For Final Fixed Data Analysis

Additional Statistical Analysis Plan

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

Mitsubishi Tanabe Pharma Corporation

Preparation date	September 06, 2019
Study protocol number	MT-6548-J01
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Approval Column

MTPC Statistics Approver	
[redacted]	

1. Introduction

This is a document that shows the contents of the additional analysis for the statistical analysis plan in the final fixed data of "A phase III, confirmatory study of MT-6548 in patients with anemia associated with nondialysis-dependent chronic kidney disease (open-label comparative study with darbepoetin alfa [recombinant]" (hereinafter, the final fixed data).

1.1 Review of the effect on the change of data in the treatment period phase 1 (addition)

In the "(1) Summary of adverse events and adverse drug reactions", differences from the treatment period phase 1 would be categorized by SOC and PT and tabulated separately; however, no differences were found in "(1) Summary of adverse events and adverse drug reactions" because subjects with an additional adverse event had other adverse events. Therefore, in order to evaluate the effect of the single additional adverse event, a tabulation of the individual adverse events classified by SOC and PT below is added.

The derivation and analysis method should be based on the description of SAP for the treatment period phase 1.

1.1.1 Individual adverse events

(1) Individual adverse events

Regarding adverse events, the number of subjects and incidence of individual adverse events classified by SOC and PT of MedDRA Version 20.1 and MedDRA/J Version 20.1. (hereinafter the same) should be calculated.

The SOC will be sorted by order of international consensus, the PT by descending order of the number of subjects with MT-6548 and by descending order of the number of subjects with darbepoetin (PT code ascending when the number is equal). No analysis will be performed for patient cohorts.

9. List of Output Tables

Table number and title
Table 14.5.1.1.2 Adverse Events by System Organ Class and Preferred Term in Period I (Safety Analysis Set)

For Final Fixed Data Analysis

Statistical Analysis Plan

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

Mitsubishi Tanabe Pharma Corporation

Preparation date	September 02, 2019
Study protocol number	MT-6548-J01
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Revision History

Version number	Content of revision
Version 1	First edition
Version 2 (final edition)	Revision after the case review meeting

For Final Fixed Data Analysis
Statistical Analysis Plan

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

Approval Column

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List of Abbreviations

Abbreviation	Full 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
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
JSDT	The Japanese society for dialysis therapy
LOCF	Last observation carried forward
MMRM	Mixed model repeated measures
MRP	Multidrug resistance-associated protein
NDD-CKD	Nondialysis dependent chronic kidney disease
OATP	Organic anion transporting polypeptide
OAT	Organic anion transporter
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Preferred term
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 the 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 scheduled tests for Week 24 of the treatment period to completion of scheduled tests for Week 52 of the treatment period
Day of completion of treatment period	Week 52 of the treatment period or the day of discontinuation during the treatment period
X weeks prior to the first day of the screening period	Same day of the week X weeks prior to the first day of the screening period
MT-6548 tablets	Each film-coated tablet contains 150 mg vadadustat
Darbepoetin alfa injection	Plastic syringe containing darbepoetin alfa (recombinant) in 1 syringe (0.5 mL)
Correction cohort	Patients who have not received ESA formulations from 8 weeks prior to the first day of the screening period
Conversion cohort	Patients who have received the same ESA formulations from 8 weeks prior to the first day of the screening period

1. Introduction

This is a document that shows more detailed contents in addition to those of the study plan on the statistical analysis plan for the efficacy and safety in the final fixed data (hereinafter, the final fixed data) of "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. Study Objectives and Design

Study objectives

The study evaluates the non-inferiority of MT-6548 in patients with anemia associated with NDD-CKD using Hb values as a measure and darbepoetin alfa (recombinant) as a control drug and also the safety of long-term administration of MT-6548.

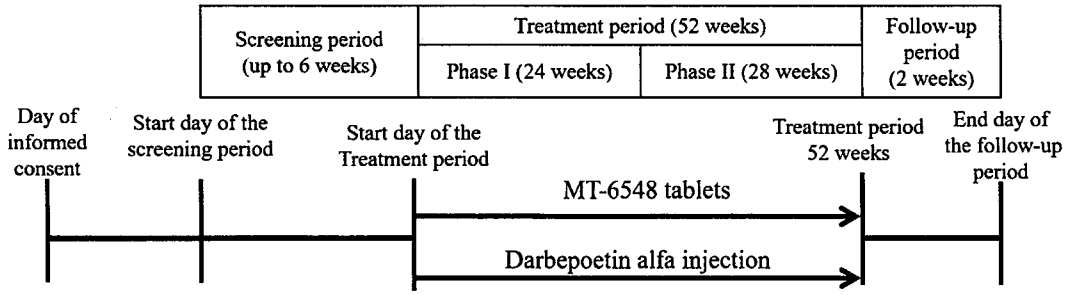
In addition, the study evaluates the effect of MT-6548 on improvement and maintenance of Hb values in a cohort of patients who have not received ESA formulations and also the effect of MT-6548 on switch maintenance of Hb values in a cohort of patients receiving ESA formulations.

2.2 Study design

Study phase: Phase III

Study type: Confirmatory study

Multicenter, randomized, open-label, active-controlled, parallel group comparative study.



2.3 Randomization methods

Personnel responsible for preparation of the allocation table should 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 who are judged eligible to enter the treatment period are assigned to treatment groups in ascending order of the randomization number based on the randomization key code table for each stratification factor, and the treatment groups assigned on the Web registration system are notified. The investigator/coinvestigator should prescribe the study drug of the treatment group notified on the Web registration system. Further details of randomization methods shall be specified in the standard operating procedure for randomization key code table preparation and storage.

Subjects should be randomly assigned in a 1:1 ratio to MT-6548 and darbepoetin groups with the following stratification factors.

✓ Correction cohort or Conversion cohort

✓ Mean Hb levels during the screening period (mean of the latest two central measurements):

- Correction cohort: <10.0 g/dL or ≥10.0 g/dL
- Conversion cohort: <11.0 g/dL or ≥11.0 g/dL

2.4 Evaluation time points

VISIT / ITEM	Informed consent	Screening period [a]		Treatment period																		Final day of follow-up observation period [b]
				Treatment period phase I										Treatment period phase II							Day of discontinuation	
		First day	Visit 2	Start day [c]	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52		
Visit No.	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	FU
Permitted range (day)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7 or +14 [d]	+7
Procedure/Evaluation																						
Informed consent	×																					
Inclusion/Exclusion criteria	×	×	×	×																		
Allocation				×																		
Patient's background and history	×			×																		
Height				×																		
Body weight				×						×			×			×				×	×	
Folate and vitamin B_{12}		×																				
Pregnancy test [e]		×											×							×	×	
Hematology tests		×	× [f]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Blood biochemistry tests and eGFR		×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
C-reactive protein		×		×									×							×	×	
Iron-related measures		×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Hepcidin				×	×	×	×			×			×			×				×	×	
Erythropoietin [g]				×	×	×	×			×			×			×				×	×	
VEGF				×						×			×			×				×	×	
DHEA-S				×						×			×			×				×	×	
Urinalysis (qualitative)		×		×	×	×	×		×	×	×	×	×	×	×	×	×	×	×	×	×	
Urine albumin/creatinine ratio		×		×						×			×			×				×	×	
Urine protein/creatinine ratio		×		×						×			×			×				×	×	
Vital signs [h]		×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
12-lead ECG [i]				×									×							×	×	
Fundoscopy [d]		×										×							×		×	
Chest X-ray [d]		×										×							×		×	
QOL measures (EQ-5D-5L, KDQOL)				×						×			×							×	×	
AE Investigation				×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Blood sampling for PK testing [j]						×				×			×									
Blood sampling for genetic analysis [k]					Blood sample for genetic analysis performed once as early as possible after Week 2 of the treatment period																	
Blood sampling for plasma protein binding [l]		×																				
Drug evaluation/procedure																						
Investigation of concomitant drugs				×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Prescription of MT-6548 tablets [m]				Administered according to the dose adjustment guideline																		
Prescribing of darbepoetin alfa injection				Administered according to the dose adjustment guideline																		
Administration of iron supplements		Administration iron supplements to maintain serum ferritin values >=100 ng/mL or TSAT at >=20%																				

[a] The screening period can be up to 6 weeks. Test results should be reviewed prior to transition 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 can be performed as necessary.

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

[c] Should be performed prior to study drug treatment (AE investigations begin after study drug treatment).

[d] Fundoscopy and chest X-ray should be performed once during the screening period. Fundoscopy and chest X-ray should be performed once during Weeks 20–24 of the treatment period, and once during Weeks 48–52 of the treatment period. Should be performed within 14 days of study withdrawal if treatment is discontinued.

[e] Only female subjects who may become pregnant.

[f] Only Hb values should be measured.

[g] Erythropoietin should be measured in subjects of the MT-6548 group only.

[h] Measurements should be made before blood sampling as much as possible. Measurements should be made in the sitting position after 5 minutes of rest.

[i] Measurements should be made before blood sampling as much as possible. Measurements should be made in the supine position after 5 minutes of rest.

[j] Blood sampling for PK testing should be performed in subjects of the MT-6548 group only.

[k] Blood should be collected once as early as possible after Week 2 of the treatment period for subjects who have given consent to the genetic analysis tests. Blood sampling for genetic analysis should be performed in subjects of the MT-6548 group only.

[l] For subjects who consent to the plasma protein binding rate study, blood should be collected once before the start of treatment with MT-6548 tablets. For subjects in the darbepoetin group, blood sampling should also be allowed during the treatment period.

[m] MT-6548 tablets should be prescribed to subjects depending on the number of their unused tablets. Subjects should be instructed to use up one bottle before opening the next.

2.5 Rationale for sample size

A total of 300 subjects (150 each for the MT-6548 and darbepoetin groups) should be enrolled in the treatment period. The target sample size for each cohort is shown below.

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

However, the maximum number of subjects 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 in the screening period in the Conversion cohort should be 120.

[Rationale]

For the primary efficacy endpoint of mean Hb values at treatment period Weeks 20 and 24, the mean Hb value in the darbepoetin group is assumed to be 12.0 g/dL, the difference between the MT-6548 and darbepoetin groups 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 to <13.0 g/dL) and non-inferiority could be established.

In addition, the target sample size was set for each of the Correction cohort, Conversion cohort, Conversion (Hb value ≥11.0 g/dL) cohort, and Conversion (Hb value <11.0) cohort so that appropriate evaluation could be made for each cohort.

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

3. Endpoints

3.1 Efficacy endpoints

3.1.1 Secondary endpoints

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

(2) Hb values at each evaluation time point in the treatment period

(3) Proportion of subjects with mean Hb values within the target range (≥11.0 to <13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each evaluation time point in the treatment period

(4) Number of days from the first day of the treatment period required to reach the target Hb range (≥11.0 g/dL to <13.0 g/dL)

3.1.2 Other endpoints

(1) Changes in mean Hb values from the first day of the treatment period at Weeks 48 and 52 of the treatment period

(2) Proportion of subjects with a ≥1.0 g/dL increase in mean Hb values from the first day of the treatment period at each time point of the treatment period.

(3) Number of days to maintain the target Hb values

(4) Proportion of subjects receiving rescue therapy with ESA formulations, red blood cell transfusion, or phlebotomy

(5) Study drug dosage

(6) Total number of dosage adjustments

(7) Iron supplement dosage

(8) Proportion of subjects receiving oral, intravenous, or (any route) administration of iron supplements

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

(10) Changes and rate of changes in iron-related indices (serum iron, TIBC, TSAT, and serum ferritin values) and hepcidin from the first day of the treatment period

(11) Changes in hematocrit, red blood cell count, reticulocytes (number and rate), mean corpuscular volume, mean corpuscular hemoglobin, and erythropoietin (MT-6548 group only) from the first day of the treatment period

(12) Changes and rate of changes in systolic blood pressure, diastolic blood pressure, lipids (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides), and blood glucose from the start of the treatment period

(13) Change in renal function-related indices (eGFR, serum creatinine, urinary albumin/creatinine ratio) from the first day of the treatment period

(14) QOL indices (EQ-5D-5L, KDQOL)

3.2 Safety endpoints

(1) Adverse events and adverse drug reactions

(2) Laboratory test values

1) Hematology tests:

Mean corpuscular volume, mean hemoglobin, mean hemoglobin concentration, RBC distribution width, WBC count, WBC fractions (neutrophils, eosinophils, monocytes, lymphocytes, basophils), platelet count.

2) Blood biochemistry tests:

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 the age at the time of informed consent acquisition.

eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age $^{-0.287}$ (× 0.739 if female)

3) C-reactive protein

4) Vascular endothelial growth factor (VEGF)

5) Dehydroepiandrosterone sulfate (DHEA-S)

6) Urine albumin/creatinine ratio and urine protein/creatinine ratio

7) Urinalysis (qualitative)

Glucose, protein, urobilinogen, occult blood

(3) Resting standard 12-lead ECG

(4) Body weight

(5) Vital signs

(6) Fundoscopy

(7) Chest X-ray

(8) Proportion of subjects with documented Hb values of ≥13.0 g/dL or ≥14.0 g/dL

(9) Proportion of subjects with documented Hb values of <9.0 g/dL or <8.0 g/dL.

(10) Proportion of subjects with a documented Hb increase rate >0.5 g/dL/week

(11) Hb level after dose reduction or interruption of the study drug

4. Definition of Derived Variables

4.1 Age at consent acquisition

Age (year) = Date of consent acquisition (year) − Date of birth (year)
However, when (Date of Consent [Months] < Date of Birth [Months]) or (Date of Consent [months] = Date of Birth [months] and Date of Consent [days] < Date of Birth [days]), 1 is subtracted from the traditional Japanese age system calculated above.

4.2 Duration of disease

The duration of disease (year) should be the period from the onset of renal anemia to the consent month and shall be the integer part + 1 digit (rounded). Duration of disease is calculated as follows:

Duration of disease (years) = (Date of consent acquisition [year] − Time of onset [year]) + (Date of consent acquisition [month] − Time of onset [month])/12

If the month of onset is unknown, the month is calculated as 1.

4.3 BMI

BMI (kg/m^2) = Body weight (kg)/(Height [m])^2

Should be rounded and displayed to one decimal place.

4.4 LDL-C/HDL-C ratio

LDL-C/HDL-C ratio = LDL-C (mg/dL)/HDL-C (mg/dL)

Should be rounded and displayed to two decimal place.

4.5 Number of days of drug interruptions

The number of days of drug interruptions does not include subject's forgetting to take the drug and is defined by the following formula. Number of days of drug interruptions (days) = Date of resumption of study drug administration − Start date of study drug interruption.

If there are multiple interruptions, the sum of them should be used.

Resumption date of study drug: After the entry of "Daily Dose" = 0 mg or 0 μg in the CRF, the first dose should be taken when a value of >0 mg is entered for the first time, or when a value of >0 μg is entered for the first time. If the drug interruption continues until Week 52 of the treatment period, days should be calculated based on the visit date after Week 52 of the treatment period as the resumption date. Specifically, if the treatment is completed or discontinued while the drug is interrupted, the day before the day of blood sampling at Week Treatment period 52 for hematology tests or the day before the day of treatment discontinuation should be used.

First day of study drug interruption: First day of administration when "Daily Dose" = 0 mg is first entered in the CRF or first day of administration when 0 μg is entered.

4.6 Study drug administration/duration

For subjects who completed treatment period:

Study drug administration/duration (days) = Day of blood sampling for hematology tests at Week 52 − First day of the treatment period.

For subjects who discontinued: Study drug administration/duration (days) = Day of discontinuation − First day of the treatment period.

4.7 Study drug administration/number of administration days

The number of days that the study drug is taken (administered) is defined by the following formula.
Number of MT-6548 administration days (days) = Period of study drug administration − Number of days of no study drug administration other than drug interruptions − Number of days of drug interruptions.
Number of darbepoetin alfa administration days (days) = Number of doses of darbepoetin alfa once every week × 7 days + Number of doses of darbepoetin alfa once every 2 weeks × 14 days + Number of doses of darbepoetin alfa once every 4 weeks × 28 days + Number of doses of darbepoetin alfa once every 3 weeks × 21 days + Number of doses of darbepoetin alfa twice every week × 3.5 days.

4.8 Study drug administration/compliance rate

Drug administration/compliance rate (%) = Number of days of study drug use (administration)/(Period of study drug use [administration] − Number of days of drug interruptions) × 100
However, if the compliance rate exceeds 100%, it should be 100%.

4.9 Mean daily dose/mean weekly dose

Mean daily dose of MT-6548 during each scheduled study visit period* = Daily dose based on the physician's prescription × Period of administration (days)*3 of the corresponding dose*2 between the scheduled study visits*/Period between the schedule study visits (days)*4.

Mean weekly dose of darbepoetin alfa during each scheduled study visit period* = (Daily dose based on the physician's prescription × Period of administration (days)*5 of the corresponding dose*2 between the scheduled study visits*/Period between the scheduled study visits (days)*4 × 7.

*: For each period between the scheduled study visits, the actual study visit dates will not be considered, and this variable should be fixed as follows:

- ✓ The first day of the treatment period to Week 2 of the treatment period: The first day of the treatment period (Day 1) to Day 14
- ✓ Week 2 of the treatment period to Week 4 of the treatment period: Day 15 to Day 28
- ✓ The same should apply thereafter, and the final period between the scheduled study visits should be Week 48 to Week 52 of the treatment period: Day 337 to the day before the day of blood sampling for hematological tests at Week 52 of the treatment period.

However, for subjects who discontinued their treatment, the final period between the scheduled study visits should be up to the day before discontinuation.

*[2]: If there are multiple applicable doses, the sum of the calculated values for each dose should be used.

*[3]: The number of days without drug administration other than drug interruption should not be excluded from the "period of administration (days)".

*[4]: 14 days up to Week 12 of the treatment period and 28 days after Week 12 of the treatment period. However, for subjects who discontinued their treatment, the final period between the scheduled study visits (days) should be the actual number of days until the day before discontinuation.

*[5]: "Period from the day of administration of darbepoetin alfa to the day of next administration of darbepoetin alfa". However, the first treatment period (days) during the scheduled study visit period should be "period from the start date during the scheduled study visit period to the day before the day of the first darbepoetin alfa administration date after the start date during the scheduled study visit period" and the last treatment period (days) should be "from the last day of darbepoetin alfa administration during the scheduled study visit period to the day before the day of the last treatment or the day before discontinuation during the scheduled study visit period".

The following formula should be used when no darbepoetin alfa is administered during the scheduled study visit period.

Mean weekly dose of darbepoetin alfa = Weekly dose of darbepoetin alfa immediately before the schedule study visit period.

4.10 Cumulative dosage

The cumulative dosage of the study drug is defined by the following formula.

Cumulative dosage of MT-6548 = 150 mg × Days of 150 mg administration + 300 mg × Days of 300 mg administration + 450 mg × Days of 450 mg administration + 600 mg × Days of 600 mg administration.

Number of administration days of X mg* = Day when dose was changed from X mg − First day of X mg administration (not excluding the number of days of no drug administration).

If there are multiple applicable periods, the sum of them should be used.

*: X indicates each dose of MT-6548.

The cumulative dosage of darbepoetin alfa is the sum of individual doses of darbepoetin alfa × the number of administrations of individual doses.

4.11 Iron supplement dosage

The dose of iron supplements is defined by the following formula. However, the dose of iron supplements will not be calculated if iron supplements are used as needed.

Mean monthly dose of iron supplements during the screening period* and each scheduled study visit period*2 (tabulation period of iron supplements) = (Daily dose based on the physician's prescription × Period of administration (days) of the corresponding dose*3 during the tabulation period of iron supplements)/Tabulation period of iron supplements (days)*4 × 30.4375*5

*: The number of days of the screening period is "First day of the treatment period − First day of the screening period".

*2: For each period between the scheduled study visits, the actual study visit dates are not considered, and this tabulation is fixed as follows:

- ✓ The first day of the treatment period to Week 2 of the treatment period: The first day of the treatment period (1 day) to 14 days.
- ✓ Week 2 of the treatment period to Week 4 of the treatment period: 15 to 28 days.
- ✓ The same should apply thereafter, and the final period between the scheduled study visits should be Week 48 to Week 52 of the treatment period: 337 days to the day before the day of blood sampling for hematological tests at Week 52 of the treatment period. However, for subjects who discontinued their treatment, the final period between the scheduled study visits should be up to the day before discontinuation.

*3: If there are multiple applicable doses, the sum of the calculated values for each dose should be used.

*4: For subjects who discontinued their treatment, the final period between the scheduled study visits (days) should be the actual number of days until the day before discontinuation.

*5: In this tabulation, 1 month is counted as 30.4375 days (365.25/12 = 30.4375).

4.12 QOL (EQ-5D-5L) index value

Responses to five questions (mobility [Mo], self care [Sc], usual activities [Ua], pain/discomfort [Pd], anxiety/depression [Ad] in 5 levels (level 1 is healthy and the level goes up to 5, and the health status decreases with increases in level) are converted into index values. The index value is calculated using the Japanese EQ-5D-5L conversion table (Table 4.12.1) [1].

(1) The responses to questions from Mo to Ad should be arranged side by side into five numbers (hereinafter, health state). The health state can exist from "11111" to "55555".

(2) If all five responses are 1, i.e. the health state is "11111", the index value is 1. If the health state is other than "11111", "Constant term: -0.060924" in Table 4.12.1 and the estimated value of the coefficient for each level of the response to each question should be used to obtain the index value using the following formula. The index value of the subject should be missing if one of the 5 questions has not been answered.

