A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis 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	Non-abbreviated term
AUC	Area under the plasma concentration-time curve
ANCOVA	Analysis of covariance
BCRP	Breast cancer resistance protein
CKD	Chronic kidney disease
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450
DHEA-S	dehydroepiandrosterone sulfate
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
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Preferred term
PT-INR	Prothrombin time-international normalized ratio
PPS	Per protocol set
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
VEGF	vascular endothelial growth factor

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
Treatment period Phase 1	From completion of scheduled tests for the first day of the treatment period to completion of scheduled tests for Week 24 of the treatment period
Treatment period Phase 2	From completion of tests specified for Week 24 of treatment period to completion of tests specified for Week 52 of treatment period
Day of completion of treatment period	Week 52 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 150 mg	Each film-coated tablet contains 150 mg vadadustat.
MT-6548 Tablet placebo	Film-coated tablets visually indistinguishable from MT-6548 Tablet 150 mg without containing vadadustat
MT-6548 Tablet	MT-6548 Tablet 150 mg and MT-6548 Tablet placebo
Darbepoetin alfa injection active comparator	Visually indistinguishable plastic syringes, each (0.5 mL) containing 5, 10, 20, 40, or 60 μg of darbepoetin alfa (recombinant)
Darbepoetin alfa injection placebo	Plastic syringes visually indistinguishable from darbepoetin alfa injection active comparator without containing darbepoetin alfa (recombinant)
Darbepoetin alfa injection	Darbepoetin alfa active comparator and darbepoetin alfa placebo

Protocol Summary

1. Study title

A phase III, double blind, confirmatory study of MT-6548 compared to darbepoetin alfa in hemodialysis subjects with anemia associated with chronic kidney disease in Japan

2. Purpose of the study

The study will verify non-inferiority of MT-6548 in patients with anemia associated with hemodialysis-dependent chronic kidney disease (HD-CKD) who are currently treated with an erythropoiesis-stimulating agent (ESA) using hemoglobin (Hb) levels as a measure and darbepoetin alfa (recombinant) as a control drug and evaluate safety of long-term administration of MT-6548.

3. Subjects

3.1 Subjects

Patients with anemia associated with HD-CKD

3.2 Inclusion criteria

Subjects must meet all inclusion criteria below and have capacity to grant informed consent. Laboratory tests related to the inclusion criteria will be assessed based on central laboratory measurements. If a given laboratory test is performed multiple times during the screening period, the most recent test will be used for assessment. If blood is drawn on the day of dialysis, data obtained before dialysis will be used for assessment. In addition, Hb values in blood collected in the supine position will be used for assessment.

(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 received either hemodialysis or hemodiafiltration three times a week for at least 12 weeks prior to the first day of the screening period; however, patients on home dialysis and those receiving a combined therapy of home hemodialysis and peritoneal dialysis are excluded

(4) 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) in the 8 weeks prior to the first day of the screening period, using the dosages described below

Dosage:

- ✓ Epoetin alpha (recombinant), epoetin beta (recombinant), and epoetin kappa (recombinant): ≤9000 IU every week
- ✓ Darbepoetin alfa (recombinant): ≤60 μg every week
- ✓ Epoetin beta pegol (recombinant): ≤250 μg every 4 weeks

(5) Patients with a mean Hb value (mean of the latest two measurements) of ≥9.5 g/dL and ≤12.0 g/dL during the screening period

(6) Patients with an Hb difference of <1.5 g/dL between the latest two measurements during the screening period

(7) Patients with a serum ferritin value of ≥100 ng/mL or a transferrin saturation (TSAT) of ≥20% during the screening period

(8) Patients with folic acid and vitamin B12 values above the lower limit of normal values during the screening period

3.3 Exclusion criteria

Patients who meet any of the following exclusion criteria will be excluded. Laboratory tests related to the exclusion criteria will be assessed based on central laboratory measurements. If a given laboratory test is performed multiple times during the screening period, the most recent test will be used for assessment. If blood is drawn on the day of dialysis, data before dialysis will be used for assessment.

(1) Patients who have anemia primarily due to diseases other than CKD (including sickle cell disease, myelodysplastic syndrome, myelofibrosis, hematopoietic malignancy, myeloma, hemolytic anemia, thalassemia, and pure red cell aplasia) after the day of informed consent

(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 who are expected to no longer require hemodialysis or hemodiafiltration due to recovery of renal function

(7) 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.

(8) Patients with poorly controlled hypertension (defined as a systolic blood pressure (BP) of >180 mmHg or diastolic BP of >110 mmHg) on the first day of the screening period and on the first day of the treatment period

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

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

(11) 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.

(12) 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).

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

(14) Patients with current or previous haemosiderosis or hemochromatosis

(15) 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

(16) Patients with an allergy to the study drugs

(17) 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)

(18) Patients who have previously used MT-6548

(19) Patients who are known not to be tolerant to hypoxia-inducible factor prolyl hydroxylase enzyme inhibitors

(20) 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

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

(22) 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 may be performed during the screening period at the discretion of the investigator/subinvestigator for any subject whose laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, and total bilirubin) or BP do not meet the inclusion criteria

or meet the exclusion criteria during the screening period.

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.

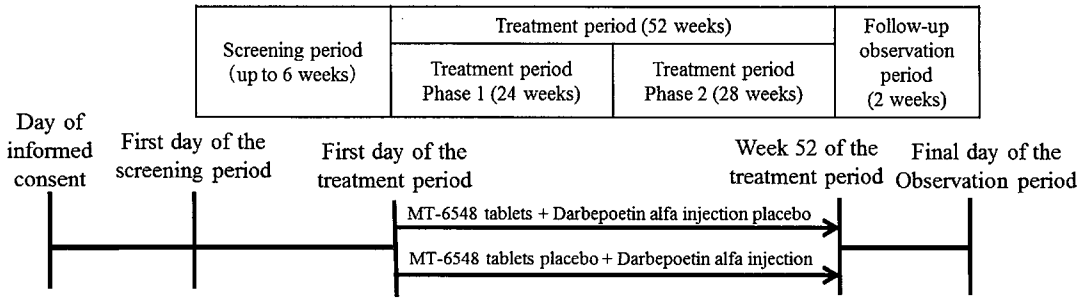
(2) Re-screening

For any subject whose laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, and total bilirubin), BP, or BP measurements on the first day of the treatment period do not meet the inclusion criteria or meet the exclusion criteria during the screening period, re-screening may be performed if the investigator/subinvestigator considers that the subject may become eligible for the study due to natural course or with drug therapy.

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

4. Study design

This is a multicenter, randomized, double-blind, active-controlled, double-dummy, parallel group comparative 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. Testing may be repeated 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 52 of the treatment period or discontinuation of treatment).

The treatment period consists of phase 1 and phase 2, as defined below.

- ✓ Treatment period Phase 1: From completion of scheduled tests for the first day of the treatment period to completion of scheduled tests for Week 24 of the treatment period. Treatment period Phase 1 will be double-blind.
- ✓ Treatment period Phase 2: From the completion of the tests specified for Week 24 of the treatment period to the completion of tests specified for Week 52 of the treatment period. Even after all subjects complete the treatment period Phase I and the key code is opened, the subjects, study institution staff members, and monitoring personnel will remain blinded to treatment. Details of the procedure of maintaining the blindness will be separately defined before opening of the key code.

During the treatment period, subjects are to visit the study site on the day of dialysis after a 2-day interdialytic interval; however, if this is difficult, subjects are to visit the study site on the day of dialysis after a 1-day interdialytic interval. After the first day of the treatment period, subjects are to visit the study site every 2 weeks until Week 12 and every 4 weeks after Week 12 to undergo the scheduled test. However, subjects are to visit the study site at shorter intervals as necessary, if excessive increases or decreases in Hb are of concern based on the time course of Hb levels, the dose interval of darbepoetin alfa injection is shorter than the scheduled visit interval, or for hemodialysis.

(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.

(2) Control drug

1) MT-6548 Tablet placebo

Dosage form and content: Film-coated tablets visually indistinguishable from MT-6548 Tablet 150 mg without containing vadadustat

2) Darbepoetin alfa injection active comparator (see Attachment 6 NESP® injection package insert for information on darbepoetin alfa [recombinant])

Name: Darbepoetin alfa injection 5 μg
Darbepoetin alfa injection 10 μg
Darbepoetin alfa injection 20 μg
Darbepoetin alfa injection 40 μg
Darbepoetin alfa injection 60 μg

Nonproprietary name: Darbepoetin alfa (recombinant)

Dosage form and content: Visually indistinguishable plastic syringes, each (0.5 mL) containing 5, 10, 20, 40, or 60 μg of darbepoetin alfa (recombinant)

3) Darbepoetin alfa injection placebo

Dosage from and content: Plastic syringes visually indistinguishable from darbepoetin alfa injection active comparator without containing darbepoetin alfa (recombinant)

5.2 Dosage and administration

The investigator/subinvestigator will administer both MT-6548 Tablets and darbepoetin alfa injection to subjects during the treatment period. Contents of the study drug are shown below; subjects, study institution staff members, and monitoring personnel will remain blinded to treatment until the final data has been fixed at the end of the study. The kit code of the study drug will be notified on the Web registration system every time the study drug is prescribed.

MT-6548 group: MT-6548 Tablet 150 mg and darbepoetin alfa injection placebo will be administered.

Darbepoetin group: MT-6548 Tablet placebo and darbepoetin alfa injection active comparator will be administered.

5.2.1 Administration method

(1) MT-6548 Tablet

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.)

(2) Darbepoetin alfa injection

Intravenous administration. Darbepoetin alfa injection should be administered on the day of dialysis after a 2-day interdialytic interval in principle. (The first dose should be administered after completion of the scheduled tests on the first day of the treatment period; however, the tests scheduled after dialysis should be performed before the first dose whenever possible.)

5.2.2 Initial dose and dose interval

(1) MT-6548 Tablet

Single daily dose of 300 mg (2 tablets)

(2) Darbepoetin alfa injection

1) Initial dosage for subjects receiving darbepoetin alfa (recombinant) prior to switching

The same pre-switching dosage of darbepoetin alfa (recombinant) will be used after switching as initial dosage. The same dose interval will be used as well. However, if pre-switching dosage of darbepoetin alfa injection does not match any of the dosages listed on the dosage adjustment table, the investigator/subinvestigator will select initial dosage from the 2 closest options on the table according to the subject's clinical status and Hb levels.

2) Initial dosage for subjects receiving epoetin alfa (recombinant), epoetin beta (recombinant), or epoetin kappa (recombinant) prior to switching

For subjects receiving epoetin alfa (recombinant), epoetin beta (recombinant), or epoetin kappa (recombinant) twice or three times a week prior to switching, the initial dosage of darbepoetin alfa injection will be selected according to Table (a) and administered using a once-weekly regimen initially. For subjects receiving epoetin alfa (recombinant), epoetin beta (recombinant), or epoetin kappa (recombinant) every week or every 2 weeks prior to switching, the initial dosage of darbepoetin alfa injection will be selected according to Table (b) and administered using a biweekly regimen initially. However, if the total dosage prior to switching does not match any of the dosages listed on Table (a) or Table (b), the investigator/subinvestigator will select initial dosage from the 2 closest ones listed on Table (a) or Table (b) considering the subject's clinical status and Hb levels.

