size as originally planned at the start of the study was found difficult because there were more than expected numbers of candidate subjects who did not provide consent and who dropped out during screening after providing consent for the study. It was therefore decided to change some of the inclusion and exclusion criteria for this study. After these changes, the ultimate number of subjects randomized and evaluable for the primary endpoints are expected to be around 53 and 51, respectively, per group.

Assuming the number of subjects per group as 51 under these assumptions, the study will provide a 70.6% power in a two-sample t-test with a significance level of 5% (two-sided).

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
Ccr	creatinine clearance
CKD	chronic kidney disease
CRO	contract research organization
DPP-4	dipeptidyl-peptidase-4
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	glucagon like peptide-1
γ-GTP	γ-glutamyl transpeptidase
hCG	human chorionic gonadotropin
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
ICH	International Conference on Harmonisation
INR	international normalized ratio
JAPIC-CTI	Japan Pharmaceutical Information Center- Clinical Trials Information
JDS	The Japan Diabetes Society
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NGSP	national glycohemoglobin standardization program
PGx	pharmacogenomics
PMDA	Pharmaceuticals and Medical Devices Agency
PTE	pretreatment event
QTcF	corrected QT interval by Fridericia formula
SGLT	sodium glucose co- transporter
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Type 2 diabetes mellitus is thought to be mainly caused by a combination of deficient insulin secretion and insulin resistance. Currently used oral medications for type 2 diabetes mellitus (oral hypoglycemic drugs) include sulfonylureas (SUs), rapid-acting insulin secretagogues, and dipeptidyl peptidase-4 (DPP-4) inhibitors, which stimulate insulin secretion; α-glucosidase inhibitors, which delay glucose absorption through the digestive tract; biguanides and thiazolidinediones, which improve insulin resistance: and sodium-glucose co-transporter 2 inhibitors, which exhibit hypoglycemic effects by inhibiting glucose reabsorption in the renal proximal tubules and promoting glucose excretion into the urine.

It has been believed that deficient insulin secretion is mainly associated with the etiology of type 2 diabetes mellitus in Japanese people, and SUs and DPP-4 inhibitors are widely used in the Japanese clinical setting. Compared with other oral hypoglycemic drugs, SUs exhibit more potent hypoglycemic effects, but have longer-lasting insulinotropic effects; therefore, several issues such as hypoglycemic risk and secondary failure resulting from pancreatic beta cell exhaustion associated with long-term treatment have been pointed out.

Meanwhile, DPP-4 inhibitors are oral hypoglycemic drugs that increase the blood concentrations of glucagon-like peptide-1 (GLP-1), and thereby stimulate insulin secretion glucose-dependently. GLP-1 is an incretin hormone that has a crucial role in glucose metabolism, and stimulates insulin secretion glucose-dependently. It is also reported that GLP-1 has a protective effect on pancreatic beta cells and an inhibitory effect on glucagon secretion [1][2].

SYR-472, a DPP-4 inhibitor synthesized by Takeda California, Inc, is expected to stimulate insulin secretion glucose-dependently via an increase of GLP-1 concentration and preserve pancreatic function. SYR-472 is also expected to be useful as a once-weekly oral antidiabetic drug, since prolonged inhibition of DPP-4 activity has been shown in pharmacodynamic assessments.

Of clinical studies conducted in Japan, non-inferiority of SYR-472 100 mg once weekly to alogliptin 25 mg once daily has been assessed in a confirmatory study conducted in Japanese patients with type 2 diabetes mellitus using the once-daily DPP-4 inhibitor alogliptin 25 mg as a comparator (Study CCT-002). In addition, the efficacy and safety of SYR-472 in long-term monotherapy and combination therapy with SYR-472 and other approved oral hypoglycemic drug shaving different mechanisms of action, such as α-glucosidase inhibitors, thiazolidinediones, sulfonylureas, biguanides, and rapid-acting insulin secretagogues have been confirmed (Study-OCT 001, SYR-472 administered 100 mg/week).

Based on these findings, the manufacture and marketing approval of SYR-472 was obtained in March 2015 as a drug for the treatment of type 2 diabetes mellitus administered once weekly.

Currently, a confirmatory and long-term study to evaluate the efficacy and safety of SYR-472 in combination with insulin preparations in patients with type 2 diabetes mellitus (Study CCT-101) is ongoing.

4.2 Rationale for the Proposed Study

The clinical dose of SYR-472 is 100 mg once weekly as a usual dose [3].

Meanwhile, in an overseas clinical pharmacology study in subjects with renal impairment (Study 101; SYR-472 50 mg given as a single dose), the AUC(0-tlqc) of unchanged SYR-472 (SYR-472Z) was 1.56, 2.06, 3.01, and 3.68 times higher in subjects with mild renal impairment (Ccr: >50 to ≤80 mL/min), subjects with moderate renal impairment (Ccr: ≥30 to ≤50 mL/min), subjects with severe renal impairment (Ccr: <30 mL/min, but not performing hemodialysis), and subjects with end-stage renal failure requiring hemodialysis, respectively, as compared with healthy adults (Ccr: >80 mL/min).

Based on this result, there is no need to adjust the SYR-472 dose for patients with mild renal impairment, while half the usual dose (50 mg once weekly) is recommended suitable for patients with moderate renal impairment, and the manufacture and marketing approval of SYR-472 50 mg and 100 mg tablets was obtained. In addition, SYR-472 is contraindicated in patients with severe renal impairment and end-stage renal failure for whom 1-quarter of the usual dose (25 mg once weekly) is considered appropriate [3].

However, since patients with type 2 diabetes mellitus often have renal impairment, it was decided to develop SYR-472 25 mg tablets to contribute to the treatment of diabetes mellitus in patients with severe or more severe renal impairment.
Therefore a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study and a phase 3, multicenter, open-label, long-term study to evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure was planned. Currently, a clinical pharmacology study (Study 1005) to evaluate the bioequivalence of SYR-472 25 mg tablets and 50 mg tablets in healthy adults is ongoing.

Pharmacogenomic (PGx) analysis may be conducted to investigate a possible contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study subjects in PGx sample collection is optional.

As PGx is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research on stored samples.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly using placebo as a control in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and with inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug in addition to diet and/or exercise therapy (if any); and to evaluate the long-term safety and efficacy of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure.

5.2 Endpoints

5.2.1 Primary Endpoints

Efficacy: Change in Hemoglobin A1c (HbA1c) at the end of Treatment Period I from the end of the screening period (Week 0)

Safety: Adverse Events (AEs)

5.2.2 Secondary Endpoints

Efficacy: HbA1c, fasting blood glucose, glycoalbumin

Safety: Vital signs, 12-lead ECG, clinical laboratory values

5.2.3 Additional Endpoints

Efficacy : Fasting C-peptide, fasting glucagon, DPP-4 activity, weight

Safety : Hypoglycemia (only for subjects using insulin preparations)

Pharmacokinetics : Plasma concentration of SYR-472Z

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study (Treatment Period I) and a phase 3, multicenter, open-label, long-term study (Treatment Period II) using placebo as a control to evaluate the efficacy and safety of SYR-472 when administered orally at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure and with inadequate glycemic control despite diet and/or exercise therapy (if any) or despite treatment with 1 antidiabetic drug (Table 6.a) in addition to diet and/or exercise therapy (if any).

Table 6.a Concomitant Antidiabetic Drugs Permitted in the Study

Type	Drug Name (Nonproprietary Name or Class)
Rapid-acting insulin secretagogues	Mitiglinide calcium hydrate, repaglinide
α-glucosidase inhibitors	Acarbose, miglitol, voglibose
Insulin preparations	Mixed, intermediate-acting, or long-acting soluble insulin (40 units/day or less*)

*: For change in the dosing unit of insulin preparations, see 2 (2) in Section 7.3.

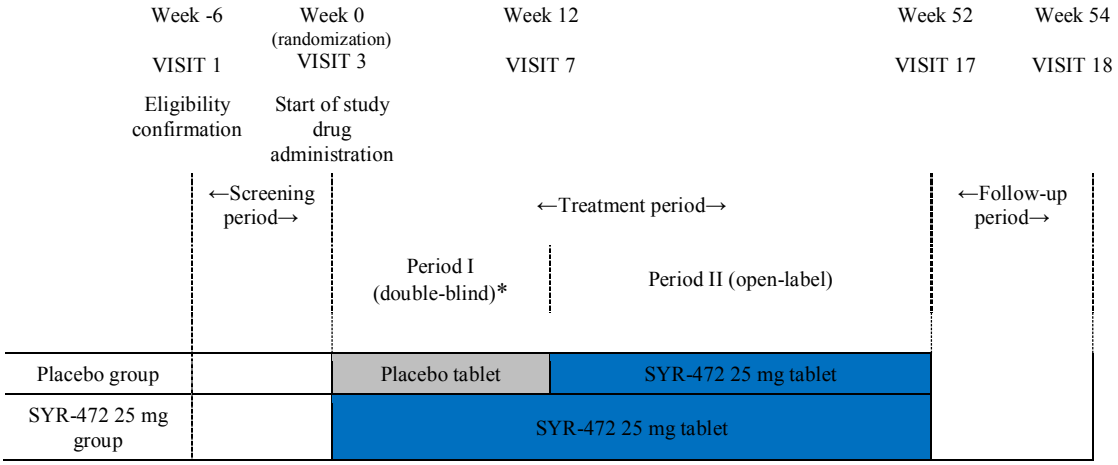
Subjects who enter the screening period after signing informed consent and are considered eligible according to the inclusion and exclusion criteria will be randomly assigned to either of the SYR-472 25 mg group or placebo group. Subjects who are assigned to the SYR-472 25 mg group in Treatment Period I will continue to be treated with SYR-472 25 mg in Treatment Period II, while those assigned to the placebo group will be switched to SYR-472 25 mg in Treatment Period II.

