Statistical Analysis Plan

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A Randomized, Double-blind, Placebo-controlled Study to Evaluate Efficacy and Safety of Canagliflozin (TA-7284) in Patients With Diabetic Nephropathy

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Revision History

Version Number	Details of Revision
Final draft version	First Version
Version 1	Information about the analysis that was provided in the Final Draft version was revised and finalized. The results of the case review board were reflected in the final version.

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Approval Information

Preparer	**Date (Month Day, Year)**
Approver	**Date (Month Day, Year)**

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List of Abbreviation

Abbreviation	Unabbreviated expression
ACE-I	Angiotensin-converting-enzyme Inhibitor
ACR	Urine Albumin-to-Creatinine Ratio
ALT	Alanine Aminotransferase
ARB	Angiotensin II Receptor Blocker
AUC	Area under the plasma concentration-time curve
C_{max}	Maximum plasma concentration
Cr	Creatinine
CV	Cardiovascular
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage renal disease
FAS	Full Analysis Set
GCP	Good clinical practice
GFR	Glomerular Filtration Rate
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HDL-C	High density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
LOCF	Last observation carried forward
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PPS	Per Protocol Set
PTP	Press-through sheets
PVD	Peripheral Vascular Disease
SGLT	Sodium glucose co-transporter
SMBG	Self-monitoring of blood glucose
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximum plasma concentration

Definition of Terms

Term	Definition
Screening period	The period from the first day of the screening period until the completion of the scheduled tests on the first day of the run-in period, 4 weeks at most.
Run-in period	The 2-week period from the completion of the scheduled tests on the first day of the run-in period until the completion of the scheduled tests on the first day of the treatment period.
Treatment period	The period from the completion of the scheduled tests on the first day of the treatment period until the completion of the scheduled tests on the last day of the treatment period (Week 104 of the treatment period or the day of treatment period discontinuation).
Follow-up observation period	The 4-week period from the completion of the scheduled tests on the last day of the treatment period.
Pre-treatment period discontinuation	Discontinuation in the period between informed consent acquisition and the end of the run-in period.
Treatment period discontinuation	Discontinuation during the treatment period
Proportion of subjects achieving a 30% decline in the eGFR	The proportions of subjects at the end of the treatment period with a decline of 30% in the eGFR or more compared to the average of the values on the first days of the run-in and treatment periods
Proportion of subjects achieving a 40% decline in the eGFR	The proportions of subjects at the end of the treatment period with a decline of 40% in the eGFR or more compared to the average of the values on the first days of the run-in and treatment periods

1. Introduction

This document describes the sponsor's plans for the statistical analyses in the "a randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of canagliflozin (TA-7284) in patients with diabetic nephropathy," and covers the information that is included in the study protocol, but in greater detail.

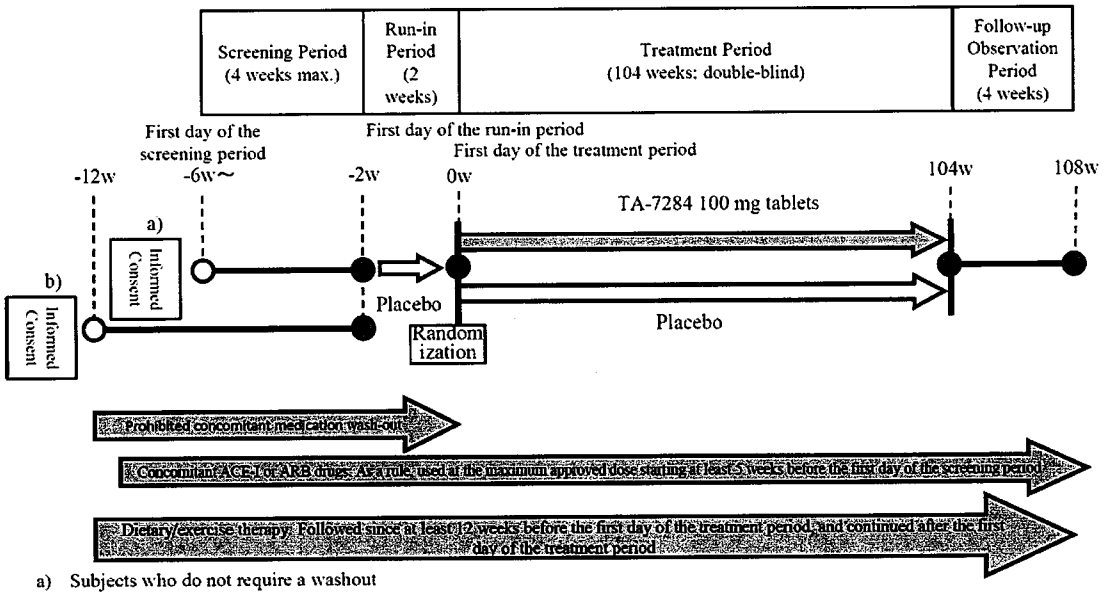
2. Study Objective And Study Design

2.1. Objectives

To compare the efficacy and safety of the administration of TA-7284 100 mg once a day for 104 weeks to those of placebo in type 2 diabetes mellitus patients with Stage 3 diabetic nephropathy (overt nephropathy).

2.2. Study Design

Multicenter, randomized, double-blind, placebo-controlled, parallel-group, comparative study



a) Subjects who do not require a washout
b) Subjects who required a washout

Definitions of Periods

Periods	Definitions
Screening period	The period from the first day of the screening period until the completion of the scheduled tests on the first day of the run-in period, 4 weeks at most.
Run-in period	The 2-week period from the completion of the scheduled tests on the first day of the run-in period until the completion of the scheduled tests on the first day of the treatment period. The run-in period will be a single-blind period, and a placebo will be administered.
Treatment period	The period from the completion of the scheduled tests on the first day of the treatment period until the completion of the scheduled tests on the last day of the treatment period (Week 104 of the treatment period or the day of treatment period discontinuation). The treatment period will be a double-blind period, and TA-7284 100 mg tablets or a placebo will be administered.
Follow-up observation period	The 4-week period from the completion of the scheduled tests on the last day of the treatment period. No investigational product will be administered in the follow-up observation period. If a patient discontinues from the study before the treatment period, then no follow-up observation period will be needed.

2.3. Randomization Procedures

Subjects will be randomly assigned in a 1:1 ratio to the TA-7284 100 mg tablet group or the TA-7284 tablet placebo group based on stratified randomization, with eGFR on the first day of the run-in period as the stratification factor (≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and < 90).

2.4. Assessment Time Point

2.4.1. Test/Observation Schedule

Time point a) / Parameter		Screening Period b) (4 weeks max.)	Run-in Period (2 weeks)	Treatment Period (104 weeks)																											Follow-up observation period (4 weeks)
	Date of informed consent acquisition	First day of the screening period	First day of the run-in period	First day of the treatment period (Week 2 of run-in period)	Week 4 of the treatment period	Week 8 of the treatment period	Week 12 of the treatment period	Week 16 of the treatment period	Week 20 of the treatment period	Week 24 of the treatment period	Week 28 of the treatment period	Week 32 of the treatment period	Week 36 of the treatment period	Week 40 of the treatment period	Week 44 of the treatment period	Week 48 of the treatment period	Week 52 of the treatment period	Week 56 of the treatment period	Week 60 of the treatment period	Week 64 of the treatment period	Week 68 of the treatment period	Week 72 of the treatment period	Week 76 of the treatment period	Week 80 of the treatment period	Week 84 of the treatment period	Week 88 of the treatment period	Week 92 of the treatment period	Week 96 of the treatment period	Week 100 of the treatment period	Week 104 of the treatment period	At discontinuation	Week 4 of the follow-up observation period
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	–	–	V18	–	–	V19	–	–	V20	–	–	–	V21	–	V22
Telephone follow-up																		●	●		●	●		●	●		●	●	●			
Allowable window c)	–	–	±3 d	–	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	+7 d	+14 d
Informed consent acquisition	●																															
Subject baseline characteristics	●	●	●	●																												
Run-in period investigational product administration d)			↔																													
Treatment period investigational product administration d)				←																										→		
Investigation of treatment adherence			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Height				●																												
Weight			●	●			●			●			●				●			●			●			●				●		
Vital sign			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●			●			●				●	●	
Standard 12-lead ECG			●	●						●							●						●							●	●	
Pregnancy test e)			●							●							●						●							●	●	
Clinical laboratory tests f)g)			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●			●			●				●	●	
eGFR g)			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●			●			●				●	●	●
Urine ACR (first morning void urine) h)		•i)		●	●	●	●			●			●				●			●			●			●				●	○	●
HbA1c			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●			●			●				●	○	●
Fasting blood glucose			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●			●			●				●	○	
Fasting urine glucose/creatinine ratio				●	●	●	●			●			●				●			●			●			●				●	○	
Renal function biomarker				●	•j)												●													●	○	
Investigation of adverse events k)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Investigation of hypoglycemia (SMBG, survey form) l)			←																													→

a) On scheduled visit days, subjects will fast (including juice and alcohol) for at least 10 hours starting on the night before, and will come to the hospital in the morning with an empty stomach (except for on the first day of the screening period, at the visit at Week 4 of the follow-up observation period, and at discontinuation). However, patients will be allowed to drink water and other beverages that do not contain any calories.