Table (a)

Total dosage 1 week prior to switching	Initial dosage of darbepoetin alfa injection
≤3,000 IU	15 μg or placebo
4,500 IU	20 μg or placebo
6,000 IU	30 μg or placebo
9,000 IU	40 μg or placebo

Table (b)

Total dosage 2 weeks prior to switching	Initial dosage of darbepoetin alfa injection
≤3,000 IU	15 μg or placebo
4,500 IU	20 μg or placebo
6,000 IU	30 μg or placebo
9,000 IU	40 μg or placebo
12,000 IU	60 μg or placebo

3) Initial dosage for subjects receiving epoetin beta pegol (recombinant) prior to switching

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

5.2.3 Maintenance dosage and dosage adjustments

(1) MT-6548 Tablet

Maintenance dosage is 150–600 mg once daily and adjusted according to the dosage

adjustment guideline below.

(2) Darbepoetin alfa injection

The maintenance dosage is 5–180 μg per dose once a week, once every 2 weeks, or once every 4 weeks, which will be adjusted as appropriate according to the dosage adjustment guidelines below.

[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 adjustment will be performed at scheduled visits or on the day of darbepoetin alfa injection; however, an additional visit may be provided for dosage adjustment, if considered necessary, in cases where excessive increases or decreases in Hb levels are of concern based on the Hb time course. In principle, dosage of MT-6548 Tablets and darbepoetin alfa injection will be adjusted simultaneously. If interruption of study drug administration is necessary, administration of MT-6548 Tablets and darbepoetin alfa injection should be discontinued, and if study drug administration is resumed, administration of both drugs should be resumed.

Hb levels will be measured in samples collected in the supine position using a HemoCue® Hb201 DM analyzer; and in principle, these measurements will be used to determine dosage adjustments. Hb levels on the day of dialysis will be measured in samples collected before dialysis. Hb measurements used for dosage adjustment determinations will be recorded in the subject's 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 10.0–12.0 g/dL during the study. Dosage steps are defined in the dosage adjustment table below.

MT-6548 Tablet dosage adjustment table

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

Darbepoetin alfa injection dosage adjustment table

Step	Dosage
1	5 μg or placebo
2	10 μg or placebo
3	15 μg or placebo
4	20 μg or placebo
5	30 μg or placebo
6	40 μg or placebo
7	50 μg or placebo
8	60 μg or placebo
9	80 μg or placebo
10	100 μg or placebo
11	120 μg or placebo
12	140 μg or placebo
13	160 μg or placebo
14	180 μg or placebo

*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 table 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.

<u>Dosage adjustment algorithm</u>

- ✓ Dosage increases of MT-6548 Tablets should be performed at intervals of at least 4 weeks in principle, and dosage decreases at intervals of at least 2 weeks. Dosage increases and decreases of darbepoetin alfa injection should be performed at intervals of 2 weeks in principle.
- ✓ If Hb levels suddenly increase (>2.0 g/dL change in the past 4 weeks*), the dose should be decreased by 1 step.
- ✓ The dose should be increased by 1 step if Hb levels are <10.0 g/dL. However, decrease by 1 step instead of increasing in cases of sudden increase in Hb (more than 2.0 g/dL change

in past 4 weeks*).

- ✓ The dose should be decreased by 1 step if Hb levels are >11.5 g/dL.
- ✓ If Hb levels are >12.0 g/dL and ≤13.0 g/dL with a rapid increase in Hb levels (>2.0 g/dL change in the past 4 weeks*), study drug administration should be discontinued, and the dose should be decreased by 1 step and administration resumed after Hb levels decrease to ≤12.0 g/dL.
- ✓ If Hb levels are >13.0 g/dL, study drug administration should be discontinued, and the dose should be decreased by 1 step and administration resumed after Hb levels decrease to ≤12.0 g/dL.
- ✓ (Criteria only for darbepoetin alfa injection) If Hb levels are maintained in the range of 10.0–11.5 g/dL, the dose may be twice the single dose at that time, and the dose interval changed from once every week to once every 2 weeks, or from once every 2 weeks to once every 4 weeks.
- ✓ (Criteria only for darbepoetin alfa injection) If Hb levels do not reach the target levels even after doses of 180 μg, the dose should be either 80 or 100 μg per occasion, and dose interval should be changed from once every 4 weeks to once every 2 weeks, or from once every 2 weeks to once every week. Whether the dose should be 80 or 100 μg per occasion will be selected at the discretion of the investigator/coinvestigator.

*The rate of increase in Hb levels will be calculated using the Hb levels at the time points closest to 4 weeks among those measured 3–5 weeks prior to the day of dosage adjustment. A rate of change greater than 0.5 g/dL/week will be regarded as a rapid increase in Hb levels. If no Hb levels were measured 3–5 weeks prior to the day of dosage adjustment, the Hb levels measured at most recent time points prior to 5 weeks before the day of dosage adjustment will be used to calculate the rate of increase in Hb levels.

5.3 Duration of treatment

MT-6548 Tablets and darbepoetin alfa injection will be administered from the first day of the treatment period to the day before Week 52 of the treatment period.

6. Concomitant medications/therapies and rescue therapy

6.1 Prohibited concomitant medications and therapies

(1) ESA formulations

Concomitant use of epoetin alpha (recombinant), epoetin beta (recombinant), epoetin kappa (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant) is prohibited for the period from the first day of the treatment period to the completion of blood sampling for hematology tests on the final day of the treatment period, excluding the

study drug darbepoetin alfa injection. These restrictions do not apply to rescue therapy.

(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 concomitant medications and therapies

(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.

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.

(3) Hemodialysis

The type of hemodialysis is either hemodialysis or hemodiafiltration with a frequency of three times a week. In principle, a change in the type and frequency of hemodialysis is prohibited from the first day of the screening period to the completion of blood sampling for hematology tests on the final day of the treatment period; however, the type (hemodialysis and hemodiafiltration) and frequency may be changed if the investigator/subinvestigator considers it clinically necessary.

6.3 Rescue therapy

The following rescue therapy options will be provided as needed for subject safety. If any of the following rescue therapies is performed prior to the completion of the scheduled tests at Week 24 of the treatment period, that subject will be withdrawn from the study. If rescue therapies are performed after scheduled tests at Week 24 of the treatment period, the subject can 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 Tablets or darbepoetin alfa injection for ≥2 weeks and meets all criteria below, the investigator/subinvestigator may administer an ESA as a rescue therapy to improve Hb levels if necessary in order to secure subject safety. An ESA-based rescue therapy may also be provided without meeting the criteria below if the investigator/subinvestigator considers it necessary to secure subject safety, such as in cases of acute decreases in Hb levels. Study drug administration (MT-6548 Tablets or darbepoetin alfa injection) will be discontinued when an ESA-based rescue therapy is provided. Study drug treatment may be resumed after an improvement in Hb levels and should not be coadministered with a rescue therapy with an ESA. Subjects who are not expected to resume study drug treatment will be withdrawn from the study.

Administration of any ESA formulation other than the study drug is considered a rescue therapy. Dosage increase of darbepoetin alfa injection (including an increase not in accordance with the dosage adjustment algorithm) is not considered a rescue therapy.

- ✓ 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

Usually, RBC transfusions are performed when clinically necessary in instances of acute or major bleeding. For less sever anemia, which may be exacerbated, or moderate to severe anemia symptoms, RBC transfusions may be performed as needed clinically at the discretion of the investigator/subinvestigator.

(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 endpoint

Mean Hb at treatment period Weeks 20 and 24

(2) Secondary endpoints

1) Mean Hb at treatment period Weeks 48 and 52
2) Hb at each treatment period timepoint
3) Proportion of subjects with mean Hb levels within the target range (10.0–12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each timepoint in the treatment period

(3) Other endpoints

1) Ratio of subjects who received ESA rescue therapy
2) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.
3) Study drug dosage
4) MT-6548 group only: cumulative number of MT-6548 Tablet dosage adjustments
5) Quantity of iron administered
6) Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20%.
7) Change from baseline of iron-related measures (serum iron, total iron binding capacity (TIBC), TSAT, and serum ferritin) and hepcidin.

8) Changes from baseline in haematocrit, RBC count, reticulocytes (count and fraction), and erythropoietin (EPO)
9) 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) Dry weight
(5) Body weight
(6) Vital signs
(7) Fundoscopy
(8) Chest X-ray
(9) Proportion of subjects with documented Hb levels of ≥12.0 or ≥13.0 g/dL
(10) Ratio of subjects with Hb increase rates exceeding 0.5 g/dL/week.

7.3 Pharmacokinetic endpoints

Plasma concentration of unchanged MT-6548.

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 the subject meets one of the following criteria regarding hepatic function abnormalities during the study.
   1) ALT or AST > 3x ULN and total bilirubin > 2x ULN
   2) ALT or AST > 3x ULN and INR > 1.5*1
   3) ALT or AST > 8x ULN
   4) ALT or AST remains > 5x ULN over 2 weeks*2
   5) ALT or AST > 3x ULN with symptoms including e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia

   *1: The subject should be withdrawn from the study if the measurement of PT-INR is performed besides this study and the value meets the criterion.

   *2: Administration of the study drug should be avoided with ALT or AST > 5x ULN unless there are no other good therapeutic options.

(5) If rescue therapy is performed prior to conclusion of scheduled tests at Week 24.
(6) 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.
(7) If the subject no longer requires hemodialysis or hemodiafiltration.
(8) If the subject has undergone renal transplantation.
(9) If pregnancy of the subject is discovered.
(10) If the investigator/subinvestigator determines a subject should withdraw from the study for any other reason.

9. The criteria of the temporary discontinuation of study drugs

Subjects will temporary discontinue the study drug if either of the following criteria is met:

(1) Based on the dosage adjustment guideline.
(2) ALT or AST > 3x ULN without total bilirubin > 2x ULN during the study.

10. Target sample size

The number of subjects registered in the treatment period will be 300 in total (150 each for the MT-6548 and darbepoetin groups).

10.1 Rationale for target sample size

The primary endpoint of mean Hb levels in the darbepoetin group at Weeks 20 and 24 of the treatment period are assumed to be 11.0 g/dL with a difference in the Hb levels between the MT-6548 and darbepoetin groups of 0 g/dL and a common standard deviation of 1.73 g/dL. The non-inferiority margin is set at -0.75 g/dL. When the detection power was calculated based on these assumptions, 150 sujbects per group were required to ensure that the mean of mena Hb levels in the MT-6548 group and its 95% confidence interval are included within the target Hb range (10.0–12.0 g/dL) with a probability of achieving non-inferiority being >95%.

The assumed standard deviation of 1.73 g/dL was based on the upper limit of the 95% confidence interval (two-sided) for the standard deviation in the MT-6548 300 mg group at Week 6 in Study CI-0022.

11. Study period

[redacted]

12. Test and observation schedule

Item \ Visit	Informed consent	Screening period [a]		Treatment period [b]																		Final day of the follow-up observation [c]
				Treatment period Phase 1										Treatment period Phase 2								
		First day	Visit 2	First day	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	Day of discontinuation	
Visit number	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	FU
Permitted range (days)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7 or +14 [d]	+7
Procedure/evaluation																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X	X	X																		
Allocation				X																		
Patient background and history	X			X																		
Height				X																		
Dry weight, body weight [e]				X						X			X			X				X	X	
Forlic acid and vitamin B_{12} [f]		X																				
Pregnancy test [h]		X											X							X	X	
Hematology tests [f], [g], [i]		X	X [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry test [f], [g], [k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein [f], [g]		X		X									X							X	X	
Iron-related measures [f], [g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepcidin [g]				X	X	X	X			X			X			X				X	X	
EPO [g]				X	X	X	X			X			X			X				X	X	
VEGF [g]				X						X			X			X				X	X	
DHEA-S [g]				X						X			X			X				X	X	
Vital signs [f], [g], [l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Resting standard 12-lead ECG [g], [m]				X									X							X	X	
Fundoscopy [d]		X										X							X		X	
Chest X-ray [d]		X										X							X		X	
Duration of hemodialysis				X									X							X	X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X							X	X	
AE investigation [n]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK testing						X				X			X									
Blood sampling for genetic analysis [o]				Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period																		
Blood sampling for plasma protein binding test [p]		X																				
Product evaluatio/procedure																						
Investigation of concomitant medications/therapies				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MT-6548 tablets [q], [r], [s]				Administered according to the dosage adjustment guidelines																		
Darbepoetin alfa injection [r], [t]				Administered according to the dosage adjustment guidelines																		
Iron supplements		Iron supplements administered to maintain a serum ferritin level of ≥100 ng/mL or a TSAT of ≥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] During the treatment period, subjects are to visit the study site on the day of dialysis after a 2-day interdialytic interval; however, if this is difficult, subjects are to visit the study site on the day of dialysis after a 1-day interdialytic interval.

