



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

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

STATISTICAL ANALYSIS PLAN

Study 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

Protocol No. : SYR-472-3003

Sponsor : Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

PPD  Takeda Pharmaceutical Company Limited

PPD 

Trial Statistician

PPD  Takeda Pharmaceutical Company Limited

PPD 

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

- Study Day: The day before the start of the study drug administration will be defined as Day -1 and the day of the start of the study drug administration will be defined as Day 1.
- Follow-up Day for Treatment Period I: The day after the last administration of the study drug for Treatment Period I will be defined as Follow-up Day 1 for Treatment Period I.
- Study Day for Treatment Period II: The day before the start of the study drug administration for Treatment Period II will be defined as Day -1 for Treatment Period II and the day of the start of the study drug administration for Treatment Period II will be defined as Day 1 for Treatment Period II.
- Study Day for SYR-472 25 mg tablet: The day before the start of SYR-472 25 mg tablet will be defined as Day -1 for SYR-472 25 mg tablet and the day of the start of SYR-472 25 mg tablet will be defined as Day 1 for SYR-472 25 mg tablet.
- Follow-up Day for SYR-472 25 mg tablet: The day after the last administration of SYR-472 25 mg tablet will be defined as Follow-up Day 1 for SYR-472 25 mg tablet.
- Treatment groups: SYR-472 25 mg group (subjects who received SYR-472 25 mg in both Treatment Periods I and II), placebo group (subjects who received placebo in Treatment Period I and SYR-472 25 mg in Treatment Period II).

In this statistical analysis plan (hereinafter referred to as SAP), the treatment groups will be presented as the SYR-472 25 mg/SYR-472 25 mg group and the placebo/SYR-472 25 mg group.

- Summary statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Reason for not being treated with the study drug for Treatment Period II: If the subject is “Not treated” with the study drug for Treatment Period II, the reason why the administration of study drug was discontinued will be analyzed as the reason for not being treated with the study drug for Treatment Period II.
- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of the study drug administration. Since there is a possibility that the evaluation result of an adverse event may differ before and after the start of the study drug administration for Treatment Period II, the evaluation result of adverse event to be used for analysis will be defined according to the rules below:
 - TEAEs that occur before the start of the study drug for Treatment Period II: The analysis will be performed based on the evaluation result entered in the CRF under “Pretreatment Event/Adverse Event (Period 1).”
 - TEAEs that occur after the start of SYR-472 25 mg tablet: The analysis will be performed based on the evaluation results entered in the CRFs under “Pretreatment Event/Adverse Event (Period 1)” and “Pretreatment Event/Adverse Event (Period 2 and thereafter).” If the

evaluation results differ between “Pretreatment Event/Adverse Event (Period 1)” and “Pretreatment Event/Adverse Event (Period 2 and thereafter),” the evaluation result of “Pretreatment Event/Adverse Event (Period 2 and thereafter)” will be preferentially used.

- Time of onset: In the analysis of TEAEs that occur before the start of the study drug for Treatment Period II, the time of onset will be calculated by defining the day of the start of the study drug administration as day 1. In the analysis of TEAEs that occur after the start of SYR-472 25 mg tablet, it will be calculated by defining the day of the start of SYR-472 25 mg tablet as day 1.
- Number of days from the immediate study drug administration: To be calculated by defining the day of the immediate study drug administration as Day 1. If the study drug administration and TEAE occur on the same day, the number of days from the immediate study drug administration will be defined as 1 day.
- Complications of hepatobiliary disorders: Concurrent medical conditions summarized as hepatobiliary disorders by SOC.
- MAV: An abbreviation for markedly abnormal value.
- Overall hypoglycemia: Hypoglycemia reported as “Yes” for hypoglycemic symptoms and asymptomatic hypoglycemia.
- Asymptomatic hypoglycemia: Hypoglycemia with an evaluable self-monitoring blood glucose value (i.e., non-missing and determined to be eligible based on “Handling Rules for Analysis Data”) and a measured concentration of ≤ 70 mg/dL but determined to be not accompanied by symptoms of hypoglycemia at the measurement of that blood glucose value. The presence or absence of asymptomatic hypoglycemia will be determined for each blood glucose value measured.

HANDLING OF TIME WINDOW

For each test, observation, and evaluation items, evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) will be handled according to the following rules.

The evaluable data within the acceptable window will be used. If more than one evaluable datum lies within the same acceptable window, the data whose test/observation/evaluation date is closest to the scheduled date will be used and, if there are two data equidistant to the scheduled date, the data obtained earlier will be used for efficacy endpoints and the data obtained later will be used for safety endpoints.

HbA1c

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -29			
Week -2	Study Day: -14	-28 to -8			
Week 0	Study Day: 1	-7 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	
Week 16	Study Day: 113	99 to 126		2 ~	~ 20
Week 20	Study Day: 141	127 to 154		2 ~	~ 20
Week 24	Study Day: 169	155 to 182		2 ~	~ 20
Week 28	Study Day: 197	183 to 210		2 ~	~ 20
Week 32	Study Day: 225	211 to 238		2 ~	~ 20
Week 36	Study Day: 253	239 to 266		2 ~	~ 20
Week 40	Study Day: 281	267 to 294		2 ~	~ 20
Week 44	Study Day: 309	295 to 322		2 ~	~ 20
Week 48	Study Day: 337	323 to 350		2 ~	~ 20
Week 52	Study Day: 365	351 to 378		2 ~	~ 20
At the End of Treatment Period I	Follow-up Day for Treatment Period I: 7	2 ~	~ 20	~ 1	
At the End of Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet: 7			2 ~ *	~ 20

*: At the end of Treatment Period II, "Study Day for Treatment Period II" will be assumed to be "Study Day for SYR-472 25 mg tablet."

Fasting blood glucose

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -22			
Week 0	Study Day: 1	-21 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	
Week 16	Study Day: 113	99 to 126		2 ~	~ 20
Week 20	Study Day: 141	127 to 154		2 ~	~ 20
Week 24	Study Day: 169	155 to 182		2 ~	~ 20
Week 28	Study Day: 197	183 to 210		2 ~	~ 20
Week 32	Study Day: 225	211 to 238		2 ~	~ 20
Week 36	Study Day: 253	239 to 266		2 ~	~ 20
Week 40	Study Day: 281	267 to 294		2 ~	~ 20
Week 44	Study Day: 309	295 to 322		2 ~	~ 20
Week 48	Study Day: 337	323 to 350		2 ~	~ 20
Week 52	Study Day: 365	351 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28
At the End of Treatment Period I	Follow-up Day for Treatment Period I: 7	2 ~	~ 20	~ 1	
At the End of Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet: 7			2 ~ *	~ 20

*: At the end of Treatment Period II, "Study Day for Treatment Period II" will be assumed to be "Study Day for SYR-472 25 mg tablet."