Index value = 1 + "Estimate of the constant term" + "Sum of 'estimated coefficients corresponding to levels of responses other than 1'"

Table 4.12.1 Japanese EQ-5D-5L conversion table

Item	Level	Estimate	Standard error	p value
Constant term		−0.060924	0.013625	<0.0001
Mo	2	−0.063865	0.008996	<0.0001
	3	−0.112618	0.009287	<0.0001
	4	−0.179043	0.010231	<0.0001
	5	−0.242916	0.009425	<0.0001
Sc	2	−0.043632	0.008931	<0.0001
	3	−0.076660	0.009972	<0.0001
	4	−0.124265	0.010129	<0.0001
	5	−0.159659	0.008924	<0.0001
Ua	2	−0.050407	0.009205	<0.0001
	3	−0.091131	0.010005	<0.0001
	4	−0.147929	0.009744	<0.0001
	5	−0.174786	0.009115	<0.0001
Pd	2	−0.044545	0.008354	<0.0001
	3	−0.068178	0.010052	<0.0001
	4	−0.131436	0.008985	<0.0001
	5	−0.191203	0.009604	<0.0001
Ad	2	−0.071779	0.009701	<0.0001
	3	−0.110496	0.010863	<0.0001
	4	−0.168171	0.009850	<0.0001
	5	−0.195961	0.009164	<0.0001

Mo: mobility, Sc: self care, Ua: usual activities, Pd: pain/discomfort, Ad: anxiety/depression

4.13 QOL (KDQOL) scoring

Step 1 (See Table 4.13.1[2]): The appropriate score is converted from the response choices for each item number in Table 4.13.1[2] (See Listing 16.2.4.9 for questions) for each subject.

Table 4.13.1 Step 1 in KDQOL scoring [2]

Item number	Response choices	Score
Question 4 A–D Question 5 A–C, Question 21	1	0
	2	100
Question 3 A–J	1	0
	2	50
	3	100
Question 19 A, B	1	0
	2	33.33
	3	66.66
	4	100
Question 10 Question 11 A, C Question 12 A–D	1	0
	2	25
	3	50
	4	75
	5	100
Question 9 B, C, F, G, I Question 18 B	1	0
	2	20
	3	40
	4	60
	5	80
	6	100
Question 20	1	100
	2	0
Question 1, Question 2, Question 6, Question 8 Question 11 B, D, Question 14 A–M, Question 15 A–H, Question 16 A, B Question 24 A, B	1	100
	2	75
	3	50
	4	25
	5	0
Question 7 Question 9 A, D, E, H Question 13 A–F Question 18 A, C	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
Question 23	1	100
	2	83.33
	3	66.66
	4	50
	5	33.33
	6	16.66
	7	0

Step 2 (See Table 4.13.2[2]): The mean of the scores calculated at Step 1 in the item numbers in the right column of Table 4.13.2[2] is calculated for each subject by subscale. For questions 17 and 22, the scores obtained are multiplied by 10 to convert the values from 0 to 100. The mean value should be the score for each subject by subscale. If at least one question constituting the subscale is answered,

the subscale should be tabulated without missing. If "No" is chosen in question 16, the question 16 should be treated as missing.

Table 4.13.2 Step 2 in KDQOL scoring [2]

- Each item score should be averaged to calculate each subscale score

Subscale	Number of items	After scoring according to Table 4-1, the mean of the items included in each subscale should be calculated.
Kidney disease-specific scale		
Symptoms	12	Questions 14 A–K, L (M)*
Effects of kidney disease on daily life	8	Question 15 A–H
Burden due to kidney disease	4	Question 12 A–D
Working status	2	Question 20, Question 21
Cognitive function	3	Question 13 B, D, F
Relationship with people	3	Question 13 A, C, F
Sexual function	2	Question 16 A, B
Sleep	4	Question 17, Question 18 A–C
Social support	2	Question 19 A, B
Encouragement from dialysis staff	2	Question 24 A, B
Patient satisfaction with dialysis care	1	Question 23
Comprehensive scale (SF-36)		
Physical functioning	10	Question 3 A–J
Daily role functioning (physical)	4	Question 4 A–D
Bodily pain	2	Question 7, Question 8
General health	5	Question 1, Question 11 A–D
Vitality	4	Question 9 A, E, G, I
Social functioning	2	Question 6, Question 10
Daily role functioning (emotional)	3	Question 5 A–C
Mental health	5	Question 9 B, C, D, F, H

4.14 Adverse drug reactions

Adverse events for which a causal relationship to the study drug was evaluated as "reasonable possibility" are defined as adverse drug reactions.

5. Analysis Sets

Efficacy analysis will be performed in the largest analysis set (hereinafter, FAS). Safety analysis will be performed in the safety analysis set.

The analysis sets are defined below; for details on the treatment of subjects in the final fixation data, the FAS is the analysis set consisting of subjects randomized by the sponsor until data fixation, excluding the following subjects.

5.1 Efficacy analysis set

(1) FAS

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

- ✓ Subjects who did not have anemia associated with NDD-CKD
- ✓ Subjects who have never received a dose of the study drug
- ✓ Subjects with no post-randomization efficacy data

5.2 Safety analysis set

The analysis set consisting of all randomly allocated subjects excluding the following subjects is the safety analysis set.

- ✓ Subjects who have never received a dose of the study drug
- ✓ Subjects with no post-randomization safety data

6. Patient Cohorts

The patient cohorts are defined below. Each patient cohort will be analyzed as needed.

- ✓ Correction cohort: A group of patients who have not received ESA formulations from 8 weeks prior to the first day of the screening period.
- ✓ Conversion cohort: A group of patients who have received ESA formulations from 8 weeks prior to the first day of the screening period.
- ✓ Conversion (Hb values ≥ 11.0) cohort: A subset of patients in the Conversion cohort whose mean Hb value during the last 2 screening sessions is ≥11.0 g/dL.

✓ Conversion (Hb values < 11.0) cohort: A subset of patients in the Conversion cohort whose mean Hb value during the last 2 screening sessions is <11.0 g/dL.

7. Data Handling

Final fixed data should be handled as follows:

7.1 Handling of missing data

If test measurements are missing or if problems with samples etc. result in invalid measurements or reference values, these should be handled as missing values. Derived variables should also be treated as missing if even one test value or other data required for derivation is missing or not adopted.

7.2 Handing of data for tabulation at each evaluation time point

Data that meet the permitted range specified in the "Table 9.1-1 Permitted range of study visits" section of the protocol should be used for the tabulation at each evaluation time point and should not be imputed with those outside the permitted range.

If there are multiple data within the permitted range, then the one closer to the reference date should be adopted. If the deviations from the reference date are the same, data for the efficacy and safety evaluations should be adopted before and after the reference date, respectively.

7.3 Handling of efficacy endpoints if rescue therapy is performed

If rescue therapy is performed, data from the day after rescue therapy should not be used to assess efficacy.

7.4 Imputation of missing values

The mixed repeated-measures model (MMRM) should not use data imputing missing data, except for the first day of the treatment period.

If there are missing values at the first day of the treatment period, data from the day closest to the first day of the treatment period should be used as data for the first day of the treatment period.

In the case of missing data in calculating descriptive statistics of mean Hb values at Weeks 48 and 52 of the treatment period, missing data should be imputed with data from the evaluation time point immediately before the missing evaluation time point (excluding the first day of the treatment period) (LOCF method). When any one evaluation time points has missing values, the data at the evaluation time point closest to the missing evaluation time point is adopted, and when two evaluation time points

have missing values, the data in the two different evaluation time points closest to and before the missing evaluation time points should be adopted to calculate the mean Hb value. However, Hb values at the same evaluation time point should not be used.
In addition, for clinical laboratory values, vital signs, and QOL indices among the efficacy endpoints, values at Week 52 of the treatment period imputed with data from the immediately preceding evaluation time point (excluding the first day of the treatment period) should also be output.

7.5 Handling of clinical laboratory test values, such as those less than the limit of quantification

If the measured values are reported to be not more than the limit of quantification, less than the limit of quantification, or impossible to calculate, the following handling procedures should be applied for tabulation, and missing values or zero values should not be used.
[Handling of quantification limit values]

(1) If the measurement is reported as less than the limit of quantification

The value obtained by adding the following processing to the limit of quantification value is used as an alternative value for tabulation.

1) After checking the number of significant figures of the applicable item, 1 should be subtracted from the significant figure of the lowest reported quantification limit value.

2) It should then be expanded by one digit to a smaller number and 9 is set.

Example) Report: less than 3 Effective number of the measuring facility: up to ones digit

→ Tabulation handling: 2.9

Report: less than 500 Effective number of the measuring facility: up to tens digit

→ Tabulation handling: 499

(2) When the measured value is reported as not more than the limit of quantification or not less than the upper limit of quantification, the limit of quantitation itself should be used as a substitute value for tabulation.

Example) Not more than the limit of quantification
Report: ≤10 → Tabulation handling: 10
Not less than the limit of quantification
Report: ≥20 → Tabulation handling: 20

(3) When the measured value used in the calculation is less than or not more than the quantification limit and the test result is reported as "Unable to be calculated" (Urinary albumin/creatinine ratio, urinary protein/creatinine ratio), the measured value used in the calculation is added with the above processing as an alternative value, calculation is performed using the following calculation formula, and the calculation result is used for tabulation.

[Arithmetic expression]

- Urine albumin/creatinine ratio = 100 × Urine albumin/urine creatinine
- Urine protein/creatinine ratio = 1000 × Urine protein assay (concentration)/urine creatinine

8. Statistical Method

In this trial, when the observation of all subjects is completed, the final data will be fixed and the statistical analysis should be conducted.

8.1 Basic matters

8.1.1 Level of significance and confidence coefficient

When implementing tests, level of significance should be set at 2-sided 5%. CI will be 2-sided with a confidence coefficient of 95%.

8.1.2 Descriptive statistics to calculate

Types of continuous variables to be calculated for each descriptive statistics item are provided below. Number of subjects, mean, standard deviation (SD), median, minimum, maximum, and 2-sided 95% CI of the mean

8.1.3 Number of digits displayed

The number of digits to be displayed in the analysis results will be as follows.

Numeric content	Number of display digits
p value	3 decimal places, however, when it is less than 0.001, it will be described as "< 0.001".
Proportion (percentage)	Integer part + 1 decimal place
Rate of change	Integer part + 1 decimal place
Descriptive statistics (minimum and maximum)	Same as the number of digits as original variable
Descriptive statistics (mean, SD, median)	Number of digits of the original variable + 1 digit
Rate of increase in Hb value	Integer part + 4 decimal places
QOL (EQ-5D-5L) index value	Integer part + 3 decimal places

Hepcidin will be measured in units of pg/mL; however, the unit used for tabulation should be ng/mL, and the number of displayed digits should be two decimal places.

8.2 Breakdown of subjects

8.2.1 Disposition

For subjects enrolled in the treatment period, the breakdown of each analysis set in each treatment group should be provided. The breakdown of patient cohort will also be provided.

Items: Number of subjects enrolled in treatment period, number of subjects completed treatment period phase 2, number of subjects discontinued the study, number of subjects who received rescue therapy, number and proportion of subjects in the FAS, number and proportion of subjects not included in the FAS, number and proportion of subjects in the safety analysis set, number and proportion of subjects not included in the safety analysis set

8.2.2 Subjects who discontinued or interrupted their treatment

For subjects enrolled in the treatment period, the number and proportion of discontinued subjects should be calculated in each treatment group and by reasons for discontinuation. Subjects who entered specific comments ("Criterion for liver function") according to the input rules should be counted for the number of subjects discontinued by reasons that meet the discontinuation criteria for abnormal hepatic function values.

Items: Number and proportion of discontinued subjects by treatment group and the number and proportion of reasons for discontinuation for subjects enrolled in treatment period,

In addition, for subjects enrolled in the treatment period, the number and proportion of discontinued subjects should be calculated in each treatment group and in every 12 weeks (unit: from first day of the treatment period [Day 1] to Day 84, Days 85–168, Days 169–252, and after Day 253.

Items: Number and proportion of subjects discontinued in each treatment group in subjects enrolled in the treatment period

For subjects enrolled in treatment period, the number cases of drug interruption should be tabulated by treatment group and the number and proportion of of cases by reasons for interruption should be tabulated. The denominator of the proportion should be the sum of the number of interruption cases. If there are multiple reasons for a single interruption, they should be counted for each reason and stated as the number of interruption cases. For drug interruption due to abnormal hepatic function, subjects who entered specific comments according to the input rules ("Criterion for liver function") should be calculated.

Items: Number of drug interruptions in subjects enrolled in the treatment period and number and ratio of drug interruptions by reasons for drug interruption

8.3 Demographic and other baseline characteristics

For each analysis set, the key demographic and other baseline characteristics for each treatment group should be summarized. Frequency and proportion will be provided for discrete variables and descriptive statistics for continuous variables (no calculation of 95% CI of the mean) . The data should also be summarized in the FAS by patient cohort.

Table 8.3.1 Demographic and other baseline characteristics

Category	Item	Type of variables
Subject background	Sex (male, female)	Dichotomous
	Age (years) as of informed consent	Continuous
	2 categories: <65, ≥65	Dichotomous
	2 categories: <75, ≥75	Dichotomous
	Duration of nephrogenic anemia (years)	Continuous
	3 categories: <1, 1 to <5, ≥5	Ordinal
	Height (cm)	Continuous
	Body weight (kg)	Continuous
	BMI (kg/m^2)	Continuous
	2 categories: <25, ≥25	Dichotomous
	Race 3 categories: not Hispanic or Latino, Hispanic or Latino, Unknown	Multiple value
	Ethnicity 3 categories: Asian (Japanese), Asian (other), other	Polytomous
Smoking status	Presence or absence of smoking status 3 categories: never smoked, ex-smoker, current smoker	Polytomous
Underlying cause of CKD	Underlying cause 8 categories: diabetes mellitus, hypertension, autoimmune/glomerulonephritis/vasculitis, interstitial nephritis/pyelonephritis, cystic/hereditary/congenital disease, neoplasm/tumor, unknown, other	Polytomous
Complication	Presence or absence of complications on the first day of the treatment period	Dichotomous
	Presence or absence of hypertension	Dichotomous
	Presence or absence of diabetes mellitus	Dichotomous
	Presence or absence of dyslipidemia	Dichotomous

Previous ESA formulation (Conversion cohort only)	Types of previous ESA formulation 4 categories: epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol, other.	Polytomous
	Frequency of administration by type of previous ESA formulation 7 categories: once a week, twice a week, three times per week, every 2 weeks, every 3 weeks, every 4 weeks, other	Polytomous
	Weekly dose (IU) of epoetin alfa or epoetin beta	Continuous
	Weekly dose of darbepoetin alfa (μg)	Continuous
	Weekly dose of epoetin beta pegol (μg)	Continuous
Evaluation data	Hb value (g/dL) on the first day of the treatment period	Continuous
	3 categories: <9, 9 to <11, ≥11	Ordinal
	eGFR on the first day of the treatment period (mL/min/1.73 m^2)	Continuous
	4 categories: <15, 15 to <30, 30 to <60, ≥60	Ordinal
	Liver function test (U/L) on the first day of the treatment period	
	3 categories: AST and ALT are both not more than the upper limit of normal, either is more than the upper limit of normal and both are not more than 2 times the upper limit of normal, either is more than 2 times the upper limit of normal	Trichotomous
	CRP (mg/dL) on the first day of the treatment period	Continuous
	Serum ferritin (ng/mL) on the first day of the treatment period	Continuous
	2 categories: <100, ≥100	Dichotomous
	TSAT (%) on the first day of the treatment period	Continuous
	2 categories: <20, ≥20	Dichotomous

	With or without iron supplements on the first day of the treatment period	Dichotomous
	2 categories: oral, intravenous	Dichotomous
	With or without iron-containing phosphate binders on the first day of the treatment period	Dichotomous

8.4 Study drug administration/treatment period and study drug administration/compliance status

For FAS and safety analysis set, the descriptive statistics of the study drug administration/compliance rate (no calculation of 95% CI of the mean) will be calculated by treatment group to provide the number and rate of subjects with study drug compliance rate of ≥80% and < 80%. Analysis should be performed by patient cohort in the FAS.

For FAS and safety analysis set, the descriptive statistics of the study drug administration/treatment period (no calculation of 95% CI of the mean) will be calculated by treatment group. Analysis should be performed by patient cohort in the FAS.

For FAS and safety analysis set, the descriptive statistics of the cumulative dosage of study drug (no calculation of 95% CI of the mean) will be calculated by treatment group.

8.5 Efficacy analysis

As a general rule, efficacy analysis will be performed on the FAS. When necessary, descriptive statistics for continuous variables should be calculated and frequency and proportion will be calculated for discrete variables. Unless otherwise specified, a similar analysis will be conducted for patient cohort. No data from the day after the rescue therapy implementation date should be included in the efficacy analysis.

8.5.1 Analysis of secondary endpoints

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

Descriptive statistics for change from Hb on the first day of the treatment period to mean Hb at Week 48 and Week 52 in the treatment period should be calculated by treatment group. The MMRM is used to model the mean Hb values at each evaluation time point based on the following model, and the mean Hb values at Week 48 and Week 52 of the treatment period for each treatment group should be obtained, and the least squares mean (LSMean), its standard error, and 2-sided 95% CIs for the mean Hb values should be calculated, and the point estimate of the between-group difference (MT-6548 -

darbepoetin) of LSMean, its standard error, and 2–sided 95% CI should be calculated. No analysis will be performed for patient cohorts.

[MMRM Model]

- Covariate: response variable value of the first day of the treatment period
- Fixed effects: Treatment group, evaluation time point, patient cohort (Correction or Conversion cohort), interactions of evaluation time point × treatment group, interactions of patient cohort (Correction or Conversion cohort) in evaluation time point
- Degrees of freedom adjustment: Kenward–Roger method
- Covariance matrix within subject for each subject: unstructured (type = UN; unstructured)
  When it was not converged using unstructured as a covariance matrix within subject variance, the setting of the covariance matrix within subject variance will be changed in the following order, and the analysis will be carried out using the covariance matrix within subject variance converged first.
  Heterogeneous Toeplitz (TOEPH) → Heterogeneous AR (1) (ARH [1]) → Heterogeneous CS (CSH) → Toeplitz (TOEP) → First-order autoregressive (AR [1]) → Compound symmetry (CS)
- Random effects: subjects

(2) Hb values at each evaluation time point in the treatment period

1) Hb values at each evaluation time point in the treatment period

Hb value and change of Hb values from the first day of the treatment period at each evaluation time point of the treatment period will be obtained, and its descriptive statistics should be calculated for each treatment group. Before and after comparison will be conducted for changes of Hb from the first day of the treatment period to each evaluation time using the paired t-test. In the Conversion and Conversion (Hb ≥ 11.0 g/dL) cohorts, no test will be conducted for the difference between the baseline value and each evaluation time point during the treatment period in the darbepoetin alfa group.

A group comparison should be conducted using an MMRM (with compound symmetry [CS] for a covariance matrix within subject variance) similar to the analysis of "(1) Mean Hb values at Week 48 and Week 52 of treatment". LSMean, its standard errors, and 2-sided 95% CI will be calculated for Hb value at each evaluation time point of the treatment period, and the point estimate, its standard errors, 2-sided 95% CI, and p-value will be calculated for the group difference (MT-6548 − darbepoetin) of the LSMean by treatment group.

A group comparison should be conducted for the change from the first day of the treatment period using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI should be calculated for change at each evaluation

time point from the first day of the treatment period, and point estimate, its standard errors, 2-sided 95% CI, and p-value should be calculated for the group difference (MT-6548 − darbepoetin).

The time course diagram will be prepared for mean Hb values in each evaluation time point in the treatment period by treatment group. 95% CI of the mean will be represented by an error bar.
In the Conversion and Conversion (Hb ≥ 11.0 g/dL) cohorts, no test will be conducted for the group difference.

2) Analysis of timing of administration of MT-6548 tablets (before meal, after meal, other)

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted by the timing of administration of MT-6548 tablets (before meal, after meal, other). However, this analysis is only for the MT-6548 group; neither tabulation in the darbepoetin group nor comparison with the darbepoetin group is performed. No analysis will be performed for patient cohorts.

3) Analysis by previous ESA formulation type

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted by the type of previous ESA formulation (epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol). Only Conversion, Conversion (Hb ≥11.0 g/dL), and Conversion (Hb <11.0 g/dL) cohorts should be analyzed, and the data should be summarized in the , MT-6548 group only.

4) Analysis by dose of previous ESA formulation types

An analysis similar to " 1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted for weekly dose of previous ESA formulation (darbepoetin alfa, epoetin beta pegol: ≥15 μg, <15 μg; 2 categories) by type of previous ESA formulation (darbepoetin alfa, epoetin beta pegol). The number of patients classified by dose was set to be almost equal.
Only Conversion, Conversion (Hb ≥11.0 g/dL), and Conversion (Hb <11.0 g/dL) cohorts should be analyzed, and the data should be summarized in the MT-6548 group only.

5) Analysis of Hb value on the first day of the treatment period

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted for the Hb value on the first day of the treatment period (divided the number of subject into 3 categories at tertiles). The Conversion (Hb <11.0 g/dL) cohort should be summarized in the MT-6548 group only. Time course diagram for mean and 95% CI should be prepared separately by treatment group. No statistical test will be conducted for the group difference and the difference between baseline and each evaluation time point in the treatment period for the darbepoetin alfa group in the Conversion cohort and Conversion (Hb ≥11.0 g/dL) cohort.

6) Analysis with or without iron supplements and iron-containing phosphate binders

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period (LSMean, standard error, and two-sided 95% CIs will not be calculated for changes from the start of

the treatment period.)" should be conducted for subjects continuously using iron supplements or iron-containing phosphate binders and subjects never using iron supplements and iron-containing phosphate binders during the treatment period. Analysis should be performed only in the MT-6548 group, and no analysis using the MMRM model will be conducted for patient cohorts. However, subjects who uses intravenous iron at least once should be excluded from the tabulation.

Since intravenous iron should be included in the tabulation for treatment period phase 1, the tabulation for treatment period phase 1 should be output again.

7) Analysis by iron supplements and iron-containing phosphate binders formulations

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" except for the analysis using the MMRM should be conducted for subjects continuously using iron supplements or iron-containing phosphate binders during the treatment period. Analysis should be performed only in the MT-6548 group, and no analysis will be performed for patient cohorts However, subjects who uses intravenous iron at least once should be excluded from the tabulation.

