A Phase III, Open-label Study of MT-6548 in Peritoneal Dialysis Subjects With Anemia Associated With Chronic Kidney Disease in Japan

Study Protocol

Study sponsor:

Mitsubishi Tanabe Pharma Corporation

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CONFIDENTIALITY

This study protocol contains information which should be viewed only by those directly involved with the study. The contents of this document should only be published or disclosed to third parties with the express written consent of Mitsubishi Tanabe Pharma Corporation.

The study will be performed in compliance with the Pharmaceutical Affairs Law, Ordinance on Good Clinical Practice (GCP), related regulations, and this study protocol.

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List of abbreviations

Abbreviation	Expanded term
AUC	Area under the plasma concentration-time curve
BCRP	Breast Cancer Resistance Protein
CKD	Chronic kidney disease
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
EDC	Electronic data capture/ Systems for using electronic devices and software to collect data on clinical study subjects from study centers or contract testing laboratories
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
FAS	Full analysis set
GFR	Glomerular filtration rate
GCP	Good Clinical Practice
HD-CKD	Hemodialysis dependent chronic kidney disease
HIF-PH	Hypoxia inducible factor prolyl hydroxylase
IC_{50}	Median inhibitory concentration
JSDT	The Japanese Society for Dialysis Therapy
LOCF	Last observation carried forward
MMRM	Mixed model repeated measures
MRP	Multidrug resistance-associated protein
NDD-CKD	Nondialysis dependent chronic kidney disease
OATP	Organic anion transporting polypeptide
OAT	Organic anion transporter
PD	Pharmacodynamics
PD-CKD	Peritoneal dialysis chronic kidney disease
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Preferred term
QOL	Quality of life
SOC	System organ class
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach maximum plasma concentration
TIBC	Total iron binding capacity
TSAT	Transferrin saturation

Definitions of terms

Term	Definitions
Study period	From the day of informed consent to the final day of follow.up observation period
Treatment period	From the first day of the treatment period to the final day of the treatment period
Day of completion of treatment period	Week 24 of treatment period or day of discontinuation of treatment
X weeks prior to the first day of the screening period.	Same day of week from X weeks prior to the first day of the screening period
MT-6548 Tablet	Each film-coated tablet contains 150 mg vadadustat.
Correction cohort	Patients who have not received ESA treatment from 8 weeks prior to the first day of the screening period
Conversion cohort	Patients who have received the same ESA treatment from 8 weeks prior to the first day of the screening period

Protocol Summary

1. Study title

A phase III, open-label study of MT-6548 in peritoneal dialysis subjects with anemia associated with chronic kidney disease in Japan

2. Purpose of the study

The purpose of the study is to evaluate efficacy and safety of MT-6548 in patients with CKD-related anaemia undergoing peritoneal dialysis.

3. Subjects

3.1 Subjects

Patients with CKD-related anaemia undergoing peritoneal dialysis

3.2 Inclusion criteria

Subjects must meet all inclusion criteria below and have capacity to grant informed consent. Laboratory tests to determine inclusion criteria will be performed at a central testing facility. If a given laboratory test is performed multiple times during the screening period, the most recent test will be used for determination.

(1) Patients at least 20 years of age as of the day of consent (either sex)

(2) Patients with CKD diagnosed according to the Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" as of the day of consent.

(3) Patients who have been receiving peritoneal dialysis for at least 4 weeks prior to the first day of the screening period, but excluding patients also receiving haemodialysis.

(4) Patients expected to initiate haemodialysis during the treatment period.

(5) Correction cohort: Patients who have not received erythropoiesis-stimulating agent (ESA) treatment from 8 weeks prior to the first day of the screening period. However, patients receiving ESA treatment at consent may join the study if they discontinue this treatment after consent and have a washout period of at least 8 weeks.

Conversion cohort Patients receiving the same formulation of ESA using the same administration route and the same dose interval (the dose interval should be the one described in the package insert for the ESA formulation) within 8 weeks prior to the first day of the screening period, using the dosages described below.

Dosage:

- ✓ Epoetin alfa (recombinant) and epoetin beta (recombinant) ≤12,000 IU every 2 weeks
- ✓ Darbepoetin alfa (recombinant): ≤120 μg every 2 weeks

- ✓ Epoetin beta pegol (recombinant): ≤250 μg every 4 weeks

(6) Patients with the following mean Hb values during screening, using the mean of the latest two tests:
- ✓ Correction cohort: ≥8.0 g/dL, <11.0 g/dL
- ✓ Conversion cohort: ≥9.0 g/dL, <12.5 g/dL

(7) Patients with a difference of <1.5 g/dL in Hb for the latest two tests in the screening period

(8) Patients with serum ferritin values of ≥100 ng/mL or transferrin saturation (TSAT) of ≥20% during the screening period.

(9) Patients with folic acid and vitamin B_{12} values above standard minimum values during the screening period.

3.3 Exclusion criteria

Patients who meet any of the following exclusion criteria will be excluded. Laboratory tests to determine exclusion criteria will be performed at a central testing facility. If blood pressure measurements or a given laboratory test is performed multiple times during the screening period, the most recent test will be used for determination.

(1) Patients with anaemia resulting primarily from a disease other than CKD after date of consent (e.g., sickle-cell syndrome, myelodysplastic syndrome, myelofibrosis, haematopoietic malignancy, myeloma, haemolytic anaemia, thalassemia, or aplasia pure red cell)

(2) Patients with active haemorrhaging or exsanguination within 8 weeks prior to the first day of the screening period.

(3) Patients who have received RBC transfusion within 8 weeks prior to the first day of the screening period.

(4) Patients who have received testosterone enanthate or mepitiostane within 8 weeks prior to the first day of the screening period.

(5) Patients determined by investigators/subinvestigators to likely require immediate rescue therapy or drug holiday of the study drug after initiation of treatment period.

(6) Patients expected to no longer require peritoneal dialysis during the study period due to recovery of renal function.

(7) Patients with peritonitis within 4 weeks of the first day of the screening period.

(8) Patients with AST, ALT, or total bilirubin values of 2.5 times or greater the upper limit of standard during the screening period. This does not apply to patients with Gilbert's syndrome.

(9) Patients with uncontrolled hypertension (defined as systolic BP >180 mmHg or diastolic BP >110 mmHg) during the screening period or on the first day of the treatment period.

(10) Patients for whom any of the following apply upon fundoscopy during the screening period:
- ✓ No ocular fundus findings are possible.

- ✓ Active ocular fundus disease.

(11) Patients with severe cardiac failure from the day of consent (Class IV according to severity classification of the New York Heart Association (NYHA))

(12) Patients with cerebrovascular disorders or acute coronary syndromes (hospitalization for unstable angina or myocardial infarction, etc.) within 12 weeks prior to the first day of the screening period. Patients who have been hospitalized due to acute coronary angioplasty or cardiac failure.

(13) Patients with malignant tumors or a history of such. However, this does not apply to patients with no relapse for 5 or more years (5 or more years with no relapse from last administration of chemotherapy if chemotherapy was used).

(14) Patients with incidence or relapse of deep vein thrombosis or pulmonary embolism within 12 weeks prior to the first day of the screening period.

(15) Patients with current or previous haemosiderosis or hemochromatosis.

(16) Patients with a history of or plans for organ transplant (not including being on a waiting list for renal transplant), haematopoietic stem cell transplant, or bone marrow transplant.

(17) Patients with an allergy to the study drugs.

(18) Patients who have participated in another clinical study and received study drugs within 12 weeks prior to informed consent, or within 5 times the half-life of the study drug (whichever is longer).

(19) Patients who have previously used MT-6548.

(20) Patients with known low tolerance to hypoxia-inducible factor prolyl hydroxylase enzyme (HIF-PH) inhibitors.

(21) Patients who are unwilling to consent to use contraception from the beginning of the study period to 30 days following the final dose of the study drug for women who may become pregnant, or from the beginning of the study period to 90 days following the final dose of the study drug for men.

(22) Female patients who are or may be pregnant, or women who are nursing.

(23) Other patients judged by investigators/subinvestigators to be inappropriate as a subject in this study.

3.4 Re-testing/re-screening

(1) Re-testing

Re-testing during the screening period may be performed at the discretion of investigators/subinvestigators for subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, or total bilirubin) or blood pressure.

Subjects with blood pressure measurements on the first day of the treatment period which

meet exclusion criteria may be re-tested at the discretion of investigators/subinvestigators, and processed for treatment period initiation if they no longer meet exclusion criteria.

However, the maximum time from the first day of the screening period to the first day of the treatment period is 6 weeks.

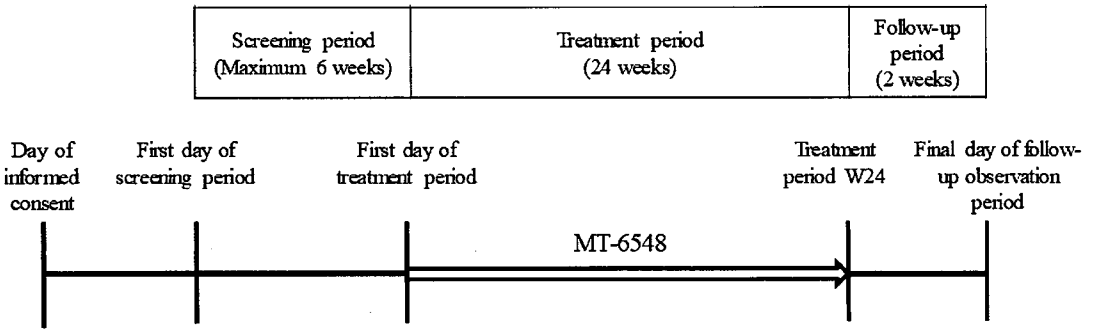
(2) Re-screening

Re-screening may be performed at the discretion of investigators/subinvestigators if subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, or total bilirubin), blood pressure, or blood pressure on the first day of the treatment period, may have become eligible for the study due to natural course or drug treatment.

However, re-screening may only be performed once for any given subject.

4. Study design

Multicenter, uncontrolled open-label study



(1) Screening period

The screening period begins on the first day of the screening period, and ends upon completion of tests required on the first day of the treatment period. Maximum screening period time is 6 weeks. Two visits will be made during the screening period; the first (SV1) is the first day of the screening period. The second screening period visit (SV2) occurs after results from laboratory tests performed on the first day of the screening period have been obtained. Re-testing will be performed as necessary.

(2) Treatment period

The treatment period will last from completion of scheduled tests on the first day of the treatment period to completion of blood sampling for haematology tests on the final day of the treatment period (Week 24 of the treatment period or discontinuation of treatment).

Treatment period study visits will be made every 2 weeks up until Week 12, and every

4 weeks thereafter for scheduled tests. However, study visits may be more frequent if variation in Hb levels causes concern for excessive increase or decrease in Hb, or for other reasons.

(3) Follow-up observation period

The follow-up observation period consists of 2 weeks from completion of blood sampling for haematology tests on the final day of the treatment period. The final day of the follow-up observation period is 2 weeks from the completion of blood sampling for haematology tests on the final day of the treatment period, regardless of whether a study visit is made on that day.

Subjects should make study visits as close to the same time as possible during the study period for scheduled tests.

5. Study drug, dosage, and administration

5.1 Study drug names

(1) Investigational product

Name: MT-6548 Tablet 150 mg

Nonproprietary name: vadadustat

Dosage form and content: Each film-coated tablet contains 150 mg vadadustat.

5.2 Treatment period, dosage, and administration

(1) Treatment period

From the first day of the treatment period to the day prior to Week 24 of the treatment period.

(2) Initial dosage levels

1) Initial dosage for correction cohort

Single daily dose of 300 mg (2 tablets)

2) Initial dosage for conversion cohort

Single daily dose of 300 mg (2 tablets)

(3) Maintenance dosage and dosage adjustments

Maintenance dosage is 150 to 600 mg once daily and adjusted according to the dosage adjustment guideline below.

MT-6548 Tablet dosage adjustment guidelines

Investigators/subinvestigators will monitor Hb levels throughout the treatment period, and determine whether to adjust study drug dosage or discontinue administration as required. In

principle dosage adjustments are to be performed at scheduled study visits, but they may also be performed at unscheduled visits if considered necessary, for example if Hb level variation gives concern for excessive increases or decreases.

Hb levels will be measured on scheduled study visit with the HemoCue® Hb201 DM analyzer; in principle these measurements will be used for determinations regarding dosage adjustments. Hb measurements used for dosage adjustment determinations will be recorded in the subject's case report form (CRF). Measurement results from the HemoCue® Hb201 DM will be used solely for determination of study drug dosage adjustments, and will not be used for efficacy or safety analysis.

The dosage adjustment algorithm below will be followed in order to achieve and maintain Hb levels of 11.0–13.0 g/dL during the study. Dosage adjustment steps are defined in the chart below.

MT-6548 Tablet dosage adjustment chart

Step	No. of tablets	Dosage
1	1	150 mg
2	2	300 mg
3	3	450 mg
4	4	600 mg

*It is permitted for dosage adjustments not to comply with the dosage adjustment algorithm for safety reasons depending on factors such as clinical status (e.g., AEs, volume depletion, or volume overload), Hb elevation rate, decrease rate, or fluctuations. In such cases, clinical status will be recorded in CRFs. All dosage increases of MT-6548 will be in increments of 1 tablet at a time.

If a dosage increase or reduction according to the dosage adjustment algorithm is impossible because the maximum or minimum dosage on the dosage adjustment chart is already being administered, it is permitted to not alter the dosage at that point. However, in this case it will be confirmed whether withdrawal criteria are met, and treatment discontinued if so.

Dosage adjustment algorithm for MT-6548 Tablet

- ✓ Dosage increases are in principle separated by at least 4 weeks. There are no set intervals for dosage decreases, but frequent dosage adjustments are to be avoided.
- ✓ Decrease MT-6548 dosage by 1 tablet if Hb levels suddenly increase (more than 2.0 g/dL change in past 4 weeks*).
- ✓ Increase MT-6548 dosage by 1 tablet if Hb levels are <11.0 g/dL. However, decrease by 1 tablet instead of increasing in cases of sudden increase in Hb (more than 2.0 g/dL

change in past 4 weeks*).

- ✓ Decrease MT-6548 dosage by 1 tablet if Hb is >12.5 g/dL.
- ✓ If Hb is >13.0 g/dL and ≤13.5 g/dL, and there has been a sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*), discontinue MT-6548 administration and resume at 1 tablet reduced dosage after Hb falls to ≤13.0 g/dL.
- ✓ If Hb is >13.5 g/dL, discontinue MT-6548 administration and resume at 1 tablet reduced dosage after Hb falls to ≤13.0 g/dL.

*Calculate Hb change rate using the Hb measurement closest to 4 weeks prior to the day of dosage adjustment (in the range of 3 to 5 weeks). A rate of change greater than 0.5 g/dL/week constitutes "sudden increase." If Hb was not measured 3 to 5 weeks prior to the day of dosage adjustment, use the measurement made immediately prior to 5 weeks before the day of dosage adjustment.