b) The screening period will be at most 4 weeks long.

c) The first day of the treatment period will be the starting point for calculating the run-in and treatment periods, and the final assessment day in the treatment period will be the starting point for calculating the follow-up observation period (including for cases who discontinued from the study).

d) Investigational product will start being administered on the first day of the run-in period and on the first day of the treatment period. Subjects will come in for the scheduled study visits without taking the investigational product.

e) Pregnancy tests will be required for all females of childbearing potential.

f) During the treatment period, urine glucose tests performed at the study sites will be prohibited.

g) If a patient has an eGFR < 15 mL/min/1.73 m^2, or if the patient's serum creatinine value more than doubles compared to the average of the values on the first day of the run-in period and the first day of the treatment period, then the measurement will be performed at least 30 days, and preferably within 60 days, after the assessment time point at which this criterion will be met. If there is no scheduled visit during this period, then one is to be scheduled if possible.

h) Collect first-morning void urine samples on 3 days within a one-week period that includes the scheduled visit day.

i) If the urine ACR does not satisfy the inclusion criterion, retesting may be performed during the screening period if the (sub)investigator judges it to be medically

appropriate. Furthermore, no restrictions will be placed on the number of retests that may be performed.

j) Only erythropoietin will be measured.

k) Serious adverse events will be investigated from informed consent acquisition up until Week 4 of the follow-up observation period. Other adverse events will be investigated from after the start of the administration of the treatment period investigational product up until Day 14 of the follow-up observation period.

l) The instructions on blood glucose self-measurement (SMBG) and on completing the hypoglycemia symptoms survey form will be given on the first day of the run-in period. Blood glucose self-measurements will be performed whenever possible when the patient experiences symptoms of hypoglycemia.

2.5. Sample Size Justification

300 subjects (150 subjects per group) as the number of subjects who will start the treatment period

[redacted]

Rationale

[redacted]

3. Endpoints

3.1. Efficacy Endpoints

3.1.1. Primary endpoint

Proportion of subjects achieving a 30% decline in the eGFR (The proportions of subjects at the end of the treatment period with a decline of 30% in the eGFR or more compared to the average of the values on the first days of the run-in and treatment periods)

3.1.2. Secondary endpoints

(1) Proportion of subjects achieving a 40% decline in the eGFR (The proportions of subjects at the end of the treatment period with a decline of 40% in the eGFR or more compared to the average of the

values on the first days of the run-in and treatment periods)

(2) The change and percent change in the eGFR at each assessment time point compared to the average of the values on the first days of the run-in and treatment periods

(3) Composite endpoint of end-stage renal disease (ESRD), doubling of serum creatinine, renal death, and cardiovascular (CV) death

(4) Composite endpoint of CV death and hospitalized congestive heart failure

(5) Composite endpoint of CV death, non-fatal myocardial infarction, and non-fatal stroke

(6) Hospitalized congestive heart failure

(7) Composite renal endpoint of end-stage renal disease (ESRD), doubling of serum creatinine, and renal death

(8) CV death

(9) All-cause death

(10) The CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina

(11) Percent change from the first day of the treatment period in urine ACR (first morning void urine) at each assessment time point

(12) Change from the first day of the treatment period in the HbA1c at each assessment time point

(13) Change from the first day of the treatment period in fasting blood glucose at each assessment time point

(14) Change from the first day of the treatment period in blood pressure (systolic blood pressure, diastolic blood pressure) at each assessment time point

(15) Change and percent change from the first day of the treatment period in the lipid levels (HDL-C, fasting neutral lipids) at each assessment time point

(16) Change and percent change from the first day of the treatment period in body weight at each assessment time point

(17) Change from the first day of the treatment period in the fasting urine glucose/creatinine ratio at each assessment time point

3.2. Safety Endpoints

(1) Adverse event

(2) Hypoglycemia

(3) Clinical laboratory test values

(4) Standard 12-lead ECG

(5) Vital signs

4. Definitions of Derived Variables

4.1. BMI

BMI (kg/m^2) = Body weight (kg)/{Height (m)}^{2}

The number of digits displayed will consist of the values rounded off to the first decimal point. Furthermore, the height and weight from the first day of the treatment period will be used.

4.2. Duration of Illness of the Primary Disease (Stage 3 Diabetic Nephropathy)

Duration of illness (in years) of the primary disease (Stage 3 diabetic nephropathy)

(First day of the treatment period – Time of diagnosis of the primary disease + 1)/365.25

The number of digits displayed will consist of the values rounded off to the first decimal point. If only the month is known for the time of onset, then the date will be reclassified as the fifteenth of the month for the purposes of this calculation. Also, if only the year is known, then the date will be reclassified as July 1.

4.3. Duration of Illness of Diabetes

Duration of illness of diabetes (in years)

(First day of the treatment period – Diagnosis date of diabetes mellitus + 1)/365.25

The number of digits displayed will consist of the values rounded off to the first decimal point. If only the month is known for the time of onset, then the date will be reclassified as the fifteenth of the month for the purposes of this calculation. Also, if only the year is known, then the date will be reclassified as July 1.

4.4. Blood Pressure (Systolic Blood Pressure, Diastolic Blood Pressure)

The median of 3 measured values will be used. If only 2 measured values are available, then the mean of these 2 values will be used, and if only 1 measured value is available, then this value will be used. These values will be displayed rounded off to the first decimal place.

4.5. Change and Percent Change

4.5.1. Parameters other than the eGFR

・Change

Change = Value at the measurement time point in question – value on the first day of the treatment

period

・Percent Change

Percent change = [(Value at the measurement time point in question – value on the first day of the treatment period)/Value on the first day of the treatment period] × 100

The values will be displayed rounded off to the first decimal place.

4.5.2. eGFR

・Change

Change = eGFR value at the measurement time point in question – Mean of the eGFR value on the first day of the run-in period and the eGFR value on the first day of the treatment period

・Percent Change

Percent change = [(eGFR value at the measurement time point in question – Mean of the eGFR value on the first day of the run-in period and the eGFR value on the first day of the treatment period) / Mean of the eGFR value on the first day of the run-in period and the eGFR value on the first day of the treatment period] × 100

The values will be displayed rounded off to the first decimal place.

4.6. Duration of Investigational Product Administration

4.6.1. Duration of Investigational Product Administration in the Run-in Period

For completers: Duration of investigational product administration in the run-in period (in days) = (First day of the treatment period – 1) – First day of the run-in period + 1

For discontinuations: Duration of investigational product administration in the run-in period (in days) = Day of discontinuation – First day of the run-in period + 1

4.6.2. Duration of Investigational Product Administration in the Treatment Period

For completers: Duration of investigational product administration in the treatment period (in days) =

(Day of the visit at Week 104 of the treatment period – 1) – First day of the treatment period + 1

For discontinuations: Duration of investigational product administration in the treatment period (in days) = Day of discontinuation – First day of the treatment period + 1

4.7. Study Treatment Compliance (%)

4.7.1. Study Treatment Compliance in the Run-in Period

Run-in period study treatment compliance (%) = [(Quantity of run-in period investigational product prescribed – Quantity of run-in period investigational product returned)]/(Duration of administration of investigational product in the run-in period) x 100

The values will be displayed rounded off to the first decimal place.

4.7.2. Study Treatment Compliance in the Treatment Period

Treatment period study treatment compliance (%) = [(Quantity of treatment period investigational product prescribed – Quantity of treatment period investigational product returned)]/(Duration of administration of investigational product in the treatment period) x 100

The values will be displayed rounded off to the first decimal place.

4.8. eGFR

eGFR (mL/min/1.73 m^2) = 194 x Serum creatinine$^{-1.094}$ x Actual age of the subject in years$^{-0.287}$ (females: x 0.739)

4.9. eGFR % Decline

eGFR % decline = [(eGFR value at the measurement time point in question – Mean of the eGFR value on the first day of the run-in period and the eGFR value on the first day of the treatment period) / Mean of the eGFR value on the first day of the run-in period and the eGFR value on the first day of the treatment period] × 100

The values will be displayed rounded off to the first decimal place.