In Treatment Period I, 1 SYR-472 25 mg tablet or placebo tablet will be orally administered once weekly before breakfast. In Treatment Period II, 1 SYR-472 25 mg tablet will be orally administered once weekly before breakfast.

The study period consists of 6 weeks of screening, 52 weeks of treatment, and 2 weeks of follow-up, a total of 60 weeks. The treatment period consists of Treatment Period I (double-blind) between Week 0 and Week 12 and Treatment Period II (open-label) between Week 12 and Week 52. Subjects will visit the site at the start of the screening period (Week -6), Week -2 of the screening period, end of the screening period (Week 0), Week 2 and Week 4 of the treatment period, and at every 4 weeks until Week 52 of the treatment period, and at the end of the follow-up period (Week 54) (total of 18 visits).

The planned sample size is 106 randomized subjects (53 per group).

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



*: The study drug blind in Treatment Period I will be maintained until the end of the study.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

(1) Justification for the study design

This study, which aims to evaluate the efficacy and safety of SYR-472 when administered at a dose of 25 mg once weekly in patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure, will be conducted in a double-blind manner until Week 12 of the treatment period (Treatment Period I) to evaluate the efficacy and safety of SYR-472 by comparing the SYR-472 25 mg group and placebo group. Subsequently, it will be conducted in an open-label manner between Week 12 and Week 52 of the treatment period (Treatment Period II) to evaluate the long-term safety of SYR-472.

(2) Justification for the dose and regimen

The usual dose of SYR-472 is 100 mg once weekly; however, since Study 101 showed that the AUC of SYR-472Z in patients with severe renal impairment and end-stage renal failure was 3.01 and 3.68 times higher than that in healthy adults, respectively, 1-quarter of the usual dose is considered appropriate for patients with severe to end-stage renal failure, and a dose of 25 mg once weekly has thus been selected for the study.

(3) Justification for the study period

1) Justification for the Screening Period

The duration of the screening period was set at 6 weeks to select subjects who meet all of the inclusion criteria and none of the exclusion criteria, and to select subjects with a stable HbA1c value in reference to the “the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)” [4].

2) Justification for the treatment period

<Justification for Treatment Period I (double-blind period)>

In Study CCT-002, the change (mean) in HbA1c at Week 8, 12, 16, 20, and 24 of the treatment period following oral administration of SYR-472 at a dose of 100 mg once weekly was -0.39%, -0.40%, -0.38%, -0.34%, and -0.31%, respectively, and the

difference from the placebo group (SYR-472 100 mg group - placebo group) was -0.42%, -0.53%, -0.59%, -0.63%, and -0.52%, respectively. These results suggest that the HbA1c-lowering effect of SYR-472 almost reaches a plateau by Week 12 of treatment. The incidence of AEs including hypoglycemia did not increase depending on the duration of treatment. In addition, the results of Study 101 suggest that administration of 1-quarter (25 mg/week) of the usual dose to patients with severe renal impairment or end-stage renal failure will result in a similar exposure level to that observed in patients with normal renal function. Based on these results, the HbA1c-lowering effect in patients with severe renal impairment or end-stage renal failure will almost reach a plateau by Week 12 when treated at 1-quarter (25 mg/week) of the usual dose, just as observed in patients with normal renal function.

Furthermore, the basic treatment (diet and/or exercise therapy and an antidiabetic drug) of subjects is required to remain fixed from at least 6 weeks prior to the start of the screening period (Week -6) through the end of Treatment Period I in principle, with respect to the possible influence on assessments in the study. However, since strict glycemic control is required especially for patients with type 2 diabetes mellitus complicated by renal impairment, it is considered difficult to continue with fixed fundamental treatment over a long period.

Based on the above considerations, the duration of Treatment Period I was set at 12 weeks as a period during which the efficacy and safety of SYR-472 25 mg can be evaluated in patients with severe renal impairment or end-stage renal failure and with respect to the safety of the subjects.

<Justification for Treatment Period II (open-label period)>

Treatment Period II was set as an open-label period and the total duration of Treatment Periods I and II was set at 1 year (52 weeks) in reference to the “The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions” [5] and “the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)” [4].

<Justification for Follow-up Period>

In Study 101, the elimination half-life (mean) of unchanged SYR-472 following the administration of SYR-472 50 mg under fasted conditions (without breakfast) to patients with severe renal impairment and end-stage renal failure was 88.45 and 107.97 hours, respectively, which were longer than those in matched healthy adults (56.43 and 56.75 hours). Based on these results, the time of assessment at the end of the follow-up period was set at Week 54 by reference to 5 times the elimination half-life (18.4 and 22.5 days, or longer) from the last administration of SYR-472 25 mg tablets (Week 51).

(4) Justification for the primary endpoints

According to “the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)” [4], HbA1c should be used as an efficacy endpoint in phase 3 studies in principle. In addition, the safety of the study drug should be used as the primary endpoint in long-term studies. Therefore, HbA1c at the end of Treatment Period I will be evaluated as the efficacy endpoint and AEs throughout the treatment period will be evaluated as the safety endpoint.

(5) Justification for the secondary endpoints

In reference to "the Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)" [4] and based on the results of clinical studies of SYR-472 conducted so far, HbA1c, fasting blood glucose, and glycoalbumin were set as efficacy endpoints, and vital signs, 12-lead ECG, and clinical laboratory test values were set as safety endpoints to evaluate the efficacy and safety of SYR-472 25 mg.

(6) Justification for the inclusion criteria

See Section 7.1.

(7) Justification for the exclusion criteria

See Section 7.2.

(8) Justification for the excluded medications and other exclusions

See Section 7.3.

(9) Justification for the sample size

See Section 13.3.

6.3 Premature Termination or Suspension of Study or Investigational 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 medication 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 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 Investigational Sites

A study site may be terminated prematurely or suspended if the study 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 Investigational Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

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

1. The subject has a diagnosis of type 2 diabetes mellitus.
2. The subject has a fasting C-peptide value of 0.6 ng/mL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
3. The subject has a hemoglobin value of 10.0 g/dL or higher at the start of the screening period (Week -6) and Week -2 of the screening period.
4. The subject has an HbA1c value of 7.0% or higher but less than 10.0% at Week -2 of the screening period. However, subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% at Week -2 of the screening period are permitted to be enrolled if they have a glycoalbumin value of 20% or higher.
5. <Subjects with a HbA1c value of 7.0% or higher but less than 10.0% at Week -2 of the screening period>

   The subject has an HbA1c value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the HbA1c value at the start of the screening period (Week -6).

   <Subjects on hemodialysis (patients with end-stage renal failure) with an HbA1c value of less than 7.0% and glycoalbumin value of 20% or higher at Week -2 of the screening period>

   The subject has a glycoalbumin value difference between the start of the screening period (Week -6) and Week -2 of the screening period within 10.0%* of the glycoalbumin value at the start of the screening period (Week -6).

   *: rounded to one decimal place
6. The subject has been on a fixed diet and/or exercise therapy (if any) from at least 6 weeks prior to the start of the screening period (Week -6).
7. The subject meets any of the following:

   - The subject has not received any antidiabetic medications (including insulin preparations) from at least 6 weeks prior to the start of the screening period (Week -6).
   - The subject is being treated with 1 oral hypoglycemic drug* starting from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen.

     *: Any of the following medications: mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or voglibose

- The subject is being treated with 1 insulin preparation** from at least 6 weeks prior to the start of the screening period (Week -6) at a fixed dose and regimen (≤40 units/day).

  **: Any of the following insulin monotherapies: mixed (rapid-acting or ultrarapid-acting insulin containing no more than 30% of volume), intermediate-acting, or long-acting soluble insulin preparations

8. The subject is not undergoing hemodialysis or peritoneal dialysis and has severe renal impairment (Ccr <30 mL/min at the start of the screening period [Week -6]), or the subject is undergoing hemodialysis and has end-stage renal failure.
9. In the opinion of the investigator or sub-investigator, the initiation of hemodialysis or peritoneal dialysis within 12 weeks after the initiation of the study drug is not expected. (in cases where the subject is not undergoing hemodialysis or peritoneal dialysis [patients with severe renal impairment])
10. The subject has been undergoing hemodialysis started from at least 6 months prior to informed consent and, in the opinion of the investigator or sub-investigator, the subject is clinically stable. (in cases where the subject is undergoing hemodialysis [patient with end-stage renal failure])
11. The subject is male or female and is aged 20 years or older at the time of informed consent.
12. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use adequate contraception from signing of informed consent until 1 month after the end of the study.

Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

13. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
14. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.

<Justification of Inclusion Criteria>

1. The criterion was set as the target disease of the study.
2. In order to select subjects who maintain capacity for secreting intrinsic insulin, the lower limit of the fasting C-peptide value was set at 0.6 ng/mL based on Training Guidebook for Board Certified Diabetologists (the revised 6th edition)[6].
3. The criterion was set to require a blood hemoglobin value of 10.0 g/dL or higher in reference to the therapeutic target for renal anemia provided in the "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" [7] and "Evidence-based Clinical Practice Guideline for CKD 2013" [8] because a low blood hemoglobin level may affect HbA1c, which is defined as an efficacy endpoint.

4. The criterion was set to define a lower limit of 7.0% because The Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 [9] recommends that the target value of HbA1c should be less than 7.0% from the perspective of prevention of complications. However, since subjects on hemodialysis (patients with end-stage renal failure) may have a low HbA1c level because of factors such as increased immature erythrocytes and shorter erythrocyte lifespan [8], it was decided to take glycoalbumin value additionally into consideration in evaluating subjects with the lower limit of HbA1c level of less than 7.0%. The acceptable glycoalbumin level for such subjects was set at 20% or higher in reference to Best Practice for Diabetic Patients on Hemodialysis 2012 [10]. In addition, the upper limit of HbA1c level was set at 10.0% to exclude subjects with very poor glycemic control with respect to the safety of the subjects.