(4) Administration method

The study drug is taken once-daily orally. The drug does not need to be taken with meals, but timing should be as consistent as possible throughout the treatment period, both in relation to meals and time of day. The first dose will be taken after required tests are finished on the first day of the treatment period.

6. Concomitant medications and therapies

6.1 Prohibited concomitant medications and therapies

(1) ESA formulations

Concomitant use of epoetin alfa (recombinant), epoetin beta (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant) is prohibited for the period described below. These restrictions do not apply to rescue therapy.

- ✓ Correction cohort: Concomitant use is prohibited from 8 weeks prior to the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period.
- ✓ Conversion cohort: Concomitant use is prohibited from the first day of the treatment period to completion of blood sampling for haematology tests on the final day of the treatment period.

(2) Testosterone enanthate and mepitiostane

Concomitant use is prohibited from 8 weeks prior to the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period.

(3) Blood transfusion

Prohibited from 8 weeks prior to the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period. These restrictions do not apply to rescue therapy.

6.2 Restricted drugs

(1) Iron supplements

From the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period, administer iron supplements to maintain serum ferritin values of ≥100 ng/mL or TSAT of ≥20%. Iron supplements may be omitted for subjects who respond poorly to them, such as those with an allergy or those with adverse drug reaction (ADRs) to iron (vomiting, etc.).

Investigators/subinvestigators will determine iron supplement dosage and administration route.

Important: Oral iron supplements may impair MT-6548 bioavailability, so oral iron supplements must not be taken at the same time as MT-6548 Tablet. Subjects taking oral iron supplements will be instructed not to take any within 2 hours before or after taking MT.6548 Tablet.

(2) Iron-containing phosphate binders (ferric citrate hydrate, sucroferric oxyhydroxide)

New use of iron-containing phosphate binders is fundamentally prohibited from the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period. If iron-containing phosphate binders are used by a subject on the first day of the screening period, then the same dosage of the same type should fundamentally be continued from the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period. If investigators/subinvestigators determine that a dosage increase is required for iron-containing phosphate binders, then additional treatment will be performed with hyperphosphatemia drugs containing no iron, or treatment switched to hyperphosphatemia drugs containing no iron. Dosage of iron-containing phosphate binders may also be reduced if determined necessary according to the subject's condition. For subjects in the correction cohort, there must be no switching to other hyperphosphatemia drugs containing no iron from the first day of the screening period to completion of scheduled tests at Week 4 of the treatment period.

Important: As with oral iron supplements, iron-containing phosphate binders may impair MT-6548 bioavailability, so iron-containing phosphate binders must not be taken at the

same time as MT-6548 Tablet. Subjects taking iron-containing phosphate binders will be instructed not to take any within 2 hours before or after taking MT-6548 Tablet.

6.3 Rescue therapy

The following rescue therapy options will be available for subject safety. If rescue therapies are performed, the subject may continue in the study unless investigators/subinvestigators determine study withdrawal is appropriate. Details of any rescue therapy implemented will be recorded in the subject's CRF.

(1) ESA formulations

If a subject has received maximum dosages of MT-6548 for ≥2 weeks and meets all criteria below, investigators/subinvestigators may administer ESA as rescue therapy to improve Hb levels if necessary in order to secure subject safety. ESA rescue therapy may also be administered without meeting the criteria below if deemed necessary by investigators/subinvestigators in order to secure subject safety, such as in cases of acute decreases in Hb. MT-6548 administration will be discontinued if implementing ESA rescue therapy. Study drug treatment may resume if Hb levels improve, as long as there is no concomitant use with ESA. Subjects who are not expected to resume study drug treatment will be withdrawn from the study.

- ✓ Anaemia or anaemia symptoms (e.g., fatigue, weakness, shortness of breath, chest pain, confusion, dizziness) become aggravated compared to the first day of the treatment period to the point they are clinically problematic.
- ✓ Hb levels drop to <8.0 g/dL.

(2) RBC transfusion

Normally RBC transfusions are performed when clinically necessary in instances of acute or major haemorrhaging. RBC transfusion may be performed at investigator/subinvestigator discretion if deemed clinically necessary in cases of potentially worsening anaemia, even if that anaemia is not severe, or in cases of moderate to severe anaemia symptoms.

(3) Phlebotomy

Phlebotomy may be performed at investigator/subinvestigator discretion in cases of hyperviscosity syndrome, if the rate of Hb increase is concerning to investigators/subinvestigators, or if Hb levels are high enough to warrant concern to investigators/subinvestigators.

7. Endpoints

7.1 Efficacy endpoints

(1) Primary endpoints

1) Mean Hb of treatment period Weeks 20 and 24
2) Hb at each treatment period timepoint
3) Ratios of subjects with mean Hb within the target range (11.0–13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each timepoint in treatment period
4) Correction cohort only: Days from initiation of treatment period required to reach target Hb range (11.0–13.0 g/dL)
5) Correction cohort only: Rate of increase of Hb levels

(2) Other endpoints

1) Correction cohort only: Change from baseline in mean Hb of Weeks 20 and 24 of treatment period.
2) Correction cohort only: Ratio of subjects with an increase of ≥1.0 g/dL of mean Hb from baseline at each timepoint in treatment period.
3) Ratio of subjects who received ESA rescue therapy
4) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.
5) Study drug dosage
6) total number of dosage adjustments
7) Quantity of iron administered
8) Ratio of subjects who received IV iron
9) Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20%.
10) Change from baseline of iron-related measures (serum iron, total iron binding capacity (TIBC), TSAT, and serum ferritin) and hepcidin.
11) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and erythropoietin (EPO).
12) QOL measures (EQ-5D-5L, KDQOL)

7.2 Safety endpoints

(1) Adverse events and adverse drug reactions
(2) Laboratory test values
(3) Resting standard 12-lead ECG
(4) Body weight (excluding dialysis solution)
(5) Vital signs
(6) Fundoscopy
(7) Chest X-ray

(8) Ratio of subjects with Hb levels of ≥13.0 g/dL or ≥14.0 g/dL.

(9) Ratio of subjects with Hb increase rates exceeding 0.5 g/dL/week.

8. Withdrawal criteria

Subjects will be withdrawn from the study if the following criteria are met:

(1) If the subject expresses a desire to withdraw from the study.

(2) If it is discovered that the subject is clearly ineligible for study participation.

(3) If investigators/subinvestigators determine that AEs make continued participation in the study difficult.

(4) If investigators/subinvestigators determine that continuation of the study is inappropriate for a subject, such as if hyperviscosity syndrome occurs or if control of Hb within the target range is impossible.

(5) If continuous haemodialysis is initiated, or if the subject receives a renal transplant.

(6) If renal function recovers such that peritoneal dialysis is discontinued.

(7) If pregnancy of the subject is discovered.

(8) If the investigator/subinvestigator determines a subject should withdraw from the study for any other reason.

9. Target sample size

Forty subjects enrolled in treatment period.

9.1 Rationale for target sample size

Assuming a SD of 1.78 for mean Hb, which is one of the efficacy endpoints for the study, a sample size of 40 subjects allows for value estimation with a precision of mean±0.57 g/dL (95% CI). The SD of 1.78 was calculated from the upper limit of the 80% CI in the MT-6548 300 mg group at the end of the primary efficacy evaluation period of 6 weeks in study CI-0021, a dose-finding study in Japanese patients with NDD-CKD-related anaemia. According to JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015," Hb values vary in a range of about 1 g/dL in normal clinical contexts, so a level of precision of mean Hb±0.57 g/dL (95% CI) should allow for a clinically meaningful analysis. A sample size of 40 subjects should also enable analysis of safety.

10. Study period

[redacted]

11. Test and observation schedule

Item \ VISIT	Informed consent	Screening period [a]		Treatment period											Final day of follow-up observation period [b]
		First day	Visit 2	First day [c]	W2	W4	W6	W8	W10	W12	W16	W20	W24	Day of discontinuation	
Visit no.	**IC**	**SV1**	**SV2**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**TV7**	**TV8**	**TV9**	**TV10**	**TV11**	**FU**
Permitted range (day)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	+ 7 or + 14 [d]	+7
Procedure/evaluation															
Informed consent	X														
Inclusion/exclusion criteria	X	X	X	X											
Patient's background and history	X			X											
Height				X											
Body weight (weight excluding dialysis solution)				X						X			X	X	
Folic acid and vitamin B_{12}		X													
Pregnancy test [e]		X											X	X	
Haematology test		X	X [f]	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry test		X		X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein		X		X									X	X	
Iron-related measures		X		X	X	X	X	X	X	X	X	X	X	X	
Hepcidin				X	X	X	X			X			X	X	
Erythropoietin				X	X	X	X			X			X	X	
VEGF				X						X			X	X	
Urinalysis (qualitative)		X		X	X	X	X	X	X	X	X	X	X	X	
Vital signs [g]		X		X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [h]				X									X	X	
Fundoscopy [d]		X										X		X	
Chest X-ray [d]		X										X		X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X	X	
AE investigations				X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for genetic analysis [i]					Blood sampling should be performed once as early as possible after 2 weeks of										
Drug evaluation/procedure															
Investigation of concomitant drugs				X	X	X	X	X	X	X	X	X	X	X	X
Prescribing MT-6548 tablets [j]				Administration according to the dosage adjustment guideline											
Administration of iron supplements		Administer iron supplements to maintain serum ferritin values ≥100 ng/mL or TSAT ≥20%.													

[a] Maximum screening period length is 6 weeks. Test results will be reviewed prior to transitioning from the first day of the screening period to screening period Visit 2, and from screening period Visit 2 to the first day of the treatment period. Re-testing will be performed as necessary.

[b] Not required if withdrawing prior to treatment period.

[c] Perform prior to study drug treatment (AE investigations begin after study drug treatment)

[d] Fundoscopy and chest X-ray performed once during screening period and during Weeks 20 and 24 of treatment period. Also performed to extent possible within 14 days of study withdrawal.

[e] Only female subjects who may become pregnant.

[f] Hb only measured.

[g] Measured to extent possible prior to blood sampling. Measured with subject sitting after 5 minutes of rest.

[h] Measured to extent possible prior to blood sampling. Measured with subject in supine position after 5 minutes of rest.

[i] Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period in subjects who have granted consent.

[j] Prescribe MT-6548 Tablet depending on quantity of subject's remaining study drug. Subjects are

instructed to open new bottles of study drug only after completing previous bottle.

1. Protocol history and background information

(1) Target disease and treatment methods

Chronic kidney disease (CKD) is defined in Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012"[1] as renal disorders (e.g., proteinuria) or renal impairment with glomerular filtration rate (GFR) of <60 mL/min/1.73m^2 for 3 or more months.

CKD is a significant public health problem throughout the world, and in Japan alone 20% of adults are estimated[2] to have GFR of <60 mL/min/1.73m^2. In Japan there are more than 300,000 CKD patients requiring dialysis, a number which has increased in the past 30 years[3].

Anaemia is a well-known complication of renal disease, and occurs early after onset of CKD[4]. Prevalence of anaemia increases as CKD progresses, with 53% to 89% of dialysis patients affected by the disease[5, 6]. Causes of anaemia in CKD patients include exsanguination, reduced RBC (red blood cell) lifespan, iron deficiency, erythropoietin (EPO) deficiency, [redacted]. The primary cause of nephrogenic anaemia is EPO deficiency, which results from hypoxic disorders or cells surrounding renal tubules or cell decrease in cells surrounding renal tubules[4, 7]. [redacted]

Further, iron loss due to dialysis is an extremely important cause of anaemia in CKD and requires iron supplementation[7]. Anaemia significantly affects organ function by decreasing oxygen transport to tissue, resulting in various symptoms such as fatigue, shortness of breath, and exercise intolerance[6]. Compensatory changes occur in the structure and function of the heart in these anaemia patients, including increased cardiac output and left ventricular hypertrophy, which can ultimately result in cardiac failure[8]. Other anaemia-related disorders observed in CKD patients include cognitive function disorders, sleep disorders, and impaired immune function, sometimes resulting in reduced quality of life (QOL)[4, 9]. Anaemia is also a factor related to poor prognosis in CKD patients[4, 7]. Improving anaemia results particularly in markedly improved QOL in terms of energy, fatigue, and physical function[4, 7, 10].

Peritoneal dialysis involves injecting dialysis solution into the peritoneal cavity and allowing it to remain for a period of time so that the peritoneum may purify the blood. As of the end of 2015, 2.9% of all dialysis patients in Japan were using this method (according to the JSDT's "Summary of Chronic Dialysis Treatment in Japan 2015".) Peritoneal dialysis is fundamentally positioned as initial comprehensive renal replacement therapy for Stage 5 CKD patients. Beginning the treatment in a planned manner while the patient still maintains renal function is considered crucial for avoiding complications during introduction and improving prognosis (2009 JSDT "Guideline for Peritoneal Dialysis"). Further, the clinical status of patients with peritoneal dialysis-related chronic kidney disease (PD-CKD) is extremely similar to that of

non-dialysis-dependent CKD (NDD-CKD) patients, so fundamental dosing approaches for erythropoiesis-stimulating agents (ESA) and target Hb values in PD-CKD patients are considered similar to those for NDD-CKD patients (JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015").

ESA formulations include epoetin alfa (recombinant), epoetin beta (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant); these are standard therapy for anaemia in CKD patients, but require IV or subcutaneous administration.