8) Analysis of Hb value at Week 52 and CRP values on the first day of the treatment period

For MT-6548 group only, a scatter plot chart should be provided after linear regression with the following variables. No analysis will be performed for patient cohorts.

x: Logarithmic CRP value on the first day of the treatment period

y: Hb values at Week 52 of the treatment period

(3) Proportion of subjects whose Hb level during the treatment period is within the target range (11.0 g/dL to <13.0 g/dL) or outside the target range (<10.0 g/dL or ≥13.0 g/dL)

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of subjects with Hb value within the target range (11.0 g/dL to <13.0 g/dL, within), <11.0 g/dL (below), and ≥13.0 g/dL (above) at each time point of the treatment period should be provided by treatment group. McNemar tests should be used for before and after comparison (ratio of subjects within the target range and out of target range) on the first day and each evaluation time point of the treatment period.

Point estimate, its 95% CI (exact method), and p-value (Fisher's exact test) of subject proportions should be calculated for the between-group difference (MT-6548 − darbepoetin) of Hb values in each category (within the target range [11.0 g/dL to <13.0 g/dL]), <11.0 g/dL or ≥13.0 g/dL) at each evaluation time point of the treatment period.

The proportion of subjects in each Hb category (within the target range [11.0 g/dL to <13.0 g/dL], <11.0 g/dL or ≥13.0 g/dL) at each evaluation time point of the treatment period should be provided as a stacked bar graph assuming that the number subjects of each treatment group at the evaluation time point is 100% . Stacked bar charts should be generated separately for each treatment group. No statistical test will be conducted for the group difference and the difference between baseline and each

evaluation time point in the treatment period for the darbepoetin alfa group in the Conversion cohort and Conversion (Hb ≥11.0 g/dL) cohort.

(4) Number of days from the first day of the treatment period required to reach the target Hb range (≥11.0 g/dL to <13.0 g/dL)

Descriptive statistics should be calculated for number of days required from the first day to reach target Hb range (11.0 g/dL to <13.0 g/dL) of the treatment period. The number of days should be calculated as the first evaluation day when the target Hb range (11.0 g/dL to <13.0 g/dL) is reached minus first day of the treatment period plus 1. If target Hb range (11.0 g/dL to <13.0 g/dL) is not reached, it should be calculated as the final day of evaluations minus first day of the treatment period plus 1.

Kaplan–Meier plots for the number of days required from the first day to reach target Hb range (11.0 g/dL to <13.0 g/dL) of the treatment period should be provided for each treatment group.

No subjects with an Hb value of ≥11.0 g/dL on the first day of the treatment period will be included in the tabulation.

Only the Correction and Conversion (Hb <11.0 g/dL) cohorts should be analyzed. The Conversion (Hb <11.0 g/dL) cohort should be summarized in the MT-6548 group only.

8.5.2 Analysis of other endpoints

(1) Changes in mean Hb values from the first day of the treatment period at Weeks 48 and 52 of the treatment period

Descriptive statistics for change from Hb on the first day of the treatment period to mean Hb at Week 48 and Week 52 in the treatment period should be calculated by treatment group. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.

A group comparison should be conducted for the change from the first day of the treatment period using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI for change from Hb on the first day of the treatment period to mean Hb at Week 48 and Week 52 in the treatment period should be calculated by treatment group. The point estimate, its standard errors, 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin) of LSMean should be calculated.

Only the Correction and Conversion (Hb <11.0 g/dL) cohorts should be analyzed. The Conversion (Hb <11.0 g/dL) cohort should be summarized in the MT-6548 group only.

(2) Proportion of subjects with a ≥1.0 g/dL increase in mean Hb values from the first day of the treatment period at each time point of the treatment period.

The number and proportion of subjects and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with an Hb value increase of ≥1.0 g/dL from the first day to each evaluation time point of the treatment period should be provided.
The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects whose Hb level increased by ≥ 1.0 g/dL at each evaluation time point from the first day of the treatment period.
Only the Correction and Conversion (Hb <11.0 g/dL) cohorts should be analyzed. The Conversion (Hb <11.0 g/dL) cohort should be summarized in the MT-6548 group only.

(3) Number of days to maintain the target Hb values

The number of maintenance days should be calculated from reaching to leaving the target Hb range for each subject, and the descriptive statistics should be calculated. Only the MT-6548 group is analyzed. However, if treatment period is completed in 52 weeks, the maintenance days should be until Week 52 of the treatment period. No analysis will be performed for patient cohorts.

(4) Proportion of subjects receiving rescue therapy with ESA formulations, red blood cell transfusion, or phlebotomy

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects receiving rescue therapy with an ESA preparation should be provided by treatment group, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period.
The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects receiving rescue therapy.
The analyses same to the above subjects receiving rescue therapy with ESA formulation should be performed for subjects receiving rescue therapy with RBC transfusion or receiving phlebotomy.

(5) Study drug dosage

1) Study drug dosage

Descriptive statistics of the average daily dose of MT-6548 and mean weekly dose of darbepoetin alfa injection (recombinant) should be calculated, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period. The time course diagram for mean daily dose of MT-6548 and mean weekly dose of darbepoetin alfa injection (recombinant) should be separately prepared by treatment group. 95% CI of the mean will be represented by an error bar. Each period between scheduled study visits is defined as the period between the scheduled visit and the day before the next scheduled visit.

2) Distribution of MT-6548 tablets and darbepoetin alfa injection

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) of proportion per daily dose of MT-6548 tablets and per weekly dose of darbepoetin alfa (recombinant) during the treatment period should be provided by treatment group.

The proportion of subjects receiving each dose of MT-6548 tablets and darbepoetin alfa injection (recombinant) at each evaluation time point of the treatment period should be provided as a stacked bar graph with the number of subjects in each treatment group as 100%. Stacked bar charts should be generated separately for each treatment group.

If no prescription is available on the day of each evaluation timepoint of the treatment period, the dose should be based on the immediately before prescription.

3) Analysis of timing of administration of MT-6548 tablets (before meal, after meal, other)

An analysis similar to "1) Study drug dosage" should be conducted according to the timing of administration of MT-6548 tablets (before meal, after meal, other). Only the MT-6548 group is analyzed. No analysis will be performed for patient cohorts.

4) Analysis by previous ESA formulation type

An analysis similar to "1) Study drug dosage" should be conducted by the type of previous ESA formulation (epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol).

Conversion, Conversion (Hb ≥11.0 g/dL), and Conversion (Hb <11.0 g/dL) cohorts will be analyzed in the MT-6548 group only.

5) Analysis by dose of previous ESA formulation types

An analysis similar to "1) Study drug dosage" should be conducted for weekly dose (darbepoetin alfa, epoetin beta pegol: ≥15 μg, <15 μg) of previous ESA formulation by type (darbepoetin alfa, epoetin beta pegol). The number of patients classified by dose was set to be almost equal.

Conversion, Conversion (Hb ≥11.0 g/dL), and Conversion (Hb <11.0 g/dL) cohorts will be analyzed in the MT-6548 group only.

6) Analysis of Hb values on the first day of the treatment period

An analysis similar to "1) Study drug dosage" should be conducted for the Hb value on the first day of the treatment period (divided the number of subject into 3 categories at tertiles).

7) Analysis with or without iron supplements and iron-containing phosphate binders

An analysis similar to "1) Study drug dosage" should be conducted for subjects continuously using iron supplements or iron-containing phosphate binders and subjects never using iron supplements and iron-containing phosphate binders during the treatment period. Only the MT-6548 group is analyzed. However, subjects who uses intravenous iron at least once should be excluded from the tabulation. Since intravenous iron should be included in the tabulation for treatment period phase 1, the tabulation for treatment period phase 1 should be output again.

8) Analysis by iron supplements and iron-containing phosphate binders formulations

An analysis similar to "1) Study drug dosage" should be conducted for subjects using iron supplements or iron-containing phosphate binders continuously during the treatment period. Analysis should be performed only in the MT-6548 group, and no analysis will be performed for patient cohorts However, subjects who uses intravenous iron at least once should be excluded from the tabulation.

9) Analysis of the mean dose of the study drug at Week 48 to Week 52 of the treatment period and CRP values on the first day of the treatment period

For MT-6548 group only, a scatter plot chart should be provided after linear regression with the following variables. No analysis will be performed for patient cohorts.

x: Logarithmic CRP value on the first day of the treatment period

y: Study drug average dosage at Week 48 to Week 52 of the treatment period

(6) Total number of dosage adjustments

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects receiving dose adjustment should be provided, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period.

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects should be provided for the proportion of subjects defined below in each period between scheduled study visits. If a subject is included in more than one definition, the subject should be counted in each definition.

No dose adjustment: No change

With dose adjustment: dose adjustment (Dose adjustment), dose increase (Increase), dose decrease (Decrease). drug interruption (Interrupt)

Dose adjustment (Dose adjustment) should include the number of times of increase, decrease, and interruption, and should not count the increase when it is resumed after interruption. Only the MT-6548 group will be tabulated.

(7) Iron supplement dosage

The following should be provided according to the 3 categories of oral iron supplement, intravenous iron supplement, and iron supplement (any route).

Descriptive statistics of the mean dose of iron supplement per month for each treatment group should be calculated for the screening period, and after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period.

Descriptive statistics of the change in the mean dose of iron supplement per month from the baseline (mean dose of iron during the screening period) should be calculated, after the first day of the treatment

period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period. Before and after comparison should be conducted for changes from baseline using the paired t-test. The changes should be compared between groups using the Student-t test. The mean value of the between-group difference (MT-6548 – darbepoetin), its two-sided 95% CI, t-statistic, and p-value should be provided.

The dosage of iron supplement should be calculated using the dose as iron.

If no iron supplement is administered, the dose should be tabulated as 0 mg. Subjects who changed the administration route of an iron supplement during the treatment period and subjects who had never received an iron supplement during the treatment period should be excluded from the tabulation.

(8) Proportion of subjects receiving oral, intravenous, or (any route) administration of iron supplements

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects treated with oral, intravenous, or oral iron supplement (any route) should be provided by treatment group for screening period, and after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period. McNemar tests should be used to compare baseline values (proportion of subjects receiving iron supplements by the aforementioned route in the screening period) with those before and after each period between scheduled study visits. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 – darbepoetin) should be calculated for the proportion of subjects receiving oral, intravenous, or (any route) iron supplement.

Subjects who have not received an iron supplement are to be subjects who have never received an iron supplement during the relevant period, and subjects who have received an oral, intravenous, or (any route) iron supplement are to be subjects who have received an iron supplement at least once during the relevant period.

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

The number and proportion of subjects and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with serum ferritin values of ≥100 ng/mL or TSAT of ≥20% should be provided at each evaluation time point of the treatment period for each treatment group. Before and after comparison should be conducted for changes between the first day of the treatment period and each period between scheduled study visits using the McNemar test. Changes in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin should be calculated from the first day of the treatment period to each evaluation time point of the treatment period.

(10) Changes and rate of changes in iron-related indices (serum iron, TIBC, TSAT, and serum ferritin values) and hepcidin from the first day of the treatment period

Changes in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin should be calculated from the first day of the treatment period to each evaluation time point of the treatment period. A paired t-test should be performed for before and after comparison of changes and change rates from the first day of the treatment period.

A group comparison should be conducted for the change in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin from the first day of the treatment period to each evaluation time point using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI should be calculated, and the point estimate, its standard errors, 2-sided 95% CI, and p-value should be provided for the group difference (MT- 6548 − darbepoetin) of the LSMean by treatment group. Only the serum ferritin value at each evaluation time point of the treatment period should be similarly compared between groups.

The time course diagram of changes in the iron-related measures (serum iron, TIBC, TSAT, and serum ferritin values) and hepcidin from the first day of the treatment period to each evaluation time point should be prepared for each treatment group. The 95% CI of LSMean will be represented by an error bar. For only the serum ferritin value, a time course diagram should be prepared for mean ferritin values and 95% CI at each evaluation time point of the treatment period.

The serum ferritin values should be shown as follows.

An analysis similar to the above should be conducted for serum ferritin at baseline (divided the number of subject into 3 categories at tertiles). Time course diagram for mean and 95% CI should be prepared separately by treatment group.

The following scatter plot chart should be provided by treatment group. Linear regression should be performed to calculate the p-value and correlation coefficient of the test with zero slope as the null hypothesis.

x: Serum ferritin at baseline

y: Serum ferritin at Week 52 of the treatment period

(11) Change in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean cell hemoglobin, and EPO (MT-6548 group only) from the first day of the treatment period

Descriptive statistics of hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean cell hemoglobin, and EPO (MT-6548 group only) at each evaluation time point should be calculated for each dose group. And, the change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each dose group. A

paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.

A group comparison should be conducted for the change in hematocrit, red blood cell count, reticulocyte (number and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO (MT-6548 group only) from the first day of the treatment period to each evaluation time point using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI should be calculated, and the point estimate, its standard errors, 2-sided 95% CI, and p-value should be provided for the group difference (MT-6548 − darbepoetin) of the LSMean by treatment group. EPO will be analyzed in the MT-6548 group only. Hematocrit, RBC count, and reticulocytes (number and rate) in the Conversion (Hb < 11.0 g/dL) cohort should be analyzed only in the MT-6548 group. No statistical test should be conducted for hematocrit, RBC count, and reticulocytes (number and rate) in the Conversion cohort and Conversion (Hb ≥ 11.0 g/dL) cohort for group differences and the difference between baseline and each evaluation time point in the treatment period for the darbepoetin alfa group.

A histogram of EPO measurements should be prepared for evaluation time point at Week 52 of the treatment period.

(12) Changes in systolic blood pressure, diastolic blood pressure, and blood glucose from the start of the treatment period, changes and the rate of change in lipid (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides) from the start of the treatment period

Systolic blood pressure, diastolic blood pressure, lipids (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides), and blood glucose should be analyzed in the same manner as hematocrit, red blood cell count, and reticulocyte (number and rate) in the preceding section.

Descriptive statistics for each measurement at the evaluation time point of Week 52 of the treatment period should be calculated by baseline value (divided the number of subject into 3 categories at tertiles). And, the change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each dose group. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period. A group comparison should be conducted for the change from the first day of the treatment period using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI should be calculated, and the point estimate, its standard errors, 2-sided 95% CI, and p-value should be provided for the group difference (MT-6548 − darbepoetin) of the LSMean by treatment group.

The descriptive statistics should be similarly calculated for each administration group on the rate of change from the first day of the treatment period at each evaluation time point of the lipid (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides), and a group comparison should be

conducted using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance.

No analysis will be performed for patient cohorts.

(13) Renal function-related measures (eGFR, serum creatinine, urinary albumin/creatinine ratio) should be analyzed in the same way as hematocrit, red blood cell count, and reticulocyte (count and rate) in the previous section.

Renal function-related measures (eGFR, serum creatinine, urinary albumin/creatinine ratio) should be analyzed in the same way as hematocrit, red blood cell count, and reticulocyte (count and rate) in the previous section.

Descriptive statistics for changes in eGFR and urinary albumin/creatinine ratio from the first day of the treatment period to each evaluation time point should be similarly calculated for each administration group, and a group comparison should be conducted using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance.

The following items should also be calculated.

- The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of subjects with a ≥30% decrease in eGFR from the start of the treatment period during the evaluation time point of Week 52 of the treatment period should be provided for each treatment group.

  The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for rate of subjects with a ≥30% decrease in eGFR from the start of the treatment period at the evaluation time point of Week 52 of the treatment period.
- The same analysis as above should be performed for the number of subjects with an eGFR decrease of ≥40% from the start of the treatment period at the evaluation time point of Week 52 of the treatment period.
- The same analysis as above should be conducted for the number of subjects with serum creatinine ≥2-fold from the start of the treatment period at evaluation time point of Week 52 of the treatment period.
- The shift table for the urinary albumin/creatinine ratio (mg/g Cr), which consists of the first day of treatment and Week 52 of the treatment period, should be provided for each treatment group. Classification follows CKD severity classification. (normal, <30; microalbuminuria, ≥30 and <300; macroalbuminuria, ≥300). No analysis will be performed for patient cohorts.

(14) QOL indices (EQ-5D-5L, KDQOL)

The score of the QOL index should be calculated and provided by treatment group.

EQ-5D-5L

The number, proportion, and their two-sided 95% CI (Clopper-Pearson [Exact] method) of subjects in responses in 5 levels to the 5 questions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) should be provided at each evaluation time point.

For Index value and VAS score, descriptive statistics of measured values and descriptive statistics of changes from the first day of the treatment period should be provided for each treatment group at each evaluation time point. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.

A group comparison should be conducted for the changes in Index value and VAS score from the first day of the treatment period at each evaluation time point using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI should be calculated, and the point estimate, its standard errors, 2-sided 95% CI, and p-value should be provided for the group difference (MT-6548 − darbepoetin) of the LSMean by treatment group.

The correlations of Hb value and Index Value, and Hb value and VAS score at all evaluation time points should be evaluated using linear regression and Emax model. For linear regression, the estimated items analyzed by the following model (refer to "linear regression model") should be output, and the p-value of the test with 0 slope as the null hypothesis should be calculated. Scatter plots and regression lines should be prepared separately for each treatment group. On the Emax model, estimated items (refer to "Emax model") analyzed by the following model should be output. Scatter plots and regression curves should be prepared separately for each treatment group. No analysis will be performed for patient cohorts.

The correlation between the change in Hb from the first day of the treatment period and the change in Index Value from the first day of the treatment period and the correlation between the change in Hb from the first day of the treatment period and the change in VAS score from the first day of the treatment period should be analyzed in linear regression in the same way as the correlation between Hb value and Index Value and between Hb value and VAS score, respectively. Only the Correction and Conversion (Hb <11.0 g/dL) cohorts should be analyzed

[Linear regression model]

regression equation $Y = aX + b$

X: Hb value, or change in Hb value from the first day of the treatment period

Y: Index Value, or VAS score, or change from the first day of the treatment period on the left

Estimated items (output item): a: slope of the regression line and its standard error, b: intercept of the regression line and its standard error, r: correlation coefficient

[Emax model]

Model 4-parameter logistic model

X: Hb value

Y: Index Value or VAS score

Estimates (output item): EC_{50} with its standard errors and 2-sided 95% CI, Emax with its standard errors and 2-sided 95% CI, min with its standard errors and 2-sided 95% CI, slope with its standard errors and 2-sided 95% CI, R-Square (contribution ratio).

KDQOL

Descriptive statistics of KDQOL should be calculated by subscale (Section 4.13 [Table 4.13.2] "subscale") for measured values and changes from the first day of the treatment period at each evaluation time point by treatment group. Scores by subscale should be calculated using a scoring method (Section 4.13). Scores by subscale should be calculated using a scoring method (Section 4.13). A paired t-test should be performed for before and after comparison of changes in KDQOL from the first day of the treatment period.

A group comparison should be conducted for the change in KNDQOL from the first day of the treatment period at each evaluation time point using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). The point estimate of LSMean, its standard errors, and 2-sided 95% CI should be calculated by treatment group, and the point estimate, its standard errors, 2-sided 95% CI, and p-value should be provided for the group difference (MT-6548 − darbepoetin) of the LSMean.

8.5.4 Statistical analysis issues

8.5.4.1 Adjustment for covariates

In the analysis of efficacy, in order to consider the effect of the measurement value of the first day of the treatment period on the change of each measurement in the group comparison, the analysis using the MMRM should be conducted using the measurement value of the first day of the treatment period as a covariate in the general analysis.

8.5.4.2 Handling of dropout or missing data

Provided in "7. Data handling".

8.5.4.3 Interim analysis and data monitoring

The statistical analysis plan for the fixed data for the treatment period phase 1 was prepared separately, and the statistical analysis was conducted. In this statistical analysis plan, statistical analysis plan for the final fixed data was prepared.

8.5.4.4 Multicenter trial

For FAS, the following analysis should be conducted for each following endpoint for each facilities. Descriptive statistics of Hb values should be calculated at Week 52 of the treatment period (imputed by the LOCF method) for each treatment group. Descriptive statistics of mean dose of the study drug should be calculated for the Week 48 to Week 52 of the treatment period in the treatment group.
No analysis will be performed for patient cohorts.

8.5.4.5 Subgroup analyses

The following analyses should be conducted for subpopulations based on the stratification factor for each endpoint in the Table below (Table 8.5.4.5.1) in the FAS. Unless otherwise specified, no analysis will be performed for patient cohorts.

(1) Hb value at Week 52 of the treatment period

LSMean, standard error, and 2-sided 95% CI should be calculated for each treatment group using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). The point estimate, its standard errors, 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin) of LSMean should be calculated.

(2) 2. Study drug average dosage at Week 48 to Week 52 of the treatment period

Descriptive statistics should be calculated for each treatment group.

(3) With respect to the responder rate at Week 52 of the treatment period (proportion of subjects with increased Hb level by ≥1.0 g/dL from the first day of the treatment period), number of responders in subject, the percentage of responders, and 95% of responders in CI (Clopper-Pearson [Exact] method) are provided in by treatment group.

The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for group difference (MT-6548 − darbepoetin) should be calculated. Only the Correction and Conversion (Hb <11.0 g/dL) cohorts should be analyzed.

(4) Target Hb achievement rate at Week 52 of the treatment period

The number, proportion, and 95% CI (Clopper-Pearson [Exact)] method) for the proportion of subjects with Hb values within the target range (11.0 g/dL to <13.0 g/dL) should be provided for each treatment group. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for group difference (MT-6548 − darbepoetin) should be calculated.

