

**A Phase III, Open-label, Confirmatory Study of MT-6548 Compared to
Darbepoetin Alfa in Non-dialysis Subjects With Anemia Associated With
Chronic Kidney Disease in Japan**

Study Protocol

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CONFIDENTIALITY

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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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- Appendix 4 EQ-5D-5L questionnaire
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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
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
eGFR	Estimated glomerular filtration rate
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
JSĐT	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

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	Each film-coated tablet contains 150 mg vadadustat.
Darbepoetin alfa injection	Each plastic syringe (0.5 mL) contains darbepoetin alfa (recombinant).
Correction cohort	Patients who have not received ESA treatment from 8 weeks prior to the first day of the screening period
Conversion cohort	Patients who have received the same ESA treatment from 8 weeks prior to the first day of the screening period

Protocol Summary

1. Study title

A Phase III, open-label, confirmatory study of MT-6548 compared to darbepoetin alfa in non-dialysis subjects with anemia associated with chronic kidney disease in Japan

2. Purpose of the study

The study will assess non-inferiority of MT-6548 in patients with anaemia accompanying chronic kidney disease (CKD) using haemoglobin (Hb) values as a measure and darbepoetin alfa (recombinant) as a control drug, as well as safety of long-term administration of MT-6548.

The study will also evaluate MT-6548's Hb improvement maintenance effects in a cohort of patients who have not received (erythropoiesis-stimulating agent) ESA treatment, as well as switching maintenance effects in a cohort of patients receiving ESA treatment.

3. Subjects

3.1 Subjects

Patients with anaemia due to non-dialysis-dependent chronic kidney disease

3.2 Inclusion criteria

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

- (1) Patients at least 20 years of age as of the day of consent (either sex)
- (2) Patients with CKD diagnosed according to the Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" as of the day of consent.
- (3) Patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² in the screening period.
eGFR is calculated according to the following formula using age as of informed consent:
$$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{serum creatinine-1.094} \times \text{age-0.287 (females: } \times 0.739)$$
- (4) Patients who have not received dialysis 8 weeks prior to the first day of the screening period, and who are not expected to begin dialysis during the treatment period
- (5) Correction cohort: Patients who have not received ESA treatment 8 weeks prior to the first day of the screening period. However, patients receiving ESA treatment at consent may join the study if they discontinue this treatment after consent and have a washout period of at least 8 weeks.

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

Dosage:

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

- (6) Patients with the following mean Hb values during screening, using the mean of the latest two tests:
 - ✓ Correction cohort: ≥ 8.0 g/dL, < 11.0 g/dL
 - ✓ Conversion cohort: ≥ 9.0 g/dL, < 12.5 g/dL
- (7) Patients with a difference of < 1.5 g/dL in Hb for the latest two tests in the screening period
- (8) Patients with serum ferritin values of ≥ 100 ng/mL or transferrin saturation (TSAT) of $\geq 20\%$ during the screening period.
- (9) Patients with folic acid and vitamin B₁₂ values above standard minimum values during the screening period.

3.3 Exclusion criteria

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

- (1) Patients with anaemia resulting primarily from a disease other than CKD after date of consent (e.g., sickle-cell syndrome, myelodysplastic syndrome, myelofibrosis, haematopoietic malignancy, myeloma, haemolytic anaemia, thalassemia, or aplasia pure red cell)
- (2) Patients with active haemorrhaging or exsanguination within 8 weeks prior to the first day of the screening period.
- (3) Patients who have received RBC transfusion within 8 weeks prior to the first day of the screening period.
- (4) Patients who have received testosterone enanthate or mepitiostane within 8 weeks prior to the first day of the screening period.
- (5) Patients determined by investigators/subinvestigators to likely require immediate rescue therapy or drug holiday of the study drug after initiation of treatment period.
- (6) Patients 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.

- (7) Patients with uncontrolled hypertension (defined as systolic BP >180 mmHg or diastolic BP >110 mmHg) during the screening period or on the first day of the treatment period.
- (8) Patients for whom any of the following apply upon fundoscopy during the screening period:
 - ✓ No ocular fundus findings are possible.
 - ✓ Active ocular fundus disease.
- (9) Patients with severe cardiac failure from the day of consent (Class IV according to severity classification of the New York Heart Association (NYHA))
- (10) 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.
- (11) 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).
- (12) Patients with incidence or relapse of deep vein thrombosis or pulmonary embolism within 12 weeks prior to the first day of the screening period.
- (13) Patients with current or previous haemosiderosis or hemochromatosis.
- (14) 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.
- (15) Patients with an allergy to the study drugs.
- (16) 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).
- (17) Patients who have previously used MT-6548.
- (18) Patients with known low tolerance to hypoxia-inducible factor prolyl hydroxylase enzyme (HIF-PH) inhibitors.
- (19) 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.
- (20) Women who are or may be pregnant, or women who are nursing.
- (21) Other patients judged by investigators/subinvestigators to be inappropriate as a subject in this study.

3.4 Re-testing/re-screening

(1) Re-testing

Re-testing during the screening period may be performed at the discretion of

investigators/subinvestigators for subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, eGFR, serum ferritin, TSAT, folic acid, vitamin B₁₂, AST, ALT, or total bilirubin) or blood pressure.

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

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

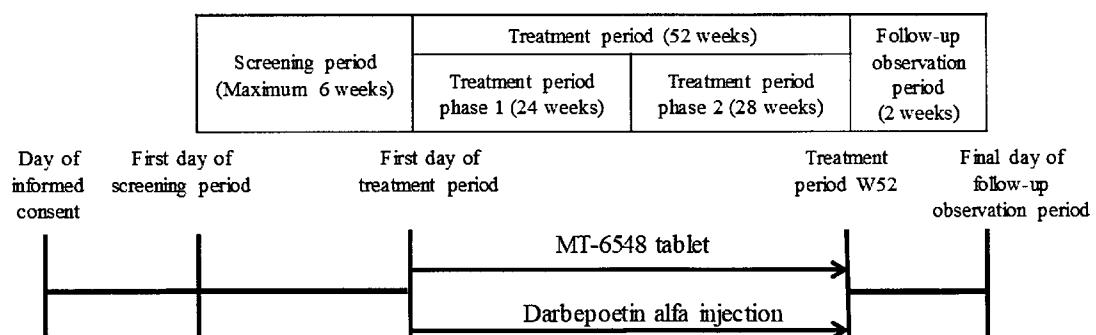
(2) Re-screening

Re-screening may be performed at the discretion of investigators/subinvestigators if subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, eGFR, serum ferritin, TSAT, folic acid, vitamin B₁₂, AST, ALT, or total bilirubin), blood pressure, or blood pressure on the first day of the treatment period, may have become eligible for the study due to natural course or drug treatment.

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

4. Study design

The current study is a multicenter, randomized, open-label, active-controlled, 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. Re-testing will be performed as necessary.

(2) Treatment period

The treatment period will last from completion of scheduled tests on the first day of the treatment period to completion of blood sampling for haematology tests on the final day of the treatment period (Week 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 2: From completion of tests specified for Week 24 of treatment period to completion of tests specified for Week 52 of treatment period

Subjects will be randomly allocated to the MT-6548 group or the darbepoetin group on the first day of the treatment period. Allocation ratios will be 1:1 for both groups.

Stratification factors are as below.

- ✓ Correction cohort or conversion cohort
- ✓ Mean Hb during screening period (mean of latest two measurements from central testing facility):
 - Correction cohort: <10.0 g/dL or ≥ 10.0 g/dL
 - Conversion cohort: <11.0 g/dL or ≥ 11.0 g/dL

Treatment period study visits will be made every 2 weeks up until Week 12, and every 4 weeks thereafter for scheduled tests. However, study visits may be more frequent if variation in Hb levels causes concern for excessive increase or decrease in Hb, if the dose interval for darbepoetin alfa injection is shorter than the study visit interval, or for other reasons.

(3) Follow-up observation period

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

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

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

5. Study drug, dosage, and administration

5.1 Study drug names

(1) Investigational product

Name: MT-6548 Tablet 150 mg

Nonproprietary name: vadadustat

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

(2) Control drug

Name: Darbepoetin alfa injection 15 µg

Darbepoetin alfa injection 20 µg

Darbepoetin alfa injection 30 µg

Darbepoetin alfa injection 40 µg

Darbepoetin alfa injection 60 µg

Darbepoetin alfa injection 120 µg

Darbepoetin alfa injection 180 µg

Nonproprietary name: Darbepoetin alfa (recombinant)

Dosage form and content: Each plastic syringe (0.5 mL) contains darbepoetin alfa (recombinant) in dosages of 15, 20, 30, 40, 60, 120, or 180 µg.

5.2 Treatment period, dosage and administration

5.2.1 MT-6548 Tablet

(1) Treatment period

MT-6548 group: From the first day of the treatment period to the day prior to Week 52 of the treatment period.

(2) Initial dosage levels

1) Initial dosage for correction cohort

Single daily dose of 300 mg (2 tablets)

2) Initial dosage for conversion cohort

Single daily dose of 300 mg (2 tablets)

(3) Maintenance dosage and dosage adjustments

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

MT-6548 Tablet dosage adjustment guidelines

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

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

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

MT-6548 Tablet dosage adjustment chart

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

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

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

Dosage adjustment algorithm for MT-6548 Tablet

- ✓ Dosage increases are in principle separated by at least 4 weeks. There are no set intervals for

dosage decreases, but frequent dosage adjustments are to be avoided.

- ✓ Decrease MT-6548 dosage by 1 tablet if Hb levels suddenly increase (more than 2.0 g/dL change in past 4 weeks*).
- ✓ Increase MT-6548 dosage by 1 tablet if Hb levels are <11.0 g/dL. However, decrease by 1 tablet instead of increasing in cases of sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*).
- ✓ Decrease MT-6548 dosage by 1 tablet if Hb is >12.5 g/dL.
- ✓ If Hb is >13.0 g/dL and ≤13.5 g/dL, and there has been a sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*), discontinue MT-6548 administration and resume at 1 tablet reduced dosage after Hb falls to ≤13.0 g/dL.
- ✓ If Hb is >13.5 g/dL, discontinue MT-6548 administration and resume at 1 tablet reduced dosage after Hb falls to ≤13.0 g/dL.

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

(4) Administration method

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

5.2.2 Darbepoetin alfa injection

(1) Treatment period

Darbepoetin group: From the first day of the treatment period to the day prior to Week 52 of the treatment period.

(2) Initial dose and dose interval

1) Initial dosage for correction cohort

One 30 µg dose every 2 weeks

2) Initial dosage for conversion cohort: 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 chart, investigators/subinvestigators will select initial dosage from the 2 closest options on the chart according to the subject's clinical status and Hb levels.

3) Initial dosage for conversion cohort: initial dosage for subjects receiving epoetin alfa (recombinant) or epoetin beta (recombinant) prior to switching

Determine initial dosage of darbepoetin alfa injection according to the chart below and begin treatment at 1 dose every 2 weeks. However, if total dosage 2 weeks prior to switching does not match any of the dosages listed on the chart below, investigators/subinvestigators will select initial dosage from the 2 closest options on the chart according to the subject's clinical status and Hb levels.