5. The criterion was set to select subjects with stable glycemic control.

6. The Evidence-based Practice Guideline for the Treatment of Diabetes 2013 [9] recommends to change treatment for patients who cannot achieve the target glucose level despite continuous diet and exercise therapy for 2 to 3 months; therefore, patients who have been on a fixed diet and/or exercise therapy (if any) from at least 6 weeks prior to the start of the screening period (Week -6), i.e., at least 12 weeks prior to the start of Treatment Period I, will be included in this study.

7. The Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)" [4] stipulates that subjects for phase 3 confirmatory and long-term studies should be "adults patients with type 2 diabetes mellitus who are stable and are not treated with any hypoglycemic drugs," while subjects for long-term combination therapy studies should be "adult patients with type 2 diabetes mellitus refractory to 1 of commercially available hypoglycemic drugs treated over a certain period." Therefore, patients who are not using antidiabetic drugs (including insulin preparations) from at least 6 weeks prior to the start of the screening period (Week -6) (i.e., at least 12 weeks prior to the start of Treatment Period I) or those who are using 1 antidiabetic drug (including insulin preparations) at a fixed dose and regimen will be included in this study.
With respect to the safety of the subjects, the antidiabetic drug should be any 1 of mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, voglibose, or insulin preparations, which can be used for patients with severe renal impairment or end-stage renal failure according to the package insert. Similar DPP-4 inhibitors and GLP-1 receptor agonists are excluded with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety.

8. The criterion was set to exclude patients with moderate or milder renal impairment in reference to the "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" [7]. In addition, hemodialysis was set as the only dialysis method permitted for patients with

end-stage renal failure with respect to the possible influence on the evaluation of efficacy and safety in the study.

9. The criterion was set to select subjects who are not receiving hemodialysis and do not have the possibility of starting hemodialysis during Treatment Period I with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety in the study.

10. The criterion was set to select subjects showing stable effects of hemodialysis with respect to the possible influence on the evaluation of efficacy and safety in the study.

11 The criterion was set to define a minimum of 20 years of age at which subjects can voluntarily consent to participation in the study. An upper limit of age was not set in order to collect results in elderly patients as much as possible.

12. to 14. These criteria were set as basic matters to conduct clinical studies.

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 clinically evident hepatic impairment (e.g., AST or ALT >=2.5 times the upper limit of normal or total bilirubin of >=2.0 mg/dL at the start of the screening period [Week -6] or at Week -2 of the screening period).
2. The subject has any serious cardiac diseases, cerebrovascular disorders, or serious pancreatic or hematological diseases (e.g., subjects who require inpatient treatment or had been hospitalized for treatment within 24 weeks prior to the start of the screening period).
3. The subject has severe ketosis, diabetic coma or pre coma, type 1 diabetes, severe infection, or severe external injury, or immediately before or after surgery.
4. The subject has hemoglobinopathy (sickle cell disease, thalassemia, etc.).
5. The subject experienced hypoglycemia (subjects with a blood glucose value of ≤70 mg/dL or hypoglycemic symptoms) within 6 weeks prior to the start of the screening period or during the screening period (at least twice per week).
6. The subject has inadequately controlled hypertension.
7. For subjects who are being treated with 1 antidiabetic agent, the subject had been treated with at least 2 antidiabetic agentss on the day before 6 weeks prior to the start of the screening period (Week -6) (43 days prior to the start of the screening period).
8. The subject has malignancies.
9. The subject has a history of hypersensitivity or allergies to dipeptidyl peptidase-4 (DPP-4) inhibitors.
10. The subject has a history of gastrectomy or small intestinal resection.
11. The subject is a habitual drinker and consumes a daily average of more than 100 mL of alcohol.

12. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse.
13. The subject is required to take excluded medications during the study period.
14. The subject has received SYR-472 in a previous clinical study.
15. The subject received any investigational products (including investigational drugs in a post-marketing clinical study) within 12 weeks prior to the start of the screening period.
16. The subject is participating in other clinical studies at the time of informed consent.
17. If female, the subject is pregnant or lactating or intending to become pregnant from the time of informed consent to within 1 month after the end of the study; or intending to donate ova during such time period.
18. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
19. The subject is hospitalized during the screening period or is deemed as requiring hospitalization during the study period by the investigator or sub-investigator, unless the hospitalization is for short-term evaluations including complete health checkups or for short-term admission for shunt operation (including shunt maintenance).
20. The subject is deemed ineligible for the study for any other reason by the investigator or sub-investigator.

Reference) Alcohol Conversion Chart

Type	Type	Alcohol Content	Volume Equivalent to 100 mL of Alcohol
Brewages	Sake	15%	670 mL (approximately 3 gou)
	Beer	5%	2000 mL (approximately 3 beer bottles in large size)
	Low-malt beer	5%	2000 mL
	Wine	12%	830 mL
	Shaoxing rice wine	18%	560 mL
Distilled liquors	Distilled spirit (Kou-type shouchu)	35%	290 mL
	Distilled spirit (Otsu-type shouchu)	25%	400 mL
	Whiskey	40%	250 mL (approximately 3 double shots)
	Brandy	40%	250 mL (approximately 3 double shots)
	Vodka	40%	250 mL (approximately 3 double shots)
Mixed liquors	Plum wine	13%	770 mL
	Synthetic sake	16%	630 mL

<Justification of Exclusion Criteria>

1., 2., 6., 8., and 9.

These criteria were set with respect to the safety of the subjects.

3. The criterion was set with respect to the safety of the subjects and possible influence on the evaluation of efficacy in the study.

4., 10. to 12., and 14.
These criteria were set because they could influence the evaluation of efficacy and safety in the study.

5. The criterion was set with respect to the safety of the subjects and possible influence on the evaluation of safety in the study.

7. The criterion was set because if excluded antidiabetic drugs are discontinued in order to participate in the study under informed consent, the discontinuation of 2 or more drugs may jeopardize the safety of the subject.

13. The criterion was set with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety in the study.

15. to 18. and 20.
These criteria were set as basic requirements to conduct clinical studies.

19. The criterion was set because intervention in lifestyles due to hospitalization is likely to influence the glucose metabolism of subjects.

7.3 Excluded Medications and Treatments

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

1. Excluded Medications

Use of the following medications is prohibited in each period:

(1) Screening Period and Treatment Period I

- New antidiabetic drugs*
- Other DPP-4 inhibitors and GLP-1 receptor agonists
- Sulfonylureas, biguanides, thiazolidinediones, nateglinide, and SGLT-2 inhibitors

*: Except for antidiabetic drugs that are being used at the start of the screening period (Week -6) and will be concomitantly used during the study period

(2) Treatment Period II and Follow-up Period

- New insulin preparations*
- Other DPP-4 inhibitors and GLP-1 receptor agonists
- Sulfonylureas, biguanides, thiazolidinediones, nateglinide, and SGLT-2 inhibitors

*: Except for insulin preparations that are being used at the start of the screening period (Week -6) and will be concomitantly used during the study period

<Justification for Excluded Medications>

In the screening period and Treatment Period I, changes in the basic treatment are prohibited with respect to the possible influence on the efficacy and safety evaluation of SYR-472. However, the addition of new insulin preparations is only prohibited in Treatment Period II and thereafter with respect to the safety of the subjects. In addition, the use of antidiabetic drugs that are contraindicated in patients with serious renal impairment and SGLT-2 inhibitors that cannot be used over a long period as of the start of the study is prohibited with respect to the safety of the subjects. Furthermore, the use of similar DPP-4 inhibitors and GLP-1 receptor agonists is prohibited with respect to the safety of the subjects and possible influence on the evaluation of efficacy and safety.

2. Restricted Medications

(1) Oral Hypoglycemic Agents

1) Screening Period and Treatment Period I

Changes in the dose/regimen or discontinuations/interruptions of oral hypoglycemic drugs that are being used at the start of the screening period (Week -6) and will be concomitantly used in the study period are prohibited.

2) Treatment Period II and Follow-up Period

- Changes in the dose/regimen or discontinuations/interruptions of oral hypoglycemic drugs that are being used at the start of the screening period (Week -6) and will be concomitantly used in the study period are allowed.
- For subjects who are not using any other antidiabetic drug in Treatment Period I (those who are only treated with the study drug), the use of 1 new oral hypoglycemic drug* is allowed at Week 16 of the treatment period and thereafter.

  *: Any 1 of the following medications: mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or voglibose

(2) Insulin Preparations

For subjects who are receiving insulin preparations at the start of the screening period (Week -6) and continue to receive in the study period, insulin preparations should be administered as specified below.

- Type of Insulin Preparation

Any 1 of the mixed (rapid-acting or ultrarapid insulin containing no more than 30% of volume), intermediate-acting, or long-acting soluble insulin preparations should be used alone, and should not be changed throughout the study period.

- Daily Dose (Unit) of Insulin Preparation

1) Screening Period

The daily dose (unit) of insulin preparation should be 40 units/day or less at the start of the screening period (Week -6), and the dose and regimen should not be changed during the screening period (for subjects on hemodialysis who receive different daily doses [unit] of insulin preparation on days of hemodialysis and on other days, each dose and regimen of insulin preparation should not be changed).

2) Treatment Period I

The dose and regimen of insulin preparations at the start of the screening period (Week -6) should be maintained and no changes will allowed, in principle.

However, the investigator or sub-investigator should consider reduction or increase in the daily dose (unit) of insulin preparation if the criteria described below are met. After dose reduction or increase, the unit after reduction or increase should be continued.

Even if reduction in the daily dose (unit) of insulin preparation results in the discontinuation of insulin use, the study may be continued. If increase in the daily dose (unit) of insulin preparation results in a dose exceeding 40 units/day on a continuing basis, the investigator or sub-investigator should determine whether the study should be continued or discontinued, with respect to the safety of the subject.