(2) Study drug names and explanations

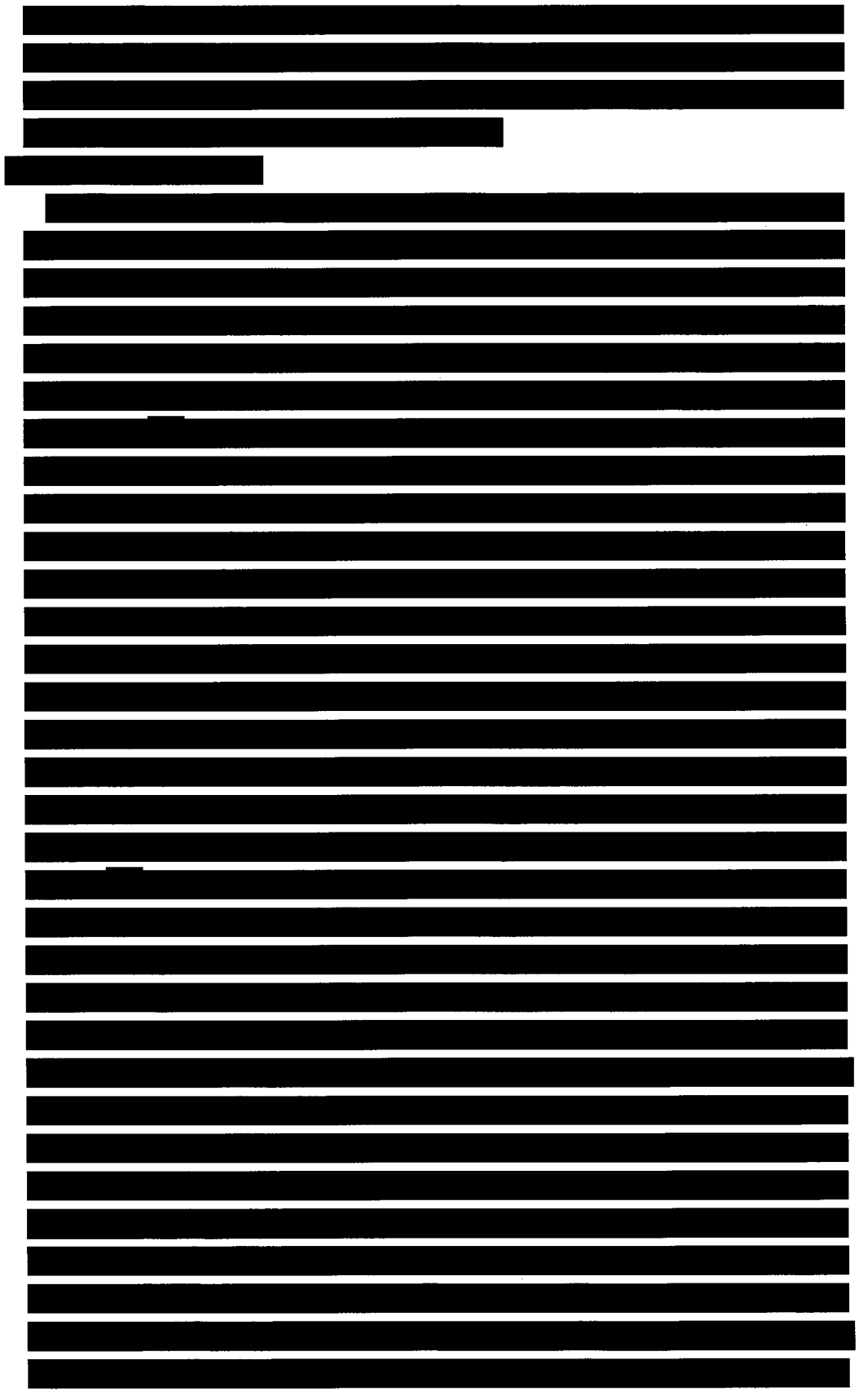
MT-6548 is a hypoxia-inducible factor prolyl hydroxylase enzyme (HIF-PH) inhibitor currently under development for treatment of anaemia in CKD patients either using or not using dialysis. It is a novel small-molecule compound which can be taken orally.

HIF-PH causes hydroxylation of HIF-α in normoxic conditions, with VHL (von Hippel-Lindau)-dependent breakdown of HIF-α reducing HIF-α levels. However, in hypoxic conditions HIF-PH activity is reduced, causing stabilized HIF-α to be transported to the cellular nucleus, where it forms a dimer with HIF-β and binds with hypoxia response elements (HRE) to control various target genes, such as activation of EPO genes which increase EPO protein production. By inhibiting HIF-PH activity, MT-6548 creates a physiological response similar to that of hypoxic conditions, thereby increasing EPO protein production [redacted] resulting in increased Hb and RBC production11).

(3) Nonclinical and clinical study results

Refer to the latest MT-6548 investigator's brochure for details.

[redacted]



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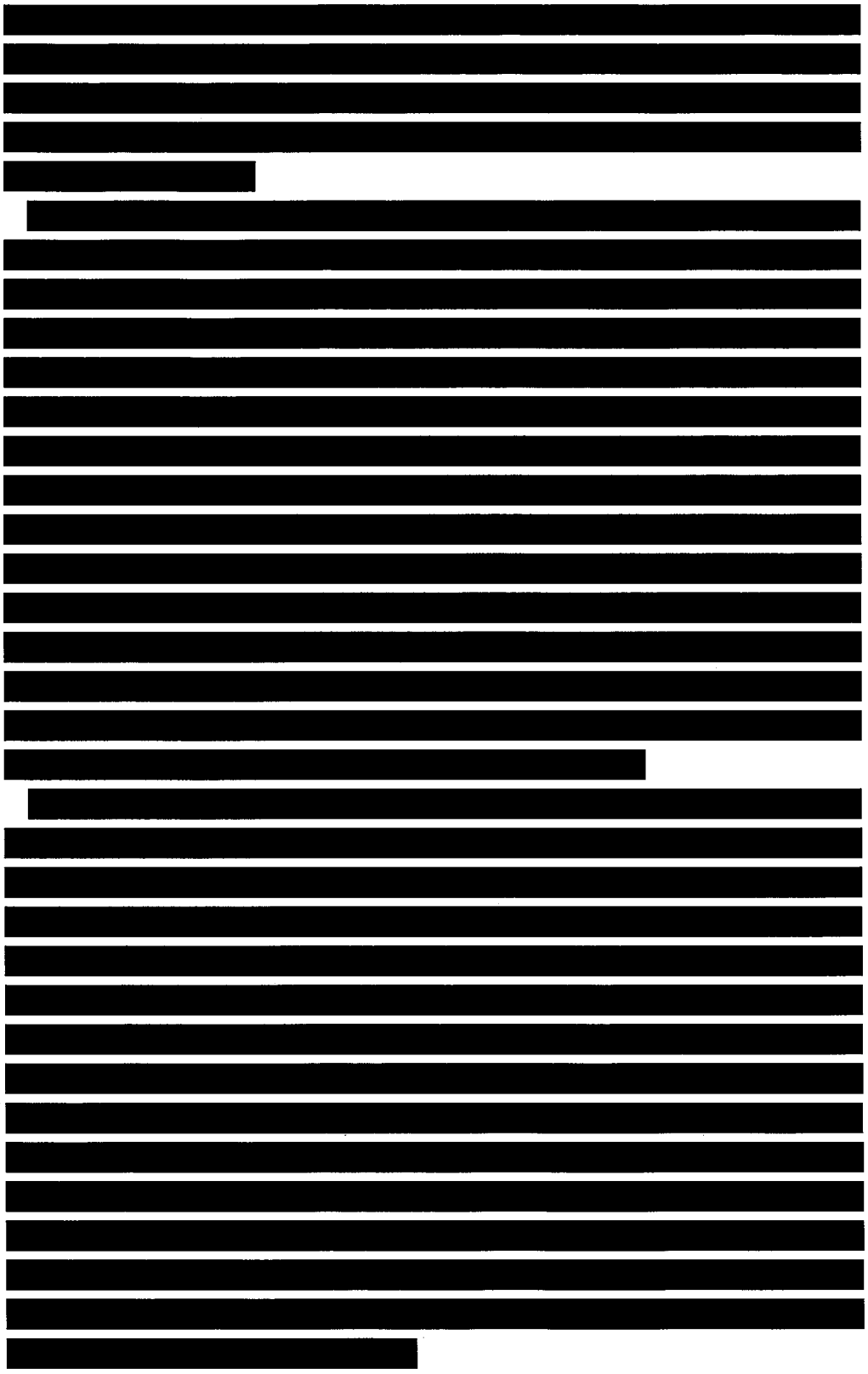


(4) Investigational plan

The current study will evaluate efficacy and safety of MT-6548 in patients with PD-CKD-related anaemia.

Based on results of clinical studies to date, the treatment period is set at 24 weeks, an appropriate period to enable evaluation of MT-6548 efficacy in terms of Hb improvement maintenance and switching maintenance.

MT-6548 dosage is set based on results to date at an initial dosage of 300 mg, with maintenance dosages of 150–600 mg.

2. Study objectives.

The purpose of the study is to evaluate efficacy and safety of MT-6548 in patients with PD-CKD-related anaemia.

3. Subjects

3.1 Subjects

Patients with PD-CKD-related anaemia

3.2 Inclusion criteria

Subjects must meet all inclusion criteria below and have capacity to grant informed consent. Laboratory tests to determine inclusion criteria will be performed at a central testing facility. If a given laboratory test is performed multiple times during the screening period, the most recent test will be used for determination.

(1) Patients at least 20 years of age as of the day of consent (either sex)

(2) Patients with CKD diagnosed according to the Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" as of the day of consent.

(3) Patients who have been receiving peritoneal dialysis for at least 4 weeks prior to the first day of the screening period, but excluding patients also receiving haemodialysis.

(4) Patients expected to initiate haemodialysis during the treatment period.

(5) Correction cohort: Patients who have not received ESA treatment 8 weeks prior to the first day of the screening period. However, patients receiving ESA treatment at consent may join the study if they discontinue this treatment after consent and have a washout period of at least 8 weeks.

Conversion cohort: Patients receiving the same formulation of ESA using the same administration route and the same dose interval (the dose interval should be the one described in the package insert for the ESA formulation) within 8 weeks prior to the first day of the screening period, using the dosages described below.

Dosage:

- ✓ Epoetin alfa (recombinant) and epoetin beta (recombinant): ≤12,000 IU every 2 weeks
- ✓ Darbepoetin alfa (recombinant): ≤120 μg every 2 weeks
- ✓ Epoetin beta pegol (recombinant): ≤250 μg every 4 weeks

(6) Patients with the following mean Hb values during screening, using the mean of the latest two tests:

- ✓ Correction group: ≥8.0 g/dL, <11.0 g/dL
- ✓ Conversion group: ≥9.0 g/dL, <12.5 g/dL

(7) Patients with a difference of <1.5 g/dL in Hb for the latest two tests in the screening period

(8) Patients with serum ferritin values of ≥100 ng/mL or transferrin saturation (TSAT) of ≥20% during the screening period.

(9) Patients with folic acid and vitamin B_{12} values above standard minimum values during the screening period.

Rationale

(1) Individuals are legally capable of granting consent as of 20 years of age. There is no particular basis for limiting participation to either sex.

(2) To ensure that subjects have the target disease of CKD.

(3) (4) Set because target patients are those receiving peritoneal dialysis with no concomitant haemodialysis

(5) The 8-week timespan was set in consideration of ESA's half-life and RBC life-span. ESA type, route of administration, and dose interval were restricted in order to control Hb value fluctuations. ESA dosage may be adjusted to maintain Hb levels as required, but only patients whose dosage does not exceed the normal maintenance dosage described in the package insert are eligible for the study.

(6) Set with reference to target Hb values in nephrogenic anaemia therapy according to JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015."

(7) Set to ensure appropriate efficacy evaluation by targeting patients without significant fluctuations in Hb levels.

(8) Set to ensure patients without iron insufficiency, using as reference criteria for initiating iron supplementation therapy according to the JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015."

(9) Set to ensure appropriate efficacy evaluation by targeting patients without insufficiencies in folic acid or vitamin B_{12}, required for hematopoiesis.

3.3 Exclusion criteria

Patients who meet any of the following exclusion criteria will be excluded. Laboratory tests to determine exclusion criteria will be performed at a central testing facility. If blood pressure measurements or a given laboratory test is performed multiple times during the screening period, the most recent test will be used for determination.

(1) Patients with anaemia resulting primarily from a disease other than CKD after date of consent (e.g., sickle-cell syndrome, myelodysplastic syndrome, myelofibrosis, haematopoietic malignancy, myeloma, haemolytic anaemia, thalassemia, or aplasia pure red cell)

(2) Patients with active haemorrhaging or exsanguination within 8 weeks prior to the first day of the screening period.

(3) Patients who have received RBC transfusion within 8 weeks prior to the first day of the screening period.

(4) Patients who have received testosterone enanthate or mepitiostane within 8 weeks prior to the first day of the screening period.

(5) Patients determined by investigators/subinvestigators to likely require immediate rescue therapy or drug holiday of the study drug after initiation of treatment period.

(6) Patients expected to no longer require peritoneal dialysis during the study period due to recovery of renal function.

(7) Patients with peritonitis within 4 weeks of the first day of the screening period.

(8) Patients with AST, ALT, or total bilirubin values of 2.5 times or greater the upper limit of standard during the screening period. This does not apply to patients with Gilbert's syndrome.

(9) Patients with uncontrolled hypertension (defined as systolic BP >180 mmHg or diastolic BP >110 mmHg) during the screening period or on the first day of the treatment period.

(10) Patients for whom any of the following apply upon fundoscopy during the screening period:

- ✓ No ocular fundus findings are possible.
- ✓ Active ocular fundus disease.

(11) Patients with severe cardiac failure from the day of consent (Class IV according according to severity classification of the New York Heart Association (NYHA))

(12) Patients with cerebrovascular disorders or acute coronary syndromes (hospitalization for unstable angina or myocardial infarction, etc.) within 12 weeks prior to the first day of the screening period. Patients who have been hospitalized due to acute coronary angioplasty or cardiac failure.

(13) Patients with malignant tumors or a history of such. However, this does not apply to patients with no relapse for 5 or more years (5 or more years with no relapse from last administration of chemotherapy if chemotherapy was used).

(14) Patients with incidence or relapse of deep vein thrombosis or pulmonary embolism within 12 weeks prior to the first day of the screening period.

(15) Patients with current or previous haemosiderosis or hemochromatosis.

(16) Patients with a history of or plans for organ transplant (not including being on a waiting list for renal transplant), haematopoietic stem cell transplant, or bone marrow transplant.

(17) Patients with an allergy to the study drugs.

(18) Patients who have participated in another clinical study and received study drugs within 12 weeks prior to informed consent, or within 5 times the half-life of the study drug (whichever is longer).

(19) Patients who have previously used MT-6548.

(20) Patients with known low tolerance to HIF-PH inhibitors.

(21) Patients who are unwilling to consent to use contraception from the beginning of the study period to 30 days following the final dose of the study drug for women who may become pregnant, or from the beginning of the study period to 90 days following the final dose of the study drug for men.

(22) Female patients who are or may be pregnant, or women who are nursing.

(23) Other patients judged by investigators/subinvestigators to be inappropriate as a subject in this study.

Rationale

(1)–(4) (6) (19) These were considered likely to affect drug efficacy evaluation of MT-6548.

(5)–(7) (17) (20) Set in regard for patient safety and ethics.

(18) Set in regard to ethical performance of study. Also, unevaluated drugs may affect efficacy or safety in unpredictable ways.

(21) (22) Reproductive and developmental toxicity safety has not been established in humans, and the possibility that the study drug may transfer to human sperm cannot be ruled out. Therefore, this was set for safety reasons.

(23) Set in order to allow determinations regarding study participation in regard for patient safety for reasons other than the general factors listed above.

3.4 Re-testing/re-screening

(1) Re-testing

Re-testing during the screening period may be performed at the discretion of investigators/subinvestigators for subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, or total bilirubin) or blood pressure.

Subjects with blood pressure measurements on the first day of the treatment period which meet exclusion criteria may be re-tested at the discretion of investigators/subinvestigators, and processed for treatment period initiation if they no longer meet exclusion criteria.

However, the maximum time from the first day of the screening period to the first day of the treatment period is 6 weeks.