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

4) Initial dosage for conversion cohort: initial dosage for subjects receiving epoetin beta pegol (recombinant) prior to switching

(3) Maintenance dosage and dosage adjustments

Maintenance dosage is 15–180 µg per dose. Treatment intervals are 1 dose per 1 week, 2 weeks, or 4 weeks.

Maintenance dosage is adjusted according to the dosage adjustment guideline below.

[Dosage adjustment guideline for darbepoetin alfa injection]

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 timing should coincide with days of darbepoetin alfa injection administration. Hb levels will be measured prior to administration of darbepoetin alfa injection with the HemoCue® Hb201 DM analyzer; in principle these measurements will be used for determinations regarding dosage adjustments. Hb measurements used for dosage adjustment determinations will be recorded in the subject's case report form (CRF). Measurement results from the HemoCue® Hb201 DM will be used solely for determination of study drug dosage adjustments, and will not be used for efficacy or safety analysis.

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

Darbepoetin alfa injection dosage adjustment chart

Step	Dosage
1	15 µg
2	30 µg
3	60 µg
4	90 µg
5	120 µg
6	180 µg

*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.

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

Dosage adjustment algorithm for darbepoetin alfa injection

- ✓ Dosage increases are in principle separated by at least 2 weeks. There are no set intervals for dosage decreases, but frequent dosage adjustments are to be avoided.
- ✓ Decrease darbepoetin alfa injection dosage by 1 step if Hb levels suddenly increase (more

than 2.0 g/dL change in past 4 weeks*).

- ✓ Increase darbepoetin alfa injection by 1 step if Hb levels are <11.0 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*).
- ✓ Decrease darbepoetin alfa injection by 1 step if Hb levels are >12.5 g/dL.
- ✓ If Hb is >13.0 g/dL and ≤13.5 g/dL, and there has been a sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*), discontinue darbepoetin alfa injection and resume at 1 step reduced dosage after Hb falls to ≤13.0 g/dL.
- ✓ If Hb is >13.5 g/dL, discontinue darbepoetin alfa injection and resume at 1 step reduced dosage after Hb falls to ≤13.0 g/dL.
- ✓ If Hb is maintained in the range of 11.0–12.5 g/dL, existing dosage may be doubled and dose interval extended from once every 1 week to once every 2 weeks, or from once every 2 weeks to once every 4 weeks.
- ✓ If Hb levels do not reach target levels even with dosage of 180 µg, halve existing dosage and reduce dose interval from once every 4 weeks to once every 2 weeks, or from once every 2 weeks to once every 1 week.

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

(4) Administration method

Subcutaneous administration (initial dose after completion of scheduled tests on the first day of the treatment period)

6. Concomitant medications and therapies

6.1 Prohibited concomitant medications and therapies

(1) ESA formulations

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

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

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

(2) Testosterone enanthate and mepirostane

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

(3) Blood transfusion

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

6.2 Restricted drugs

(1) Iron supplements

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

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

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

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

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

day of the screening period to completion of scheduled tests at Week 4 of the treatment period.

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

6.3 Rescue therapy

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

(1) ESA formulations

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

Administration of any ESA formulation aside from darbepoetin alfa injection is considered rescue therapy for subjects in the darbepoetin group. Dosage increase of darbepoetin alfa injection (regardless of adherence to the dosage adjustment algorithm) does not constitute 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

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

(3) Phlebotomy

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

7. Endpoints

7.1 Efficacy endpoints

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

(3) Other endpoints

- 1) Correction cohort only: Change from mean baseline value in mean Hb of Weeks 20 and 24, and Weeks 48 and 52, of treatment period.
- 2) Correction cohort only: Ratio of subjects with an increase of ≥1.0 g/dL of mean Hb from baseline at each timepoint in treatment period.
- 3) Ratio of subjects who received ESA rescue therapy
- 4) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.
- 5) Study drug dosage
- 6) MT-6548 group only: total number of dosage adjustments
- 7) Quantity of iron administered
- 8) Ratio of subjects who received IV iron
- 9) Ratio of subjects with serum ferritin of ≥100 ng/mL or TSAT ≥20%.
- 10) Change from baseline of iron-related measures (serum iron, total iron binding capacity (TIBC), TSAT, and serum ferritin) and hepcidin.
- 11) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and erythropoietin (EPO) (MT-6548 group only).
- 12) QOL measures (EQ-5D-5L, KDQOL)

7.2 Safety endpoints

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

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 continuous haemodialysis or peritoneal dialysis is initiated, or if the subject receives a renal transplant.
- (8) If pregnancy of the subject is discovered.
- (9) 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 $> 3 \times$ ULN without total bilirubin $> 2 \times$ ULN during the study.

10. Target sample size

Target sample size is 300 total subjects enrolled in treatment period (150 subjects each in MT-6548 group and darbepoetin group). Target sample sizes for each cohort are as follows.

- ✓ Correction cohort: 100 subjects
- ✓ Conversion cohort: 200 subjects

The maximum number of subjects in the conversion cohort with mean screening period Hb values (mean of 2 most recent central testing facility results) of < 11.0 g/dL and ≥ 11.0 g/dL is 120 each.

10.1 Rationale for target sample size

For the primary efficacy endpoint of mean Hb at treatment period Weeks 20 and 24, mean Hb in the darbepoetin group is assumed to be 12.0 g/dL, the difference between the MT-6548 group and darbepoetin group is assumed to be 0 g/dL, and the standard deviation for both is assumed to be 1.78 g/dL. The non-inferiority margin is set at -0.75 g/dL. Calculation of statistical power from these assumptions shows that a sample size of 150 subjects in each group would ensure greater than 95% probability that the mean of mean Hb values in the MT-6548 group and its 95% CI would fall within the target Hb range (11.0–13.0 g/dL) and non-inferiority could be established.

Target sample sizes for each cohort were also set to enable appropriate evaluation of the correction cohort, the conversion cohort, and subjects with Hb of < 11.0 g/dL or ≥ 11.0 g/dL in the conversion cohort.

The assumed standard deviation of 1.78 g/dL was calculated from the upper limit of the 80% CI in the MT-6548 300 mg group at Week 6 in study CI-0021.

11. Study period



12. Test and observation schedule

VIST	Item	Screening period [a]	Treatment period												Final day of follow-up observation period [b]				
			Treatment period phase 1						Treatment period phase 2						Day of discontinuation				
First day	Visit 2	First day [c]	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Visit no.	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16
Permitted range (day)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	TV17
Procedure/evaluation																			+7 or +14 [d]
Informed consent	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Allocation																			
Patient's background and history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																	
Body weight		X																	
Folate acid and vitamin B ₁₂	X																		
Pregnancy test [e]	X																		
Haematology test	X	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood biochemistry test and eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-reactive protein	X																		
Iron-related measures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haptocritin		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Erythropoietin [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VEGF		X																	
DHEA-S	X																		
Urinalysis (qualitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine albumin/creatinine ratio	X																		
Urine protein/creatinine ratio	X																		
Vital signs [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [i]		X																	
Fundoscopy [d]	X																		
Chest X-ray [d]	X																		
QOL measures (EQ-5D-5L, KIDQOL)		X																	
AE investigations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK testing [j]																			
Blood sampling for genetic analysis [k]																			
Blood sampling for plasma protein binding [l]																			
Drug evaluation/procedure																			
Investigation of concomitant drugs																			
Prescribing M-6548 tablets																			
Prescribing Darbepoetin Alfa injection																			
Administration of iron supplements																			

Administration according to the dosage adjustment guideline
Administration according to the dosage adjustment guideline
Administer iron supplements to maintain serum ferritin values ≥100 ng/mL or TSAT ≥20%.

- [a] Maximum screening period length is 6 weeks. Test results will be reviewed prior to transitioning from the first day of the screening period to screening period Visit 2, and from screening period Visit 2 to the first day of the treatment period. Re-testing will be performed as necessary.
- [b] Not required if withdrawing prior to treatment period.
- [c] Perform prior to study drug treatment (AE investigations begin after study drug treatment)
- [d] Fundoscopy and chest X-ray performed once during screening period, once during Weeks 20–24 of treatment period, and once during Weeks 48–52 of treatment period. Also performed to extent possible within 14 days of study withdrawal.
- [e] Only female subjects who may become pregnant.
- [f] Hb only measured.
- [g] Erythropoietin measured only for subjects in MT-6548 group.
- [h] Measured to extent possible prior to blood sampling. Measured with subject sitting after 5 minutes of rest.
- [i] Measured to extent possible prior to blood sampling. Measured with subject in supine position after 5 minutes of rest.
- [j] Blood sampling for PK testing only for subjects in MT-6548 group.
- [k] Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period in subjects who have granted consent. Blood sampling for genetic analysis only for subjects in MT-6548 group.
- [l] Blood sampling for plasma protein binding ratio study performed once in subjects who have granted consent. Sample must be collected before starting MT-6548 Tablet for subjects in MT-6548 group, but may be collected during screening period or treatment period for subjects in darbepoetin group.
- [m] Prescribe MT-6548 Tablet depending on quantity of subject's remaining study drug. Subjects are instructed to open new bottles of study drug only after completing previous bottle.

1. Protocol history and background information

(1) Target disease and treatment methods

Chronic kidney disease (CKD) is defined in Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012"¹⁾ as renal disorders (e.g., proteinuria) or renal impairment with glomerular filtration rate (GFR) of <60 mL/min/1.73m² for 3 or more months.

CKD is a significant public health problem throughout the world, and in Japan alone 20% of adults are estimated²⁾ to have GFR of <60 mL/min/1.73m². In Japan there are more than 300,000 CKD patients requiring dialysis, a number which has increased in the past 30 years³⁾.

Anaemia is a well-known complication of renal disease, and occurs early after onset of CKD⁴⁾. 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]
[REDACTED] Further, iron loss due to dialysis is an extremely important cause of anaemia in CKD and requires iron supplementation⁷⁾. Anaemia significantly affects organ function by decreasing oxygen transport to tissue, resulting in various symptoms such as fatigue, shortness of breath, and exercise intolerance⁶⁾. 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 failure⁸⁾. 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)}. ESA formulations include epoetin alfa (recombinant), epoetin beta (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant); these are standard therapy for anaemia in CKD patients, but require IV or subcutaneous administration.