[c] Not required if withdrawn prior to the treatment period.

[d] Fundoscopy and chest X-ray performed once during screening period, once during Weeks 20–24 of treatment period, and once during Weeks 48–52 of treatment period. In the case of discontinuation of the treatment period, fundoscopy and chest X-ray should be performed within 14 days after discontinuation whenever possible.

[e] Body weights should be measured before and after dialysis.

[f] To be measured before dialysis on the day of dialysis during the screening period.

[g] Tests during the treatment period should be performed before dialysis on the day of dialysis.

[h] To be performed only in female subjects of childbearing potential.

[i] Hb levels should be measured in blood collected in the supine position.

[j] Only Hb levels should be measured.

[k] Only urea nitrogen levels should be measured before and after dialysis on the first day, Weeks 24 and 52 of the treatment period, and on the day of treatment discontinuation.

[l] To be measured in the sitting position after a 5-minute rest before blood sampling whenever possible.

[m] To be measured in the supine position after a 5-minute rest before blood sampling whenever possible.

[n] AE investigation begins after study drug administration.

[o] For subjects giving consent to blood sampling for genetic analysis, blood will be collected once as early as possible after Week 2 of the treatment period.

[p] For subjects giving consent to the plasma protein binding rate study, blood will be collected once before study drug administration on the day of dialysis before dialysis.

[q] MT-6548 Tablets should be prescribed depending on the number of unused tablets by the subject. Subjects should be instructed to open a new bottle after using up the tablets in one bottle.

[r] In principle, dosage adjustments should be performed at scheduled visits or on the day of darbepoetin alfa injection; however, an additional visit may be provided for dosage adjustment, if considered necessary, in cases where excessive increases or decreases in Hb levels are of concern based on the Hb time course.

[s] The first dose should be administered after completion of the scheduled tests on the first day of

the treatment period.

[t] The first dose should be administered after completion of the scheduled tests on the first day of the treatment period; however, the tests scheduled after dialysis should be performed before the first dose whenever possible.

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].

Dialysis is the most popular treatment for end-stage renal disease in Japan, and hemodialysis and hemodiafiltration are particularly common modalities. A survey by the Japanese Society for Dialysis Therapy (JSDT) ("An overview of regular dialysis treatment in Japan as of December 31, 2015") showed that 79.5% of all patients on dialysis at the end of 2015 were on hemodialysis, and 17.0% were on hemodiafiltration.

Erythropoiesis-stimulating agents (ESAs), which include epoetin alfa (recombinant), epoetin beta (recombinant), epoetin kappa (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant), are the standard therapy for anemia in patients with hemodialysis-dependent chronic kidney disease (HD-CKD).

(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, reducing HIF-α levels with von Hippel-Lindau (VHL)-dependent breakdown of HIF-α. 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 production[11].

(3) Nonclinical and clinical study results

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

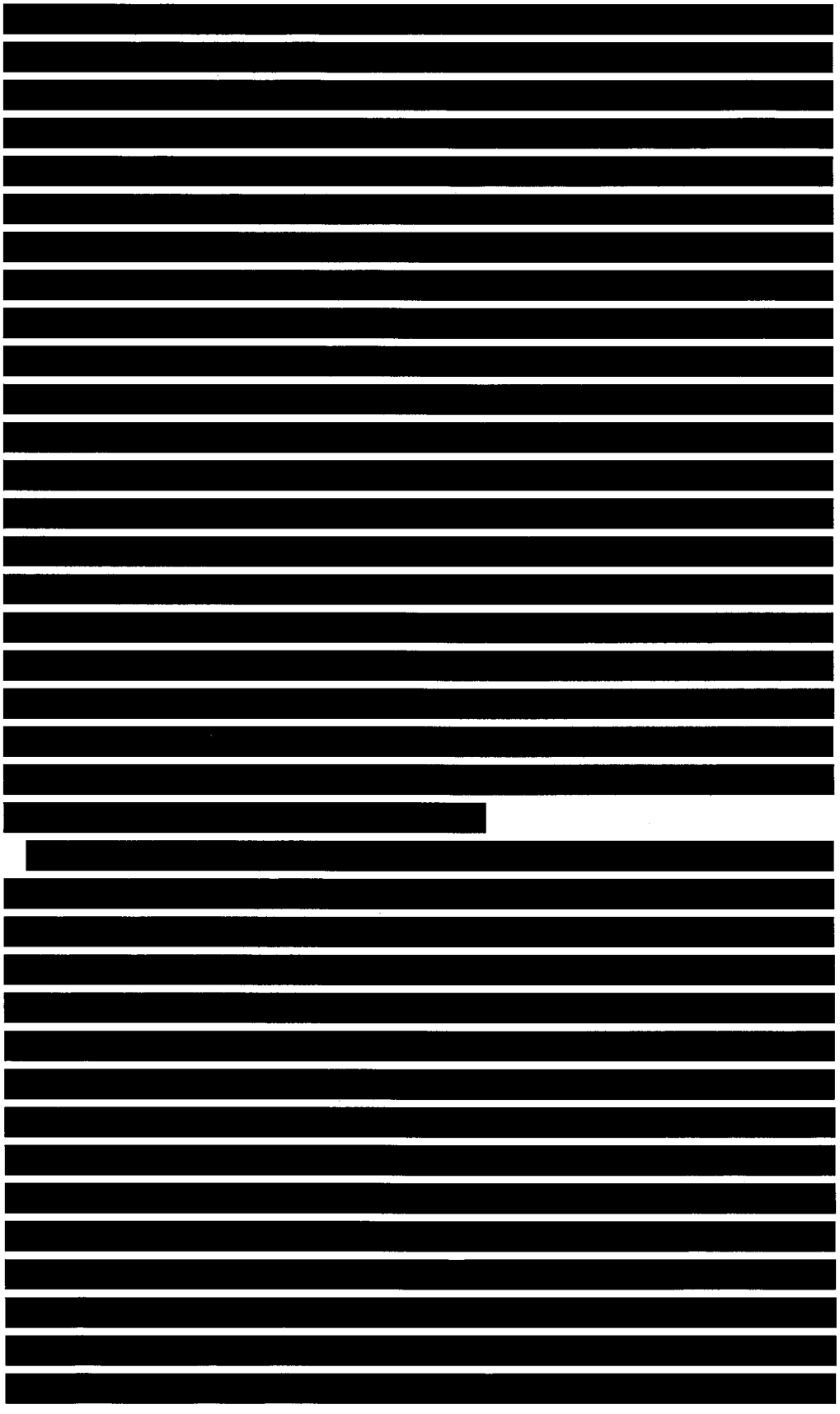
[redacted]

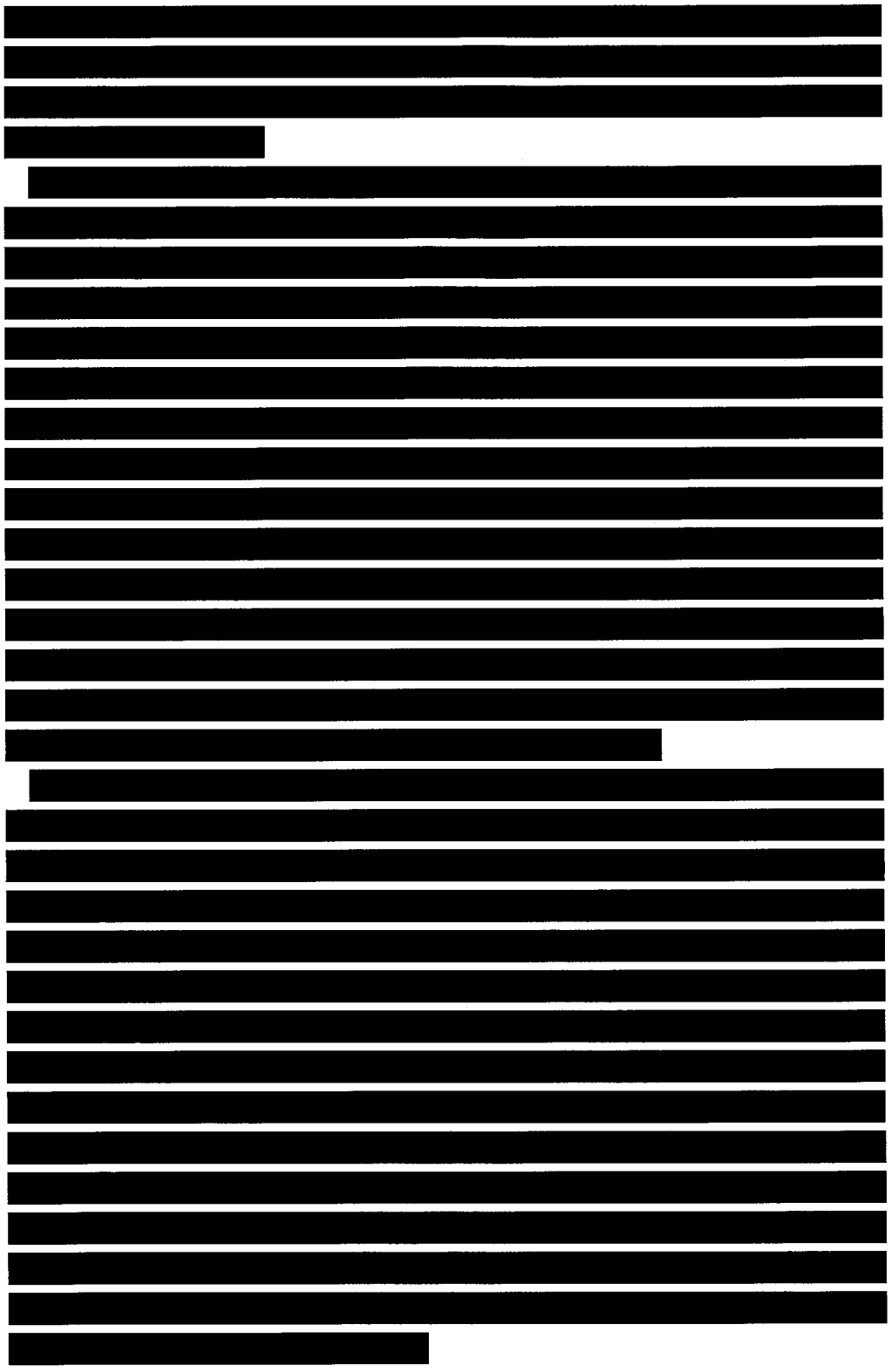
[redacted]

hemoglobinuric nephropathy in a 7-day repeated-dose toxicity study in rats, and vomiting

[redacted]

[redacted]





(4) Investigational plan

The current study will evaluate efficacy and safety of MT-6548 in patients with

HD-CKD-related anaemia who are receiving ESA treatment.

Darbepoetin alfa (recombinant), which is a standard therapy for nephrogenic anaemia, is used as a control drug. Hb levels are used as a measure of efficacy in order to evaluate non-inferiority of MT-6548 with darbepoetin alfa (recombinant).

