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

Protocol

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Sponsor

Mitsubishi Tanabe Pharma Corporation

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Confidentiality Notice

This protocol contains information to be provided only to people directly related to the study. The information contained in this document must not be published or disclosed to any third parties without the prior written consents of Mitsubishi Tanabe Pharma Corporation.

This study will be conducted in compliance with the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, the Pharmaceutical Affairs Law of Japan, the Ministerial Order on Good Clinical Practice (GCP), and related laws, and this protocol.

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List of Abbreviations

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
ULN	Upper limit of normal

Definitions of Terminology

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 proportion 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 proportion 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.

Protocol Synopsis

1 Study Title

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

2 Objective

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).

3 Subjects

3.1 Subjects

Type 2 diabetes mellitus patients with Stage 3 diabetic nephropathy (overt nephropathy)

3.2 Inclusion Criteria

Patients will be eligible for enrollment in the study if all of the following criteria apply, and the patients are capable of providing consent. Furthermore, the clinical laboratory test values that have been centrally measured at a central laboratory will be used for the inclusion criteria assessments.

(1) Japanese patients with age ≥ 30 years at written informed consent acquisition.
(2) Patients who have received diagnoses of type 2 diabetes based on the diagnosis criteria of the Japan Diabetes Society by the time of written informed consent acquisition.
(3) Sex: Either
(4) Inpatient/outpatient status: Outpatient
(5) Patients who have been receiving dietary and exercise therapy for diabetes without any changes to the regimens since at least 12 weeks before the first day of the treatment period. However, this restriction will not apply if the exercise therapy cannot be continued because of a complication.
(6) Patients who have been receiving angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) drugs at the maximum approved dose since at least 5 weeks before the first day of the screening period (or at the maximum approved dose for hypertension if the drug has not been approved for an indication of diabetic nephropathy). However, this restriction will not apply if the (sub) investigator determines that for medical reasons it would not be appropriate to use the maximum approved dose. Furthermore, the concomitant use of ACE-I and ARB drugs will not be permitted.
(7) Patients with HbA1c ≥ 6.5% and ≤ 12.0% on the first day of the run-in period.
(8) Patients with estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2 on the first day of the run-in period.
(9) Patients with a median urine albumin/creatinine ratio (urine ACR) for 3 days' worth of first morning void urine collected within 1 week that includes the visit day on the first day of the screening period that is at least 300 mg/g Cr and not more than 5,000 mg/g Cr. Furthermore, if this criterion is not satisfied, the (sub) investigator may perform retesting during the

screening period if he/she determines that it is medically appropriate. No rule is being established regarding the number of times retesting may be performed.

(10)Patients who have not been using any prohibited concomitant medications (see "6.1 Prohibited Concomitant Medications") since at least 12 weeks before the first day of the treatment period. Furthermore, if a patient is receiving a prohibited concomitant medication at informed consent acquisition, its use must be discontinued following informed consent acquisition, and a wash-out of at least 12 weeks implemented.

(11)Patients who have not deviated from the restrictions on concomitant use if they are being treated with a restricted concomitant medication (see "6.2 Restricted Concomitant Drugs/Therapies").

(12)Patients who have an adherence rate of at least 80% with the treatment of the run-in period investigational product treatment.

3.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria between the day of informed consent acquisition and the first day of the treatment period will be excluded from the study. Furthermore, clinical laboratory test values that have been assessed at a central laboratory will be used in the exclusion criteria assessments.

(1) Patients with type 1 diabetes mellitus, diabetes mellitus resulting from pancreatic disorder, or secondary forms of diabetes (e.g., Cushing's syndrome, acromegaly).
(2) Patients with genetic glucose/galactose absorption deficiencies or renal glycosuria.
(3) Patients with conditions requiring strict blood glucose monitoring, such as patients with severe ketosis, diabetic coma or precoma, severe infection, or severe trauma, or pre- or post-operative patients; or patients with a history of diabetic ketoacidosis.
(4) Patients undergoing dietary therapy that strictly restrict sugar intake.
(5) Patients diagnosed with non-diabetic kidney disease.
(6) Patients with a history of nephrectomy or renal transplant or patients who have received dialysis treatment.
(7) Patients with resting systolic blood pressure $\geq$ 180 mmHg or resting diastolic blood pressure $\geq$ 100 mmHg measured by the study site on the first day of the run-in period or the first day of the treatment period.
(8) Patients who are human immunodeficiency virus antibody (HIV) positive.
(9) Patients with serious (e.g., requiring hospitalization for treatment or eligible for surgery) liver or kidney disease.
(10)Patients with ALT > 2 x ULN or total bilirubin > 1.5 x ULN on the first day of the run-in period.
(11)Patients with serum potassium > 5.5 mmol/L on the first day of the run-in period.
(12)Patients with current or prior symptoms of Class IV cardiac failure according to the functional classifications of the New York Heart Association (NYHA).
(13)Patients who develop myocardial infarction or cerebrovascular disorders in the 12 weeks before the first day of the treatment period. Patients who have undergone revascularization (e.g., stent placement or bypass surgery). Patients with concurrent unstable angina pectoris.
(14)Patients with ECG findings requiring urgent diagnosis/assessment or intervention in the 12 weeks before the first day of the treatment period (e.g., newly emergent clinically significant arrhythmias or conduction disorders).

(15)Patients with malignant tumors or with a past history of malignant tumors. However, patients with a past history of malignant tumors who have not experienced a recurrence for at least 5 years prior to the date of informed consent acquisition (patients for whom at least 5 years have passed between the date of the last dose and the date of informed consent acquisition for patients who had been receiving anticancer agents) are exempt from this restriction.

(16)Patients who have participated in clinical trials or other studies or who have received investigational products or other study drugs in the 12 weeks before the first day of the treatment period, or patients who are currently participating in clinical trials or other studies.

(17)Males and females of childbearing potential (patients who have not undergone sterilization procedures such as surgical hysterectomy or bilateral ovariectomy, or patients who are pre-menopausal [with post-menopausal being defined as not having menstruated for at least 1 year]) who do not consent to practice contraception during the term of the study.

(18)Female patients who are pregnant, nursing, or possibly pregnant.

(19)Patients who have been treated with canagliflozin hydrate (either as an investigational product or as the commercial product) in the past.

(20)Patients otherwise found by the (sub) investigator to be ineligible for the study.

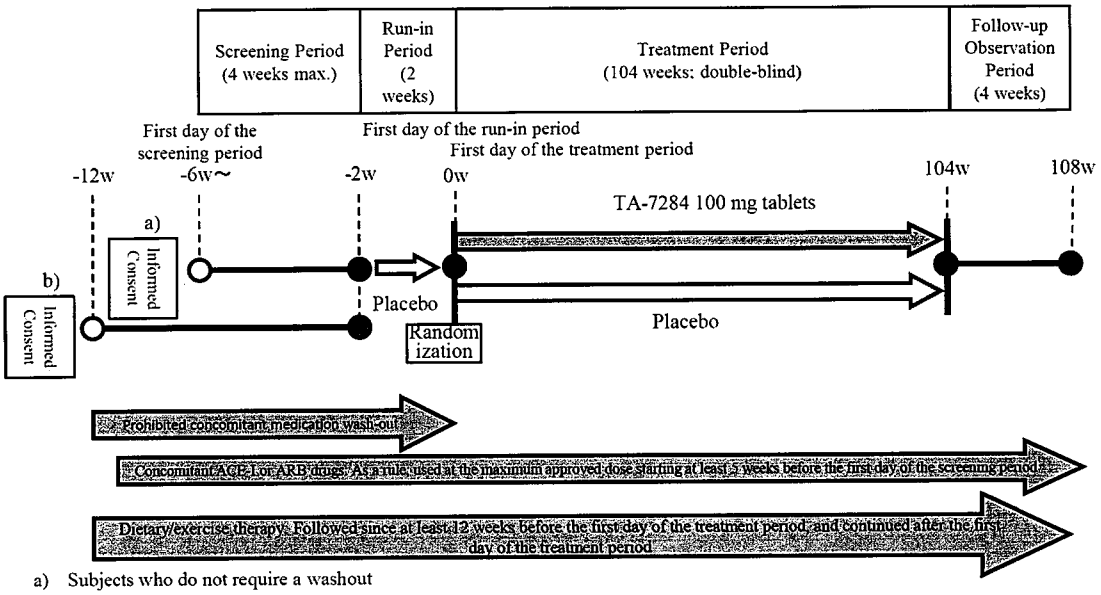
(21)Patients with a history of non-traumatic amputation within 12 months prior to the day of informed consent, or with a history of lower limb active skin ulcer, osteomyelitis, gangrene, or severe ischemic within 6 months prior to the day of informed consent.

4 Study Design

Phase of study : Phase III

Study type : Long-term study

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



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

Period	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. 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.

5 Investigational Product Dosage and Administration

5.1 Name of Investigational Product

(1) Study drug

Name	: TA-7284 Tablets 100 mg
Nonproprietary name	: Canagliflozin hydrate (JAN)
Dosage form and strength	: Film-coated tablets containing canagliflozin 100 mg per tablet

(2) Control agent

Name	: TA-7284 Tablets placebo
Dosage form and strength	: Placebo tablets that are externally indistinguishable from the TA-7284 100 mg tablets

5.2 Dosage and Administration

(1) In the run-in period, one tablet of the run-in period investigational product (TA-7284 placebo tablets) will be administered by mouth with water once a day before or after breakfast.
(2) In the treatment period, one tablet of the treatment period investigational product (TA-7284 100 mg tablets or TA-7284 placebo tablets) will be administered by mouth with water once a day before or after breakfast.

5.3 Treatment/Assessment Periods

(1) Screening period : 4 weeks maximum
(2) Run-in period : 2 weeks
(3) Treatment period : 104 weeks
(4) Follow-up observation period : 4 weeks

6 Concomitant Drugs/Therapies

6.1 Prohibited Concomitant Drugs

The concomitant use of the drugs listed below will be prohibited from 12 weeks before the first day of the treatment period until Week 4 of the follow-up observation period. However, the drugs listed in (1) through (3) may be used after the completion of the scheduled tests on the last day of the treatment period if the (sub) investigator judges it to be necessary.

(1) Aldosterone antagonists
(2) Direct renin inhibitors
(3) SGLT2 inhibitors other than the investigational product (including commercially available canagliflozin hydrate)
(4) Other investigational products (including placebos)

6.2 Restricted Concomitant Drugs/Therapies

6.2.1 ACE-I or ARB

One ACE-I or ARB drug may be used concomitantly at the maximum approved dose (if the drug is

not indicated for diabetic nephropathy, then at the maximum approved dose for hypertension) from at least 5 weeks before the first day of the screening period through Week 4 of the follow-up observation period. However, this restriction will not apply if the (sub) investigator determines that for medical reasons it would not be appropriate to use the maximum approved dose. Furthermore, the concomitant use of ACE-I and ARB drugs will not be permitted. If blood pressure control becomes inadequate, another antihypertensive agent may be added and the regimen thereof modified, without changing the dosing regimen of the ACE-I or ARB drug.

6.2.2 Antihypertensive Agents and Lipid Lowering Drugs Other Than ACE-I or ARB Drugs

If an antihypertensive agent other than an ACE-I or ARB drug (excluding diuretics) or a lipid lowering agent (e.g., a statin, ezetimibe, a fibrate, nicotinic acid) is concomitantly used, whenever possible the dosing regimen should remain unchanged from at least 4 weeks before the first day of the screening period until the first day of the treatment period. The additional use of these concomitant drugs, the discontinuation of the concomitant use of these drugs, or the modification of the dosing regimens thereof will be permitted provided that the (sub) investigator has determined that it is appropriate after referring to, for example, guidelines that have been prepared by a Japanese academic society.

6.2.3 Diabetes Medications

If a diabetes medication is going to be used concomitantly, then whenever possible the dosing regimen should remain unchanged from at least 4 weeks before the first day of the screening period until the first day of the treatment period. However, the additional use of these drugs, the discontinuation of the use of these drugs, or the modification of the dosing regimens thereof will be permitted provided that the (sub) investigator has determined that it is appropriate after referring to, for example, guidelines that have been prepared by a Japanese academic society.

6.2.4 Drugs with the Potential to Affect the Serum Creatinine Level

Drugs with the potential to affect the serum creatinine level (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], trimethoprim, cimetidine, probenecid, aminoglycoside antibiotics, amphotericin, ketoconazole, clofibrate) should whenever possible be administered without changing the dosing regimens thereof for the 2 weeks before all of the clinical laboratory tests that are conducted from the first day of the run-in period until Week 4 of the follow-up observation period.

6.2.5 Diuretics

The use of diuretics in combination with TA-7284 is not recommended. On the day of informed consent acquisition, consideration should be given to switching subjects who are receiving diuretics to alternative medications.

6.2.6 Concomitant Therapies

Dietary and exercise therapies should be continued without any changes to the regimens thereof from at least 12 weeks before the first day of the treatment period until Week 4 of the follow-up observation period. However, this restriction will not apply if the (sub) investigator determines that it would be difficult to continue the dietary or exercise therapy because of a complication or adverse event.

7 Endpoints

7.1 Efficacy Endpoints

7.1.1 Primary Endpoint

The proportion of subjects with a 30% decline in the eGFR (the proportion of subjects with a decline of at least 30% in the eGFR at the end of the treatment period compared to the average of the values on the first days of the run-in and treatment periods).

7.1.2 Secondary Endpoints

(1) The proportion of subjects with a 40% decline in the eGFR (the proportion of subjects with a decline of at least 40% in the eGFR at the end of the treatment period 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) The renal composite endpoint of 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

For the events described in (3) through (10), both the proportion of subjects with such events and the time to initial onset will be assessed.

7.2 Safety Endpoints

(1) Adverse events
(2) Hypoglycemia
(3) Clinical laboratory test values
(4) Standard 12-lead electrocardiography
(5) Vital signs

8 Discontinuation criteria

Subjects meeting any of the following discontinuation criteria will be discontinued from the study.

(1) If the subject requests discontinuation.
(2) If it is determined that the subject is clearly ineligible to participate in the study.
(3) If the (sub) investigator determines that it would be difficult to continue the study because of the emergence of, for example, an adverse event.
(4) If the (sub) investigator determines that it would not be appropriate to continue the study because of a worsening of the patient's primary disease.
(5) If it is discovered that the subject is pregnant.
(6) If the (sub) investigator determines that the study should be discontinued for some other reason.