(2) Re-screening

Re-screening may be performed at the discretion of investigators/subinvestigators if subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, or total bilirubin), blood pressure, or blood pressure on the first day of the treatment period, may have become eligible for the study due to natural course or drug treatment.

However, re-screening may only be performed once for any given subject.

4. Explanations to subjects and consent

4.1 Informed consent forms and written information

Study investigators will draft informed consent forms and written information for patients. These will be either a single form, or a set of forms, and will be revised as required.

Authored or revised consent forms will be submitted to study sponsor and approved by the Institutional Review Board (IRB) prior to study initiation.

4.2 Content of written information

Written information for subjects must contain at least the following items:

(1) The study is for research purposes.

(2) Study objectives.

(3) Names, titles, and addresses of investigators and subinvestigators.

(4) Study methodology (trial aspects and subject inclusion criteria).

(5) Expected clinical benefits, risks, and inconveniences (subjects must also be informed if there are no expected benefits for them).

(6) If enrolling a patient into the trial, explanation of other therapeutic options for the patient and expected risks/rewards associated with these.

(7) Expected period of study participation for the subject.

(8) Participation in the study is purely voluntary, and the subject or his/her agent may rescind agreement to participate at any time. If the subject determines not to participate in the study or withdraws consent, he/she will not be disadvantaged in anyway, and will not forego any benefits from not participating.

(9) Study monitors, auditors, IRB members, and regulatory authorities may view source documents from the study. In this event, subject confidentiality will be preserved. The subject or his/her agent consents to this viewing of source documents by signing (or printing name and affixing personal seal) the consent form.

(10) Subject confidentiality will be preserved even if study results are published.

(11) Contact information for consultations with the study center for when subjects wish to learn more information about the study or their rights, or for when study-related damage to health occurs.

(12) Financial reimbursements or treatments available to subjects in the event of damage to health resulting from the study.

(13) Types of IRBs that will investigate and determine issues related to appropriate performance of the study, types of issues which fall under IRB purview, and other study-related issues concerning the IRB.

(14) Planned number of subjects in the study.

(15) If any information comes to light which may affect the willingness of the subject or his/her agent to continue study participation, that information will be rapidly shared with the subject or his/her agent.

(16) Conditions and reasons leading to study withdrawal.

(17) Details of any costs to be borne by the subject, if applicable.

(18) Details of any money to be paid to the subject, if applicable (agreements for determining amounts, etc.)

(19) Behaviors or rules to be followed by the subject.

(20) Other necessary items or information related to the study.

4.3 Method of obtaining consent

(1) Prior to initiating study, the investigator/subinvestigator will hand the informed consent forms and written information approved by the IRB to each patient in person, and conduct a full explanation. Clinical coordinators may also perform supplementary explanations. Explanations will be based on written information for the study and use as simple language as possible to ensure patient understanding. All patient questions will be answered fully. After confirming that the patient understands fully, he/she may freely grant informed consent for participation in the study in writing.

(2) The informed consent form will be signed (or names printed and personal seals affixed) and dated by both the patient and the investigator/subinvestigator who performed the explanation. If clinical coordinators performed supplementary explanations, he/she will also sign (or print name and affix personal seal) and date the form.

(3) If the patient is incapable of reading the written information, the investigator/subinvestigator will arrange for a fair witness to be present when performing the explanation and obtaining consent. In this case, the witness will also sign (or print name and affix personal seal) and date the consent form.

(4) Before each subject begins participation in the study, the investigator/subinvestigator will issue hand him or her a signed (or names printed and personal seals affixed) and dated copy of the informed consent forms and written information. Originals of the consent forms will be stored at each study center in accordance with that center's regulations.

(5) The date of informed consent will be recorded on each CRF.

4.4 Revision of informed consent forms and written information

(1) If new significant information is obtained which may impact a subject's consent, investigators/subinvestigators will verbally convey this information to each subject participating in the study in a timely manner, confirm whether the subject wishes to continue participation, and record these actions in the medical records.

(2) In this event, investigators will determine in a timely manner whether this new information requires revision of informed consent forms and written information.

(3) If it is determined that informed consent forms and written information must be revised, investigators must make said revisions in a timely manner and obtain approval from the IRB.

(4) The investigator/subinvestigator must explain relevant information to subjects already participating in the study using revised informed consent forms and written information newly approved by the IRB, and obtain freely-given consent in writing.

(5) As with the initial informed consent, the revised informed consent form will be signed (or names printed and personal seals affixed) and dated by both the subject and the investigator/subinvestigator who performed the explanation. If clinical coordinators performed supplementary explanations, he/she will also sign (or print name and affix personal seal) and date the form.

(6) As with the initial informed consent, if the subject is incapable of reading the written information, the investigator/subinvestigator will arrange for a fair witness to be present when performing the explanation and obtaining consent. In this case, the witness will also sign (or print name and affix personal seal) and date the consent form.

(7) Investigators/subinvestigators will give subjects a signed (or names printed and personal seals affixed) and dated copy of the informed consent forms and written information. Originals of the consent forms will be stored at each study center in accordance with that center's regulations.

5. Study design

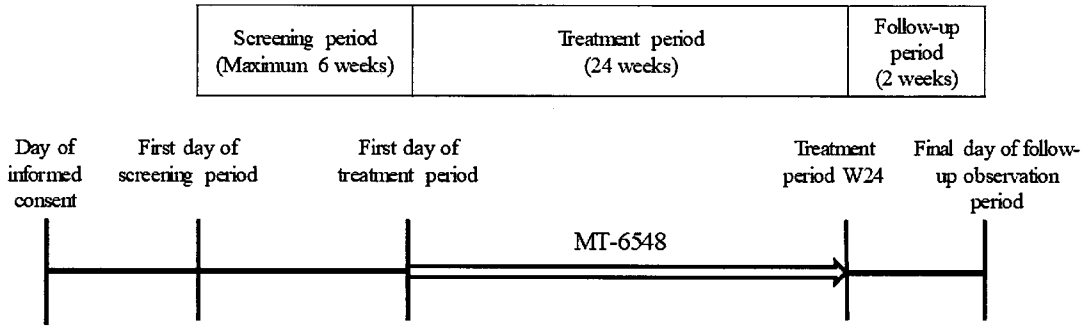
5.1 Study phase and type

Study phase: Phase 3

Study type: Confirmatory study

5.2 Study design

Multicenter, uncontrolled open-label study



(1) Screening period

The screening period begins on the first day of the screening period, and ends upon completion of tests required on the first day of the treatment period. Maximum screening period time is 6 weeks. Two visits will be made during the screening period; the first (SV1) is the first day of the screening period. The second screening period visit (SV2) occurs after results from laboratory tests performed on the first day of the screening period have been obtained. Re-testing will be performed as necessary.

(2) Treatment period

The treatment period will last from completion of scheduled tests on the first day of the treatment period to completion of blood sampling for haematology tests on the final day of the treatment period (Week 24 of the treatment period or discontinuation of treatment).

Treatment period study visits will be made every 2 weeks up until Week 12, and every 4 weeks thereafter for scheduled tests. However, study visits may be more frequent if variation in Hb levels causes concern for excessive increase or decrease in Hb, or for other reasons.

(3) Follow-up observation period

The follow-up observation period consists of 2 weeks from completion of blood sampling for haematology tests on the final day of the treatment period. The final day of the follow-up

observation period is 2 weeks from the completion of blood sampling for haematology tests on the final day of the treatment period, regardless of whether a study visit is made on that day.

Subjects should make study visits as close to the same time as possible during the study period for scheduled tests.

Rationale

Screening period: Established to confirm subject suitability for the study.

Treatment period: There are very few PD-CKD patients in Japan, so an uncontrolled study was considered more pragmatic.

Follow-up observation period: A 2-week follow-up observation period was established considering MT-6548's elimination half-life in order to study AEs occurring after completion of administration.

5.3 Endpoints

5.3.1 Efficacy endpoint

(1) Primary endpoints

1) Mean Hb at treatment period Weeks 20 and 24
2) Hb at each treatment period timepoint
3) Ratios of subjects with mean Hb within the target range (11.0–13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each timepoint in treatment period
4) Correction cohort only: Days from initiation of treatment period required to reach target Hb range (11.0–13.0 g/dL)
5) Correction cohort only: Rate of increase of Hb levels

(2) Other endpoints

1) Correction cohort only: Change from baseline in mean Hb of Weeks 20 and 24 of treatment period.
2) Correction cohort only: Ratio of subjects with an increase of ≥1.0 g/dL of mean Hb from baseline at each timepoint in treatment period.
3) Ratio of subjects who received ESA rescue therapy
4) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.
5) Study drug dosage
6) total number of dosage adjustments
7) Quantity of iron administered
8) Ratio of subjects who received IV iron
9) Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20%.

10) Change from baseline of iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin.
11) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and EPO.
12) QOL measures (EQ-5D-5L, KDQOL)

Rationale

(1) Primary endpoint

These were set as primary efficacy endpoints in order to comprehensively evaluate effects on Hb, which is already established as the standard assessment measure for nephrogenic anaemia treatment.

(2) Other endpoints

Other endpoints were set in order to enable multifaceted evaluation of changes in iron-related measures, RBC-related parameters, QOL measures, and concomitant therapies.

5.3.2 Safety endpoints

(1) Adverse events and adverse drug reactions
(2) Laboratory test values
(3) Resting standard 12-lead ECG
(4) Body weight (excluding dialysis solution)
(5) Vital signs
(6) Fundoscopy
(7) Chest X-ray
(8) Ratio of subjects with Hb levels of ≥13.0 g/dL or ≥14.0 g/dL.
(9) Ratio of subjects with Hb increase rates exceeding 0.5 g/dL/week.

Rationale

(1)–(5) (7) Set to evaluate general safety for nephrogenic anaemia patients.
(6) Set to evaluate effects of MT-6548 on fundus oculi.
(8) (9) Set to evaluate excessive or acute increase of Hb levels.

6. Target sample size and study period

6.1 Target sample size

Forty subjects enrolled in treatment period.

Rationale

Assuming a SD of 1.78 for mean Hb, which is one of the efficacy endpoints for the study, a sample size of 40 subjects allows for value estimation with a precision of mean ± 0.57 g/dL (95% CI). The SD of 1.78 was calculated from the upper limit of the 80% CI in the MT-6548 300 mg group at the end of the primary efficacy evaluation period of 6 weeks in study CI-0021, a dose-finding study in Japanese patients with NDD-CKD-related anaemia. According to JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015," Hb values vary in a range of about 1 g/dL in normal clinical contexts, so a level of precision of mean Hb ± 0.57 g/dL (95% CI) should allow for a clinically meaningful analysis. A sample size of 40 subjects should also enable analysis of safety.

6.2 Study period

7. Study drug

7.1 Study drug names

(1) Investigational product

Name: MT-6548 Tablet 150 mg

Nonproprietary name: vadadustat

Dosage form and content: Each film-coated tablet contains 150 mg vadadustat.

7.2 Study drug packaging and labelling

(1) Packaging

Each bottle contains 100 tablets of MT-6548.

(2) Labelling

Clinical Study Drugs MT-6548 Tablet 150 mg 100 tablets
Study no.: MT-6548-J02 Lot no.: XXXXX
Storage method: Please store at 1–30°C.
Dosage and administration: Please follow your doctor's instructions.
*Please return empty bottles and unused study drug.
*Those not participating in the MT-6548 study must not take the study drugs.
Mitsubishi Tanabe Pharma Corporation. 3-2-10 Dosho-machi, Chuo-ku, Osaka

7.3 Storage method

Store between 1–30°C.

7.4 Study drug handling, storage, and management methods

The study sponsor will supply study drugs to each study center after conclusion of the study agreement. Study drug managers will follow the Procedures for Management of Study Drug provided by the study sponsor in storage and management of the study drugs, then return all unused study drugs to the monitor.

Investigators/subinvestigators and study drug managers will notify the study sponsor immediately if any abnormalities in study drug quality are discovered. Any such study drug will be returned to the study sponsor as necessary in accordance with the Procedures for Management of Study Drug.

Study drugs must not be used for any other purpose than those described in this protocol (other clinical studies, animal experiments, basic research experiments, etc.).

8. Subject-related test methods

8.1 Lists of screened subjects, enrolled subjects, and identification codes

The investigator will prepare a list of all patients who received an explanation of the study. All subjects on this list who have granted consent will be assigned an identification code, and a subject identification code list prepared. Key information for comparisons with source documents will be included.

The investigator will also prepare a list of enrolled subjects (including those who withdrew or dropped out), including sex, date of consent, subject identification code, and other information.

8.2 Subject enrollment

8.2.1 Consent processing and enrollment

(1) Investigators/subinvestigators will determine which patients are eligible for participation in the study, and obtain written consent as described in "4. Explanations to Subjects and Consent."
(2) Investigators/subinvestigators will contact the study sponsor by fax.
(3) Subjects planned for the correction cohort who are using ESA formulations will discontinue ESA use and undergo a wash-out period of at least 8 weeks.

8.2.2 Screening period

(1) Investigators/subinvestigators will confirm subject suitability on the first day of the screening period, make a determination regarding screening period enrollment, and notify the study sponsor by fax.
* Contact by fax is not required for re-screening.

8.2.3 Treatment period enrollment

(1) Investigators/subinvestigators will review all laboratory tests and other tests performed up to the first day of the treatment period, and make a suitability determination prior to initiating the treatment period.
(2) Investigators/subinvestigators will contact the study sponsor by fax on the first day of the treatment period.
(3) Investigators/subinvestigators will take the following actions toward the subject depending on their final determination regarding suitability for the study.
✓ Subject is suitable for initiation of treatment period: Transition subject to the treatment

period.

✓ Subject is not suitable for initiation of treatment period: Explain to the subject that they did not meet inclusion criteria, and withdraw the subject from the study.

8.2.4 Withdrawal processing

(1) Investigators/subinvestigators will contact the study sponsor by fax regarding any subjects who withdraw from the study after granting informed consent.

8.3 Dosage and administration

(1) Initial dosage levels

1) Initial dosage for correction cohort

Single daily dose of 300 mg (2 tablets)

2) Initial dosage for conversion cohort

Single daily dose of 300 mg (2 tablets)

(2) Maintenance dosage and dosage adjustments

Maintenance dosage is 150 to 600 mg once daily and adjusted according to the dosage adjustment guideline below.

MT-6548 Tablet dosage adjustment guidelines

Investigators/subinvestigators will monitor Hb levels throughout the treatment period, and determine whether to adjust study drug dosage or discontinue administration as required. In principle dosage adjustments are to be performed at scheduled study visits, but they may also be performed at unscheduled visits if considered necessary, for example if Hb level variation gives concern for excessive increases or decreases.

Hb levels will be measured on scheduled study visit with the HemoCue® Hb201 DM analyzer; in principle these measurements will be used for determinations regarding dosage adjustments. Hb measurements used for dosage adjustment determinations will be recorded in the subject's case report form (CRF). Measurement results from the HemoCue® Hb201 DM will be used solely for determination of study drug dosage adjustments, and will not be used for efficacy or safety analysis.