(2) Study drug names and explanations

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

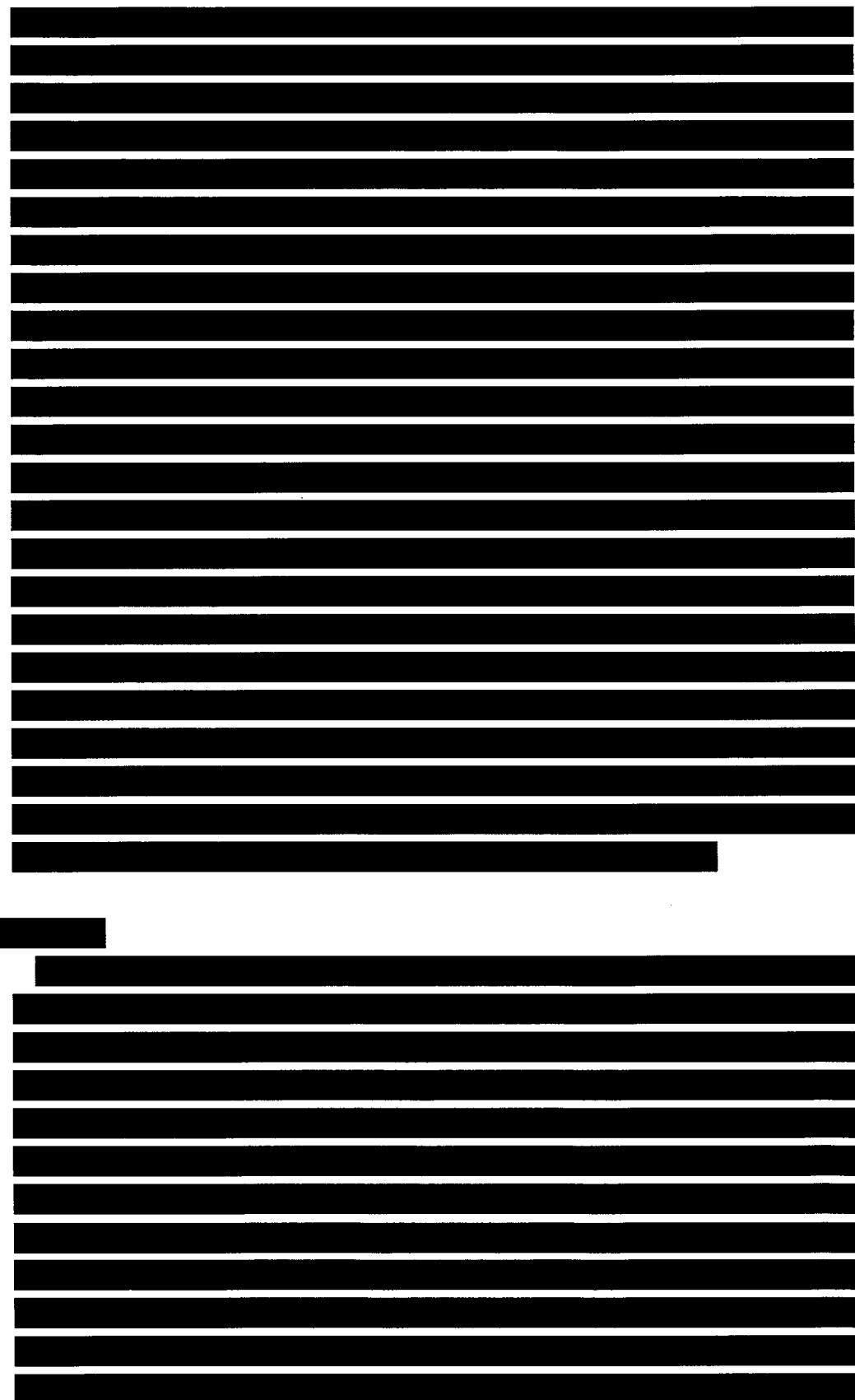
HIF-PH causes hydroxylation of HIF- α in normoxic conditions, with VHL (von Hippel-Lindau)-dependent breakdown of HIF- α reducing HIF- α levels. However, in hypoxic conditions HIF-PH activity is reduced, causing stabilized HIF- α to be transported to the cellular nucleus,

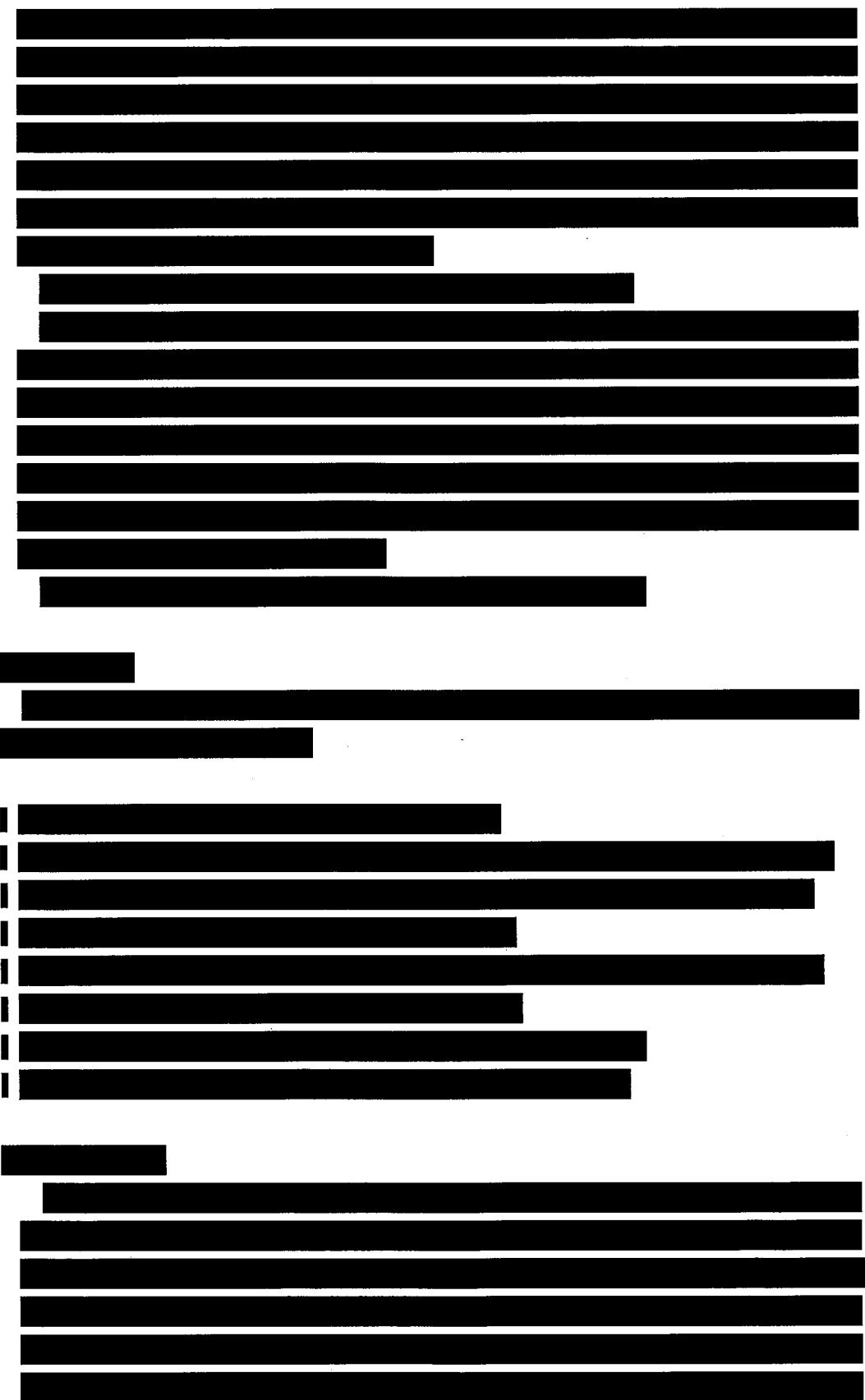
where it forms a dimer with HIF- β and binds with hypoxia response elements (HRE) to control various target genes, such as activation of EPO genes which increase EPO protein production. By inhibiting HIF-PH activity, MT-6548 creates a physiological response similar to that of hypoxic conditions, thereby increasing EPO protein production and [REDACTED], resulting in increased Hb and RBC production¹¹⁾.

(3) Nonclinical and clinical study results

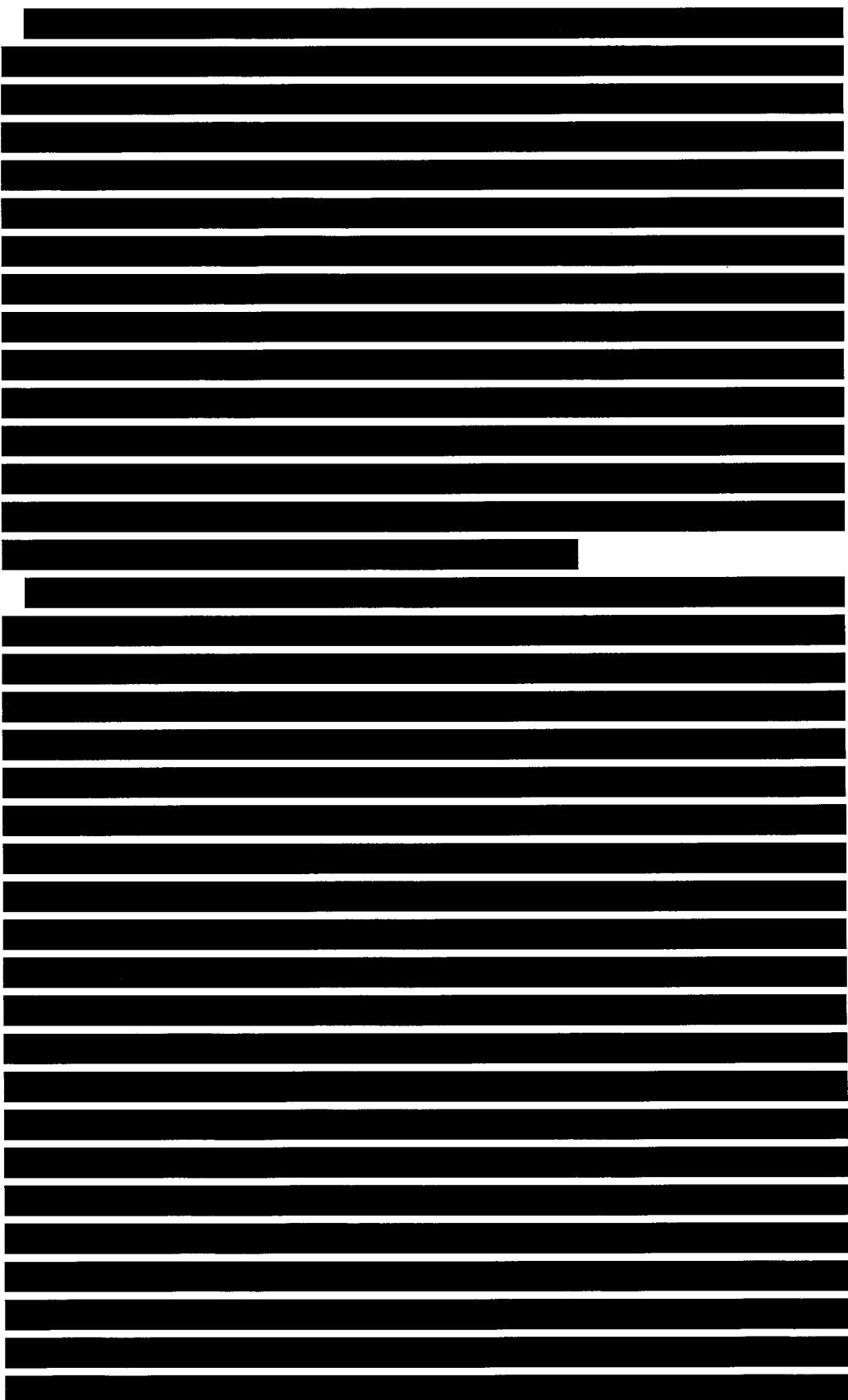
Refer to the latest MT-6548 investigator's brochure for details.