9 Target Sample Size

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

10 Duration of Study

December 2017 through September 2021

11 Test and Observation Schedule

Time point a) / Parameter	Date of informed consent	Screening Period b) (4 weeks max.)	Run-in Period (2 weeks)	Treatment Period (104 weeks)																														Follow-up observation period
		First day of the screening period	First day of the run-in period	First day of the treatment period (Week 2 of the 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 n)																		●	●		●	●		●	●		●	●	●			
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 to +56 d m)	+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)			←																														→

●: Required ○: Implemented when possible

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 discontinue 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 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 was 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.
m) If the (sub)investigator determines that it would not be possible for a subject to come in for a study visit because of the impact of the COVID-19 pandemic, then the investigator will conduct a survey by telephone of, for example, the investigational product dosing compliance conditions and adverse events, and then may prescribe more investigational product based on the results thereof, and may postpone the deadline for performing the visit beyond Week 104 of the treatment period.
n) If the (sub)investigator determines that it would not be possible for a subject to come in for a study visit because of the impact of the COVID-19 pandemic then, even if the tests/observations can not be performed on the scheduled visit date, the investigator

will conduct a survey by telephone of, for example, the investigational product dosing compliance conditions and adverse events, and then may prescribe more investigational product based on the results thereof. In addition, if this is done, and if the deadline for performing the visit is extended beyond Week 104 of the treatment period, then the investigator will conduct a survey by telephone of, for example, the investigational product dosing compliance conditions and adverse events, every 14 days, as a rule.

1. History of Protocol and Background Information

(1) Disease Studied and Available Treatments

Diabetic nephropathy accounts for the majority of chronic kidney disease. In Japan, it has been the main primary disease leading to the introduction of maintenance dialysis (hemodialysis, peritoneal dialysis) since 1998[2] and accounted for 43.7% of the total number of patients on dialysis in 2015.[3] In Japan, the total costs of artificial dialysis are around 1.4 trillion yen (2009),[4] meaning that dialysis accounts for 4% of Japan's total health care costs. Controlling the number of patients who receive dialysis is therefore a significant societal issue. Patients receiving dialysis face many employment and lifestyle restrictions, and the burden on their caregivers (e.g., families) is also considerable. In addition, the five-year survival rate of patients who have been started on dialysis has been reported to be 60.8%.[3] Thus, it is important for patients with diabetes to diagnose and treat nephropathy early to inhibit its progression from the viewpoint of the prognosis of patients, the quality of life of patients and caregivers, and health economics. In early (Stage 2) nephropathy, in which the urine albumin level is 30 mg/gCr or above, if treatment is not administered, the urine albumin level will rise at a rate of around 10 to 20% a year until after 10 to 15 years the patient has progressed to overt (Stage 3) nephropathy. The patient's glomerular filtration rate (GFR) will then gradually decrease (by between 2 and 20 mL/min/1.73 m^2 per year), ultimately resulting in end-stage renal failure (renal failure stage, dialysis therapy stage).[5] It has been reported that as the urine albumin level increases, the incidence of cardiovascular events increases,[2,6] and the prognosis for renal function worsens.[7] Thus, treatment guidelines recommend starting treatment in the early stage, i.e., early nephropathy stage. In addition, it has been reported that improving blood pressure management even in the overt nephropathy stage can result in remission from macroalbuminuria to normal urine albumin levels, and intensive therapy therefore is believed to be critical for patients with overt nephropathy as well.[8,9]

At present, the only drugs that are indicated for diabetic nephropathy in Japan are losartan potassium, an ARB drug the use of which is limited to type 2 diabetes patients with hypertension and proteinuria (urine ACR $\geq$ 300 mg/g), and imidapril hydrochloride, and ACE-I drug the use of which is limited to type 1 diabetes patients.

(2) Name and Description of Investigational Product

TA-7284 (nonproprietary name: canagliflozin hydrate) is a sodium glucose co-transporter (SGLT) 2 inhibitor for which Mitsubishi Tanabe Pharma Corporation obtained marketing approval in Japan in July 2014 for an indication for type 2 diabetes for Canaglu 100 mg Tablets.

[redacted]

SGLT2 is distributed in the renal tubules and is involved in the reabsorption of around 90% of the glucose that is filtered from the blood by the glomerulus and that subsequently passes into the glomerular filtrate. SGLT2 inhibitors selectively inhibit SGLT2 and thereby inhibit urinary glucose reabsorption, normalizing blood glucose levels. It appears that SGLT2 inhibitors, by effecting a correction in the hyperglycemic state, will alleviated "glucose toxicity" and help to inhibit the progression of diabetes and/or help to prevent the emergence and progression of complications.

In addition, independent of its blood glucose lowering effects, which result from its increasing of urinary glucose excretion, TA-7284 appears to also act to reduce intraglomerular pressure via an intrarenal mechanism (the promotion of tubuloglomerular feedback [a mechanism in which both glomerular filtration and Na^+ and body fluid renal tubule reabsorption are involved]) that results in a rapid and slight reduction in the estimated glomerular filtration rate, and thus results in a decrease in hyperfiltration and albuminuria. TA-7284 therefore inhibits the progression of diabetic nephropathy by effects that are different from those of ACE-I and ARB drugs, and it is therefore expected that this mechanism will be additive to the renal protective effects of ACE-I and ARB drugs. Figure 1.1 shows the hypothesized mechanism of renal protection of ACE-I and ARB drugs as well as the hypothesized mechanism of pharmacological action for TA-7284.

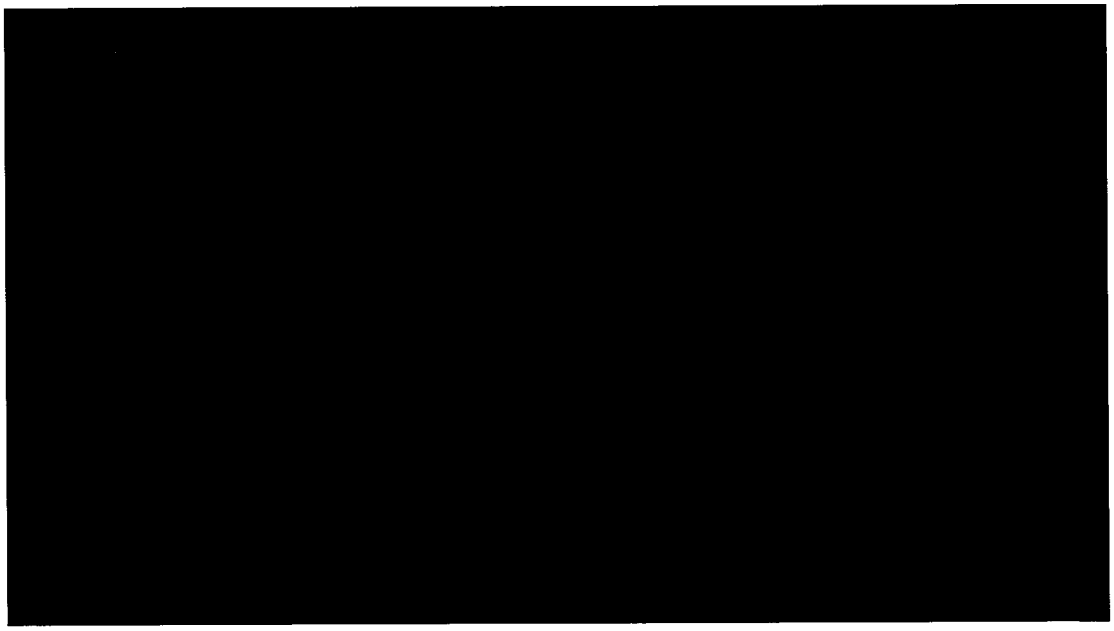


Figure 1.1: Hypothesized Mechanism of Pharmacological Action of TA-7284

As shown above, TA-7284's inhibition of SGLT2 increases glomerular afferent arteriole tonus and thereby reduces intraglomerular pressure, and therefore appears to result in a

hemodynamically mediated reduction in intraglomerular pressure that is reflected in a sudden, slight decrease in the GFR. It appears possible that the reduction in intraglomerular pressure inhibits the progression of diabetic nephropathy through the reduction in urine albumin levels that is seen in treatment with TA-7284.

(3) Summary of Nonclinical and Clinical Findings

1) Nonclinical findings

In diabetic db/db mice that were given a selected SGLT2 inhibitor [redacted] blood glucose control was improved after 12 weeks, and the urine albumin levels were reduced (207 ± 5 mg/g in the treatment group compared to 745 ± 36 mg/g in the control group; $P < 0.001$). In addition, the administration of [redacted] reduced the tissue changes that are characteristic of diabetic nephropathy, such as mesangial proliferation, fibronectin and type IV collagen accumulation, and podocyte loss, and were inhibited macrophage accumulation aggregation and neutral lipid accumulation in the kidneys.[10] In a different rat model of diabetes in which a different selective SGLT2 inhibitor [redacted] was used (rats administered streptomycin), as well, similar reductions were observed in blood glucose and urinary albumin excretion.[11] Furthermore, caution needs to be exercised regarding the fact that an improvement in blood glucose control will also reduce the extent of the decline in renal function. In other words, it is necessary to pay close attention to the fact that in these studies it is not possible to distinguish the effects that result from improved blood glucose control from the hemodynamically mediated effects on the kidneys.

The effects of luseogliflozin (an SGLT2 inhibitor), lisinopril (an ACE-I), the concomitant use of lisinopril and luseogliflozin, and insulin or a placebo have been investigated in a rat model of diabetic nephropathy (T2DN rats). T2DN rats administered placebos exhibited progressive proteinuria, decreased GFR, focal glomerulosclerosis, kidney fibrosis, and tubular necrosis. By contrast, when lisinopril and luseogliflozin were each administered alone, this inhibited the reduction in the GFR and alleviated the progression of glomerular injury, kidney fibrosis, and tubular necrosis. The administration of insulin, on the other hand, had no effect on the progression of kidney disease in the T2DN rats. The administration of lisinopril in combination with luseogliflozin substantially alleviated the progression of glomerular injury, kidney fibrosis, and tubular necrosis compared to the administration of either of these drugs alone. These results suggest that SGLT2 inhibition delays the progression of diabetic nephropathy compared to insulin, and that the use of an SGLT2 inhibitor in combination with an ACE-I drug has a greater kidney protective effect than the use of either of these types of drugs alone.[12]

A kidney micropuncture test was conducted using diabetic Wistar rats in order to evaluate the hemodynamic effects of dapagliflozin, a selective SGLT2 inhibitor, in early diabetic

nephropathy. The administration of dapagliflozin increased the influx of Na^+ into the distal renal tubule and alleviated the increase in the GFR in the single nephron involved in diabetes.[13)]

These results in nonclinical rodent studies suggest that SGLT2 inhibition by TA-7284 may reduce glomerular hyperfiltration and thereby delay the onset and progression of diabetic nephropathy.

2) Clinical findings

Pharmacokinetics

The results of the Japanese clinical studies are described below.

When single oral doses of TA-7284 100 mg were administered to type 2 diabetes patients (study TA-7284-02), the C_{max} was 1126 ng/mL, the $AUC_{0-\infty}$ was 6561 ng•h/mL, the t_{max} was 1.0-1.5 hours, and the $t_{1/2}$ was 10.2 hours. When repeated oral doses of TA-7284 100 mg were administered once a day for 14 days to type 2 diabetes patients (study TA-7284-02), the C_{max} was 1136 ng/mL, the AUC_{0-24} was 6635 ng•h/mL, the t_{max} was 1.0-1.5 hours, the $t_{1/2}$ was 11.8 hours, and a steady state therefore appeared to be reached by Day 4 after treatment initiation.

When single oral doses of TA-7284 200 mg were administered to healthy adults in a fasted state or 10 minutes after food (study TA-7284-08), the C_{max} and $AUC_{0-\infty}$ geometric mean fed/fasted ratios, and the 90% confidence intervals thereof, were 0.843 [0.790, 0.900] and 0.977 [0.945, 1.011], respectively. The median t_{max} of TA-7284 was prolonged by around 1.0 hour by fed dosing compared to fasted dosing.

When single oral doses of TA-7284 100 mg were administered to type 2 diabetes patients with moderate renal impairment (study TA-7284-07), the $AUC_{0-\infty}$ was increased by around 26% compared to that of type 2 diabetes patients with normal renal function.

In a dose-finding study in type 2 diabetes patients (study TA-7284-04), the dose-adjusted trough plasma concentration of TA-7284 and the $AUC_{0-2.17h}$ at after 12 weeks of treatment in elderly subjects (age $\geq$ 65 years, 71 to 73 subjects) were compared to those in non-elderly subjects (age < 65 years, 217 to 225 subjects). It was found as a result that the mean trough concentration in the elderly was around 10% to 30% higher than that in the non-elderly.

The results of overseas clinical studies are described below.

When single oral doses of TA-7284 300 mg were administered to healthy adults (9 non-Japanese subjects) (study [redacted]), absolute bioavailability was around 65%. When single oral doses of ^{14}C-labeled TA-7284 192 mg were administered to healthy adults (6 non-Japanese subjects) (study [redacted]), unchanged TA-7284 (45.4-98.7%), the glucuronide conjugation metabolites M5 (1.9-29.6%) and M7 (16.0-28.8%), and the oxidation metabolite M9 (2.42-3.70%) were observed in plasma through 24 hours postdose. In addition, by 168 hours postdose, 32.5% of all administered radioactivity was excreted in urine, and 60.4% in

feces.

When single oral doses of TA-7284 300 mg were administered to patients with hepatic impairment (study [redacted]), it was found that the TA-7284 C_{max} in patients was around 7% higher in patients with mild hepatic impairment (Child-Pugh total score: 5-6) and was around 4% lower in patients with moderate hepatic impairment (Child-Pugh total score: 7-9) than in patients with normal hepatic function. The $AUC_{0-\infty}$ values in these groups, moreover, were around 10% and 11% higher, respectively, than that in persons with normal hepatic function.

When repeated oral doses of rifampicin 600 mg were administered once a day for 9 days to healthy adults (14 subjects) and single doses of TA-7284 300 mg were concomitantly administered to these same subjects (on Day 7 of rifampicin administration) (study [redacted]), the TA-7284 C_{max} and $AUC_{0-\infty}$ geometric mean ratios and 90% confidence intervals thereof, relative to the oral administration of TA-7284 alone, were 0.72 [0.61, 0.84] and 0.49 [0.44, 0.54], respectively.

When repeated oral doses of digoxin 0.25 mg (0.5 mg on the first day) were administered once a day for 7 days to healthy adults (16 subjects) and repeated doses of TA-7284 300 mg were concomitantly administered to these same subjects (study [redacted]), the digoxin C_{max} and AUC_{0-24h} geometric mean ratios and 90% confidence intervals thereof, relative to the oral administration of digoxin alone, were 1.36 [1.21, 1.53] and 1.20 [1.12, 1.28], respectively.

Interactions with the following drugs were investigated, but the concomitant use of these drugs was not found to have any clear effects: teneligliptin (Japanese data), glibenclamide (Glyburide), metformin, cyclosporine, probenecid, oral contraceptives (ethinyl estradiol and levonorgestrel), hydrochlorothiazide, simvastatin, acetaminophen, and warfarin potassium.

Efficacy

At the present time, no results are available from clinical studies in Japanese patients with Stage 3 diabetic nephropathy (overt nephropathy). The results of an investigation based on Japanese clinical studies in type 2 diabetes patients are described below.