Glycoalbumin

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -29			
Week -2	Study Day: -14	-28 to -8			
Week 0	Study Day: 1	-7 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	
Week 16	Study Day: 113	99 to 126		2 ~	~ 20

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week 20	Study Day: 141	127 to 154		2 ~	~ 20
Week 24	Study Day: 169	155 to 182		2 ~	~ 20
Week 28	Study Day: 197	183 to 210		2 ~	~ 20
Week 32	Study Day: 225	211 to 238		2 ~	~ 20
Week 36	Study Day: 253	239 to 266		2 ~	~ 20
Week 40	Study Day: 281	267 to 294		2 ~	~ 20
Week 44	Study Day: 309	295 to 322		2 ~	~ 20
Week 48	Study Day: 337	323 to 350		2 ~	~ 20
Week 52	Study Day: 365	351 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28
At the End of Treatment Period I	Follow-up Day for Treatment Period I: 7	2 ~	~ 20	~ 1	
At the End of Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet: 7			2 ~ *	~ 20

*: At the end of Treatment Period II, "Study Day for Treatment Period II" will be assumed to be "Study Day for SYR-472 25 mg tablet."

Fasting C-peptide

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -29			
Week -2	Study Day: -14	-28 to -8			
Week 0	Study Day: 1	-7 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	
Week 24	Study Day: 169	99 to 210		2 ~	~ 20
Week 36	Study Day: 253	211 to 308		2 ~	~ 20
Week 52	Study Day: 365	309 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
At the End of Treatment Period I	Follow-up Day for Treatment Period I: 7	2 ~	~ 20	~ 1	
At the End of Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet: 7			2 ~ *	~ 20

*: At the end of Treatment Period II, "Study Day for Treatment Period II" will be assumed to be "Study Day for SYR-472 25 mg tablet."

Fasting glucagon, DPP-4 activity

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week 0	Study Day: 1	-49 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	
Week 24	Study Day: 169	99 to 210		2 ~	~ 20
Week 36	Study Day: 253	211 to 308		2 ~	~ 20
Week 52	Study Day: 365	309 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28
At the End of Treatment Period I	Follow-up Day for Treatment Period I: 7	2 ~	~ 20	~ 1	
At the End of Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet: 7			2 ~ *	~ 20

*: At the end of Treatment Period II, "Study Day for Treatment Period II" will be assumed to be "Study Day for SYR-472 25 mg tablet."

Weight, BMI

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -29			
Week -2	Study Day: -14	-28 to -8			
Week 0	Study Day: 1	-7 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	
Week 16	Study Day: 113	99 to 126		2 ~	~ 20
Week 20	Study Day: 141	127 to 154		2 ~	~ 20
Week 24	Study Day: 169	155 to 182		2 ~	~ 20
Week 28	Study Day: 197	183 to 210		2 ~	~ 20
Week 32	Study Day: 225	211 to 238		2 ~	~ 20
Week 36	Study Day: 253	239 to 266		2 ~	~ 20
Week 40	Study Day: 281	267 to 294		2 ~	~ 20
Week 44	Study Day: 309	295 to 322		2 ~	~ 20
Week 48	Study Day: 337	323 to 350		2 ~	~ 20
Week 52	Study Day: 365	351 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28
At the End of Treatment Period I	Follow-up Day for Treatment Period I: 7	2 ~	~ 20	~ 1	
At the End of Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet: 7			2 ~ *	~ 20

*: At the end of Treatment Period II, "Study Day for Treatment Period II" will be assumed to be "Study Day for SYR-472 25 mg tablet."

Vital signs, laboratory test, creatinine clearance, eGFR

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -29			
Week -2	Study Day: -14	-28 to -8			
Week 0	Study Day: 1	-7 to 1			
Week 2	Study Day: 15	2 to 22	~ 20	~ 1	
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 8	Study Day: 57	43 to 70	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week 16	Study Day: 113	99 to 126		2 ~	~ 20
Week 20	Study Day: 141	127 to 154		2 ~	~ 20
Week 24	Study Day: 169	155 to 182		2 ~	~ 20
Week 28	Study Day: 197	183 to 210		2 ~	~ 20
Week 32	Study Day: 225	211 to 238		2 ~	~ 20
Week 36	Study Day: 253	239 to 266		2 ~	~ 20
Week 40	Study Day: 281	267 to 294		2 ~	~ 20
Week 44	Study Day: 309	295 to 322		2 ~	~ 20
Week 48	Study Day: 337	323 to 350		2 ~	~ 20
Week 52	Study Day: 365	351 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28

12-lead ECG

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week -6	Study Day: -42	-49 to -22			
Week 0	Study Day: 1	-21 to 1			
Week 4	Study Day: 29	2 to 56	~ 20	~ 1	
Week 12	Study Day: 85	57 to 98	~ 20	~ 1	
Week 24	Study Day: 169	99 to 210		2 ~	~ 20
Week 36	Study Day: 253	211 to 308		2 ~	~ 20
Week 52	Study Day: 365	309 to 378		2 ~	~ 20
Week 54	Follow-up Day for SYR-472 25 mg Tablet: 21				21 to 28

Plasma concentration of SYR-472Z

Visit	Scheduled Study Day	Acceptable Window			
		Study Day	Follow-up Day for Treatment Period I	Study Day for Treatment Period II	Follow-up Day for SYR-472 25 mg Tablet
Week 4	Study Day: 29	23 to 42	~ 20	~ 1	
Week 12	Study Day: 85	71 to 98	~ 20	~ 1	

OTHER HANDLING

- Creatinine clearance (mL/min): To be calculated using the following Cockcroft-Gault equation (rounded off to the nearest integer in both cases).

Male: $([140 - \text{Age}] \times \text{Weight [kg]}) / (72 \times \text{Serum creatinine [mg/dL]})$

Female: $0.85 \times ([140 - \text{Age}] \times \text{Weight [kg]}) / (72 \times \text{Serum creatinine [mg/dL]})$

Creatinine clearance will be calculated when the variables to be used for calculation are all evaluable and measured on the same day. The age will be calculated from the test dates of variables to be used for calculation and the date of birth.
- eGFR (mL/min/1.73 m²): To be calculated using the following equation (rounded off to the nearest integer in both cases).