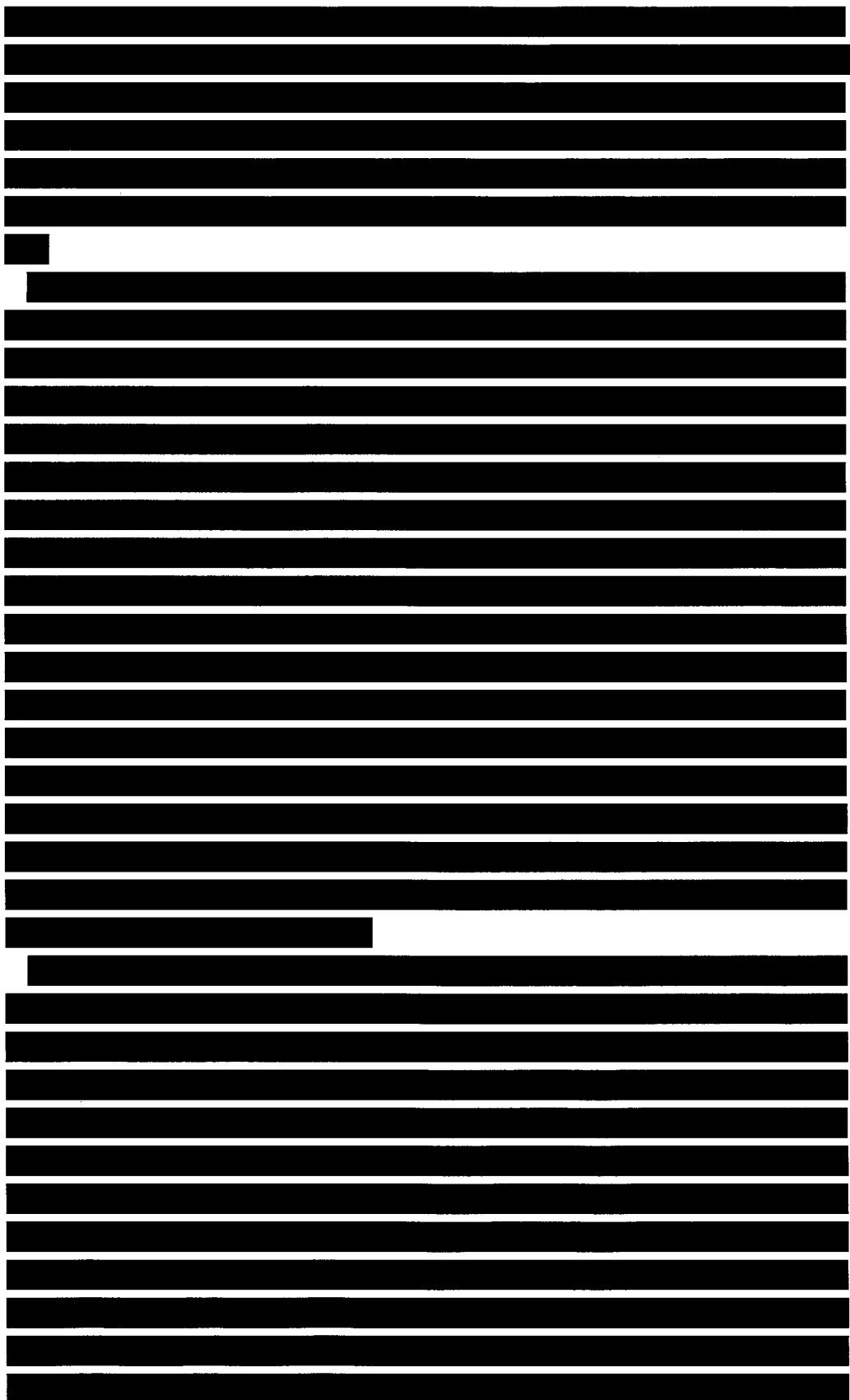
A large black rectangular redaction box covers the majority of the page content, starting below the header and ending above the footer. The redaction is composed of several horizontal black bars of varying lengths, creating a striped effect across the page.

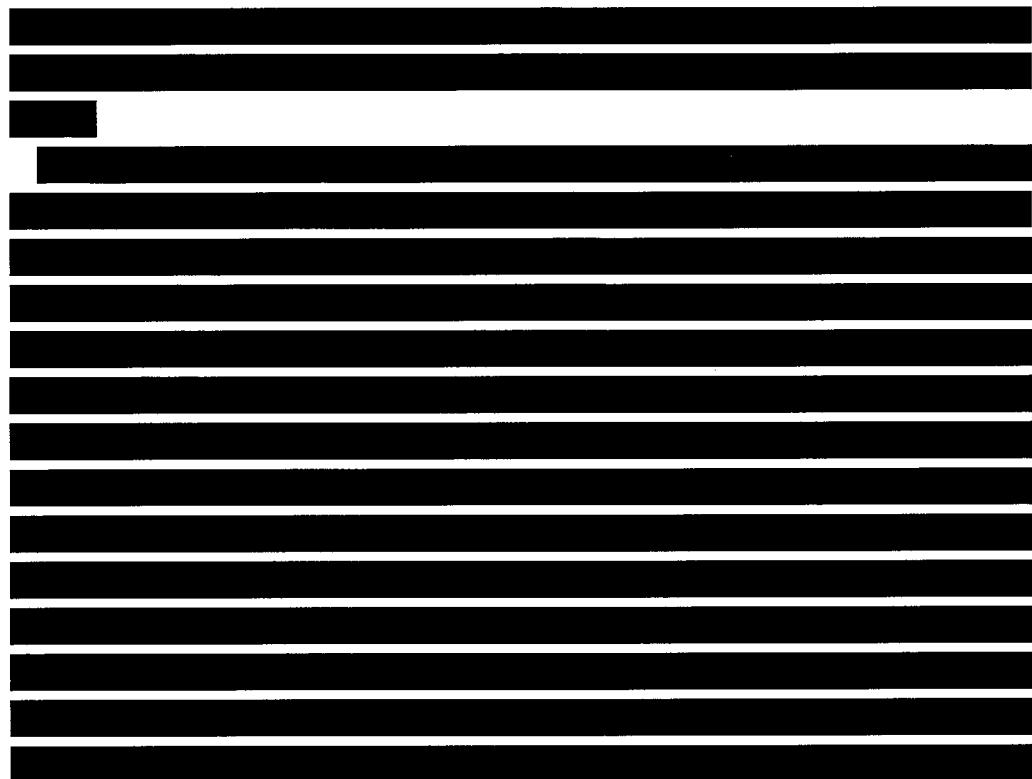




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(4) Investigational plan

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

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 Hb improvement maintenance and 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 NDD-CKD-related anaemia 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.

The study will also evaluate MT-6548's Hb improvement maintenance effects in a cohort of patients who have not received ESA treatment, as well as switching maintenance effects in a cohort of patients receiving ESA treatment.

3. Subjects

3.1 Subjects

Patients with anaemia due to NDD-CKD

3.2 Inclusion criteria

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

- (1) Patients at least 20 years of age as of the day of consent (either sex)
- (2) Patients with CKD diagnosed according to the Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012" as of the day of consent.
- (3) Patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² in the screening period.

*eGFR is calculated according to the following formula using age as of informed consent:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{serum creatinine-1.094} \times \text{age-0.287 (females: } \times 0.739)$$

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

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

Dosage:

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

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

- (7) Patients with a difference of <1.5 g/dL in Hb for the latest two tests in the screening period
- (8) Patients with serum ferritin values of ≥ 100 ng/mL or transferrin saturation (TSAT) of $\geq 20\%$ during the screening period.
- (9) Patients with folic acid and vitamin B₁₂ values above standard minimum values during the screening period.

Rationale

- (1) Individuals are legally capable of granting consent as of 20 years of age. There is no particular basis for limiting participation to either sex.
- (2) (3) To ensure that subjects have the target disease of CKD.
- (4) To ensure that patients are not dialysis-dependent.
- (5) The 8-week timespan was set in consideration of ESA's half-life and RBC life-span. ESA type, route of administration, and dose interval were restricted in order to control Hb value fluctuations. ESA dosage may be adjusted to maintain Hb levels as required, but only patients whose dosage does not exceed the normal maintenance dosage described in the package insert are eligible for the study.
- (6) Set with reference to target Hb values in nephrogenic anaemia therapy according to The Japanese Society for Dialysis Therapy's (JSDT) "Guideline for Renal Anemia in Chronic Kidney Disease 2015."
- (7) Set to ensure appropriate efficacy evaluation by targeting patients without significant fluctuations in Hb levels.
- (8) Set to ensure patients without iron insufficiency, using as reference criteria for initiating iron supplementation therapy according to the JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015."
- (9) Set to ensure appropriate efficacy evaluation by targeting patients without insufficiencies in folic acid or vitamin B₁₂, required for hematopoiesis.

3.3 Exclusion criteria

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

- (1) Patients with anaemia resulting primarily from a disease other than CKD after date of consent (e.g., sickle-cell syndrome, myelodysplastic syndrome, myelofibrosis, haematopoietic malignancy, myeloma, haemolytic anaemia, thalassemia, or aplasia pure red cell)
- (2) Patients with active haemorrhaging or exsanguination within 8 weeks prior to the first day of the screening period.

- (3) Patients who have received RBC transfusion within 8 weeks prior to the first day of the screening period.
- (4) Patients who have received testosterone enanthate or mepitiostane within 8 weeks prior to the first day of the screening period.
- (5) Patients determined by investigators/subinvestigators to likely require immediate rescue therapy or drug holiday of the study drug after initiation of treatment period.
- (6) Patients 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.
- (7) Patients with uncontrolled hypertension (defined as systolic BP >180 mmHg or diastolic BP >110 mmHg) during the screening period or on the first day of the treatment period.
- (8) Patients for whom any of the following apply upon fundoscopy during the screening period:
 - ✓ No ocular fundus findings are possible.
 - ✓ Active ocular fundus disease.
- (9) Patients with severe cardiac failure from the day of consent (Class IV according according to severity classification of the New York Heart Association (NYHA))
- (10) 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.
- (11) 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).
- (12) Patients with incidence or relapse of deep vein thrombosis or pulmonary embolism within 12 weeks prior to the first day of the screening period.
- (13) Patients with current or previous haemosiderosis or hemochromatosis.
- (14) 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.
- (15) Patients with an allergy to the study drugs.
- (16) 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).
- (17) Patients who have previously used MT-6548.
- (18) Patients with known low tolerance to HIF-PH inhibitors.
- (19) 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.

- (20) Female patients who are or may be pregnant, or women who are nursing.
- (21) Other patients judged by investigators/subinvestigators to be inappropriate as a subject in this study.