4.10.Periods of Assessment of Efficacy Endpoint Events

4.10.1. Time to Initial Event Onset (in days)

Time to initial event onset = Day of initial event onset – First day of the treatment period + 1

4.10.2. Time to Censoring (in days)

1. Subjects for whom the date of the visit at Week 4 of the follow-up observation period can be obtained

Time to censoring = Date of the visit at Week 4 of the follow-up observation period – First day of the treatment period + 1

2. Subjects for whom the date of the visit at Week 4 of the follow-up observation period can not be obtained

Time to censoring = Final assessment time point[*1] – First day of the treatment period + 1

[*1]Final assessment time point
If the day of discontinuation can be obtained: Day of discontinuation
If the day of discontinuation cannot be obtained: Day of the final scheduled visit[*2]

[*2]Day of the final scheduled visit
The latest date will be used, regardless of the allowable time window

4.11.Urine ACR (First Morning Void Urine)

- Urine ACR (First Morning Void Urine)
  The median of 3 measured values will be used. If only 2 measured values are available, then the median of these 2 measured values will be used, and if only 1 measured value is available, this value will be used. These values will be displayed rounded off to the first decimal place. Additionally, the last date of the dates on which the 3 (or 2) measurements were performed will be considered the date of measurement.

・ Log-transformed urine ACR

The natural log will be used for log transformation.

・ Geometric mean urine ACR

Geometric mean urine ACR = Value obtained by the inverse transformation of the arithmetic mean of the log-transformed urine ACR values

・ Change in the log-transformed value

Change in the log-transformed urine ACR = Value obtained by the log transformation of the urine ACR at each measurement time point – Value obtained by the log transformation of the urine ACR on the first day of the treatment period

4.12.Adverse Drug Reaction

Adverse events for which it has been determined that there is a "reasonable possibility" of there being a causal relationship to the investigational product will be handled as adverse reactions.

4.13.Period of Assessment of the Incidence Per 1000 Person-Years of Each Safety Endpoint

1. Subjects for whom the date of the visit at Week 4 of the follow-up observation period can be obtained

Period of assessment of the incidence per 1000 person-years (in years) = (Day of the visit at Week 4 of the follow-up observation period – First day of the treatment period + 1)/365.25

2. Subjects for whom the date of the visit at Week 4 of the follow-up observation period can not be obtained

Period of assessment of the incidence per 1000 person-years (in years) = (Final assessment time point[*1]– First day of the treatment period + 1)/365.25

[*1]Final assessment time point

If the day of discontinuation can be obtained: Day of discontinuation

If the day of discontinuation cannot be obtained: Day of the final scheduled visit[*2]

[*2]Day of the final scheduled visit

The latest date will be used, regardless of the allowable time window

5. Analysis Sets

The analysis of efficacy is performed in the full analysis set (FAS). In addition, a secondary analysis of the primary endpoint will be performed in the per-protocol set (PPS), as well. Safety analysis is performed in the safety analysis set. The data sets analyzed are defined below. The study sponsor finalizes the details of how the subjects are handled by the time of the database lock.

5.1. Efficacy Analysis Sets

(1) Efficacy Analysis Sets

1) FAS

The analysis sets consisting of all randomized subjects other than the following constitute the FAS.

- Subjects who were not type 2 diabetes mellitus patients with Stage 3 diabetic nephropathy (overt nephropathy)
- All subjects who did not take the investigational product at all
- All subjects for which no post-randomization efficacy data are available

2) PPS

The PPS is the FAS, minus the following subjects.

- Subjects who have deviated from the inclusion criteria
- Subjects who have met the exclusion criteria
- Subjects who have violated the stipulations about the prohibited concomitant drugs
- Subjects with a rate of compliance with the investigational product of 75% or lower
- Subjects with treatment periods shorter than 52 weeks

5.2. Safety Analysis Sets

The analysis sets consisting of all randomized subjects other than the following constitute the safety analysis sets.

- All subjects who did not take the investigational product at all
- All subjects for which no post-randomization safety data are available

6. Handling of Data

The data handling procedures are described below, except for issues that are determined by the study sponsor's case review board.

6.1. Handling of Missing Values

When test values are missing or reported as reference data, or can not be measured because of, for example, a problem with the test sample, this parameter will be handled as missing. If the data (e.g., test

values) required for derivation include even 1 missing or uncollected value, the derived variable will be considered missing.

6.2. Handling of Time Point Data When Tabulating the Data by Evaluation Time Point

Table 6.2: Test/Observation Schedule Allowable Time Windows

Assessment Time Point		Reference Date	Allowable Window
Screening period	First day of the screening period	–	*1
Run-in period	First day of the run-in period	-14 days	-17 days to -11 days
Treatment period	First day of the treatment period*2 (Week 2 of the run-in period)	0 days	–
	Week 4 of the treatment period	28 days	14 days to 42 days
	Week 8 of the treatment period	56 days	43 days to 70 days
	Week 12 of the treatment period	84 days	71 days to 98 days
	Week 16 of the treatment period	112 days	99 days to 126 days
	Week 20 of the treatment period	140 days	127 days to 154 days
	Week 24 of the treatment period	168 days	155 days to 182 days
	Week 28 of the treatment period	196 days	183 days to 210 days
	Week 32 of the treatment period	224 days	211 days to 238 days
	Week 36 of the treatment period	252 days	239 days to 266 days
	Week 40 of the treatment period	280 days	267 days to 294 days
	Week 44 of the treatment period	308 days	295 days to 322 days
	Week 48 of the treatment period	336 days	323 days to 350 days
	Week 52 of the treatment period	364 days	351 days to 378 days
	Week 56 of the treatment period	392 days	379 days to 406 days
	Week 60 of the treatment period	420 days	407 days to 434 days
	Week 64 of the treatment period	448 days	435 days to 462 days
	Week 68 of the treatment period	476 days	463 days to 490 days
	Week 72 of the treatment period	504 days	491 days to 518 days
	Week 76 of the treatment period	532 days	519 days to 546 days
	Week 80 of the treatment period	560 days	547 days to 574 days
	Week 84 of the treatment period	588 days	575 days to 602 days
	Week 88 of the treatment period	616 days	603 days to 630 days
	Week 92 of the treatment period	644 days	631 days to 658 days
	Week 96 of the treatment period	672 days	659 days to 686 days
	Week 100 of the treatment period	700 days	687 days to 714 days
	Week 104 of the treatment period	728 days	715 days to 742 days
	Treatment period discontinuation	The day of treatment period discontinuation	Within 7 days of the day of treatment period discontinuation
Week 4 of the follow-up observation period		Week 104 of the treatment period (or the day of treatment period discontinuation)	28 to 42 days after the last day of the treatment period

*1: The first day of the run-in period should be within 4 weeks of the first day of the screening period.

*2: The first day of the treatment period is the day of the initial prescription of the treatment period investigational product.

6.2.1. Tabulation by eGFR Assessment Time Point

When tabulating the eGFR at each assessment time point, data that fall within the allowable time windows defined in "Table 6.2: Test/Observation Schedule Allowable Time Windows" will be used. For data that have been reported as having been collected at treatment period discontinuation, data that were collected within the allowable time window for the day of treatment period discontinuation will be used. Although a data tabulation at discontinuation will not be performed, data that have been collected within the allowable time window for the day of treatment period discontinuation that are also within the allowable time window for the time point in question will as a rule be used as data for that time point. In addition, if multiple measurements have been taken within an allowable time window, data from the test that was performed on the day closest to the target day will be used. If there are multiple measurements, and the difference in the numbers of days between the day of each measurement and the target day are the same, then the data that were collected earlier will be used.

6.2.2. Tabulation of the eGFR at Each Assessment Time Point When Imputing Data Outside the Allowable Time Window

When tabulating the eGFR data for each assessment time point, the data stipulated in 6.2.1 will be combined with data imputed by means of multiple imputation ([redacted]) for data for which the assessment time point was outside the allowable time window. A linear regression model with the data at each assessment time point from the first day of the treatment period until Week 88 of the treatment period as the explanatory variable will be used to replace missing values for each assessment time point from Week 4 of the treatment period through Week 104 of the treatment period. It will be assumed that the pattern of missing values is non-monotonic.

6.2.3. Tabulation of Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point

When tabulating the data for endpoints other than the eGFR and urine ACR, data that have been collected within the allowable time windows defined in "Table 6.2: Test/Observation Schedule Allowable Time Windows" will be used. For data that have been reported as having been collected at treatment period discontinuation, data that were collected within the allowable time window for the day of treatment period discontinuation will be used. Although a data tabulation at discontinuation will not be performed, data that have been collected within the allowable time window at discontinuation that are also within the allowable time window for the time point in question will be used as data for that time point. Data will not be replaced with data from outside the allowable time windows. In addition, if multiple measurements have been taken within an allowable time window, data from the test that was performed on the day closest to the target day will be used. If the differential number of days from the

reference date is equal, the data obtained before the reference date will be used to evaluate efficacy, and the data obtained after the reference date will be used to evaluate safety.

6.2.4. Tabulation of the Urine ACR Endpoints at Each Assessment Time Point

When tabulating the urine ACR endpoints at each assessment time point, if the date of the visit falls within the allowable time window defined in "Table 6.2: Test/Observation Schedule Allowable Time Windows," then data that have been collected within a 1-week period that includes the visit day will be used as data for that time point. Also, if the day of the visit at discontinuation falls within the allowable time window of the day of discontinuation in the treatment period and the allowable time window for the time point data, then data that were obtained within a 1-week period that includes the day of the visit at discontinuation will be used as the data for that time point. Data will not be replaced with data from outside the allowable time windows. In addition, if multiple measurements were taken within the allowable time window, then the visit day that was closest to the target date will be used. If the difference (in the number of days) between the day of the measurement and the target day is the same for each of two measurements, then the earlier day will be used.