Table 8.5.4.5.1 Subgroup analysis of efficacy

Endpoints	**Stratification factor**	**Stratified category**
1. Hb values at Week 24 of the treatment period 2. Study drug average dosage at Week 20 to Week 24 of the treatment period 3. Responder rates at Week 24 of the treatment period 4. Target Hb achievement rate at Week 24 of the treatment period	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65
		<75, ≥75
	Body weight (kg) on the first day of the treatment period	<60, ≥60
	Body mass index (kg/m^2) on the first day of the treatment period	<25, ≥25
	Underlying cause of CKD	Diabetes, hypertension, autoimmune/glomerulonephritis/vasculitis, interstitial nephritis/pyelonephritis, cystic/hereditary/congenital disease, neoplasm/tumor
	Duration of nephrogenic anaemia (years)	<1, 1 to <5, ≥5
	Complication	hypertension, diabetes, dyslipidemia
	Hb value (g/dL) on the first day of the treatment period	<9, 9 to <11, ≥11
	eGFR on the first day of the treatment period ($mL/min/1.73\ m^2$)	<15, 15 to <30, 30 to <60, ≥60
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both below the upper limit of normal, either above the upper limit of normal and both ≤2 times the

		upper limit of normal, either >2 times the upper limit of normal
	CRP (mg/dL) on the first day of the treatment period	<0.31, ≥0.31
	Serum ferritin (ng/dL) on the first day of the treatment period	Divide the number of subjects into three categories based on the tertile
	TSAT (%) on the first day of the treatment period	Divide the number of subjects into three categories based on the tertile
	Smoking status	3 categories: never smoked, ex-smoker, current smoker
	Administration of oral iron on the first day of the treatment period	Yes or No
	Treatment with oral iron supplement at Week 24 of the treatment period	Yes or No
	Iron-containing phosphate binders on the first day of the treatment period	Yes or No
	Iron-containing phosphate binders at Week 24 of the treatment period	Yes or No
	Previous ESA formulation (Conversion cohort only)	Epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol, other
	Epoetin alfa or epoetin beta weekly dose (IU) (Conversion cohort only)	Divide the number of subjects into three categories based on the tertile
	Darbepoetin alfa weekly dose (μg) (Conversion cohort only)	Divide the number of subjects into three categories based on the tertile
	Epoetin beta pegol dose (μg) (Conversion cohort only)	Divide the number of subjects into three categories based on the tertile
	CYP2B6 inducer combination *	Yes or No

* List of CYP2B6 substrates obtained from The Metabolism and Transport Drug Interaction Database (DIDB®)

8.5.4.6 Multiple comparison and multiplicity

Since the mean Hb values at Week 20 and Week 24 of the treatment period, the primary endpoints of this study, should be evaluated in the analysis of the fixed data of the treatment period phase 1, there is no need to consider multiplicity in the analysis of the final fixed data.

8.5.4.7 A study with active control intended to demonstrate equivalence. This is a non-inferiority study with an active control.

8.6 Safety analysis

The safety analysis set should be analyzed for each treatment group. When necessary, frequency and proportion should be calculated for discrete variables and descriptive statistics for continuous variables. Unless otherwise specified, no analysis will be performed for patient cohorts.

8.6.1 Adverse events and adverse drug reactions

8.6.1.1 Summary of adverse events and adverse drug reactions

The number (number of subjects with adverse events) and proportion of subjects in whom the following adverse events are observed at least once after the administration of the study drug to the end of the follow-up period should be calculated for each treatment group. The same analyses should be performed for the Correction and the Conversion cohorts.

- Adverse event
- Adverse drug reaction
- Serious adverse event
- Serious adverse drug reaction
- Adverse event leading to discontinuation
- Adverse events leading to dose reduction or interruption of study drug
- Adverse events treated with rescue therapy

- Adverse event leading to death (adverse event of fatal outcome)

8.6.1.2 Individual adverse events

For adverse events, adverse drug reactions, serious adverse events, serious adverse events, non-serious adverse events, adverse events leading to discontinuation, adverse events leading to dose reduction or interruption of study drug, adverse events treated with rescue therapy, and adverse events leading to death, the number and proportion of subjects with each adverse event classified by SOC and PT in MedDRA/J version: 20.1 (hereinafter the same) should be calculated. The same analyses should be performed for the Correction and Conversion cohorts except non-serious adverse events.
The SOC will be sorted by order of international consensus, the PT by descending order of the number of subjects with MT-6548 and by descending order of the number of subjects with darbepoetin (PT code ascending when the number is equal).

8.6.1.3 Adverse events by severity

The number of subjects and incidence rate should be calculated for adverse event and adverse drug reaction by severity for the overall and for individual events classified by SOC and PT.
The tabulation method by severity (severe, moderate, mild) is as follows.
When adverse events of different severity occur in the same subject, the most severe adverse event should be counted as one subject.
When multiple adverse events of the same severity occur in the same subject, the same severity should be counted as 1 subject.
When the same subject experienced the same adverse event multiple times, the most severe adverse event should be counted as 1 subject.

8.6.1.4 Adverse events by the time of onset

The number and incidence rate of subjects with adverse events and adverse drug reactions should be calculated for adverse event and adverse drug reaction by time of onset (every 12 weeks) for the overall and for individual events classified by SOC and PT. For the calculation of the incidence rate, the number of subjects at each evaluation time point is used as the denominator. (Tabulation unit: from the first day of the treatment period [Day 1] to Day 84, Days 85–168, Days 169–252, Days 253–364, and after Day 365)
However, if the same adverse event occurs in different categories in the same subject, it is counted as 1 subject in each category.

8.6.1.5 Adverse events by dose immediately before onset

The number and incidence rate of adverse events and adverse drug reactions in overall and individual events classified by SOC and PT per total exposure period should be calculated for each treatment group by dose immediately before onset*. The total exposure period is defined as the total number of months (months) that each dose was administered during the study period.
The following formula is used to calculate the number of months of exposure. Number of months of exposure = number of days of exposure/30.4375
*The tabulation unit for each event by dose immediately before onset should be as follows:
MT-6548 group: daily dose (tabulation unit: 0 mg, 150 mg, 300 mg, 450 mg, 600 mg)
Darbepoetin group: weekly dosage (tabulation unit: 0 μg, >0 μg to ≤30 μg, >30 μg to ≤60 μg, >60 μg to ≤90 μg, >90 μg to ≤120 μg, >120 μg)

8.6.1.6 Adverse events by cumulative dosage

The number of subjects and incidence rate should be calculated for adverse event and adverse drug reaction by cumulative dosage before onset for the overall and for individual events classified by SOC and PT. The cumulative dosage will be divided into 4 categories at quartiles (0 to 1/4 of the maximum cumulative dosage, 1/4 to 2/4 of the maximum cumulative dosage, 2/4 to 3/4 of themaximum cumulative dosage, and ≥3/4 of the maximum cumulative dosage). In addition, the average number of exposure days per person should be calculated for each category. (Average number of exposure days: in the case of "0–x/4 of the Maximum Cumulative dosage", the number of days until the subject concerned reaches x/4of the maximum cumulative dosage should be calculated for each subject. In the case of ≥3/4 of the maximum cumulative dosage, the number of days to final administration for each subject and the mean should be calculated.)

The tabulation unit by cumulative dosage is as follows: However, if the same adverse event occurs in different categories in the same subject, it is counted as 1 subject in each category.
4 categories (cumulative unit: ≥0 to <1/4* maximum cumulative dosage, ≥1/4 to < 2/4* maximum cumulative dosage, ≥2/4 to <3/4* maximum cumulative dosage, ≥3/4* maximum cumulative dosage).

8.6.1.7 Adverse events before and after drug interruption

The number of subjects and incidence rate should be calculated for adverse event and adverse drug reaction by before and after drug interruption for the overall and for individual events classified by SOC and PT. It should be classified to 2 categories: 4 weeks before drug interruption and 4 weeks after

drug interruption (4 weeks after the start of drug interruption). If a subject had multiple drug interruptions and the adverse event occurred within 4 weeks after the drug interruption and within 4 weeks before the drug interruption, the subject should be counted as 1 subject for both periods.
Drug interruption period is defined as the period when "Yes" was selected in the question of "Did you choose the dosage according to the dosage adjustment algorithm?" and "0 mg" for the MT-6548 group or "0 μg" for the darbepoetin group was selected in the question of "Whether the dose was changed" in the "Administration status" of the case report form. If "No" is selected in the question of "Did you choose dosage according to dosage adjustment algorithm?", the subject should not be included in the calculation.

8.6.2 Laboratory test values

Descriptive statistics (except 2-sided 95% CI of the mean) should be calculated by treatment group at each evaluation time point for haematology tests, blood biochemistry tests, C-reactive protein, VEGF, dehydroepiandrosterone sulfate (DHEA-S), urine albumin/creatinine ratio, and urine protein/creatinine ratio. Changes from the first day of the treatment period at each evaluation time point should also be summarized. As for qualitative urinalysis, a shift table which consists of frequency tabulation by category at each evaluation time point and the start date of the treatment period and the decision results on the first day of the treatment period and each evaluation time point should be provided.

8.6.3 Number and proportion of subjects whose hepatic function values met the criteria for drug interruption or discontinuation

For AST and ALT, the number and proportion of subjects who meet the following conditions should be provided in each period between scheduled study visits from the first day to Week 52 week of the treatment period and during the entire treatment period from the first day to Week 52 of the treatment period. However, the conditions of each laboratory test values should be as shown in Table 8.6.3.1

Table 8.6.3.1 Definition of tabulation conditions for liver function values

Tabulation condition	Definitions

AST, ALT	AST >3.0 × ULN and total bilirubin ≤2.0 × ULN ALT >3.0 × ULN and total bilirubin ≤2.0 × ULN AST >3.0 × ULN and total bilirubin >2.0 × ULN ALT >3.0 × ULN and total bilirubin >2.0 × ULN AST >5.0 × ULN ALT >5.0 × ULN AST >8.0 × ULN ALT >8.0 × ULN

8.6.4 Resting standard 12-lead ECG

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be calculated at each evaluation time point, and a shift table composed of the decision results on the first day of the treatment period and each evaluation period should be provided.

8.6.5 Body weight

Descriptive statistics (except for two-sided 95% CIs of mean) should be calculated for each treatment group by evaluation time point. Changes from the first day of the treatment period at each evaluation time point should also be summarized.

8.6.6 Vital signs

Descriptive statistics (except for two-sided 95% CIs of mean) should be calculated for each treatment group by evaluation time point for the items of blood pressure and pulse rate. Changes from the first day of the treatment period at each evaluation time point should also be summarized.

8.6.7 Fundoscopy

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal [Presence or absence of retinal hemorrhage, presence or absence of retinal oedema]) should be calculated at each evaluation time point, and a shift table composed of the decision results (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be provided on the first day of the treatment period and each evaluation time point.

8.6.8 Chest X-ray

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be calculated at each evaluation time point, and a shift table composed of the decision results on the first day of the treatment period and each evaluation period should be provided.

8.6.9 Proportion of subjects with documented Hb values of ≥13.0 g/dL or ≥14.0 g/dL

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of subjects with confirmed Hb values of ≥13.0 g/dL or ≥14.0 g/dL, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period should be provided for each treatment group. If Hb is >13.0 g/dL and 14.0 g/dL in the same subject, the subject should be counted in both categories.
The similar analysis should be conducted for each patient cohort.

8.6.10 Proportion of subjects with documented Hb values of <9.0 g/dL or <8.0 g/dL.

Subjects with confirmed Hb values <9.0 g/dL or <8.0 g/dL should be analyzed in the same manner as in Section 8.6.9.

8.6.11 Proportion of subjects with a documented Hb increase rate >0.5 g/dL/week

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of subjects in whom the Hb increase rate is confirmed to be >0.5 g/dL/week, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 52 of the treatment period should be provided in each treatment group. The Hb increase rate in this tabulation should be calculated based on the difference in Hb values between the 2 time points measured on the scheduled study visit day in every 4 weeks and the Hb value measurement interval obtained from the actual study visit date. A similar analysis should be performed for each patient cohort.

8.6.12 Hb level after dose reduction or interruption of the study drug

Descriptive statistics of Hb values at dose reduction/drug interruption and after dose reduction/drug interruption of the study drug should be calculated for each treatment group. In addition, the change

of Hb after dose reduction/drug interruption of the study drug should be determined, and descriptive statistics should be calculated for each treatment group.

In the MT-6548 group, since there may be a certain number of cases where the "administration status" form is entered as "0 μg" one day after the study visit, Hb value on the day or the day before when the "administration status" form is entered as "0 μg", whichever is closer, should be adopted as the Hb data at the time of dose reduction or discontinuation of the study drug. For the Hb value after dose reduction/drug interruption of the study drug, the data of the day closest to 4 weeks (28 days) after the Hb measurement day at dose reduction/drug interruption should be adopted. If no study drug data at the time of dose reduction/drug interruption are available, subjects should be excluded from the Hb value analysis.

In addition, the interval (days) from the Hb measurement in dose reduction/drug interruption of the study drug to the Hb measurement after dose reduction/drug interruption should be calculated, and the descriptive statistics should be provided in each treatment group.

Drug interruption period is defined as the period when "Yes" was selected in the question of "Did you choose the dosage according to the dosage adjustment algorithm?" and "0 mg" for the MT-6548 group or "0 μg" for the darbepoetin group was selected in the question of "Whether the dose was changed" in the "Administration status" of the case report form. If "No" is selected in the question of "Did you choose the dosage according to the dosage adjustment algorithm?", or if rescue therapy was performed from the time of drug interruption of the study drug to the day of blood collection for data of Hb after drug interruption, the subject should not be included in the calculation.

A similar analysis should be performed for each patient cohort.

8.6.13 Subgroup analyses

In the safety analysis set, the number and incidence ratio of subjects with adverse events and adverse drug reactions should be calculated by treatment group for each subgroup based on the stratification factors for each endpoint in the table below (Tables 8.6.13.1 and 8.6.13.2).

Table 8.6.13.1 Intrinsic subgroup analysis of safety

Endpoints	Stratification factor	Stratified category
Adverse events and adverse	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65 <75, ≥75

drug reactions	Body weight (kg) on the first day of the treatment period	<60, ≥60
	Hb value (g/dL) on the first day of the treatment period	<9, 9 to <11, ≥11
	eGFR on the first day of the treatment period (mL/min/1.73 m^2)	<15, 15 to <30, 30 to <60, ≥60
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both below the upper limit of normal, either above the upper limit of normal and both ≤ 2 times the upper limit of normal, either > 2 times the upper limit of normal

Table 8.6.13.2 Extrinsic subgroup analysis of safety

Endpoints	Stratification factor	Stratified category
Adverse events and adverse drug reactions	Timing of taking (MT-6548 group only)	Before meal, after meal, other *If the timing of administration of MT-6548 tablets differs between the treatment period phase 1 and treatment period phase 2, the subjects should be excluded from the analysis.
	Patient cohort	Correction cohort, Conversion cohort, Conversion (Hb value ≥11.0 g/dL) cohort, Conversion (Hb value <11.0 g/dL) cohort

8.7 Review of the effect on the change of data in the treatment period phase 1

Since the data of iron supplement dosage in the treatment period phase 1 was changed in the treatment period phase 2, the data of the treatment period phase 1 should be tabulated again to check the effect on the results. The derivation and analysis method should be based on the description of SAP for the treatment period phase 1.

8.7.1 Iron supplement dosage

The following should be provided according to the 3 categories of oral iron supplement, intravenous iron supplement, and iron supplement (any route).

Descriptive statistics of the mean dose of iron supplement per month for each treatment group should be calculated for the screening period, and after the first day of the treatment period, in each period

between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period.

Descriptive statistics of the change in the mean dose of iron supplement per month from the baseline (mean dose of iron during the screening period) should be calculated, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period. Before and after comparison should be conducted for changes from baseline using the paired t-test. The changes should be compared between groups using the Student-t test. The mean value of the between-group difference (MT-6548 − darbepoetin), its two-sided 95% CI, t-statistic, and p-value should be provided. The dosage of iron supplement should be calculated using the dose as iron. If no iron supplement is administered, the dose should be tabulated as 0 mg. Subjects who changed the administration route of an iron supplement during the treatment period and subjects who had never received an iron supplement during the treatment period should be excluded from the tabulation.

Analysis should be performed for each patient cohort of the overall cohort, the correction cohort, and the conversion cohort.

8.7.2 Proportion of subjects receiving oral, intravenous, or iron supplement (any route)

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects treated with oral, intravenous, or oral iron supplement (any route) should be provided by treatment group for screening period, and after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period. McNemar tests should be used to compare baseline values (proportion of subjects receiving iron supplements by the aforementioned route in screening period) with before and after each period between scheduled study visits. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects receiving oral, intravenous, or (any route) iron supplement.

Subjects who have not received an iron supplement are to be subjects who have never received an iron supplement during the relevant period, and subjects who have received an oral, intravenous, or (any route) iron supplement are to be subjects who have received an iron supplement at least once during the relevant period.

Analysis should be performed for each patient cohort of the overall cohort, the Correction cohort, and the Conversion cohort.

8.7.3 Subgroup analyses

The following analyses should be conducted for subpopulations based on the stratification factor for each endpoint in the below (Table 8.7.3.1) in the FAS. Unless otherwise specified, no analysis will be performed for patient cohorts.

(1) Hb value at Week 24 of the treatment period

LSMean, standard error, and 2-sided 95% CI should be calculated for each treatment group using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance). The point estimate, its standard errors, 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin) of LSMean should be calculated.

(2) Mean dose of the study drug for the Week 20 to Week 24.

Descriptive statistics should be calculated for each treatment group.

(3) Target Hb value achievement rate at Week 24 of the treatment period

The number, proportion, and 95% CI (Clopper-Pearson [Exact)] method) for the proportion of subjects with Hb values within the target range (10.0 g/dL to <12.0 g/dL) should be provided for each treatment group. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for group difference (MT-6548 − darbepoetin) should be calculated.

Table 8.8.3.1 Subgroup analysis on efficacy

Endpoints	Stratification factor	Stratified category
1. Hb value at Week 24 of the treatment period 2. Study drug mean dose at Week 20 to Week 24 of the treatment period 3. Target Hb achievement rate at Week 24 of the treatment period	Treatment with oral iron supplement at Week 24 of the treatment period	Yes or No
	Iron-containing phosphate binders at Week 24 of the treatment period	Yes or No

8.7.4 Individual adverse events

(1) Summary of adverse events and adverse drug reactions

The number (number of subjects with adverse events) and proportion of subjects in whom the following adverse events are observed at least once after the administration of the study drug to the end of the follow-up period should be calculated for each treatment group. Unless otherwise specified, no analysis will be performed for patient cohorts.

- Adverse event
- Adverse drug reaction
- Serious adverse event
- Serious adverse drug reaction
- Adverse event leading to discontinuation
- Adverse events leading to dose reduction or interruption of the study drug (active drug)
- Adverse events resulting in death (adverse event leading to death)

(2) Individual adverse events

If a difference from treatment period 1 occurs in "(1) Summary of adverse events and adverse reactions", the number of subjects and the incidence rate of individual adverse events classified by SOC and PT in MedDRA Version 20.1 and MedDRA/J Version 20.1. (hereinafter the same) should be calculated.

The SOC will be sorted by order of international consensus, the PT by descending order of the number of subjects with MT-6548 and by descending order of the number of subjects with darbepoetin (PT code ascending when the number is equal). Unless otherwise specified, no analysis will be performed for patient cohorts.

(3) Fundoscopy

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal [Presence or absence of retinal hemorrhage, presence or absence of retinal oedema]) should be calculated at each evaluation time point, and a shift table composed of the decision results (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be provided on the first day of the treatment period and each evaluation time point.

9. Software to Use

SAS for Windows (Release 9.4) will be used for statistical analysis.

10. Changes in the Statistical Analysis Plan from the Study Protocol

No change from the study protocol.

11. References

[1]: Shinya I, Takeru S, Ataru I, Shinichi N, Takashi F, et al. Developing a Japanese version of the EQ-5D-5L value set. J. Natl. Inst. Public Health 2015.; 64 (1): 47-55.

[2]: Miura Y, Green J, Fukuhara S. KDQOL-SF version 1.3 Japanese manual. iHope International Inc.; 2016. p. 13-16.

Errata

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 Number	MT-6548-J01

Date of Errata preparation	April 2, 2019
Errata prepared by	[redacted]

Object document	Statistical Analysis Plan
Object document version number	Version 2
Signature date	February 12, 2019

The Statistical Analysis Plan (Version 2) in "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" is corrected as follows:

Applicable part	Correct
4.12 Iron supplement dosage	(Error) *5: In this tabulation, 1 month month is counted as 30.4375 days (365.25/12 = 30.4375). (Correct) *5: In this tabulation, 1 month ~~month~~ is counted as 30.4375 days (365.25/12 = 30.4375).
	(Reason) Due to typographical error.

Applicable part	Correct
8.2.2 Subjects who discontinued or interrupted their treatment	(Error) Item: Number and proportion of drug interruptions among subjects enrolled in the treatment period (Correct) Item: Number of ~~and proportion~~ drug interruptions among subjects enrolled in the treatment period
	(Reason) Deleted because it was an unnecessary description

Applicable part	Correct
Table 8.5.4.6 Subgroup analysis on efficacy	(Error) CYP2B6 inducer coadministration * List of CYP2B6 inducers obtained from The Metabolism and Transport Drug Interaction Database (DIDB®). (Correct) CYP2B6 substrates * List of CYP2B6 substrates obtained from The Metabolism and Transport Drug Interaction Database (DIDB®).
	(Reason) Due to typographical error

Applicable part	Correct
8.6.1.2. Individual adverse events	(Error) For adverse events, adverse drug reactions, serious adverse events, non-serious adverse events, serious adverse events, adverse events leading to discontinuation, dose reduction or interruption of study drug, and adverse events leading to death, the number of subjects with individual adverse events classified by SOC and PT in MedDRA/J version: 2x.x (hereinafter the same) and the incidence should be calculated. (Correct) For adverse events, adverse drug reactions, serious adverse events, non-serious adverse events, serious adverse drug reactions, adverse events leading to discontinuation, adverse events leading to dose reduction or interruption of study drug, and adverse events leading to death, the number of subjects and incidence rate will be calculated for each adverse event classified by SOC and PT in MedDRA/J 20.1 (hereinafter the same).
	(Reason) Due to typographical error.