Male: $194 \times \text{Serum creatinine (mg/dL)}^{-1.094} \times \text{Age}^{-0.287}$

Female: $194 \times \text{Serum creatinine (mg/dL)}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$

The age will be calculated from the test dates of variables to be used for calculation and the date of birth.
- Duration of disease (months): Period from the onset time of type 2 diabetes until the time of informed consent.
- Duration of study drug exposure for Treatment Period I: Date of the last administration of the study drug for Treatment Period I – Date of the start of the study drug administration for Treatment Period I + 1
- Compliance with study drug for Treatment Period I: Number of study drug administrations for Treatment Period I / (Smallest integer of \geq [(Date of the last administration of the study drug for Treatment Period I – Date of the start of the study drug administration for Treatment Period I + 7) / 7]) $\times 100$ (rounded off to the first decimal place)
- Duration of exposure to SYR-472 25 mg tablet: Date of the last administration of SYR-472 25 mg tablet – Date of the start of SYR-472 25 mg tablet + 1
- Compliance with SYR-472 25 mg tablet: Number of administrations of SYR-472 25 mg tablet / (Smallest integer of \geq [(Date of the last administration of SYR-472 25 mg tablet – Date of the start of SYR-472 25 mg tablet + 7) / 7]) $\times 100$ (rounded off to the first decimal place)

1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS

1.1 Disposition of Subjects

1.1.1 Study Information

Analysis set: All subjects who signed the informed consent form

Analysis variables: Date first subject signed the informed consent form
Date of last visit or contact, whichever comes later
MedDRA version
WHO Drug version
SAS version used for creating the datasets

Analysis methodology: The following analysis will be performed for the above analysis variables.
(1) Display of the analysis variables

1.1.2 Disposition of All Subjects Who Were Not Randomized

Analysis set: All subjects who were not randomized

Analysis variables: Categories in brackets [] (hereinafter the same)
Age (years) [Min≤ - <65, 65≤ - ≤Max]
Sex [Male, Female]

Analysis methodology: The following analysis will be performed for the above analysis variables.
(1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.1.3 Subject Eligibility

Analysis set: All subjects who signed the informed consent form

Analysis variables: Eligibility for randomization [Eligible, Not eligible]
Reason for not being randomized [Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Did not meet inclusion criteria or did meet exclusion criteria, Other]

Analysis methodology: The following analysis will be performed for the above analysis variables.
When calculating percentages for the reasons for not being

randomized, the number of subjects who were not randomized will be used as the denominator.

(1) Frequency distribution

1.1.4 Number of Subjects Who Were Randomized by Site

Analysis set:	All subjects who were randomized
Analysis variables:	Eligibility for randomization
Stratum:	Study site
	[Site numbers will be used as categories]

Analysis methodology: The following analysis will be performed for the above analysis variables for each stratum by each treatment group and in the consolidated treatment groups.

(1) Frequency distribution

1.1.5 Disposition of Subjects

1.1.5.1 Disposition of Subjects in Treatment Period I

Analysis set:	All subjects who were randomized
Analysis variables:	Study drug administration status
	Reason for not being treated
	[Not treated] [Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study drug administration status for Treatment Period II
	Reason for not being treated
	[Treated, Not treated] [Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]

Analysis methodology: The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups. When calculating percentages of the reasons for not being treated, the number of subjects who did not receive with the study

drug will be used as the denominator.

(1) Frequency distribution

1.1.5.2 Disposition of Subjects in the Entire Study

Analysis set:	All subjects who were randomized	
Analysis variables:	Study drug administration status	[Not treated]
	Reason for not being treated	[Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study drug completion status	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Completion status of the follow-up period	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]

Analysis methodology: The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups. When calculating percentages of the reasons for not being treated, the number of subjects who did not receive the study drug will be used as the denominator. When calculating percentages of the reasons for not being completed, the number of subjects who did not complete the study drug/follow-up period will be used as the denominator.

(1) Frequency distribution

1.1.6 Study Drug Completion Status

Analysis set:	All subjects who were randomized	
Analysis variables:	Study drug completion status	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Significant protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Categories:	Number of study drug administrations	[0, 1-4, 5-8, 9-12, 13-24, 25-36, 37-48, 49-52, 53-Max]
Analysis methodology:	<p>The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups.</p> <p>(1) Frequency distribution by number of study drug administrations</p>	

1.1.7 Protocol Deviations and Analysis Sets

1.1.7.1 Protocol Deviations

Analysis set:	All subjects who were randomized	
Analysis variables:	Protocol deviations	[Major GCP violations, Deviations of protocol entry criteria, Deviations of discontinuation criteria, Deviations related to treatment procedure or dose, Deviations concerning excluded medication or therapy, Deviations to avoid emergency risk, Other]
Analysis methodology:	<p>The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups.</p> <p>Frequency distribution of subjects with protocol deviations will be provided for each deviation category above. A subject who has several deviations that can be classified into the same category will be counted once in each appropriate category (overlapped counting).</p> <p>(1) Frequency distribution</p>	

1.1.7.2 Analysis Sets

Analysis set:	All subjects who were randomized	
Analysis variables:	Handling of subjects and subject data in analysis sets	[Categories are based on the specifications in “Handling Rules for Analysis Data”]
Inclusion/Exclusion of analysis sets		
	Full analysis set	[Included]
	Per protocol set	[Included]
	Safety analysis set	[Included]
Analysis methodology:	<p>The following analyses of (1) and (2) will be performed for the above analysis variables by treatment group and the following analysis of (3) will be performed by each treatment group and in the consolidated treatment groups.</p> <p>A subject who corresponds to several categories in (1) and (2) will be counted once in each appropriate category (overlapped counting).</p> <ol style="list-style-type: none"> (1) Frequency distributions concerning the handling of subjects in each analysis set (2) Frequency distributions concerning the handling of subject data in each analysis set (3) Frequency distributions concerning the number of subjects included in each analysis set 	