6.3. Handling of eGFR Data at the End of the Treatment Period (Analysis of 7.6.1.3)

When tabulating eGFR data at the end of the treatment period, the data collected at Week 104 of the treatment period, as defined in "Table 6.2: Test/Observation Schedule Allowable Time Windows" will be used. However, if any data from Week 104 of the treatment period are missing, then these data will be imputed as indicating that an eGFR decline has occurred.

6.4. Handling of Event Endpoint Data

The time to initial event onset (in days)[*1] and the time to censoring (in days)[*2] will be used for the event data described in 1 through 14 below.

*1 and *2 are defined in "4.10 Periods of Assessment of Efficacy Endpoint Events."

1. Composite endpoint of end-stage renal disease (ESRD) onset, doubling of serum creatinine, renal death, and cardiovascular (CV) death
2. Composite endpoint of CV death and hospitalized congestive heart failure
3. Composite endpoint of CV death, non-fatal myocardial infarction, and non-fatal stroke
4. Hospitalized congestive heart failure
5. Composite renal endpoint of end-stage renal disease (ESRD), doubling of serum creatinine, and renal death

6. CV death
7. All-cause death
8. The CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina
9. ESRD
10. Doubling of serum creatinine
11. Renal death
12. Non-fatal myocardial infarction
13. Non-fatal stroke
14. Hospitalized unstable angina

6.5. Handling of Clinical Laboratory Values Below and Above the Lower Limit of Quantitation

For values that are at or below the lower limit of quantitation, the lower limit of quantitation will be included in the tabulation. Also, if a measured value has been reported as being below the lower limit of quantitation, a value equal to one-half of the lower limit of quantitation will be included in the tabulation; it will not be considered missing or treated as zero.

For values that are at or above the upper limit of quantitation, the upper limit of quantitation will be included in the tabulation. If a measured value has been reported as being above the upper limit of quantitation*, it will be replaced with a value obtained by adding a 1 to the decimal place after the number of reported digits of the upper limit of quantitation; it will not be considered missing or treated as zero.

*If the upper limit of quantitation is "1000," and the value is above the upper limit of quantitation, then "1000.1" will be used as the value above the upper limit of quantitation.

7. Statistical Methods

7.1. General Methods

7.1.1. Calculated Descriptive Statistics

The types of descriptive statistics that will be calculated for each continuous data parameter are shown in Table 7-1.

Table7-1. Types of Descriptive Statistics Calculated

Parameter	Calculated Descriptive Statistics
Descriptive Statistics	Numbers of subjects, mean values, SDs, medians, minimums, maximums

7.1.2. Number of Display Digits

Table 7-2 shows the number of display digits that will be included in the analysis results. Additionally, the digits after the number of display digits will be rounded off (or up), except for the minimum and maximum values.

Table 7-2. Number of Display Digits

Description of Value	Number of Display Digits
p value	Values rounded off to the third decimal place However, if the value is below 0.001, then it will be shown as "< 0.001."
Odds ratio	To the second decimal place
Proportion (percent)	To the first decimal place
Person-years	To the second decimal place
Hazard ratio	To the second decimal place
Descriptive statistics of measured values and changes therein (mean, SD, median)	To 1 decimal place more than that of the original variable
Descriptive statistics of percent changes (mean, SD, median)	To the second decimal place
Descriptive statistics (minimum and maximum values)	Same as the number of digits of the original variable
LS mean, LS mean SE	To 1 decimal place more than that of the original variable
Geometric Mean, Geometric Mean 95% CI, Geometric LS Mean, Geometric LS Mean 95% CI	To the third decimal place
Ratio of Geometric LS Mean, Ratio of Geometric LS Mean 95% CI	To the third decimal place
Percent change of the endpoint in question (Geometric LS Mean of the ratio of the endpoint in question to the baseline value – 1) x 100	To the first decimal place

7.1.3. Significance Level and Confidence Coefficient

The tests will be all two-sided, with a significance level of 5%. The confidence intervals will be two-sided, and the confidence coefficient will be 95%.

7.2. Subject Disposition

7.2.1. Disposition of the Subjects From Whom Written Consent Was Obtained

Analysis population(s): Subjects who progressed to the run-in period

Analysis parameter(s): Number of subjects who discontinued from the run-in period, number of subjects randomized

Analysis method: For each analysis parameter, the number and proportion of subjects will be tabulated.

Listings

Analysis population(s): Subjects who progressed to the run-in period

7.2.2. Disposition of the Randomized Subjects

Analysis population(s): Randomized subjects

Analysis parameter(s): Number of subjects who completed the treatment period, number of subjects discontinued from the treatment period, reasons for discontinuation from the treatment period, number of subjects who completed the follow-up observation period, number of subjects who discontinued from the follow-up observation period (subjects who were not subjects who completed the follow-up observation period will be tabulated as subjects who discontinued from the follow-up observation period)

Analysis method: For each analysis parameter, the number and proportion of subjects will be tabulated by treatment group.

Listings

Analysis population(s): Randomized subjects

7.2.3. Disposition of Randomized Subjects for Each Analysis Set

Analysis population(s): Randomized subjects

Analysis parameter(s): Number of subjects in the safety analysis set, number of subjects in the FAS, number of subjects in the PPS

Analysis method: For each analysis parameter, the number and proportion of subjects will be tabulated by treatment group.

Listings

Analysis population(s): Randomized subjects

7.3. Demographic and Other Baseline Characteristics

Analysis population(s): FAS, safety analysis set

Analysis parameter(s): See Table 7-3.

Analysis method: The key demographic and other baseline characteristics of each analysis population will be summarized, both overall and by treatment group. For two-value, multivalue, and ordered category variables, the number and proportion of subjects will be tabulated. For

continuous variables, the descriptive statistics will be calculated. Additionally, for the FAS, the values will also be tabulated by eGFR category (eGFR ≥ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2, eGFR ≥ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2, eGFR ≥ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2) on the first day of the run-in period.

Table7-3. Investigation of Demographic and Other Baseline Characteristics

Endpoints		Data Category
Sex	Male/Female	Two-value
Age at informed consent (years)		Continuous
Age at informed consent (years)	< 55, ≥ 55 and < 65, ≥ 65 and < 75, ≥ 75	Ordered category
Height (cm)		Continuous
Body Weight (kg)		Continuous
BMI (kg/m^2)		Continuous
BMI (kg/m^2)	< 30, ≥ 30	Two-value
Race	Asian (Japanese), Asian (Other), Other	Multivalue
Disease duration of Diabetic Nephropathy		Continuous
Disease duration of Diabetic Nephropathy	< 10, ≥ 10, Unknown	Multivalue
Disease duration of Type2 Diabetes		Continuous
Disease duration of Type2 Diabetes	< 10, ≥ 10, Unknown	Multivalue
Medical Conditions		
Dyslipidaemia	Yes/No	Two-value
Hypertension	Yes/No	Two-value
Information about the subject's past history of fractures	Yes/No	Two-value
Average number of cigarettes smoked per day		Continuous
Smoking status	Never, Former, Current	Multivalue
eGFR (mL/min/1.73 m^2) on the first day of the run-in period		Continuous
eGFR (mL/min/1.73 m^2) on the first day of the run-in period	≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and < 90	Ordered category
eGFR (mL/min/1.73 m^2) on the first day of the treatment period		Continuous
Urine ACR (first morning void urine) (mg/g Cr)		Continuous
Urine ACR (first morning void urine) (mg/g Cr)	≤ 1000, > 1000	Two-value
HbA1c (%)		Continuous
HbA1c (%)	< 7, ≥ 7 and < 8, ≥ 8 and < 9, ≥ 9 and ≤ 10, > 10	Ordered category
Fasting blood glucose (mg/dL)		Continuous
Systolic blood pressure (mmHg)		Continuous
Systolic blood pressure (mmHg)	≤ 140, > 140	Two-value
Diastolic blood pressure (mmHg)		Continuous
Diastolic blood pressure (mmHg)	≤ 90, > 90	Two-value
HDL-C (mg/dL)		Continuous
LDL-C (mg/dL)		Continuous
Fasting triglycerides (mg/dL)		Continuous
Fasting urine glucose/creatinine ratio		Continuous

Endpoints		Data Category
(mg/mg Cr)		
Renal function biomarkers eGFRcys, serum cysteine C, erythropoietin, c-peptide, high sensitivity CRP, urine transferrin, NAG, L-FABP, TNFR1, TNFR2		Continuous
eGFRcys (mL/min/1.73 m^2)	< 45, ≥ 45 and < 60, ≥ 60	Ordered category

Listings

Analysis population(s): Randomized subjects

7.4. Concomitant Medications

Analysis population(s): FAS

Analysis parameter(s): Concomitant medications

Analysis method: For both the population overall and by treatment group, the number and proportion of subjects concomitantly receiving ACE inhibitors or ARB drugs will be tabulated for subjects "who have been concomitantly receiving ACE inhibitors or ARB drugs from at least 5 weeks before the start of the screening period," "who have been concomitantly receiving ACE inhibitors or ARB drugs from at least 4 weeks before the start of the screening period," "who have been concomitantly receiving ACE inhibitors or ARB drugs from before the day of the first dose," or for whom the first day of administration of the concomitant medication (before the first day of the run-in period) is the same day as the day of randomization, or earlier.