Applicable part	Correct
Appendix	(Error) List of CYP2B6 inducers obtained from The Metabolism and Transport Drug Interaction Database (DIDB®) (Correct) List of CYP2B6 substrates obtained from The Metabolism and Transport Drug Interaction Database (DIDB®).
	(Reason) Due to typographical error.

End

For Fixed Data Analysis of Treatment Period Phase 1

Statistical Analysis Plan

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

Mitsubishi Tanabe Pharma Corporation

Preparation date	February 12, 2019
Study protocol number	MT-6548-J01
Version number	Version 2.0

Revision History

Version number	Content of revision
Version 1	First edition
Version 2 (final edition)	Reflection of case review meeting and preparation of description

For Fixed Data Analysis of Treatment Period Phase 1

Statistical Analysis Plan

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

Approval Column

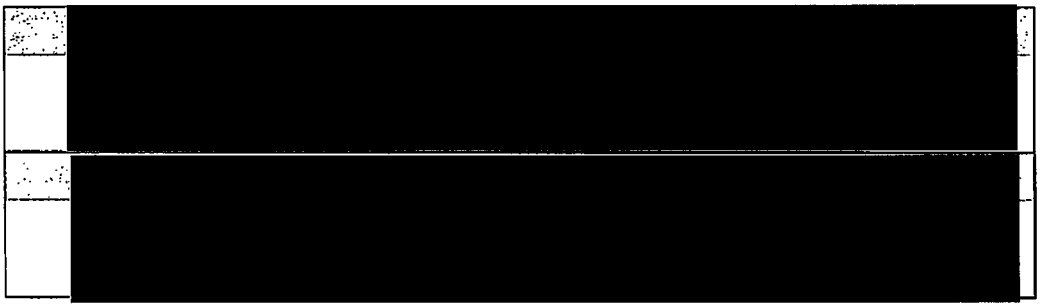


Table of Contents

List of Abbreviations

Abbreviation	Full 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
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
JSDT	The Japanese society for dialysis therapy
LOCF	Last observation carried forward
MMRM	Mixed model repeated measures
MRP	Multidrug resistance-associated protein
NDD-CKD	Nondialysis dependent chronic kidney disease
OATP	Organic anion transporting polypeptide
OAT	Organic anion transporter
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Preferred term
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 the 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 scheduled tests for Week 24 of the treatment period to completion of scheduled tests for Week 52 of the treatment period
Day of completion of treatment period	Week 52 of the treatment period or the day of discontinuation during the treatment period
X weeks prior to the first day of the screening period	Same day of the week X weeks prior to the first day of the screening period
MT-6548 tablets	Each film-coated tablet contains 150 mg vadadustat
Darbepoetin alfa injection	Plastic syringe containing darbepoetin alfa (recombinant) in 1 syringe (0.5 mL)
Correction cohort	Patients who have not received ESA formulations from 8 weeks prior to the first day of the screening period
Conversion cohort	Patients who have received the same ESA formulations from 8 weeks prior to the first day of the screening period

1. Introduction

This is a document that shows more detailed contents in addition to those of the study protocol on the statistical analysis plan for the efficacy and safety in the treatment period phase 1 fixed data (hereinafter, phase 1 fixed data) of "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. Study Objectives and Design

2.1 Study objectives

The study evaluates the non-inferiority of MT-6548 in patients with anemia associated with NDD-CKD using Hb values as a measure and darbepoetin alfa (recombinant) as a control drug and also the safety of long-term administration of MT-6548.

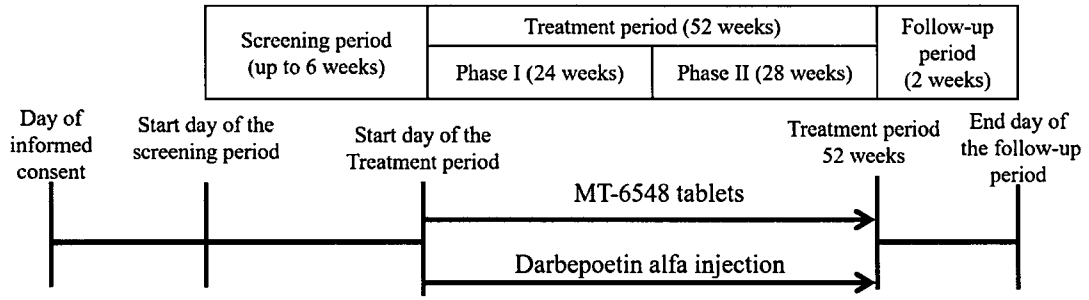
In addition, the study evaluates the effect of MT-6548 on improvement and maintenance of Hb values in a cohort of patients who have not received ESA formulations and also the effect of MT-6548 on switch maintenance of Hb values in a cohort of patients receiving ESA formulations.

2.2 Study design

Study phase: Phase III

Study type: Confirmatory study

Multicenter, randomized, open-label, active-controlled, parallel group comparative study.



2.3 Randomization methods

Personnel responsible for preparation of the allocation table should 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 who are judged eligible to enter the treatment period are assigned to treatment groups in ascending order of the randomization number based on the randomization key code table for each stratification factor, and the treatment groups assigned on the Web registration system are notified. The investigator/coinvestigator should prescribe the study drug of the treatment group notified on the

Web registration system. Further details of randomization methods shall be specified in the standard operating procedure for randomization key code table preparation and storage.
Subjects should be randomly assigned in a 1:1 ratio to MT-6548 and darbepoetin groups with the following stratification factors.

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

2.4 Evaluation time point

VISIT / ITEM	Informed consent	Screening period [a]		Treatment period																		Final day of follow-up observation period [b]
				Treatment period phase I										Treatment period phase II							Day of discontinuation	
		First day	Visit 2	Start day [c]	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52		
Visit No.	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	FU
Permitted range (day)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7 or +14 [d]	+7
Procedure/Evaluation																						
Informed consent	×																					
Inclusion/Exclusion criteria	×	×	×	×																		
Allocation				×																		
Patient's background and history	×			×																		
Height				×																		
Body weight				×						×			×			×				×	×	
Folate and vitamin B_{12}		×																				
Pregnancy test [e]		×											×							×	×	
Hematology tests		×	× [f]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Blood biochemistry tests and eGFR		×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
C-reactive protein		×		×									×							×	×	
Iron-related measures		×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Hepcidin				×	×	×	×			×			×			×				×	×	
Erythropoietin [g]				×	×	×	×			×			×			×				×	×	
VEGF				×						×			×			×				×	×	
DHEA-S				×						×			×			×				×	×	
Urinalysis (qualitative)		×		×	×	×	×		×	×	×	×	×	×	×	×	×	×	×	×	×	
Urine albumin/creatinine ratio		×		×						×			×			×				×	×	
Urine protein/creatinine ratio		×		×						×			×			×				×	×	
Vital signs [h]		×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
12-lead ECG [i]				×									×							×	×	
Fundoscopy [d]		×										×							×		×	
Chest X-ray [d]		×										×							×		×	
QOL measures (EQ-5D-5L, KDQOL)				×						×			×							×	×	
AE Investigation				×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Blood sampling for PK testing [j]						×				×			×									
Blood sampling for genetic analysis [k]				Blood sample for genetic analysis performed once as early as possible after Week 2 of the treatment period																		
Blood sampling for plasma protein binding [l]		×																				
Drug evaluation/procedure																						
Investigation of concomitant drugs				×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Prescription of MT-6548 tablets [m]				Administered according to the dose adjustment guideline																		
Prescribing of darbepoetin alfa injection				Administered according to the dose adjustment guideline																		
Administration of iron supplements		Administration iron supplements to maintain serum ferritin values >=100 ng/mL or TSAT at >=20%																				

[a] The screening period can be up to 6 weeks. Test results should be reviewed prior to transition 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 can be performed as necessary.

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

[c] Should be performed prior to study drug treatment (AE investigations begin after study drug treatment)

[d] Fundoscopy and chest X-ray should be performed once during the screening period. Fundoscopy and chest X-ray should be performed once during Weeks 20–24 of the treatment period, and once during Weeks 48–52 of the treatment period. Should be performed within 14 days of study withdrawal if treatment is discontinued.

[e] Only female subjects who may become pregnant.

[f] Only Hb values should be measured.

[g] Erythropoietin should be measured in subjects of the MT-6548 group only.

[h] Measurements should be made before blood sampling as much as possible. Measurements should be made in the sitting position after 5 minutes of rest.

[i] Measurements should be made before blood sampling as much as possible. Measurements should be made in the supine position after 5 minutes of rest.

[j] Blood sampling for PK testing should be performed in subjects of the MT-6548 group only.

[k] Blood should be collected once as early as possible after Week 2 of the treatment period for subjects who have given consent to the genetic analysis tests. Blood sampling for genetic analysis should be performed in subjects of the MT-6548 group only.

[l] For subjects who consent to the plasma protein binding rate study, blood should be collected once before the start of treatment with MT-6548 tablets. For subjects in the darbepoetin group, blood sampling should also be allowed during the treatment period.

[m] MT-6548 tablets should be prescribed to subjects depending on the number of their unused tablets. Subjects should be instructed to use up one bottle before opening the next.

2.5 Rationale for sample size

A total of 300 subjects (150 each for the MT-6548 and darbepoetin groups) should be enrolled in the treatment period. The target sample size for each cohort is shown below.

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

However, the maximum number of subjects 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 in the screening period in the Conversion cohort should be 120.

[Rationale]

For the primary efficacy endpoint of mean Hb values at treatment period Weeks 20 and 24, the mean Hb value in the darbepoetin group is assumed to be 12.0 g/dL, the difference between the MT-6548 and darbepoetin groups 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 to <13.0 g/dL) and non-inferiority could be established.

In addition, the target sample size was set for each of the Correction cohort, Conversion cohort, Conversion (Hb value ≥11.0 g/dL) cohort, and Conversion (Hb value <11.0) cohort so that appropriate evaluation could be made for each cohort.

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

3. Endpoints

3.1 Efficacy endpoints

3.1.1 Primary endpoint

Mean Hb values at Weeks 20 and 24 of the treatment period

3.1.2 Secondary endpoints

Hb values at each evaluation time point in the treatment period

(1) Proportion of subjects with mean Hb values within the target range (≥11.0 to <13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each evaluation time point in the treatment period

(2) Number of days from the first day of the treatment period required to reach the target Hb range (≥11.0 g/dL to <13.0 g/dL)

(3) Hb increase rate

3.1.3 Other endpoints

(1) Changes in mean Hb values from the first day of the treatment period at Weeks 20 and 24 of the treatment period

(2) Proportion of subjects with a ≥1.0 g/dL increase in mean Hb values from the first day of the treatment period at each time point of the treatment-period

(3) Number of days to maintain the target Hb values

(4) Proportion of subjects receiving rescue therapy with ESA formulations, red blood cell transfusion, or phlebotomy

(5) Study drug dosage

(6) Total number of dosage adjustments

(7) Iron supplement dosage

(8) Proportion of subjects receiving oral, intravenous, or (any route) administration of iron supplements

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

(10) Changes and rate of changes in iron-related indices (serum iron, TIBC, TSAT, and serum ferritin values) and hepcidin from the first day of the treatment period

(11) Changes in hematocrit, red blood cell count, reticulocytes (number and rate), mean corpuscular volume, mean corpuscular hemoglobin, and erythropoietin (MT-6548 group only) from the first day of the treatment period

(12) Changes and rate of changes in systolic blood pressure, diastolic blood pressure, lipids (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides), and blood glucose from the first day of the treatment period

(13) Change in renal function-related indices (eGFR, serum creatinine, urinary albumin/creatinine ratio) from the first day of the treatment period

(14) QOL indices (EQ-5D-5L, KDQOL)

3.2 Safety endpoints

(1) Adverse events and adverse drug reactions

(2) Laboratory test values

1) Hematology tests:

Mean corpuscular volume, mean hemoglobin, mean hemoglobin concentration, RBC distribution width, WBC count, WBC fractions (neutrophils, eosinophils, monocytes, lymphocytes, basophils), platelet count

2) Blood biochemistry tests:

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 the age at the time of informed consent acquisition.

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

3) C-reactive protein

4) Folic acid and vitamin B12

5) Vascular endothelial growth factor (VEGF)

6) Dehydroepiandrosterone sulfate (DHEA-S)

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

8) Urinalysis (qualitative)

9) Glucose, protein, urobilinogen, occult blood

(3) Resting standard 12-lead ECG

(4) Body weight
(5) Vital signs
(6) Fundoscopy
(7) Chest X-ray
(8) Proportion of subjects with documented Hb values of ≥13.0 g/dL or ≥14.0 g/dL
(9) Proportion of subjects with documented Hb values of <9.0 g/dL or <8.0 g/dL
(10) Proportion of subjects with a documented Hb increase rate >0.5 g/dL/week
(11) Hb level after dose reduction or interruption of the study drug

3.3 Pharmacokinetic endpoints

Plasma concentration of unchanged MT-6548

4. Definition of Derived Variables

4.1 Age at consent acquisition

Age (year) = Date of consent acquisition (year) − Date of birth (year)
However, when (Date of Consent [Months] < Date of Birth [Months]) or (Date of Consent [months] = Date of Birth [months) and Date of Consent [days] < Date of Birth [days]), 1 is subtracted from the traditional Japanese age system calculated above.

4.2 Duration of disease

The duration of disease (year) should be the period from the onset of renal anemia to the consent month and shall be the integer part + 1 digit (rounded). Duration of disease is calculated as follows:
Duration of disease (years) = (Date of consent acquisition [year] − Time of onset [year]) + (Date of consent acquisition [month] − Time of onset [month])/12
If the month of onset is unknown, the month is calculated as 1.

4.3 BMI

BMI (kg/m^2) = Body weight (kg)/(Height [m])^2
Should be rounded and displayed to one decimal place.

4.4 LDL-C/HDL-C ratio

LDL-C/HDL-C ratio = LDL-C (mg/dL)/HDL-C (mg/dL)
Should be rounded and displayed to two decimal places.

4.5 Number of days of drug interruptions

The number of days of drug interruptions does not include subject's forgetting to take the drug and is defined by the following formula.

Number of days of drug interruptions (days) = Date of resumption of study drug administration − Start date of study drug interruption; If there are multiple interruptions, the sum of them is used.

Resumption date of study drug: After the entry of "Daily Dose" = 0 mg or 0 μg in the CRF, the first dose should be taken when a value of >0 mg is entered for the first time, or when a value of >0 μg is entered for the first time. If the drug interruption continues until Week 24 of the treatment period, days should be calculated based on the visit date after Week 24 of the treatment period as the resumption date. Specifically, if the treatment is completed or discontinued while the drug is interrupted, the day before the day of blood sampling at Week 24 for hematology tests or the day before the day of treatment discontinuation should be used.

Start date of study drug interruption: The dose start date when "Daily Dose" = 0 mg is first entered in the CRF or the administration date when 0 μg is entered.

4.6 Study drug administration/duration

For subjects who completed treatment period phase I:

Study drug administration/duration (days) = Day of blood sampling for hematology tests at Week 24 − First day of the treatment period

For subjects who discontinued: Study drug administration/duration (days) = Day of discontinuation − First day of the treatment period

4.7 Study drug administration/number of administration days

The number of days that the study drug is taken (administered) is defined by the following formula.

Number of MT-6548 administration days (days) = Period of study drug administration − Number of days of no study drug administration other than drug interruptions − Number of days of drug interruptions

Number of darbepoetin alfa administration days (days) = Number of doses of darbepoetin alfa once every week × 7 days + Number of doses of darbepoetin alfa once every 2 weeks × 14 days + Number of doses of darbepoetin alfa once every 4 weeks × 28 days + Number of doses of darbepoetin alfa once every 3 weeks × 21 days + Number of doses of darbepoetin alfa twice every week × 3.5 days

4.8 Study drug administration/compliance rate

Drug administration/compliance rate (%) = Number of days of study drug use (administration)/(Period of study drug use [administration] − Number of days of drug interruptions) × 100

However, if the compliance rate exceeds 100%, it should be 100%.

4.9 Mean daily dose/mean weekly dose

Mean daily dose of MT-6548 during each scheduled study visit period* = (Daily dose based on the physician's prescription × Period of administration (days)*3 of the corresponding dose*2 between the scheduled study visits*/Period between the schedule study visits (days)*4

Mean weekly dose of darbepoetin alfa during each scheduled study visit period* = Daily dose based on the physician's prescription × Period of administration (days)*5 of the corresponding dose*2 between the scheduled study visits*/Period between the scheduled study visits (days)*4 × 7

*: For each period between the scheduled study visits, the actual study visit dates will not be considered, and this variable should be fixed as follows:

- ✓ The first day of the treatment period to Week 2 of the treatment period: The first day of the treatment period (Day 1) to Day 14
- ✓ Week 2 of the treatment period to Week 4 of the treatment period: Day 15 to Day 28
- ✓ The same shall apply thereafter, and the final period between the scheduled study visits should be Week 20 to Week 24 of the treatment period: Day 141 to a blood sampling day for hematological tests at Week 24 of the treatment period.

However, for subjects who discontinued their treatment, the final period between the scheduled study visits should be up to the day before discontinuation.

*2: If there are multiple applicable doses, the sum of the calculated values for each dose should be used.

*3: The number of days without drug administration other than drug interruption should not be excluded from the "period of administration (days)".

*4: 14 days up to Week 12 of the treatment period and 28 days after Week 12 of the treatment period. However, for subjects who discontinued their treatment, the final period between the scheduled study visits (days) should be the actual number of days until the day before discontinuation.

*5: "Period from the day of administration of darbepoetin alfa to the day of next administration of darbepoetin alfa". However, the first treatment period (days) during the scheduled study visit period should be "period from the start date during the scheduled study visit period to the day before the day of the first darbepoetin alfa administration date after the start date during the scheduled study visit period" and the last treatment period (days) should be "from the last day of darbepoetin alfa administration during the scheduled study visit period to the day before the day of the last treatment or the day before discontinuation during the scheduled study visit period".

The following formula should be used when no darbepoetin alfa is administered during the scheduled study visit period.

Mean weekly dose of darbepoetin alfa = Weekly dose of darbepoetin alfa immediately before the schedule study visit period

4.10 Cumulative dosage

The cumulative dosage of the study drug is defined by the following formula.

Cumulative dosage of MT-6548 = 150 mg × Days of 150 mg administration + 300 mg × Days of 300 mg administration + 450 mg × Days of 450 mg administration + 600 mg × Days of 600 mg administration

Number of administration days of X mg* = Day when dose was changed from X mg − First day of X mg administration (not excluding the number of days of no drug administration)

If there are multiple applicable periods, the sum of them should be used.

*: X indicates each dose of MT-6548.

The cumulative dosage of darbepoetin alfa is the sum of individual doses of darbepoetin alfa × the number of administrations of individual doses.

4.11 Hb value increase rate

The Hb value increase rate is defined as the rate calculated using the following method.

- ✓ Hb value increase rate (g/dL/week):

  (Hb value at Week 4 of the treatment period − Hb value at the start of the treatment period)/([Hb value measurement day at Week 4 of the treatment period − Hb value measurement day at the start of the treatment period)]/7)

- ✓ Hb value increase rate (regression) (g/dL/week):

  The slope of the regression line calculated based on the Hb values measured from the first day of the treatment period to Week 6 of the treatment period 6 and the measurement day (weeks from the first day of the treatment period) is defined as the Hb value increase rate (regression). Subjects without data at the first day and Week 6 of the treatment period should be excluded from the tabulation. The number of weeks from the first day of the treatment period used to obtain the regression line is defined by the following formula.

  First day of the treatment period: 0

  Week 2 of the treatment period: (Measurement day at Week 2 of the treatment period − the first day of the treatment period)/7

  Week 4 of the treatment period: (Measurement day at Week 4 of the treatment period − the first day of the treatment period)/7

  Week 6 of the treatment period: (Measurement day at Week 6 of the treatment period − the first day of the treatment period)/7

  Unscheduled study visit from the first day of the treatment period to Week 6 of the treatment period: (Day of unscheduled study visit − the first day of the treatment period)/7

4.12 Iron supplement dosage

The dose of iron supplements is defined by the following formula. However, the dose of iron supplements will not be calculated if iron supplements are used as needed.

Mean monthly dose of iron supplements during the screening period* and each scheduled study visit period*2 (tabulation period of iron supplements) = (Daily dose based on the physician's prescription × Period of administration (days) of the corresponding dose*3 during the tabulation period of iron supplements)/Tabulation period of iron supplements (days)*4 × 30.4375*5

*: The number of days of the screening period is "First day of the treatment period − First day of the screening period".

*2: For each period between the scheduled study visits, the actual study visit dates are not considered, and this tabulation is fixed as follows:

- ✓ The first day of the treatment period to Week 2 of the treatment period: The first day of the treatment period (1 day) to 14 days
- ✓ Week 2 of the treatment period to Week 4 of the treatment period: 15 to 28 days
- ✓ The same shall apply thereafter, and the final period between the scheduled study visits should be Week 20 to Week 24 of the treatment period: 141 days to a blood sampling day for hematological tests at Week 24 of the treatment period. However, for subjects who discontinued their treatment, the final period between the scheduled study visits should be up to the day before discontinuation.

*3: If there are multiple applicable doses, the sum of the calculated values for each dose should be used.

*4: For subjects who discontinued their treatment, the final period between the scheduled study visits (days) should be the actual number of days until the day before discontinuation.

*5: In this tabulation, 1 month month is counted as 30.4375 days (365.25/12 = 30.4375).

4.13 QOL (EQ-5D-5L) index value

Responses to five questions (mobility [Mo], self care [Sc], usual activities [Ua], pain/discomfort [Pd], anxiety/depression [Ad] in 5 levels (level 1 is healthy and the level goes up to 5, and the health status decreases with increases in level) are converted into index values. The index value is calculated using the Japanese EQ-5D-5L conversion table (Table 4.12.1) [1].

(1) The responses to questions from Mo to Ad should be arranged side by side into five numbers (hereinafter, health state). The health state can exist from "11111" to "55555".