Based on results of clinical studies to date, the treatment period is set at 24 weeks, considered treatment period Phase 1, an appropriate period to enable evaluation of MT-6548 efficacy in terms of switching maintenance. Meanwhile, total treatment period is set at 52 weeks in order to evaluate safety in long-term administration, with the period from Week 24 to Week 52 of treatment period considered treatment period Phase 2.

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 study will assess non-inferiority of MT-6548 in patients with HD-CKD-related anaemia receiving ESA treatment using Hb values as a measure and darbepoetin alfa (recombinant) as a control drug, as well as safety of long-term administration of MT-6548.

3. Subjects

3.1 Subjects

Patients with anemia associated with HD-CKD

3.2 Inclusion criteria

Subjects must meet all inclusion criteria below and have capacity to grant informed consent. Laboratory tests related to the inclusion criteria will be assessed based on central laboratory measurements. If a given laboratory test is performed multiple times during the screening period, the most recent test will be used for assessment. If blood is drawn on the day of dialysis, data obtained before dialysis will be used for assessment. In addition, Hb values in blood collected in the supine position will be used for assessment.

(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 received either hemodialysis or hemodiafiltration three times a week for at least 12 weeks prior to the first day of the screening period; however, patients on home dialysis and those receiving a combined therapy of home hemodialysis and peritoneal dialysis are excluded

(4) 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) in the 8 weeks prior to the first day of the screening period, using the dosages described below

Dosage:

- ✓ Epoetin alpha (recombinant), epoetin beta (recombinant), and epoetin kappa (recombinant): ≤9000 IU every week
- ✓ Darbepoetin alfa (recombinant): ≤60 μg every week
- ✓ Epoetin beta pegol (recombinant): ≤250 μg every 4 weeks

(5) Patients with a mean Hb value (mean of the latest two measurements) of ≥9.5 g/dL and ≤12.0 g/dL during the screening period

(6) Patients with an Hb difference of <1.5 g/dL between the latest two measurements during the screening period

(7) Patients with a serum ferritin value of ≥100 ng/mL or a transferrin saturation (TSAT) of ≥20% during the screening period

(8) Patients with folic acid and vitamin B_{12} values above the lower limit of normal 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) Set to ensure patients stable on hemodialysis or hemodiafiltration with reference to the "Guidelines for Clinical Evaluation of Therapeutic Drugs" for Renal Anemia (PFSB/ELD Notification No. 0930-2).
(4) 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 the upper limit of dosage was set because only patients whose dosage does not exceed the normal maintenance dosage described in the package insert are eligible for the study.
(5) Set to ensure patients with controlled Hb with reference to target Hb values in nephrogenic anaemia therapy in the JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015".
(6) Set to ensure appropriate efficacy evaluation by targeting patients without significant fluctuations in Hb levels.
(7) 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."
(8) 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 related to the exclusion criteria will be assessed based on central laboratory measurements. If a given laboratory test is performed multiple times during the screening period, the most recent test will be used for assessment. If blood is drawn on the day of dialysis, data before dialysis will be used for assessment.

(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 who are expected to no longer require hemodialysis or hemodiafiltration due to recovery of renal function

(7) 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.

(8) Patients with poorly controlled hypertension (defined as a systolic blood pressure [BP] of >180 mmHg or diastolic BP of >110 mmHg) on the first day of the screening period and on the first day of the treatment period

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

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

(11) 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.

(12) 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).

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

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

(15) 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.

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

(17) 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).

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

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

(20) 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.

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

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

Rationale

(1)–(4), (6), (18) These were considered likely to affect drug efficacy evaluation of MT-6548.

(5), (7)–(16), (19) Set in regard for patient safety and ethics.

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

(20) (21) 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.

(22) 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 may be performed during the screening period at the discretion of the investigator/subinvestigator for any subject whose laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, and total bilirubin) or BP do not meet the inclusion criteria or meet the exclusion criteria during the screening period.

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

For any subject whose laboratory values (Hb, serum ferritin, TSAT, folic acid, vitamin B_{12}, AST, ALT, and total bilirubin), BP, or BP measurements on the first day of the treatment period do not meet the inclusion criteria or meet the exclusion criteria during the screening period, re-screening may be performed if the investigator/subinvestigator considers that the

subject may become eligible for the study due to natural course or with drug therapy. 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, subject inclusion criteria, and probabilities of being assigned to different study groups).
(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

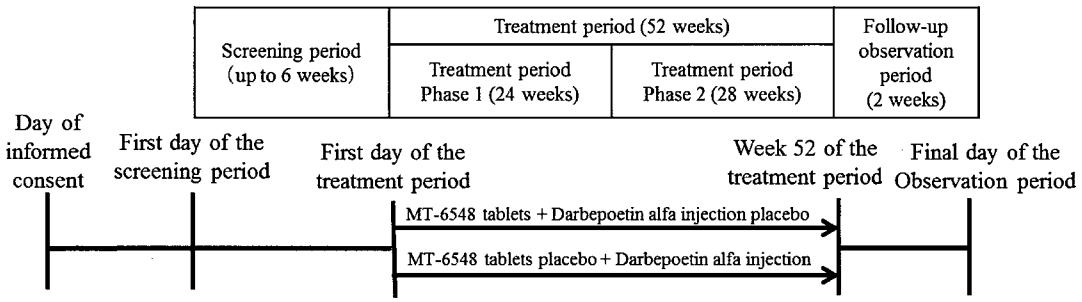
5.1 Study phase and type

Study phase: Phase 3

Study type: Confirmatory study

5.2 Study design

This is a multicenter, randomized, double-blind, active-controlled, double-dummy, parallel group comparative 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. Testing may be repeated 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 52 of the treatment period or discontinuation of treatment).

The treatment period consists of phase 1 and phase 2, as defined below.

- ✓ Treatment period Phase 1: From completion of scheduled tests for the first day of the treatment period to completion of scheduled tests for Week 24 of the treatment period. Treatment period Phase 1 will be double-blind.
- ✓ Treatment period Phase 2: From the completion of the tests specified for Week 24 of the treatment period to the completion of tests specified for Week 52 of the treatment period. Even after all subjects complete the treatment period Phase I and the key

code is opened, the subjects, study institution staff members, and monitoring personnel will remain blinded to treatment. Details of the procedure of maintaining the blindness will be separately defined before opening of the key code.

During the treatment period, subjects are to visit the study site on the day of dialysis after a 2-day interdialytic interval; however, if this is difficult, subjects are to visit the study site on the day of dialysis after a 1-day interdialytic interval. After the first day of the treatment period, subjects are to visit the study site every 2 weeks until Week 12 and every 4 weeks after Week 12 to undergo the scheduled test. However, subjects are to visit the study site at shorter intervals as necessary, if excessive increases or decreases in Hb are of concern based on the time course of Hb levels, the dose interval of darbepoetin alfa injection is shorter than the scheduled visit interval, or for hemodialysis.

(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: The treatment period is set at 24 weeks, considered treatment period Phase 1, an appropriate period to enable evaluation of MT-6548 efficacy in terms of switching maintenance. Meanwhile, total treatment period is set at 52 weeks in order to evaluate safety in long-term administration, with the period from Week 24 to Week 52 of treatment period considered treatment period Phase 2.

Follow-up observation period: The follow-up observation period for MT-6548 Tablet and darbepoetin alfa injection was set at 2 weeks considering the elimination half-life of these drugs in order to investigate AEs occurring after completion of treatment.

5.3 Randomization methods

5.3.1 Blinding methods

Treatment period Phase 1 of the main study will be double-blind. Blinding for the main study will be performed by not informing those involved in conducting the study of which study drug is being administered and by using a placebo indistinguishable from the active comparator. The key code for data up to Week 24 of treatment period Phase 1 will be opened after data are fixed. However, even after that point, blinding of subjects, study center staff, and monitoring staff will be maintained until completion of the final data are fixed at the end of the study. Details of the procedure of maintaining the blindness will be separately defined before opening of the key code.

The organization contracted to perform randomization will create one original and one copy of the material list and one original each of the randomized key code list and allocation number list. To prevent disclosure of key code information to unauthorized parties, they will store and manage originals of the material list, randomized key code list, and allocation number list in a secure manner until the key code is opened. One original each of the material list, randomized key code list, and allocation number list will be opened when all CRFs for treatment period Phase 1 have been completed, data lock has occurred, and the manner of handling the data has been determined.

Upon receiving a request from the sponsor, the organization contracted to perform randomization will submit one copy of the material list to the sponsor's investigational drug QA manager for allocation of the study drugs. The sponsor's investigational drug manufacturing control manager will prepare study drugs with affixed kit codes based on the material list. They will prepare MT-6548 Tablet in such a way that the placebo and active comparator cannot be distinguished by their external appearance. They will also prepare darbepoetin alfa injection in such a way that the placebo and active comparator, as well as the different strengths, cannot be distinguished by their external appearance. To prevent disclosure of key code information to parties not involved in study drug allocation, the sponsor's investigational drug QA manager will store and manage the copy of the material list in a secure manner until the key code is opened.

The organization contracted to perform randomization will create an emergency key for addressing emergency situations and will provide this key to the emergency call center. To prevent disclosure of key code information to unauthorized parties, the emergency call center will store and manage the key in a secure manner until completion of the study. The organization contracted to perform randomization will create a key code for suspected unexpected serious adverse reaction (SUSAR) unblinding in the event that [redacted] the company conducting clinical studies of MT-6548 outside Japan, must submit a SUSAR report to foreign regulatory authorities, and will provide this key code to the emergency call center. To prevent disclosure of key code information to unauthorized parties, the emergency call center will store and manage the key code for SUSAR unblinding and reporting to foreign regulatory authorities in a secure manner until the key code is

opened.

The organization contracted to perform randomization will provide key code information to the contract testing laboratory. The contract testing laboratory will use this information to only send samples from the MT-6548 group to the drug concentration measurement laboratory. To prevent disclosure of key code information to unauthorized parties, the contract testing laboratory will store and manage key code information in a secure manner until the key code is opened. To prevent disclosure of plasma drug concentration measurements to unauthorized parties, the drug concentration measurement laboratory will store plasma drug concentration measurements in a secure manner until the key code is opened. Plasma drug concentration measurements will not be disclosed to subjects, study center staff, or monitoring staff until completion of the final data lock at the end of the study.

To prevent disclosure of EPO measurements to unauthorized parties, the contract testing laboratory will store and manage EPO measurements in a secure manner until the key code is opened. EPO measurements will not be disclosed to subjects, study center staff, or monitoring staff until completion of the final data lock at the end of the study. Study centers are prohibited from measuring EPO during the treatment period in order to maintain blinding.

5.3.2 Randomization and allocation methods

The organization contracted to perform randomization will create a randomized key code list in accordance with predefined procedures for creation and storage of randomized key code lists. When a subject is judged to be eligible to transition to the treatment period, the online enrollment system will allocate a treatment group on the basis of the randomized key code list and send a notification with the allocation number. Specifics of randomization will be defined in the enrollment center subject allocation specifications.

Randomized allocation will be performed such that the MT-6548 group and the darbepoetin groups are the same size.

5.4 Endpoints

5.4.1 Efficacy endpoint

(1) Primary endpoint

Mean Hb at treatment period Weeks 20 and 24

(2) Secondary endpoints

1) Mean Hb at treatment period Weeks 48 and 52
2) Hb at each treatment period timepoint

3) Proportion of subjects with mean Hb levels within the target range (10.0–12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each timepoint in the treatment period

(3) Other endpoints

1) Ratio of subjects who received ESA rescue therapy
2) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.
3) Study drug dosage
4) MT-6548 group only: cumulative number of MT-6548 Tablet dosage adjustments
5) Quantity of iron administered
6) Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20%.
7) Change from baseline of iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin.
8) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and EPO.
9) QOL measures (EQ-5D-5L, KDQOL)

Rationale

(1) Primary endpoint

Hb level was set as the primary endpoint because this is already established as the standard assessment measure for nephrogenic anaemia treatment. Mean Hb levels at treatment period Weeks 20 and 24 was set because of possible fluctuations in Hb levels.