A post-hoc analysis of the Japanese phase 3 long-term study was performed to investigate the effects of TA-7284 in patients with Stage 2 diabetic nephropathy (early nephropathy). The percent change in the urine ACR (casual urine) in subjects exhibiting microalbuminuria (urine ACR $\geq$ 50 mg/gCr and < 300 mg/gCr) at baseline revealed significant decreases from baseline from Week 24 on in the TA-7284 100 mg group. The percent change in the urine ACR from baseline at Week 52 was -38.9% in the TA-7284 100 mg group and -43.9% in the TA-7284 200 mg group. Furthermore, the percent change in the urine ACR when missing data from Week 52 were imputed using LOCF was -35.5% in the TA-7284 100 mg group and -43.3% in the TA-7284 200 mg group.

The results of an investigation performed based on overseas clinical studies are described

below.

The CANVAS study is an event study conducted to verify the effects of TA-7284 on the cardiovascular (CV) risks in patients with type 2 diabetes with poor blood glucose control who are at high risk for or have a past history of cerebrovascular/cardiovascular disease using the hazard ratio relative to placebo in a composite endpoint as the outcome measure. The percent change in the urine ACR after 52 weeks of treatment in subjects with macroalbuminuria (baseline urine ACR > 300 mg/gCr) in this CANVAS study was -15.4% in the placebo group, -67.3% in the TA-7284 100 mg group, and -59.7% in the TA-7284 300 mg group. Furthermore, when missing data from Week 52 were imputed using LOCF, the percent change in the urine ACR was -17.6% in the placebo group, -65.2% in the TA-7284 100 mg group, and -58.6% in the TA-7284 300 mg group.

The effects of TA-7284 on renal function parameters were investigated in the CANVAS program, which was conducted in 10,142 type 2 diabetes patients with poor blood glucose control who are at high risk for or have a past history of cerebrovascular/cardiovascular disease, and which consisted of a pooled analysis of the CANVAS study (in which subjects were randomly assigned in a 1:1:1 ratio to 3 groups, (1) a placebo group, (2) a TA-7284 100 mg group, and (3) a TA-7284 300 mg group), and the CANVAS-R study (in which subjects were randomly assigned in a 1:1 ratio to 2 groups, (1) a placebo group, and (2) a TA-7284 100 mg group [with dose adjustment to 300 mg permitted]). Although these are reference data, progression of albuminuria was less in the TA-7284 group than in the placebo group (number of patients per 1000 person-years: 89.4 vs. 128.7; hazard ratio = 0.73; 95% confidence interval: 0.67 to 0.79). In addition, the composite endpoint of a decline of 40% in the eGFR, the initiation of renal replacement therapy, and mortality due to kidney disease was also less frequent in the TA-7284 group than in the placebo group (number of patients per 1000 person-years: 5.5 vs. 9.0; hazard ratio: 0.60; 95% confidence interval: 0.47 to 0.77).

The change in the eGFR when TA-7284 was administered in combination with metformin for 104 weeks was investigated in the CANTASA-SU study (study [redacted]) in type 2 diabetes patients, in which glimepiride was used as the control. Although the TA-7284 group exhibited a transient decrease in the eGFR immediately after administration, a constant eGFR level was subsequently maintained, and the change in the eGFR from baseline was -2.7 ml/min/1.73 m^2 (95% confidence interval, -3.5 to -1.9) in the TA-7284 100 mg group and -3.9 ml/min/1.73 m^2 (95% confidence interval, -4.7 to -3.0) in the TA-7284 300 mg group. In the glimepiride group, on the other hand, the eGFR decreased at a constant rate after the start of the study, and the change in the eGFR from baseline was -5.4 ml/min/1.73 m^2 (95% confidence interval, -6.2 to -4.5). These results suggested that the long-term use of TA-7284 may inhibit the reduction in the eGFR compared to patients receiving glimepiride, in whom the eGFR continues to fall at a constant rate.

Safety

There are at present no results from clinical studies in patients with Stage 3 diabetic nephropathy (overt nephropathy). The results of Japanese clinical pharmacology studies conducted in type 2 diabetes patients with moderate renal impairment and Japanese clinical studies in type 2 diabetes patients are described below.

In a Japanese phase 2 dose-finding study and phase 3 studies that were conducted in type 2 diabetes patients, 953 adverse reactions (including clinical laboratory abnormalities) were reported in 474 of 1629 subjects (29.1%). The most common adverse reactions included asymptomatic hypoglycemia, hypoglycemia, pollakiuria, increased blood ketone bodies, and constipation. The package insert lists the following as "clinically significant adverse reactions": hypoglycemia, dehydration, ketoacidosis, septicemia, and pyelonephritis. In addition, the following are listed as "other adverse reactions" that occur in at least 1% of patients: constipation, thirst, cystitis, pollakiuria, vulvovaginal candidiasis, ketosis, asymptomatic hypoglycemia, and increased blood ketone bodies.

In a clinical pharmacology study (a randomized, open-label, 2-step crossover study) that was conducted in Japan in 12 type 2 diabetes patients with moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73 m^2 and < 50 mL/min/1.73 m^2), the safety of single doses of TA-7284 100 mg and 200 mg was evaluated. The following adverse events were reported in this study: nasopharyngitis in 1 subject, urine protein positive in 1 subject, and pollakiuria in 1 subject in the TA-7284 100 mg group, and nasopharyngitis in 1 subject in the TA-7284 200 mg group. Of these events, it was determined that the pollakiuria that occurred in 1 subject in the TA-7284 100 mg group was causally related to the investigational product. No adverse events resulting in discontinuation or serious adverse events were reported. No other abnormal changes or findings that would pose a problem from a safety standpoint were reported in any other clinical laboratory test, vital sign, 12-lead ECG, or kidney function test parameters.

The results of an investigation conducted based on overseas clinical studies are described below.

In clinical studies that were conducted overseas (studies [redacted] and [redacted]) and in overseas DS2 (moderate renal impairment data set), the safety of TA-7284 in patients with moderate renal impairment was generally similar to that in patients with normal kidney function and that in patients with mild renal impairment. In both the TA-7284 100 mg group and the TA-7284 300 mg group, the incidence per person-year of adverse events associated with total fluid volume decreased was higher in the overseas DS2 than in either overseas DS1 (the placebo-controlled study data set) or DS3 (the extensive active-controlled and placebo-controlled study data set). In addition, although moderate or greater renal impairment (< 60 mL/min/1.73 m^2) was found to be an important risk factor for adverse events associated

with total fluid volume decreased in subjects receiving TA-7284 300 mg, no marked increase in the incidence was found in subjects receiving TA-7284 100 mg.

(4) Study Plan

The CREDENCE study of TA-7284, a global study in patients with type 2 diabetes, Stage 2 or 3 chronic nephropathy, and macroalbuminuria who are receiving standard therapy, is currently being conducted. This study will be a placebo-controlled study to investigate the efficacy and safety of the administration of TA-7284 100 mg once a day for 104 weeks in type 2 diabetes patients with Stage 3 diabetic nephropathy (overt nephropathy) in order to obtain an indication in Japan for Stage 3 diabetic nephropathy (overt nephropathy).

2. Objective

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).

3. Subjects

3.1 Subjects

Type 2 diabetes mellitus patients with Stage 3 diabetic nephropathy (overt nephropathy)

3.2 Inclusion Criteria

Patients will be eligible for enrollment in the study if all of the following criteria apply, and the patients are capable of providing consent. Furthermore, the clinical laboratory test values that have been centrally measured at a central laboratory will be used for the inclusion criteria assessments.

(1) Japanese patients with age $\geq$ 30 years at written informed consent acquisition.
(2) Patients who have received diagnoses of type 2 diabetes based on the diagnosis criteria of the Japan Diabetes Society by the time of written informed consent acquisition.
(3) Sex: Either
(4) Inpatient/outpatient status: Outpatient
(5) Patients who have been receiving dietary and exercise therapy for diabetes without any changes to the regimens since at least 12 weeks before the first day of the treatment period. However, this restriction will not apply if the exercise therapy cannot be continued because of a complication.
(6) Patients who have been receiving angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) drugs at the maximum approved dose since at least 5 weeks before the first day of the screening period (or at the maximum approved dose for hypertension if the drug has not been approved for an indication of diabetic nephropathy).

However, this restriction will not apply if the (sub) investigator determines that for medical reasons it would not be appropriate to use the maximum approved dose. Furthermore, the concomitant use of ACE-I and ARB drugs will not be permitted.

(7) Patients with HbA1c $\geq$ 6.5% and $\leq$ 12.0% on the first day of the run-in period.

(8) Patients with eGFR $\geq$ 30 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2 on the first day of the run-in period.

(9) Patients with a median urine albumin/creatinine ratio (urine ACR) for 3 days' worth of first morning void urine collected within 1 week that includes the visit day on the first day of the screening period that is at least 300 mg/g Cr and not more than 5,000 mg/g Cr. Furthermore, if this criterion is not satisfied, the (sub) investigator may perform retesting during the screening period if he/she determines that it is medically appropriate. No rule is being established regarding the number of times retesting may be performed.

(10) Patients who have not been using any prohibited concomitant medications (see "8.5.1 Prohibited Concomitant Medications") since at least 12 weeks before the first day of the treatment period. Furthermore, if a patient is receiving a prohibited concomitant medication at informed consent acquisition, its use must be discontinued following informed consent acquisition, and a wash-out of at least 12 weeks implemented.

(11) Patients who have not deviated from the restrictions on concomitant use if they are being treated with a restricted concomitant medication (see "8.5.2 Restricted Concomitant Drugs/Therapies").

(12) Patients who have an adherence rate of at least 80% with the treatment of the run-in period investigational product treatment.

Rationale

(1) The same criterion as that used in the CREDENCE study was established because the applicant is planning to compare the results of the present study to the results of the CREDENCE study, the global study that is currently underway.

(2) This criterion was established because this study is being conducted in type 2 diabetes patients with Stage 3 diabetic nephropathy (overt nephropathy).

(3) This criterion was included because there are no reasons for specifying patients of either gender.

(4) Only outpatients were chosen as being eligible to participate in this study because of the different natures of the dietary and exercise therapies that are administered to patients requiring inpatient care, including inpatient education, and those that are administered to patients receiving outpatient care.

(5) This criterion was established because the 2016-2017 Diabetes Treatment Guidelines[14] state that "drug therapy should be administered when the blood glucose control target has not been achieved despite 2 or 3 months of dietary and exercise therapy."

(6), (10)-(12) These criteria were established because it is believed that these factors would affect the evaluation of the pharmacological activity of TA-7284.

(7) [redacted] and the upper limit was established for

the purpose of ensuring subject safety.

(8) The lower limit was established based on the Diabetic Nephropathy Classifications[15] and for the upper limit the same CKD Stage 2 or 3 criterion that was used in the CREDENCE study was established.

(9) The lower limit was established based on the Diabetic Nephropathy Classifications[15] and the upper limit was established for the purpose of ensuring subject safety.

3.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria between the day of informed consent acquisition and the first day of the treatment period will be excluded from the study. Furthermore, clinical laboratory test values that have been assessed at a central laboratory will be used in the exclusion criteria assessments.

(1) Patients with type 1 diabetes mellitus, diabetes mellitus resulting from pancreatic disorder, or secondary forms of diabetes (e.g., Cushing's syndrome, acromegaly).
(2) Patients with genetic glucose/galactose absorption deficiencies or renal glycosuria.
(3) Patients with conditions requiring strict blood glucose monitoring, such as patients with severe ketosis, diabetic coma or precoma, severe infection, or severe trauma, or pre- or post-operative patients; or patients with a history of diabetic ketoacidosis.
(4) Patients undergoing dietary therapy that strictly restrict sugar intake.
(5) Patients diagnosed with non-diabetic kidney disease.
(6) Patients with a history of nephrectomy or renal transplant or patients who have received dialysis treatment.
(7) Patients with resting systolic blood pressure $\geq$ 180 mmHg or resting diastolic blood pressure $\geq$ 100 mmHg measured by the study site on the first day of the run-in period or the first day of the treatment period.
(8) Patients who are human immunodeficiency virus (HIV) antibody positive.
(9) Patients with serious (e.g., requiring hospitalization for treatment or eligible for surgery) liver or kidney disease.
(10) Patients with ALT > 2 x ULN or total bilirubin > 1.5 x ULN on the first day of the run-in period.
(11) Patients with serum potassium > 5.5 mmol/L on the first day of the run-in period.
(12) Patients with current or prior symptoms of Class IV cardiac failure according to the functional classifications of the New York Heart Association (NYHA).
(13) Patients who develop myocardial infarction or cerebrovascular disorders in the 12 weeks before the first day of the treatment period. Patients who have undergone revascularization (e.g., stent placement or bypass surgery). Patients with concurrent unstable angina pectoris.
(14) Patients with ECG findings requiring urgent diagnosis/assessment or intervention in the 12 weeks before the first day of the treatment period (e.g., newly emergent clinically significant arrhythmias or conduction disorders).
(15) Patients with malignant tumors or with a past history of malignant tumors. However, patients with a past history of malignant tumors who have not experienced a recurrence for at least 5 years prior to the date of informed consent acquisition (patients for whom at least 5 years

have passed between the date of the last dose and the date of informed consent acquisition for patients who had been receiving anticancer agents) are exempt from this restriction.

(16) Patients who have participated in clinical trials or other studies or who have received investigational products or other study drugs in the 12 weeks before the first day of the treatment period, or patients who are currently participating in clinical trials or other studies.

(17) Males and females of childbearing potential (patients who have not undergone sterilization procedures such as surgical hysterectomy or bilateral ovariectomy, or patients who are pre-menopausal [with post-menopausal being defined as not having menstruated for at least 1 year]) who do not consent to practice contraception during the term of the study.

(18) Female patients who are pregnant, nursing, or possibly pregnant.

(19) Patients who have been treated with canagliflozin hydrate (either as an investigational product or as the commercial product) in the past.

(20) Patients otherwise found by the (sub) investigator to be ineligible for the study.

(21) Patients with a history of non-traumatic amputation within 12 months prior to the day of informed consent, or with a history of lower limb active skin ulcer, osteomyelitis, gangrene, or severe ischemic within 6 months prior to the day of informed consent.

Rationale

(1)(2)(5)(19) These criteria were established because it is believed that these factors would affect the evaluation of the pharmacological activity of TA-7284.

(3)(4)(6)-(15)(20)(21) These criteria were established out of consideration for patient safety and for ethical considerations.

(16) This criterion was established to ensure that the study is conducted in an ethical manner. This criterion was also established because it is not possible to predict what effects drugs without established assessments will have on the efficacy and safety of TA-7284.

(17)(18) These criteria were established for the sake of protecting subject safety, because the safety of TA-7284 in pregnant women, unborn children, and nursing infants has not been confirmed.

4. Subject Informed Consent

4.1 Authoring of Written Information and Informed Consent Form

The investigator will author the written information and informed consent form (which are collectively referred to as "informed consent form"). The informed consent form will be a single document or set of documents and may be amended as necessary.

The document and its amendments will be submitted to the sponsor and be approved by the institutional review board before the study begins.