1.2 Demographic and Other Baseline Characteristics

1.2.1 Distribution of Baseline Demographics

Analysis set:	All subjects who were randomized	
Analysis variables:	Age (years)	[Min \leq - <65, 65 \leq - \leq Max]
		[Min \leq - <75, 75 \leq - \leq Max]
	Sex	[Male, Female]
	Height (cm)	
	Weight (kg) (Week 0)	
	BMI (kg/m ²) (Week 0)	[Min \leq - <18.5, 18.5 \leq - <25.0, 25.0 \leq - <30.0, 30.0 \leq - \leq Max]
	Duration of disease (months)	[Min \leq - \leq 24, 24< - \leq 60, 60< - \leq 120, 120< - \leq Max]
	Smoking status	[Never smoked, Current smoker, Ex-smoker]
	Alcohol use	[Yes, No]

Exercise therapy	[Yes, No]
Hemodialysis	[Yes (end-stage renal failure), No (severe renal impairment)]
Use of antidiabetic drugs (Week -6)	[Yes, No]
Rapid-acting insulin	[Yes, No]
secretagogues	
Details of rapid-acting insulin secretagogues	
Mitiglinide calcium hydrate	[Yes]
Repaglinide	[Yes]
α -glucosidase inhibitors	[Yes, No]
Details of α -glucosidase inhibitors	
Acarbose	[Yes]
Miglitol	[Yes]
Voglibose	[Yes]
Insulin preparations	[Yes, No]
Types of insulin preparations	[Mixed, intermediate-acting, Long-acting soluble]
Reason for concomitant use of antidiabetic drugs being judged to be appropriate	[Combination therapy is expected to be more effective, Development of AEs due to dose increase is concerned, Maximum dose has already been administered, Other]
Creatinine (mg/dL) (Week 0)	Male
Male	[Min \leq - \leq 2.4, 2.4 $<$ - \leq Max]
Female	Female
	[Min \leq - \leq 2.0, 2.0 $<$ - \leq Max]
Creatinine clearance (mL/min) (Week 0)	
eGFR (mL/min/1.73 m ²) (Week 0)	[Min \leq - $<$ 15, 15 \leq - $<$ 30, 30 \leq - \leq Max]
HbA1c (%) (Week 0)	[Min \leq - $<$ 7.0, 7.0 \leq - \leq Max]
	[Min \leq - $<$ 8.0, 8.0 \leq - \leq Max]

Fasting blood glucose (mg/dL) (Week 0)	[Min≤ - <130, 130≤ - <160, 160≤ - ≤Max]
Glycoalbumin (%) (Week 0)	[Min≤ - <24, 24≤ - ≤Max]
Fasting C-peptide (ng/mL) (Week 0)	[Min≤ - <1.0, 1.0≤ - <2.0, 2.0≤ - ≤Max]
Fasting glucagon (pg/mL) (Week 0)	
DPP-4 activity (nmol/min/mL) (Week 0)	
Analysis methodology:	The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups. (1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.2.2 Medical History and Concurrent Medical Conditions

Analysis set:	Safety analysis set
Analysis variables:	Medical history Concurrent medical conditions
Analysis methodology:	The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups. The analysis variables will be coded using MedDRA dictionary and will be summarized based on the SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. (1) Frequency distributions for medical history (by SOC and PT) (2) Frequency distributions for concurrent medical conditions (by SOC and PT) The frequency distributions will be provided according to the rules below: [Number of subjects] A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

1.2.3 Medication History and Concomitant Medications

Analysis set:	Safety analysis set
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Analysis variables: Medication history
Concomitant medications

Analysis methodology: The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups.
The analysis variables will be coded by use of WHO Drug and summarized based on Preferred Name, which will be sorted in decreasing frequency.
A subject who has been administered several medications with the same Preferred Name will be counted only once for that Preferred Name.

- (1) Frequency distributions for medication history
- (2) Frequency distributions for concomitant medications that were discontinued prior to the first dose of the study drug
- (3) Frequency distributions for concomitant medications that were ongoing at the first dose of the study drug and continued in the treatment period
- (4) Frequency distributions for concomitant medications that started after the first dose of the study drug
- (5) Frequency distributions for concomitant medications that were ongoing at the first dose of the study drug and continued in the treatment period, and concomitant medications that started after the first dose of the study drug

1.2.4 Concomitant Antidiabetic Drugs Permitted in the Study

Analysis set: Full analysis set

Analysis variables: Newly added oral hypoglycemic drug [Yes, No]
in Treatment Period II (at Week 16
and thereafter)
Any change in antidiabetic drugs that [Yes, No]
are being used at Week -6 and will be
concomitantly used during the study
period in Treatment Period II

Stratum: Types of antidiabetic drugs [Rapid-acting insulin
secretagogues,
 α -glucosidase inhibitors,
Insulin preparations]

Analysis methodology: The following analysis will be performed for the newly added oral hypoglycemic drug in Treatment Period II (at Week 16 and thereafter) in subjects who are not using any antidiabetic drug at Week -16 among the full analysis set by treatment group. Also, the following analysis will be performed for any change in antidiabetic drugs that are being used at Week -6 and will be concomitantly used during the study period in Treatment Period II in subjects who are using antidiabetic drugs at Week -16 among the full analysis set by treatment group. Treatment Period II is the period from the start of the study drug administration for Treatment Period II until 20 days after the last administration of the study drug for Treatment Period II.

(1) Frequency distribution

1.3 Measurement of Compliance Status for Treatment

1.3.1 Study Drug Exposure and Compliance in the Treatment Period

Analysis set:	Safety analysis set	
Analysis variables:	Number of study drug administrations	[1-12, 13-24, 25-36, 37-48, 49-52, 53-Max]
	Number of study drug administrations in Treatment Period I	[1-4, 5-8, 9-12, 13-Max]
	Duration of study drug exposure in Treatment Period I (days)	[1-28, 29-56, 57-84, 85-Max]
	Compliance with study drug for Treatment Period I (%)	[Min≤ - ≤50.0, 50.0< - ≤70.0, 70.0< - ≤90.0, 90.0< - ≤Max]
	Number of administrations of SYR-472 25 mg tablet	[1-12, 13-24, 25-36, 37-48, 49-52, 53-Max]
	Duration of exposure to SYR-472 25 mg tablet (days)	[1-84, 85-168, 169-252, 253-336, 337-364, 365-Max]
	Compliance with SYR-472 25 mg tablet (%)	[Min≤ - ≤50.0, 50.0< - ≤70.0, 70.0< - ≤90.0, 90.0< - ≤Max]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups.	
	(1) Frequency distributions for categorical variables and summary statistics for continuous variables	

1.3.2 Compliance of Antidiabetic Drugs

Analysis set: Full analysis set

Analysis variables: Compliance with antidiabetic drugs [Fully complied (90% or more), Almost complied (70% or more), Occasionally complied (50% or more), Rarely complied (less than 50%)]

Visits: Weeks -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 or at discontinuation, and 54

Analysis methodology: The following analysis will be performed for the above analysis variables in subjects who are using antidiabetic drugs at Week -16 among the full analysis set by each treatment group and in the consolidated treatment groups.