(2) Secondary endpoints

Secondary endpoints were set in order to comprehensively evaluate effects on Hb levels.

(3) 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.

5.4.2 Safety endpoints

(1) Adverse events and adverse drug reactions
(2) Laboratory test values
(3) Resting standard 12-lead ECG
(4) Dry weight
(5) Body weight
(6) Vital signs
(7) Fundoscopy
(8) Chest X-ray
(9) Proportion of subjects with documented Hb levels of ≥12.0 or ≥13.0 g/dL

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

Rationale

(1)–(6) (8) Set to evaluate general safety for HD-CKD patients.

(7) Set to evaluate effects of MT-6548 on fundus oculi.

(9) (10) Set to evaluate excessive or acute increase of Hb levels.

5.4.3 Pharmacokinetic endpoints

Plasma concentration of unchanged MT-6548.

Rationale

Set to evaluate pharmacokinetic parameters of MT-6548 in HD-CKD patients.

6. Target sample size and study period

6.1 Target sample size

The number of subjects registered in the treatment period will be 300 in total (150 each for the MT-6548 and darbepoetin groups).

Rationale

The primary endpoint of mean Hb levels in the darbepoetin group at Weeks 20 and 24 of the treatment period are assumed to be 11.0 g/dL with a difference in the Hb levels between the MT-6548 and darbepoetin groups of 0 g/dL and a common standard deviation of 1.73 g/dL. The non-inferiority margin is set at -0.75 g/dL. When the detection power was calculated based on these assumptions, 150 sujbects per group were required to ensure that the mean of Hb levels in the MT-6548 group and its 95% confidence interval are included within the target Hb range (10.0–12.0 g/dL) with a probability of achieving non-inferiority being >95%.

The assumed standard deviation of 1.73 g/dL was based on the upper limit of the 95% confidence interval (two-sided) for the standard deviation in the MT-6548 300 mg group at Week 6 in Study CI-0022.

6.2 Study period

[redacted]

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.

(2) Control drug

1) MT-6548 Tablet placebo

Dosage form and content: Film-coated tablets visually indistinguishable from MT-6548 Tablet 150 mg without containing vadadustat

2) Darbepoetin alfa injection active comparator (see Attachment 6 NESP® injection package insert for information on darbepoetin alfa [recombinant])

Name: Darbepoetin alfa injection 5 μg
Darbepoetin alfa injection 10 μg
Darbepoetin alfa injection 20 μg
Darbepoetin alfa injection 40 μg
Darbepoetin alfa injection 60 μg

Nonproprietary name: Darbepoetin alfa (recombinant)

Dosage form and content: Visually indistinguishable plastic syringes, each (0.5 mL) containing 5, 10, 20, 40, or 60 μg of darbepoetin alfa (recombinant)

3) Darbepoetin alfa injection placebo

Dosage form and content: Plastic syringes visually indistinguishable from darbepoetin alfa injection active comparator without containing darbepoetin alfa (recombinant)

7.2 Study drug packaging and labelling

(1) Packaging

1) MT-6548 Tablet

Each bottle contains 100 tablets of MT-6548.

2) Darbepoetin alfa injection

Each darbepoetin alfa injection syringe is packaged inside a single bag inside a single box.

(2) Labelling

1) MT-6548 Tablet

Clinical Study Drugs MT-6548 Tablet 150 mg or Placebo 100 tablets
Study no.: MT-6548-J01 Kit code: XXXXXX
Storage method: Please store at 1–30°C. Lot no.: XXXXX
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

2) Darbepoetin alfa injection

Top

Clinical Study Drugs Darbepoetin alfa injection or Placebo
Study no.: MT-6548-J03 Lot no.: XXXXXXX
Storage method: Store at 2–8°C away from light. Avoid freezing. Expiration date: 20XX /

* See separate instructions for handling, storage, management, etc. of the study drugs.
* Unused study drug will be collected after the study.
Mitsubishi Tanabe Pharma Corporation, 3-2-10 Dosho-machi, Chuo-ku, Osaka

Side

Clinical Study Drugs Darbepoetin alfa injection or Placebo
Study no.: MT-6548-J01 Kit code: XXXXXXX

7.3 Storage method

(1) MT-6548 Tablet

Store between 1–30°C.

(2) Darbepoetin alfa injection

Store at 2–8°C away from light. Avoid freezing.

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.).

7.5 Procedure for opening the emergency key

In the event of an SAE or other such situation in which urgent identification of the allocated study drug would be necessary to ensure subject safety, investigators will address the situation by following the "Procedures for Opening the Emergency Key". That subject will be withdrawn from the study after opening of their emergency key. The investigator opening the key should promptly make a written record of the reason for doing so and submit that information to the sponsor.

In the event it is necessary to identify the allocated study drug due to safety concerns that would affect the risk-benefit balance of that study drug, the sponsor's investigational drug safety manager will address the situation by following the "Procedures for Opening the Emergency Key". The sponsor's investigational drug safety manager will record the reason for key opening and items discussed and store that information in accordance with internal corporate procedures.

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 or clinical coordinators will input necessary information about subjects who have granted informed consent in the online enrollment system.

(3) The online enrollment system will determine whether consent processing and enrollment is possible based on the input information, and inform the investigators/subinvestigators, clinical coordinators, and study sponsor of the result online.

8.2.2 Screening period

(1) Investigators/subinvestigators will confirm subject suitability on the first day of the screening period.

(2) Investigators/subinvestigators or clinical coordinators will input necessary information into the online enrollment system on the first day of the screening period.

(3) The online enrollment system will determine whether screening period enrollment is possible based on the input information, and inform the investigators/subinvestigators, clinical coordinators, and study sponsor of the result online.

Enrollment using the online enrollment system 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 or clinical coordinators will input necessary information into the online enrollment system on the first day of the treatment period.
(3) The online enrollment system will determine whether or not a subject can transition to the treatment period on the basis of input information and test results obtained from the contract testing laboratory. A notification with the result of this determination, along with the allocation number and kit code if the result was "eligible", will be sent to investigators/subinvestigators, clinical coordinators, and the sponsor through the online enrollment system.
(4) Investigators/subinvestigators will take the following actions toward the subject depending on the determination of the online enrollment system.
   ✓ 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 or clinical coordinators will input necessary information in the online enrollment system about subjects who are withdrawn from the study after granting informed consent.
(2) The online enrollment system will inform the investigators/subinvestigators, clinical coordinators, and study sponsor of the processing.

8.3 Dosage and administration

The investigator/subinvestigator will administer both MT-6548 Tablets and darbepoetin alfa injection to subjects during the treatment period. Contents of the study drug are shown below; subjects, study institution staff members, and monitoring personnel will remain blinded to treatment until the final data has been fixed at the end of the study. The kit code of the study drug will be notified on the Web registration system every time the study drug is prescribed.

MT-6548 group: MT-6548 Tablet 150 mg and darbepoetin alfa injection placebo will be administered.

Darbepoetin group: MT-6548 Tablet placebo and darbepoetin alfa injection active comparator will

be administered.

8.3.1 Administration method

(1) MT-6548 Tablet

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.)

(2) Darbepoetin alfa injection

Intravenous administration. Darbepoetin alfa injection should be administered on the day of dialysis after a 2-day interdialytic interval in principle. (The first dose should be administered after completion of the scheduled tests on the first day of the treatment period; however, the tests scheduled after dialysis should be performed before the first dose whenever possible.)

8.3.2 Initial dose and dose interval

(1) MT-6548 Tablet

Single daily dose of 300 mg (2 tablets)

(2) Darbepoetin alfa injection

1) Initial dosage for subjects receiving darbepoetin alfa (recombinant) prior to switching

The same pre-switching dosage of darbepoetin alfa (recombinant) will be used after switching as initial dosage. The same dose interval will be used as well. However, if pre-switching dosage of darbepoetin alfa injection does not match any of the dosages listed on the dosage adjustment table, the investigator/subinvestigator will select initial dosage from the 2 closest options on the table according to the subject's clinical status and Hb levels.

2) Initial dosage for subjects receiving epoetin alfa (recombinant), epoetin beta (recombinant), or epoetin kappa (recombinant) prior to switching

For subjects receiving epoetin alfa (recombinant), epoetin beta (recombinant), or epoetin kappa (recombinant) twice or three times a week prior to switching, the initial dosage of darbepoetin alfa injection will be selected according to Table (a) and administered using a once-weekly regimen initially. For subjects receiving epoetin alfa (recombinant), epoetin beta (recombinant), or epoetin kappa (recombinant) every week or every 2 weeks prior to

switching, the initial dosage of darbepoetin alfa injection will be selected according to Table (b) and administered using a biweekly regimen initially. However, if the total dosage prior to switching does not match any of the dosages listed on Table (a) or Table (b), the investigator/subinvestigator will select initial dosage from the 2 closest ones listed on Table (a) or Table (b) considering the subject's clinical status and Hb levels.

Table (a)

Total dosage 1 week prior to switching	Initial dosage of darbepoetin alfa injection
≤3,000 IU	15 μg or placebo
4,500 IU	20 μg or placebo
6,000 IU	30 μg or placebo
9,000 IU	40 μg or placebo

Table (b)

Total dosage 2 weeks prior to switching	Initial dosage of darbepoetin alfa injection
≤3,000 IU	15 μg or placebo
4,500 IU	20 μg or placebo
6,000 IU	30 μg or placebo
9,000 IU	40 μg or placebo
12,000 IU	60 μg or placebo

3) Initial dosage for subjects receiving epoetin beta pegol (recombinant) prior to switching

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

8.3.3 Maintenance dosage and dosage adjustments

(1) MT-6548 Tablet

Maintenance dosage is 150–600 mg once daily and adjusted according to the dosage

adjustment guideline below.

(2) Darbepoetin alfa injection

The maintenance dosage is 5–180 μg per dose once a week, once every 2 weeks, or once every 4 weeks, which will be adjusted as appropriate according to the dosage adjustment guidelines below.

[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 adjustment will be performed at scheduled visits or on the day of darbepoetin alfa injection; however, an additional visit may be provided for dosage adjustment, if considered necessary, in cases where excessive increases or decreases in Hb levels are of concern based on the Hb time course. In principle, dosage of MT-6548 Tablets and darbepoetin alfa injection will be adjusted simultaneously. If interruption of study drug administration is nececcary, administration of MT-6548 Tablets and darbepoetin alfa injection should be discontinued, and if study drug administration is resumed, administration of both drugs should be resumed.

Hb levels will be measured in samples collected in the supine position using a HemoCue® Hb201 DM analyzer; and in principle, these measurements will be used to determine dosage adjustments. Hb levels on the day of dialysis will be measured in samples collected before dialysis. Hb measurements used for dosage adjustment determinations will be recorded in the subject's 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 10.0–12.0 g/dL during the study. Dosage steps are defined in the dosage adjustment table below.