4.2 Information to Include in Written Information

The written information must include at least the following:

(1) A statement that the study involves research.

(2) Study objectives

(3) The name, title, and contact information of the (sub)investigator

(4) The study methods (including the aspects of the study that are experimental, subject eligibility criteria, and the probability for random randomization to each treatment, if applicable).

(5) The foreseeable clinical benefits, risks, and inconveniences of the clinical research (including a statement that the research provides no benefits to the subject if applicable).

(6) The availability of other treatments for the patient and foreseeable major benefits and risks of these treatments.

(7) The scheduled duration of study participation by the subjects.

(8) That participation in the study is voluntary and that the subject or legally acceptable representative may refuse to participate or stop participating in the study at any time. Also that the subject would not be treated disadvantageously for refusing to participate or withdrawing consent and would not lose benefits to which the subject would be otherwise entitled for not participating.

(9) A statement that monitors, auditors, the institutional review board, and regulatory authorities are allowed to view medical source documents. Patient privacy would be maintained in such instances. By signing or affixing the name and the seal to the informed consent form, the subject or legally acceptable representative allows this viewing of documents.

(10) That the subject's personal information will remain confidential if the study results are published.

(11) Whom the subject should contact at the study site to obtain further information regarding the study and the rights of subjects, or if the subject experiences a study-related injury.

(12) The compensation and treatment available to the subject in the event of study related injury.

(13) The type of institutional review board responsible for determining whether the study should be conducted, information about the reviews conducted by the institutional review board, and other study-related information about the institutional review board.

(14) The number of subjects scheduled to participate in the study.

(15) That the subject or legally acceptable representative will be promptly informed if information becomes available that may be relevant to the subject's or legally acceptable representative's willingness to continue study participation.

(16) The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.

(17) The expenses, if any, required of the subject.

(18) The monetary and other payments, if any, to the subject (including how amounts to be paid are determined).

(19) Rules with which the subject is expected to comply.

(20) Other necessary information about the study

4.3 Obtaining Informed Consent

(1) The (sub) investigator will give the informed consent form as approved by the institutional review board to each patient who is to become a subject in the study and sufficiently inform the patient. Clinical research coordinators may provide supplementary explanations. When informing the patient, the (sub) investigator will use plain language easily understandable to the patient that is grounded in the written information related to the study and must sufficiently answer all patient questions. After confirming that the patient understands what has been described, the (sub) investigator will obtain voluntary written consent from the patient to participate in the study.

(2) The informing (sub) investigator and the patient will sign or affix the name and the seal to the informed consent form, and date it. If a clinical research coordinator provides a supplementary explanation, that clinical research coordinator will also sign or affix the name and the seal to the document, and date it.

(3) Before the subject participates in the study, the (sub) investigator will give the name and the seal affixed or signed and dated informed consent form to the subject and appropriately retained the original informed consent form according to study site procedures.

(4) The date of informed consent acquisition will be recorded in the case report form.

4.4 Amending the Informed Consent Form

(1) Whenever important new information becomes available that may be relevant to the subject's consent, the (sub) investigator will promptly orally inform the subjects already participating in the study about this information, ascertain their willingness to continue participating in the study, and document this process in the medical records.

(2) The investigator will promptly determine whether the informed consent form should be amended to reflect this information.

(3) If determining that the informed consent form should be amended, the investigator must promptly amend the informed consent form and must again obtain the approval of the institutional review board.

(4) The (sub) investigator will inform the subjects already participating in the study using the amended informed consent form approved by the institutional review board and obtain voluntary written consent from the subjects to continue participating in the study.

(5) The informing (sub) investigator and the patient will sign or affix the name and the seal to the informed consent form, and date it as they did when consent was first obtained. If a clinical research coordinator provides a supplementary explanation, that clinical research coordinator will also sign or affix the name and the seal to the document, and date it.

(6) The (sub) investigator will give the name and the seal affixed or signed and dated informed consent form to the subject and appropriately retained the original informed consent form according to study site procedures.

5. Study Design

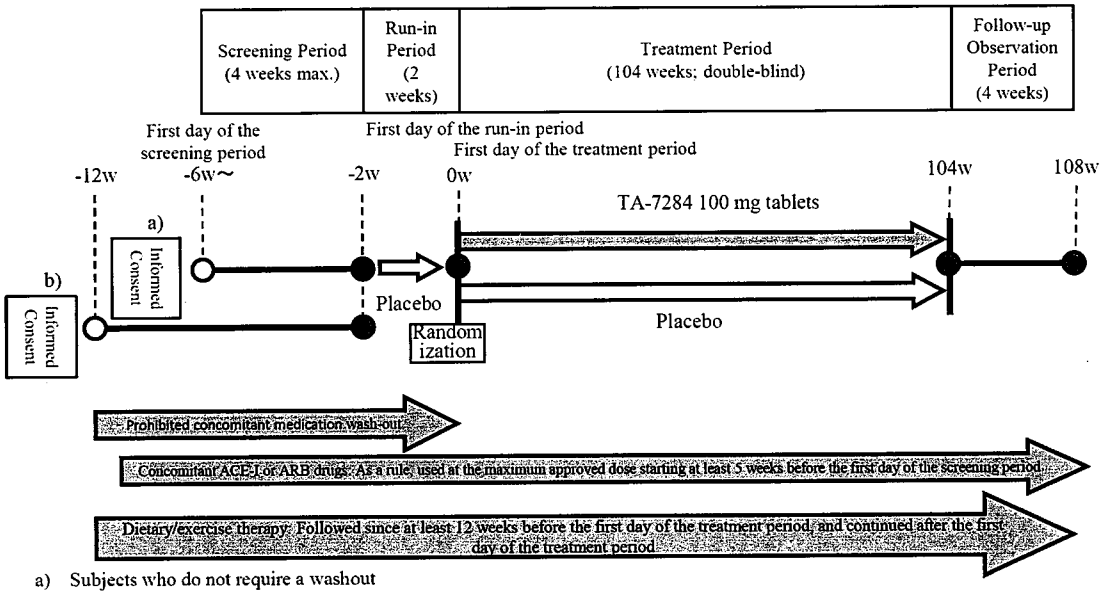
5.1 Phase and Type of the Study

Phase of study : Phase III

Study type : Long-term study

5.2 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

Figure 5.1: Study Design

Table 5.1: 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.

Rationale

Screening period: The screening period was established to confirm the eligibility of the subjects for participation in the study.

Run-in period: The run-in period was established in order to exclude the effects of placebo administration and in order to confirm the eligibility of the subjects for participation in the study.

Treatment period: The treatment period was established to investigate the efficacy and safety of TA-7284 in 2 groups, a TA-7284 100 mg group and a control, placebo group. The subjects will be randomized to ensure similarity of the patient populations in TA-7284 group and placebo group. Double blinding will be used to minimize bias in subject control, treatment, and evaluation.

Follow-up observation period: The follow-up observation period was established as a period for monitoring the patients for adverse events and hypoglycemia occurring after the end of treatment, and for monitoring the patients for changes in their eGFR, urine ACR, and HbA1c levels after the end of treatment.

5.3 Blinding and Randomization Procedures

5.3.1 Blinding Procedures

[redacted]

5.3.2 Randomization and Assignment Procedures

[redacted]

[redacted]

5.4 Endpoints

5.4.1 Efficacy Endpoints

5.4.1.1 Primary Endpoint

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

Rationale

It was reported as a result of a meta-analysis of multiple clinical studies in patients with chronic nephropathy that there is a correlation between the proportion of patients with a 30% decline in the eGFR over 2 to 3 years and the proportion of patients with end-stage kidney disease.[16] It has also been reported that there is a similar relationship in Japanese, as a result of an analysis of a cohort study that was conducted in Japan (CKD-JAC),[17] and the company therefore chose the proportion of subjects with a 30% decline in the eGFR as the primary endpoint because the company believed that this could be used as a surrogate endpoint for end-stage kidney disease.

5.4.1.2 Secondary Endpoints

(1) The proportion of subjects with a 40% decline in the eGFR (the proportion of subjects with a decline of at least 40% in the eGFR at the end of the treatment period 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) The renal composite endpoint of 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

For the events described in (3) through (10), both the proportion of subjects with such events and the time to initial onset will be assessed.

Rationale

(1)-(15) These endpoints were chosen for the purpose of evaluating the efficacy of TA-7284 from various perspectives.

5.4.2 Safety Endpoints

(1) Adverse events
(2) Hypoglycemia
(3) Clinical laboratory test values
(4) Standard 12-lead electrocardiography
(5) Vital signs

Rationale

(1)-(5) These were chosen because they are common safety endpoints.

6. Target Sample Size and Duration of Study

6.1 Target Sample Size

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

[redacted]

Rationale

[redacted]

6.2 Duration of Study

December 2017 through September 2021

7. Investigational Product

7.1 Name of Investigational Product

(1) Study drug

Name:	TA-7284 Tablets 100 mg
Nonproprietary name:	Canagliflozin hydrate (JAN)
Dosage form and strength:	Film-coated tablets containing canagliflozin 100 mg per tablet

(2) Control agent

Name:	TA-7284 Tablets Placebo
Dosage form and strength:	Placebo tablets that are externally indistinguishable from the

7.2 Investigational Product Packaging and Labeling

(1) Packaging

Run-in period investigational product:	One sheet of PTP tablets will contain 14 TA-7284 placebo tablets (14 days' worth), and 4 such sheets (8 weeks' worth) will be packaged in a single carton.
Treatment period investigational product placebo group:	One sheet of PTP tablets will contain 14 TA-7284 placebo tablets (14 days' worth), and 14 such sheets (28 weeks' worth) will be packaged in a single carton.
Treatment period investigational product TA-7284 group:	One sheet of PTP tablets will contain 14 TA-7284 100 mg tablets (14 days' worth), and 14 such sheets (28 weeks' worth) will be packaged in a single carton.

(2) Labeling

1) Run-in period investigational product

For Studies

Study TA-7284-14 < Run-in Period >
8 Weeks' Worth [56 Tablets]

Storage: Store at room temperature; Manufacturing number: XXXXX

Mitsubishi Tanabe Pharma Corporation
[redacted]

• See separately provided procedures on handling, storing, and controlling this investigational product.
• Any unused medication and the empty box will be collected after the study is over.

2) Treatment period investigational product

For Studies Kit Code: XXXXX

Study TA-7284-14 < Treatment period >
26 Weeks' Worth [182 Tablets] + 2 Weeks' Worth [14 Tablets] as Spares

Subject Identification Code:_____

Storage: Store at room temperature; Manufacturing number: XXXXX

Mitsubishi Tanabe Pharma Corporation
[redacted]

• See separately provided procedures on handling, storing, and controlling this investigational product.
• Any unused medication and the empty box will be collected after the study is over.

7.3 Storage Conditions

The investigational product should be stored at room temperature in a specified location.

7.4 Handling, Storage, and Control of Investigational Product

After concluding a contract with the study site, the sponsor will dispense the investigational product to that study site.

The investigational product controller will store and control the investigational product and, after the conclusion of the study, return all unused investigational product to the sponsor according to the "Investigational Product Management Procedures" specified by the sponsor.

The investigational product may not be used for any purpose not allowed in the protocol (e.g., another clinical study, animal studies, basic research).

7.5 Emergency Key Unblinding Procedures

If it becomes necessary to urgently identify the relevant investigational product (when a serious adverse event occurs, for instance) in order to ensure the safety of the subject, the investigator must take appropriate action according to the "Procedures for Unblinding of the Emergency Key." After the emergency key has been opened, the administration of the investigational product for that subject will be discontinued. The investigator will promptly record the reasons for unblinding in a document, and submit the document to the sponsor.

Study sponsor employees who are involved in managing the safety of the clinical study will take action in accordance with the "Emergency Key Unblinding Procedures" whenever a safety concern arises that appears likely to affect the risk/benefit balance of the investigational product and it therefore becomes necessary to urgently identify an investigational product. Furthermore, study sponsor employees who are involved in managing the safety of the clinical study will record the reason for the unblinding and the deliberations that were conducted, and will store said records, in accordance with the study sponsor's procedures.

8. Study Procedures for Subjects

8.1 Subject Screening and Creation of Enrollment Log and Identification Code List

The investigator will list all patients to whom information for informed consent has been given and prepare a subject screening list. The investigator will assign identification codes to the listed subjects who have given a written consent and prepare a list of subject identification code. In the list, key information to be used in the verification with source documents will be described.

The investigator will also prepare a subject registration list for subjects included in the study (including subjects who discontinue permanently) with sex, date of informed consent, subject identification code, etc.

8.2 Enrollment of Subjects

The (sub) investigator will enroll subjects into the study using the web-based subject enrollment system in accordance with the following procedures. Information may be entered into the web-based subject enrollment system by a clinical research coordinator provided approval has been obtained from the (sub) investigator and provided the required information has been recorded on the source documents (e.g., the patient's medical records).

8.2.1 Registration of Consent

(1) The (sub) investigator will select patients that appear to be eligible for study participation and will then obtain their written consent to participation in the study in accordance with "4. Subject Explanation and Consent."

(2) The (sub) investigator will enter the required information about subjects from whom written consent has been obtained into the web-based subject enrollment system and register their consent. Once registration of subject consent has been received, the results of the assessment will be sent to the (sub) investigator and the study sponsor via e-mail via the web-based subject enrollment system. The investigator will confirm the results of the assessment by e-mail or via the web-based subject enrollment system.

8.2.2 Registration of the Start of the Screening Period

(1) The (sub) investigator will confirm the eligibility of the subject on the first day of the screening period, and will enter the required information into the web-based subject enrollment system and register the start of the screening period for the subject. Once the registration of the start of the screening period has been accepted, the (sub) investigator and the study sponsor will receive the results of the assessment via e-mail from the web-based subject enrollment system. The (sub) investigator will confirm the results of the assessment by e-mail or via the web-based subject enrollment system.

(2) If re-screening is performed, the date of re-screening will be entered into the web-based subject enrollment system (at the time of registration of the start of the run-in period).

8.2.3 Registration of the Start of the Run-in Period

(1) The (sub) investigator will confirm the eligibility of the subject on the first day of the run-in period, and will enter the required information into the web-based subject enrollment system and register the start of the run-in period for the subject. Once the registration of the start of the run-in period has been accepted, the (sub) investigator and the study sponsor will receive the results of the assessment via e-mail from the web-based subject enrollment system. The investigator will confirm the results of the assessment by e-mail or via the web-based subject enrollment system.

(2) If the results of the assessment of the registration of the start of the run-in period show that the subject is eligible to participate in the study, the (sub) investigator will prescribe the run-in period investigational product to the subject and instruct the subject to start taking the investigational product on the day of the initial prescription.

8.2.4 Registration of the Start of the Treatment Period

(1) The (sub) investigator will confirm the eligibility of the subject on the first day of the treatment period, and will enter the required information into the web-based subject enrollment system and register the start of the treatment period for the subject. Once the registration of the start of the treatment period has been accepted, the (sub) investigator and the study sponsor will receive the results of the assessment via e-mail from the web-based subject enrollment system. The (sub) investigator will confirm the results of the assessment by e-mail or via the web-based subject enrollment system.