Listings

Analysis population(s): Randomized subjects

7.5. Status of Treatment Compliance

7.5.1. Duration of Study Treatment in the Treatment Period

Analysis population(s): FAS

Analysis parameter(s): Duration of study treatment (weeks)

Analysis method: Descriptive statistics are presented for the administration duration (in weeks), both overall and by treatment group. The number and proportion of subjects are tabulated by administration duration category.

Treatment duration categories (weeks)

< 13, ≥ 13 and < 26, ≥ 26 and < 52, ≥ 52 and < 78, ≥ 78

Listings

Analysis population(s): Randomized subjects

7.5.2. Treatment Period Treatment Compliance

Analysis population(s): FAS

Analysis parameter(s): Study treatment compliance (%)

Analysis method: Both for the population overall and by treatment group, descriptive statistics will be presented for treatment compliance (%) in the treatment period. The number and proportion of subjects will be tabulated for each of the following treatment compliance (%) categories.

Treatment Compliance (%) Categories

$< 75, \geq 75$ and $< 90, \geq 90$ and $< 100, =100, > 100$

Listings

Analysis population(s): Randomized subjects

7.6. Analysis of Efficacy

7.6.1. Primary Endpoints

7.6.1.1. Primary Analysis

Analysis population(s): FAS, PPS

Analysis parameter(s): Proportion of subjects with a decline of 30% in the eGFR at Week 104 of the treatment period

Analysis method:

In accordance with "6.2.2. Tabulation of the eGFR at Each Assessment Time Point When Imputing Data Outside the Allowable Time Window," a dataset will be prepared using [redacted]. The estimated values from this dataset, and the variance thereof, will be combined using Rubin's rule, and the proportion of subjects with a decline of 30% in the eGFR at Week 104 of the treatment period, and the 95% confidence interval thereof, will be shown for each treatment group. The point estimate for the difference between the groups (placebo group minus TA-7284 group) and the 95% confidence interval according to the Farrington-Manning method will also be shown.

Listings

Analysis population(s): Randomized subjects

7.6.1.2. Secondary Analysis

Analysis population(s): FAS, PPS

Analysis parameter(s): Proportion of subjects with a decline of 30% in the eGFR at Week 104 of the treatment period

Analysis method:

In accordance with "6.2.2. Tabulation of the eGFR at Each Assessment Time Point When Imputing Data Outside the Allowable Time Window," a dataset will be prepared using [redacted]. The estimated values from this dataset, and the variance thereof, will be combined using Rubin's rule, and the proportion of subjects with a decline of 30% in the eGFR at Week 104 of the treatment period, and the 95% confidence interval thereof, will be shown for each treatment group.

In addition, for each of these datasets, a logistic regression model will be applied with a decline of 30% in the eGFR at Week 104 of the treatment period as the target variable, treatment group and the stratification factor eGFR on the first day of the run-in period (≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and < 90) as factors, and the urine ACR (first morning void urine) as covariates, and the estimates and variances thereof will be calculated and combined in accordance with Rubin's rule. An intergroup comparison of these results will be performed, and the odds ratio of a 30% decline in the eGFR in the TA-7284 group relative to the placebo group at Week 104 of the treatment period, and the 95% confidence interval thereof, will be presented.

Listings

Analysis population(s): Randomized subjects

7.6.1.3. Other Analysis 1

Analysis population(s): FAS, PPS

Analysis parameter(s): Proportion of subjects with a decline of 30% in the eGFR at Week 104 of the treatment period

Analysis method:

The proportion of subjects with a 30% decline in the eGFR at Week 104 of the treatment period, and the 95% confidence interval thereof, will be presented for each treatment group for the dataset obtained through the replacement of missing values at Week 104 of the treatment period in accordance with "6.3 Handling of eGFR Data at the End of the Treatment Period." The point estimate for the difference between the groups (placebo group minus TA-7284 group) and the 95% confidence interval according to the Farrington-Manning method will also be shown.

An intergroup comparison using a logistic regression model will be performed with a decline of 30% in the eGFR at Week 104 of the treatment period as the target variable, treatment group and the stratification factor eGFR on the first day of the run-in period (≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and $<$

90) as factors, and the urine ACR (first morning void urine) as covariates. Thereafter, the odds ratio of a 30% decline in the eGFR in the TA-7284 group relative to the placebo group at Week 104 of the treatment period, and the 95% confidence interval thereof, will be presented.

Listings

Analysis population(s): Randomized subjects

7.6.1.4. Other Analysis 2

Analysis population(s): FAS, PPS

Analysis parameter(s): Proportion of subjects with a decline of 30% in the eGFR at Week 104 of the treatment period

Analysis method:

The proportion of subjects with a 30% decline in the eGFR at Week 104 of the treatment period, and the 95% confidence interval thereof, will be presented for each treatment group in accordance with "6.2.1 Tabulation by eGFR Assessment Time Point." The point estimate for the difference between the groups (placebo group minus TA-7284 group) and the 95% confidence interval according to the Farrington-Manning method will also be shown.

Listings

Analysis population(s): Randomized subjects

7.6.2. Secondary endpoints

7.6.2.1. The proportion of subjects achieving a 40% decline in the eGFR

Analysis population(s): FAS, PPS

Analysis parameter(s): Proportion of subjects with a decline of 40% in the eGFR at Week 104 of the treatment period

Analysis method: Analyses similar to those described in 7.6.1.1, 7.6.1.2, 7.6.1.3, and 7.6.1.4 will be performed for these analysis parameters.

Listings

Analysis population(s): Randomized subjects

7.6.2.2. Percent Changes in the Urine ACR (First Morning Void Urine) and Fasted Urine

Glucose/Creatinine Ratio

Analysis population(s): FAS

Analysis parameter(s): Urine ACR (first morning void urine), fasted urine glucose/creatinine ratio

Analysis method:

For the data described in "6.2.3. Tabulation of Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point" and "6.2.4. Tabulation of the Urine ACR Endpoints at Each Assessment Time Point," for each analysis parameter at each assessment time point in each group, the geometric mean and 95% confidence interval at the start of the treatment period and at follow-up (Week 108) (Week 104 for the fasted urine glucose/creatinine ratio) will be presented. For each treatment group, time profiles will be prepared showing the geometric mean and 95% confidence interval thereof along the y-axis and each measurement time point up through Week 104 along the x-axis. In addition, for the log-transformed values of each assessment parameter for each treatment group, the mean change and 95% confidence interval at each assessment time point from the first day of the treatment period through follow-up (Week 108) (Week 104 for the fasted urine glucose/creatinine ratio) will be calculated. These values will be inverse transformed, and the geometric mean and 95% confidence interval of the ratio for each assessment parameter will be presented.

For the data described in "6.2.3. Tabulation of Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point" and "6.2.4. Tabulation of the Urine ACR Endpoints at Each Assessment Time Point," the mean changes in the log-transformed values of each analysis parameter at each assessment time point from Week 4 to Week 104 will be analyzed in a mixed model for repeated measures using a restricted maximum likelihood (REML) approach, with treatment group, assessment time point, treatment group—assessment time point interaction, and the stratification factor of the eGFR on the first day of the run-in period (≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and < 90) as factors, and the log-transformed values of the assessment parameters on the first day of the treatment period and the interactions between the assessment time points and the log-transformed values of the assessment parameters on the first day of the treatment period as covariates. For each treatment group at each assessment time point, the LS mean and standard error, 95% confidence interval, difference between the groups (the TA-7284 group minus the placebo group) in the LS mean, and the standard error and 95% confidence interval thereof, will be calculated. Additionally, the LS means and 95% confidence intervals of the changes in the log-transformed values will be back-transformed, and the geometric LS means and 95% confidence intervals of the ratios of each analysis parameter will be presented. The values obtained from the following formula will be presented as the percent change from baseline: (geometric LS mean of the ratio in the analysis parameter – 1) x 100. Also, the differences between the groups (the TA-7284 group minus the placebo group) in the LS means, and the 95% confidence intervals thereof, will be back-transformed, and the ratios of the geometric LS means of the ratios of the analysis parameters, and the 95% confidence intervals and P values, will be presented. The percent changes relative to placebo [(ratio of the geometric LS means of the ratio of each analysis parameter – 1) x 100] will also be presented.

The Kenward-Roger method will be used to adjust the degrees of freedom, and an unstructured covariance structure will be used for within-subject error modeling.