Rationale

- (1)–(4) These were considered likely to affect drug efficacy evaluation of MT-6548.
- (5)–(15) (18) Set in regard for patient safety and ethics.
- (16) Set in regard to ethical performance of study. Also, unevaluated drugs may affect efficacy or safety in unpredictable ways.
- (19) (20) 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.
- (21) Set in order to allow determinations regarding study participation in regard for patient safety for reasons other than the general factors listed above.

3.4 Re-testing/re-screening

(1) Re-testing

Re-testing during the screening period may be performed at the discretion of investigators/subinvestigators for subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, eGFR, serum ferritin, TSAT, folic acid, vitamin B₁₂, AST, ALT, or total bilirubin) or blood pressure.

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

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

(2) Re-screening

Re-screening may be performed at the discretion of investigators/subinvestigators if subjects who did not meet inclusion criteria, or who met exclusion criteria, for reasons such as laboratory values (Hb, eGFR, serum ferritin, TSAT, folic acid, vitamin B₁₂, AST, ALT, or total bilirubin), blood pressure, or blood pressure on the first day of the treatment period, may have become eligible for the study due to natural course or drug treatment.

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

4. Explanations to subjects and consent

4.1 Informed consent forms and written information

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

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

4.2 Content of written information

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

- (1) The study is for research purposes.
- (2) Study objectives
- (3) Names, titles, and addresses of investigators and subinvestigators.
- (4) Study methodology (trial aspects, 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

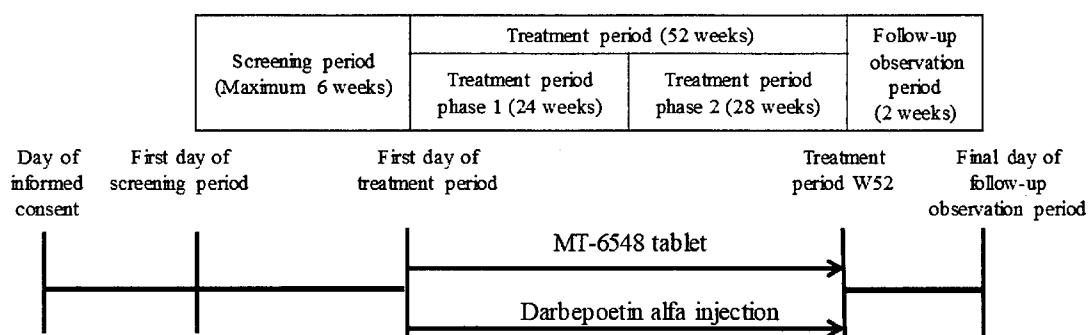
5.1 Study phase and type

Study phase: Phase 3

Study type: Confirmatory study

5.2 Study design

The current study is a multicenter, randomized, open-label, active-controlled, 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. Re-testing will be performed as necessary.

(2) Treatment period

The treatment period will last from completion of scheduled tests on the first day of the treatment period to completion of blood sampling for haematology tests on the final day of the treatment period (Week 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 2: From completion of tests specified for Week 24 of treatment period to completion of tests specified for Week 52 of treatment period

Treatment period study visits will be made every 2 weeks up until Week 12, and every 4 weeks thereafter for scheduled tests. However, study visits may be more frequent if variation in Hb levels causes concern for excessive increase or decrease in Hb, if the dose interval for darbepoetin alfa injection is shorter than the study visit interval, or for other reasons.

(3) Follow-up observation period

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

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

Rationale

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

Treatment period: 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 Hb improvement maintenance and 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 and darbepoetin alfa (recombinant) 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 Randomization and allocation methods

Personnel responsible for preparation of the allocation table will prepare a randomized key code table using block allocation according to stratification factors in accordance with the standard operating procedure for randomized key code table preparation and storage. Subjects deemed eligible to transition to the treatment period will be assigned to treatment groups, lower randomized number first, in accordance with the randomized key code table for each stratification factor. The online enrollment system will then issue a notification of treatment group allocation. The investigator/subinvestigator will prescribe to each subject the correct study drug for his or her treatment group. Further details regarding randomization methods are enumerated in the standard operating procedure for randomized key code table preparation and storage.

Randomized allocation will be performed according to the stratification factors described below such

that the MT-6548 group and the darbepoetin groups are the same size.

- ✓ Correction cohort or conversion cohort
- ✓ Mean Hb during screening period (mean of latest two measurements from central testing facility):
 - Correction cohort: <10.0 g/dL or ≥ 10.0 g/dL
 - Conversion cohort: <11.0 g/dL or ≥ 11.0 g/dL

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

(3) Other endpoints

- 1) Correction cohort only: Change from baseline in mean Hb of Weeks 20 and 24, and Weeks 48 and 52, of treatment period.
- 2) Correction cohort only: Ratio of subjects with an increase of ≥ 1.0 g/dL of mean Hb from baseline at each timepoint in treatment period.
- 3) Ratio of subjects who received ESA rescue therapy
- 4) Ratio of subjects who received red blood cell (RBC) transfusion rescue therapy.
- 5) Study drug dosage
- 6) MT-6548 group only: total number of dosage adjustments
- 7) Quantity of iron administered
- 8) Ratio of subjects who received IV iron
- 9) Ratio of subjects with serum ferritin of ≥ 100 ng/mL or TSAT $\geq 20\%$.
- 10) Change from baseline of iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin.
- 11) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and EPO (MT-6548 group only).
- 12) 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) Body weight
- (5) Vital signs
- (6) Fundoscopy
- (7) Chest X-ray
- (8) Ratio of subjects with Hb levels of ≥ 13.0 g/dL or ≥ 14.0 g/dL.
- (9) Ratio of subjects with Hb increase rates exceeding 0.5 g/dL/week.

Rationale

(1)–(5) (7) Set to evaluate general safety for nephrogenic anaemia patients.

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

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

5.4.3 Pharmacokinetic endpoints

Plasma concentration of unchanged MT-6548.

Rationale

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

6. Target sample size and study period

6.1 Target sample size

Target sample size is 300 total subjects enrolled in treatment period (150 subjects each in MT-6548 group and darbepoetin group). Target sample size for each cohort is as follows.

- ✓ Correction cohort: 100 subjects
- ✓ Conversion cohort: 200 subjects

The maximum number of subjects in the conversion cohort with mean screening period Hb values (mean of 2 most recent central testing facility results) of <11.0 g/dL and ≥ 11.0 g/dL is 120 each.

Rationale

For the primary efficacy endpoint of mean Hb at treatment period Weeks 20 and 24, mean Hb in the darbepoetin group is assumed to be 12.0 g/dL, the difference between the MT-6548 group and darbepoetin group is assumed to be 0 g/dL, and the standard deviation for both is assumed to be 1.78 g/dL. The non-inferiority margin is set at -0.75 g/dL. Calculation of statistical power from these assumptions shows that a sample size of 150 subjects in each group would ensure greater than 95% probability that the mean of mean Hb values in the MT-6548 group and their 95% CI would fall within the target Hb range (11.0–13.0 g/dL) and non-inferiority could be established.

Target sample sizes for each cohort were also set to enable appropriate evaluation of the correction cohort, the conversion cohort, and subjects with Hb of <11.0 g/dL or ≥ 11.0 g/dL in the conversion cohort.

The assumed standard deviation of 1.78 g/dL was calculated from the upper limit of the 80% CI in the MT-6548 300 mg group at Week 6 in study CI-0021.

6.2 Study period

7. Study drug

7.1 Study drug names

(1) Investigational product

Name: MT-6548 Tablet 150 mg

Nonproprietary name: vadadustat

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

(2) Control drug (for details, refer to “Appendix 6 Package Insert for Nesp® Injection”)

Name: Darbepoetin alfa injection 15 µg

 Darbepoetin alfa injection 20 µg

 Darbepoetin alfa injection 30 µg

 Darbepoetin alfa injection 40 µg

 Darbepoetin alfa injection 60 µg

 Darbepoetin alfa injection 120 µg

 Darbepoetin alfa injection 180 µg

Nonproprietary name: Darbepoetin alfa (recombinant)

Dosage form and content: Each plastic syringe (0.5 mL) contains darbepoetin alfa (recombinant) in dosages of 15, 20, 30, 40, 60, 120, or 180 µg.

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 100 tablets
Study no.: MT-6548-J01 Lot no.: XXXXXXXX
Storage method: Please store at 1–30°C.
Dosage and administration: Please follow your doctor's instructions.
*Please return empty bottles and unused study drug.
*Those not participating in the MT-6548 study must not take the study drugs.
Mitsubishi Tanabe Pharma Corporation, 3-2-10 Dosho-machi, Chuo-ku, Osaka

2) Darbepoetin alfa injection

Clinical Study Drugs Darbepoetin alfa injection • μ g
Study no.: MT-6548-J01 Lot no.: XXXXXXXX
Storage method: Store at 2–8°C away from light. Avoid freezing. Expiration date: 20XX /

* Inner packaging and the syringe have the same labels as commercially-available drugs, so please be careful not to mix them up.
* 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

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.).

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.
- (4) Subjects in the correction cohort who have been determined suitable for participation based on consent processing and enrollment and who are using ESA will discontinue ESA treatment and implement a wash-out period of at least 8 weeks.

8.2.2 Screening period

- (1) Investigators/subinvestigators will confirm subject suitability on the first day of the screening period.
- (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 transitioning to the treatment period is possible based on the input information as well as test results obtained from the contract testing laboratory, and inform the investigators/subinvestigators, clinical coordinators, and study sponsor of the result online.
- (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

8.3.1 MT-6548 Tablet

- (1) Initial dosage levels
 - 1) Initial dosage for correction cohort
Single daily dose of 300 mg (2 tablets)
 - 2) Initial dosage for conversion cohort
Single daily dose of 300 mg (2 tablets)
- (2) Maintenance dosage and dosage adjustments
Maintenance dosage is 150 to 600 mg once daily and adjusted according to the dosage adjustment guideline below.

MT-6548 Tablet dosage adjustment guidelines

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

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

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

MT-6548 Tablet dosage adjustment chart

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

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

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

Dosage adjustment algorithm for MT-6548 Tablet

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

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

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

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

(3) Administration method

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

8.3.2 Darbepoetin alfa injection

(1) Initial dose and dose interval

- 1) Initial dosage for correction cohort
One 30 μ g dose every 2 weeks

2) Initial dosage for conversion cohort: initial dosage for subjects receiving darbepoetin alfa (recombinant) prior to switching

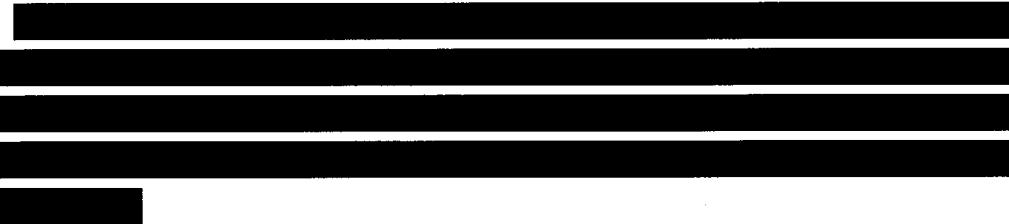
The same pre-switching dosage of darbepoetin alfa (recombinant) will be used after switching as initial dosage. The same dose interval will be used as well. However, if pre-switching dosage of darbepoetin alfa injection does not match any of the dosages listed on the dosage adjustment chart, investigators/subinvestigators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

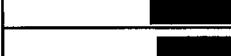
3) Initial dosage for conversion cohort: initial dosage for subjects receiving epoetin alfa (recombinant) or epoetin beta (recombinant) prior to switching

Determine initial dosage of darbepoetin alfa injection according to the chart below and begin treatment at 1 dose every 2 weeks. However, if total dosage 2 weeks prior to switching does not match any of the dosages listed on the chart below, investigators/subinvestigators will select initial dosage from the 2 closest options on the chart according to the subject's clinical status and Hb levels.