(2) If the results of the assessment of the registration of the start of the treatment period show that the subject is eligible to participate in the study, the (sub) investigator will prescribe the treatment period investigational product to the subject in accordance with the kit code noted in the results of the assessment of the registration of the start of the treatment period and instruct the subject to take the first dose on the day of the initial prescription.

8.2.5 Registration of Discontinuation

(1) If it is determined before the treatment period that a subject is ineligible to participate in the study because, for example, the subject does not meet the conditions at randomization, or if the administration of the investigational product is discontinued after randomization, the (sub) investigator will enter the required information into the web-based subject enrollment system and register the discontinuation of the subject from the study. Once the subject's discontinuation has been accepted, the (sub) investigator and the study sponsor will be notified of the results of the assessment via e-mail from the web-based subject enrollment system. The (sub) investigator will confirm the results either via e-mail or using the web-based subject enrollment system.

(2) If the administration of the investigational product is going to be discontinued after a subject has been randomized, the (sub) investigator will inform the monitor promptly of the fact that the subject is being discontinued, and will record the date of discontinuation on the case report form.

8.3 Dosage and Administration

In the run-in period, one tablet of the run-in period investigational product (TA-7284 placebo tablets) will be administered by mouth with water once a day before or after breakfast.
In the treatment period, one tablet of the treatment period investigational product (TA-7284 100 mg tablets or TA-7284 placebo tablets) will be administered by mouth with water once a day before or after breakfast.

Rationale

The daily dose was set at 100 mg, and administration before or after breakfast was specified because the approved dosage and administration in Japan for Canaglu 100 mg Tablets is "The usual adult dose is 100 mg as canagliflozin administered once a day by mouth either before or after breakfast."

8.4 Duration of Study

(1) Run-in period : 2 weeks
(2) Treatment period : 104 weeks

Rationale

(1) Run-in period

A single-blind run-in period with placebo administration was established in order to confirm the eligibility of the subjects for participation in the study.

(2) Treatment period

It was reported as a result of a meta-analysis of multiple clinical studies in patients with chronic nephropathy that there is a correlation between the proportion of patients with a 30% decline in the eGFR after 2 years and the proportion of patients with end-stage kidney disease.[16] It has also been reported that there is a similar relationship in Japanese, as a result of an analysis of a cohort study that was conducted in Japan (CKD-JAC),[17] and the company therefore chose the proportion of subjects with a 30% decline in the eGFR after 2 years as the primary endpoint because the company believed that this could be used as a surrogate endpoint.

8.5 Concomitant Drugs/Therapies

8.5.1 Prohibited Concomitant Medication

The concomitant use of the drugs listed below will be prohibited from 12 weeks before the first day of the treatment period until Week 4 of the follow-up observation period. However, the drugs listed in (1) through (3) may be used after the completion of the scheduled tests on the last day of the treatment period if the (sub) investigator judges it to be necessary.

(1) Aldosterone antagonists
(2) Direct renin inhibitors
(3) SGLT2 inhibitors other than the investigational product (including commercially available canagliflozin hydrate)
(4) Other investigational products (including placebos)

Rationale

(1)-(4) These drugs were established as prohibited concomitant medications because it is believed that their use would affect the assessment of the pharmacological activity of TA-7284.

8.5.2 Restricted Concomitant Drugs/Therapies

8.5.2.1 ACE-I or ARB

One ACE-I or ARB drug may be used concomitantly at the maximum approved dose (if the drug is

not indicated for diabetic nephropathy, then at the maximum approved dose for hypertension) from at least 5 weeks before the first day of the screening period through Week 4 of the follow-up observation period. However, this restriction will not apply if the (sub) investigator determines that for medical reasons it would not be appropriate to use the maximum approved dose. Furthermore, the concomitant use of ACE-I and ARB drugs will not be permitted. If blood pressure control becomes inadequate, another antihypertensive agent may be added and the regimen thereof modified, without changing the dosing regimen of the ACE-I or ARB drug.

Rationale

These drugs were established as restricted concomitant medications in order to investigate in this study the effects of TA-7284 in addition to ACE-I or ARB drugs, which are used as standard first-line therapies for renal protection and cardiac protection, in type 2 diabetes patients with diabetic nephropathy. It was decided that the dosages should not be changed during the treatment period because of concerns about how this would affect the assessment of the pharmacological activity of TA-7284.

8.5.2.2 Antihypertensive Agents and Lipid Lowering Drugs Other Than ACE-I or ARB Drugs

If an antihypertensive agent other than an ACE-I or ARB drug (excluding diuretics) or a lipid lowering agent (e.g., a statin, ezetimibe, a fibrate, nicotinic acid) is concomitantly used, whenever possible the dosing regimen should remain unchanged from at least 4 weeks before the first day of the screening period until the first day of the treatment period. The additional use of these concomitant drugs, the discontinuation of the concomitant use of these drugs, or the modification of the dosing regimens thereof will be permitted provided that the (sub) investigator has determined that it is appropriate after referring to, for example, guidelines that have been prepared by a Japanese academic society.

Rationale

It was decided that during the term of the study the dosing regimens of these drugs should not be changed to the extent possible, out of consideration for the effects this could have on the assessment of the pharmacological activity of TA-7284.

8.5.2.3 Diabetes Medications

If a diabetes medication is going to be used concomitantly, then whenever possible the dosing regimen should remain unchanged from at least 4 weeks before the first day of the screening period until the first day of the treatment period. However, the additional use of these drugs, the

discontinuation of the use of these drugs, or the modification of the dosing regimens thereof will be permitted provided that the (sub) investigator has determined that it is appropriate after referring to, for example, guidelines that have been prepared by a Japanese academic society.

Rationale

It was decided that during the term of the study the dosing regimens of these drugs should not be changed to the extent possible, out of consideration for the effects this could have on the assessment of the pharmacological activity of TA-7284.

8.5.2.4 Drugs with the Potential to Affect the Serum Creatinine Level

Drugs with the potential to affect the serum creatinine level (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], trimethoprim, cimetidine, probenecid, aminoglycoside antibiotics, amphotericin, ketoconazole, clofibrate) should whenever possible be administered without changing the dosing regimens thereof for the 2 weeks before all of the clinical laboratory tests that are conducted from the first day of the run-in period until Week 4 of the follow-up observation period.

Rationale

It was decided that a fixed dosing regimen should be used to the extent possible for the 2 weeks before the conduction of clinical laboratory tests out of consideration for the possible effects on the assessment of the pharmacological activity of TA-7284.

8.5.2.5 Diuretics

The use of diuretics in combination with TA-7284 is not recommended. On the day of informed consent acquisition, consideration should be given to switching subjects who are receiving diuretics to alternative medications.

Rationale

This stipulation was included out of consideration for subject safety and for ethical reasons, because there is the risk of the coadministration of a diuretic resulting in an excessive diuretic effect emerging, and caution should therefore be exercised regarding the possibility of patients becoming dehydrated.

8.5.2.6 Concomitant Therapies

Dietary and exercise therapies should be continued without any changes to the regimens thereof from at least 12 weeks before the first day of the treatment period until Week 4 of the follow-up

observation period. However, this restriction will not apply if the (sub) investigator determines that it would be difficult to continue the dietary or exercise therapy because of a complication or adverse event.

Rationale

It was decided that dietary and exercise therapy should be continued without any changes to the regimens because of the potential effects on the evaluation of the pharmacological activity of TA-7284.

8.5.3 Records of Concomitant Drugs and Therapies

The (sub) investigator or a clinical research coordinator will enter in the case report form the following information about any concomitantly received drugs or therapies from the first day of the treatment period until Week 4 of the follow-up observation period. Saline and similar products used to dissolve injectable products need not be entered.

(1) Concomitant drugs: Drug name, daily dose, route of administration, duration of use, reason for use
(2) Concomitant therapies: Name of therapy, duration of use, reason for use

8.6 Subject Management

The (sub) investigator, a clinical research coordinator, or the investigational product controller will manage the subjects paying particular attention to the following matter. Furthermore, the (sub) investigator and study support staff will solicit information from the subject about the subject's condition and adherence to the following stipulations.

8.6.1 Treatment Adherence

The (sub) investigator or investigational product controller will instruct the subject to pay attention to the following points, in accordance with the written descriptions contained in the document that explains the proper investigational product handling procedures.

(1) Administration of the investigational product will begin on the first day of the run-in period. Subjects will come in to the study sites on the scheduled visit days without taking the investigational product, and will take the investigational product after the scheduled tests have been performed.
(2) Subjects will take the investigational product every day either before or after breakfast. If a subject forgets to take the investigational product, then the subject should take the investigational product as soon as possible. Subjects should not day multiple days' worth of investigational product in a single day (see "8.3 Dosage and Administration").

(3) If any investigational product remains because, for example, the subject forgot to take it, the subject should bring this remaining investigational product in to the study site when he or she comes in for the next study visit.
(4) If a subject is unclear about anything regarding the taking of the investigational product, the subject should ask the (sub) investigator or the investigational product controller.

8.6.2 Control of Study Visits

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.

8.6.3 Lifestyle Guidance

The (sub) investigator or a clinical research coordinator will provide lifestyle guidance to the subjects, focusing on the following points:

(1) Any dietary or exercise therapies should be continued without any changes to the treatment regimens from at least 12 weeks before the first day of the treatment period until Week 4 of the follow-up observation period.
(2) Subjects are to undergo observations and tests on the specified days. If a subject is unable to visit on a specified day, the subject should be sure to contact the (sub) investigator or clinical research coordinator for instructions.
(3) Subjects should not overindulge in either food or drink during the study.
(4) Always carry subjects' study participation card and present it when receiving care at another medical institution or department. Be sure to tell the (sub) investigator or clinical research coordinator if subjects are using a drug prescribed by a doctor not involved in the study or purchased at a pharmacy. Be sure to tell the (sub) investigator or clinical research coordinator before starting to take a new drug during the study.
(5) Avoid changing lifestyle of subjects (e.g., routine exercise and eating habits) to the maximum extent possible.
(6) Promptly notify the (sub) investigator for instructions if subjects notice any physical change.
(7) The (sub) investigator or a clinical research coordinator should instruct subjects to use one of the following reliable methods of contraception during the study. Calendar-based contraception, ovulation-based contraceptive method, ovulation-based temperature monitoring contraception, post ovulation-based contraception, extravaginal ejaculation, and similar methods are not appropriate as contraception. Furthermore, post-menopausal females (females who have not menstruated for at least 1 year) and females who have undergone sterilization, such as surgical hysterectomy or bilateral ovariectomy, are excluded from this requirement.
    1) Abstinence
    2) The use of 2 effective contraceptive methods. The use of a barrier method (male latex condom/cap/diaphragm with spermicide) with a more effective contraceptive method (e.g., oral contraceptives, intrauterine ring, tubal ligation, vasectomy) is recommended.

8.6.4 Hypoglycemia Instructions

On the first day of the run-in period, the (sub) investigator will supply the subject with a "Hypoglycemia Symptom Survey Form" and the "Glutest Neo Alpha," a simple blood glucose measuring device, and will instruct the subject in how to fill out the survey form and in how to use the measuring device. The subject will be told that if the subject experiences symptoms of hypoglycemia between the first day of the run-in period and Day 14 of the follow-up observation period, the subject should enter the required information in the "Hypoglycemia Symptom Survey Form" and if possible measure his or her own blood glucose using the "Glutest Neo Alpha" device, and should be seen by a doctor promptly if the symptoms are not alleviated by taking sucrose (sugar) or the like.

8.6.5 Urine Collection Instructions

The (sub) investigator or a clinical research coordinator will provide the subject with the materials the subject needs to perform urine collection, and will instruct the subject in how to perform urine collection, paying attention to the following points.

(1) Three days' worth of first morning void urine will be collected within a 1-week period that includes the scheduled study visit.
(2) The first morning void urine should be collected by the subject at home.
(3) The subject should not take the investigational product before collecting the first morning void urine.
(4) The first morning void urine that has been collected should be transferred into a spitz tube and stored under refrigeration until the day of the visit, and brought to the study site at the time of the visit under refrigeration (e.g., by placing the spitz tube into a cooling bag).

8.6.6 Foot Care

The (sub)investigators will instruct the subjects on the importance of foot care, and closely monitor the condition of subjects' feet during the study. If any new lesions, such as skin ulcers, infections, osteomyelitis, or gangrene, will be found, they will be treated appropriately and, depending on the subject's condition, an investigation into whether or not the subject should be discontinued from the study will be performed.

9. Tests and Observations

9.1 Test and Observation Schedule

Time point a) / Parameter	Date of informed consent	Screening Period b) (4 weeks max.)	Run-in Period (2 weeks)	Treatment Period (104 weeks)																														Follow-up observation period
		First day of the screening period	First day of the run-in period	First day of the treatment period (Week 2 of the 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 n)																		●	●		●	●		●	●		●	●	●			
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 to +36 d m)	+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)			←→																														

●: Required ○: Implemented when possible

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 discontinue 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 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 was 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.
m) If the (sub)investigator determines that it would not be possible for a subject to come in for a study visit because of the impact of the COVID-19 pandemic, then the investigator will conduct a survey by telephone of, for example, the investigational product dosing compliance conditions and adverse events, and then may prescribe more investigational product based on the results thereof, and may postpone the deadline for performing the visit beyond Week 104 of the treatment period.
n) If the (sub)investigator determines that it would not be possible for a subject to come in for a study visit because of the impact of the COVID-19 pandemic then, even if the tests/observations can not be performed on the scheduled visit date, the investigator

will conduct a survey by telephone of, for example, the investigational product dosing compliance conditions and adverse events, and then may prescribe more investigational product based on the results thereof. In addition, if this is done, and if the deadline for performing the visit is extended beyond Week 104 of the treatment period, then the investigator will conduct a survey by telephone of, for example, the investigational product dosing compliance conditions and adverse events, every 14 days, as a rule.

Furthermore, if the specified observations/tests cannot be performed in accordance with the schedule, then these observations/tests will be performed within the allowable time windows shown in Table 9.1 below.

Table 9.1: 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	21 days to 35 days
	Week 8 of the treatment period	56 days	49 days to 63 days
	Week 12 of the treatment period	84 days	77 days to 91 days
	Week 16 of the treatment period	112 days	105 days to 119 days
	Week 20 of the treatment period	140 days	133 days to 147 days
	Week 24 of the treatment period	168 days	161 days to 175 days
	Week 28 of the treatment period	196 days	189 days to 203 days
	Week 32 of the treatment period	224 days	217 days to 231 days
	Week 36 of the treatment period	252 days	245 days to 259 days
	Week 40 of the treatment period	280 days	273 days to 287 days
	Week 44 of the treatment period	308 days	301 days to 315 days
	Week 48 of the treatment period	336 days	329 days to 343 days
	Week 52 of the treatment period	364 days	357 days to 371 days
	Week 56 of the treatment period	392 days	385 days to 399 days
	Week 60 of the treatment period	420 days	413 days to 427 days
	Week 64 of the treatment period	448 days	441 days to 455 days
	Week 68 of the treatment period	476 days	469 days to 483 days
	Week 72 of the treatment period	504 days	497 days to 511 days
	Week 76 of the treatment period	532 days	525 days to 539 days
	Week 80 of the treatment period	560 days	553 days to 567 days
	Week 84 of the treatment period	588 days	581 days to 595 days
	Week 88 of the treatment period	616 days	609 days to 623 days
	Week 92 of the treatment period	644 days	637 days to 651 days
	Week 96 of the treatment period	672 days	665 days to 679 days
	Week 100 of the treatment period	700 days	693 days to 707 days
	Week 104 of the treatment period	728 days	721 days to 735 days to 784 days*3
	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.