However, in within-subject error modeling, if the model fails to converge when using an unstructured covariance matrix, the covariance matrix will be changed according to the following procedure, and the first covariance matrix with successful convergence will be used to perform the analysis.

Heterogeneous Toeplitz (TOEPH) → Heterogeneous AR(1) (ARH(1)) → Heterogeneous CS (CSH) → Toeplitz (TOEP) → First-order autoregressive (AR(1)) → Compound symmetry (CS)

Listings

Analysis population(s): Randomized subjects

7.6.2.3. The Change in eGFR, HbA1c, Fasting Blood Glucose, Blood Pressure (Systolic Blood Pressure, Diastolic Blood Pressure), Lipids (HDL-C, Fasting Neutral Lipids), and Body Weight, and the Percent Change in eGFR, Lipids (HDL-C, Fasting Neutral Lipids), and Body Weight

Analysis population(s): FAS

Analysis parameter(s): eGFR, HbA1c, fasting glucose, blood pressure (systolic blood pressure, diastolic blood pressure), lipids (HDL-C, fasting neutral lipids), body weight

Analysis method:

For the data in "6.2.1. Tabulation by eGFR Assessment Time Point" and "6.2.3. Tabulation of Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point," for each treatment group, descriptive statistics will be provided for the values of each assessment parameter both on the first day of the treatment period (for the eGFR, this will be the mean of the value obtained on the first day of the run-in period and the value obtained on the first day of the treatment period) and at each of the assessment time points until follow-up (Week 108) (Week 104 for all parameters other than the eGFR and HbA1c). For each treatment group, the mean change and standard deviation at each assessment time point from the first day of the treatment period (for the eGFR, the mean of the value on the first day of the run-in period and the value on the first day of the treatment period) until follow-up (Week 108) (Week 104 for all of the parameters other than the eGFR and HbA1c) will be calculated for each of the eGFR, HbA1c, fasting glucose, blood pressure (systolic blood pressure, diastolic blood pressure), lipids (HDL-C, fasting neutral lipids), and body weight. Also, for each treatment group, the mean percent change and standard deviation at each assessment time point from the first day of the treatment period (for the eGFR, the mean of the value on the first day of the run-in period and the value on the first day of the treatment period) until follow-up (Week 108) (Week 104 for all of the parameters other than the eGFR and HbA1c) will be calculated for each of the eGFR, lipids (HDL-C, fasting neutral lipids), and body weight.

For the data in "6.2.1. Tabulation by eGFR Assessment Time Point" and "6.2.3. Tabulation of

Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point," each of the mean changes at each assessment time point from Week 4 to Week 104 in the eGFR, HbA1c, fasting glucose, blood pressure (systolic blood pressure, diastolic blood pressure), lipids (HDL-C, fasting neutral lipids), and body weight, and the mean percent changes at each assessment time point from Week 4 to Week 104 in the eGFR, lipids (HDL-C, fasting neutral lipids), and body weight will be analyzed in a mixed model for repeated measures using a restricted maximum likelihood (REML) approach, with treatment group, assessment time point, treatment group—assessment time point interaction, and the stratification factor of the eGFR on the first day of the run-in period (≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and < 90) as factors, and the values of the assessment parameters on the first day of the treatment period and the interactions between the assessment time points and the values of the assessment parameters on the first day of the treatment period as covariates. The LS means and standard errors at each measurement time point for each treatment group will be presented. The differences between the groups in the LS mean (the TA-7284 group minus the placebo group) and the 95% confidence intervals and P values will also be presented. In addition, time profiles will be prepared for each treatment group for each of the mean change and the mean percent change, with the LS means and standard errors, calculated based on MMRM, along the y-axis and each measurement time point up through Week 104 along the x-axis.

The Kenward-Roger method will be used to adjust the degrees of freedom, and an unstructured covariance structure will be used for within-subject error modeling.

However, in within-subject error modeling, if the model fails to converge when using an unstructured covariance matrix, the covariance matrix will be changed according to the following procedure, and the first covariance matrix with successful convergence will be used to perform the analysis.

Heterogeneous Toeplitz (TOEPH) → Heterogeneous AR(1) (ARH(1)) → Heterogeneous CS (CSH) → Toeplitz (TOEP) → First-order autoregressive (AR(1)) → Compound symmetry (CS)

Listings

Analysis population(s): Randomized subjects

7.6.2.4. Efficacy Event Endpoints

Analysis population(s): FAS

Analysis parameter(s): Event categories 1 through 14 below

1. Composite endpoint of end-stage renal disease (ESRD) onset, doubling of serum creatinine, renal death, and cardiovascular (CV) death
2. Composite endpoint of CV death and hospitalized congestive heart failure
3. Composite endpoint of CV death, non-fatal myocardial infarction, and non-fatal stroke
4. Hospitalized congestive heart failure

5. Composite renal endpoint of end-stage renal disease (ESRD), doubling of serum creatinine, and renal death
6. CV death
7. All-cause death
8. The CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina
9. ESRD
10. Doubling of serum creatinine
11. Renal death
12. Non-fatal myocardial infarction
13. Non-fatal stroke
14. Hospitalized unstable angina

Analysis method:

For the data in "6.4 Handling of Event Endpoint Data," for each of the endpoint event categories 1 through 14, the number and proportion of subjects experiencing the events in question, as well as the event incidence per 1000 person-years, will be calculated for each treatment group. Kaplan-Meier curves will be presented for each treatment group for endpoint event categories 1 through 8.

Endpoint event categories 1 through 14 will be analyzed using a stratified Cox proportional hazard model in which the baseline hazard is stratified based on the eGFR on the first day of the run-in period ($\geq$ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2, $\geq$ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2, $\geq$ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2), with treatment group included as a factor, and the hazard ratios, 95% confidence intervals, and P values will be presented.

For the endpoint event categories 1 through 14, the number and proportion of subjects experiencing the events in question, as well as the hazard ratios and 95% confidence intervals thereof, will be presented in forest plots for each treatment group.

Listings

Analysis population(s): Randomized subjects

7.6.3. Issues in Statistical Analyses

7.6.3.1. Adjustments for Covariates

An analysis using a logistic regression model was performed in "7.6.1.2. Secondary Analysis" and "7.6.1.3. Other Analyses," and the log-transformed urine ACR level (first morning void urine) on the first day of the treatment period was used as a covariate.

An analysis using a mixed model for repeated measures was performed in "7.6.2.2. Percent Changes

in the Urine ACR (First Morning Void Urine) and Fasted Urine Glucose/Creatinine Ratio," and the log-transformed value of the analysis parameter on the first day of the treatment period and the interaction between the assessment time point and the log-transformed value of the analysis parameter on the first day of the treatment period were used as covariates.

An analysis using a mixed model for repeated measures was performed in "7.6.2.3. The Change in eGFR, HbA1c, Fasting Blood Glucose, Blood Pressure (Systolic Blood Pressure, Diastolic Blood Pressure), Lipids (HDL-C, Fasting Neutral Lipids), and Body Weight, and the Percent Change in eGFR, Lipids (HDL-C, Fasting Neutral Lipids), and Body Weight," and the value of the analysis parameter on the first day of the treatment period and the interaction between the assessment time point and the value of the analysis parameter on the first day of the treatment period were used as covariates.

7.6.3.2. Handling of Dropouts or Missing Data

See "6. Data Handling."

7.6.3.3. Interim Analyses and Data Monitoring

Not applicable

7.6.3.4. Multicenter Studies

This study is not a multicenter study.

7.6.3.5. Multiple Comparison/Multiplicity

Not applicable

7.6.3.6. Comparisons of Subject "Efficacy Assessment Subgroups"

The analyses described in "7.6.1.1 Primary analysis," "7.6.1.2 Secondary analyses," "7.6.1.3 Other analysis 1," "7.6.1.4 Other analysis 2," and "7.6.2.1 Proportion of subjects with a 40% decline in the eGFR" will be performed, using the PPS as the analysis population.

7.6.3.7. Active-Control Studies Intended to Show Equivalence

Not applicable

7.6.3.8. Analyses of Subgroups

The following subgroup analyses will be performed for the analysis described in 7.6.1.1.

Analysis population(s): FAS

Subgroups: Sex (male, female), age (< 65 years, ≥ 65 years), disease duration of type2 diabetes (< median in years, ≥ median in years), BMI (< 30, ≥ 30), HbA1c on the first day of the treatment period (< 8, ≥ 8), eGFR on the first day of the run-in period (≥ 30 and < 45, ≥ 45

and < 60, ≥ 60 and < 90), mean of the eGFR on the first day of the run-in period and that on the first day of the treatment period (< 45, ≥ 45 and < 60, ≥ 60), urine ACR on the first day of the treatment period (≤ 1000, > 1000), systolic blood pressure on the first day of the treatment period (≤ median value, > median value)

Analysis parameter(s): Proportions of subjects with declines of 30% and 40% in the eGFR at Week 104 of the treatment period

Analysis method:

In accordance with "6.2.2. Tabulation of the eGFR at Each Assessment Time Point When Imputing Data Outside the Allowable Time Window," a dataset will be prepared using [redacted] by subgroup. The estimates and variances for this dataset will be combined using Rubin's rule, and the proportions of subjects with declines of 30% and 40% in the eGFR at Week 104 of the treatment period, the point estimates for the differences between the groups (placebo group minus TA-7284 group), and the 95% confidence intervals based on the Farrington-Manning method, will be calculated for each treatment group. These figures, along with the numbers and proportions of subjects in each of these subgroups, will be presented in forest plots.