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

4) Initial dosage for conversion cohort: initial dosage for subjects receiving epoetin beta pegol (recombinant) prior to switching





(2) Maintenance dosage and dosage adjustments

Maintenance dosage is 15–180 µg per dose. Treatment intervals are 1 dose per 1 week, 2 weeks, or 4 weeks.

Maintenance dosage is adjusted according to the dosage adjustment guideline below.

[Dosage adjustment guideline for darbepoetin alfa injection]

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 timing should coincide with days of darbepoetin alfa injection administration. Hb levels will be measured prior to administration of darbepoetin alfa injection with the HemoCue® Hb201 DM analyzer; in principle these measurements will be used for determinations regarding dosage adjustments. Hb measurements used for dosage adjustment determinations will be recorded in the subject's CRF. Measurement results from the HemoCue® Hb201 DM will be used solely for determination of study drug dosage adjustments, and will not be used for efficacy or safety analysis.

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

Darbepoetin alfa injection dosage adjustment chart

Step	Dosage
1	15 µg
2	30 µg
3	60 µg
4	90 µg
5	120 µg
6	180 µg

*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.

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

Dosage adjustment algorithm for darbepoetin alfa injection

- ✓ Dosage increases are in principle separated by at least 2 weeks. There are no set intervals for dosage decreases, but frequent dosage adjustments are to be avoided.
- ✓ Decrease darbepoetin alfa injection dosage by 1 step if Hb levels suddenly increase (more than 2.0 g/dL change in past 4 weeks*).
- ✓ Increase darbepoetin alfa injection by 1 step if Hb levels are <11.0 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*).
- ✓ Decrease darbepoetin alfa injection by 1 step if Hb levels are >12.5 g/dL.

- ✓ If Hb is >13.0 g/dL and ≤ 13.5 g/dL, and there has been a sudden increase in Hb (more than 2.0 g/dL change in past 4 weeks*), discontinue darbepoetin alfa injection and resume at 1 step reduced dosage after Hb falls to ≤ 13.0 g/dL.
- ✓ If Hb is >13.5 g/dL, discontinue darbepoetin alfa injection and resume at 1 step reduced dosage after Hb falls to ≤ 13.0 g/dL.
- ✓ If Hb is maintained in the range of 11.0–12.5 g/dL, existing dosage may be doubled and dose interval extended from once every 1 week to once every 2 weeks, or from once every 2 weeks to once every 4 weeks.
- ✓ If Hb levels do not reach target levels even with dosage of 180 µg, halve existing dosage and reduce dose interval from once every 4 weeks to once every 2 weeks, or from once every 2 weeks to once every 1 week.

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

(3) Administration method

Subcutaneous administration (initial dose after completion of scheduled tests on the first day of the treatment period)

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

- (1) MT-6548 group: From the first day of the treatment period to the day prior to Week 52 of the treatment period.
- (2) Darbepoetin group: From the first day of the treatment period to the day prior to 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 alfa (recombinant), epoetin beta (recombinant), darbepoetin alfa (recombinant), and epoetin beta pegol (recombinant) is prohibited for the period described below. This excludes darbepoetin alfa injection in the darbepoetin group. These restrictions do not apply to rescue therapy.

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

(2) Testosterone enanthate and mepitiostane

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

(3) Blood transfusion

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

Rationale

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

8.5.2 Restricted drugs

(1) Iron supplements

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

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

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

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

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

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

Rationale

- (1) Set with reference to criteria for initiating iron supplementation therapy in JSDT's "Guideline for Renal Anemia in Chronic Kidney Disease 2015."
- (2) Continuation of therapy without changing dosage will avoid affecting evaluation of MT-6548 efficacy.

8.5.3 Rescue therapy

The following rescue therapy options will be available for subject safety. If any of the following rescue therapies are performed prior to 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 or darbepoetin alfa injection for ≥ 2 weeks and meets all criteria below, investigators/subinvestigators may administer ESA as rescue therapy to improve Hb levels if necessary in order to secure subject safety. ESA rescue therapy may also be administered without meeting the criteria below if deemed necessary by investigators/subinvestigators in order to secure subject safety, such as in cases of acute decreases in Hb. Study drug administration (MT-6548 or darbepoetin alfa injection) will be discontinued if implementing ESA rescue therapy. Study drug treatment may resume if Hb levels improve, as long as there is no concomitant use with ESA. Subjects who are not expected to resume study drug treatment will be withdrawn from the study.

Administration of any ESA formulation aside from darbepoetin alfa injection is considered rescue therapy for subjects in the darbepoetin group. Dosage increase of darbepoetin alfa injection (regardless of adherence to the dosage adjustment algorithm) does not constitute 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

Normally RBC transfusions are performed when clinically necessary in instances of acute or major haemorrhaging. RBC transfusion may be performed at investigator/subinvestigator discretion if deemed clinically necessary in cases of potentially worsening anaemia, even if that

anaemia is not severe, or in cases of moderate to severe anaemia symptoms.

(3) Phlebotomy

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

Rationale

Set out of consideration for subject safety.

8.5.4 Recording of concomitant drugs and therapies

The following information will be recorded regarding all concomitant drugs and therapies performed from the first day of the treatment period to completion of the follow-up observation period in the subject's CRF. Information for the screening period will also be recorded in CRFs regarding drugs described in "8.5.2 Restricted drugs." Physiological saline used for dissolving injectable formulations will not be recorded.

- (1) Concomitant drugs: Drug name, daily dosage, administration route, duration of administration, purpose
- (2) Concomitant therapies: Name/details of therapy, duration of treatment, purpose

8.6 Subject oversight

Investigators/subinvestigators, clinical coordinators, or study drug managers will oversee subjects with attention to the following points. Investigators/subinvestigators or clinical coordinators will question subjects about their adherence to the items below.