(2) If all five responses are 1, i.e. the health state is "11111", the index value is 1. If the health state is other than "11111", "Constant term: −0.060924" in Table 4.12.1 and the estimated value of the coefficient for each level

of the response to each question should be used to obtain the index value using the following formula. The index value of the subject should be missing if one of the 5 questions has not been answered.

Index value = 1 + "Estimate of the constant term" + "Sum of 'estimated coefficients corresponding to levels of responses other than 1'"

Table 4.12.1 Japanese EQ-5D-5L conversion table

Item	Level	Estimate	Standard error	p value
Constant term		-0.060924	0.013625	<0.0001
Mo	2	-0.063865	0.008996	<0.0001
	3	-0.112618	0.009287	<0.0001
	4	-0.179043	0.010231	<0.0001
	5	-0.242916	0.009425	<0.0001
Sc	2	-0.043632	0.008931	<0.0001
	3	-0.076660	0.009972	<0.0001
	4	-0.124265	0.010129	<0.0001
	5	-0.159659	0.008924	<0.0001
Ua	2	-0.050407	0.009205	<0.0001
	3	-0.091131	0.010005	<0.0001
	4	-0.147929	0.009744	<0.0001
	5	-0.174786	0.009115	<0.0001
Pd	2	-0.044545	0.008354	<0.0001
	3	-0.068178	0.010052	<0.0001
	4	-0.131436	0.008985	<0.0001
	5	-0.191203	0.009604	<0.0001
Ad	2	-0.071779	0.009701	<0.0001
	3	-0.110496	0.010863	<0.0001
	4	-0.168171	0.009850	<0.0001
	5	-0.195961	0.009164	<0.0001

Mo: mobility, Sc: self care, Ua: usual activities, Pd: pain/discomfort, Ad: anxiety/depression

4.14 QOL (KDQOL) scoring

Step 1 (See Table 4.13.1[2]): The appropriate score is converted from the response choices for each item number in Table 4.13.1 [2] (See Listing 16.2.4.9 for questions) for each subject.

Table 4.13.1 Step 1 in KDQOL scoring [2]

Item number	Response choices	Score
Question 4, A–D Question 5 A–C, Question 21	1	0
	2	100
Question 3 A–J	1	0
	2	50
	3	100
Question 19 A, B	1	0
	2	33.33
	3	66.66
	4	100
Question 10 Question 11 A, C Question 12, A–D	1	0
	2	25
	3	50
	4	75
	5	100
Question 9 B, C, F, G, I Question 18 B	1	0
	2	20
	3	40
	4	60
	5	80
	6	100
Question 20	1	100
	2	0
Question 1, Question 2, Question 6, Question 8 Question 11 B, D, Question 14 A–M, Question 15 A–H, Question 16 A, B Question 19 A, B	1	100
	2	75
	3	50
	4	25
	5	0
Question 7 Question 9 A, D, F, H Question 13 A–F Question 18 A, C	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
Question 23	1	100
	2	83.33
	3	66.66
	4	50
	5	33.33
	6	16.66
	7	0

Step 2 (See Table 4.13.2[2]): The mean of the scores calculated at Step 1 in the item numbers in the right column of Table 4.13.2 [2] is calculated for each subject by subscale. For questions 17 and 22, the scores obtained are multiplied by 10 to convert the values from 0 to 100. The mean value should be the score for each subject by subscale. If at least one question constituting the subscale is answered, the subscale should be tabulated without missing. If "No" is chosen in question 16, the question 16 should be treated as missing.

Table 4.13.2 Step 2 in KDQOL scoring [2]

Each item score should be averaged to calculate each subscale score

Subscale	Number of items	After scoring according to Table 4-1, the mean of the items included in each subscale should be calculated.
Kidney disease-specific scale		
Symptoms	12	Questions 14 A–K, L (M)*
Effects of kidney disease on daily life	8	Question 15 A–H
Burden due to kidney disease	4	Question 12 A–D
Working status	2	Question 20, Question 21
Cognitive function	3	Question 13 B, D, F
Relationship with people	3	Question 13 A, C, F
Sexual function	2	Question 16 A, B
Sleep	4	Question 17, Question 18 A–C
Social support	2	Question 19 A, B
Encouragement from dialysis staff	2	Question 24 A, B
Patient satisfaction with dialysis care	1	Question 23
Comprehensive scale (SF-36)		
Physical functioning	10	Question 3 A–J
Daily role functioning (physical)	4	Question 4 A–D
Bodily pain	2	Question 7, Question 8
General health	5	Question 1, Question 11 A–D
Vitality	4	Question 9 A, E, G, I
Social functioning	2	Question 6, Question 10
Daily role functioning (emotional)	3	Question 5 A–C
Mental health	5	Question 9 B, C, D, F, H

4.15 Adverse drug reactions

Adverse events for which a causal relationship to the study drug was evaluated as "reasonable possibility" are defined as adverse drug reactions.

5. Analysis Sets

Efficacy analysis will be performed in the largest analysis set (hereinafter, 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 in the safety analysis set. Pharmacokinetic analysis will be performed in the pharmacokinetics analysis set.

The analysis sets are defined below; Details of treatment period phase 1 fixed data and treatment of subjects with final fixed data will be determined by the sponsor by the time the data are fixed.

5.1 Efficacy analysis set

(1) FAS

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

- ✓ Subjects who did not have anemia associated with NDD-CKD
- ✓ Subjects who have never received a dose of the study drug
- ✓ Subjects with no post-randomization efficacy data

(2) PPS

PPS is defined as the analysis set consisting of subjects excluding the following subjects from the FAS.

- ✓ Subjects who deviated from inclusion criteria
- ✓ Subjects who met any of the exclusion criteria
- ✓ Subjects who violated rules concerning prohibited concomitant drugs or therapies
- ✓ Subjects with a <80% compliance rate for either MT-6548 tablets or darbepoetin alfa injection

5.2 Safety analysis set

The analysis set consisting of all randomly allocated subjects excluding the following subjects is the safety analysis set.

- ✓ Subjects who have never received a dose of the study drug
- ✓ Subjects with no post-randomization safety data

5.3 Pharmacokinetics analysis set

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

- ✓ Subjects who have never received a dose of MT-6548 tablets
- ✓ Subjects with no post-randomization plasma drug concentration data

6. Patient Cohort

The patient cohort is defined as follows: Analyses will be performed for each patient cohort as needed.

- ✓ Correction cohort: A group of patients who have not received ESA formulations from 8 weeks prior to the first day of the screening period.
- ✓ Conversion cohort: A group of patients who have received ESA formulations from 8 weeks prior to the first day of the screening period.
- ✓ Conversion (Hb level ≥ 11.0) cohort: A subset of patients in the Conversion cohort whose mean Hb level during the last 2 screening sessions is ≥11.0 g/dL.
- ✓ Conversion (Hb level < 11.0) cohort: A subset of patients in the Conversion cohort whose mean Hb level during the last 2 screening sessions is <11.0 g/dL.

7. Data Handling

The fixed data of the treatment period phase 1 should be handled as follows: The handling of data other than the following (excluding handling of data related to pharmacokinetic assessment) should be decided in the case review meeting and specified in the statistical analysis plan that will be fixed finally by the data fixation.

7.1 Handling of missing data

If test measurements are missing or if problems with samples etc. result in invalid measurements or reference values, these should be handled as missing values. Derived variables should also be treated as missing if even one test value or other data required for derivation is missing or not adopted.

7.2 Handing of data for tabulation at each evaluation time point

Data that meet the permitted range specified in the "Table 9.1-1 Permitted range of study visits" section of the protocol should be used for the tabulation at each evaluation time point and should not be imputed with those outside the permitted range.

If there are multiple data within the permitted range, then the one closer to the reference date should be adopted. If the deviations from the reference date are the same, data for the efficacy and safety evaluations should be adopted before and after the reference date, respectively.

7.3 Handling of efficacy endpoints if rescue therapy is performed

If rescue therapy is performed, data from the day after rescue therapy should not be used to assess efficacy.

7.4 Imputation of missing data

The mixed repeated-measures model (MMRM) used to analyze the primary efficacy endpoint should not use data imputing missing data, except for the first day of the treatment period.

If there are missing values at the first day of the treatment period, data from the day closest to the first day of the treatment period should be used as data for the first day of the treatment period.

Mean Hb values at Weeks 20 and 24 of the treatment period should be derived as data for analysis of covariance (ANCOVA), which is performed as a sensitivity analysis for the primary efficacy endpoint. Missing data are imputed with data from the evaluation time point immediately before the missing evaluation time point (excluding the first day of the treatment period) (LOCF method). When any one evaluation time points has missing values, the data at the evaluation time point closest to the missing evaluation time point is adopted, and when two evaluation time points have missing values, the data in the two different evaluation time points closest to and before the missing evaluation time points should be adopted to calculate the mean Hb value. However, Hb values at the same evaluation time point should not be used.

In addition, for clinical laboratory values, vital signs, and QOL indices among the efficacy endpoints, values imputed by the LOCF method at Week 24 of the treatment period should also be output. Data obtained by imputing missing values at Week 24 of the treatment period should be used as data at the end of the treatment period phase 1.

7.5 Handling of clinical laboratory test values less than the limit of quantification

If the measured values are reported to be not more than the limit of quantification, less than the limit of quantification, or impossible to calculate, the following handling procedures should be applied for tabulation, and missing values or zero values should not be used.

[Handling of quantification limit values]

(1) If the measurement is reported as less than the limit of quantification

The value obtained by adding the following processing to the limit of quantification value is used as an alternative value for tabulation.

1) After checking the number of significant figures of the applicable item, 1 should be subtracted from the significant figure of the lowest reported quantification limit value.
2) It should then be expanded by one digit to a smaller number and 9 is set.

Example) Report: less than 3 Effective number of the measuring facility: up to ones digit

→ Tabulation handling: 2.9

Report: less than 500 Effective number of the measuring facility: up to tens digit

→ Tabulation handling: 499

(2) When the measured value is reported as not more than the limit of quantification or not less than the upper limit of quantification, the limit of quantitation itself should be used as a substitute value for tabulation.

Example) Not more than the limit of quantification

Report: 10 or less→ Tabulation handling: 10 Not less than the limit of quantification

Report: ≥20 → Tabulation handling: 20

(3) When the measured value used in the calculation is less than or not more than the quantification limit and the test result is reported as "Unable to be calculated" (Urinary albumin/creatinine ratio, urinary protein/creatinine ratio), the measured value used in the calculation is added with the above processing as an alternative value, calculation is performed using the following calculation formula, and the calculation result is used for tabulation.

[Arithmetic expression]

- Urine albumin/creatinine ratio = 100 × Urine albumin/urine creatinine
- Urine protein/creatinine ratio = 1000 × Urine protein assay (concentration)/Urine creatinine

7.6 Handling of PK-related data

Blood sampling days for plasma drug concentration measurements should be set as described in "Table 9.1-1 Permitted ranges for study visits" in the study protocol When it is necessary to examine the handling of data, such as when the day of blood sampling is outside the permitted range, when there is a deviation from the study protocol, or when the plasma collection procedure is not observed, the sponsor should decide whether to collect and analyze drug concentration data after the case review meeting.

8. Statistical Method

Data for up to Week 24 of the treatment period phase 1 will be fixed when all subjects have completed treatment period Phase 1. Statistical analysis will be conducted for the treatment period phase 1 fixed data.

8.1 Basic Matters

8.1.1 Level of significance and confidence coefficient

When implementing tests, level of significance should be set at 2-sided 5%. Confidence interval will be 2-sided with a confidence coefficient of 95%.

8.1.2 Descriptive statistics to calculate

Types of continuous variables to be calculated for each descriptive statistics item are provided below.
Number of subjects, mean, standard deviation (SD), median, minimum, maximum, and 2-sided 95% CI of the mean

8.1.3 Number of digits displayed

The number of digits to be displayed in the analysis results will be as follows.

Numeric content	Number of display digits
p value	3 decimal places, however, when it is less than 0.001, it will be described as "< 0.001".
Proportion (percentage)	Integer part + 1 decimal places
Rate of change	Integer part + 1 decimal places
Descriptive statistics (minimum and maximum)	Same as the number of digits as original variable
Descriptive statistics (mean, SD, median)	Number of digits of the original variable + 1 digit
Hb increase rate	Integer part + 4 decimal places
QOL (EQ-5D-5L) index value	Integer part + 3 decimal places

Hepcidin will be measured in units of pg/mL; however, the unit used for tabulation should be ng/mL, and the number of displayed digits should be two decimal places.

8.2 Breakdown of subjects

8.2.1 Disposition

For subjects enrolled in the treatment period, the breakdown of each analysis set in each treatment group should be provided. The breakdown of patient cohort will also be provided.

Item: Number of subjects enrolled in treatment period, FAS subject number and its proportion, FAS exclusion subject number and its proportion, PPS subject number and its proportion, PPS exclusion subject number and its proportion, safety analysis set subject number and its proportion, safety analysis set exclusion subject number and its proportion, drug concentration analysis sets and its proportion, drug concentration analysis sets exclusion subject number and its proportion

8.2.2 Subjects who discontinued or interrupted their treatment

For subjects enrolled in the treatment period, the number and proportion of discontinued subjects should be calculated in each treatment group and by reasons for discontinuation.

Item: Number and proportion of discontinued subjects by treatment group and the number and proportion of reasons for discontinuation for subjects enrolled in treatment period,

For subjects enrolled in the treatment period, the number of cases of drug interruptions should be tabulated by treatment group and the number and proportion of reasons for interruption should be tabulated. The denominator of the proportion should be the sum of the number of interruption cases. If there are multiple reasons for a single interruption, they should be counted for each reason and stated as the number of interruption cases.

Item: Number and proportion of cases of drug interruptions in subjects enrolled in the treatment period and the number and proportion of reasons for drug interruptions

8.3 Demographic and other baseline characteristics

For each analysis sets (except PK analysis set), the major demographic and other baseline characteristics should be summarized by treatment group. Frequency and proportion will be provided for discrete variables and descriptive statistics for continuous variables (no calculation of 95% CI of the mean). If the PPS or safety analysis set is the

same as the FAS, the results for the analysis sets will not be presented. The data should also be summarized in the FAS by patient cohort.

Table 8.3 Characteristics of demographic and other baseline characteristics

Category	Item	Type of variables
Subject background	Sex (male, female)	Dichotomous
	Age (years) as of informed consent	Continuous
	2 categories: <65, ≥65	Dichotomous
	2 categories: <75, ≥75	Dichotomous
	Duration of nephrogenic anemia (years)	Continuous
	3 categories: <1, 1 to <5, ≥5	Ordinal
	Height (cm)	Continuous
	Body weight (kg)	Continuous
	BMI (kg/m²)	Continuous
	2 categories: <25, ≥25	Dichotomous
	Race 3 categories: not Hispanic or Latino, Hispanic or Latino, Unknown	Polytomous
	Ethnicity 3 categories: Asian (Japanese), Asian (other), other	Polytomous
Smoking status	Presence or absence of smoking status 3 categories: never smoked, ex-smoker, current smoker	Polytomous
Underlying cause of CKD	Underlying cause 8 categories: diabetes mellitus, hypertension, autoimmune/glomerulonephritis/vasculitis, interstitial nephritis/pyelonephritis, cystic/hereditary/congenital disease, neoplasm/tumor, unknown, other	Polytomous
Complication	Presence or absence of complications on the first day of the treatment period	Dichotomous
	Presence or absence of hypertension	Dichotomous
	Presence or absence of diabetes mellitus	Dichotomous
	Presence or absence of dyslipidemia	Dichotomous

Previous ESA formulation (Conversion cohort only)	Types of previous ESA formulation 4 categories: epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol, other.	Polytomous
	Frequency of administration by type of previous ESA formulation 7 categories: once a week, twice a week, three times per week, every 2 weeks, every 3 weeks, every 4 weeks, other	Polytomous
	Weekly dose (IU) of epoetin alfa or epoetin beta	Continuous
	Weekly dose of darbepoetin alfa (μg)	Continuous
	Weekly dose of epoetin beta pegol (μg)	Continuous
Evaluation data	Hb value (g/dL) on the first day of the treatment period	Continuous
	3 categories: <9, 9 to <11, ≥11	Ordinal
	eGFR on the first day of the treatment period (mL/min/1.73 m^2)	Continuous
	4 categories: <15, 15 to <30, 30 to <60, ≥60	Ordinal
	Liver function test (U/L) on the first day of the treatment period 3 categories: AST and ALT are both not more than the upper limit of normal, either is more than the upper limit of normal and both are not more than 2 times the upper limit of normal, either is more than 2 times the upper limit of normal	Trichotomous
	CRP (mg/dL) on the first day of the treatment period	Continuous
	Serum ferritin (ng/mL) on the first day of the treatment period	Continuous
	2 categories: <100, ≥100	Dichotomous
	TSAT (%) on the first day of the treatment period	Continuous
	2 categories: <20, ≥20	Dichotomous
	With or without iron supplements on the first day of the treatment period	Dichotomous
	2 categories: oral, intravenous	Dichotomous
	With or without iron-containing phosphate binders on the first day of the treatment period	Dichotomous

8.4 Study drug administration/treatment period and study drug administration/compliance status

For FAS and safety analysis set, the descriptive statistics of the study drug administration/compliance rate (no calculation of 95% CI of the mean) will be calculated by treatment group to provide the number and rate of subjects with study drug compliance rate of ≥80% and < 80% . Analysis will be performed by patient cohort in the FAS.

For FAS and safety analysis set, the descriptive statistics of the study drug administration/treatment period (no calculation of 95% CI of the mean) will be calculated by treatment group. Analysis will be performed by patient cohort in the FAS.

For FAS and safety analysis set, the descriptive statistics of the cumulative dosage of study drug (no calculation of 95% CI of the mean) will be calculated by treatment group.

8.5 Efficacy analysis

As a general rule, efficacy analysis will be performed on the FAS. When necessary, descriptive statistics for continuous variables should be calculated and frequency and proportion will be calculated for discrete variables. Unless otherwise specified, a similar analysis will be conducted for patient cohort. No data from the day after the rescue therapy implementation date should be included in the efficacy analysis.

8.5.1 Analysis of primary endpoint

Descriptive statistics will be calculated for the primary efficacy endpoint of the mean Hb level at Week 20 and 24 of the treatment period. Mean Hb at each evaluation time point will be modeled using the MMRM based on the following model. The mean Hb level at Week 20 and Week 24 of the treatment period should be calculated by treatment group; least squares mean (LSMean) for the mean Hb level at Week 20 and Week 24 of the treatment period , its standard errors, and 2-sided 95% CI should be calculated by treatment group; and point estimate, its standard errors, and 2-sided 95% CI of the difference of LSMean between the groups (MT-6548 − darbepoetin) should be calculated. When the lower limit of 95% CI of the difference between the groups is not more than −0.75 g/dL, MT-6548 will be considered noninferior to darbepoetin alfa (recombinant). The robustness of the results will be examined by the same analysis for PPS. No analysis will be performed for patient cohorts.

[MMRM Model]

- Covariate: response variable value of the first day of the treatment period

- Fixed effects: Treatment group, evaluation time point, patient cohort (Correction or Conversion cohort), interactions of evaluation time point × treatment group, interactions of patient cohort (Correction or Conversion cohort) in evaluation time point
- Degrees of freedom adjustment: Kenward-Roger method
- Covariance matrix within subject variance for each subject: unstructured (type = UN; unstructured)
  When it was not converged using unstructure as a covariance matrix within subject variance, the setting of the covariance matrix within subject variance will be changed in the following order, and the analysis will be carried out using the covariance matrix within subject variance converged first.
  Heterogeneous Toeplitz (TOEPH) → Heterogeneous AR (1) (ARH [1]) → Heterogeneous CS (CSH) → Toeplitz (TOEP) → First-order autoregressive (AR [1]) → Compound symmetry (CS)
- Random effects: subjects

- Sample SAS code

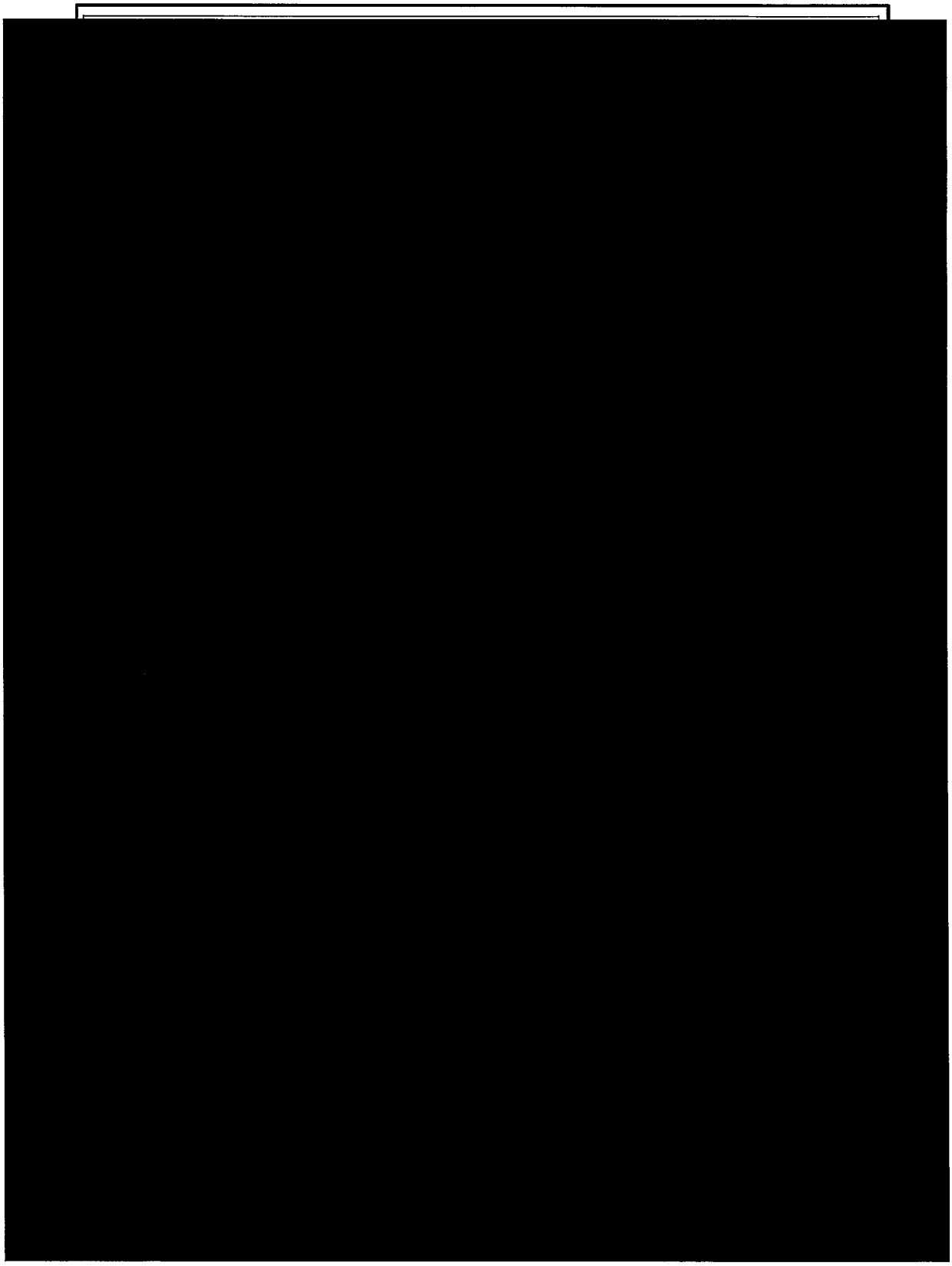
The non-inferiority of MT-6548 to darbepoetin should be assessed after confirming that the mean Hb and its 95% CI of MT-6548 cohort at Weeks 20 and 24 of the treatment period are included within the target range (≥11.0 g/dL and <13.0 g/dL) based on the MMRM model.