Criteria for dose reduction: If either criterion (i) or (ii) described below is met, the daily dose (unit) of insulin preparation may be reduced from the unit administered at the start of the screening period (Week -6) by up to 4 units (regardless of the number of changes).

If it is necessary to reduce the dose from the unit administered at the start of the screening period (Week -6) by more than 4 units/day, the study should be discontinued and appropriate measures should be taken.

i) A subject shows hypoglycemic symptoms, and the investigator or sub-investigator considers that the dose reduction of insulin preparation is necessary in view of the safety of the subjects.

ii) Hypoglycemia is suspected since a subject has had 2 or more consecutive self-monitoring blood glucose values of ≤70 mg/dL, and the investigator or sub-investigator considers that the risk of developing hypoglycemia is high.

Criteria for dose increase: If a subject has had 2 or more consecutive self-monitoring blood glucose values of >240 mg/dL and the investigator or sub-investigator considers that the increase of insulin preparation is necessary in view of the safety of the subjects, the daily dose (units) of insulin preparation at the start of the screening period (Week -6) can be increased by up to 4 units (regardless of the number of dose changes).

If dose increase greater than 4 units/day from the unit administered at the start of the screening period (Week -6) is required, the subject will be withdrawn from the study and receive appropriate treatment.

3) Treatment Period II and Follow-up Period

The investigator or sub-investigator should consider reduction or increase in the daily dose (unit) of insulin preparation if the criteria described below are met. After dose reduction or increase, the unit after reduction or increase should be continued.

Even if reduction in the daily dose (unit) of insulin preparation results in the discontinuation of insulin use, the study may be continued. If increase in the daily dose (unit) of insulin preparation results in a dose exceeding 40 units/day on a continuing basis, the investigator or sub-investigator should determine whether the study should be continued or discontinued, with respect to the safety of the subject.

Criteria for dose reduction: If either criterion (i) or (ii) described below is met, reduction in the daily dose (unit) of insulin preparation should be considered.

i) A subject shows hypoglycemic symptoms, and the investigator or sub-investigator considers that the dose reduction of insulin preparation is necessary in view of the safety of the subjects.

ii) Hypoglycemia is suspected since the subject has had 2 or more consecutive self-monitoring blood glucose values of ≤70 mg/dL, and the investigator or sub-investigator considers that the risk of developing hypoglycemia is high.

Criteria for dose increase: If a subject has had 2 or more consecutive self-monitoring blood glucose values of >200 mg/dL and the investigator or sub-investigator considers that the increase of insulin preparation is necessary in view of the safety of the subjects, whether or not to increase the daily dose (units) of insulin preparation should be considered.

<Justification of Restricted Medications>

For oral hypoglycemic drugs, changes in the basic treatment are prohibited in the screening period and Treatment Period I with respect to the possible influence on the efficacy and safety evaluation of SYR-472. In Treatment Period II and the follow-up period, changes in the dose or regimen as well as discontinuations and interruptions are allowed due to ethical considerations on the state of glycemic control for patients with type 2 diabetes mellitus complicated by renal impairment during the 54-week study period. In addition, for subjects who do not receive any other antidiabetic drug in Treatment Period I and still show inadequate glycemic control after 4 weeks following entry into Treatment Period II (Week 16 of the treatment period or thereafter), 1 oral hypoglycemic drug only may be additionally administered at the discretion of the investigator and sub-investigator.

For insulin preparations, changes in the daily dose (unit) are permitted according to the fixed criteria for dose reduction or increase, if the investigator or sub-investigator considers it necessary from the perspective of the safety of the subject.

3. Other medications

For medications other than those specified in 1 and 2 above, the daily dose administered at the start of the screening period (Week -6) should not be changed in Treatment Period I, in principle. However, if deemed necessary for treatment by the investigators due to the occurrence of an AE or other reasons, changes in the daily dose and administration of a new medication are permitted. It should be confirmed that the medication can administered to individuals with renal impairment. Caution should be exercised for medications that require careful use with the study drug and/or antidiabetic drug that is used at the start of the screening period (Week -6) and continued during the study period as recommended in the package insert.

<Justification for Medications Other Than Excluded Medications and Restricted Medications>

The use of other medications is permitted because they are unlikely to influence the evaluation of drug effects unless the daily dose is changed. The daily dose of such medications should not be changed in principle; however, changes in the daily dose and administration of a new medication due to the onset of an AE or other reasons are permitted for ethical considerations.

4. Other prohibitions

Hospitalization is prohibited during the study period, excluding short-term hospitalization for medical evaluations including complete health checkups or for short-term admission for shunt operation (including shunt maintenance).

<Justification for Other prohibitions>

Hospitalization during the study period is prohibited because intervention in lifestyle due to hospitalization is likely to influence glucose metabolism (for example, continued hospitalization for 1 week or longer), possibly affecting the evaluation of drug effects.

7.4 Diet, Fluid, Activity Control

The investigator, sub-investigator, and study coordinator will pay attention to the following requirements and provide necessary instructions to subjects:

1. For diet and/or exercise therapy (if any), the investigator or sub-investigator should provide fixed instructions on diet and/or exercise therapy throughout the study period. In addition, subjects should be instructed to follow instructions on diet and/or exercise therapy.
2. Subjects are required to comply with the prescribed dose and regimen of the study drug. Subjects are required to bring study drug sheet to the study site at each visit.

   Study drug administration should be started after all procedures scheduled for the end of the screening period (Week 0) are completed (the day when study drug administration is started is defined as the first day of dosing). The SYR-472 25 mg or placebo tablets should be taken once weekly (on the same day of the week as the day of the first dose). If a dose is missed, just 1 tablet for the last missed dose should be taken immediately after the subject notices it. Subjects should not take more than 1 SYR-472 25 mg or placebo tablet for several missed doses prior to the next scheduled dosing day.
3. Subjects should be instructed to ingest glucose or sucrose (sugar) in case any hypoglycemic symptom (e.g., unusual hunger, weakness, finger tremor, cold sweat, or palpitations) appears, and to visit the study site immediately if the symptom does not improve despite glucose or sucrose ingestion.
4. For subjects using insulin preparations, the investigator or sub-investigator should provide explanations and instructions about the method and timing of self-monitoring of blood glucose at the end of the screening period (Week 0). Subjects should also be instructed to report the results of self-monitoring of blood glucose to the investigator or sub-investigator at each visit. In particular, they should be instructed to report to the investigator or sub-investigator whether or not they have experienced a blood glucose value exceeding 240 mg/dL (Treatment Period I) or 200 mg/dL (Treatment Period II and follow-up period), or a blood glucose value of 70 mg/dL or less as measured by self-monitoring, and whether or not they have experienced any hypoglycemic symptoms.

   For the time points of self-monitoring of blood glucose, refer to Section 9.1.21.
5. If a subject plans to use any drugs (including over-the-counter [OCT] drugs) other than those prescribed by the investigator or sub-investigator, he/she should consult

with the investigator or sub-investigator in advance, whenever possible. In case these drugs have already been used, immediate notification is required.

6. If a subject plans to visit another physician, prior notification to the investigator or sub-investigator is required. If a subject has already been treated by another physician, immediate notification is required.
7. Subjects are required to be punctual for visit appointments and undergo physical examinations and prescribed tests as scheduled. If a subject cannot visit the study site on the scheduled day, immediate contact to the study site is required.
8. Subjects should be instructed to avoid excessive drinking and eating, extreme changes in diet (e.g. ingestion of a high-fat diet), or excessive exercises and live as usual on the days before the study visit.
9. On the day of the visit, subjects should visit the site under fasted conditions (at least 10 hours of fasting). Subjects using oral hypoglycemic drugs or insulin preparations should visit the site without taking them on the day of the visit.
10. Subjects are required to undergo routine ophthalmologic examination and pay attention to complications including diabetic retinopathy.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.25.

1. **Pretreatment event (PTE) or AE**
   The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   Liver Function Test (LFT) Abnormalities

   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status [value at immediately after the inforned consent for PTEs and at immediately before the initiation of the study drug for AEs], see Section 9.1.9), if the following circumstances occur at any time during study drug treatment:

   – alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
   – ALT or AST >5 × ULN and persists for more than 2 weeks, or
   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
   – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

- Renal Function Test Abnormalities

  For subjects not on hemodialysis at the start of the screening period (Week -6) (patients with severe renal impairment), the study drug should be discontinued with

appropriate clinical follow-up until a subject's laboratory profile has returned to normal/baseline status for subjects not on hemodialysis at the start of the screening period (Week -6) (patients with severe renal impairment) if the subject shows worsening of renal function that may necessitate hemodialysis in Treatment Period I and is considered inappropriate to continue the study in the opinion of the investigator or sub-investigator, or if the subject shows rapid worsening of Ccr (e.g., reduction of 30% or more) on 2 consecutive post dose measurements, as compared with the value at the end of the screening period (Week 0), and is considered inappropriate to continue the study in the opinion of the investigator or sub-investigator.

- Serious hypoglycemia

  A serious hypoglycemic symptom (coma, depressed consciousness, etc.; severe enough to require active sugar or glucagon administration or other resuscitation by other people) appears. For reporting in the event of serious hypoglycemia, refer to Section 10.2.1.3 and Section 10.2.2.

- Serious hyperglycemia

  A serious hyperglycemic symptom (coma, ketosis, ketoacidosis, etc.; severe enough to require assistance by other people) appears. For reporting in the event of serious hyperglycemia, refer to Section 10.2.2.

- Acute pancreatitis

  Acute pancreatitis is conclusively diagnosed. For reporting in the event of acute pancreatitis, refer to Section 10.2.1.3.