8.6.1 Drug use guidance for MT-6548 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

VISIT	Informed consent	Screening period [s]	Treatment period												Final day of follow-up/observation period [h]																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
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			First day	First day	W2	W4	W6	W8	W10	W12	W14	W23	W32	W40	W44	W52																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																							
Item			First day	Visit 2	W2	W4	W6	W8	W10	W12	W14	W23	W32	W40	W44	W48	Final day of follow-up/observation period [h]																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
Visit no.	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	TV19	TV20	TV21	TV22	TV23	TV24	TV25	TV26	TV27	TV28	TV29	TV30	TV31	TV32	TV33	TV34	TV35	TV36	TV37	TV38	TV39	TV40	TV41	TV42	TV43	TV44	TV45	TV46	TV47	TV48	TV49	TV50	TV51	TV52	TV53	TV54	TV55	TV56	TV57	TV58	TV59	TV60	TV61	TV62	TV63	TV64	TV65	TV66	TV67	TV68	TV69	TV70	TV71	TV72	TV73	TV74	TV75	TV76	TV77	TV78	TV79	TV80	TV81	TV82	TV83	TV84	TV85	TV86	TV87	TV88	TV89	TV90	TV91	TV92	TV93	TV94	TV95	TV96	TV97	TV98	TV99	TV100	TV101	TV102	TV103	TV104	TV105	TV106	TV107	TV108	TV109	TV110	TV111	TV112	TV113	TV114	TV115	TV116	TV117	TV118	TV119	TV120	TV121	TV122	TV123	TV124	TV125	TV126	TV127	TV128	TV129	TV130	TV131	TV132	TV133	TV134	TV135	TV136	TV137	TV138	TV139	TV140	TV141	TV142	TV143	TV144	TV145	TV146	TV147	TV148	TV149	TV150	TV151	TV152	TV153	TV154	TV155	TV156	TV157	TV158	TV159	TV160	TV161	TV162	TV163	TV164	TV165	TV166	TV167	TV168	TV169	TV170	TV171	TV172	TV173	TV174	TV175	TV176	TV177	TV178	TV179	TV180	TV181	TV182	TV183	TV184	TV185	TV186	TV187	TV188	TV189	TV190	TV191	TV192	TV193	TV194	TV195	TV196	TV197	TV198	TV199	TV200	TV201	TV202	TV203	TV204	TV205	TV206	TV207	TV208	TV209	TV210	TV211	TV212	TV213	TV214	TV215	TV216	TV217	TV218	TV219	TV220	TV221	TV222	TV223	TV224	TV225	TV226	TV227	TV228	TV229	TV230	TV231	TV232	TV233	TV234	TV235	TV236	TV237	TV238	TV239	TV240	TV241	TV242	TV243	TV244	TV245	TV246	TV247	TV248	TV249	TV250	TV251	TV252	TV253	TV254	TV255	TV256	TV257	TV258	TV259	TV260	TV261	TV262	TV263	TV264	TV265	TV266	TV267	TV268	TV269	TV270	TV271	TV272	TV273	TV274	TV275	TV276	TV277	TV278	TV279	TV280	TV281	TV282	TV283	TV284	TV285	TV286	TV287	TV288	TV289	TV290	TV291	TV292	TV293	TV294	TV295	TV296	TV297	TV298	TV299	TV300	TV301	TV302	TV303	TV304	TV305	TV306	TV307	TV308	TV309	TV310	TV311	TV312	TV313	TV314	TV315	TV316	TV317	TV318	TV319	TV320	TV321	TV322	TV323	TV324	TV325	TV326	TV327	TV328	TV329	TV330	TV331	TV332	TV333	TV334	TV335	TV336	TV337	TV338	TV339	TV340	TV341	TV342	TV343	TV344	TV345	TV346	TV347	TV348	TV349	TV350	TV351	TV352	TV353	TV354	TV355	TV356	TV357	TV358	TV359	TV360	TV361	TV362	TV363	TV364	TV365	TV366	TV367	TV368	TV369	TV370	TV371	TV372	TV373	TV374	TV375	TV376	TV377	TV378	TV379	TV380	TV381	TV382	TV383	TV384	TV385	TV386	TV387	TV388	TV389	TV390	TV391	TV392	TV393	TV394	TV395	TV396	TV397	TV398	TV399	TV400	TV401	TV402	TV403	TV404	TV405	TV406	TV407	TV408	TV409	TV410	TV411	TV412	TV413	TV414	TV415	TV416	TV417	TV418	TV419	TV420	TV421	TV422	TV423	TV424	TV425	TV426	TV427	TV428	TV429	TV430	TV431	TV432	TV433	TV434	TV435	TV436	TV437	TV438	TV439	TV440	TV441	TV442	TV443	TV444	TV445	TV446	TV447	TV448	TV449	TV450	TV451	TV452	TV453	TV454	TV455	TV456	TV457	TV458	TV459	TV460	TV461	TV462	TV463	TV464	TV465	TV466	TV467	TV468	TV469	TV470	TV471	TV472	TV473	TV474	TV475	TV476	TV477	TV478	TV479	TV480	TV481	TV482	TV483	TV484	TV485	TV486	TV487	TV488	TV489	TV490	TV491	TV492	TV493	TV494	TV495	TV496	TV497	TV498	TV499	TV500	TV501	TV502	TV503	TV504	TV505	TV506	TV507	TV508	TV509	TV510	TV511	TV512	TV513	TV514	TV515	TV516	TV517	TV518	TV519	TV520	TV521	TV522	TV523	TV524	TV525	TV526	TV527	TV528	TV529	TV530	TV531	TV532	TV533	TV534	TV535	TV536	TV537	TV538	TV539	TV540	TV541	TV542	TV543	TV544	TV545	TV546	TV547	TV548	TV549	TV550	TV551	TV552	TV553	TV554	TV555	TV556	TV557	TV558	TV559	TV560	TV561	TV562	TV563	TV564	TV565	TV566	TV567	TV568	TV569	TV570	TV571	TV572	TV573	TV574	TV575	TV576	TV577	TV578	TV579	TV580	TV581	TV582	TV583	TV584	TV585	TV586	TV587	TV588	TV589	TV590	TV591	TV592	TV593	TV594	TV595	TV596	TV597	TV598	TV599	TV600	TV601	TV602	TV603	TV604	TV605	TV606	TV607	TV608	TV609	TV610	TV611	TV612	TV613	TV614	TV615	TV616	TV617	TV618	TV619	TV620	TV621	TV622	TV623	TV624	TV625	TV626	TV627	TV628	TV629	TV630	TV631	TV632	TV633	TV634	TV635	TV636	TV637	TV638	TV639	TV640	TV641	TV642	TV643	TV644	TV645	TV646	TV647	TV648	TV649	TV650	TV651	TV652	TV653	TV654	TV655	TV656	TV657	TV658	TV659	TV660	TV661	TV662	TV663	TV664	TV665	TV666	TV667	TV668	TV669	TV670	TV671	TV672	TV673	TV674	TV675	TV676	TV677	TV678	TV679	TV680	TV681	TV682	TV683	TV684	TV685	TV686	TV687	TV688	TV689	TV690	TV691	TV692	TV693	TV694	TV695	TV696	TV697	TV698	TV699	TV700	TV701	TV702	TV703	TV704	TV705	TV706	TV707	TV708	TV709	TV710	TV711	TV712	TV713	TV714	TV715	TV716	TV717	TV718	TV719	TV720	TV721	TV722	TV723	TV724	TV725	TV726	TV727	TV728	TV729	TV730	TV731	TV732	TV733	TV734	TV735	TV736	TV737	TV738	TV739	TV740	TV741	TV742	TV743	TV744	TV745	TV746	TV747	TV748	TV749	TV750	TV751	TV752	TV753	TV754	TV755	TV756	TV757	TV758	TV759	TV760	TV761	TV762	TV763	TV764	TV765	TV766	TV767	TV768	TV769	TV770	TV771	TV772	TV773	TV774	TV775	TV776	TV777	TV778	TV779	TV780	TV781	TV782	TV783	TV784	TV785	TV786	TV787	TV788	TV789	TV790	TV791	TV792	TV793	TV794	TV795	TV796	TV797	TV798	TV799	TV800	TV801	TV802	TV803	TV804	TV805	TV806	TV807	TV808	TV809	TV810	TV811	TV812	TV813	TV814	TV815	TV816	TV817	TV818	TV819	TV820	TV821	TV822	TV823	TV824	TV825	TV826	TV827	TV828	TV829	TV830	TV831	TV832	TV833	TV834	TV835	TV836	TV837	TV838	TV839	TV840	TV841	TV842	TV843	TV844	TV845	TV846	TV847	TV848	TV849	TV850	TV851	TV852	TV853	TV854	TV855	TV856	TV857	TV858	TV859	TV860	TV861	TV862	TV863	TV864	TV865	TV866	TV867	TV868	TV869	TV870	TV871	TV872	TV873	TV874	TV875	TV876	TV877	TV878	TV879	TV880	TV881	TV882	TV883	TV884	TV885	TV886	TV887	TV888	TV889	TV890	TV891	TV892	TV893	TV894	TV895	TV896	TV897	TV898	TV899	TV900	TV901	TV902	TV903	TV904	TV905	TV906	TV907	TV908	TV909	TV910	TV911	TV912	TV913	TV914	TV915	TV916	TV917	TV918	TV919	TV920	TV921	TV922	TV923	TV924	TV925	TV926	TV927	TV928	TV929	TV930	TV931	TV932	TV933	TV934	TV935	TV936	TV937	TV938	TV939	TV940	TV941	TV942	TV943	TV944	TV945	TV946	TV947	TV948	TV949	TV950	TV951	TV952	TV953	TV954	TV955	TV956	TV957	TV958	TV959	TV960	TV961	TV962	TV963	TV964	TV965	TV966	TV967	TV968	TV969	TV970	TV971	TV972	TV973	TV974	TV975	TV976	TV977	TV978	TV979	TV980	TV981	TV982	TV983	TV984	TV985	TV986	TV987	TV988	TV989	TV990	TV991	TV992	TV993	TV994	TV995	TV996	TV997	TV998	TV999	TV1000	TV1001	TV1002	TV1003	TV1004	TV1005	TV1006	TV1007	TV1008	TV1009	TV1010	TV1011	TV1012	TV1013	TV1014	TV1015	TV1016	TV1017	TV1018	TV1019	TV1020	TV1021	TV1022	TV1023	TV1024	TV1025	TV1026	TV1027	TV1028	TV1029	TV1030	TV1031	TV1032	TV1033	TV1034	TV1035	TV1036	TV1037	TV1038	TV1039	TV1040	TV1041	TV1042	TV1043	TV1044	TV1045	TV1046	TV1047	TV1048	TV1049	TV1050	TV1051	TV1052	TV1053	TV1054	TV1055	TV1056	TV1057	TV1058	TV1059	TV1060	TV1061	TV1062	TV1063	TV1064	TV1065	TV1066	TV1067	TV1068	TV1069	TV1070	TV1071	TV1072	TV1073	TV1074	TV1075	TV1076	TV1077	TV1078	TV1079	TV1080	TV1081	TV1082	TV1083	TV1084	TV1085	TV1086	TV1087	TV1088	TV1089	TV1090	TV1091	TV1092	TV1093	TV1094	TV1095	TV1096	TV1097	TV1098	TV1099	TV1100	TV1101	TV1102	TV1103	TV1104	TV1105	TV1106	TV1107	TV1108	TV1109	TV1110	TV1111	TV1112	TV1113	TV1114	TV1115	TV1116	TV1117	TV1118	TV1119	TV1120	TV1121	TV1122	TV1123	TV1124	TV1125	TV1126	TV1127	TV1128	TV1129	TV1130	TV1131	TV1132	TV1133	TV1134	TV1135	TV1136	TV1137	TV1138	TV1139	TV1140	TV1141	TV1142	TV1143	TV1144	TV1145	TV1146	TV1147	TV1148	TV1149	TV1150	TV1151	TV1152	TV1153	TV1154	TV1155	TV1156	TV1157	TV1158	TV1159	TV1160	TV1161	TV1162	TV1163	TV1164	TV1165	TV1166	TV1167	TV1168	TV1169	TV1170	TV1171	TV1172	TV1173	TV1174	TV1175	TV1176	TV1177	TV1178	TV1179	TV1180	TV1181	TV1182	TV1183	TV1184	TV1185	TV1186	TV1187	TV1188	TV1189	TV1190	TV1191	TV1192	TV1193	TV1194	TV1195	TV1196	TV1197	TV1198	TV1199	TV1200	TV1201	TV1202	TV1203	TV1204	TV1205	TV1206	TV1207	TV1208	TV1209	TV1210	TV1211	TV1212	TV1213	TV1214	TV1215	TV1216	TV1217	TV1218	TV1219	TV1220	TV1221	TV1222	TV1223	TV1224	TV1225	TV1226	TV1227	TV1228	TV1229	TV1230	TV1231	TV1232	TV1233	TV1234	TV1235	TV1236	TV

- [a] Maximum screening period length is 6 weeks. Test results will be reviewed prior to transitioning from the first day of the screening period to screening period Visit 2, and from screening period Visit 2 to the first day of the treatment period. Re-testing will be performed as necessary.
- [b] Not required if withdrawing prior to treatment period.
- [c] Perform prior to study drug treatment (AE investigations begin after study drug treatment)
- [d] Fundoscopy and chest X-ray performed once during screening period, once during Weeks 20–24 of treatment period, and once during Weeks 48–52 of treatment period. Also performed to extent possible within 14 days of study withdrawal.
- [e] Only female subjects who may become pregnant.
- [f] Hb only measured.
- [g] Erythropoietin measured only for subjects in MT-6548 group.
- [h] Measured to extent possible prior to blood sampling. Measured with subject sitting after 5 minutes of rest.
- [i] Measured to extent possible prior to blood sampling. Measured with subject in supine position after 5 minutes of rest.
- [j] Blood sampling for PK testing only for subjects in MT-6548 group.
- [k] Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period in subjects who have granted consent. Blood sampling for genetic analysis only for subjects in MT-6548 group.
- [l] Blood sampling for plasma protein binding ratio study performed once in subjects who have granted consent. Sample must be collected before starting MT-6548 Tablet for subjects in MT-6548 group, but may be collected during screening period or treatment period for subjects in darbepoetin group.
- [m] Prescribe MT-6548 Tablet depending on quantity of subject's remaining study drug. Subjects are instructed to open new bottles of study drug only after completing previous bottle.

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

Table 9.1-1 Permitted ranges for study center visits

Evaluation timepoint		Reference date	Permitted range
Screening period ^{*1}	Initiation date	—	—
	Visit 2	—	—
Treatment period Phase 1	Initiation date ^{*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) Body weight
- (5) Race
- (6) Ethnicity
- (7) Smoking status
- (8) Underlying cause of CKD
- (9) Time of onset of nephrogenic anaemia
- (10) Concomitant illnesses (illnesses present on the first day of the treatment period)
- (11) Correction group or conversion group
- (12) Yes/no for wash-out period for ESA (correction cohort only)
- (13) Details of washed-out ESA formulation (type, administration route, dose interval, dosage, and final day) (correction cohort only)
- (14) Details of previous ESA formulation (type, administration route, dose interval, dosage, and final day) (conversion cohort only)

9.2.2 Treatment status

9.2.2.1 MT-6548 Tablet

Subjects will be asked the following information to be recorded in CRFs.

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

If darbepoetin alfa injection was administered, record dates of treatment, dosage, and dose interval 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. All measurement results will be reported to each study center and the study sponsor.