Sensitivity analysis should be evaluated using following analysis methods for FAS.

- The defect mechanism of the missing not at random is be assumed, and the tipping point analysis will be performed after 1000 times of multiple imputation using the fully conditional specification regression method. For the data with multiple imputation, a similar analysis should be performed using the same MMRM model as that used for the primary efficacy endpoint, mean Hb at Week 20 and Week 24 of the treatment period. When non-inferiority is not established in the results of the tipping point analysis, LSMean, its standard errors, and 2-sided 95% CI of the mean Hb of Week 20 and Week 24 of the treatment period should be provided by

treatment group. Furthermore, point estimate, its standard errors, and 2-sided 95% CI should be provided for LSMean of between-group differences (MT-6548 – darbepoetin).

- **Sample SAS code**



- Using analysis of covariance (ANCOVA) with the Hb value on the first day of the treatment period as a covariate, the LSMean, its standard errors, and 2-sided 95% of mean Hb at Week 20 and Week 24 should be provided by treatment group. Furthermore, point estimate, its standard errors, and 2-sided 95% CI should be provided for the between-group differences (MT-6548 – darbepoetin) of LSMean. If data from Week 20 and Week 24 of the treatment period are missing, data should be imputed by the methods described in "7.4 Imputation of missing values".

8.5.2 Analysis of secondary endpoints

(1) Hb values at each evaluation time point in the treatment period

1) Hb values at each evaluation time point in the treatment period

Hb value and change of Hb from the first day of the treatment period at each evaluation time point of the treatment period will be obtained, and its descriptive statistics should be calculated for each treatment group. Before and after comparison will be conducted for changes of Hb from the first day of the treatment period to each evaluation time using the paired t-test.

Group comparison will be conducted using an MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance) similar to the analysis of primary endpoint. LSMean, its standard errors, and 2-sided 95% CI will be calculated for Hb value at each evaluation time point of the treatment period, and the point estimate, its standard errors, 2-sided 95% CI, and p-value will be calculated for the group difference (MT-6548 – darbepoetin) of the LSMean by treatment group.

A group comparison will be conducted for the change from the first day of the treatment period using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean of the change from the first day of the treatment period will be calculated at each evaluation time point of the treatment period, and point estimate, its standard errors, 2-sided 95% CI, and p-value will be calculated for the between-group difference of the LSMean by treatment group.

The time course diagram will be prepared for mean Hb values in each evaluation time point in the treatment period by treatment group. 95% CI of the mean will be represented by an error bar.

The Conversion (Hb value <11.0 g/dL) cohort should be analyzed only in the MT-6548 cohort. No statistical test will be conducted for group differences and the difference between baseline and each evaluation time point in the treatment period for the darbepoetin alfa group in the Conversion cohort and Conversion (Hb value ≥ 11.0 g/dL) cohort.

2) Analysis of timing of administration of MT-6548 tablets (before meal, after meal, other)

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted by the timing of administration of MT-6548 tablets (before meal, after meal, other). However, this

analysis is only for the MT-6548 group; neither tabulation in the darbepoetin group nor comparison with the darbepoetin group is performed. No analysis will be performed for patient cohorts.

3) Analysis by previous ESA formulation type

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted by the type of previous ESA formulation (epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol). Conversion, Conversion (Hb value ≥11.0 g/dL), and Conversion (Hb value <11.0 g/dL) cohorts should be analyzed, and the data should be summarized in the MT-6548 group only. The time course diagram of the means should be prepared separately by treatment group.

4) Analysis by dose of previous ESA formulation types

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted for weekly dose (darbepoetin alfa, epoetin beta pegol: ≥15 μg and <15 μg, 2 classifications) of previous ESA formulation by type (epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol). The number of patients classified by dose was set to be almost equal.

Conversion, Conversion (Hb value ≥11.0 g/dL), and Conversion (Hb value <11.0 g/dL) cohorts should be analyzed, and the data should be summarized in the MT-6548 group only. The time course diagram of the means should be prepared separately by treatment group.

5) Analysis of Hb value on the first day of the treatment period

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted for the Hb value on the first day of the treatment period (divided the number of subjects into 3 categories at tertiles). The Conversion (Hb value <11.0 g/dL) cohort should be summarized in the MT-6548 group only. Time course diagram for mean and 95% CI should be prepared separately by treatment group. No statistical test will be conducted for group differences and the difference between baseline and each evaluation time point in the treatment period for the darbepoetin alfa group in the Conversion cohort and Conversion (Hb value ≥ 11.0 g/dL) cohort.

6) MT-6548 group only: analysis with or without iron supplements and iron-containing phosphate binders

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted for subjects continuously using iron supplements or iron-containing phosphate binders and subjects never using iron supplements and iron-containing phosphate binders during the treatment period. No analysis using the MMRM model will be conducted for patient cohorts.

7) MT-6548 group only: analysis by iron supplements and iron-containing phosphate binders formulations

An analysis similar to "1) Treatment period Hb at each evaluation time point in the treatment period" should be conducted for subjects using iron supplements or iron-containing phosphate binders continuously during the treatment period, except for the analysis using the MMRM model. No analysis will be performed for patient cohorts.

8) Analysis of Hb value at Week 24 and CRP values on the first day of the treatment period

For MT-6548 group only, a scatter plot chart should be provided after linear regression with the following variables. No analysis will be performed for patient cohorts.

x: Logarithmic CRP value on the first day of the treatment period

y: Hb value at Week 24 of the treatment period

(2) Proportion of subjects with mean Hb values within the target range (≥11.0 to <13.0 g/dL), <11.0 g/dL, and ≥13.0 g/dL at each evaluation time point in the treatment period

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects with Hb values within the target range (11.0 g/dL to <13.0 g/dL, within), <11.0 g/dL (below), and ≥13.0 g/dL (above) at each time point of the treatment period should be provided by treatment group. McNemar tests should be used for before and after comparison (ratio of subjects within the target range and out of target range) on the first day and each evaluation time point of the treatment period.

Point estimate, its 95% CI (exact method), and p-value (Fisher's exact test) of subject proportions should be calculated for the between-group difference (MT-6548 − darbepoetin) of Hb values in each category (within the target range [11.0 g/dL to <13.0 g/dL]), <11.0 g/dL or ≥13.0 g/dL) at each evaluation time point of the treatment period.

The proportion of subjects in each Hb category (within the target range [11.0 g/dL to <13.0 g/dL], <11.0 g/dL or ≥13.0 g/dL) at each evaluation time point of the treatment period should be provided as a stacked bar graph assuming that the number subjects of each treatment group at the evaluation time point is 100% . Stacked bar charts should be generated separately for each treatment group. The Conversion (Hb value <11.0 g/dL) cohort should be analyzed only in the MT-6548 cohort. No statistical test will be conducted for the group difference and the difference between baseline and each evaluation time point in the treatment period for the darbepoetin alfa group in the Conversion cohort and Conversion (Hb value ≥11.0 g/dL) cohort.

(3) Number of days from the first day of the treatment period required to reach the target Hb range (≥11.0 g/dL to <13.0 g/dL)

Descriptive statistics should be calculated for number of days required from the first day to reach target Hb range (11.0 g/dL to <13.0 g/dL) of the treatment period. The number of days should be calculated as the first evaluation date reached target Hb range (11.0 g/dL to <13.0 g/dL) − first date of the treatment period + 1. If target Hb range (11.0 g/dL to <13.0 g/dL) is not reached, the final date of evaluations − first date of the treatment period + 1 should be assumed.

Kaplan-Meier plots for the number of days required from the first day to reach target Hb range (11.0 g/dL to <13.0 g/dL) of the treatment period should be provided by treatment group.
No subjects with an Hb value of ≥11.0 g/dL on the first day of the treatment period will be included in the calculation.
Only the Correction and Conversion (Hb value <11.0 g/dL) cohorts will be analyzed. The Conversion (Hb value < 11.0 g/dL) cohort will be tabulated in the MT-6548 group only.

(4) Hb increase rate

Descriptive statistics should be calculated for the Hb increase rate (g/dL/week) by treatment group. Between-group comparisons by analysis of covariance (ANCOVA) should be performed using Hb on the first day of the treatment period as a covariate. LSMean, its standard errors, and 2-sided 95% CI of Hb increase rate (g/dL/week) should be calculated by treatment group. The point estimate of the between-group difference (MT-6548 − darbepoetin) of LSMean, its standard errors, 2-sided 95% CI, and p-value should be calculated.
The Hb increase rate should be analyzed by 2 methods defined in the "4.10 Hb increase rate".
Only the Correction and Conversion (Hb value <11.0 g/dL) cohorts will be analyzed. The Conversion (Hb value < 11.0 g/dL) cohort will be tabulated in the MT-6548 group only.

8.5.3 Analysis of other endpoints

(1) Changes in mean Hb values from the first day of the treatment period at Weeks 20 and 24 of the treatment period

Descriptive statistics for change from Hb on the first day of the treatment period to mean Hb at Week 20 and Week 24 in the treatment period should be calculated by treatment group. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.
A group comparison should be conducted for the change from the first day of the treatment period using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). LSMean, its standard errors, and 2-sided 95% CI for change from Hb on the first day of the treatment period to mean Hb at Week 20 and Week 24 in the treatment period should be calculated by treatment group. The point estimate, its standard errors, 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin) of LSMean should be calculated.
Only the Correction and Conversion (Hb value <11.0 g/dL) cohorts will be analyzed. The Conversion (Hb value <11.0 g/dL) cohort should be summarized in the MT-6548 group only.

(2) Ratio of subjects with an increase of ≥1.0 g/dL of mean Hb values from the first day to each time point of the treatment period The number and proportion of subjects and 95% CI (Clopper-Pearson [exact] method) for the proportion of subjects with an Hb increase of ≥1.0 g/dL from the first day to each evaluation time point of the treatment period. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects whose Hb level increased

by ≥ 1.0 g/dL at each evaluation time point from the first day of the treatment period. Only Correction and Conversion (Hb value <11.0 g/dL) cohorts will be analyzed. The Conversion (Hb value <11.0 g/dL) cohort will be calculated in the MT-6548 group only.

(3) Number of days to maintain the target Hb values

The number of maintenance days should be calculated from reaching to leaving the target Hb range for each subject. The total number of maintenance days should be calculated for each subject, and the descriptive statistics should be calculated. Only the MT-6548 group is analyzed. However, if treatment period is completed in 24 weeks, the maintenance days should be until Week 24 of the treatment period.

No analysis will be performed for patient cohorts.

(4) Proportion of subjects receiving rescue therapy with ESA formulations, red blood cell transfusion, or phlebotomy

The number and proportion of subjects and the 95% confidence interval (Clopper-Pearson [Exact] method) for the proportion of subjects receiving rescue therapy with an ESA preparation should be provided by treatment group, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period.

The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects receiving rescue therapy.

The analyses same to the above subjects receiving rescue therapy with ESA formulation should be performed for subjects receiving rescue therapy with RBC transfusion or receiving phlebotomy.

(5) Study drug dosage

1) Study drug dosage

Descriptive statistics of the average daily dose of MT-6548 tablets and mean weekly dose of darbepoetin alfa injection should be calculated, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period. The time course diagram for mean daily dose of MT-6548 tablets and mean weekly dose of darbepoetin alfa injection should be separately prepared by treatment group. 95% CI of the mean will be represented by an error bar. Each period between scheduled study visits is defined as the period between the scheduled visit and the day before the next scheduled visit.

2) Distribution of MT-6548 tablets and darbepoetin alfa injection

The number and proportion of subjects and the 95% CI (Clopper-Pearson [Exact] method) for the proportion per daily dose of MT-6548 tablets and per weekly dose of darbepoetin alfa during the treatment period should be provided by treatment group.

The proportion of subjects receiving each dose of MT-6548 tablets and darbepoetin alfa injection at each evaluation time point of the treatment period should be provided as a stacked bar graph with the number of subjects in each treatment group as 100%. Stacked bar charts should be generated separately for each treatment group.
If no prescription is available on the day of each evaluation timepoint of the treatment period, the dose should be based on the immediately before prescription.

3) Analysis of timing of administration of MT-6548 tablets (before meal, after meal, other)
An analysis similar to "1) Study drug dosage" should be conducted according to the timing of administration of MT-6548 tablets (before meal, after meal, other). Only the MT-6548 group is analyzed. No analysis will be performed for patient cohorts.

4) Analysis by previous ESA formulation type
An analysis similar to "1) Study drug dosage" should be conducted by the type of previous ESA formulation (epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol).
Conversion, Conversion (Hb value ≥11.0 g/dL), and Conversion (Hb value <11.0 g/dL) cohorts should be analyzed in the MT-6548 group only.

5) Analysis by dose of previous ESA formulation types
An analysis similar to "1) Study drug dosage" should be conducted for weekly dose (darbepoetin alfa, epoetin beta pegol: ≥15 μg, <15 μg) of previous ESA formulation by type (darbepoetin alfa, epoetin beta pegol). The number of patients classified by dose was set to be almost equal.
Conversion, Conversion (Hb value ≥11.0 g/dL), and Conversion (Hb value <11.0 g/dL) cohorts should be analyzed in the MT-6548 group only.

6) Analysis of Hb value on the first day of the treatment period
An analysis similar to "1) Study drug dosage" should be conducted for the Hb value on the first day of the treatment period (divided the number of subjects into 3 categories at tertiles).

7) MT-6548 group only: analysis with or without iron supplements and iron-containing phosphate binders
An analysis similar to "1) Study drug dosage" should be conducted for subjects continuously using iron supplements or iron-containing phosphate binders and subjects never using iron supplements and iron-containing phosphate binders during the treatment period.

8) MT-6548 group only: analysis by iron supplements and iron-containing phosphate binders formulations
An analysis similar to "1) Study drug dosage" should be conducted for subjects using iron supplements or iron-containing phosphate binders continuously during the treatment period.

9) Analysis of the mean dose of the study drug at Week 20 to Week 24 of the treatment period and CRP values on the first day of the treatment period

For MT-6548 group only, a scatter plot chart should be provided after linear regression with the following variables.

x: Logarithmic CRP value on the first day of the treatment period

y: Study drug average dosage at Week 20 to Week 24 of the treatment period

(6) Total number of dosage adjustments

The number and proportion of subjects and the 95% confidence interval (Clopper-Pearson [Exact] method) for the proportion of subjects receiving dose adjustment should be provided, after the first day of the treatment period, between each scheduled study visit and during the entire treatment period from the first day to Week 24 of the treatment period.

The number and proportion of subjects and the 95% confidence interval (Clopper-Pearson [Exact] method) should be provided for the proportion of subjects defined below in each period between scheduled study visits. If a subject is included in more than one definition, the subject should be counted in each definition.

- ✓ No dose adjustment: No change
- ✓ With dose adjustment: dose adjustment (Dose adjustment), dose increase (Increase), dose decrease (Decrease). drug interruption (Interrupt)

Dose adjustment (Dose adjustment) should include the number of times of increase, decrease, and interruption, and should not count the increase when it is resumed after interruption. Only the MT-6548 group will be tabulated.

(7) Iron supplement dosage

The following should be provided according to the 3 categories of oral iron supplement, intravenous iron supplement, and iron supplement (any route).

Descriptive statistics of the mean dose of iron supplement per month for each treatment group should be calculated for the screening period, and after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period.

Descriptive statistics of the change in the mean dose of iron supplement per month from the baseline (mean dose of iron during the screening period) should be calculated, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period. Before and after comparison should be conducted for changes from baseline using the paired t-test The changes should be compared between groups using the Student-t test. The mean value of the between-group difference (MT-6548 − darbepoetin), its two-sided 95% confidence interval, t-statistic, and p-value should be provided.

The dosage of iron supplement should be calculated using the dose as iron.

If no iron supplement is administered, the dose should be tabulated as 0 mg. Subjects who changed the administration route of an iron supplement during the treatment period and subjects who had never received an iron supplement during the treatment period should be excluded from the tabulation.

(8) Proportion of subjects receiving oral, intravenous, or (any route) administration of iron supplements

The number and proportion of subjects and the 95% confidence interval (Clopper-Pearson [Exact] method) for the proportion of subjects treated with oral, intravenous, or oral iron supplement (any route) should be provided by treatment group for screening period, and after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period. A McNemar tests should be used for before and after comparison between baseline (ratio of subjects receiving iron supplements by the aforementioned route in screening period) and each period between scheduled study visits. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects receiving oral, intravenous, or (any route) iron supplement.

Subjects who have not received an iron supplement are to be subjects who have never received an iron supplement during the relevant period, and subjects who have received an oral, intravenous, or (any route) iron supplement are to be subjects who have received an iron supplement at least once during the relevant period.

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

The number and proportion of subjects and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with serum ferritin values of ≥100 ng/mL or TSAT values of ≥20% should be provided at each evaluation time point of the treatment period for each treatment group. Before and after comparison should be conducted for changes between the first day of the treatment period and each period between scheduled study visits using the McNemar test. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated for the proportion of subjects with serum ferritin ≥100 ng/mL or TSAT ≥20%.

(10) Changes and rate of changes in iron-related indices (serum iron, TIBC, TSAT, and serum ferritin values) and hepcidin from the first day of the treatment period

Changes in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin should be calculated from the first day of the treatment period to each evaluation time point of the treatment period. A paired t-test should be performed for before and after comparison of changes and change rates from the first day of the treatment period. A group comparison should be conducted for the change in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin from the first day of the treatment period to each evaluation time point using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). The LSMean of by treatment group should be calculated, and the point estimate of between-group differences (MT-6548 −

darbepoetin), its standard errors, 2-sided 95% CI, and p-value of LSMean should be provided. Only the serum ferritin value at each evaluation time point of the treatment period should be similarly compared between groups.
The time course diagram of changes in the iron-related measures (serum iron, TIBC, TSAT, and serum ferritin values) and hepcidin from the first day of the treatment period to each evaluation time point should be prepared for each treatment group. The 95% CI of LSMean will be represented by an error bar. For only the ferritin value, a time course diagram should be prepared for mean and 95% CI of ferritin values at each evaluation time point of the treatment period.
The serum ferritin values should be shown as follows.

- ✓ An analysis similar to the above should be conducted for serum ferritin at baseline (divided the number of subjects into 3 categories at tertiles). Time course diagram for mean and 95% CI should be prepared separately by treatment group.
- ✓ The following scatter plot chart should be provided by treatment group. Linear regression should be performed to calculate the p-value and correlation coefficient of the test with zero slope as the null hypothesis.
  x: Serum ferritin at baseline
  y: Serum ferritin at Week 24 of the treatment period

(11) Change in hematocrit, red blood cell count, reticulocyte (count and rate), mean cell volume, mean cell hemoglobin, and EPO (MT-6548 group only) from the first day of the treatment period
Descriptive statistics of hematocrit, red blood cell count, reticulocyte (count and rate), mean cell volume, mean cell hemoglobin, and EPO (MT-6548 group only) at each evaluation time point should be calculated for each dose group. And, the change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each dose group. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.
A group comparison should be conducted for the change in hematocrit, red blood cell count, reticulocyte (count and rate), mean cell volume, mean cell hemoglobin, and EPO (MT-6548 group only) from the first day of the treatment period to each evaluation time point using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). The LSMean of by treatment group should be calculated, and the point estimate of between-group differences (MT-6548 − darbepoetin), its standard errors, 2-sided 95% CI, and p-value of LSMean should be provided. EPO will be analyzed in the MT-6548 group only. Hematocrit, RBC count, and reticulocytes (count and rate) in the Conversion (Hb value < 11.0 g/dL) cohort should be analyzed only in the MT-6548 group. No statistical test will be conducted for hematocrit, red blood cell count, and reticulocytes (count and rate) in the Conversion cohort and Conversion (Hb value ≥ 11.0 g/dL) cohort for group differences and the difference between baseline and each evaluation time point in the treatment period for the darbepoetin alfa group.
A histogram of EPO measurements should be prepared for evaluation time point at Week 24 of the treatment period.

(12) Changes in systolic blood pressure, diastolic blood pressure, and blood glucose from the start of the treatment period, changes and the rate of change in lipid (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides) from the start of the treatment period

Systolic blood pressure, diastolic blood pressure, lipids (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides), and blood glucose should be analyzed in the same manner as hematocrit, red blood cell count, and reticulocyte (count and rate) in the preceding section.