The following subgroup analyses will be performed for the analysis described in 7.6.2.2 and 7.6.2.3.

Analysis population(s): FAS

Subgroups: eGFR on the first day of the run-in period (≥ 30 and < 45, ≥ 45 and < 60, ≥ 60 and < 90)

Analysis parameter(s): Urine ACR (first morning void urine), eGFR, HbA1c, blood pressure (systolic blood pressure, diastolic blood pressure)

Analysis method:

Urine ACR (First Morning Void Urine)

For the data described in "6.2.4. Tabulation of the Urine ACR Endpoints at Each Assessment Time Point," for the urine ACR (first morning void urine) at each assessment time point in each group, the geometric mean and 95% confidence interval at the start of the treatment period and up through follow-up (Week 108) will be presented. For each treatment group, time profiles will be prepared showing the geometric mean and 95% confidence interval thereof along the y-axis and each measurement time point up through Week 104 along the x-axis. In addition, for the log-transformed values of the urine ACR (first morning void urine) for each treatment group, the mean change and 95% confidence interval at each assessment time point from Week 4 through follow-up (Week 108) will be calculated. These values will be inverse transformed, and the geometric mean and 95% confidence interval of the ratio for urine ACR (first morning void urine) will be presented.

For the data in "6.2.4. Tabulation of the Urine ACR Endpoints at Each Assessment Time Point," the mean change at each assessment time point from Week 4 to Week 104 in the log-transformed values of the urine ACR (first morning void urine) will be analyzed in a mixed model for repeated measures using a restricted maximum likelihood (REML) approach, with treatment group, assessment time point,

treatment group—assessment time point interaction, log-transformed value of the urine ACR (first morning void urine) on the first day of the treatment period, and interaction between the assessment time point and the log-transformed value of the urine ACR (first morning void urine) on the first day of the treatment period as covariates. For each treatment group at each assessment time point, the LS mean and standard error, 95% confidence interval, difference between the groups (the TA-7284 group minus the placebo group) in the LS mean, and the standard error and 95% confidence interval thereof, will be calculated. Additionally, the LS means and 95% confidence intervals of the changes in the log-transformed values will be back-transformed, and the geometric LS means and 95% confidence intervals of the ratios of the urine ACR (first morning void urine) will be presented. The values obtained from the following formula will be presented as the percent change from baseline: (geometric LS mean of the ratio of urine ACR [first morning void urine] – 1) x 100. Also, the differences between the groups (the TA-7284 group minus the placebo group) in the LS means, and the 95% confidence intervals thereof, will be back-transformed, and the ratios of the geometric LS means of the ratios of the urine ACR (first morning void urine) and the 95% confidence intervals and P values, will be presented. The percent changes relative to placebo [(ratio of the geometric LS means of the ratio of urine ACR (first morning void urine) – 1) x 100] will also be presented.

The Kenward-Roger method will be used to adjust the degrees of freedom, and an unstructured covariance structure will be used for within-subject error modeling.

However, in within-subject error modeling, if the model fails to converge when using an unstructured covariance matrix, the covariance matrix will be changed according to the following procedure, and the first covariance matrix with successful convergence will be used to perform the analysis.

Heterogeneous Toeplitz (TOEPH) → Heterogeneous AR(1) (ARH(1)) → Heterogeneous CS (CSH) → Toeplitz (TOEP) → First-order autoregressive (AR(1)) → Compound symmetry (CS)

eGFR, HbA1c, blood pressure (systolic blood pressure, diastolic blood pressure)

For the data in "6.2.1. Tabulation by eGFR Assessment Time Point" and "6.2.3. Tabulation of Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point," for each treatment group, descriptive statistics will be provided for the values of each assessment parameter both on the first day of the treatment period (for the eGFR, this will be the mean of the value obtained on the first day of the run-in period and the value obtained on the first day of the treatment period) and at each of the assessment time points until follow-up (Week 108) (Week 104 for the parameter of blood pressure). For each treatment group, the mean change and standard deviation at each assessment time point from the first day of the treatment period (for the eGFR, the mean of the value on the first day of the run-in period and the value on the first day of the treatment period) until follow-up (Week 108) (Week 104 for the parameter of blood pressure) will be calculated for each of the eGFR, HbA1c, and blood pressure

(systolic blood pressure, diastolic blood pressure). In addition, the mean percent changes (and standard deviations) from the mean of the eGFR value on the first day of the run-in period and that on the first day of the treatment period to each assessment time point through follow-up (Week 108) will be calculated for each treatment group.

For the data in "6.2.1. Tabulation by eGFR Assessment Time Point" and "6.2.3. Tabulation of Endpoints Other Than the eGFR and Urine ACR at Each Assessment Time Point," each of the mean changes at each assessment time point from Week 4 to Week 104 in the eGFR, HbA1c, and blood pressure (systolic blood pressure, diastolic blood pressure), and each of the mean percent changes at each assessment time point from Week 4 to Week 104 in the eGFR will be analyzed in a mixed model for repeated measures using a restricted maximum likelihood (REML) approach, with treatment group, assessment time point, treatment group—assessment time point interaction as factors, and the values of the assessment parameters on the first day of the treatment period and the interactions between the assessment time points and the values of the assessment parameters on the first day of the treatment period as covariates. The LS means and standard errors at each measurement time point for each treatment group will be presented. The differences between the groups in the LS mean (the TA-7284 group minus the placebo group) and the 95% confidence intervals and P values will also be presented. In addition, time profiles will be prepared for each treatment group for each of the mean change and the mean percent change, with the LS means and standard errors, calculated based on MMRM, along the y-axis and each measurement time point up through Week 104 along the x-axis, for the eGFR.

The Kenward-Roger method will be used to adjust the degrees of freedom, and an unstructured covariance structure will be used for within-subject error modeling.

However, in within-subject error modeling, if the model fails to converge when using an unstructured covariance matrix, the covariance matrix will be changed according to the following procedure, and the first covariance matrix with successful convergence will be used to perform the analysis.

Heterogeneous Toeplitz (TOEPH) → Heterogeneous AR(1) (ARH(1)) → Heterogeneous CS (CSH) → Toeplitz (TOEP) → First-order autoregressive (AR(1)) → Compound symmetry (CS)

7.7. Safety Analysis

7.7.1. Adverse Events

- Reported adverse events will be reclassified using MedDRA version 20.1.
- Events newly occurring following the administration of the investigational product and events that have worsened compared to their status prior to treatment initiation will be tabulated as treatment-emergent adverse events (TEAEs).
- SOCs will be tabulated and displayed in the internationally recognized order, and PTs will be tabulated and displayed in descending order of the number of subjects with said events in the active drug group, in descending order of the number of subjects with said events in the placebo group,

and in PT code ascending order.

- When counting the number of subjects with a particular event by PT, if the same subject experienced a different PT adverse event, then this subject will be counted once for each PT. If the same subject experiences the same PT adverse event multiple times, then this subject will be counted only one time for this PT.
- When counting the number of subjects with a particular event by SOC, if the same subject experienced a different SOC adverse event, then this subject will be counted once for each SOC. If the same subject experiences the same SOC adverse event multiple times, then this subject will be counted only one time for this SOC.
- When tabulating events by severity (severe, moderate, mild), subjects will be counted as described below.

(1) If the same subject experiences adverse events at different levels of severity, then this subject will be counted once, at the highest level of severity.

(2) If the same subject experiences multiple adverse events at the same level of severity, then this subject will be counted once, at this level of severity.

(3) If the same subject experiences the same adverse event multiple times, this subject will be counted once at the highest level of severity.

- Calculation of the incidence per 1000 person-years

Safety Endpoints

Adverse events, adverse reactions, serious adverse events, serious adverse reactions, adverse events leading to study treatment discontinuation, adverse reactions leading to study treatment discontinuation, adverse events leading to death, adverse reactions leading to death, hypoglycemia, severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia, the adverse events in the PT list for hypoglycemia in the attachment, lower limb amputation, volume depletion, fracture, osmotic diuresis, renal-related adverse events, diabetic ketoacidosis, acute pancreatitis, urinary tract infection, upper urinary tract infection, female mycotic genital infection, male mycotic genital infection, hypoglycemia, malignancy

N: Safety endpoint sample size

P: Sum total of the assessment period (in years) of the incidence per 1000 person-years for each subject in the safety analysis population

Incidence per 1000 person-years = N/P x 1000 (1000 subject-years)

7.7.1.1. Adverse Event Incidences

Analysis population(s): Safety analysis set

Analysis parameter(s): Adverse events, adverse reactions, serious adverse events, serious adverse reactions, adverse events leading to study treatment discontinuation, adverse reactions leading to study treatment discontinuation, adverse events leading to death, adverse reactions leading to death

Analysis method:

For events occurring in the adverse event tabulation period, the numbers and proportions of subjects experiencing said events, as well as the incidence per 1000 person-years, will be presented for each treatment group.