(1) Frequency distributions at each visit

1.3.3 Compliance of Diet and/or Exercise Therapy

Analysis set: Full analysis set

Analysis variables: Compliance with diet [Fully complied (90% or more), Almost complied (70% or more), Occasionally complied (50% or more), Rarely complied (less than 50%)]

Compliance with exercise therapy [Fully complied (90% or more), Almost complied (70% or more), Occasionally complied (50% or more), Rarely complied (less than 50%)]

Visits: Weeks -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 or at discontinuation, and 54

Analysis methodology: The following analysis will be performed for the above analysis variables by each treatment group and in the consolidated treatment groups.

(1) Frequency distributions at each visit

2 EFFICACY ANALYSIS

The “full analysis set” based on the specifications in the protocol and the “Handling Rules for Analysis Data” will be the main analysis set. For the sensitivity point of view, the “per protocol set” will be used for an analysis performed secondarily on the primary endpoint in order to examine the robustness of the results.

2.1 Primary Endpoints and Analysis Methodology

2.1.1 Primary Analysis

Analysis set: Full analysis set

Analysis variables: Change in HbA1c at the end of Treatment Period I from Week 0

Analysis methodology: The population mean change in HbA1c at the end of Treatment Period I from Week 0 will be compared between the SYR-472 25 mg/SYR-472 25 mg group and placebo/SYR-472 25 mg group based on an analysis of covariance (ANCOVA) model for the change in HbA1c at the end of Treatment Period I from Week 0 with factors of treatment group and HbA1c at 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/SYR-472 25 mg group – placebo/SYR-472 25 mg group) and the two-sided 95% CI.

2.1.2 Secondary Analysis

Analysis set: Full analysis set
Per protocol set

Analysis variables: Change in HbA1c at the end of Treatment Period I from Week 0

Analysis methodology: The analysis (1) will be performed in the “full analysis set” and (2) in the “per protocol set” for the above analysis variables.

- (1) Summary statistics and the 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/SYR-472 25 mg group – placebo/SYR-472 25 mg group) and the two-sided 95% CI.
- (2) In addition, the same analyses as 2.1.1 Primary Analysis and 2.1.2 Secondary Analysis (1) will be performed to evaluate the robustness of the results in terms of a sensitivity analysis.

2.2 Secondary Endpoints and Analysis Methodology

2.2.1 HbA1c, Fasting Blood Glucose, Glycoalbumin

Analysis set:	Full analysis set
Analysis variables:	HbA1c Fasting blood glucose Glycoalbumin
Visits:	HbA1c Weeks -6, -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, at the end of Treatment Period I, and at the end of Treatment Period II Fasting blood glucose Weeks -6, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 54, at the end of Treatment Period I, and at the end of Treatment Period II Glycoalbumin Weeks -6, -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 54, at the end of Treatment Period I, and at the end of Treatment Period II
Analysis methodology:	<p>The following analyses (1) and (2) will be performed for the above analysis variables. Also, the following analysis (3) will be performed for HbA1c.</p> <p>For the mean and standard deviation plot, a plot until Treatment Period I and a plot for the entire study will be created, respectively, but the plot for the entire period will not be output at Week 54 or at the end of Treatment Period I.</p> <p>(1) Summary statistics and the two-sided 95% CI for the mean will be calculated for each visit and the mean and standard deviation plot by treatment group will be prepared. Also, the intergroup difference in the mean between treatment groups (SYR-472 25 mg/SYR-472 25 mg group – placebo/SYR-472 25 mg group) and the two-sided 95% CI will be calculated for each visit during the Screening and Treatment Period I.</p> <p>(2) The same analysis as the above (1) will be performed for changes from Week 0 at each visit after Treatment Period I.</p> <p>(3) 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%</p>

CIs will be calculated for each treatment group, and the intergroup difference in the proportions between treatment groups (SYR-472 25 mg/SYR-472 25 mg group – placebo/SYR-472 25 mg 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 Week 0 will be included in the analysis.

2.3 Other Endpoints and Analysis Methodology

2.3.1 Fasting C-peptide, Fasting Glucagon, DPP-4 Activity, Weight

Analysis set:	Full analysis set
Analysis variables:	Fasting C-peptide Fasting glucagon DPP-4 activity Weight
Visits:	Fasting C-peptide Weeks -6, -2, 0, 2, 4, 8, 12, 24, 36, 52, 54, at the end of Treatment Period I, and at the end of Treatment Period II Fasting glucagon, DPP-4 activity Weeks 0, 2, 4, 8, 12, 24, 36, 52, 54, at the end of Treatment Period I, and at the end of Treatment Period II Weight Weeks -6, -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 54, at the end of Treatment Period I, and at the end of Treatment Period II
Analysis methodology:	The following analyses (1) and (2) will be performed for the above analysis variables. For the mean and standard deviation plot, a plot until Treatment Period I and a plot for the entire study will be created respectively and the plot for the entire period will not be output at Week 54 and at the end of Treatment Period I. (1) Summary statistics and the two-sided 95% CI for the mean will be calculated for each visit and the mean and standard deviation plot by treatment group will be prepared. Also, the intergroup difference in the mean between treatment groups (SYR-472 25 mg/SYR-472 25 mg group – placebo/SYR-472

25 mg group) and the two-sided 95% CI will be calculated for each visit during the Screening and Treatment Period I.

(2) The same analysis as the above (1) will be performed for changes from Week 0 at each visit after Treatment Period I (for DPP-4 activity, inhibition rate $[100 \times (\text{Week 0} - \text{each visit after Treatment Period I}) / \text{Week 0}]$, rounded off to the first decimal place]).

2.4 Statistical and Analytical Issues

2.4.1 Adjustments for Covariates

See 2.1.1 Primary Analysis.