Descriptive statistics for each measurement at the evaluation time point of Week 24 of the treatment period should be calculated by baseline value (divided the number of subjects into 3 categories at tertiles). In addition, the change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each dose group. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period. A group comparison should be conducted for the change from the first day of the treatment period using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). The LSMean of by treatment group should be calculated, and the point estimate of between-group differences (MT-6548 – darbepoetin), its standard errors, 2-sided 95% CI, and p-value of LSMean should be provided.

The descriptive statistics should be similarly calculated for each administration group on the rate of change from the first day of the treatment period at each evaluation time point of the lipid (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides), and a group comparison should be conducted using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance).

No analysis will be performed for patient cohorts.

(13) Change in renal function-related measures (eGFR, serum creatinine, urinary albumin/creatinine ratio) from the first day of the treatment period

Renal function-related measures (eGFR, serum creatinine, urinary albumin/creatinine ratio) should be analyzed in the same way as hematocrit, red blood cell count, and reticulocyte (count and rate) in the previous section.

Descriptive statistics for changes in eGFR and urinary albumin/creatinine ratio from the first day of the treatment period to each evaluation time point should be similarly calculated for each administration group, and a group comparison should be conducted using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance).

The following items should also be calculated.

- The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) for the proportion of subjects with a ≥30% decrease in eGFR from the start of the treatment period during the evaluation time point of Week 24 of the treatment period should be provided for each treatment group.

  The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 – darbepoetin) should be calculated for rate of subjects with a ≥30% decrease in eGFR from the start of the treatment period at the evaluation time point of Week 24 of the treatment period.

- The same analysis as above should be performed for the number of subjects with an eGFR decrease of ≥40% from the start of the treatment period at the evaluation time point of Week 24 of the treatment period.
- The same analysis as above should be conducted for the number of subjects with serum creatinine ≥2-fold from the start of the treatment period at evaluation time point of Week 24 of the treatment period.
- The shift table for the urinary albumin/creatinine ratio (mg/g Cr), which consists of the first day of treatment and Week 24 of the treatment period, should be provided for each treatment group. Classification follows CKD severity classification. (normal, <30; microalbuminuria, ≥30 and <300; macroalbuminuria, ≥300)
  No analysis will be performed for patient cohorts.

(14) QOL indices (EQ-5D-5L, KDQOL)

The score of the QOL index should be calculated and provided by treatment group.

1) EQ-5D-5L

The number, proportion, and their two-sided 95% CI (Clopper-Pearson [Exact] method) of subjects in responses in 5 levels to the 5 questions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) should be provided at each evaluation time point.

For Index value and VAS score, descriptive statistics of measured values and descriptive statistics of changes from the first day of the treatment period should be provided for each treatment group at each evaluation time point. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.

A group comparison should be conducted for the changes in Index value and VAS score from the first day of the treatment period at each evaluation time point using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). The LSMean of by treatment group should be calculated, and the point estimate of between-group differences (MT-6548 − darbepoetin), its standard errors, 2-sided 95% CI, and p-value of LSMean should be provided.

The correlations of Hb value and Index Value, and Hb value and VAS score at all evaluation time points should be evaluated using linear regression and Emax model. For linear regression, the estimated items analyzed by the following model (Refer to "linear regression model") should be output, and the p-value of the test with 0 slope as the null hypothesis should be calculated. Scatter plots and regression lines should be prepared separately for each treatment group. On the Emax model, estimated items (Refer to "Emax model") analyzed by the following model should be output. Scatter plots and regression curves should be prepared separately for each treatment group. No analysis will be performed for patient cohorts.

The correlation between the change in Hb from the first day of the treatment period and the change in Index Value from the first day of the treatment period and the correlation between the change in Hb from the first day of the treatment period and the change in VAS score from the first day of the treatment period should be analyzed in linear regression in the same way as the correlation between Hb value and Index Value and between Hb value and VAS score, respectively. Only the Correction and Conversion (Hb value <11.0 g/dL) cohorts will be analyzed.

[Linear regression model]

- regression equation $Y = aX + b$
- X: Hb value, or change in Hb value from the first day of the treatment period
- Y: Index Value, or VAS score, or change from the first day of the treatment period on the left
- Estimated items (output item): a: slope of the regression line and its standard error, b: intercept of the regression line and its standard error, r: correlation coefficient

[Emax model]

- Model 4-parameter logistic model
- X: Hb value
- Y: Index Value or VAS score
- Estimated item (output item): EC_{50} with its standard errors and 2-sided 95% CI, Emax with its standard errors and 2-sided 95% CI, min with its standard errors and 2-sided 95% CI, slope with its standard errors and 2-sided 95% CI, R-Square (contribution ratio).

2) KDQOL

Descriptive statistics of KDQOL should be calculated by subscale (Section 4.13 [Table 4.13.2] "subscale") for measured values and changes from the first day of the treatment period at each evaluation time point by treatment group. Scores by subscale should be calculated using a scoring method (Section 4.13). Dialysis staff assessment and patient satisfaction, subscales for dialysis patients, will not be calculated.

A paired t-test should be performed for before and after comparison of changes in KDQOL from the first day of the treatment period.

A group comparison should be conducted for the change in KNDQOL from the first day of the treatment period at each evaluation time point using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). The LSMean of by treatment group should be calculated, and the point estimate of between-group differences (MT-6548 − darbepoetin), its standard errors, 2-sided 95% CI, and p-value of LSMean should be provided.

8.5.4 Statistical issues

8.5.4.1 Adjustment for covariates

In the analysis of efficacy, in order to consider the effect of the measurement value of the first day of the treatment period on the change of each measurement in the group comparison, the analysis using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance) should be conducted using the measurement value of the first day of the treatment period as a covariate in the general analysis including the analysis

of the primary endpoint. A sensitivity analysis of the primary endpoint should be similarly conducted using ANCOVA with the measurement value of the first day of the treatment period as a covariate. In addition, the group comparison of Hb increase rate should be similarly conducted using ANCOVA with the measured value of the first day of the treatment period as a covariate.

8.5.4.2 Use of the "Subpopulation for efficacy evaluation" of patients

The primary analysis for the primary endpoint should also be performed for the PPS to examine the robustness of the results.

8.5.4.3 Handling of dropout or missing data

Provided in "7. Data handling".

8.5.4.4 Interim analysis and data monitoring

This statistical analysis plan regulates statistical analysis plan of fixed data in the treatment period 1. In the final fixed data, a separate statistical analysis plan should be prepared to perform statistical analysis.

8.5.4.5 Multicenter trial

For FAS, the following analysis should be conducted for each following endpoint for each facilities. Descriptive statistics of Hb values should be calculated at Week 24 of the treatment period (imputed by the LOCF method) for each treatment group.
Descriptive statistics of mean dose of the study drug should be calculated for the Week 20 to Week 24 of the treatment period in the treatment group.
No analysis will be performed for patient cohorts.

8.5.4.6 Subgroup analyses

The following analyses should be conducted for subpopulations based on the stratification factor for each endpoint in the Table below (Table 8.5.4.6) in the FAS. Unless otherwise specified, no analysis will be performed for patient cohorts.
On the Hb value at Week 24 of the treatment period, LSMean, standard error, and 2-sided 95% CI should be calculated for each treatment group using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance). The point estimate, its standard errors, 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin) of LSMean should be calculated.

Descriptive statistics of mean dose of the study drug should be calculated for the Week 20 to Week 24 of the treatment period in the treatment group.

With respect to the responder rate at Week 24 of the treatment period (proportion of subjects with increased Hb level by ≥1.0 g/dL from the first day of the treatment period), the number of responders, proportion, and 95% CI (Clopper-Pearson [Exact] method) for the proportion should be provided for each treatment group. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for between-group difference (MT-6548 − darbepoetin) should be calculated. Only the Correction and Conversion (Hb value <11.0 g/dL) cohorts should be analyzed.

With respect to the achievement rate of target Hb at Week 24 of the treatment period, the number, rate and 95% CI (Clopper-Pearson [Exact)] method) for the rate of subjects with Hb values within the target range (11.0 g/dL to <13.0 g/dL) should be provided for each treatment group. The estimate, its 95% CI (exact method), and p-value (Fisher's exact test) for group difference (MT-6548 − darbepoetin) should be calculated.

Table 8.5.4.6 Subgroup analyses in efficacy

Endpoints	Stratification factor	Stratified category
1. Hb values at Week 24 of the treatment period 2. Study drug average dosage at Week 20 to Week 24 of the treatment period 3. Responder rates at Week 24 of the treatment period 4. Target Hb achievement rate at Week 24 of the treatment period	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65
		<75, ≥75
	Body weight (kg) on the first day of the treatment period	<60, ≥60
	Body mass index (kg/m^2) on the first day of the treatment period	<25, ≥25
	Underlying cause of CKD	Diabetes, hypertension, autoimmune/glomerulonephritis/vasculitis, interstitial nephritis/pyelonephritis, cystic/hereditary/congenital disease, neoplasm/tumor
	Duration of nephrogenic anemia (years)	<1, 1 to <5, ≥5
	Complication	hypertension, diabetes, dyslipidemia
	Hb value (g/dL) on the first day of the treatment period	<9, 9 to <11, ≥11
	eGFR on the first day of the treatment period (mL/min/1.73 m^2)	<15, 15 to <30, 30 to <60, ≥60
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both below the upper limit of normal, either above the upper limit of normal and both ≤ 2 times the upper limit of normal, either > 2 times the upper limit of normal
	CRP (mg/dL) on the first day of the treatment period	<0.31, ≥0.31
	Serum ferritin (ng/dL) on the first day of the treatment period	Divide the number of subjects into three categories based on the tertile
	TSAT (%) on the first day of the treatment period	Divide the number of subjects into three categories based on the tertile
	Smoking status	3 categories: never smoked, ex-smoker, current smoker
	Administration of oral iron on the first day of the treatment period	Yes or No
	Treatment with oral iron supplement at Week 24 of	Yes or No

	the treatment period	
	Iron-containing phosphate binders on the first day of the treatment period	Yes or No
	Iron-containing phosphate binders at Week 24 of the treatment period	Yes or No
	Previous ESA formulation (Conversion cohort only)	Epoetin Alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol, other
	Epoetin alfa or epoetin beta weekly dose (IU) (Conversion cohort only)	Divide the number of subjects into three categories based on the tertile
	Darbepoetin alfa weekly dose (μg) (Conversion cohort only)	Divide the number of subjects into three categories based on the tertile
	Epoetin beta pegol dose (μg) (Conversion cohort only)	Divide the number of subjects into three categories based on the tertile
	CYP2B6 inducer combination *	Yes or No

* List of CYP2B6 inducers obtained from The Metabolism and Transport Drug Interaction Database (DIDB ®).

8.5.4.7 Multiple comparison and multiplicity

In this study, separately analyzing treatment period 1 fixed data and final fixed data does not pose the problem of the multiplicity because mean Hb value at Week 20 and Week 24 of the treatment period is the primary endpoint. The problem of the multiple comparison does not arise, since 2-group comparison should be conducted in the primary analysis of the primary efficacy endpoint and all analyses of the secondary endpoints. In addition, since the analyses of secondary endpoints and other endpoints should be conducted in the exploratory standpoint, no adjustment of the multiplicity between endpoints and between evaluation time points should be conducted.

8.5.4.8 A study with active control intended to demonstrate equivalence

This is a non-inferiority study with an active control.

8.6 Safety analysis

The safety analysis set should be analyzed for each treatment group. When necessary, frequency and proportion should be calculated for discrete variables and descriptive statistics for continuous variables. Unless otherwise specified, no analysis will be performed for patient cohorts.

8.6.1 Adverse events and adverse drug reactions

8.6.1.1 Summary of adverse events and adverse drug reactions

The number (number of subjects with adverse events) and proportion of subjects in whom the following adverse events are observed at least once after the administration of the study drug to Week 24 of the treatment period (if discontinued, end of the follow-up period) should be calculated for each treatment group.

- Adverse event
- Adverse drug reaction
- Serious adverse event
- Serious adverse drug reaction
- Adverse event leading to discontinuation
- Adverse events leading to dose reduction or interruption of study drug
- Adverse event leading to death (adverse event of fatal outcome)

8.6.1.2 Individual adverse events

For adverse events, adverse drug reactions, serious adverse events, serious adverse events, non-serious adverse events, adverse events leading to discontinuation, adverse events leading to dose reduction or interruption of study drug, and adverse events leading to death, the number and rate of subjects with each adverse event classified by SOC and PT in MedDRA/J version: 2x.x (hereinafter the same) should be calculated. The SOC will be sorted by order of international consensus, the PT by descending order of the number of subjects with MT-6548 and by descending order of the number of subjects with darbepoetin (PT code ascending when the number is equal).

8.6.1.3 Adverse events by severity

The number of subjects and incidence rate should be calculated for adverse events and adverse drug reactions by severity for the overall and for individual events classified by SOC and PT.

The tabulation method by severity (severe, moderate, mild) is as follows.

(1) When adverse events of different severity occur in the same subject
The most severe adverse event should be counted as 1 subject.

(2) When multiple adverse events with the same degree occur in the same subject
The same severity should be counted as 1 subject.

(3) When multiple same adverse events occur in the same subject
The most severe adverse event should be counted as 1 subject.

8.6.1.4 Adverse events by time of onset

The number and incidence rate of subjects with adverse events and adverse drug reactions should be calculated for adverse event and adverse drug reaction by time of onset (every 12 weeks) for the overall and for individual events classified by SOC and PT. For the calculation of the incidence rate, the number of subjects at each evaluation time point is used as the denominator. (Tabulation unit: from the first day of the treatment period [Day 1] to Day 84, after Day 85)

8.6.1.5 Adverse events by dose immediately before onset

The number and incidence rate to total exposure period of adverse events and adverse drug reactions in overall and individual events classified by SOC and PT should be calculated for each treatment group by dose immediately before onset*. The total exposure period is defined as the total number of days (days) that each dose was administered during the study period.

*The tabulation unit by dose immediately before onset should be as follows:

MT-6548 group: daily dose (tabulation unit: 0 mg, 150 mg, 300 mg, 450 mg, 600 mg)

Darbepoetin group: weekly dosage (tabulation unit: 0 μg, >0 μg to ≤30 μg, >30 μg to ≤60 μg, >60 μg to ≤90 μg, >90 μg to ≤120 μg, >120 μg)

8.6.1.6 Adverse events by cumulative dosage

The number of subjects and incidence rate should be calculated for adverse events and adverse drug reactions by cumulative dosage before onset of AE for the overall events and for individual events classified by SOC and PT. The cumulative dosage will be divided into 4 categories at quartiles (0 to 1/4 of the maximum cumulative dosage, 1/4 to 2/4 of the maximum cumulative dosage, 2/4 to 3/4 of the maximum cumulative dosage, ≥3/4 of the maximum cumulative dosage). In addition, the average number of exposure days per person should be calculated for each category. (Average number of exposure days: in the case of "0–x/4 of the Maximum Cumulative dosage", the number of days until the subject concerned reaches x/4 of the maximum cumulative dosage should be calculated for each subject. In the case of ≥3/4 of the maximum cumulative dosage, the number of days to final administration for each subject and the mean should be calculated.)

8.6.1.7 Adverse events before and after drug interruption

The number of subjects and incidence rate should be calculated for adverse event and adverse drug reaction by before and after drug interruption for the overall and for individual events classified by SOC and PT. It should be classified to 2 categories: 4 weeks before drug interruption and 4 weeks after drug interruption (4 weeks after the start of drug interruption). If a subject had multiple drug interruptions and the adverse event occurred within 4 weeks

after the drug interruption and within 4 weeks before the drug interruption, the subject should be counted as 1 subject for both periods.

Drug interruption period is defined as the period when "Yes" was selected in the question of "Did you choose the dosage according to the dosage adjustment algorithm?" and "0 mg" for the MT-6548 group or "0 μg" for the darbepoetin group was selected in the question of "Whether the dose was changed" in the "Administration status" of the case report form. If "No" is selected in the question of "Did you choose dosage according to dosage adjustment algorithm?", the subject should not be included in the calculation.

8.6.2 Laboratory test values

Descriptive statistics (except 2-sided 95% CI of the mean) should be calculated by treatment group at each evaluation time point for hematology tests, blood biochemistry tests, C-reactive protein, VEGF, dehydroepiandrosterone sulfate (DHEA-S), urine albumin/creatinine ratio, and urine protein/creatinine ratio. Changes from the first day of the treatment period at each evaluation time point should also be summarized. As for qualitative urinalysis, a shift table which consists of frequency tabulation by category at each evaluation time point and the start date of the treatment period and the decision results on the first day of the treatment period and each evaluation time point should be provided.

8.6.3 Resting standard 12-lead ECG

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be calculated at each evaluation time point, and a shift table composed of the decision results on the first day of the treatment period and each evaluation period should be provided.

8.6.4 Body weight

Descriptive statistics (except for two-sided 95% CIs of mean) should be calculated for each treatment group by evaluation time point. Changes from the first day of the treatment period at each evaluation time point should also be summarized.

8.6.5 Vital signs

Descriptive statistics (except for two-sided 95% CIs of mean) should be calculated for each treatment group by evaluation time point for the items of blood pressure and pulse rate. Changes from the first day of the treatment period at each evaluation time point should also be summarized.

8.6.6 Fundoscopy

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal [Presence or absence of retinal hemorrhage, presence or absence of retinal oedema]) should be calculated at each

evaluation time point, and a shift table composed of the decision results (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be provided on the first day of the treatment period and each evaluation time point.

8.6.7 Chest X-ray

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be calculated at each evaluation time point, and a shift table composed of the decision results on the first day of the treatment period and each evaluation period should be provided.

8.6.8 Proportion of subjects with documented Hb values of ≥13.0 g/dL or ≥14.0 g/dL

The number and proportion of subjects with confirmed Hb ≥13.0 g/dL or ≥14.0 g/dL, after the first day of the treatment period, between each scheduled study visit and during the entire treatment period from the first day to Week 24 of the treatment period should be provided for each treatment group. If Hb is >13.0 g/dL and 14.0 g/dL in the same subject, the subject should be counted in both categories.
The similar analysis should be conducted for each patient cohort.

8.6.9 Proportion of subjects with documented Hb values of <9.0 g/dL or <8.0 g/dL.

Subjects with confirmed Hb values <9.0 g/dL or <8.0 g/dL should be analyzed in the same manner as in Section 8.6.8.

8.6.10 Proportion of subjects with a documented Hb increase rate >0.5 g/dL/week

The number and proportion of subjects in whom the Hb increase rate is confirmed to be >0.5 g/dL/week, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period should be provided in each treatment group. The Hb increase rate in this tabulation should be calculated based on the difference in Hb values between the 2 time points measured on the scheduled study visit day in every 4 weeks (first day of the treatment period, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 of the treatment period) and the Hb value measurement interval obtained from the actual study visit date. A similar analysis should be performed for each patient cohort.
In addition, for the Correction cohort and Conversion (Hb <11.0 g/dL) cohort, the number and proportion of subjects in whom the Hb increase rate calculated by the 2 methods defined in "4.10 Hb increase rate" was confirmed to be >0.5 g/dL/week should also be provided for each treatment group. For the Conversion (Hb <11.0 g/dL) cohort, only the MT-6548 group will be tabulated.

8.6.11 Hb level after dose reduction or interruption of the study drug

Descriptive statistics of Hb values at dose reduction/drug interruption and after dose reduction/drug interruption of the study drug should be calculated for each treatment group. In addition, the change of Hb after dose reduction/drug interruption of the study drug should be determined, and descriptive statistics should be calculated for each treatment group. For the Hb value after dose reduction/drug interruption of the study drug, the data of the day closest to 4 weeks (28 days) after the Hb measurement day at dose reduction/drug interruption should be adopted. If no study drug data at the time of dose reduction/drug interruption are available, subjects should be excluded from the Hb value analysis. In addition, the interval (days) from the Hb measurement in dose reduction/drug interruption of the study drug to the Hb measurement after dose reduction/drug interruption should be calculated, and the descriptive statistics should be provided in each treatment group. A similar analysis should be performed for each patient cohort.

8.6.12 Subgroup analyses

In the safety analysis set, the number and incidence ratio of subjects with adverse events and adverse drug reactions should be calculated by treatment group for each subgroup based on the stratification factors for each endpoint in the table below (Tables 8.6.12.1 and 8.6.12.2).

Table 8.6.12.1 Intrinsic subgroup analysis of safety

Endpoints	Stratification factor	Stratified category
Adverse events and adverse drug reactions	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65 <75, ≥75
	Body weight (kg) on the first day of the treatment period	<60, ≥60
	Hb value (g/dL) on the first day of the treatment period	<9, 9 to <11, ≥11
	eGFR on the first day of the treatment period (mL/min/1.73m²)	<15, 15 to <30, 30 to <60, ≥60
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both below the upper limit of normal, either above the upper limit of normal and both ≤ 2 times the upper limit of normal, either > 2 times the upper limit of normal

Table 8.6.12.2 Extrinsic subgroup analysis of safety

Endpoints	Stratification factor	Stratified category
	Timing of taking (MT-6548 group only)	Before meal, after meal, other

Adverse events and adverse drug reactions	Patient cohort	Correction cohort, Conversion cohort, Conversion (Hb value≥11.0 g/dL) cohort, Conversion (Hb value <11.0 g/dL) cohort

8.7 Pharmacokinetics analysis

[redacted]

8. Software to Use

SAS for Windows (Release 9.4) will be used for statistical analysis.

9. Changes in the Statistical Analysis Plan from the Study Protocol

No change from the study protocol.

10. References

[1] : Shinya I, Takeru S, Ataru I, Shinichi N, Takashi F, et al. Developing a Japanese version of the EQ-5D-5L value set. J. Natl. Inst. Public Health 2015.; 64 (1): 47-55.

[2] : Miura Y, Green J, Fukuhara S. KDQOL-SF version 1.3 Japanese manual. iHope International Inc.; 2016. p. 13-16.