MT-6548 Tablet dosage adjustment table

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

Darbepoetin alfa injection dosage adjustment table

Step	Dosage
1	5 μg or placebo
2	10 μg or placebo
3	15 μg or placebo
4	20 μg or placebo
5	30 μg or placebo
6	40 μg or placebo
7	50 μg or placebo
8	60 μg or placebo
9	80 μg or placebo
10	100 μg or placebo
11	120 μg or placebo
12	140 μg or placebo
13	160 μg or placebo
14	180 μg or placebo

*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 table 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

- ✓ Dosage increases of MT-6548 Tablets should be performed at intervals of at least 4 weeks in principle, and dosage decreases at intervals of at least 2 weeks. Dosage increases and decreases of darbepoetin alfa injection should be performed at invervals of 2 weeks in principle.
- ✓ If Hb levels suddenly increase (>2.0 g/dL change in the past 4 weeks*), the dose should be decreased by 1 step.
- ✓ The dose should be increased by 1 step if Hb levels are <10.0 g/dL. However, decrease by

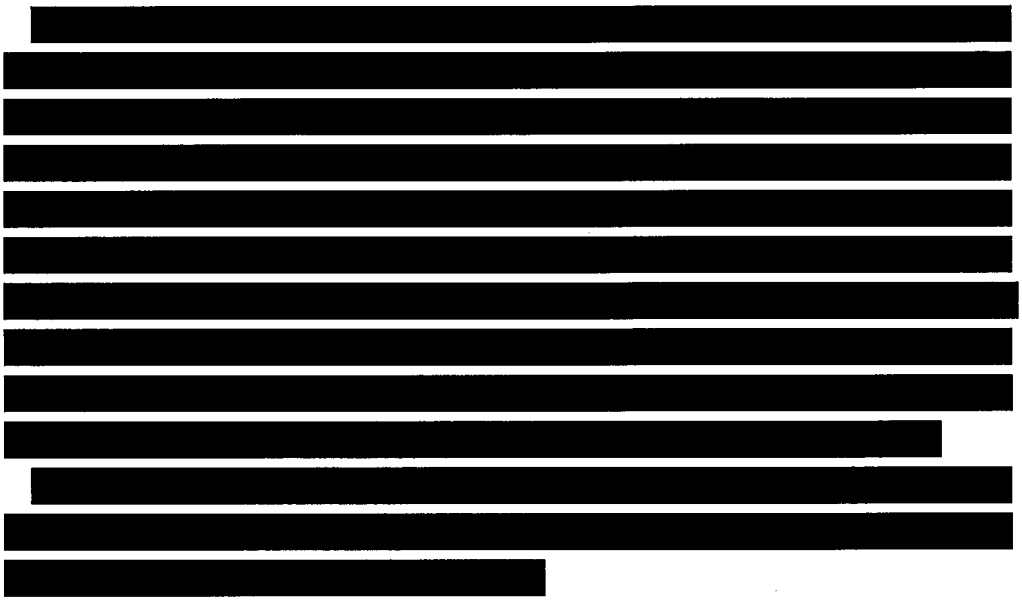
1 step instead of increasing in cases of sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*).

- ✓ The dose should be decreased by 1 step if Hb levels are >11.5 g/dL.
- ✓ If Hb levels are >12.0 g/dL and ≤13.0 g/dL with a rapid increase in Hb levels (>2.0 g/dL change in the past 4 weeks*), study drug administration should be discontinued, and the dose should be decreased by 1 step and administration resumed after Hb levels decrease to ≤12.0 g/dL.
- ✓ If Hb levels are >13.0 g/dL, study drug administration should be discontinued, and the dose should be decreased by 1 step and administration resumed after Hb levels decrease to ≤12.0 g/dL.
- ✓ (Criteria only for darbepoetin alfa injection) If Hb levels are maintained in the range of 10.0–11.5 g/dL, the dose may be twice the single dose at that time, and the dose interval changed from once every week to once every 2 weeks, or from once every 2 weeks to once every 4 weeks.
- ✓ (Criteria only for darbepoetin alfa injection) If Hb levels do not reach the target levels even after doses of 180 μg, the dose should be either 80 or 100 μg per occasion, and dose interval should be changed from once every 4 weeks to once every 2 weeks, or from once every 2 weeks to once every week. Whether the dose should be 80 or 100 μg per occasion will be selected at the discretion of the investigator/coinvestigator.

*The rate of increase in Hb levels will be calculated using the Hb levels at the time points closest to 4 weeks among those measured 3–5 weeks prior to the day of dosage adjustment. A rate of change greater than 0.5 g/dL/week will be regarded as a rapid increase in Hb levels. If no Hb levels were measured 3–5 weeks prior to the day of dosage adjustment, the Hb levels measured at most recent time points prior to 5 weeks before the day of dosage adjustment will be used to calculate the rate of increase in Hb levels.

Rationale

(1) MT-6548 Tablet



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."

(2) Darbepoetin alfa injection

Dosage for darbepoetin alfa (recombinant) (product name: Nesp® Injection) was set according to the drug's package insert.

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

MT-6548 Tablets and darbepoetin alfa injection will be administered from the first day of the treatment period to the day before Week 52 of the treatment period.

8.5 Concomitant medications and therapies and rescue therapy

8.5.1 Prohibited concomitant medications and therapies

(1) ESA formulations

Concomitant use of epoetin alpha (recombinant), epoetin beta (recombinant), epoetin kappa (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant)

is prohibited for the period from the first day of the treatment period to the completion of blood sampling for hematology tests on the final day of the treatment period, excluding the study drug darbepoetin alfa injection. These restrictions do not apply to rescue therapy.

(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 concomitant medications and therapies

(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.

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.

(3) Hemodialysis

The type of hemodialysis is either hemodialysis or hemodiafiltration with a frequency of three times a week. In principle, a change in the type and frequency of hemodialysis is prohibited from the first day of the screening period to the completion of blood sampling for hematology tests on the final day of the treatment period; however, the type (hemodialysis and hemodiafiltration) and frequency may be changed if the investigator/subinvestigator considers it clinically necessary.

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.
(3) It was determined that subjects should continue the same type of hemodialysis at the same frequency due to potential effects of changes in these items on evaluation of MT-6548 efficacy.

8.5.3 Rescue therapy

The following rescue therapy options will be provided as needed for subject safety. If any of the following rescue therapies is performed prior to the completion of the scheduled tests at Week 24 of the treatment period, that subject will be withdrawn from the study. If rescue therapies are performed after scheduled tests at Week 24 of the treatment period, the subject can 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 Tablets and darbepoetin alfa injection for ≥2 weeks and meets all criteria below, the investigator/subinvestigator may administer an ESA as a rescue therapy to improve Hb levels if necessary in order to secure subject safety. An ESA-based rescue therapy may also be provided without meeting the criteria below if the investigator/subinvestigator considers it necessary to secure subject safety, such as in cases of acute decreases in Hb levels. Study drug administration (MT-6548 Tablets and darbepoetin alfa injection) will be discontinued when an ESA-based rescue therapy is provided. Study drug treatment may be resumed after an improvement in Hb levels and should not be coadministered with a rescue therapy with an ESA. Subjects who are not expected to resume study drug treatment will be withdrawn from the study.

Administration of any ESA formulation other than the study drug is considered a rescue therapy. Dosage increase of the study drug darbepoetin alfa injection (including an increase not in accordance with the dosage adjustment algorithm) is not considered a rescue therapy.

- ✓ 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

Usually, RBC transfusions are performed when clinically necessary in instances of acute or major bleeding. For less severe anemia, which may be exacerbated, or moderate to severe anemia symptoms, RBC transfusions may be performed as needed clinically at the discretion of the investigator/subinvestigator.

(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 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 concomitant medications and therapies."

The only information recorded about dialysis, drugs commonly used for dialysis (e.g., dialysate, anticoagulants, and substitution fluid), and physiological saline used for dissolving injectable formulations will be that specified in "9.2.1 Subject Background".

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

(2) Concomitant therapies: Name 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 Tablet

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

(1) MT-6548 Tablets 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 throughout the treatment period, both in relation to meals and time of day. 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

Item \ Visit	Informed consent	Screening period [a]		Treatment period [b]																	Final day of the follow-up observation [c]
				Treatment period Phase 1										Treatment period Phase 2							
		First day	Visit 2	First day	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	Day of discontinuation	
Visit number	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	FU
Permitted range (days)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7 or +14 [d]	-7
Procedure/evaluation																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X	X	X																		
Allocation				X																		
Patient background and history	X			X																		
Height				X																		
Dry weight, body weight [e]				X						X			X			X				X	X	
Forlic acid and vitamin B_{12} [f]		X																				
Pregnancy test [h]		X											X							X	X	
Hematology tests [f], [g], [i]		X	X [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry test [f], [g], [k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein [f], [g]		X		X									X							X	X	
Iron-related measures [f], [g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepcidin [g]				X	X	X	X			X			X			X				X	X	
EPO [g]				X	X	X	X			X			X			X				X	X	
VEGF [g]				X						X			X			X				X	X	
DHEA-S [g]				X						X			X			X				X	X	
Vital signs [f], [g], [l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Resting standard 12-lead ECG [g], [m]				X									X							X	X	
Fundoscopy [d]		X										X							X		X	
Chest X-ray [d]		X										X							X		X	
Duration of hemodialysis				X									X							X	X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X							X	X	
AE investigation [n]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK testing						X				X			X									
Blood sampling for genetic analysis [o]					Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period																	
Blood sampling for plasma protein binding test [p]		X																				
Product evaluatio/procedure																						
Investigation of concomitant medications/therapies				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MT-6548 tablets [q], [r], [s]				Administered according to the dosage adjustment guidelines																		
Darbepoetin alfa injection [r], [t]				Administered according to the dosage adjustment guidelines																		
Iron supplements		Iron supplements administered to maintain a serum ferritin level of ≥100 ng/mL or a TSAT of ≥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] During the treatment period, subjects are to visit the study site on the day of dialysis after a 2-day interdialytic interval; however, if this is difficult, subjects are to visit the study site on the day of dialysis after a 1-day interdialytic interval.

[c] Not required if withdrawn prior to the treatment period.

[d] Fundoscopy and chest X-ray performed once during screening period, once during Weeks 20–24 of treatment period, and once during Weeks 48–52 of treatment period. In the case of discontinuation of the treatment period, fundoscopy and chest X-ray should be performed within 14 days after discontinuation whenever possible.

[e] Body weights should be measured before and after dialysis.

[f] To be measured before dialysis on the day of dialysis during the screening period.

[g] Tests during the treatment period should be performed before dialysis on the day of dialysis.

[h] To be performed only in female subjects of childbearing potential.

[i] Hb levels should be measured in blood collected in the supine position.

[j] Only Hb levels should be measured.

[k] Only urea nitrogen levels should be measured before and after dialysis on the first day, Weeks 24 and 52 of the treatment period, and on the day of treatment discontinuation.

[l] To be measured in the sitting position after a 5-minute rest before blood sampling whenever possible.

[m] To be measured in the supine position after a 5-minute rest before blood sampling whenever possible.

[n] AE investigation begins after study drug administration.

[o] For subjects giving consent to blood sampling for genetic analysis, blood will be collected once as early as possible after Week 2 of the treatment period.

[p] For subjects giving consent to the plasma protein binding rate study, blood will be collected once before study drug administration on the day of dialysis before dialysis.

[q] MT-6548 Tablets should be prescribed depending on the number of unused tablets by the subject. Subjects should be instructed to open a new bottle after using up the tablets in one bottle.

[r] In principle, dosage adjustments should be performed at scheduled visits or on the day of darbepoetin alfa injection; however, an additional visit may be provided for dosage adjustment, if considered necessary, in cases where excessive increases or decreases in Hb levels are of concern based on the Hb time course.

[s] The first dose should be administered after completion of the scheduled tests on the first day of

the treatment period.

[t] The first dose should be administered after completion of the scheduled tests on the first day of the treatment period; however, the tests scheduled after dialysis should be performed before the first dose whenever possible.