- Abnormal QT/QTc interval

  Serious arrhythmia or significant QT interval prolongation (e.g., an absolute QTcF interval of >500 msec or a change of >60 msec from the end of the screening period [Week 0]) is observed, and the investigator or sub-investigator considers it inappropriate for the subject to continue the study. For reporting in the event of abnormal QT/QTc interval, refer to Section 10.2.1.3.

2. **Significant protocol deviation.**
   The discovery postrandomization 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 study site and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

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 (i.e., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

5. **Study termination.**
   The sponsor, IRB, or regulatory agency terminates the study.

6. **Pregnancy**.
   The subject is found to be pregnant.

   NOTE: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. **Lack of efficacy.**
   The investigator or sub-investigator has determined that the subject is not benefiting from the study drug treatment; and, continued participation would pose an unacceptable risk to the subject.

8. **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 or sub-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 or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

8.1 Study Drug

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study drug

The study drug refers to SYR-472DB tablets (SYR-472 25 mg tablets or placebo tablets) for Treatment Period I and SYR-472 25 mg tablets for Treatment Period II.

1. Dosage Form

(i) SYR-472DB tablets (for Treatment Period I)

Genetic name: Trelagliptin Succinate (JAN)

Chemical name: 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)-4-fluorobenzonitrile monosuccinate

Dose:

- SYR-472 25 mg tablets: 1 tablet contains 25 mg of SYR-472 (as free base).
- SYR-472 placebo tablets: the placebo tablet does not contain SYR-472.

Dosage form: Yellow-red film-coated tablets

The appearance of SYR-472 25 mg tablets and SYR-472 placebo tablets is mutually indistinguishable.

(ii) SYR-472 25 mg tablets (for Treatment Period II)

Genetic name: Trelagliptin Succinate (JAN)

Chemical name: 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)-4-fluorobenzonitrile monosuccinate

Dose:

- SYR-472 25 mg tablets: 1 tablet contains 25 mg of SYR-472 (as free base).

Dosage form: Yellow-red film-coated tablets

2. Manufacturing

SYR-472 25 mg and placebo tablets were manufactured by Takeda Pharmaceutical Company Limited.

3. Packaging and Labeling

For Treatment Period I, 2 AL-AL blister sheets each containing 8 tablets (12 tablets for 12 weeks and 4 spare tablets for 4 weeks) are packed in a carton for 1 subject. For Treatment Period II, 16 AL-AL blister sheets each containing 8 tablets (128 tablets) are packed in a carton. The study drug for Treatment Period II can be used in common among all subjects in each study site.

The outer carton is labeled with a statement that it is for clinical study use, and with information such as the name of the study drug, quantity, sponsor's name and address, manufacturing number, and storage conditions.

8.1.2 Storage

The study drug will be stored at room temperature (1 to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All drugs provided by the sponsor 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.

8.1.3 Dose and Regimen

In Treatment Period I, 1 tablet of SYR-472 25 mg or placebo will be orally administered once weekly before breakfast. In Treatment Period II, 1 tablet of SYR-472 25 mg tablet will be orally administered once weekly before breakfast.

Subjects will start study drug administration after all procedures scheduled for the end of the screening period (Week 0) are completed. At subsequent visits when the study drug is administered, all specified procedures should be performed prior to study drug administration.

Table 8.a describes the dose and regimen that will be provided to each group in Treatment Period I.

Table 8.a Dose and Regimen (Treatment Period I)

Treatment Group	Dose	Treatment Description	
		SYR-472 25 mg tablet	SYR-472 placebo tablet
SYR-472 25 mg group	SYR-472 25 mg tablet once weekly	×1	×0
Placebo group	SYR-472 placebo tablet once weekly	×0	×1

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. AEs associated with an overdose will be documented on AE CRFs according to Section 10.0, PRETREATMENT EVENTS AND ADVERSE EVENTS.

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

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

8.2 Study drug Assignment and Dispensing Procedures

After judging and confirming eligibility of a subject, the investigator or sub-investigator will assign the subject to receive the study drugs for Treatment Period I which have been allocated to each study site (SYR-472DB tablets) in consecutive order of medication ID number. The investigator or investigator's designee will record the medication ID number in the eCRF.

In Treatment Period II, the investigator or sub-investigator will start administration of the study drug for Treatment Period II (SYR-472 25 mg tablet) after performing all physical examinations/examinations/assessments scheduled for Week 12 in the treatment period.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

Emergency Key Code Administration Center will maintain the subject's study drug blind information until emergency key code breaking or data lock of all subjects.

Since the measured values of study drug concentration and DPP-4 may hinder study drug blind maintenance in this study, the central laboratory institute should retain the final results of these parameters until the key code breaking without disclosing them externally; the final results will be reported to the investigator via the sponsor after the code breaking.

The study blind in Treatment Period I will be maintained until the end of the study.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator or sub-investigator unless information concerning the study drug is necessary for the medical treatment of the subject.

For unblinding a subject, the study drug blind can be obtained by contacting the Emergency Key Code Administration Center (Annex 1).

If the study drug blind is broken, the date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and submitted to the sponsor. The same information (except the time) must be recorded on the eCRF.

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

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and

collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

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 sub-investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

If a subject undergoing hemodialysis (patients with end-stage renal failure) receive hemodialysis on the day of study site visit, all procedures should be performed before hemodialysis.

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.

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

PGx Informed Consent Procedure

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting a blood sample for PGx Research for this study. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, height, weight, body mass index (BMI), alcohol use, smoking status, onset time of type 2 diabetes, presence or absence of hemodialysis and diet and/or exercise therapy.

The BMI will be calculated by the sponsor using the formula provided below:

Metric: BMI = weight (kg)/[height (m)]^2

Height should be measured in centimeters without decimal places (rounding off the first decimal place). For measurement of weight, refer to Section 9.1.5.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes drug name, route of administration, daily dose, and end date of any antidiabetic drug stopped between 24 weeks prior to the end of the screening period (Week 0) and the start of the screening period (Week -6).

9.1.3 Antidiabetic Drugs Administered During the Study

1. Screening Period

For antidiabetic drugs administered at the start of the screening period (Week -6) and concomitantly used during the study period, the drug name, type (for insulin preparations), and daily dose of antidiabetic drugs used at the start of the screening period (Week -6) and concomitantly used during the study will be recorded in the eCRF.

2. Treatment Period I

For antidiabetic drugs administered at the start of the screening period (Week -6) and concomitantly used during the study period, the drug name, type (for insulin preparations), and daily dose of antidiabetic drugs used at the start of the screening period (Week -6) and concomitantly used during the study period will be recorded in the eCRF.

In case concomitant use of other antidiabetic drugs in addition to an antidiabetic drug used at the start of the screening period (Week -6) is judged to be appropriate, the investigator or sub-investigator should record the reason for the judgment in the eCRF according to the following categories:

- Combination therapy is expected to be more effective.
- Development of AEs due to dose increase is concerned.
- The maximum dose has already been administered.
- Others

3. Treatment Period II

For subjects who do not receive 1 antidiabetic drug other than the study drug in Treatment Period I and start the administration of 1 new oral hypoglycemic drug from Week 16 of the Treatment Period II (or thereafter), the drug name, daily dose, date of the start and end of administration, will be recorded in the eCRF.

9.1.4 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.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to the first dose examination.

9.1.5 Weight

Weight should be measured in kilograms to one decimal place (rounding off the second decimal place) under fasting conditions (at least 10 hours of fasting) to avoid the effect of meal. For subjects receiving hemodialysis (patients with end-stage renal failure), dry weight should be used.

9.1.6 Vital Sign Procedure

Vital signs will include sitting or supine blood pressure (resting more than 5 minutes) (systolic and diastolic) and pulse.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug and antidiabetic drugs. 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 drug (including vitamin supplements, over-the-counter medications, and herbal preparations) used from the start of the screening period (Week -6) through the end of the study, and the drug name, route of administration, dates of the start and end of administration, and purpose of use must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

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

9.1.9 Procedures for Clinical Laboratory Samples

Clinical laboratory tests that will be performed in this study are shown in Table 9.a.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 27 mL, and the approximate total volume of blood for the study is 322 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry
Red blood cells	Alanine aminotransferase
Reticulocytes	Aspartate aminotransferase
White blood cells	γ-Glutamyl transferase
Hemoglobin	Alkaline phosphatase
Hematocrit	Total bilirubin
Platelets	Total protein
White blood cells with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Albumin
	Creatinine
	Amylase
Erythrocyte indices (MCV, MCH, MCHC)	Lipase
	Blood urea nitrogen
	Uric acid
	Creatine kinase
	Lactate dehydrogenase
	Total cholesterol
	Triglyceride (fasting)
	Low-density lipoprotein (LDL) cholesterol (direct measurement)
	High-density lipoprotein (HDL) cholesterol
	high-sensitivity CRP
	Potassium
	Sodium
	Calcium
	Chloride
	Phosphate
	Ferrum
Other:	
Pregnancy test (serum or urine human chorionic gonadotropin [hCG]) (female subjects of childbearing potential)	

The central laboratory (Annex 1) will perform laboratory tests listed above except for the pregnancy test. Creatinine clearance (Ccr) will be calculated by the sponsor using the Cockcroft-Gault equation.

Cockcroft-Gault equation
Male: Ccr = {(140 - age) × weight (kg)} / {72 × serum creatinine (mg/dL)}
Female: Ccr = 0.85 × {(140 - age) × weight (kg)} / {72 × serum creatinine (mg/dL)}

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3)

The results of laboratory tests will be returned to the investigator or sub-investigator, who is responsible for reviewing and filing these results. The investigator will also maintain a copy of the reference ranges including their amendment for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent and throughout the duration of the study and for 1 month after the end of the study, female subjects of childbearing potential (i.e.,

nonsterilized, premenopausal female subjects) who are sexually active must use acceptable methods of contraception. Such subjects will be provided with information on acceptable 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 during the course of the study. During the course of the study, regular serum/urine hCG pregnancy tests will be performed, and subjects will receive continued guidance with respect to avoiding pregnancy as part of the study procedures (Appendix A).