*3: If postpone because of the effects of the COVID-19 pandemic.

9.2 Tests/Observations and Timing

9.2.1 Subject Baseline Characteristics

The (sub) investigator will determine the following baseline characteristics of subjects by the first day of the treatment period and enter the information in the case report form:

(1) Sex
(2) Date of birth (Western calendar format)
(3) Height
(4) Weight
(5) Race
(6) Diagnosis date of diabetes mellitus
(7) Diagnosis date of primary disease
(8) Concurrent illnesses (diseases or disorders present on the first day of the treatment period)
(9) Information about the subject's past history of bone fractures
(10) Smoking status

9.2.2 Treatment Adherence

The (sub) investigator will at each subject visit investigate the subject's treatment adherence based on the number of tablets of the investigational product that remain and through questioning of the subject, and will record in the case report form the day the investigational product was first taken, the amount prescribed, the amount returned, the remaining drug, and the day on which the investigational product was last taken. Furthermore, if the subject has not taken the investigational product for 7 or more days in a row, the (sub) investigator will enter the date that this period began and the reason therefor in the case report form.

9.2.3 Efficacy Evaluation

9.2.3.1 eGFR

Blood samples will be collected at the following visits, and the eGFR measured at a central laboratory: the first day of the run-in period; the first day of the treatment period; Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation); and Week 4 of the follow-up observation period.

The blood samples will be collected at the study sites, and the measurements and calculations will be performed at the central laboratory. The collection of the specimens will be performed by the central laboratory. The test result printouts that are provided by the central laboratory will be retained by the study sites.

The eGFR will be calculated using the following formula, which is the formula for estimating the GFR in Japanese:

eGFR (mL/min/1.73m^2) = 194 x Serum creatinine$^{-1.094}$ x Age$^{*-0.287}$ (females: x 0.739)

*Age: Subject's biological age in years

9.2.3.2 Initial Onset of End-Stage Renal Disease (ESRD)

Subjects will be monitored for the initial onset of end-stage renal disease from the first day of the treatment period through Week 4 of the follow-up observation period.

ESRD is defined as the start of maintenance dialysis for at least 1 month, renal transplantation, or a sustained eGFR of < 15 mL/min/1.73 m^2 (this should be confirmed by remeasurement by the central laboratory after at least 30 days but preferably within 60 days; the results of measurements taken within 30 days of the assessment time point at which this criterion was first met may not be used for this assessment). The (sub) investigator will record the results in the case report form.

9.2.3.3 Doubling of Serum Creatinine

Blood samples will be collected at the following visits, and serum creatinine measurements will be performed at a central laboratory: the first day of the run-in period; the first day of the treatment period; Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation); and Week 4 of the follow-up observation period.

A doubling of serum creatinine is defined as a sustained doubling of the serum creatinine value compared to the average of the values on the first day of the run-in period and the first day of the treatment period that lasts from the visit on which the doubling is first noted until confirmation based on a test performed by the central laboratory at least 30 days later, but preferably within 60 days. Furthermore, the results of any measurements performed less than 30 days after the initial measurement that met the criteria will not be used for the assessment. The (sub) investigator will record the result in the case report form.

9.2.3.4 Renal Death

Subjects will be monitored for renal death from the first day of the treatment period until Week 4 of the follow-up observation period.

Renal death is defined as the death of a subject who develops ESRD and dies without beginning renal replacement therapy with no other identified cause of death. The (sub) investigator will record the details in the case report form.

9.2.3.5 Cardiovascular (CV) Death

Subjects will be monitored for CV death from the first day of the treatment period until Week 4 of

the follow-up observation period.

CV death is defined as death due to myocardial infarction, stroke, or cardiac failure, death during the treatment of a cardiovascular disorder or due to a complication arising from said treatment, suspected cardiovascular sudden death, death of unknown etiology, or death due to a confirmed CV event other than those described above (artery aneurysm, peripheral vascular disease). The (sub) investigator will record the details in the case report form.

9.2.3.6 Other Events

Subjects will be monitored for the emergence of other events from the first day of the treatment period until Week 4 of the follow-up observation period.

The (sub) investigator will evaluate all individually diagnosed cases of hospitalized congestive heart failure, hospitalized unstable angina, all-cause death, non-fatal myocardial infarction, and non-fatal stroke, and will record the details in the case report form.

9.2.3.7 Urine ACR (First Morning Void Urine)

Three days' worth of first morning void urine samples for urine ACR measurements will be collected within a 1-week period that includes the day of the scheduled visit at the following time points: the screening period, the first day of the treatment period, Weeks 4, 8, 12, 24, 36, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation, whenever possible), and at Week 4 of the follow-up observation period.

Each subject will perform urine collection at home, and will give the collected urine to the study site for collection and measurement by the central laboratory. The test result printouts provided by the central laboratory will be retained by the study site.

9.2.3.8 HbA1c

Blood samples will be collected at the following visits for the measurement of HbA1c at the central laboratory: the first day of the run-in period; the first day of the treatment period; Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation, whenever possible); and Week 4 of the follow-up observation period.

The blood samples will be collected by the individual study sites, and the measurements will be performed by the central laboratory, which will collect the samples from the study sites. The test result printouts provided by the central laboratory will be retained by the study sites.

9.2.3.9 Fasting Blood Glucose

Blood samples will be collected at the following visits for the measurement of fasting blood glucose at the central laboratory: the first day of the run-in period; the first day of the treatment period; and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation, whenever possible).

The blood samples will be collected by the individual study sites, and the measurements will be performed by the central laboratory, which will collect the samples from the study sites. The test result printouts provided by the central laboratory will be retained by the study sites.

9.2.3.10 Blood Pressure (Systolic Blood Pressure, Diastolic Blood Pressure)

Blood pressure (systolic blood pressure, diastolic blood pressure) will be measured in accordance with "9.2.4.4 Vital Signs."

9.2.3.11 Lipids (HDL-C, Fasting Neutral Lipids)

Blood samples will be collected at the following visits for the measurement of lipids at the central laboratory: the first day of the run-in period; the first day of the treatment period; and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation, whenever possible).

The blood samples will be collected by the individual study sites, and the measurements will be performed by the central laboratory, which will collect the samples from the study sites. The test result printouts provided by the central laboratory will be retained by the study sites.

9.2.3.12 Body Weight

Body weight measurements will be performed in accordance with "9.2.4.5 Height and Weight."

9.2.3.13 Fasting Urine Glucose/Creatinine Ratio

Urine samples will be collected at the following visits for measurement at the central laboratory: the first day of the treatment period; and Weeks 4, 8, 12, 24, 36, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation, whenever possible). The urine samples will be collected by the central laboratory, and the test results printouts provided by the central laboratory will be retained by the study sites.

[redacted]

9.2.4 Safety Assessment Parameters

9.2.4.1 Clinical Laboratory Tests

Blood samples will be collected at the following visits for the measurement of the following parameters at the central laboratory: the first day of the run-in period; the first day of the treatment period; and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation).

(1) Hematology test parameters

White blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)

(2) Blood biochemistry test parameters (except for the parameters for the efficacy assessments)

AST (GOT), ALT (GPT), ALP, LDH, gamma-GTP, total cholesterol, LDL-C, CPK, Na, K, Cl, Ca, inorganic phosphorus, Mg, HCO_3, ketone body differential (total ketone bodies, acetoacetic acid, 3-hydroxybutyric acid), total protein, urea nitrogen, serum creatinine, uric acid, total bilirubin, direct bilirubin, albumin

Urine samples will be collected at the following time points for the measurement of the following parameters: the first day of the treatment period, and Weeks 4, 8, 12, 24, 36, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation).

(3) Urinalysis (quantitative) (except for the parameters for the efficacy assessments)

Urine creatinine, urine Na,* urine K,* urine Cl,* urine Ca,* urine inorganic phosphorus,* urine Mg*

*: Creatinine adjusted value

Urine samples will be collected at the following study visits for the measurement of the following parameters: the first day of the treatment period, and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation).

(4) Urinalysis (qualitative)

Specific gravity, pH, urine protein, urine occult blood, urine ketones, urine bilirubin, urine urobilinogen, nitrite, white blood cell esterase

The blood and urine samples will be collected by the individual study sites, and will then be collected from the study sites by the central laboratory for measurement. The test result printouts provided by the central laboratory will be retained by the study sites.

The clinical laboratory test results will be considered abnormal values if they deviate from the central laboratory's reference values.

If a urinary tract infection or genital infection is suspected, the necessary tests (e.g., bacteria tests) will be performed in order to arrive at a diagnosis.

9.2.4.2 Renal Function Biomarkers

Blood and urine samples will be collected at the study visits on the first day of the treatment period and at the visits at Weeks 52 and 104 of the treatment period (and at treatment period discontinuation whenever possible) for the measurement of the following parameters.

(1) Blood biochemistry parameters:
Serum cysteine C,[*1] erythropoietin,[*2] c-peptide, high sensitivity CRP

*1: The following formulas, which are formulas that use the serum cysteine C levels in Japanese, will be used to calculate the eGFRcys at the central laboratory.
Males: eGFRcys (mL/min/1.73 m^2) = (104 x serum cysteine $C^{-1.019}$ x 0.996^{Age}) – 8
Females: eGFRcys (mL/min/1.73 m^2) = (104 x serum cysteine $C^{-1.019}$ x 0.996^{Age} x 0.929) - 8
Age: The subject's biological age in years

*2: Blood samples will also be collected for measurement at the visit at Week 4 of the treatment period.

(2) Urinalysis (quantitative):
Urine transferrin, NAG, L-FABP

(3) Other:
TNFR1, TNFR2

9.2.4.3 Pregnancy Tests (Women of Childbearing Potential Only)

A urine human chorionic gonadotropin (hCG) pregnancy test will be performed at the study visits on the first day of the run-in period and Weeks 24, 52, 76, and 104 of the treatment period (or at treatment period discontinuation), and the results will be entered in the case report form.

9.2.4.4 Vital Signs

Blood pressure and pulse rate will be measured, and the results entered into the case report form, at the study visits on the first day of the run-in period, the first day of the treatment period, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 64, 76, 88, and 104 of the treatment period (or at treatment period discontinuation). The measurements will be taken before blood sample collection, with the patient sitting down and having rested for at least 5 minutes. On the first day of the run-in period, blood pressure will be measured at both arms, and if the difference between the arms exceeds

10 mmHg for either the diastolic blood pressure or the systolic blood pressure, then the value from the arm with the higher reading will be used. If the difference between the arms is 10 mmHg or less, then the value from either arm may be used. As a rule, subsequent measurements will be taken using the same arm. In addition, whenever possible the same person should take the measurements each time to minimize inter-rater variability. Three blood pressure measurements will be taken at each visit, at intervals of at least 1 minute.

9.2.4.5 Height and Weight

Height will be measured on the first day of the treatment period at the study site, and the result entered in the case report form.

Weight will be measured at the study site on the first day of the run-in period, the first day of the treatment period, and at Weeks 12, 24, 36, 52, 64, 76, 88, and 104 of the treatment period, and the results entered into the case report form.

9.2.4.6 Resting Standard 12-Lead ECG

A resting standard 12-lead ECG will be measured at the subject visits on the first day of the run-in period, the first day of the treatment period, and Weeks 24, 52, 76, and 104 of the treatment period (or at treatment period discontinuation). The results of, for example, the arrhythmia and waveform diagnoses from the ECG results will be comprehensively assessed and classified according to the following 3 levels, and the result entered into the case report form.

(1) Normal
(2) Abnormal, NCS (Clinically insignificant abnormality)
(3) Abnormal, CS (Clinically significant abnormality)

9.2.4.7 Hypoglycemia

The (sub) investigator will monitor the subject for hypoglycemia from the first day of the run-in period until Day 14 of the follow-up observation period based on Appendix 4, "Hypoglycemia Symptom Survey Form" and the blood glucose measurement results.

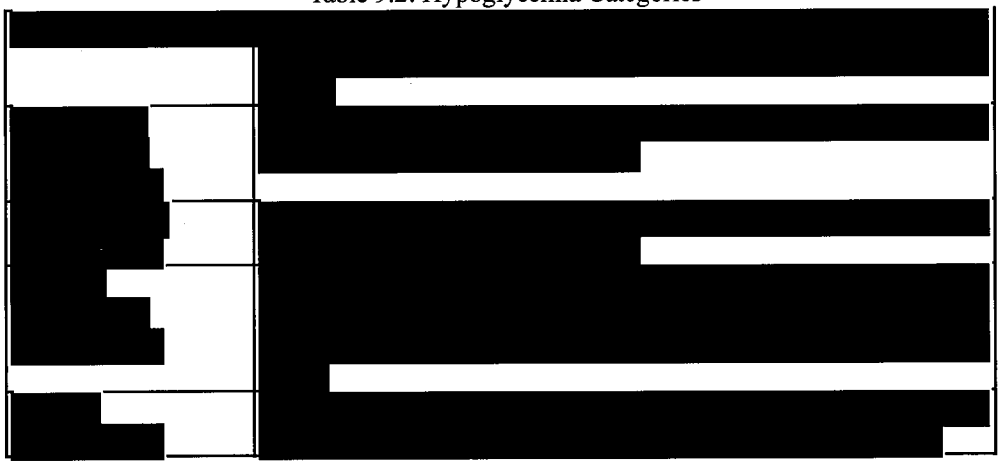
At each subject visit, the (sub) investigator will have the subject bring in the "Hypoglycemia Symptom Survey Form," and will check its contents. If the (sub) investigator determines, on the basis of the "Hypoglycemia Symptom Survey Form" and the blood glucose measurement results, that the subject has developed hypoglycemia, the (sub) investigator will note this in the hypoglycemia space on the case report form. If the (sub) investigator determines that a symptom that is not judged to constitute hypoglycemia is an adverse event, the (sub) investigator will enter this information in the

adverse event section of the case report form.

The (sub) investigator will obtain the following information about events that have been judged to constitute hypoglycemia, and will record this information in the case report form in accordance with "9.2.4.8 Adverse Events." Furthermore, if the (sub) investigator determines that an event constitutes asymptomatic hypoglycemia, then the (sub) investigator will promptly check the subject's condition.

(1) Hypoglycemia symptoms: Details of observed symptoms of hypoglycaemia.
(2) Hypoglycemia categories: Hypoglycemia will be classified based on the categories shown in Table 9.2 below.