If tests and observations cannot be performed on the scheduled day, they may be performed within the permitted ranges shown below. During the treatment period, subjects are to visit the study site on the day of dialysis after a 2-day interdialytic interval; however, if this is difficult, subjects are to visit the study site on the day of dialysis after a 1-day interdialytic interval.

Table 9.1-1 Permitted ranges for study center visits

Evaluation timepoint		Reference date	Permitted range
Screening period*1	First day	–	–
	Visit 2	–	–
Treatment period Phase 1	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
Treatment period Phase 2	Week 28	Day 196	Day 189–203
	Week 32	Day 224	Day 217–231
	Week 36	Day 252	Day 245–259
	Week 40	Day 280	Day 273–287
	Week 44	Day 308	Day 301–315
	Week 48	Day 336	Day 329–343
	Week 52	Day 364	Day 357–371
Day of discontinuation of treatment		Day of discontinuation	Within 7 days of discontinuation*3
Follow-up observation period	Day of completion	Week 52 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 notification of subject suitability is received from the online enrollment system.

*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) Race
(5) Ethnicity
(6) Smoking status
(7) Underlying cause of CKD
(8) Time of onset of nephrogenic anaemia
(9) Concomitant illnesses (illnesses present on the first day of the treatment period)
(10) Start time of hemodialysis
(11) Type of hemodialysis*1 (hemodialysis or hemodiafiltration)
(12) Frequency of hemodialysis*1 (times/week)
(13) Hemodialysis conditions (dialyzer, dialysate, type of anticoagulant)
(14) Type, administration route, dose interval, dosage, and final day of previous ESA formulation

*1: If the type of hemodialysis is changed at any point from the first day of the treatment period to the final day of the follow-up observation period, the date of the change and the type after the change should be recorded in the CRF.

*2: If the frequency of hemodialysis is changed at any point from the first day of the treatment period to the final day of the follow-up observation period, the date of the change and the frequency after the change should be recorded in the CRF.

9.2.2 Treatment status

9.2.2.1 MT-6548 Tablet

The following information should 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, 12, 24, 36, 52, and day of discontinuation. Also, date and time for 2 doses immediately prior to blood collection for PK at treatment period Weeks 4, 12, and 24.

9.2.2.2 Darbepoetin alfa injection

Record dates of treatment, dosage, and dose interval of darbepoetin alfa injection in the CRF. If changes were made to dosage and administration of darbepoetin alfa injection (including drug holiday), record reasons for changes in the CRF.

9.2.3 Efficacy endpoints

Blood sampling will be performed at each study center for measurement by the contract laboratory testing facility. Study centers will store test reports issued by the contract testing laboratory. EPO measurements will be disclosed to the sponsor after key code opening, but will not be disclosed to subjects, study center staff, or monitoring staff until completion of the final data lock at the end of the study.

During the screening period, blood will be collected before dialysis whenever the subject makes a study visit on the same day they are scheduled for dialysis. During the treatment period, blood will be collected before dialysis on days the subject is scheduled for dialysis.

(1) Hb value

Blood sampling and Hb measurement will be performed in the supine position 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, 24, 28, 32, 36, 40, 44, 48, and 52 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) 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, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

(8) 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, 24, 36, and 52, and the day of discontinuation of treatment.

(9) 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, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

(10) 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, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

(11) 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, 24, 36, and 52, and the day of discontinuation of treatment. Blood sampling time will be recorded in CRFs.

EPO measurements will be disclosed to the sponsor after key code opening, but will not be disclosed to subjects, study center staff, or monitoring staff until completion of the final data

lock at the end of the study. Study centers are prohibited from measuring EPO during the treatment period in order to maintain blinding.

(12) 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, 24, and 52, 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 collection at the study center. Study centers will store test reports issued by the contract testing laboratory.

During the screening period, blood will be collected before dialysis whenever the subject makes a study visit on the same day they are scheduled for dialysis. During the treatment period, blood will be collected before dialysis on days the subject is scheduled for dialysis. Only urea nitrogen levels should be measured before and after dialysis on the first day, Weeks 24 and 52 of the treatment period, and on the day of treatment discontinuation.

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, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

Parameters: 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, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment. Only urea nitrogen levels should be measured before and after

dialysis on the first day, Weeks 24 and 52 of the treatment period, and on the day of treatment discontinuation.

Parameters: 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 Weeks 24 and 52, 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, 24, 36, and 52, and the day of discontinuation of treatment.

6) Dehydroepiandrosterone sulfate (DHEA-S):

Blood sampling and measurement of DHEA-S will be performed on the first day of the screening period, treatment period Weeks 12, 24, 36, and 52, and the day of discontinuation of treatment.

(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 Weeks 24 and 52, and the day of discontinuation of treatment. ECG diagnosis consists of a comprehensive evaluation including arrhythmia and wave-form diagnoses.

Measured to extent possible prior to blood sampling before dialysis on the day of dialysis. 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) Dry weight

Dry weight will be measured during study visits on the first day of the treatment period, treatment period Weeks 12, 24, 36, and 52, and the day of discontinuation of treatment. Measurements are recorded in CRFs.

(4) Body weight

Body weight will be measured before and after dialysis during study visits on the first day of the treatment period, treatment period Weeks 12, 24, 36, and 52, and the day of discontinuation of treatment. Measurements are recorded in CRFs.

(5) Duration of hemodialysis

The duration of hemodialysis during visits on the first day, Weeks 24 and 52 of the treatment period, and on the day of treatment discontinuation should be recorded in CRFs.

(6) 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, 24, 28, 32, 36, 40, 44, 48, and 52, and the day of discontinuation of treatment.

During the screening period, measurements will be made before dialysis whenever the subject makes a study visit on the same day they are scheduled for dialysis. During the treatment period, measurements will be made before dialysis on days the subject is scheduled for dialysis. Measurements will be made before blood sampling when possible, and after 5 minutes at rest.

(7) Fundoscopy

Fundoscopy will be performed once each within the screening period, from treatment period Week 20 to Week 24, treatment period Week 48 to Week 52, 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 and need to be submitted if requested by the study sponsor.

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

(8) Chest X-ray

Fundoscopy will be performed once each within the screening period, from treatment period

Week 20 to Week 24, treatment period Week 48 to Week 52, 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

(9) 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 52, 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 MT-6548 Tablet or darbepoetin alfa injection 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 of a causal relationship with MT-6548 Tablet exists will be treated as ADRs of MT-6548 Tablet, and AEs for which a logical possibility of a causal relationship with darbepoetin alfa injection

exists will be treated as ADRs of darbepoetin alfa injection.

(a) Causal relationship with MT-6548 Tablet

1. Logical possibility
2. No logical possibility

(b) Causal relationship with darbepoetin alfa injection

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 MT-6548 Tablet and darbepoetin alfa injection fall into the 6 categories listed below.

(a) Actions taken to MT-6548 Tablet

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)

(b) Actions taken to darbepoetin alfa injection

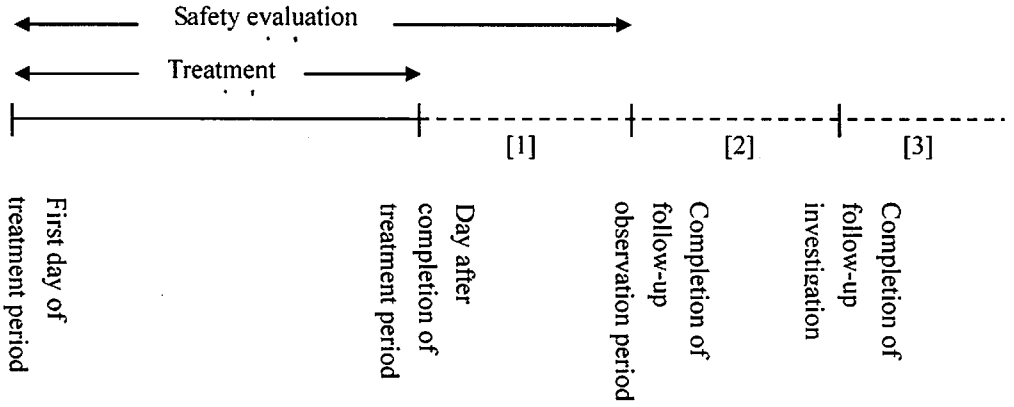
1. Discontinuation of administration (study withdrawal)
2. Drug holiday
3. Dosage increase
4. Dosage reduction
5. No action
6. Not applicable (occurred after final administration of study drug)

8) Actions 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 Pharmacokinetic-related endpoints

(1) Measuring plasma concentration

1) Blood sampling timing and volume

(a) Blood sampling timing: Treatment period Weeks 2, 12, and 24. [redacted]

(b) Blood sampling volume: [redacted]

(c) Number of times blood is sampled: 3 times

2) Blood processing

[redacted]

(2) Sample transport and storage

After the plasma drug concentration measurement sample is collected by the contract testing laboratory, it will be cryopreserved at -20°C or below. The contract testing laboratory will only send samples from subjects in the MT-6548 group to the drug concentration measurement laboratory, and will dispose of samples from subjects in the darbepoetin group.

Rationale

Blood will be sampled multiple times from each subject in order to evaluate fluctuation of levels within the body in a full population PK analysis. Three samples are to be collected from each subject also because of the paucity of data in Japanese people.

9.2.6 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").

9.2.7 Blood sampling for the plasma protein binding ratio study

Investigators/subinvestigators will collect [redacted] in subjects who have granted consent to the plasma protein binding rate study. [redacted] (refer to "26. Plasma protein binding ratio study" for details).

10. Evaluation methods and standards

10.1 Efficacy

10.1.1 Primary efficacy endpoint

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.

10.1.2 Secondary endpoints

The following endpoints will also be studied.

(1) Mean Hb at treatment period Weeks 48 and 52

Mean Hb of treatment period Weeks 48 and 52 will be calculated.

(2) Hb at each treatment period timepoint

Hb at each timepoint in treatment period will be calculated.

(3) Proportion of subjects with mean Hb levels within the target range (10.0–12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each timepoint in the treatment period

Ratios of subjects with mean Hb within the target range (10.0–13.0 g/dL), <10.0 g/dL, and >12.0 g/dL at each timepoint in treatment period will be calculated.

10.1.3 Other endpoints

The following endpoints will also be studied.

(1) 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 and 52 will be calculated.

(2) 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 and 52 will be calculated.

(3) Study drug dosage

MT-6548 Tablet: Mean daily dosage will be calculated for each scheduled study visit from the first day of the treatment period up to treatment period Week 52.

Darbepoetin alfa injection: Mean weekly dosage will be calculated for each scheduled

study visit from the first day of the treatment period up to treatment period Week 52.

(4) MT-6548 group only: cumulative number of MT-6548 Tablet dosage adjustments

The total number of dosage adjustments from the first day of the treatment period to treatment period Weeks 24 and 52 will be calculated.

(5) 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 52.

(6) 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.

(7) 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.

(8) 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.

(9) 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) Dry weight
(5) Body weight
(6) Vital signs

(7) Fundoscopy

(8) Chest X-ray

(9) Proportion of subjects with documented Hb levels exceeding 12.0 or 13.0 g/dL

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

10.3 Pharmacokinetics

Scatter plot diagrams for plasma concentrations of unchanged drug over time following MT-6548 Tablet treatment will be created.

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, temporary discontinuation of study drugs 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 the subject meets one of the following criteria regarding hepatic function abnormalities during the study.

1) ALT or AST > 3x ULN and total bilirubin > 2x ULN

2) ALT or AST > 3x ULN and INR > 1.5*1

3) ALT or AST > 8x ULN

4) ALT or AST remains > 5x ULN over 2 weeks*2

5) ALT or AST > 3x ULN with symptoms including e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia

*1: The subject should be withdrawn from the study if the measurement of PT-INR is performed besides this study and the value meets the criterion.