2.4.2 Handling of Dropouts or Missing Data

Missing test results and ineligible data according to the “Handling Rules for Analysis Data” or the SAP will be excluded from statistical analyses and estimations.

2.4.3 Interim Analysis and Data Monitoring

No interim analysis is planned.

2.4.4 Multicenter Studies

Although this is a multicenter study, interactions between treatment and the study site will not be investigated since the target number of subjects per study site is not sufficiently large for meaningful analyses of the interactions.

2.4.5 Multiple Comparisons/Multiplicity

The main focuses will be placed on the results of the primary analysis performed for the primary endpoint defined as “change in HbA1c at the end of Treatment Period I from Week 0” in the “full analysis set.” Other analytical results will be interpreted to support the results of the primary endpoint or to explore the characteristics of efficacy of the study drug. These results will be considered one measure suggesting the trends or characteristics of efficacy. Thus, no adjustment for multiplicity will be performed.

2.4.6 Use of an “Efficacy Subset of Subjects”

To confirm the robustness of the primary analysis results for the primary endpoint for the sensitivity point of view, the same analysis as for the “full analysis set” will be performed secondarily in the “per protocol set.”

2.4.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority

Not applicable.

2.4.8 Examination of Subgroups

Analysis set:	Full analysis set
Analysis variables:	Change in HbA1c at the end of Treatment Period I from Week 0
Stratum:	<p>Age (years) [Min≤ - <65, 65≤ - ≤Max]</p> <p>Sex [Male, Female]</p> <p>BMI (kg/m²) (Week 0) [Min≤ - <25.0, 25.0≤ - <30.0, 30.0≤ - ≤Max]</p> <p>Duration of disease (months) [Min≤ - ≤120, 120< - ≤Max]</p> <p>Medication history [Yes, No]</p> <p>Hemodialysis [Yes (end-stage renal failure), No (severe renal impairment)]</p>
	<p>Use of antidiabetic drugs (Week -6) [Yes, No]</p> <p>Rapid-acting insulin secretagogues [Yes, No]</p> <p>α-glucosidase inhibitors [Yes, No]</p> <p>Insulin preparations [Yes, No]</p>
	<p>eGFR (mL/min/1.73 m²) (Week 0) [Min≤ - <15, 15≤ - ≤Max]</p> <p>HbA1c (%) (Week 0) [Min≤ - <7.0, 7.0≤ - ≤Max] [Min≤ - <8.0, 8.0≤ - ≤Max]</p> <p>Fasting blood glucose (mg/dL) [Min≤ - <160, 160≤ - =Max] (Week 0)</p>
	<p>Glycoalbumin (%) (Week 0) [Min≤ - <24, 24≤ - ≤Max]</p> <p>Fasting C-peptide (ng/mL) [Min≤ - <2.0, 2.0≤ - ≤Max] (Week 0)</p>
Analysis methodology:	<p>The following analyses will be performed for the above analysis variables.</p> <p>(1) Summary statistics and the two-sided 95% CI for the mean will be calculated for each stratum by treatment group, as well as the intergroup difference in the mean between treatment groups (SYR-472 25 mg/SYR-472 25 mg group – placebo/SYR-472 25 mg group) and the two-sided 95% CI.</p> <p>(2) The ANCOVA will be performed for each stratum with the change in HbA1c at the end of Treatment Period I from Week 0 as the response and with treatment group, stratum, and</p>

interactions of treatment group and stratum as factors. The stratum will be included in the ANCOVA model as category variables based on the above category and analyzed.

2.5 Plasma Concentration of SYR-472Z

Analysis set: Full analysis set

Analysis variables: Plasma concentration of SYR-472Z

Stratum: Hemodialysis [Yes (end-stage renal failure), No (severe renal impairment)]

Visits: Weeks 4 and 12

Analysis methodology: Summary statistics will be calculated for the above analysis variables for each visit in the SYR-472 25 mg/SYR-472 25 mg group among the full analysis set.
The same analysis as the above will be performed for each stratum.

3 SAFETY ANALYSIS

3.1 Treatment-Emergent Adverse Event

3.1.1 Overview of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set	
Analysis variables:	TEAEs that occur before the start of the study drug for Treatment Period II	
	TEAEs that occur after the start of SYR-472 25 mg tablet	
Categories:	Causality [Related, Not related] Intensity [Mild, Moderate, Severe]	
Analysis methodology:	<p>The following summaries will be provided for the above analysis variables by treatment group.</p> <p>In the analysis of TEAEs occurring after the start of SYR-472 25 mg tablet, subjects who received SYR-472 25 mg tablet in the safety analysis set will be included in the analyses and the summaries in the consolidated treatment groups will be also provided.</p>	
	<p>(1) Overview of TEAEs</p> <ol style="list-style-type: none"> 1) All TEAEs (number of events, number and percentage of subjects) 2) Causal relationship between all TEAEs and study drug (number of events, number and percentage of subjects) 3) Intensity of all TEAEs (number of events, number and percentage of subjects) 4) TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects) 5) Serious TEAEs (number of events, number and percentage of subjects) 6) Causal relationship between serious TEAEs and study drug (number of events, number and percentage of subjects) 7) Serious TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects) 8) TEAEs leading to death (number of events, number and percentage of subjects) 	
	<p>TEAEs will be counted according to the rules below:</p> <p>[Number of subjects]</p> <ul style="list-style-type: none"> • In the case of “summaries by causality” <p>A subject with occurrences of TEAE in both categories (i.e.,</p>	

“Related” and “Not related”) will be counted once in the “Related” category.