The dosage adjustment algorithm below will be followed in order to maintain Hb levels of 11.0–13.0 g/dL during the study. Dosage adjustment steps are defined in the chart below.

MT-6548 Tablet dosage adjustment chart

Step	No. of tablets	Dosage
1	1	150 mg
2	2	300 mg
3	3	450 mg
4	4	600 mg

*It is permitted for dosage adjustments not to comply with the dosage adjustment algorithm for safety reasons depending on factors such as clinical status (e.g., AEs, volume depletion, or volume overload), Hb elevation rate, decrease rate, or fluctuations. In such cases, clinical status will be recorded in CRFs. All dosage increases of MT-6548 will be in increments of 1 tablet at a time.

If a dosage increase or reduction according to the dosage adjustment algorithm is impossible because the maximum or minimum dosage on the dosage adjustment chart is already being administered, it is permitted to not alter the dosage at that point. However, in this case it will be confirmed whether withdrawal criteria are met, and treatment discontinued if so.

Dosage adjustment algorithm for MT-6548 Tablet

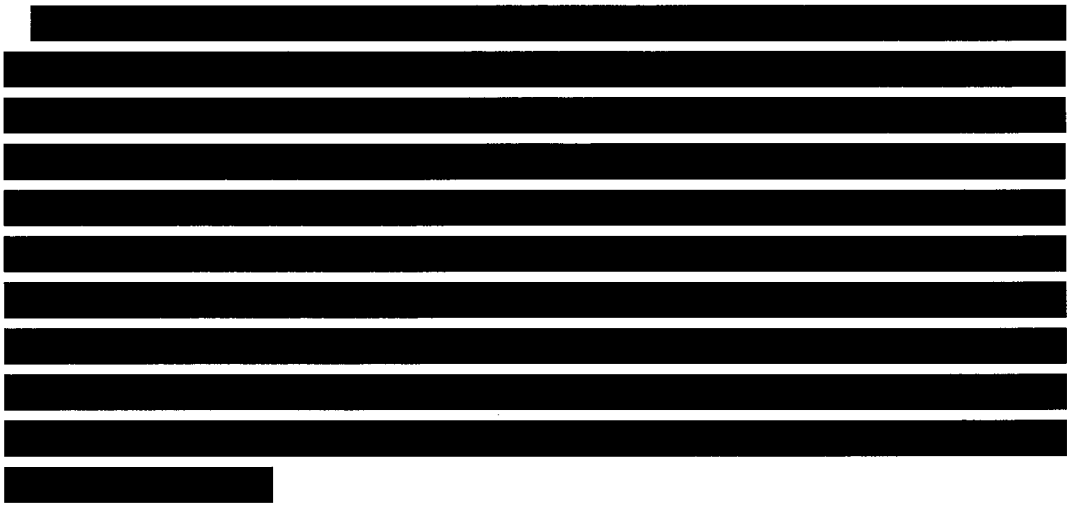
- ✓ Dosage increases are in principle separated by at least 4 weeks. There are no set intervals for dosage decreases, but frequent dosage adjustments are to be avoided.
- ✓ Decrease MT-6548 dosage by 1 tablet if Hb levels suddenly increase (more than 2.0 g/dL change in past 4 weeks*).
- ✓ Increase MT-6548 dosage by 1 tablet if Hb levels are <11.0 g/dL. However, decrease by 1 tablet instead of increasing in cases of sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*).
- ✓ Decrease MT-6548 dosage by 1 tablet if Hb is >12.5 g/dL.
- ✓ If Hb is >13.0 g/dL and ≤13.5 g/dL, and there has been a sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*), discontinue MT-6548 administration and resume at 1 tablet reduced dosage after Hb falls to ≤13.0 g/dL.
- ✓ If Hb is >13.5 g/dL, discontinue MT-6548 administration and resume at 1 tablet reduced dosage after Hb falls to ≤13.0 g/dL.

*Calculate Hb change rate using the Hb measurement closest to 4 weeks prior to the day of dosage adjustment (in the range of 3 to 5 weeks). A rate of change greater than 0.5 g/dL/week constitutes "sudden increase." If Hb was not measured 3 to 5 weeks prior to the day of dosage adjustment, use the measurement made immediately prior to 5 weeks before the day of dosage adjustment.

(3) Administration method

The study drug is taken once-daily orally. The drug does not need to be taken with meals, but timing should be as consistent as possible throughout the treatment period, both in relation to meals and time of day. The first dose will be taken after required tests are finished on the first day of the treatment period.

Rationale



The dosage adjustment algorithm was set in order to avoid excessive Hb increase with reference to target Hb values in nephrogenic anaemia therapy according to JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015."

8.4 Treatment period

From the first day of the treatment period to the day prior to Week 24 of the treatment period.

8.5 Concomitant medications and therapies

8.5.1 Prohibited concomitant medications and therapies

(1) ESA therapies

Concomitant use of epoetin alfa (recombinant), epoetin beta (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant) is prohibited for the period described below. These restrictions do not apply to rescue therapy.

- ✓ Correction cohort: Concomitant use is prohibited from 8 weeks prior to the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period.
- ✓ Conversion cohort: Concomitant use is prohibited from the first day of the treatment

period to completion of blood sampling for haematology tests on the final day of the treatment period.

(2) Testosterone enanthate and mepitiostane

Concomitant use is prohibited from 8 weeks prior to the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period.

(3) Blood transfusion

Prohibited from 8 weeks prior to the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period. These restrictions do not apply to rescue therapy.

Rationale

(1) – (3) Medications and therapies considered likely to affect evaluation of MT-6548 efficacy are prohibited for concomitant use.

8.5.2 Restricted drugs

(1) Iron supplements

From the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period, administer iron supplements to maintain serum ferritin values of ≥100 ng/mL or TSAT of ≥20%. Iron supplements may be omitted for subjects who respond poorly to them, such as those with an allergy or those with adverse drug reaction (ADRs) to iron (vomiting, etc.).

Investigators/subinvestigators will determine iron supplement dosage and administration route.

Important: Oral iron supplements may impair MT-6548 bioavailability, so oral iron supplements must not be taken at the same time as MT-6548 Tablet. Subjects taking oral iron supplements will be instructed not to take any within 2 hours before or after taking MT.6548 Tablet.

(2) Iron-containing phosphate binders (ferric citrate hydrate, sucroferric oxyhydroxide)

New use of iron-containing phosphate binders is fundamentally prohibited from the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period. If iron-containing phosphate binders are used by a subject on the first day of the screening period, then the same dosage of the same type should fundamentally be

continued from the first day of the screening period to completion of blood sampling for haematology tests on the final day of the treatment period. If investigators/subinvestigators determine that a dosage increase is required for iron-containing phosphate binders, then additional treatment will be performed with hyperphosphatemia drugs containing no iron, or treatment switched to hyperphosphatemia drugs containing no iron. Dosage of iron-containing phosphate binders may also be reduced if determined necessary according to the subject's condition. For subjects in the correction cohort, there must be no switching to other hyperphosphatemia drugs containing no iron from the first day of the screening period to completion of scheduled tests at Week 4 of the treatment period.

Important: As with oral iron supplements, iron-containing phosphate binders may impair MT-6548 bioavailability, so iron-containing phosphate binders must not be taken at the same time as MT-6548 Tablet. Subjects taking iron-containing phosphate binders will be instructed not to take any within 2 hours before or after taking MT-6548 Tablet.

Rationale

(1) Set with reference to criteria for initiating iron supplementation therapy in JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015."

(2) Continuation of therapy without changing dosage will avoid affecting evaluation of MT-6548 efficacy.

8.5.3 Rescue therapy

The following rescue therapy options will be available for subject safety. If rescue therapies are performed, the subject may continue in the study unless investigators/subinvestigators determine study withdrawal is appropriate. Details of any rescue therapy implemented will be recorded in the subject's CRF.

(1) ESA formulations

If a subject has received maximum dosages of MT-6548 for ≥2 weeks and meets all criteria below, investigators/subinvestigators may administer ESA as rescue therapy to improve Hb levels if necessary in order to secure subject safety. ESA rescue therapy may also be administered without meeting the criteria below if deemed necessary by investigators/subinvestigators in order to secure subject safety, such as in cases of acute decreases in Hb. MT-6548 administration will be discontinued if implementing ESA rescue therapy. Study drug treatment may resume if Hb levels improve, as long as there is no concomitant use with ESA. Subjects who are not expected to resume study drug treatment will

be withdrawn from the study.

- ✓ Anaemia or anaemia symptoms (e.g., fatigue, weakness, shortness of breath, chest pain, confusion, dizziness) become aggravated compared to the first day of the treatment period to the point they are clinically problematic.
- ✓ Hb levels drop to <8.0 g/dL.

(2) RBC transfusion

Normally RBC transfusions are performed when clinically necessary in instances of acute or major haemorrhaging. RBC transfusion may be performed at investigator/subinvestigator discretion if deemed clinically necessary in cases of potentially worsening anaemia, even if that anaemia is not severe, or in cases of moderate to severe anaemia symptoms.

(3) Phlebotomy

Phlebotomy may be performed at investigator/subinvestigator discretion in cases of hyperviscosity syndrome, if the rate of Hb increase is concerning to investigators/subinvestigators, or if Hb levels are high enough to warrant concern to investigators/subinvestigators.

Rationale

Set out of consideration for subject safety.

8.5.4 Recording of concomitant drugs and therapies

The following information will be recorded regarding all concomitant drugs and therapies performed from the first day of the treatment period to the date of completion of the follow-up observation period in the subject's CRF. Information for the screening period will also be recorded in CRFs regarding drugs described in "8.5.2 Restricted drugs." Peritoneal dialysis and drugs such as dialysis solutions normally used in peritoneal dialysis, as well as physiological saline used for dissolving injectable formulations, will not be recorded.

(1) Concomitant drugs: Drug name, daily dosage, administration route, duration of administration, purpose

(2) Concomitant therapies: Name/details of therapy, duration of treatment, purpose

8.6 Subject oversight

Investigators/subinvestigators, clinical coordinators, or study drug managers will oversee subjects with attention to the following points. Investigators/subinvestigators or clinical coordinators will

question subjects about their adherence to the items below.

8.6.1 Drug use guidance for MT-6548 Tablets

Investigators/subinvestigators or study drug managers will give guidance to subjects covering the following items.

(1) MT-6548 will be issued to subjects in bottles containing 100 tablets. If multiple bottles are issued at a time, subjects will open new bottles only after finishing the MT-6548 from the existing bottle. Subjects will bring all bottles of MT-6548 to each study visit for study drug control purposes, including unused bottles, bottles being used, and empty bottles.

(2) MT-6548 tablets are to be taken with water once-daily, without chewing. The drug does not need to be taken with meals, but timing should be as consistent as possible. Timing of drug doses should be kept as consistent as possible throughout the treatment period. If a subject forgets to take the study drug on a given day, they should resume taking the study drug as normal on the next day.

(3) Oral iron supplements and iron-containing phosphate binders may impair MT-6548 bioavailability, so these must not be taken at the same time as MT-6548 Tablet. Subjects taking oral iron supplements or iron-containing phosphate binders will not take any within 2 hours before or after taking MT-6548 Tablet.

8.6.2 Visits

Subjects should make study visits as close to the same time as possible during the study period for scheduled tests.

8.6.3 Lifestyle guidance

Investigators/subinvestigators or clinical coordinators will give guidance to subjects covering the following points.

(1) Subjects receive examinations and tests on scheduled days. Subjects should always contact the study center if unable to make a scheduled study visit, and follow instructions.

(2) Subjects should contact investigators/subinvestigators in a timely manner if they experience abnormal symptoms.

(3) Subjects will receive a study participation card to show when receiving care at other departments or hospitals. Subjects should always inform investigators/subinvestigators or clinical coordinators if they are using any drugs prescribed by other doctors or purchased at a pharmacy. Subjects should always consult with investigators/subinvestigators or clinical coordinators before using any new drugs during the study.

(4) Maintain the same lifestyle (daily activities, food, etc.) as before to the extent possible.

(5) Investigators/subinvestigators or clinical coordinators will instruct women who may become pregnant to use the contraception methods described below during the study period and up to 30 days following the final dose of the study drug, and men during the study period and up to 90 days following the final dose of the study drug. Calendar, anovulation, ovulation detection through body temperature, post-ovulation, and withdrawal do not constitute appropriate forms of contraception. This does not apply to postmenopausal women with absence of menstruation for more than 1 year, women with surgical hysterectomy, or women with bilateral ovariectomy.

1) Abstain from intercourse

2) Use two effective types of contraception. Joint use of a barrier method (latex condoms for men or diaphragm) in conjunction with a highly effective method such as oral contraceptives, IUD, tubal ligation, or vasectomy is recommended.

9. Tests and observations

9.1 Test and observation schedule

VISIT / Item	Informed consent	Screening period [a]		Treatment period										Final day of follow-up observation period [b]
		First day	Visit 2	First day [c]	W2	W4	W6	W8	W10	W12	W16	W20	W24	Day of discontinuation
Visit no.	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	FU
Permitted range (day)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	+ 7 or + 14 [d]	+7
Procedure/evaluation															
Informed consent	X														
Inclusion/exclusion criteria	X	X	X	X											
Patient's background and history	X			X											
Height				X											
Body weight (weight excluding dialysis solution)				X						X			X	X	
Folic acid and vitamin B_{12}		X													
Pregnancy test [e]		X											X	X	
Haematology test		X	X [f]	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry test		X		X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein		X		X									X	X	
Iron-related measures		X		X	X	X	X	X	X	X	X	X	X	X	
Hepcidin				X	X	X	X			X			X	X	
Erythropoietin				X	X	X	X			X			X	X	
VEGF				X						X			X	X	
Urinalysis (qualitative)		X		X	X	X	X	X	X	X	X	X	X	X	
Vital signs [g]		X		X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [h]				X									X	X	
Fundoscopy [d]		X										X		X	
Chest X-ray [d]		X										X		X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X	X	
AE investigations				X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for genetic analysis [i]					Blood sampling should be performed once as early as possible after 2 weeks of										
Drug evaluation/procedure															
Investigation of concomitant drugs				X	X	X	X	X	X	X	X	X	X	X	X
Prescribing MT-6548 tablets [j]				Administration according to the dosage adjustment guideline											
Administration of iron supplements		Administer iron supplements to maintain serum ferritin values ≥100 ng/mL or TSAT ≥20%.													

[a] Maximum screening period length is 6 weeks. Test results will be reviewed prior to transitioning from the first day of the screening period to screening period Visit 2, and from screening period Visit 2 to the first day of the treatment period. Re-testing will be performed as necessary.

[b] Not required if withdrawing prior to treatment period.

[c] Perform prior to study drug treatment (AE investigations begin after study drug treatment)

[d] Fundoscopy and chest X-ray performed once during screening period. Also performed once between treatment period Weeks 20 and 24, and to extent possible within 14 days of study withdrawal.