(1) Hb value

Blood sampling and Hb measurement will be performed on the first day of the screening period, screening period Visit 2, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 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 (MT-6548 group only)

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

(6) Quantity of iron administered

Iron dosage will be recorded in CRFs.

(7) Ratio of subjects who received IV iron

Iron administration route will be recorded in CRFs.

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

Blood sampling and measurement will be performed for serum iron, TIBC, TSAT, and serum ferritin on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

(9) Hepcidin

Blood sampling and measurement of hepcidin will be performed on the first day of the treatment period, treatment period Weeks 2, 4, 6, 12, 24, 36, and 52, and the day of discontinuation of treatment.

(10) Haematocrit, RBC count

Blood sampling and measurement will be performed for haematocrit and RBC count on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

(11) Reticulocytes (counts and fractions)

Blood sampling and measurement will be performed for reticulocytes (counts and fractions) on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

(12) EPO (MT-6548 group only)

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.

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

Subjects will fill out EQ-5D-5L and KDQOL questionnaires (Appendices 4 and 5) on the first day of the treatment period, treatment period Weeks 12, 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 and urine collection at the study center. All measurement results will be reported to each study center and the study sponsor. Study centers will store test reports issued by the contract testing laboratory. Investigators/subinvestigators will record day of confirmation and confirmation results (clinical significance) for the following tests.

1) Haematology tests:

Blood sampling and measurement will be performed for the following parameters on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

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

2) Blood biochemistry tests:

Blood sampling and measurement will be performed for the following parameters on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

Total protein, albumin, blood glucose, urea nitrogen, creatinine, eGFR, 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

eGFR is calculated according to the following formula using age as of informed consent:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine} - 1.094 \times \text{age} - 0.287 \text{ (females: } \times 0.739\text{)}$$

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 B₁₂:

Blood sampling and measurement of folic acid and vitamin B₁₂ 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.

7) Urine albumin/creatinine ratio and urine protein/creatinine ratio:

Urine sampling and measurement Urine albumin/creatinine ratio and urine protein/creatinine ratio will be performed on the first day of the screening period, the first day of the treatment period, treatment period Weeks 12, 24, 36, and 52, and the day of discontinuation of treatment.

8) Urinalysis (qualitative):

Urine sampling and measurement will be performed for the following parameters on the first day of the screening period, the first day of the treatment period, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 of the treatment period, and the day of discontinuation of treatment.

Glucose, protein, urobilinogen, occult blood

(2) Resting standard 12-lead ECG

Resting standard 12-lead ECG will be measured in the supine position during hospital visits on the first day of the treatment period, treatment period Weeks 24 and 52, and the day of discontinuation of treatment. ECG diagnosis consists of a comprehensive evaluation including arrhythmia and wave-form diagnoses.

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

1) Normal

2) Clinically non-problematic abnormality

3) Clinically problematic abnormality

(3) Body weight

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

(4) Vital signs

Sitting blood pressure and pulse rate will be measured during study visits on the first day of the

treatment period, treatment period Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, and the day of discontinuation of treatment. Measurements are recorded in CRFs.

Measurements will be made before blood sampling when possible, and after 5 minutes at rest.

(5) Fundoscopy

Fundoscopy will be performed once each within the screening period, from treatment period Week 20 to Week 24, 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)

(6) 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

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

Blood sampling and pregnancy testing will be performed on the first day of the screening period, treatment period Weeks 24 and 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 the study drug caused the AE. This assessment will take into account factors not related to the study drug, including risk factors such as natural course and concurrent treatments for underlying or concomitant diseases, as well as the temporal relationship between the study drugs and the event (recurrence after resuming administration, elimination after discontinuation, etc.). AEs for which a logical possibility exists for causal relationship with the study drug are treated as ADRs.

1. Logical possibility
2. No logical possibility

5) Outcome

AE outcomes are classified as follows:

1. Recovery
2. Relief
3. Not recovered
4. Recovered with sequelae
5. Death
6. Unknown

6) Date of outcome

Date of outcome is determined according to the following criteria:

Recovery: Date of recovery. If date of recovery is not known, use date on which recovery was confirmed or determined.

Relief: Date on which relief was confirmed or determined.

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

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

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

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

7) Action taken with the study drug

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

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

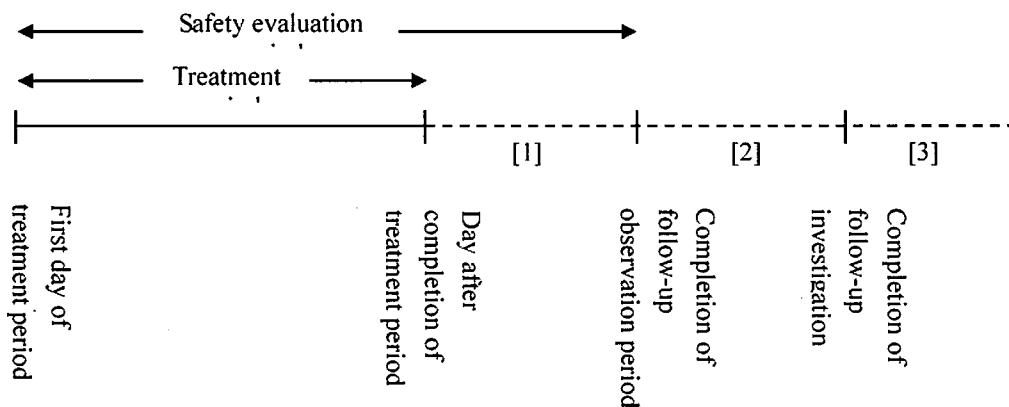
8) Action taken other than with the study drug

Actions taken other than with the study drug are classified into the following two categories:

If actions other than with the study drug were taken, details of these will be investigated and recorded in the CRF.

1. No
2. Yes

9) Follow-up investigation



- Period [1] above is the 14 days from the day after completion of the treatment period, during which any AEs will be investigated.
- Period [2] above is the 28 days from the day after completion of the follow-up observation period; it is the period for follow-up investigations of AEs occurring during the safety evaluation period (treatment period + Period [1]).

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

(4) Recording information in CRFs

If an AE is observed, investigators/subinvestigators will record the following information in the subject'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

Plasma drug concentration will be measured only in subjects in the MT-6548 group.

(1) Measuring plasma concentration

1) Blood sampling timing and volume

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) Blood sampling volume: [REDACTED]

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

2) Blood processing

[REDACTED]

[REDACTED]

[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.

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 of the MT-6548 group who have granted consent to genetic analysis. The blood sampling volume will be about [REDACTED] (refer to “25. Genetic Analysis Study”).

9.2.7 Blood sampling for the plasma protein binding ratio study

Investigators/subinvestigators will collect [REDACTED] for the plasma protein binding ratio study [REDACTED] in subjects who have granted consent. [REDACTED] [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) Ratios of subjects with mean Hb within the target range (11.0–13.0 g/dL), <11.0 g/dL, and ≥ 13.0 g/dL at each timepoint in treatment period

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

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

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

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

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

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

10.1.3 Other endpoints

The following endpoints will also be studied.

- (1) Correction cohort only: Change from baseline in mean Hb of Weeks 20 and 24, and Weeks 48 and 52, of treatment period.

Change from baseline in mean Hb of Weeks 20 and 24, and Weeks 48 and 52 of treatment period, will be calculated.

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

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

- (3) Ratio of subjects who received ESA rescue therapy

Ratio of subjects who received ESA rescue therapy from the first day of the treatment period to treatment period Weeks 24 and 52 will be calculated.

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

Ratio of subjects who received RBC transfusion from the first day of the treatment period to treatment period Weeks 24 and 52 will be calculated.

- (5) 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.

- (6) MT-6548 group only: total number of 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.

- (7) Quantity of iron administered

Mean weekly dosage will be calculated for each scheduled study visit from the first day of the treatment period up to treatment period Week 52.

- (8) Ratio of subjects who received IV iron

Ratio of subjects who received IV iron from the first day of the treatment period to treatment

period Weeks 24 and 52 will be calculated.

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

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

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

Changes in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin from baseline will be calculated for each evaluation timepoint.

(11) Change from baseline of haematocrit, RBC count, reticulocytes (counts and fractions), and EPO (MT-6548 group only).

Changes in haematocrit, RBC count, reticulocytes (counts and fractions), and EPO (MT-6548 group only) from baseline will be calculated for each evaluation timepoint.

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

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

10.2 Safety

The following endpoints will also be studied.

(1) AEs and ADRs (refer to “9.2.4.2 Adverse events” for details)

(2) Laboratory test values

(3) Resting standard 12-lead ECG

(4) Body weight

(5) Vital signs

(6) Fundoscopy

(7) Chest X-ray

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

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

10.3 Pharmacokinetics

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 continuous haemodialysis or peritoneal dialysis is initiated, or if the subject receives a renal transplant.
- (8) If pregnancy of the subject is discovered.
- (9) 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) Set in order to prevent study drug administration to subjects unsuitable for inclusion in safety

or efficacy evaluation.

- (3) (4) (6) (8) Set out of safety considerations.
- (5) Set because evaluating efficacy of MT-6548 accurately would be difficult.
- (9) 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 withdrawal 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 Dosage and administration” 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 NDD-CKD-related anaemia
- ✓ Subjects who did not receive 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 or darbepoetin alfa injection

(2) Safety analysis set

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

- ✓ Subjects who did not receive 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
- ✓ 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 closest 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 be 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.

The same analyses will be performed for the conversion cohort and the conversion cohort unless otherwise specified. 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, patient cohort (correction or conversion cohort), interactions of evaluation period \times treatment group, interactions of evaluation period \times patient cohort (correction or conversion cohort)
- 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 (11.0–13.0 g/dL).

Sensitivity analysis will be performed using the following analysis methods.

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

Numbers and ratios of subjects with mean Hb at each treatment period timepoint within the target range (11.0–13.0 g/dL), <11.0 g/dL, and ≥ 13.0 g/dL will be shown.
- 4) Correction cohort only: Days from initiation of treatment period required to reach target Hb range (11.0–13.0 g/dL)

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

Descriptive statistics will be calculated for rate of Hb increase and treatment groups compared with ANCOVA using baseline values as covariates. Point estimates and their standard errors and their 95% CI will be calculated for differences in mean values between the MT-6548 group and the darbepoetin group.

(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, 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 ≥ 13.0 g/dL or ≥ 14.0 g/dL.

Numbers and ratios of subjects with Hb levels of ≥ 13.0 g/dL or ≥ 14.0 g/dL at each timepoint will be shown 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]
[REDACTED] . [REDACTED]
[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 cancellation 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 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

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

25.4.2 Storage and transport conditions

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

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.

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 in subjects with different levels of renal function. 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]
[REDACTED]
[REDACTED]
[REDACTED]
[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) eGFR
- (7) Concomitant medications in use at time of blood sampling

26.6 Sample handling

26.6.1 Blood sampling dates

26.6.2 Storage and transport conditions

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

[Contract Monitoring Organization]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Night/Holiday Contact Information

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

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

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]