- In the case of “summaries by intensity”

A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- In the case of summaries other than the above

A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

3.1.2 Displays of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set	
Analysis variables:	TEAEs that occur before the start of the study drug for Treatment Period II	
	TEAEs that occur after the start of SYR-472 25 mg tablet	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of onset (day)	TEAEs that occur before the start of the study drug for Treatment Period II
		[1-28, 29-56, 57-Max]
		[1-14, 15-28, 29-Max]
		TEAEs that occur after the start of SYR-472 25 mg tablet
		[1-84, 85-168, 169-252, 253-336, 337-Max]
		[1-14, 15-28, 29-Max]
	Number of days from the immediate study drug administration (days)	[1, 2, 3, 4, 5, 6, 7, 8-Max]
Analysis methodology:	<p>The following summaries will be provided for the above analysis variables using frequency distributions by treatment group.</p> <p>In the analysis of TEAEs occurring after the start of SYR-472 25 mg tablet, subjects who received SYR-472 25 mg tablet in the safety analysis set will be included in the analyses and the summaries in the consolidated treatment groups will be also provided concerning (1) and (4).</p>	

TEAEs will be coded using MedDRA dictionary and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

- (1) All TEAEs by SOC and PT
- (2) All TEAEs by SOC
- (3) All TEAEs by PT
- (4) Drug-related TEAEs by SOC and PT
- (5) Intensity of all TEAEs by SOC and PT
- (6) Intensity of drug-related TEAEs by SOC and PT
- (7) TEAEs leading to study drug discontinuation by SOC and PT
- (8) Serious TEAEs by SOC and PT
- (9) All TEAEs by SOC and PT over time
- (10) Number of days from the immediate study drug administration for all TEAEs by SOC and PT
- (11) TEAEs whose incidence summarized by PT is 2% or higher (rounded off to the first decimal place) in either treatment group by SOC and PT
- (12) Intestinal obstruction-related TEAEs by SOC and PT
- (13) Acute pancreatitis-related TEAEs by SOC and PT
- (14) QT/QTc interval prolongation-related TEAEs by SOC and PT
- (15) Hypersensitivity-related TEAEs by SOC and PT
- (16) Cardiovascular TEAEs by SOC and PT
- (17) Pemphigoid TEAEs by SOC and PT
- (18) Renal impairment TEAEs by SOC and PT
- (19) Hypoglycemia-related TEAEs by SOC and PT

The frequency distribution and incidence will be provided according to the rules below:

[Number of subjects]

- In the case of “summaries by SOC and PT, by SOC, and by PT” A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages of TEAEs will be based on the number of subjects in the analysis set.
- In the case of “summaries of intensity by SOC and PT”

A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages of TEAEs will be based on the number of subjects in the analysis set.

- In the case of “summaries by SOC and PT over time”

A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.

When calculating percentages of TEAEs for each time interval, the number of subjects at risk (i.e., “subjects who either have an exposure in the study or have an occurrence of TEAE, during or after the corresponding time interval”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAEs is within the time interval” will be used as the numerator.

- In the case of “summaries of number of days from the immediate study drug administration” by SOC and PT

A subject with a TEAE that occurs in more than one category of number of days is counted in all the categories that the TEAE occurs. For each category of number of days, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. Percentages of TEAEs will be based on the number of subjects in the analysis set.

3.1.3 Subgroup Analysis of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set	
Analysis variables:	TEAEs that occur before the start of the study drug for Treatment Period II	
	TEAEs that occur after the start of SYR-472 25 mg tablet	
Stratum:	Age (years)	[Min≤ - <65, 65≤ - ≤Max] [Min≤ - <75, 75≤ - ≤Max]
	Hemodialysis	[Yes (end-stage renal failure), No (severe renal impairment)]
	Complications of hepatobiliary disorders	[Yes, No]

Use of antidiabetic drugs (Week -6) [Yes, No]

Rapid-acting insulin [Yes, No]

secretagogues

α -glucosidase inhibitors [Yes, No]

Insulin preparations [Yes, No]

eGFR (mL/min/1.73 m²) (Week 0) [Min≤ - <15, 15≤ - ≤Max]

Analysis methodology: The following summaries will be provided for the above analysis variables using frequency distributions for each stratum by treatment group for TEAEs occurring before the start of the study drug for Treatment Period II and in the consolidated treatment groups for TEAEs occurring 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 in the safety analysis set will be included in the analyses. TEAEs will be coded using MedDRA dictionary and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

- (1) All TEAEs by SOC and PT
- (2) Drug-related TEAEs by SOC and PT

The frequency distributions will be provided according to the rules below:

[Number of subjects]

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

3.2 Pretreatment Event

3.2.1 Display of Pretreatment Events

Analysis set: All subjects who signed the informed consent form

Analysis variables: PTE

Analysis methodology: The following summaries will be provided for the above analysis variables using frequency distributions.

PTEs will be coded using MedDRA dictionary and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

- (1) All PTEs by SOC and PT

(2) Serious PTEs by SOC and PT

The frequency distributions will be provided according to the rules below:

[Number of subjects]

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

3.3 Clinical Laboratory Evaluations and Other Safety Endpoints

3.3.1 Clinical Laboratory Evaluations

3.3.1.1 Hematology and Serum Chemistry

Analysis set:	Safety analysis set		
Analysis variables:	Hematology		
	Red blood cells	Reticulocytes	White blood cells
	Hemoglobin	Hematocrit	Platelets
	Neutrophils	Lymphocytes	Monocytes
	Eosinophils	Basophils	MCV
	MCH	MCHC	
	Serum chemistry		
	ALT	AST	
	γ-GTP	ALP	
	Total bilirubin	Total protein	
	Albumin	Creatinine	
	Amylase	Lipase	
	Blood urea nitrogen	Uric acid	
	Creatine kinase	LDH	
	Total cholesterol	Triglyceride	
	LDL cholesterol	HDL cholesterol	
	High-sensitivity CRP	K	
	Na	Ca	
	Cl	P	
	Fe	Creatinine clearance	
Categories:	Adjudication results based on the normal reference ranges [Low, Normal, High]		
Visits:	Weeks -6, -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and		

Analysis methodology: The following analysis will be performed for the above analysis variables except for high-sensitivity CRP and creatinine clearance by treatment group. The following analyses of (1) to (2) will be performed for high-sensitivity CRP and creatinine clearance by treatment group.

When the analysis of MAV is performed, if both “upper” and “lower” criteria in the MAV Criteria are applicable to the same test item, the analysis will be performed for each criterion separately. See Appendix 2 of this SAP for the definitions of test items subject to this analysis and the MAV Criteria.

- (1) Summary statistics for each visit and summary statistics for change from Week 0 at each visit after Treatment Period I
- (2) Case plots
- (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each visit after Treatment Period I
- (4) Frequency distributions for MAV before the start of the study drug administration for Treatment Period II and after the start of SYR-472 25 mg tablet

3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety

3.3.2.1 Vital Signs

Analysis set: Safety analysis set

Analysis variables: Systolic blood pressure
Diastolic blood pressure
Pulse

Visits: Weeks -6, -2, 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 54

Analysis methodology: The following analysis will be provided for the above analysis variables by treatment group.