[e] Only female subjects who may become pregnant.

[f] Hb only measured.

[g] Measured to extent possible prior to blood sampling. Measured with subject sitting after 5 minutes of rest.

[h] Measured to extent possible prior to blood sampling. Measured with subject in supine position after 5 minutes of rest.

[i] Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period in subjects who have granted consent.

[j] Prescribe MT-6548 Tablet depending on quantity of subject's remaining study drug. Subjects are instructed to open new bottles of study drug only after completing previous bottle.

If tests and observations cannot be performed on the scheduled day, they may be performed within the permitted ranges shown below.

Table 9.1-1 Permitted ranges for study center visits

Evaluation timepoint		Reference date	Permitted range
Screening period[*1]	Initiation date	–	–
	Visit 2	–	–
Treatment period	First day[*2]	Day 0	–
	Week 2	Day 14	Day 11–17
	Week 4	Day 28	Day 25–31
	Week 6	Day 42	Day 39–45
	Week 8	Day 56	Day 53–59
	Week 10	Day 70	Day 67–73
	Week 12	Day 84	Day 81–87
	Week 16	Day 112	Day 105–119
	Week 20	Day 140	Day 133–147
	Week 24	Day 168	Day 161–175
Day of discontinuation of treatment		Day of discontinuation	Within 7 days of discontinuation[*3]
Follow-up observation period	Day of completion	Week 24 of treatment period (or day of discontinuation of treatment period)	14–21 days

*1: Maximum screening period length is 6 weeks. Re-testing may be performed as necessary.

*2: The first day of the treatment period is the day that investigators/subinvestigators determine the subject is eligible to begin treatment.

*3: Fundoscopy and chest X-ray to be performed to extent possible within 14 days of study withdrawal.

9.2 Test and observation timepoints

9.2.1 Subject background

The following subject background factors will be determined and recorded in the CRF.

(1) Sex
(2) Date of birth (western calendar)
(3) Height
(4) Body weight (excluding dialysis solution)
(5) Race
(6) Ethnicity
(7) Smoking status
(8) Underlying cause of CKD
(9) Time of onset of nephrogenic anaemia
(10) Concomitant illnesses (illnesses present on the first day of the treatment period)
(11) Time of initiation of peritoneal dialysis
(12) Peritoneal dialysis conditions
(13) Correction group or conversion group
(14) Yes/no for wash-out period for ESA (correction cohort only)
(15) Details of washed-out ESA formulation (type, administration route, dose interval, dosage, and final day) (correction cohort only)
(16) Details of previous ESA formulation (type, administration route, dose interval, dosage, and final day) (conversion cohort only)

9.2.2 Treatment status

During the treatment period, investigators/subinvestigators or clinical coordinators will ask subjects about the following information, to be recorded in CRFs.

1) MT-6548 dosage (details and reasons for change if there was a change of dosage or drug holiday)
2) First day of MT-6548 treatment and final day of MT-6548 treatment
3) MT-6548 treatment compliance status
4) Timing of MT-6548 doses (pre-prandial: within 30 minutes prior to eating; post-prandial: within 30 minutes of eating (including eating); other)
5) MT-6548 dose date and time*

* Date and time of dose immediately prior to blood sampling for EPO measurement at treatment period Weeks 2, 4, 6, 12, 24, and day of discontinuation.

9.2.3 Efficacy endpoints

Blood sampling will be performed at each study center for measurement by the contract laboratory testing facility. All measurement results will be reported to each study center and the study sponsor.

(1) Hb value

Blood sampling and Hb measurement will be performed on the first day of the screening period, screening period Visit 2, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

(2) Ratio of subjects who received ESA rescue therapy

If ESA rescue therapy is performed, type of ESA formulation used, administration route, dose interval, and dosage will be recorded in the CRF.

(3) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.

If RBC transfusion rescue therapy is performed, type of RBC formulation used and dosage will be recorded in the CRF.

(4) Study drug dosage

Study drug dosage will be recorded in CRFs.

(5) total number of dosage adjustments

Yes/no for MT-6548 dosage adjustments and post-adjustment dosage will be recorded in the CRF.

(6) Quantity of iron administered

Iron dosage will be recorded in CRFs.

(7) Ratio of subjects who received IV iron

Iron administration route will be recorded in CRFs.

(8) Iron-related measures (serum iron, TIBC, TSAT, and serum ferritin)

Blood sampling and measurement will be performed for serum iron, TIBC, TSAT, and serum ferritin on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

(9) Hepcidin

Blood sampling and measurement of hepcidin will be performed on the first day of the treatment period, treatment period Weeks 2, 4, 6, 12, and 24, and the day of discontinuation of treatment.

(10) Haematocrit, RBC count

Blood sampling and measurement will be performed for haematocrit and RBC count on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

(11) Reticulocytes (counts and fractions)

Blood sampling and measurement will be performed for reticulocytes (counts and fractions) on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

(12) EPO

Blood sampling and measurement of EPO will be performed on the first day of the treatment period, treatment period Weeks 2, 4, 6, 12, and 24, and the day of discontinuation of treatment. Blood sampling time will be recorded in CRFs.

(13) QOL measures (EQ-5D-5L, KDQOL)

Subjects will fill out EQ-5D-5L and KDQOL questionnaires (Appendices 4 and 5) on the first day of the treatment period, treatment period Weeks 12 and 24, and the day of discontinuation of treatment, and results recorded in CRFs.

9.2.4 Safety endpoints

9.2.4.1 Objective findings

(1) Laboratory tests

The following laboratory parameters will be measured at a contract testing laboratory following blood and urine collection at the study center. All measurement results will be reported to each study center and the study sponsor. Study centers will store test reports issued by the contract testing laboratory. Investigators/subinvestigators will record day of confirmation and confirmation results (clinical significance) for the following tests.

1) Haematology tests:

Blood sampling and measurement will be performed for the following parameters on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

Mean corpuscular volume, mean cell haemoglobin, mean cell haemoglobin concentration, red cell distribution width, WBC count, WBC fraction (neutrophils, eosinophils, monocytes, lymphocytes, basophils), platelet count

2) Blood biochemistry tests:

Blood sampling and measurement will be performed for the following parameters on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

Total protein, albumin, blood glucose, urea nitrogen, creatinine, uric acid, CPK, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, Na, K, Cl, Ca, P, Mg, bicarbonate, total cholesterol, LDL-C, HDL-C, triglycerides

3) C-reactive protein:

Blood sampling and measurement of C-reactive protein will be performed on the first day of the screening period, the first day of the treatment period, treatment period Week 24, and the day of discontinuation of treatment.

4) Folic acid and vitamin B_{12}:

Blood sampling and measurement of folic acid and vitamin B_{12} will be performed on the first day of the screening period.

5) Vascular endothelial growth factor (VEGF):

Blood sampling and measurement of VEGF will be performed on the first day of the screening period, treatment period Weeks 12 and 24, and the day of discontinuation of treatment.

6) Urinalysis (qualitative):

Urine sampling and measurement will be performed for the following parameters on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 of the treatment period, and the day of discontinuation of treatment.

Glucose, protein, urobilinogen, occult blood

(2) Resting standard 12-lead ECG

Resting standard 12-lead ECG will be measured in the supine position during hospital visits on the first day of the treatment period, treatment period Week 24, and the day of discontinuation of treatment. ECG diagnosis consists of a comprehensive evaluation including arrhythmia and wave-form diagnoses.

Determinations are made according to the 3-point scale below and recorded on CRFs. Measurements will be made before blood sampling when possible, and after 5 minutes at rest.

1) Normal
2) Clinically non-problematic abnormality
3) Clinically problematic abnormality

(3) Body weight (excluding dialysis solution)

Body weight will be measured during study visits on the first day of the treatment period, treatment period Weeks 12 and 24, and the day of discontinuation of treatment. Measurements are recorded in CRFs.

(4) Vital signs

Sitting blood pressure and pulse rate will be measured during study visits on the first day of the treatment period, treatment period Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24, and the day of discontinuation of treatment. Measurements are recorded in CRFs.

Determinations are made according to the 3-point scale below and recorded on CRFs. Measurements will be made before blood sampling when possible, and after 5 minutes at rest.

(5) Fundoscopy

Fundoscopy will be performed once each within the screening period, from treatment period Week 20 to Week 24, and to extent possible within 14 days of study withdrawal. An ophthalmologist will perform the fundoscopy and make evaluations according to the 3-point scale below. Ophthalmologist evaluations will be recorded in CRFs. Fundoscopy images and ophthalmologist evaluations will be stored at study centers.

1) Normal
2) Clinically non-problematic abnormality
3) Clinically problematic abnormality (retinal hemorrhage yes/no, retinal oedema yes/no)

(6) Chest X-ray

Fundoscopy will be performed once each within the screening period, from treatment period Week 20 to Week 24, and to extent possible within 14 days of study withdrawal. Investigators/subinvestigators will evaluate test results according to the 3-point scale below. Evaluation results will be recorded in CRFs. Chest X-rays will be stored at the study center.

1) Normal

2) Clinically non-problematic abnormality
3) Clinically problematic abnormality

(7) Pregnancy tests (only for women who may become pregnant)

Blood sampling and pregnancy testing will be performed on the first day of the screening period, treatment period Weeks 24, and the day of discontinuation of treatment. Investigators/subinvestigators will evaluate pregnancy based on test results and interview when appropriate. Evaluation results will be recorded in CRFs. If the subject is incapable of becoming pregnant, the reason for this will be recorded in CRFs (women only).

9.2.4.2 Adverse events

AEs are all clinically problematic or unplanned signs (including clinically significant abnormal laboratory values), symptoms, or illnesses occurring after administration of the study drug during the safety evaluation period, regardless of causal relationship with the study drug. Instances of aggravation of events (in terms of severity or seriousness) are treated as new AEs.

However, AEs occurring from informed consent to the first day of the treatment period which match criteria for serious adverse events are still reported to the study sponsor according to "11.1 Responses to Occurrence of Serious Adverse Events."

(1) Symptoms and diseases

Investigators/subinvestigators will confirm AEs through interviews and examinations.

(2) Objective findings

Objective findings determined clinically problematic abnormalities* by investigators/subinvestigators are treated as AEs.

*Clinically problematic abnormalities are determined according to the following criteria.

- If related to clinical signs or symptoms.
- However, if the sign or symptom has already been separately reported as an AE, the relevant laboratory test abnormality does not require treatment as adverse event.
- If the relevant laboratory test abnormality was treated medically or surgically.
- If the relevant laboratory test abnormality causes a change in method of administration of the study drug (dosage change, drug holiday, discontinuation, etc.).
- If investigators/subinvestigators otherwise determine the abnormality to be clinically problematic.

(3) Adverse event evaluation and standards

1) Date of onset

Date the symptom or laboratory test abnormality was observed.

2) Severity

Adverse event severity is classified as follows:

1. Mild: No effect on activities of daily life
2. Moderate: Moderate impairment of activities of daily life caused by event
3. Severe: Event prevents performing activities of daily life

3) Seriousness

AE seriousness is classified as follows:

1. Not serious: Any events other than 2 below.
2. Serious: Any events (a) to (f):
   (a) Fatal
   (b) Life-threatening
   (c) Necessitating hospitalization or prolongation of hospitalization for treatment
   (d) Events leading to permanent or clear dysfunction or disability
   (e) Other events or reactions judged medically significant
   (f) Causing congenital anomalies or defects

4) Causal relationship with the study drug

The investigator/subinvestigator will assess whether or not there is a logical possibility that the study drug caused the AE. This assessment will take into account factors not related to the study drug, including risk factors such as natural course and concurrent treatments for underlying or concomitant diseases, as well as the temporal relationship between the study drugs and the event (recurrence after resuming administration, elimination after discontinuation, etc.). AEs for which a logical possibility exists for causal relationship with the study drug are treated as ADRs.

1. Logical possibility
2. No logical possibility

5) Outcome

AE outcomes are classified as follows:

1. Recovery
2. Relief

3. Not recovered
4. Recovered with sequelae
5. Death
6. Unknown

6) Date of outcome

Date of outcome is determined according to the following criteria:

Recovery: Date of recovery. If date of recovery is knot known, use date on which recovery was confirmed or determined.

Relief: Date on which relief was confirmed or determined.

Not recovered: Date on which "not recovered" was confirmed or determined.

Recovered with sequelae: Date on which "recovered with sequelae" was confirmed or determined.

Death: Date of death. If date is not known, use date of confirmation or determination.

Unknown: Date of death if outcome is unknown due to death of subject for cause other than the relevant AE. For other circumstances use date of confirmation or determination.

7) Action taken with the study drug

Actions taken with the study drug are classified into the following six categories:

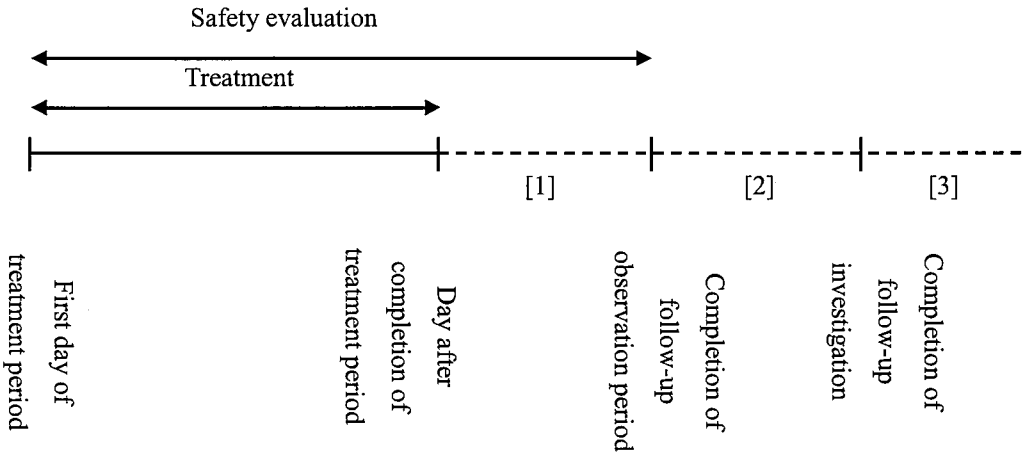
1. Discontinuation of administration (study withdrawal)
2. Drug holiday
3. Dosage increase
4. Dosage reduction
5. No action
6. Not applicable (occurred after final administration of study drug)

8) Action taken other than with the study drug

Actions taken other than with the study drug are classified into the following two categories: If actions other than with the study drug were taken, details of these will be investigated and recorded in the CRF.

1. No
2. Yes

9) Follow-up investigation



- Period [1] above is the 14 days from the day after completion of the treatment period, during which any AEs will be investigated.
- Period [2] above is the 28 days from the day after completion of the follow-up observation period; it is the period for follow-up investigations of AEs occurring during the safety evaluation period (treatment period + Period [1]).
- Course of AEs subject to follow-up investigation during Period [2] are recorded in the subject's CRF. The date of outcome written in the CRF for AEs with outcomes of relief or not recovered is the day of observation after completion of Period [2], during Period [3].
- Further investigations (Period [3]) will be performed for the course of ADRs with outcomes of relief or not recovered as of the end of Period [2].
  If there is a valid reason to halt investigations mid-way after completion of the safety evaluation period (after completion of Period [1]), record reasons for this and conclude the follow-up investigation.