Table 9.2: Hypoglycemia Categories



(3) Severity
(4) Date and time of onset: The date and time when the hypoglycemia was noticed.
(5) Outcome, date of outcome, time of recovery
(6) Blood glucose level, date and time of blood glucose level measurement: The blood glucose level at the onset of hypoglycemia, and the date and time of the measurement.
(7) The cause of the hypoglycemia: The cause of the hypoglycemia will be determined based on the following criteria.
   a) None
   b) No diet or delay of diet
   c) Performed intense exercise
   d) Other
(8) Date and time of food eaten before the onset of hypoglycemia, date and time medicine was taken
(9) Action taken with respect to TA-7284
(10) Non-investigational product action(s) taken
(11) Causal relationship to TA-7284
(12) Seriousness

9.2.4.8 Adverse Events

An adverse event refers to any clinically untoward or unintended sign (including clinically

significant test abnormalities), symptoms, or disease observed after the first day of the treatment period, regardless of the causal relationship between the event and the investigational product. In addition, if a worsening of the event (e.g., a worsening of the severity of the event) occurs, it will be handled as a new adverse event. With the elimination half-life of TA-7284 in mind, the period for the collection of information about adverse events will be from the start of the treatment period investigational product administration through Day 14 of the follow-up observation period, during which time the (sub) investigator will determine what adverse events have occurred by, for example, questioning the subject.

Because placebos are the only investigational product that is going to be administered in the run-in period of this study, information about adverse events occurring during the run-in period will not be collected. However, an adverse event that occurs between the date of informed consent acquisition and the start of the treatment period investigational product administration that meets the criteria for classification as a "serious adverse event" will be reported to the study sponsor in accordance with "11.1 Actions Taken When a Serious Adverse Event Occurs."

(1) Symptoms or diseases
The (sub) investigator will check for adverse events through interview or examination.

(2) Signs
The (sub) investigator will handle all clinically significant abnormalities* as adverse events.

* "Clinically significant abnormalities" are assessed according to the following criteria:

- The abnormality is related to a clinical sign or clinical symptom
  The test abnormality need not be classified as an adverse event if the symptom or sign has already been reported as an adverse event.
- Medical or surgical treatment is administered in response to the test abnormality
- The administration of the investigational product is changed (e.g., dosage changed, drug withdrawn, discontinued) in response to the test abnormality
- The (sub) investigator otherwise determines that the abnormality is clinically significant

(3) Adverse event assessment and criteria

1) Day of onset
   The day on which the symptom occurred or day of the test in which the laboratory abnormality was identified

2) Severity
   The severity of adverse events will be classified according to the following criteria:
   1. Mild: The event does not interfere with the daily activities of the subject.

2. Moderate: The event causes some interference with the daily activities of the subject.

3. Severe: The event makes the daily activities of the subject impossible.

3) Seriousness

The seriousness of adverse events will be classified as follows:

1. Not serious
2. Serious: (a) – (f)
   - (a) Results in death
   - (b) Is life-threatening
   - (c) Requires inpatient hospitalisation or results in prolongation of existing hospitalisation
   - (d) Results in persistent or significant disability/incapacity
   - (e) Is a medically important event or reaction
   - (f) Is a congenital anomaly / birth defect

4) Causal relationships to investigational product

The (sub) investigator will assess whether there is a reasonable possibility that the investigational product caused the adverse event. This assessment will be made in consideration of the underlying disease, concomitant medical diseases, and other aspects of the natural course of the primary disease, concomitant therapies, other risk factors and factors other than the investigational product, and the temporal relationship between investigational product dosing and adverse event onset (e.g., recurrence following rechallenge, resolution following discontinuation). Adverse events whose causal relationship with the investigational product is assessed as a reasonable possibility will be considered adverse drug reactions.

1. Reasonable possibility
2. No reasonable possibility

5) Outcome

The outcome of adverse events will be classified on the following 6-grade scale:

1. Resolved
2. Resolving
3. Not resolved
4. Resolved with sequelae
5. Fatal
6. Unknown

6) Day of outcome

The day of the outcome will be classified according to the criteria shown in Table 9.3 below.

Table 9.3: Outcome Day Criteria

Resolved	The day of resolution. However, if the day of resolution cannot be identified, then this will be the day on which the outcome was confirmed or determined.
Resolving	The day on which it was confirmed or determined that the subject was resolving.
Not resolved	The day on which it was confirmed or determined that the subject had not resolved.
Resolved with sequelae	The day on which it was confirmed or determined that sequelae were present.
Fatal	The day of death. However, if the day of death cannot be identified, then this will be the day on which the death was confirmed or determined.
Unknown	The day of death if the subject died due to a cause other than the adverse event in question and the outcome was unknown. Otherwise, the day on which this was confirmed or determined.

7) Follow-up Investigation

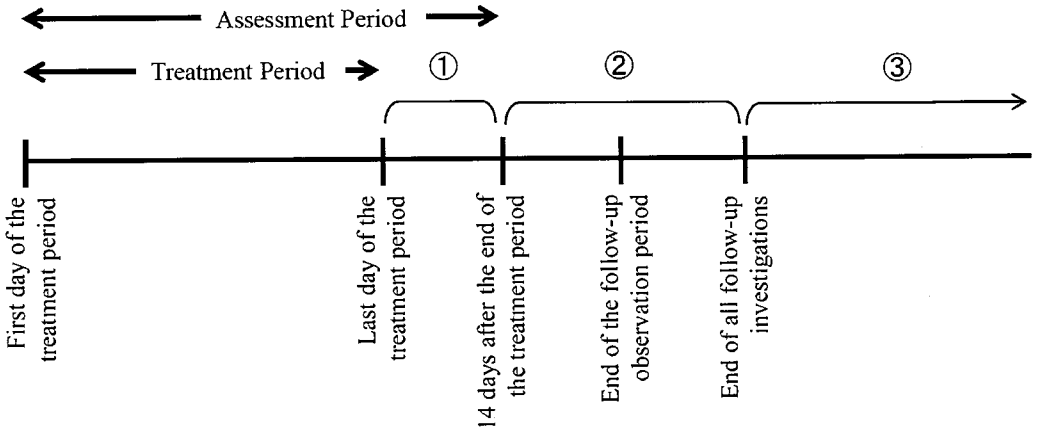


Figure 9.1: Follow-up Investigation Period

- During the 14-day period after the end of treatment denoted by ① in the figure, subjects will be monitored for the emergence of adverse events.
- The period that starts 14 days after the end of the treatment period and that is denoted by ② in the figure will be 28 days long; during this period, follow-up investigations will be performed for the adverse events that occurred during the assessment period (the treatment period + ①).
- The courses of the adverse events that were learned through the follow-up investigations that were performed during period ② will be entered in the case report form.

- If the outcome of an adverse event is "resolving" or "not resolved," the day of the outcome will be recorded in the case report form, and this will be considered the final observation day of period ②.
- The subsequent (period ③) courses of adverse reactions with an outcome of "resolving" or "did not recover" at the end of period ② will be investigated.
- If there is a valid reason for stopping the investigation after the end of the assessment period (after the end of period ①), then this reason will be recorded, and all follow-up investigations will be concluded.

(4) Information to record in case report forms

When an adverse event occurs, the (sub) investigator will enter the following information in the case report form: name of the event*, date of onset, severity, seriousness, causal relationship with the investigational product, description of any actions taken (e.g., drug name, therapy), outcome, and day of outcome.

* The names of adverse events will be selected according to the following criteria:

- The name of the diagnosis should generally be used.
- The name of the symptom or symptoms should be used when the diagnosis is unclear.
- When multiple symptoms are present and can be expressed as a singular diagnosis, that diagnosis should be used.
- When a surgical procedure is not classified as an adverse event and the disease or symptoms necessitating the surgical procedure are known, these should be classified as adverse events.

10. Evaluation Methods and Criteria

10.1 Efficacy Endpoints

10.1.1 Primary Endpoint

The proportion of subjects with a 30% decline in the eGFR (the proportion of subjects with a decline of at least 30% in the eGFR at the end of the treatment period compared to the average of the values on the first days of the run-in and treatment periods).

10.1.2 Secondary Endpoints

(1) The proportion of subjects with a 40% decline in the eGFR (the proportion of subjects with a decline of at least 40% in the eGFR at the end of the treatment period 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) The renal composite endpoint of 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

For the events described in (3) through (10), both the proportion of subjects with such events and the time to initial onset will be assessed.

10.2 Safety

Adverse events and adverse drug reactions (See Section "9.2.4.8, Adverse Events")

11. Ensuring Subject Safety

11.1 Actions to Take for Serious Adverse Events

The (sub) investigator will immediately administer appropriate treatment to any subject suffering a serious adverse event between the informed consent acquisition and Week 4 of the follow-up observation period, regardless of the causal relationship with the investigational product.

In the event of a serious adverse event, the (sub) investigator will immediately notify a monitor (in writing, as a rule) and submit detailed information in writing within 7 days of notifying the monitor. The investigator will inform the director of the study site about any such serious adverse event.

Definition of serious adverse events

(1) Results in death
(2) Is life-threatening
(3) Requires inpatient hospitalisation or results in prolongation of existing hospitalisation
(4) Results in persistent or significant disability/incapacity
(5) Is a medically important event or reaction
(6) Is a congenital anomaly / birth defect

11.2 Significant Adverse Events

There are no clinically significant adverse events that need to be defined for the purpose of investigating the safety profile.

11.3 Noteworthy Issues

The (sub) investigator will conduct the study paying close attention to safety, in accordance with the [redacted] from Appendix 2 issued by the Committee on the Appropriate Use of SGLT2 Inhibitors.

Prior to the day of informed consent acquisition, the (sub) investigator will provide subjects with guidance on getting enough fluids during the study, and will monitor the subjects closely for any decrease in total body fluid associated with polyuria/pollakiuria, and if any abnormalities, such as dehydration or decreased blood pressure are found, the (sub) investigator will initiate appropriate measures, such as fluid supplementation, and determine whether or not the study should be discontinued, depending on the patient's condition.

If a subject develops fever, diarrhea, or vomiting, or cannot consume enough food because of anorexia (sick days), TA-7284 use should be temporarily discontinued.

11.4 Pregnancy Reporting, and Other Information Affecting Safety That Needs to be Reported to the Study Sponsor

On learning that an embryo or fetus of a female subject or the female partner of a male subject has been exposed to the investigational product prior to the completion of the required period for contraception (until Week 4 of the follow-up observation period), the (sub) investigator will immediately submit the [redacted] included in Appendix 1 to the sponsor. If the female subject (or the female partner of a male subject) wishes for the pregnancy to proceed to term, the (sub) investigator will follow the subject until delivery whenever possible, determine whether the neonate has been affected by the investigational product, enter the information determined in the [redacted] in Appendix 1, and submit the report to the sponsor.

If a subject experiences an event during the safety assessment period that the study sponsor has determined needs to be reported to the sponsor, even if the event does not constitute a serious adverse event, if the study sponsor so requires, detailed information about the event should be reported promptly to the study sponsor in writing regardless of the presence or absence of a causal relationship to the investigational product.

11.5 Notifying Other Doctors of Subjects

The (sub) investigator will determine at all subject visits whether each subject has received care at a setting unrelated to this clinical study. The (sub) investigator with the permission of the subject will notify the doctor of any subject receiving care by another doctor of the subject's participation in the study. The (sub) investigator or a clinical research coordinator will provide a study participation card to subjects for notifying other doctors via the subject of subject participation in the study and instruct the subjects to present the card on receiving care at another hospital or in another department.

12. Subject Discontinuation Criteria and Procedures

12.1 Discontinuation Criteria

Subjects meeting any of the following discontinuation criteria will be discontinued from the study.

(1) If the subject requests discontinuation.
(2) If it is determined that the subject is clearly ineligible to participate in the study.
(3) If the (sub) investigator determines that it would be difficult to continue the study because of the emergence of, for example, an adverse event.
(4) If the (sub) investigator determines that it would not be appropriate to continue the study because of a worsening of the patient's primary disease.
(5) If it is discovered that the subject is pregnant.
(6) If the (sub) investigator determines that the study should be discontinued for some other reason.

Rationale

(1)-(6) These criteria were established to allow the study to be ethically conducted and in consideration of subject safety.

12.2 Discontinuation Procedures

The (sub) investigator will take the appropriate actions for any subject who is discontinued from the study and promptly notify a monitor that the subject has been discontinued. The (sub) investigator will perform the tests and observations scheduled for discontinuation within 7 days of the treatment period discontinuation.

The follow-up observation period begins once the treatment period has been discontinued.

The (sub) investigator will record the date of discontinuation and the reason for discontinuation in the case report form. Furthermore, if the study is discontinued because of an adverse event, the term of the event that resulted in discontinuation will be recorded in the case report form. The date of discontinuation is the day on which evaluations on discontinuation (evaluation day) are performed or, when evaluations on discontinuation are not possible, the day on which the decision to discontinue the

subject was made.

For subjects for whom the observations/tests that should have been conducted at discontinuation could not be conducted, and for subjects who did not visit the study site following discontinuation, the reason(s) therefor, and the courses of the subjects following discontinuation, will be determined through follow-up investigations performed through written correspondence or telephone calls, and the information obtained will be recorded.

The (sub) investigator or a clinical research coordinator will whenever possible collect the Hypoglycemia Symptom Survey Forms of subjects who do not visit to the study site by, for example, having the subjects mail them back.

13. Statistical Analysis

13.1 Analysis Populations

Efficacy analysis will be performed in the full analysis set (FAS). With respect to the primary endpoint, secondary analysis in the per protocol set (PPS) will also be performed. Safety analysis will be performed in the safety analysis set.

The data sets analyzed are defined below. The study sponsor will finalize the details of how the subjects are handled by the time of the database lock.

(1) Efficacy analysis population

1) FAS

The analysis population consisting of all randomized subjects other than the following will 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 analysis population consisting of FAS other than the following will constitute the PPS:

- 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

(2) Safety analysis population

The analysis population consisting of all randomized subjects other than the following will

constitute the safety analysis population:

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

13.2 Handling of Data

(1) Definition of missing values

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

(2) Handling of time point data tabulated at individual measurement points

When tabulating the data for each assessment time point, data that fall within the allowable time windows noted in "Table 9.1: Test/Observation Schedule Allowable Time Windows" will be used; missing data will not be replaced with data collected outside the allowable time windows.

If multiple data exist within an allowable time window, the data at the time point closest to the reference date will be used. If the degree of deviation 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.

If it is determined that data handling procedures other than those described above are required, they will be clearly described in the statistical analysis plan, which will be finalized by the time of the database lock.

13.3 Statistical Analysis Plan

Confidence intervals will be two-sided, and the confidence coefficient will be 95%. A statistical analysis plan containing more details will be prepared by the time of final database lock.

[redacted]

13.3.1 Investigation of Demographic and Other Baseline Characteristics

The demographic and other baseline characteristics of each analysis population will be summarized. The frequencies and proportions will be shown for discrete data, and for continuous data descriptive

statistics (number of subjects, mean, standard deviation, minimum, median, maximum, two-sided 95% confidence interval of the mean) will be calculated.