*2: Administration of the study drug should be avoided with ALT or AST > 5x ULN unless there are no other good therapeutic options.

(5) If rescue therapy is performed prior to conclusion of scheduled tests at Week 24.

(6) 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.

(7) If the subject no longer requires hemodialysis or hemodiafiltration

(8) If the subject has undergone renal transplantation

(9) If pregnancy of the subject is discovered.

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

Rationale

(1) Set out of ethical considerations.

(2) (7) (8) Set in order to prevent study drug administration to subjects unsuitable for inclusion in safety or efficacy evaluation.

(3) (4) (6) (9) Set out of safety considerations.

(5) Set because evaluating efficacy of MT-6548 accurately would be difficult.

(10) 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, investigators/subinvestigators will take all appropriate actions toward the subject, immediately inform the study monitor of the withdrawal, 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), and monitor the subject. If a subject meets the withdrawl criterion (4), fundamentally, repeat testing of ALT, AST, ALP and total bilirubin within 72 hours after checking the test values to confirm the abnormalities and to determine trend. Investigators/subinvestigators or clinical coordinators will also input all required information in the online enrollment system according to "8.2.4 Withdrawal processing."

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.

12.3 The criteria of the temporary discontinuation of study drugs

Subjects will temporary discontinue the study drug if either of the following criteria is met:

(1) Based on the dosage adjustment guideline. (Refer to "8.3.3 Maintenance dosage and dosage adjustments" for detail)

(2) ALT or AST > 3x ULN without total bilirubin > 2x ULN during the study.

Rationale

(1) (2) Set out of safety considerations.

12.4 Procedures for temporary discontinuation of study drugs

If a subject temporary discontinues the study drug, investigators/subinvestigators will take all appropriate actions toward the subject.

If a subject meets the criteria of the temporary discontinuation of study drugs (2), temporary discontinue the study drug immediately and fundamentally, repeat testing of ALT, AST, ALP and total bilirubin within 72 hours after checking the test values to confirm the abnormalities and to determine trend. The study drug should not be resumed until monitoring indicates abnormalities have resolved or have stabilized.

13. Statistical analysis

Data lock will occur first when all subjects have completed treatment period Phase 1 at Week 24 of the treatment period. Final data lock will occur at the completion of the study.

Data from the first data lock (Phase 1 data) and from the final data lock (final data) will be handled according to "13.2 Data Handling" and analyzed according to "13.3 Statistical Analysis Protocol."

Individual statistical analysis protocols and clinical study reports will also be drafted for Phase 1 data and final data.

13.1 Analysis sets

Efficacy analysis is performed with the full analysis set (FAS). Primary endpoint analysis will also be performed with the set of subjects conforming to the protocol, or the per-protocol set (PPS). Safety analysis will be performed with the safety analysis set.

Analysis sets are defined below; details of subject handling for Phase 1 data and final data will be determined by the study sponsor before each dataset is locked.

(1) Efficacy analysis set

1) FAS

The FAS consists of all randomly allocated subjects excluding the following subjects:

- ✓ Subjects who did not have HD-CKD-related anaemia
- ✓ Subjects who did not use a single dose of study drug
- ✓ Subjects with absolutely no post-randomization efficacy data

2) PPS

The PPS consists of the FAS with the following subjects excluded:

- ✓ Subjects with deviations from inclusion criteria
- ✓ Subjects who met exclusion criteria

- ✓ Subjects who violated rules concerning prohibited concomitant drugs or therapies
- ✓ Subjects with <80% compliance rate for either MT-6548 Tablet 150 mg or darbepoetin alfa injection active comparator

(2) Safety analysis set

The safety analysis set consists of all randomly allocated subjects excluding the following subjects:

- ✓ Subjects who did not use a single dose of study drug
- ✓ Subjects with absolutely no post-randomization safety data

(3) Drug concentration analysis set

The drug concentration analysis set consists of all randomly allocated subjects excluding the following subjects:

- ✓ Subjects who did not use a single dose of MT-6548 Tablet 150 mg
- ✓ Subjects with absolutely no post-randomization plasma drug concentration data

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

Mean Hb values for treatment period Weeks 20 and 24 imputed using LOCF, a method by

which missing timepoints are imputed using data from the immediately prior timepoint (excluding the treatment period start date), will be derived as data for analysis of covariance (ANCOVA) performed as sensitivity analysis for the primary efficacy endpoint. If 1 value is missing, then the closest value to the missing one will be used; if 2 values are missing, then mean Hb will be calculated using 2 different prior values closest to the missing value. Two values from the same timepoint will not be used.

Values imputed by LOCF will also be derived for treatment period Weeks 24 and 52. Data from treatment period Week 24 with missing values imputed will be used as data from the completion of treatment period Phase 1, and data from treatment period Week 52 with missing values imputed will be used as data from the completion of treatment period Phase 2.

(5) Handling of PK-related data

Blood sampling dates for plasma drug concentration measurements will adhere to the date ranges described in "Table 9.1-1 Permitted ranges for study center visits." If blood sampling occurred outside of the permitted range, and discussion of data handling is required (for example, if there was a deviation from the study protocol or if plasma collection procedures were not followed), the study sponsor will hold a case study committee in order to determine whether the data obtained should be used in statistical summaries or analyses. Details regarding handling are described in the statistical analysis protocol.

Required regulations for data handling other than those enumerated above will be described in the both statistical analysis protocols prior to treatment period Phase 1 and final data lock.

13.3 Statistical analysis protocol

Tests will be 2-sided, with a level of significance of 5%. 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) or tipping point analysis.

A detailed statistical analysis protocol for both Phase 1 data lock and final data lock will be authored prior to both of these.

13.3.1 Demographic and other baseline characteristics

Summary statistics will be compiled for demographic data and other baseline characteristics for all analysis sets (excluding the PK analysis set). 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

For the primary endpoint of mean Hb at treatment period Weeks 20 and 24, mean Hb at each timepoint will be modeled using MMRM with the following model, mean Hb at treatment period Weeks 20 and 24 will be calculated for each group, and point estimates and their two-sided 95% CI will be calculated for differences in mean values between the MT-6548 group and the darbepoetin group. Non-inferiority of MT-6548 to darbepoetin alfa (recombinant) will have been established if the lower limit of the 95% CI is ≥-0.75 g/dL.

[MMRM model]

- Covariates: Baseline values
- Fixed effects: Treatment group, evaluation period, interactions of evaluation period × treatment group, Random effects: Subjects
-

The non-inferiority of the MT-6548 group with the darbepoetin group will be assessed after the mean of mean Hb values at treatment period Weeks 20 and 24 and its 95% CI is confirmed to fall within the target range of Hb values (10.0–12.0 g/dL).

Sensitivity analysis will be performed using the following analysis methods.

1) Tipping point analysis
2) ANCOVA using data with missing values imputed by LOCF and baseline values as covariates

(2) Analysis methods for secondary endpoints

1) Mean Hb at treatment period Weeks 48 and 52

Treatment groups will be compared using the same analysis methods (MMRM) used for the primary endpoint. Point estimates and their standard errors and 95% CI will be calculated for differences in mean values between the MT-6548 group and the darbepoetin group.

2) Hb at each treatment period timepoint

Descriptive statistics will be calculated for Hb levels at each treatment period timepoint, and analysis performed taking into account changes over time using MMRM.

3) Proportion of subjects with mean Hb levels within the target range (10.0–12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each timepoint in the treatment period

Numbers and ratios of subjects with mean Hb at each treatment period timepoint within

the target range (10.0–12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL will be shown.

(3) Other endpoints

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

13.3.3 Safety

(1) Analysis methods for AEs and ADRs

The following statistics will be shown by treatment group: 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, dry weight, body weight, vital signs, fundoscopy, and chest X-ray

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

(3) Analysis methods for ratios of subjects with Hb levels of ≥12.0 g/dL or ≥13.0 g/dL.

Numbers and ratios of subjects with Hb levels of ≥12.0 g/dL or ≥13.0 g/dL at each timepoint will be shown by treatment group.

(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 by treatment group.

13.3.4 Pharmacokinetics

[redacted] A separate protocol will be created and [redacted]

The PK measurement center will create separate testing plans for plasma concentration measurements prior to initiating measurements, and create reports of measurement results.

13.4 Changes in statistical analysis protocol

If any portion of the 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

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

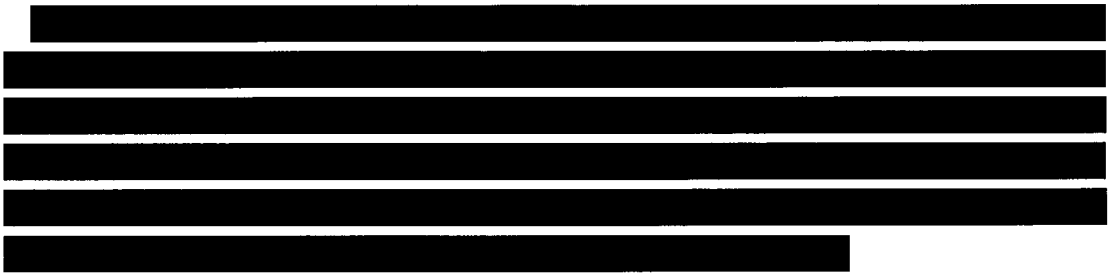
The storage facility for genetic analysis samples will issue an anonymized identification number for each blood sample received, which is separate from the subject identification code. The facility will store a table linking identification codes to subjects. Methods for anonymization and creation/storage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



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. Plasma protein binding ratio study

26.1 Purpose of the study

To measure the plasma protein binding ratio of unchanged MT-6548. Blood sampling for the plasma protein binding ratio study will only be performed at some study centers.

26.2 Eligible subjects

Subjects who have consented to participate in the main study and the plasma protein binding ratio study [redacted]

26.3 Obtaining consent

With the assistance of the study sponsor, investigators will prepare an informed consent form and written information for subjects for the plasma protein binding ratio study that is separate from the informed consent form and written information for subjects for the main study.

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

Before collecting blood samples for the plasma protein binding ratio study, investigators/subinvestigators will distribute the informed consent forms and written information for the plasma protein binding ratio study to subjects, give a full explanation of the contents, and obtain freely given consent for the plasma protein binding ratio study in writing.

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 who have granted consent for the main study may still start or continue participation in the main study even if they do not grant consent for the plasma protein binding ratio study.

26.4 Target sample size

[redacted]

26.5 Information collected

Investigators/subinvestigators will collect the following information about the plasma protein binding ratio study, record that information on a sample information report, and submit the report to the study sponsor.

(1) Subject identification code
(2) Date consent for plasma protein binding ratio study was obtained
(3) Blood sampling dates
(4) Sex
(5) Age (on day of blood sampling)
(6) Whether or not subject is on hemodialysis
(7) Concomitant medications in use at time of blood sampling

26.6 Sample handling

26.6.1 Blood sampling dates

[redacted]

26.6.2 Storage and transport conditions

[redacted]

26.7 Conduct of the plasma protein binding ratio study

Samples obtained for the plasma protein binding ratio study will only be used to measure the plasma protein binding ratio of unchanged MT-6548. The plasma protein binding ratio study will be conducted following a separately prepared protocol that includes what is to be studied, and reports will be prepared separately from clinical study reports for the main study.

26.8 Publication of results and disclosure to sample donors

Information obtained through the plasma protein binding ratio study may be published (to academic

societies, 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.

Results of the plasma protein binding ratio study will generally not be disclosed to study centers or sample donors.

27. Administrative structure

27.1 Study sponsor:

See Appendix 1.

27.2 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.

28. References

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Contact Information

[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]