(4) Recording information in CRFs

If an AE is observed, investigators/subinvestigators will record the following information in the subjec's CRF: name of AE*, date of onset, severity, seriousness, causal relationship with study drug, details of any actions taken (drug names, treatment methods, etc.), outcome, and date of outcome.

*AE names are handled in the following manner:

- Fundamentally, the name of diagnosis is used.
- The symptom name is used if a clear diagnosis has not been made.
- If there are multiple symptoms which can be expressed by a one diagnosis, that diagnosis name is used.

- Medical treatments etc. are not considered AEs; rather the disease or symptom requiring surgical treatment is considered the AE.

9.2.5 Blood sampling for genetic analysis

Blood sampling for genetic analysis will be performed once as early as possible after Week 2 of treatment period in subjects who have granted consent to genetic analysis. The blood sampling volume will be [redacted] (refer to "25. Genetic Analysis Study").

10. Evaluation methods and standards

10.1 Efficacy

10.1.1 Primary endpoints

The following endpoints will also be studied.

(1) Mean Hb at treatment period Weeks 20 and 24

Mean Hb of treatment period Weeks 20 and 24 will be calculated.

(2) Hb at each treatment period timepoint

Hb at each timepoint in treatment period will be calculated.

(3) Ratios of subjects with mean Hb within the target range (11.0–13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each timepoint in treatment period

Ratios of subjects with mean Hb within the target range (11.0–13.0 g/dL), <11.0 g/dL, and >13.0 g/dL at each timepoint in treatment period will be calculated.

(4) Correction cohort only: Days from initiation of treatment period required to reach target Hb range (11.0–13.0 g/dL)

Days from initiation of treatment period required to reach target Hb range (11.0–13.0 g/dL) will be calculated.

(5) Correction cohort only: Rate of increase of Hb levels

Rate of increase of Hb levels will be calculated according to the methods below.

- ✓ Change in Hb from the first day of the treatment period at treatment period Week 4 will be calculated.
- ✓ Calculated from slope of the regression line obtained from Hb levels on the first day of the treatment period and Weeks 2, 4, and 6 of the treatment period.

10.1.2 Other endpoints

The following endpoints will also be studied.

(1) Correction cohort only: Change from baseline in mean Hb of Weeks 20 and 24 of treatment period.

Change from baseline in mean Hb of Weeks 20 and 24 of treatment period will be calculated.

(2) Correction cohort only: Ratio of subjects with an increase of ≥1.0 g/dL of mean Hb from baseline at each timepoint in treatment period.

Ratio of subjects with an increase of ≥1.0 g/dL of mean Hb from baseline at each timepoint in treatment period will be calculated.

(3) Ratio of subjects who received ESA rescue therapy

Ratio of subjects who received ESA rescue therapy from the first day of the treatment period to treatment period Weeks 24 will be calculated.

(4) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.

Ratio of subjects who received RBC transfusion from the first day of the treatment period to treatment period Weeks 24 will be calculated.

(5) Study drug dosage

Mean daily dosage will be calculated for each scheduled study visit from the first day of the treatment period up to treatment period Week 24.

(6) total number of dosage adjustments

The total number of dosage adjustments from the first day of the treatment period to treatment period Weeks 24 will be calculated.

(7) Quantity of iron administered

Mean weekly dosage will be calculated for each scheduled study visit from the first day of the treatment period up to treatment period Week 24.

(8) Ratio of subjects who received IV iron

Ratio of subjects who received IV iron from the first day of the treatment period to treatment period Weeks 24 will be calculated.

(9) Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20%.

Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20% at each evaluation timepoint will be calculated.

(10) Change from baseline of iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin.

Changes in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin

from baseline will be calculated for each evaluation timepoint.

(11) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and EPO.

Changes in haematocrit, RBC count, reticulocytes (counts and fractions), and EPO from baseline will be calculated for each evaluation timepoint.

(12) QOL measures (EQ-5D-5L, KDQOL)

Scores for QOL measures will be calculated for each evaluation timepoint.

10.2 Safety

The following endpoints will also be studied.

(1) AEs and ADRs (refer to "9.2.4.2 Adverse events" for details)
(2) Laboratory test values
(3) Resting standard 12-lead ECG
(4) Body weight (excluding dialysis solution)
(5) Vital signs
(6) Fundoscopy
(7) Chest X-ray
(8) Ratio of subjects with Hb levels of ≥13.0 g/dL or ≥14.0 g/dL.
(9) Ratio of subjects with Hb increase rates exceeding 0.5 g/dL/week.

11. Ensuring subject safety

11.1 Responses to serious adverse events

If an SAE occurs after informed consent is granted, investigators/subinvestigators will immediately take appropriate actions toward the subject regardless of causal relationship with the study drug.

Investigators/subinvestigators will immediately notify monitors once an SAE has occurred (fundamentally in writing), and make a detailed written report to the study sponsor within 7 days of this report. Investigators/subinvestigators will also report the SAE to the director of the applicable study center.

[Definition of serious adverse events]

(1) Fatal
(2) Life-threatening
(3) Necessitating hospitalization or prolongation of hospitalization for treatment
(4) Events leading to permanent or clear dysfunction or disability
(5) Other events or reactions judged medically significant
(6) Causing congenital anomalies or defects

11.2 Significant adverse events

There are no SAEs which should be defined with regard to studying the safety profile of the drug.

11.3 Pregnancy reporting

If investigators/subinvestigators learn that a female subject or the female partner of a male subject may have exposed an embryo or fetus to the study drug from the first day of the treatment period to the end of the contraception period, they will immediately inform the study sponsor using Pregnancy Reports (Appendix 1). If the female subject or female partner of a male subject wishes to deliver the baby, investigators/subinvestigators will to the extent possible perform follow-up investigation up to birth in order to investigate effects of the study drug on the newborn. Results of the investigation will be reported to the study sponsor using Pregnancy Reports (Appendix 1).

11.4 Contacting subjects' other doctors

Investigators/subinvestigators will confirm whether or not each subject is receiving medical care other than as part of the current study during the study period. If a subject is receiving such care, the other doctor will be contacted with the consent of the subject and informed of the subject's participation in the study. In order to enlist subject aid in contacting other doctors, the

investigators/subinvestigators or clinical coordinators may give each subject a card for the current study, and request that the subject show this to other hospitals or departments.

12. Withdrawal criteria and procedures

12.1 Withdrawal criteria

Subjects will be withdrawn from the study if the following criteria are met:

(1) If the subject expresses a desire to withdraw from the study.

(2) If it is discovered that the subject is clearly ineligible for study participation.

(3) If investigators/subinvestigators determine that AEs make continued participation in the study difficult.

(4) If investigators/subinvestigators determine that continuation of the study is inappropriate for a subject, such as if hyperviscosity syndrome occurs or if control of Hb within the target range is impossible.

(5) If continuous haemodialysis is initiated, or if the subject receives a renal transplant.

(6) If renal function recovers such that peritoneal dialysis is discontinued.

(7) If pregnancy of the subject is discovered.

(8) If the investigator/subinvestigator determines a subject should withdraw from the study for any other reason.

Rationale

(1) Set out of ethical considerations.

(2) (5) (6) Set in order to prevent study drug administration to subjects unsuitable for inclusion in safety or efficacy evaluation.

(3) (4) (7) Set out of safety considerations.

(8) Set in order to allow the investigator/subinvestigator to make determinations regarding study continuation for significant safety-related reasons other than those enumerated above.

12.2 Procedures for withdrawal

If a subject withdraws from the study, the investigator/subinvestigator will take all appropriate actions toward the subject, immediately inform the study monitor of the withdrawal, and notify the study sponsor by fax according to "8.2.4 Withdrawal processing." If a subject withdraws from the study, investigators/subinvestigators will perform all tests required at discontinuation within 7 days of discontinuation (fundoscopy and chest X-rays are to be performed to extent possible within 14 days of discontinuation).

Investigators/subinvestigators will record date of withdrawal and reasons for withdrawal in the CRF for subjects who withdraw from the study following the first day of the treatment period. If the reason for withdrawal is an AE, the name of the event will be recorded in the CRF. The date of evaluations performed upon withdrawal is used as the date of withdrawal, but if these evaluations

could not be performed, the date of determination of withdrawal may be used instead. If tests and observations required on the day of withdrawal cannot be performed for a given subject, or the subject does not make any post-withdrawal visits, follow-up investigation will be performed through correspondence (sealed letters) or telephone to ascertain reasons for this and subsequent course, and information obtained recorded.

13. Statistical analysis

13.1 Analysis sets

Efficacy analysis is performed with the full analysis set (FAS). Safety analysis will be performed with the safety analysis set.

Analysis populations are defined below; details of subject handling will be determined by data lock by the study sponsor.

(1) FAS

The FAS consists of all subjects transitioned to the treatment period, excluding the following subjects:

- ✓ Subjects who did not have PD-CKD-related anaemia
- ✓ Subjects who did not use a single dose of study drug
- ✓ Subjects with absolutely no efficacy data after treatment initiation

(2) Safety analysis set

The safety analysis population consists of all subjects transitioned to the treatment period, excluding the following subjects:

- ✓ Subjects who did not use a single dose of study drug
- ✓ Subjects with absolutely no safety data after treatment initiation

13.2 Data handling

(1) Definition of missing values

If test measurements are missing or if problems with samples etc. result in invalid measurements or reference values, these are handled as missing values.

(2) Handing of timepoint data for statistical summaries at each measurement timepoint

Statistical summaries for each evaluation timepoint will use data compliant with permitted ranges as described in "Table 9.1-1 Permitted ranges for study center visits." There will be no supplementing with data from outside the permitted range.

If multiple data points exist within the permitted range, then the one closes to the scheduled day will be used. If there are deviations from the scheduled day, then data points prior to the scheduled day will be used for efficacy evaluation, and data points after the scheduled day will used for safety evaluation.

(3) Handling of efficacy endpoints if rescue therapy was implemented

No data obtained after implementation of rescue therapy will be used for efficacy evaluation.

(4) Imputation of missing values

Values imputed using LOCF will also be derived for data from treatment period Week 24. Data from treatment period Week 24 with missing values imputed will be used as data from completion of the treatment period.

Required regulations for data handling other than those enumerated above will be described in the final statistical analysis protocol prior to data lock.

13.3 Statistical analysis protocol

Confidence interval will be 2-sided, with a confidence coefficient of 95%. Data imputed using LOCF will not be used in analysis with mixed models repeated measures (MMRM).

A detailed statistical analysis protocol will be authored prior to data lock enumerating details.

13.3.1 Demographic and other baseline characteristics

Summary statistics will be compiled for demographic data and other baseline characteristics for all analysis sets. Incidence and ratios will be shown for discrete data, while descriptive statistics will be calculated for continuous data (number of subjects, mean, SD, minimum, median, maximum, and 95% CI for means, same below).

13.3.2 Efficacy

(1) Analysis methods for primary endpoint

1) Mean Hb of treatment period Weeks 20 and 24

To determine mean Hb (mean at treatment period Weeks 20 and 24), mean Hb at each timepoint will be modeled using MMRM with the following model, and mean Hb at treatment period Weeks 20 and 24 and their two-sided 95% CI will be calculated.

[MMRM model]

- Fixed effects: Evaluation period, patient cohort (correction or conversion cohort), interactions of evaluation period × patient cohort (correction or conversion cohort)
- Random effects: Subjects

2) Hb at each treatment period timepoint

Descriptive statistics will be calculated for Hb level at each treatment period timepoint,

and analysis performed taking into account changes over time using MMRM.

3) Ratios of subjects with mean Hb within the target range (11.0–13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each timepoint in treatment period

Numbers and ratios of subjects with mean Hb at each treatment period timepoint within the target range (11.0–13.0 g/dL), <11.0 g/dL, and >13.0 g/dL will be shown.

4) Correction cohort only: Days from the first day of the treatment period required to reach target Hb range (11.0–13.0 g/dL)

Descriptive statistics will be calculated for days from the first day of the treatment period required to reach target Hb range (11.0–13.0 g/dL). A Kaplan-Meier plot will be shown for days from the first day of the treatment period required to reach target Hb range (11.0–13.0 g/dL). Statistical summaries will not include subjects with Hb of ≥11.0 g/dL on the first day of the treatment period.

5) Correction cohort only: Rate of increase of Hb levels

Descriptive statistics will be calculated for rate of Hb increase.

(2) Analysis methods for other endpoints

Incidence and ratios will be shown for discrete data, while descriptive statistics will be calculated for continuous data.

13.3.3 Safety

(1) Analysis methods for adverse events and adverse drug reactions

The following statistics will be shown: numbers of subjects and incidence ratios for AEs, SAEs, AEs leading to discontinuation, AEs leading to death, ADRs, serious ADRs, ADRs leading to discontinuation, and ADRs leading to death.

(2) Analysis methods for laboratory values, resting standard 12-lead ECG, body weight (excluding dialysis solution), vital signs, fundoscopy, and chest X-ray

Descriptive statistics will be calculated for continuous data at each timepoint. Descriptive statistics will also be calculated for changes from baseline. A shift table will be shown for changes of discrete data from baseline to each timepoint.

(3) Ratio of subjects with Hb levels of ≥13.0 g/dL or ≥14.0 g/dL.

Numbers and ratios of subjects with Hb levels of ≥13.0 g/dL or ≥14.0 g/dL at each timepoint

will be shown.

(4) Ratio of subjects with Hb increase rates exceeding 0.5 g/dL/week.
Numbers and ratios of subjects with rate of Hb increase of >0.5 g/dL/week will be shown.

13.4 Changes in statistical analysis protocol

If any portion of this statistical analysis plan is modified prior to data lock, reasons for change will be described in the statistical analysis protocol and the clinical study report. If the analysis plan is modified or analyses added after data lock, reasons for modification will be described in the statistical analysis protocol and the clinical study report, and analytical results will be distinguished from the original plan.

14. Study protocol compliance, deviation, and modification

14.1 Study protocol agreement and compliance

Before each investigator agrees with the study sponsor about the study protocol, he or she will discuss it with the study sponsor based on the protocol, newest investigator's Brochure (IB), and other materials provided. The investigator must fully study the ethical and scientific validity of the study prior to agreement.

In order to demonstrate agreement with the study sponsor on the study protocol and intent to comply with it based on these considerations, the investigator will sign (or print name and affix personal seal) the Agreement and enter the date with the study sponsor.

14.2 Study protocol deviations and modifications

Investigators/subinvestigators may not deviate from or modify the study protocol without previous written permission from the study sponsor and IRB. However, if there are circumstances in which such a deviation or modification is medically necessary on an emergency basis to avoid placing subjects in danger, investigators/subinvestigators may perform such actions without prior permission from the study sponsor and IRB.