In addition to a negative serum/urine hCG pregnancy test at the start of the screening period (Week -6), subjects also must have a negative serum/urine hCG pregnancy test immediately before randomization. Subjects must also have a negative serum or urine hCG pregnancy test at Week 24 and Week 52 of the treatment period or early termination.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during the study period or within 1 month after the end of the study, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Annex 1.

Should the pregnancy occur during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator or sub-investigator. Subjects randomized to placebo who discontinued in Treatment Period I without proceeding to Treatment Period II need not be followed.

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

All reported pregnancies will be followed up to final outcome under the agreement from the female subject, 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.

9.1.12 ECG Procedure

A standard 12-lead ECG will be recorded after a rest of at least 5 minutes. The investigator or sub-investigator will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval.

9.1.13 Fasting C-peptide

Fasting C-peptide will be measured in the central laboratory. Blood samples will be collected under fasting condition (after at least 10-hour fasting).

9.1.14 HbA1c (NGSP Value)

HbA1c will be measured in the central laboratory.

9.1.15 Fasting Blood Glucose, Fasting Glucagon

Fasting blood glucose and fasting glucagon will be measured in the central laboratory. Blood samples will be collected under fasting condition (after at least 10-hour fasting).

9.1.16 Glycoalbumin

Glycoalbumin will be measured in the central laboratory.

9.1.17 DPP-4 Activity

DPP-4 activity will be measured in the central laboratory. For study drug blind maintenance, refer to Section 8.4.

9.1.18 Blood Transfusion

Whether or not the subject has received a blood transfusion from the start of the screening period (Week -6) through the end of the study (if yes, the date and type of blood transfusion [whole blood, red blood cells, plasma, or platelets]) will be recorded in the eCRF.

9.1.19 Introduction of Hemodialysis

For subjects not receiving hemodialysis (patients with severe renal impairment), whether or not hemodialysis has been introduced between the start of the study drug administration (Day 1 of administration of the study drug for Period I) through the end of the study (if yes, the date of introduction) will be recorded in the eCRF.

9.1.20 Presence or Absence of Changes and Compliance of Diet and/or Exercise Therapy

Presence or absence of changes in diet and/or exercise therapy should be recorded in the eCRFs. If any instruction for diet and/or exercise therapy has to be changed, the date, contents, and reason for the change should be recorded in the source document.

Instructions for diet and/or exercise therapy (if any) given to subjects by the investigator or sub-investigator should be consistent throughout the study.

Compliance with diet and/or exercise therapy (if any) will be monitored and rated on the 4-grade scale shown below:

1. Fully complied (90% or more)
2. Almost complied (70% or more)
3. Occasionally complied (50% or more)

4. Rarely complied (less than 50%)

9.1.21 Self-Monitoring of Blood Glucose

For subjects using insulin preparations, the investigator or sub-investigator should explain the method of self-monitoring of blood glucose to subjects at the end of the screening period (Week 0), and instruct them to perform self-monitoring of blood glucose using a finger-stick sampling method in the following occasions:

(1) At scheduled monitoring

i) 57

ii) From the end of the screening period (Week 0) to Day 7 of administration of the study drug for Treatment Period II, self-monitoring of blood glucose should be performed every day before breakfast prior to administration of the study drug and insulin preparation.

iii) From Day 8 of administration of the study drug for Treatment Period II to the end of the follow-up period, self-monitoring of blood glucose should be performed at least once weekly before breakfast prior to administration of the study drug and insulin preparation.

(2) In case any hypoglycemic symptom occurs

If case any hypoglycemic symptom (e.g., unusual hunger, weakness, finger tremor, cold sweat, or palpitations) occurs, self-monitoring of blood glucose should be performed at the time of its development (prior to treatment for hypoglycemia, if any) and disappearance.

If the blood glucose in self-monitoring is 70 mg/dL or less, presence or absence of hypoglycemic symptoms should be confirmed and recorded in the eCRF along with the blood glucose value (refer to Section 9.1.22).

The investigator or sub-investigator will record all applicable blood glucose values in the eCRFs, and report whether the case is significant hypoglycemia or not. If the case is significant hypoglycemia and treatment is required, the contents of treatment should be recorded in the eCRF.

CCI [redacted] (provided by PPD [redacted]) should be used as the self-monitoring of blood glucose kit [11][12][13][14].

9.1.22 Hypoglycemia

For subjects using insulin preparations, the investigator or sub-investigator will confirm the presence or absence of hypoglycemic symptoms that have occurred since the previous visit, at each visit in the study period. If the blood glucose in self-monitoring is 70 mg/dL or less, presence or absence of hypoglycemic symptoms should be confirmed and recorded in the eCRF along with the blood glucose value.

If any hypoglycemic symptoms are observed, values of self-monitoring of blood glucose at the time of development and disappearance of the symptom and whether the case is significant hypoglycemia or not should be recorded in the eCRF. If the case is significant

hypoglycemia and treatment is required, the contents of treatment should also be recorded in the eCRF (refer to Section 9.1.21).

If any hypoglycemic symptoms are observed and no blood glucose values have been obtained at appropriate time points, whether or not the symptoms was caused by decreased blood glucose (≤ 70 mg/dL) should be assessed and recorded in the eCRF.

Hypoglycemia will be classified according to the following definitions in reference to the "The Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised draft)" [4].

- Significant hypoglycemia: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- Symptomatic hypoglycemia: an event accompanied by typical symptoms of hypoglycemia with a measured plasma glucose concentration of ≤70 mg/dL (including self-monitoring of blood glucose values).
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration of ≤70 mg/dL (including sself-monitoring of blood glucose values).
- Probable symptomatic hypoglycemia: an event accompanied by symptoms of hypoglycemia without a plasma glucose determination but that was presumably caused by a plasma glucose concentration of ≤70 mg/dL (including self-monitoring of blood glucose values).
- Relative hypoglycemia: an event accompanied by the typical symptoms of hypoglycemia observed in patients with diabetes mellitus is assumed, but with a measured plasma glucose concentration >70 mg/dL (including self-monitoring of blood glucose values).

9.1.23 PGx Sample Collection

One 5-mL whole blood sample for PGx should be collected at the end of the screening period (Week 0) from the subject who signed PGx informed consent after the study drug was assigned for possible exploratory investigation of markers enabling the prediction of drug response.

PGx sample should not be collected from any subject who has received bone marrow transplant or whole blood transfusion within 6 months of any sample collection.

See the separately created procedure for directions on collecting, handling, and storage of PGx samples.

9.1.24 Pharmacokinetic Sample Collection and Analysis

9.1.24.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (5 mL/sample) for pharmacokinetic analysis of SYR-472Z will be collected in blood sampling tubes containing anticoagulant according to the schedule shown in Appendix A, and plasma will be taken.

Instructions for sample processing and shipment are provided in the separately prepared Procedures for Handling of Biological Samples for Drug Concentration Measurement.

The time of blood sample collection for SYR-472Z measurement, and the date and time of the latest study drug administration will be recorded in the source document and eCRF.

9.1.24.2 Bioanalytical Methods

Plasma concentration of SYR-472Z will be determined by high-performance liquid chromatography with tandem mass spectrometry at PPD (Annex 1).

Measurement will not be performed for samples collected from subjects assigned to the placebo group. In addition, measurement results will be handed as data that will not be recorded in the eCRF, and stored at the laboratory until the breaking of the study drug blind without disclosing externally. After notification of the breaking from randomization personnel, these results will be reported to the investigator through the sponsor. If measurement results are disclosed before breaking the study drug blind, these results can be reported to the sponsor through the randomization personnel after laboratory personnel makes the measurement results blind, such as re-numbering of the drug number, such that the sponsor cannot identify subjects (refer to Section 8.4).

The investigator will confirm these measurement results.

9.1.25 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

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

- PTE/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.
- Pregnancy.
- Other <specify reason>.

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

9.1.26 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment period. If the subject is found to be not eligible for randomization, the investigator or sub-investigator should record the primary reason for failure on the eCRF.

9.1.27 Hospitalization

If a subject is hospitalized for 1 week or longer during the study period due to a SAE or other reasons, the investigator or sub-investigator will record the hospitalization in the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring unused study drugs and antidiabetic drugs (if any) to the study site at each visit.

For the SYR-472DB tablets (for use in Treatment Period I) and the SYR-472 25 mg tablets (for use in Treatment Period II), the date of dosing will be recorded in the eCRFs.

For antidiabetic drugs (if any), treatment compliance during the study will be assessed and rated on the 4-point scale shown below at each visit:

1. Fully Complied (90% or more)
2. Almost complied (70% or more)
3. Occasionally complied (50% or more)
4. Rarely complied (less than 50%)

If a subject is persistently noncompliant with the study drug (e.g., 70% of the allocated medication for the period since the last visit), it may be appropriate to withdraw the subject from the study. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening (Week -6 to Week 0)

At the start of the screening period (Week -6), subjects will be screened within 49 to 35 days prior to study drug administration.

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

Subjects will be randomized at the end of the screening period (Week 0).

See Section 9.1.25 for procedures for documenting screening failures.

9.3.2 Randomization

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 instructed on when to take the first dose of study drug as described in Section 6.1.

9.3.3 Treatment Period

All specified procedures will be performed at each visit.

9.3.4 Week 52 in the Treatment Period or Early Termination

All procedures scheduled for the final visit will be performed at Week 52 of the treatment period.

For subjects prematurely withdrawn from the study during the treatment period, all procedures scheduled for Week 52 will be performed within 7 days after the final dose of the study drug (reckoned from the day after the final dose) whenever possible.