13.3.2 Efficacy

The following statistical procedure will be used for efficacy. Furthermore, subgroup analyses will be performed for some of the endpoints using stratification factors such as the eGFR ($\geq$ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2; $\geq$ 45 mL/min/1.73 m^2).

(1) Primary endpoint:
Analysis method for the proportion of subjects achieving a 30% decline in the eGFR

1) Primary analysis
The point estimate for the intergroup difference in the proportion of subjects achieving a 30% decline in the eGFR will be calculated, along with the 95% confidence interval using the Farrington-Manning method.

2) Secondary analysis
An adjusted analysis based on a logistic regression analysis model (with treatment group as a factor) that includes randomization factors as covariates will be performed for the proportion of subjects achieving a 30% decline in the eGFR, and the odds ratio and the 95% confidence interval thereof will be calculated.

Furthermore, in the aforementioned primary and secondary analyses, data will be replaced using a multiple imputation method. Detailed information about, for example, sensitivity analysis will be included in the statistical analysis plan.

(2) Analysis methods for the secondary and other endpoints

1) The Proportion of subjects achieving a 40% decline in the eGFR
An analysis similar to that performed for the proportion of subjects achieving a 30% decline in the eGFR will be performed for the proportion of subjects achieving a 40% decline in the eGFR.

2) Other efficacy endpoints
   1. Change and percent change in the eGFR
   2. Percent change in the urine ACR (first morning void urine)
   3. Change in the HbA1c
   4. Change in fasting blood glucose
   5. Change in blood pressure (systolic blood pressure, diastolic blood pressure)
   6. Change and percent change in lipids (HDL-C, fasting neutral lipids)
   7. Change and percent change in body weight
   8. Change in the fasting urine glucose/creatinine ratio

The aforementioned outcome measures for the other efficacy endpoints will be evaluated using a mixed model for repeated measures that includes treatment group, baseline value, visit, and treatment group–by-visit interactions. For the urine ACR, furthermore, the log-transformed urine ACR will be used.

3) Event endpoints

1. Composite endpoint of end-stage renal disease (ESRD), 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. The renal composite endpoint of 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

For the aforementioned event outcome measures, the event incidences will be calculated for each group. Kaplan-Meier plots will be prepared for each treatment group to analyze the time to event onset.

13.3.3 Safety

The following statistical procedure will be used for safety. Furthermore, subgroup analyses will be performed for some of the endpoints using stratification factors such as the eGFR ($\geq$ 30 mL/min/1.73 m^2 and $<$ 45 mL/min/1.73 m^2; $\geq$ 45 mL/min/1.73 m^2).

(1) Analysis of adverse events

The numbers and proportions of subjects experiencing the following categories of adverse events will be shown for each treatment group: adverse events overall, serious adverse events, adverse events resulting in discontinuation, adverse events resulting in death, adverse reactions, serious adverse reactions, adverse reactions resulting in discontinuation, and adverse reactions resulting in death.

(2) Analysis of hypoglycemia

The numbers and proportions of subjects with hypoglycemia will be shown for each treatment group.

(3) Analysis of clinical laboratory values, standard 12-lead ECG, and vital signs

For continuous data, descriptive statistics will be calculated for each treatment group for each time point. Descriptive statistics will also be calculated for each treatment group for the change from baseline. For discrete data, shift tables will be prepared for each treatment group for each time point showing the changes relative to baseline.

13.4 Changes Made to Statistical Analysis Plan

If the statistical analysis plan discussed in this section is changed before database lock, the reason for the changes made will be entered in the statistical analysis plan and in the clinical study report. Any analytical procedures changed or added after database lock will be documented along with the reason in the statistical analysis plan and clinical study report and be distinguished from the results of the planned analyses.

14. Protocol Compliance, Deviations, and Changes

14.1 Agreement to Protocol and Protocol Compliance

Before reaching an agreement with the sponsor about the protocol, the investigator must consult with the sponsor and thoroughly consider whether conducting the study is ethically and scientifically justified using the protocol, the latest version of the investigator's brochure, and other necessary data provided by the sponsor.

Based on the findings, the investigator will agree with the sponsor about the provisions of the protocol and sign or affix the name and the seal to a written agreement, and date it with the sponsor in order to certify protocol compliance.

14.2 Protocol Deviations and Changes

The (sub) investigator must not deviate from or change the protocol without prior agreement with the sponsor documented in writing and written approval based on prior review by the institutional review board. The (sub) investigator may deviate from or change the protocol without the prior written agreement of the sponsor and prior approval of the institutional review board in a medically unavoidable situation such as to avoid exposing a subject to acute risk.

In such situations, the investigator must as quickly as possible notify the sponsor, study site director, and institutional review board of the deviation or change along with the reason and, when appropriate, proposed protocol amendments. The investigator will then receive approval, the acknowledgment of the study site director, and written agreement from the sponsor.

The (sub) investigator must document all protocol deviations. The investigator will create a written record of the reason for any noncompliance with the protocol to avoid exposing a subject to acute risk or for another medically necessary reason and immediately submit this record to the sponsor and director of the study site, retaining a copy thereof.

The investigator will promptly submit a written report to the sponsor, study site director, and institutional review board about any study changes with a significant impact on the conduct of the study or that could expose the subjects to greater risk.

15. Protocol Amendment

The sponsor will amend the protocol if changes to the protocol are required during the study. The sponsor will consult and agree with the investigator about the changes, promptly notify the director of the study site in writing, and seek the approval of the institutional review board by way of the director of the study site.

The sponsor will assess the validity of any changes requested by the study site director based on the opinions of the institutional review board and amend the protocol as necessary. The sponsor will consult and agree with the investigator about the changes, promptly notify the director of the study site in writing, and seek the approval of the institutional review board by way of the director of the study site.

The sponsor will assess the validity of any changes found necessary through consultation with the investigator and amend the protocol as necessary. The sponsor will agree with the investigator about the changes, promptly notify the director of the study site in writing, and seek the approval of the institutional review board by way of the director of the study site.

16. Study Termination or Suspension

(1) Study termination/suspension criteria

The sponsor will consider whether the study should continue at all or some of the study sites in the event of any of the following:

1) Important information related to the quality, efficacy, or safety of the investigational product is learned that impacts the justification of the study.
2) A protocol change with which a study site cannot comply is required.
3) The director of the study site, based on the opinion of the institutional review board, requests a protocol revision that is unacceptable to the sponsor.
4) The study site director indicates that the study should be terminated in accordance with a decision by the institutional review board.
5) The study site is in major or continual violation of GCP, the protocol, or the study contract.

(2) Termination or suspension of the study overall by the sponsor

If determining to terminate or suspend the overall study, the sponsor will promptly notify the study site directors and regulatory authorities of this fact and the reason in writing. On receiving notification of the termination or suspension of the study by the sponsor, the study site director will promptly inform the investigator and institutional review board in writing of this fact and provide a detailed explanation of the reason.

The investigator will promptly notify the subjects and ensure they receive appropriate treatment

when notified by the sponsor by way of the director of the study site that the study will be terminated or suspended.

The subjects will be handled according to Section 12.2, Discontinuation Procedures, if the study is terminated.

(3) Termination or suspension of the study at a study site by the investigator or institutional review board

If unilaterally deciding to terminate or suspend the study, the investigator will promptly notify the study site director of this fact and provide a detailed reason in writing. The study site director will promptly inform the sponsor and institutional review board of this fact in writing.

If unilaterally deciding to terminate or suspend the study, the institutional review board will promptly notify the study site director of this fact and provide a detailed reason in writing. The study site director will promptly inform the investigator and sponsor of this fact in writing.

(4) Termination of study due to termination of contract with the study site

The sponsor will promptly notify the regulatory authorities if terminating the study, while underway, because a study site is in major or continual violation of GCP, the protocol, or the study contract.

17. About the Case Report Forms

17.1 Forms for Case Report Forms

Electronic case report forms based on an electronic data capture (EDC) system will be used in this study. Electronic case report forms reviewed and electronically signed by the investigator will be considered original documents. The results of tests conducted by the contract laboratory test facility will be obtained from the facility.

17.2 Definitions of Data Directly Entered in the Case Report Forms that are Considered Source Data

In this study, no parameters are being specified for which the data from electronic case report forms should be considered source data. Furthermore, if the data from electronic case report forms are going to be considered source data, this needs to be specified separately, in writing, before the study begins by the study sponsor and the principal investigator.

17.3 Instructions for Completing Case Report Forms

The (sub) investigator or a clinical research coordinator will complete the case report forms according to the instructions below. The procedures for completing the case report forms are specified in the "Handbook for Changing or Revising Case Report Forms"* as provided by the sponsor.

*: "Handbook for Changing or Revising Case Report Forms": EDC Manual, eCRF Entry Manual

(1) Before entries are made in the case report forms, the sponsor will engage in user control by assigning a user ID and password to the (sub) investigators and clinical research coordinators. The (sub) investigators and clinical research coordinators will keep and not share their assigned user ID and password. Data will be entered by (sub) investigators and clinical research coordinators granted entry privileges.

(2) Case report forms will be prepared for subjects receiving investigational product in the run-in period.

(3) The investigator may make entries in all case report form fields. The subinvestigators may make entries in all case report form fields other than the electronic signature field. The clinical research coordinators may transcribe information from the medical records and otherwise transcribe information from the source documents when no medical decision is required.

(4) A reason for each change or revision to case report form entries will be provided as electronic information.

(5) The investigator will electronically sign each case report form in the EDC system after confirming that the document has been accurately and completely completed and that an audit trail and electronic signature information are available for review.

(6) The investigator will archive a copy of the case report forms (a PDF version of the electronic case report forms reviewed by the investigator) saved on CD-R or other media. Electronic case report forms provided in a viewable environment (access privileges to EDC system) will serve as copies from the time after electronic signature to the time the investigator receives the CD-R or other recording media.

(7) The investigator will create a record explaining any case report form data that is inconsistent with the source documents, submit the record to the sponsor, and retain a copy.

17.4 When to Submit Case Report Forms

The (sub) investigator will as a rule prepare the case report forms within 72 hours of the completion of subject observations or assessments in each surveillance period and will submit the prepared case report forms to the study sponsor.

17.5 Handling of the Hypoglycemia Symptom Survey Forms

The Hypoglycemia Symptom Survey Forms will be retained at the study sites, in accordance with "21. Record Retention," "(1) Records Retained at Study Sites."

18. Direct Access to Source and Other Documents

The investigator and director of the study site will agree to allow monitoring and auditing by the sponsor and inspections by the institutional review board and regulatory authorities and to grant to all source documents related to the study for these purposes.

19. Study Quality Control and Quality Assurance

The sponsor must conduct the study according to "Quality Control of Clinical Studies," which is based on GCP standard operating procedures of Mitsubishi Tanabe Pharma Corporation, and "Quality Assurance for Clinical Studies," so that the quality and reliability of the study are maintained. The study site and investigator must cooperate with the study quality control and quality assurance activities of the sponsor.

During quality control activities for the study, the monitors will directly access source documents as needed and confirm that the study is being conducted in compliance with the written study-related procedures of the study site, the latest version of the protocol, and GCP. The monitors will also confirm that entries in the case report forms by the (sub) investigator are accurate and complete and agree with the source documents and other study-related records.

To ensure that the study is conducted in compliance with the protocol and GCP, auditing personnel will confirm that quality control is being appropriately performed by conducting audits according to the GCP standard operating procedures.

20. Ethics

20.1 Ethical Conduct of the Study

The study must be conducted in consideration of the principles grounded in the Declaration of Helsinki and in compliance with the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, GCP, and the protocol.

20.2 Institutional Review Boards

The institutional review boards will conduct reviews of the conduct and continuation of the study based on its ethical, scientific, medical, and pharmacological standpoints, considering the investigator's brochure, protocol, and informed consent form.

20.3 Subject Privacy

Subjects will be enrolled and identified in the case report forms using subject identification codes,

and study personnel will protect subject privacy in direct access of source documents related to the study, the presentation of results and medical journals, and the submission of data to the regulatory authorities.

21. Record Retention

(1) Records Retained at Study Sites

A record retention manager appointed by the director of each study site will retain all study-related documents and records to be maintained at the study site until the later of 1) or 2) below. If the sponsor requires the study site to retain the records for a longer period of time, the study site will consult with the sponsor about for how long and how the records should be retained.

The sponsor will submit a written explanation to the director of the study site if determining that the data related to the results of the study collected in the course of the study will not be included with the marketing application.

The sponsor will notify the director of the study site in writing if marketing approval for the investigational product is obtained or development is to be canceled.

1) The day of marketing approval of the investigational product (or the day of approval of the supplemental J-NDA in the case of an additional indication) (or the day 3 years after the day when notification is received that development is to be canceled or the study results will not be included in the marketing application)
2) The day 3 years after the termination or completion of the study

(2) Records to be retained by the sponsor

The sponsor will retain all study-related documents and records to be maintained by the sponsor until the later of 1) or 2) below.

1) The day 5 years after marketing approval for the investigational product is obtained (or the day of approval of the supplemental J-NDA in the case of an additional indication) (or the day 3 years after the decision to terminate development is made if development is terminated) or the end of reexamination
2) The day 3 years after the termination or completion of the study

22. Monetary Payments

Monetary payments to the subjects and study sites will comply with a contract or written agreement executed between each study site and the sponsor.

23. Compensation for Injuries and Insurance

23.1 Compensation for Injuries

The sponsor will provide appropriate compensation based on the established criteria for injuries any subject suffers as a result of the study unless a causal relationship with the study is ruled out. [Compensation consists of out-of-pocket medical expenses, medical allowances, and compensation.] Subjects eligible for compensation will not be required to prove a causal relationship.

23.2 Insurance

The sponsor will purchase insurance and take other necessary actions to ensure its ability to cover the expenses and compensation for subject injuries related to the study.

24. Decisions Regarding Publication

The information contained in this protocol is the property of the sponsor and is to be provided to the (sub) investigators, other study personnel, and institutional review boards. The information may not be disclosed to any third party without the written agreement of the sponsor, except as required to conduct the study.

The publication of the data obtained in the study by the (sub) investigators and other study-related personnel of the study site at conferences and other external events must be approved in advance by the sponsor.

The sponsor may freely use the data obtained in the study for any purpose, including reporting to the regulatory authorities, ensuring appropriate use, or marketing.

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Contact Information

Clinical Research & Development II Department, Ikuyaku. Integrated Value Development Division,
Mitsubishi Tanabe Pharma Corporation

[redacted]

Nighttime and Holiday Contact Information

In emergencies occurring during non-business hours (5:30 p.m. to 9:00 a.m. the following day) or on non-business days of the sponsor, such as Saturdays, Sundays, Holidays, and the New Year's break, contact the Emergency Contact Center to be transferred to a monitor.

Emergency Contact Center, Mitsubishi Tanabe Pharma Corporation

[redacted]

[redacted]