Listings

Analysis population(s): Safety Analysis Sets

7.7.1.2. Incidence of Adverse Events by eGFR on the First Day of the Run-in Period ($\geq$ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2, $\geq$ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2, $\geq$ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2)

Analysis population(s): Safety analysis set

Analysis parameter(s): Adverse events, adverse reactions, serious adverse events, serious adverse reactions, adverse events leading to study treatment discontinuation, adverse reactions leading to study treatment discontinuation, adverse events leading to death, adverse reactions leading to death

Analysis method:

For each event occurring in the adverse event tabulation period, the number and proportion of subjects experiencing the event, as well as the incidence per 1000 person-years, will be presented by eGFR category ($\geq$ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2, $\geq$ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2, $\geq$ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2) and by treatment group.

Listings

Analysis population(s): Safety Analysis Sets

7.7.1.3. Individual Adverse Events

Analysis population(s): Safety analysis set

Analysis parameter(s): Adverse events, adverse reactions, serious adverse events, serious adverse reactions, adverse events leading to study treatment discontinuation, adverse reactions leading to study treatment discontinuation, adverse events leading to death, adverse reactions

leading to death

Analysis method:

For each event occurring in the adverse event tabulation period, the number and proportion of subjects experiencing said event will be presented by treatment group and by MedDRA SOC and PT category.

Listings

Analysis population(s): Safety Analysis Sets

7.7.1.4. Adverse Events by Severity

Analysis population(s): Safety analysis set

Analysis parameter(s): Adverse events, adverse reactions

Analysis method:

For each event occurring in the adverse event tabulation period, the number and proportion of subjects experiencing said event will be presented by MedDRA PT and SOC category, by severity, and by treatment group. The severity categories will be "mild," "moderate," and "severe."

Listings

Analysis population(s): Safety Analysis Sets

7.7.1.5. Adverse Events by Causal Relationship to the Investigational Product

Analysis population(s): Safety analysis set

Analysis parameter(s): Adverse events, serious adverse events

Analysis method:

For each event occurring in the adverse event tabulation period, the number and proportion of subjects experiencing said event will be presented by MedDRA PT and SOC category, by causal relationship to the investigational product, and by treatment group. The causal relationship categories will be "reasonable possibility" and "no reasonable possibility" (of there being a causal relationship).

Listings

Analysis population(s): Safety Analysis Sets

7.7.1.6. Adverse Events by Time of Onset

Analysis population(s): Safety analysis set

Analysis parameter(s): Adverse events, adverse reactions

Analysis method:

For each event occurring in the adverse event tabulation period, the number and proportion of subjects experiencing said event will be presented by MedDRA PT and SOC category, by administration duration

(in weeks), and by treatment group.

Treatment Period Duration Categories (in weeks)
$< 13, \geq 13$ and $< 26, \geq 26$ and $< 52, \geq 52$ and $< 78, \geq 78$

Listings
Analysis population(s): Safety Analysis Sets

7.7.2. Hypoglycemia
Analysis population(s): Safety analysis set
Analysis parameter(s): Hypoglycemia
Analysis method:

The number and proportion of subjects experiencing hypoglycemia (blood glucose decreased, hypoglycemic coma, hypoglycemic unconsciousness, hypoglycemic seizure, hypoglycemia) in the adverse event tabulation period, and the incidence per 1000 person-years, will be presented by treatment group. The number and proportion of subjects and the incidence per 1000 person-years will be presented by hypoglycemia category and treatment group. The number and proportion of subjects experiencing hypoglycemia will also be presented by treatment period and treatment group. For the attached hypoglycemia PT list, the number and proportion of subjects experiencing each event, as well as the incidence per 1000 person-years, will be presented by treatment group and by SOC and PT (blood glucose decreased, hypoglycemic coma, hypoglycemic unconsciousness, hypoglycemic seizure, hypoglycemia).

Hypoglycemia Categories
Severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia

Treatment Period Categories (in weeks)
$< 13, \geq 13$ and $< 26, \geq 26$ and $< 52, \geq 52$ and $< 78, \geq 78$

Listings
Analysis population(s): Safety Analysis Sets

7.7.3. Adverse Events of Special Interest
Analysis population(s): Safety analysis set
Analysis parameter(s): Lower limb amputation, volume depletion, fracture, osmotic diuresis, renal-related adverse events, diabetic ketoacidosis, acute pancreatitis, urinary tract infection, upper

urinary tract infection, female mycotic genital infection, male mycotic genital infection, hypoglycemia, and malignancies

Analysis method:

For adverse events of special interest occurring in the adverse event tabulation period, the numbers and proportions of subjects experiencing said events, as well as the incidence per 1000 person-years, will be presented for each treatment group.

The number and proportion of subjects experiencing the event, as well as the incidence per 1000 person-years, will be presented by eGFR category ($\geq$ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2, $\geq$ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2, $\geq$ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2) and by treatment group.

In addition, for the events in the PT list of adverse events of special interest in the attachment, the numbers and proportions of subjects experiencing said events, and the incidences per 1000 person-years will be presented by treatment group and PT.

Listings

Analysis population(s): Safety Analysis Sets

7.7.4. Clinical Laboratory Tests

Analysis population(s): Safety analysis set

Analysis parameter(s): Hematology test parameters, blood biochemistry test parameters (except for the parameters for the efficacy assessments), urinalysis (quantitative) (except for the parameters for the efficacy assessments), urinalysis (qualitative), renal function biomarkers

Analysis method:

For the analysis parameters other than urinalysis (qualitative), descriptive statistics will be presented by treatment group for the values at each assessment time point and the changes therein. For the urinalysis (qualitative) parameters, the number and proportion of subjects at each assessment time point will be presented by treatment group and treatment category ((-), (+/-), (1+), (2+), (3+), (4+)). The number and proportion of subjects at each measurement time point will be presented for the change in treatment category compared to the first day of the treatment period, as well.

For analysis parameters other than urinalysis (qualitative) parameters, shift tables will be prepared by treatment group showing the treatment categories (low, normal, high) at the first day of the treatment period and at each assessment time point. For urinalysis (qualitative) parameters, shift tables will be prepared by treatment group showing the treatment categories (normal, abnormal) at the first day of the treatment period and at each assessment time point.

Listings

Analysis population(s): Safety Analysis Sets

7.7.5. Vital Signs

Analysis population(s): Safety analysis set

Analysis parameter(s): Systolic blood pressure, diastolic blood pressure, and pulse rate

Analysis method:

For the analysis parameters, descriptive statistics will be presented by treatment group for the values at each assessment time point and the changes therein.

Listings

Analysis population(s): Safety Analysis Sets

7.7.6. Resting Standard 12-Lead ECG

Analysis population(s): Safety analysis set

Analysis parameter(s): Results of ECG diagnosis (normal, abnormal but not clinically significant, abnormal and clinically significant)

Analysis method:

For each analysis parameter, the frequency of each assessment result (normal, abnormal but not clinically significant, abnormal and clinically significant) at each measurement time point will be tabulated for each treatment group, and shift tables showing the assessment results for the first day of the treatment period and the assessment time points will be prepared.

Listings

Analysis population(s): Safety Analysis Sets

8. Software Used

The SAS Windows version (release 9.4) will be used for statistical analysis.

9. Changes to Statistical Analysis Plan From The Protocol

9.1. Handling of the Fasting Urine Glucose/Creatinine Ratio

Study Protocol

Change in the fasting urine glucose/creatinine ratio

Statistical Analysis Plan

Percent change in the fasting urine glucose/creatinine ratio

9.2. Analysis Taking Into Account a Delay in Subject Visits at Week 104 of the Treatment Period Because of COVID-19 Infections

The third version of the study protocol (prepared April 17, 2020) extended the allowable time window for the visit at Week 104 of the treatment period by 56 days, to 784 days maximum, to account for cases in which subject visits at Week 104 of the treatment period would be difficult because of COVID-19 infections, and when the statistical analysis plan was being prepared, an analysis was considered that would take into account the effects of delayed subject visits. Subsequently, because no actual cases arose in which subject visits at Week 104 of the treatment period had to be delayed because of COVID-19 infections, it was decided that the allowable time window for the visit at Week 104 of the treatment period would be set at 735 days maximum, the time that had been set prior to version 3 of the study protocol, and that the analysis that takes into account the effects of delayed visits would not be conducted.

10. References

1) Matsushita K, Chen J, Sang Y, Ballew SH, Shimazaki R, Fukagawa M, et al. Risk of end-stage renal disease in Japanese patients with chronic kidney disease increases proportionately to decline in estimated glomerular filtration rate. Kidney Int. 2016;90(5):1109-14.

Appendices