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

9.3.5 Follow-up

All procedures scheduled for the end of the follow-up period will be performed at the 21st day after the final dose of the study drug (reckoned from the day after the final dose).

For subjects who discontinued study treatment, all procedures scheduled for the end of the follow-up period should be performed wherever possible.

9.3.6 Post Study Care

The study drug will not be available upon completion of the subject's participation in the study.

9.4 Biological Sample Retention and Destruction

Samples of 5-mL whole blood collected for PGx will be stored frozen at the storage site for PGx samples (Annex 1).

The collected samples will be retained for 20 years from the day when a first PGx sample was collected during the study.

When subjects request disposal of a stored sample during the retention period, the site will ask the storage site for PGx samples (Annex 1) to destroy the sample via the sponsor according to the procedure. The storage site for PGx samples (Annex 1) will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents (including medical records) have been destroyed which could identify the subject and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when PGx investigation has been conducted, the remaining samples will be destroyed and the results of PGx investigation of anonymized subject will be retained by the sponsor.

The sponsor will build a management system required for protection of the subject's personal information, define standards for collecting store and destruction of samples, and prepare appropriate procedures.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, any abnormal finding related to study procedures (e.g., bruise after blood draw) should be recorded as a PTE. If the subject experiences a worsening or complication of a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators or sub-investigator should ensure that the event term recorded captures the change in the condition from baseline (e.g., "worsening of hypertension").

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

Worsening of PTEs or AEs:

If the subject experiences a worsening or complication of a PTE after starting administration of the study drug, the worsening or complication should be recorded appropriately as an AE. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in intensity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING*
   * The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to 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

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

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

10.1.5 Adverse Events of Special Interest

An AE of Special Interest (AESI) (serious or non-serious) is 1 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 the sponsor (refer to Section 10.2.1.3).

- AESIs: hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs

<Hypoglycemia-related AEs>

Hypoglycemia-related AEs are defined as AESIs since special attention is generally paid to these events in patients with diabetes mellitus using antidiabetic drugs and severe hypoglycemia has been reported in combination therapy with other DPP-4 inhibitors and insulin preparations.

<Intestinal obstruction-related AEs>

Intestinal obstruction-related AEs are defined as AESIs since adverse reaction reports on intestinal obstruction with the use of incretin-related drugs (GLP-1 receptor agonists and other DPP-4 inhibitors) in the same class as SYR-472 have been accumulated.

<Acute pancreatitis-related AEs>

Acute pancreatitis-related AEs are defined as AESIs since adverse reaction reports on acute pancreatitis with the use of incretin-related drugs in the same class as SYR-472 have been accumulated.

<QT/QTc interval prolongation-related AEs>

In thorough QT/QTc study (Study CPH-005), QT/QTc interval prolongation was reported in the SYR-472 800 mg group, although it was not reported in the SYR-472

200 mg group; therefore, QT/QTc interval prolongation-related AEs are defined as AESIs.

10.1.6 Intensity of PTEs and AEs

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

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

10.1.7 Causality of AEs

The relationship of each AE to study drugs will be assessed using the following categories:

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

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs. The relationship should be assessed as Related if the investigator or sub-investigator considers that there is a 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 AEs/PTEs is determined based on the following criteria:

AE/PTE	Start Date
Signs, symptoms, and diseases (diagnosis)	Date when the subject and/or the investigator or sub-investigator first notices the sign or symptom of the AE.
Asymptomatic disease	Date when a definite diagnosis is determined based on the results of diagnostic testing: Even if obsolete findings are indicated based on the test findings or the approximate time of onset can be estimated, the date when a definite diagnosis is made should be recorded.
Worsening of concurrent medical conditions or PTE	Date when the subject or the investigator or sub-investigator first notices worsening of the disease or symptom.
Normal in the initial assessment after signing informed consent but abnormal in the subsequent assessment (for PTEs) Abnormal in the assessment after the start of study drug (for AEs)	Date when the test is performed in which a clinically significant abnormal test value is observed.

Abnormal in the initial assessment after signing informed consent and has worsened at the subsequent assessment (in case of PTEs) Abnormal in the assessment at the start of study drug and has worsened in the subsequent assessment (in case of AEs)	Date when the test is performed in which a medically significant elevation, reduction, increase, or decrease in clinical test values is observed.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The event not has resolved at the end of the study will be assessed as ongoing.

10.1.11 Frequency

Episodic AEs/PTEs (e.g., constipation, diarrhea, or 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

Action taken for the study drug is classified and defined as follows:

Drug withdrawn	A study drug is stopped due to the particular AE (including withdrawal at the discretion of subjects).
Dose not changed	The dose is not changed even after the occurrence of the particular AE. This shall apply in case the study drug is stopped or the dose is reduced or increased due to another AE. This shall also apply, for example, in case the study drug is stopped or the dose is reduced for any reason other than intervention for the particular AE, such as the subject's negligence.
Unknown	For example, attempts to contact the subject are unsuccessful and the course of the particular AE after the start day cannot be followed.
Not Applicable	For example, the study drug has already been completed or stopped before the onset of the particular AE.
Dose interrupted	The study drug is stopped (suspended) due to the particular AE and resumed afterwards (including temporary withdrawal at the discretion of subjects).

10.1.13 Outcome

The outcome of AEs/PTEs is classified as follows:

Classification	Assessment criteria
Recovered/resolved	•The diagnosis or signs/symptoms has disappeared or resolved. •The abnormal laboratory value has improved to the normal range or the value at baseline (AEs), or at the first assessment after signing of informed consent (PTEs). •The event was recorded as another AE in the eCRF due to increased intensity.

Classification	Assessment criteria
Recovering/resolving	•The intensity is lowered by 1 or more stages. •The diagnosis or sign/symptom has almost disappeared. •The abnormal laboratory value improved, but has not returned to the normal range or to baseline (AEs) or to the first assessment after signing of informed consent (PTEs). •The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (in this case, no need to record the date of death).
Not recovered/not resolved	•There is no change in the diagnosis or signs/symptoms, or laboratory values. •The intensity of the diagnosis or signs/symptoms, or laboratory value on the last day of the observed study period has got worse than when it started. •An irreversible congenital anomaly. •The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" (in this case, no need to record the date of death).
Resolved with sequelae	•Dysfunction that interferes with the subject's daily life is observed.
Fatal	•There is a direct relationship between the death and the AE/PTE. A "direct relationship" means that the AE/PTE caused or apparently contributed to the death. •The outcome of another AE/PTE reported in the same subject that is not determined (considered or estimated) to cause the death is not assessed as "fatal." •If the outcome is "fatal," the date of death should be recorded.
Unknown	•The course the AE/PTE after the start day cannot be followed up as specified in the protocol due to hospital change or residence change.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Visit 3). For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Visit 3). Routine collection of AEs will continue until Visit 18.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent or irreversible PTEs). Non-serious

PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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 (permanent or irreversible AEs). All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator or sub-investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date.
- Frequency.
- Intensity.
- Causal relationship between the event and administration of study drug(s) (related or not related).
- Action concerning study drug.
- Outcome of event.
- Causal relationship to study procedure(s) (if related, include the details of the suspected procedure).
- Seriousness.

AEs and serious PTEs should be followed up until the AEs/PTEs have resolved or follow-up is no longer necessary in the opinion of the investigator or sub-investigator.

10.2.1.3 AESI Reporting

If any AESI, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (Annex 1) immediately or within 1 business day of first onset or subject's notification of the event. In addition, AESI Form should be completed by the investigator, and reported to the Safety Information Emergency Call Center (Annex 1) within 10 business days.

The original AESI Form should be submitted to the sponsor.

The criteria for AESIs (hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs) are as described below. If any AE considered to be related to these condition occurs, whether or not to handle it as an AESI should be considered.

<Hypoglycemia-related AEs>

AEs related to hypoglycemia

<Intestinal obstruction-related AEs>

Intestinal obstruction, ileus, subileus, gastrointestinal obstruction, gastrointestinal motility disorder, impaired gastric emptying, and AEs related to these conditions

<Acute pancreatitis-related AEs>

AEs related to pancreatitis or acute pancreatitis

<QT/QTc interval prolongation-related AEs>

Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, disturbance of consciousness, convulsion, ECG QT prolonged, and AEs related to these conditions.

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. Any PTE which meets the SAE criteria described in Section 10.1.4 should be reported in the same manner as SAEs:

An SAE should be reported to the sponsor (Annex 1) within 1 business day of first onset or subject's notification of the event. The investigator should submit the completed SAE form within 10 calendar days.

The information to be reported within 1 business day 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 or sub-investigator's name.
- Name of the study drug(s)
- Causality assessment.

Any SAE spontaneously reported to the investigator or sub-investigator's following the AE collection period should be reported to the sponsor.

10.2.3 Reporting of Abnormal Liver Function Tests

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 or sub-investigator must contact sponsor, and investigate the details of the subject and possible alternative etiologies immediately, 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 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the detailed report becomes available at a later date, the investigator or sub-investigator should complete a follow-up SAE form or provide other written documentation and submit it to the sponsor (Annex 1) immediately. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested by the sponsor or IRB.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, 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, investigators and IRBs/the head of the study site, 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 (contract research organization [CRO]), 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. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug or that would be sufficient to consider changes in the study 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.

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, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs

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

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

The investigator or sub-investigator should complete assessments scheduled for Treatment Period I prior to starting study drug administration in Treatment Period II; the schedule of assessments should not be changed unless there is an appropriate reason.