In such cases, investigators must submit and receive approval for said deviations or modifications, reasons for these, and if appropriate revisions to the study protocol as rapidly as possible from the study sponsor, study center director, and the IRB. Approval from the study center director and agreement from the study sponsor must be obtained in writing.

Investigators/subinvestigators shall fully record all actions deviating from the study protocol. Investigators shall also draft a report detailing all medically required emergency deviations from or

modifications to the study protocol for the purpose of avoiding placing subjects in danger, including the reasons why they were necessary. Investigators will keep a copy of this report and send it to the study sponsor and study center director.

Investigators must immediately submit a report to the study sponsor, study center director, and IRB about all modifications which may significantly influence the study or increase risk to subjects.

15. Revisions to the study protocol

The study sponsor may revise the study protocol during the study if modifications are required. The study sponsor will discuss the revisions with investigators and come to agreement about them, then immediately notify the study center director in writing and obtain approval from the IRB through the study center director.

If the study center director requests modification of the protocol based on the opinion of the IRB, the study sponsor will determine whether the modification is warranted and revise the protocol as necessary. The study sponsor will discuss the revisions with investigators and come to agreement about them, then immediately notify the study center director in writing and obtain approval from the IRB through the study center director.

If investigators request modification of the protocol, the study sponsor will determine whether the modification is warranted and revise the protocol as necessary. The study sponsor will discuss the revisions with investigators and come to agreement about them, then immediately notify the study center director in writing and obtain approval from the IRB through the study center director.

16. Termination or suspension of the entire study

(1) Standards for termination or suspension of the study

In the following circumstances the study sponsor will determine whether or not continuation of the study is warranted at some or all study centers.

1) If significant information is learned about study drug quality, efficacy, or safety, or if other information about appropriate conduct of the study comes to light.
2) If modifications to the study protocol are required which study centers cannot adopt.
3) If a study center director requests modifications to the study protocol based on the opinion of the IRB, but the study sponsor cannot accept these changes.
4) If a study center director orders termination of the study based on the judgment of the IRB.
5) If a study center makes significant or continued deviations from GCP, the current study protocol, or the study contract.

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

If the study sponsor determines to terminate or suspend the entire study, study center directors and regulatory authorities will be notified immediately in writing of this decision and reasons for it. If a study center director receives notification of termination or suspension of the study from the study sponsor, they will immediately notify in writing the investigator and IRB of this fact, including detailed reasons.

If an investigator receives notification of the termination or suspension of the study from the study center director, he or she will immediately inform subjects and ensure that appropriate medical treatments are performed.

See "12.2 Procedures for Withdrawal" for actions taken related to subjects upon study termination.

(3) Termination or suspension of study at a study center by investigator or IRB

If an investigator determines on his or her own judgment to terminate or suspend the study, he or she will immediately inform the study center director in writing of the details regarding this decision. The study center director will then immediately inform the study sponsor and IRB in writing.

If the IRB determines to terminate or suspend the study, it will immediately inform the study center director in writing of the details regarding this decision. The study center director will then immediately inform the investigator and study sponsor in writing.

(4) Termination due to dissolution of contract with study center

The study sponsor will immediately inform the regulatory authorities if it terminates the study at a study center due to serious or continued violations of GCP or the study protocol during the study period.

17. Case report forms

17.1 Case report form (CRF) format

This study will use electronic CRFs using an electronic data capture (EDC) system. Electronic CRFs reviewed and digitally signed by investigators will be considered originals. Test results from clinical laboratory tests performed at the contract testing facility will be obtained from that facility.

17.2 Direct recording of information in the CRF and CRF as source documents

There is no item or category in the current study for which the electronic CRF is considered the source document. If data from an electronic CRF is to be considered the source document, this will be

agreed upon separately in writing by the study sponsor and investigator prior to initiation of the study.

17.3 Notes on making CRF entries

Investigators/subinvestigators or clinical coordinators will make CRF entries according to the following stipulations. CRFs will be created according to "Procedures for CRF modifications or revisions,"* to be supplied separately by the study sponsor.

*"Procedures for CRF modifications or revisions": eCRF operation manual and eCRF input manual

(1) The study sponsor will perform user management duties, such as giving user names and passwords to investigators/subinvestigators and clinical research staff, which will not be shared beyond the person to which they were originally assigned. Data entry will be performed only by those with authority to do so (investigators/subinvestigators and clinical research staff).

(2) CRFs will be created for all subjects who transition to the treatment period (subjects with completed treatment period enrollment).

(3) Investigators may record any information in CRFs. Subinvestigators may record any information in CRFs excluding digital signatures. Clinical research staff may transfer information from source documents to the CRF which do not require medical judgment, such as treatment records.

(4) When information recorded in CRFs is modified or revised, the reason for this will be recorded electronically in the CRF.

(5) Investigators will electronically sign the CRF on the EDC system after reviewing it and confirming accuracy and completeness, and that audit trails and electronic signature information are viewable.

(6) Investigators will retain copies of CRFs on recording media such as CDRs (stored as PDF copies of the electronic CRF after review by the investigator). Granting electronic access to CRFs (permission to view on the EDC system) may serve in lieu of submitting copies in the period from electronic signing until submission of the CDRs or other storage media.

(7) If there is conflicting data between data in the CRF and source documents, the investigator will submit a document containing the reason for this discrepancy to the study sponsor, and retain a copy.

17.4 CRF submission timepoints

Investigators/subinvestigators will make CRF entries in principle within 72 hours after each observation in the study period and after completion of evaluation, then submit these to the study sponsor.

18. Direct access to source documents

Investigators and study center directors shall grant direct access to all source documents related to the study in response to monitoring or auditing by the study sponsor, or in response to investigations by the IRB or regulatory authorities.

19. Study quality control and quality assurance

In order to ensure a high level of quality for the study, the study sponsor must perform study quality control and quality assurance based on Mitsubishi Tanabe Pharma Corporation's GCP procedures. Further, the contract research organization will perform study quality control based upon standard operating procedures agreed upon with the study sponsor. Meanwhile, study centers and investigators will grant their cooperation in performance of these duties.

As a part of quality control efforts, study monitors will directly observe activities as appropriate to ensure that the study is compliant with related procedures, the latest version of the study protocol, and GCP. Monitors will also confirm that information recorded in CRFs by investigators/subinvestigators can be compared with source documents and other related materials in order to verify accuracy and completeness.

The study auditor will audit the study in accordance with the GCP Standard Operating Procedure to ensure compliance with the study protocol and GCP, and otherwise confirm appropriate implementation of quality control measures.

20. Ethics

20.1 Ethical conduct of the study

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki, and in compliance with the Pharmaceutical Affairs Law, GCP, and the study protocol.

20.2 Institutional Review Board

The Institutional Review Board (IRB) of each study center will review the study (including its continuation) based on the investigator's Brochure (IB), study protocol, and informed consent forms and written information for subjects from ethical, scientific, medical, and pharmaceutical perspectives.

20.3 Subject confidentiality

Identification of each subject through enrollment and CRFs shall be possible only with the subject identification code. All personnel involved with the current study shall endeavor to preserve subject confidentiality during direct access to source documents, publishing in academic journals, and submissions to regulatory authorities.

21. Record storage

(1) Records stored by study centers

The records storage manager appointed by each study center director shall store all study-related documents and other records to be stored at each study center until 1) or 2) below, whichever comes later. However, if the study sponsor requests that these materials be stored for a longer period, each study center will discuss storage methods and periods with the study sponsor.

If the study sponsor determines not to include materials related to results from the clinical study in the application, it will notify study center directors of this fact and the reasons for it in writing.

Further, the study sponsor will notify study center directors in writing if marketing approval is granted for the study drug, or if approval is not granted and development is canceled.

1) Day of marketing approval for the study drug (or 3 years from receipt of notification if notified of cancelation of development, or that study results will not be included in application)
2) Three years from the day of termination or completion of the study

(2) Records stored by the study sponsor

The study sponsor shall store all study-related documents and other records to be stored by the study sponsor until 1) or 2) below, whichever comes later.

1) Five years from the day of marketing approval for the study drug , or day of completion of re-review (or 3 years from the date of cancellation of development)
2) Three years from the day of termination or completion of the study

22. Monetary compensation

Monetary compensation made to study subjects and study centers will be paid in accordance with contracts and agreements between the study centers and the study sponsor.

23. Compensation for health damage and insurance

23.1 Compensation for health damage

In the event that a subject experiences damage to health related to the study, the study sponsor shall provide compensation according to determined standards (excluding instances in which causal relationship with the study has been denied). Forms of said compensation may include the subject's portion of medical coverage, treatment allowances, or financial compensation. In these events, it shall not be the burden of the subject to prove causal relationship with the study.

23.2 Insurance

The study sponsor shall procure health insurance and take other measures to ensure fulfillment of liability and compensatory responsibilities to subjects related to damage to health arising from the study.

24. Publication policy

Information contained within this study protocol is the property of the study sponsor. Although it is provided to investigators/subinvestigators, others involved with the study, and IRBs, information contained herein shall not be disclosed to third parties without express written consent of the study sponsor, save when doing so is required for the study itself.

Information obtained through the study may be published (to academic societies, journals, etc.) by investigators/subinvestigators, or others involved with the study at study centers, only after obtaining prior consent from the study sponsor.

Finally, the study sponsor reserves the right to freely use information obtained through the study for any purpose, including reports to regulatory authorities, appropriate drug use, and sales promotions.

25. Genetic analysis study

25.1 Purpose of the study

Researching the relationship between genetic factors and drug efficacy as well as incidence of AEs is a crucial step in establishing safe, effective drugs. [redacted]

25.2 Eligible subjects

[redacted]

25.3 Obtaining consent

Investigators will obtain cooperation from the study sponsor in drafting informed consent forms and written information for the genetic analysis study separate from those required for the main study.

Authored or revised consent forms will be submitted to study sponsor and approved by the Institutional Review Board (IRB).

Investigators/subinvestigators will use the informed consent forms and written information for the genetic analysis study to fully explain the study to subjects and obtain their consent in writing prior to collecting blood samples for the genetic analysis study.

Investigators/subinvestigators and subjects will sign (or print name and affix personal seals to) and date these consent forms, after which subjects will receive a copy of the completed form. If clinical coordinators performed supplementary explanations, they will also sign (or print name and affix personal seal) and date the form.

Subjects may still participate in the main study even if they do not grant consent for the genetic analysis study.

25.4 Sample handling

25.4.1 Blood sampling dates

[redacted]

25.4.2 Storage and transport conditions

Blood samples collected will be cryopreserved until transportation. The contract testing laboratory will collect the blood samples and send them to the storage facility for genetic analysis samples. [redacted]

25.4.3 Procedures for anonymization and encoding, and preparation/storage of the identification table

The storage facility for genetic analysis samples will issue an anonymized identification number for each blood sample received, which is separate from the subject identification code. The facility will store a table linking identification codes to subjects. Methods for anonymization and creation/storage of the identity table will adhere to operating procedures of the facility or the study protocol.

25.4.4 Provision of the identity table

The storage facility for genetic analysis samples will provide a copy of the table linking subjects and identification codes to the study sponsor after storage of the final sample.

[redacted]

25.5 Performing genetic analysis

[redacted]

[redacted]

25.6 Publication of results and disclosure to sample donors

25.6.1 Publication of results and disclosure to sample donors

Information obtained through the genetic analysis study may be published (to academic societies, journals, etc.) by investigators/subinvestigators, or others involved with the study at study centers, only after obtaining prior consent from the study sponsor. Finally, the study sponsor reserves the right to freely use information obtained through the study for any purpose, including reports to regulatory authorities, appropriate drug use, and sales promotions.

In principle, genetic information about individual subjects will not be disclosed to either subjects themselves or study centers.

25.6.2 Disposal of individual genetic information

If disposal of a sample becomes necessary due to retraction of subject consent or other reasons, the genetic information manager appointed at the time of the genetic analysis study will delete data related to the relevant subject from computers where that information is stored. Paper records will be shredded to a state where restoration is impossible. However, if retraction of consent occurs after an individual's data has already been used in a group analysis, results from that analysis may be used even after the retraction. Further, it may be impossible to fully discard results if already published in papers or other forms. Details regarding disposal of genetic information will adhere to separate procedures or study protocols to be drafted.

26. Administrative structure

26.1 Study sponsor:

See Appendix 1.

26.2 Study centers and investigators

See Appendix 2.

Investigator duties: Agreeing with study protocol created by study sponsor, drafting and revising

informed consent forms and written information for subjects, selecting subjects and obtaining consent, performing study, providing medical care and information to subjects, instructing and overseeing subinvestigators and clinical coordinators, providing materials and information, cooperating with monitors and auditors, reporting deviations from the study protocol, changes from the study protocol, and AEs, making CRF entries, and storing documents or records related to the study.

27. References

(1) Japanese Society of Nephrology, "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012." Tokyo; Tokyo Igakusha; 2012.

(2) Iseki K. Chronic kidney disease in Japan. Inter Med. 2008;47(8):681-9.

(3) Imai E, Yasuda Y, Makino H. Japan association of chronic kidney disease initiatives (J-CKDI). Japan Med Assoc J. 2011;54(6):403-5.

(4) Iseki K, Kohagura K. Anemia as a risk factor for chronic kidney disease. Kidney Int Suppl. 2007;(107):S4-9.

(5) Di Iorio B, Cirillo M, Bellizzi V, Stellato D, De Santo NG; Campania Dialysis Registry Research Group. Prevalence and correlates of anaemia and uncontrolled anaemia in chronic hemodialysis patients-the Campania Dialysis Registry. Int J Artif Organs. 2007;30(4):325-33.

(6) Stauffer ME, Fan T. Prevalence of anaemia in chronic kidney disease in the United States. PLoS One. 2014;9(1):e84943.

(7) Nurko S. Anemia in chronic kidney disease: causes, diagnosis, treatment. Cleve Clin J Med. 2006;73(3):289-297.

(8) Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant. 2000;15 Suppl 3:14-8.

(9) National Institute for Health and Care Excellence. Chronic kidney disease: managing anaemia. NICE guideline. 2015. https://www.nice.org.uk/guidance/NG8

(10) KDOQI; National Kidney Foundation. Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006;47(5 Suppl 3):S11-145.

(11) Bigham AW, Lee FS. Human high-altitude adaptation: forward genetics meets the HIF pathway. Genes Dev. 2014;28(20):2189-204.

Contact Information

[redacted]

[redacted] Mitsubishi Tanabe Pharma Corporation

17-10 Nihonbashi Komai-cho, Chuo-ku, Tokyo Japan 103-8405

[redacted]

[Contract Monitoring Organization]

[redacted]

Night/Holiday Contact Information

Emergency contact for after-hours (between 5:30 PM and 9 AM), weekends, and holidays is given below.

The call center will contact study monitors on an emergency basis.

[redacted]

[redacted]