- (1) Summary statistics for each visit and summary statistics for change from Week 0 at each visit after Treatment Period I
- (2) Case plots

3.3.2.2 12-lead ECG

Analysis set: Safety analysis set

Analysis variables: Heart rate

RR interval	
PR interval	
QRS interval	
QT interval	
QTcF interval	
Findings of 12-lead ECG	[Within normal limits, Abnormal but not clinically significant, Abnormal and clinically significant]
Visits:	Weeks -6, 0, 4, 12, 24, 36, 52, and 54
Analysis methodology:	<p>The following analyses of (1) to (3) will be performed for the above analysis variables except for findings of 12-lead ECG by treatment group.</p> <p>The following analyses of (4) will be performed for findings of 12-lead ECG by treatment group.</p> <p>When the analysis of MAV is performed, if both “upper” and “lower” criteria in the MAV Criteria are applicable to the same test item, the analysis will be performed for each criterion separately.</p> <p>See Appendix 2 of this SAP for the definitions of test items subject to this analysis and the MAV Criteria.</p> <ul style="list-style-type: none"> (1) Summary statistics for each visit and summary statistics for change from Week 0 at each visit after Treatment Period I (2) Case plots (3) Frequency distributions for MAV before the start of the study drug administration for Treatment Period II and after the start of SYR-472 25 mg tablet (4) Shift tables showing at Week 0 and each visit after Treatment Period I

3.3.2.3 Hypoglycemia

Analysis set:	Safety analysis set
Analysis variables:	Hypoglycemia that occurs after the start of the study drug administration and before the start of the study drug for Treatment Period II
Analysis methodology:	Hypoglycemia that occurs after the start of SYR-472 25 mg tablet
	The following summaries will be provided for the above analysis variables using frequency distributions in subjects who

concomitantly received insulin preparations among the safety analysis set by treatment group.

In the analysis of hypoglycemia occurring after the start of SYR-472 25 mg tablet, subjects who concomitantly received insulin preparation and SYR-472 25 mg tablet in the safety analysis set will be included in the analyses.

- (1) All hypoglycemia
- (2) Severe hypoglycemia
- (3) Symptomatic hypoglycemia
- (4) Asymptomatic hypoglycemia
- (5) Probable symptomatic hypoglycemia
- (6) Relative hypoglycemia

The frequency distributions will be provided according to the rules below:

[Number of subjects]

A subject with multiple occurrences of hypoglycemia within the same classification will be counted only once in that classification.

[Number of events]

For each summary, the total number of events will be calculated.

4 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT

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

History of Revision (version management)

Version	Date	Prepared/modified by	Comments
First Version	16 April 2018	PPD	Preparation of first version
Second Version	12 June 2018		Preparation of second version

[Appendix 1] SYR-472-3003 Comparison Table for Changes

Page	Existing Text	Revised Text	Rationale for Changes
18	<p>1.2.1 Distribution of Baseline Demographics</p> <p>Rapid-acting insulin secretagogues [Yes]</p> <p>...</p> <p>α-glucosidase inhibitors [Yes]</p> <p>...</p> <p>Insulin preparations [Yes]</p> <p><u>Mixed</u> [Yes]</p> <p><u>Intermediate-acting</u> [Yes]</p> <p><u>Long-acting soluble</u> [Yes]</p>	<p>1.2.1 Distribution of Baseline Demographics</p> <p>Rapid-acting insulin secretagogues [Yes, No]</p> <p><u>Details of rapid-acting insulin secretagogues</u></p> <p>...</p> <p>α-glucosidase inhibitors [Yes, No]</p> <p><u>Details of α-glucosidase inhibitors</u></p> <p>...</p> <p>Insulin preparations [Yes, No]</p> <p><u>Types of insulin preparations</u> [Mixed, intermediate-acting, Long-acting soluble]</p>	Adjustment of descriptions and changes in the contents of distributions as a result of reexamination of contents of distributions
19	<p>1.2.1 Distribution of Baseline Demographics</p> <p>HbA1c (%) (Week 0)</p> <p>[Min\leq - <8.0, 8.0\leq - \leqMax]</p>	<p>1.2.1 Distribution of Baseline Demographics</p> <p>HbA1c (%) (Week 0)</p> <p><u>[Min\leq - <7.0, 7.0\leq - \leqMax]</u></p> <p>[Min\leq - <8.0, 8.0\leq - \leqMax]</p>	Addition of distributions as a result of reexamination of contents of distributions
20	<p>1.2.4 Concomitant Antidiabetic Drugs</p> <p>Permitted in the Study</p> <p>Any change in doses of antidiabetic drugs that are being used at Week -6 and will be concomitantly used during the study period in Treatment Period II</p>	<p>1.2.4 Concomitant Antidiabetic Drugs</p> <p>Permitted in the Study</p> <p>Any change in antidiabetic drugs that are being used at Week -6 and will be concomitantly used during the study period in Treatment Period II</p>	Adjustment of descriptions to clarify the contents of distribution

Page	Existing Text	Revised Text	Rationale for Changes
	<p>...</p> <p>Also, regarding the presence or absence of any change in doses of antidiabetic drugs that are being used at Week -6 and will be concomitantly used during the study period in Treatment Period II, ...</p>	<p>...</p> <p>Also, regarding the presence or absence of any change in antidiabetic drugs that are being used at Week -6 and will be concomitantly used during the study period in Treatment Period II, ...</p>	
27	<p>2.4.8 Examination of Subgroups</p> <p>Duration of disease (months)</p> <p>[Min≤ - ≤60, 60< - =Max]</p> <p>Fasting C-peptide (ng/mL)</p> <p>[Min≤ - <1.0, 1.0≤ - <2.0, 2.0≤ - ≤Max]</p>	<p>2.4.8 Examination of Subgroups</p> <p>Duration of disease (months)</p> <p>[Min≤ - ≤120, 120< - =Max]</p> <p>Fasting C-peptide (ng/mL)</p> <p>[Min≤ - <2.0, 2.0≤ - ≤Max]</p>	Changes in the contents of distributions as a result of reexamination of categories at the blinded review
29	<p>3.1.2 3.1.2 Displays of Treatment-Emergent Adverse Events</p>	<p>3.1.2 3.1.2 Displays of Treatment-Emergent Adverse Events</p> <p><u>(19) Hypoglycemia-related TEAEs by SOC and PT</u></p>	Addition of distributions as a result of reexamination of contents of distributions