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

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

The following data will not be recorded directly into the eCRFs:

- Laboratory parameters measured in the central clinical laboratory

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator or sub-investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed (e)CRFs 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 and the head of the institution agree to keep the records stipulated in Section 12.1 and documents include the study-specific documents, identification log of all participating subjects, medical records, source worksheets, all original signed and dated 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. The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

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

13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set (PPS), and safety analysis set. The FAS, the main analysis set used for efficacy analysis, is defined as all subjects who were randomized and received at least 1 dose of the study drug. The safety analysis set, is defined as all subjects who received at least 1 dose of the study drug. The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data and supplement descriptions about handling of the unspecified issues, consulting a medical expert as needed. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Key demographics and other baseline characteristics will be summarized for each treatment group and for overall treatment groups using the all randomized subjects.

13.1.3 Efficacy Analysis

(1) Primary endpoint and analytical methods

[Primary endpoint]

Change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0)

[Primary analysis]

The following analyses will be performed in the FAS.

The population mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) will be compared between SYR-472 25 mg group and placebo group based on an analysis of covariance (ANCOVA) model for the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) with factors of treatment group and HbA1c at the end of the screening period (Week 0).

The same ANCOVA model will be used to calculate the least square (LS) mean and the two-sided 95% confidence interval (CI) for each treatment group, as well as the intergroup difference in the LS mean between the treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI.

[Secondary analysis]

For the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0), summary statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and two-sided 95% CI for the mean will be calculated for each treatment group, as well as the intergroup difference in the mean between treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI.

In addition, the same analyses as the primary analysis and the secondary analysis described above will be performed using the PPS to evaluate the robustness of the results in terms of a sensitivity analysis.

[Adjustment for covariates]

The following analyses will be performed in the FAS.

The treatment effect of SYR-472 25 mg will be assessed in consideration of the effects of baseline characteristics based on the ANCOVA model for the change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) with factors of treatment group, HbA1c at the end of the screening period (Week 0) and baseline characteristics that may affect the primary endpoint at the blind data review.

(2) Secondary Endpoints and Analysis Methods

[Secondary endpoints]

HbA1c, fasting blood glucose, glycoalbumin

[Analytical methods]

The following analyses will be performed in the FAS.

For each endpoint, summary statistics and two-sided 95% CI for the mean will be calculated for each treatment group at each time point. In addition, summary statistics for the change from the end of the screening period (Week 0) and two-sided 95% CI for the mean will be calculated for each treatment group at each time point, and the intergroup difference in the mean between treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CI will be calculated at each time point in Treatment Period I.

For the proportions of subjects who achieved an HbA1c less than 6.0%, 7.0%, or 8.0% at the end of Treatment Period I and Treatment Period II, the proportions and the two-sided 95% CIs will be calculated for each treatment group, and the intergroup difference in the proportions between treatment groups (SYR-472 25 mg group - placebo group) and the two-sided 95% CIs will be calculated at the end of Treatment Period I. In the analysis of each proportion, subjects who did not achieve the relevant target HbA1c at the end of the screening period (Week 0) will be included in the analysis.

(3) Additional efficacy endpoints

See Section 5.2.

(4) Method of data conversion and handling of missing data

Details will be specified separately in the Handling Rules for Analysis Data and the SAP.

(5) Significance level and confidence coefficient

- Significance level: 5% (two-sided tests)
- Confidence coefficient: 95% (two-sided)

13.1.4 Safety Analysis

The following analyses will be performed in the Safety Analysis Set.

(1) Primary endpoint and analytical methods

[Primary endpoint]

AEs

[Analytical methods]

A treatment-emergent adverse event (TEAE) is defined as an AE whose date of onset occurs on or after the start of study drug administration.

The following analyses will be performed for each treatment group for TEAEs that occur before the start of the study drug for Treatment Period II, and for those that occur after the start of SYR-472 25 mg tablet. In the analysis of TEAEs occurring after the start of SYR-472 25 mg tablet, subjects who received SYR-472 25 mg tablet will be included in the analyses.

TEAEs will be coded using MedDRA dictionary. Frequency distributions will be provided using System Organ Class and Preferred Term for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

(2) Secondary endpoints and analytical methods

[Secondary endpoints]

Vital signs, 12-lead ECGs, clinical laboratory tests

[Analytical methods]

For continuous variables, the observed values and change from the end of the screening period (Week 0) will be summarized using descriptive statistics for each treatment group at each time point. In addition, case plots over time for observed values will be presented for each treatment group.

For 12-lead ECG findings and laboratory tests classified as "Low", "Normal" or "High" based on the normal reference ranges, shift tables showing the number of subjects in each

category at the end of the screening period (Week 0) and each post-baseline time point will be presented for each treatment group.

(3) Additional endpoint and analysis methods

[Additional endpoint]

Hypoglycemia

[Analytical methods]

The following analyses will be performed for hypoglycemia that occur prior to the start of the study drug for Treatment Period II by treatment group, and for those occurring after the start of SYR-472 25 mg tablet. Subjects who concomitantly receive insulin preparation will be included in these analyses of hypoglycemia, while subjects who concomitantly receive insulin preparation and SYR-472 25 mg tablet will be included in the analysis of hypoglycemia occurring after the start of SYR-472 25 mg tablet.

- Severe hypoglycemia
- Documented symptomatic hypoglycemia
- Asymptomatic hypoglycemia
- Probable symptomatic hypoglycemia
- Relative hypoglycemia

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Randomized subjects: 53 subject per group, 106 in total

(Changed as of 12 September 2016)

<Justification of sample size>

In Study CCT-002, the intergroup difference (two-sided 95% CI) in the mean change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) between the SYR-472 100 mg group and placebo group was -0.56 ([-0.753, -0.367])%. In the same study, the standard deviation of the change in HbA1c (JDS value) at the end of the treatment period (value at the end of the treatment period - value at the end of the screening period) for each treatment group ranged from 0.523% to 0.628%.

In this study, which will administer SYR-472 at a dose of 25 mg once weekly to patients with type 2 diabetes mellitus complicated by severe renal impairment or end-stage renal failure, the intergroup difference in the mean change in HbA1c at the end of Treatment Period I from the end of the screening period (Week 0) between the SYR-472 25 mg group and placebo group is assumed to be -0.40%, given that the efficacy of SYR-472 25 mg in this study is similar to that of SYR-472 100 mg administered once weekly to patients with type 2 diabetes mellitus not complicated by renal impairment. The common standard deviation in each treatment group is assumed to be 0.80%.

Based on these assumptions, 86 subjects per group will be required to provide a 90% power in a two-sample t-test with a significance level of 5% (two-sided). Therefore, the sample size was set at 90 as randomized subjects per group at the start of the study allowing for the possibility that there exit some subjects whose primary endpoint cannot be evaluated.

However, achievement of the sample size as originally planned at the start of the study was found difficult because there were more than expected numbers of candidate subjects who did not provide consent and who dropped out during screening after providing consent for the study. It was therefore decided to change some of the inclusion and exclusion criteria for this study. After these changes, the ultimate number of subjects randomized and evaluable for the primary endpoints are expected to be around 53 and 51, respectively, per group.

Assuming the number of subjects per group as 51 under these assumptions, the study will provide a 70.6% power in a two-sample t-test with a significance level of 5% (two-sided).

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 the head of the institution guarantee access to source documents by the sponsor or its designee and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator or sub-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 or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., 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 regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable 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. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from reviewing and voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB 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 for approval. The IRB'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 (i.e., before conclusion of study contract). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., 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. Until the site receives notification, no protocol activities, including the informed consent procedure, may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB 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 and sponsor.

Regarding PGx investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for PGx investigations and a research protocol will require prior approval of the company IRB in Japan.

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 describes 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 further explains the nature of the study, its objectives, and potential risks and benefits. 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 approval of the informed consent form. The informed consent form must be approved by the IRB prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

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 must be signed or signed and sealed, and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal name, not nickname, using blue or black ballpoint ink. The investigator or sub-investigator must also sign or sign and seal and date the informed consent form at the time of consent and prior to the subject entering into the study.

Once signed or signed and sealed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs or signs and seals the informed consent in the subject's medical record. Copies of the signed or signed and sealed informed consent form 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.

The informed consent form for PGx research in the clinical study of SYR-472 will be used to explain the PGx research to subjects after the study itself is explained with the informed consent form for the study. PGx samples will be collected from subjects who have consented to both the study and the PGx research.

If a subject requests disposal of stored sample, the procedures described in Section 9.4 should be followed.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited

subject attributes, such as sex, age, or date of birth 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 its monitor or designee's monitor, representatives from any regulatory authority (e.g., Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs 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 (i.e., 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 the study, only the sponsor may make study information available to other study investigators, sub-investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results 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.

The investigator or sub-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 interventional clinical trials it sponsors anywhere in the world on the publicly accessible website (ClinicalTrials.gov and Japan Pharmaceutical Information Center-Clinical Trials Information) before start of study, as defined in Takeda Policy/Standard.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator or sub-investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-57.

[2] Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153-65.

[3] Takeda Pharmaceutical Company Limited. Package Insert for Zafatek® Tablets 100 and 50. March 2015 (Version 1)

[4] "The Guideline for Clinical Evaluation of Hypoglycemic Agents (Revised Draft)" [Internet]. 2014 [cited 2014 Dec]; [30 p.]. Available from: http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495140050

[5] The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (PMSB/ELD Notification No. 592 dated 24 May 1995)

[6] The Japan Diabetes Society. Training Guidebook for Board Certified Diabetologists revised 6th Edition. Shindan to Chiryo Sha. Inc. 2014.

[7] Japanese Society of Nephrology. Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. Tokyo-igakusha. 2012.

[8] Japanese Society of Nephrology. Evidence-based Clinical Practice Guideline for CKD 2013. Tokyo-igakusha. 2013.

[9] The Japan Diabetes Society. Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013. Nankodo. 2013.

[10] The Japanese Society for Dialysis Therapy. Best Practice for Diabetic Patients on Hemodialysis 2012. Journal of Japanese Society for Dialysis Therapy. 2013;46(3):311-57.

[11] CCI

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