For Final Fixed Data Analysis

Statistical Analysis Plan

A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

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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
HD-CKD	Hemodialysis 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	Film-coated tablets containing 150 mg of vadadustat per tablet
Darbepoetin alfa injection	Plastic syringe containing darbepoetin alfa (recombinant) in 1 syringe (0.5 mL)
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 final fixed data (hereinafter, the final fixed data) of "A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan."

2. Study Objectives and Design

2.1 Study objectives

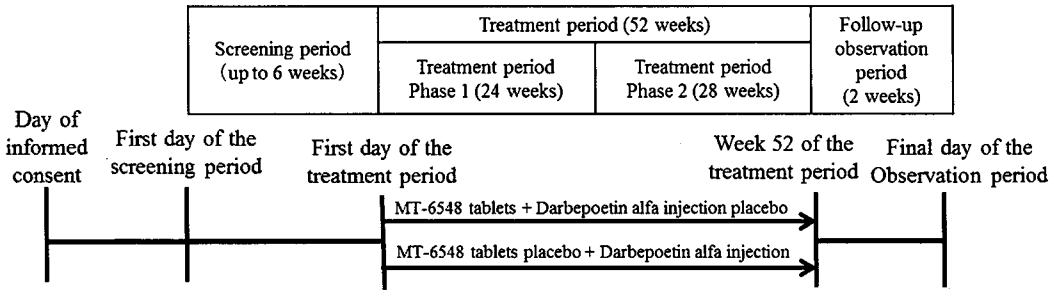
The study evaluates the non-inferiority of MT-6548 in patients with anemia associated with hemodialysis-dependent chronic kidney disease (HD-CKD) who are currently treated with an erythropoiesis-stimulating agent (ESA) using hemoglobin (Hb) levels as a measure and darbepoetin alfa (recombinant) as a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

2.2 Study design

Study phase: Phase III

Study type: Confirmatory study

Multicenter, randomized, double-blind, active-controlled, double-dummy, parallel group comparative study.



2.3 Randomization methods

2.3.1 Blinding methods

The treatment period Phase I in this study should be conducted in a double-blind manner. Blinding of this study should be achieved by not providing information to persons involved in the study as to which study drug is being administered and by using a placebo that is indistinguishable from the active drug. Data up to Week 24 of the treatment period phase 1 should be fixed and the key code should be

opened; however, the blinding of subjects, healthcare providers, and monitoring staff should be maintained until the final data fixation at the end of the study is completed. Details of the procedure of maintaining the blindness should be separately defined before opening of the key code.

The randomization business contract organization should prepare the main part and the sub part of the material list, the main part of the randomization key code table, and the allocation number list and strictly stores and manages the main part of the material list, the randomization key code table, and the allocation number list until the key code is opened so that the key code information does not leak outside. The main part of the material list, randomization key code table, and allocation number list should be opened after all case report forms for the treatment period phase 1 have been completed, data have been fixed, and their handling has been determined.

The randomization business contract organization should submit the sub part of the material list to the study drug QA director of the sponsor for the study drug allocation work after receiving the sending request from the sponsor. The study drug manufacturing management supervisor of the sponsor should prepare the study drug to which the kit code is affixed based on the material list. MT-6548 tablets should be produced so that placebo and active drug cannot be distinguished in appearance. Darbepoetin alfa Injection should be prepared so that the placebo, the active drug, and the content are visually indistinguishable. The study drug QA manager of the sponsor should strictly store and manage the sub part of the material list until the key code is opened so that the key code information does not leak to parties other than those involved in the study drug assignment work.

The randomization service contract organization should prepare emergency keys for emergency response and should provide them to the emergency contact center. The emergency contact center should strictly store and manage emergency keys until the end of the clinical trial so that the key code information does not leak outside. For reporting suspected unexpected serious adverse reactions (SUSAR) of Akebia Therapeutics Inc. which is conducting clinical studies of MT-6548 outside Japan, the randomization service contract organization should prepare key codes for SUSAR open key report of overseas regulatory authorities, and should provide them to the emergency contact center. The emergency contact center should strictly store and manage the key code for the overseas regulatory authority SUSAR open key report until the key code is opened so that the key code information does not leak outside.

The randomization service contract organization should provide key code information to the contract testing laboratory. The contract testing laboratory should use this information to send only specimen from the MT-6548 group to the drug concentration measurement laboratory. The contract testing laboratory should strictly store and manage the key code information until the key code is opened so that the key code information does not leak outside. The drug concentration measurement laboratory should strictly store and manage the plasma drug concentration measurement results until the key code is opened so that the plasma drug concentration measurement results do not leak outside. The results

of plasma drug concentration measurements shall not be disclosed to subjects, study center staff, or monitoring staff until the final data fixation at the end of the study has been completed.
The contract testing laboratory should store and control the measurement result of erythropoietin (hereinafter, EPO) strictly until the key code is opened so that the measurement result of EPO does not leak outside. The results of EPO measurements shall not be disclosed to subjects, study center staff, or monitoring staff until completion of the final data lock at the end of the study. The measurement of EPO in the study centers should be prohibited for blind maintenance during the treatment period.

2.3.2 Randomization and allocation methods

The randomization service contract organization should prepare randomization key code tables in accordance with predefined procedures for creation and storage of randomization key code tables. Subjects who are judged to be eligible for transition to the treatment period will be assigned to treatment groups based on the randomization key code table in the Web registration system, and the assignment number should be notified on the Web registration system. Details of the randomization shall be specified in the enrollment center subject allocation specifications. Subjects should be randomly assigned in a 1:1 ratio to MT-6548 and darbepoetin groups.

Evaluation time point

Item \ Visit	Informed consent	Screening period [a]		Treatment period [b]																		Final day of the follow-up observation [c]
				Treatment period Phase 1											Treatment period Phase 2							
		First day	Visit 2	First day	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	Day of discontinuation	
Visit number	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	FU
Permitted range (days)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7 or +14 [d]	+7
Procedure/evaluation																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X	X	X																		
Allocation				X																		
Patient background and history	X			X																		
Height				X																		
Dry weight, body weight [e]				X						X			X			X				X	X	
Forlic acid and vitamin B_{12} [f]		X																				
Pregnancy test [h]		X											X							X	X	
Hematology tests [f], [g], [i]		X	X [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry test [f], [g], [k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein [f], [g]		X		X									X							X	X	
Iron-related measures [f], [g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepcidin [g]				X	X	X	X			X			X			X				X	X	
EPO [g]				X	X	X	X			X			X			X				X	X	
VEGF [g]				X						X			X			X				X	X	
DHEA-S [g]				X						X			X			X				X	X	
Vital signs [f], [g], [l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Resting standard 12-lead ECG [g], [m]				X									X							X	X	
Fundoscopy [d]		X										X							X		X	
Chest X-ray [d]		X										X							X		X	
Duration of hemodialysis				X									X							X	X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X							X	X	
AE investigation [n]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK testing						X				X			X									
Blood sampling for genetic analysis [o]					Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period																	
Blood sampling for plasma protein binding test [p]		X																				
Product evaluatio/procedure																						
Investigation of concomitant medications/therapies				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MT-6548 tablets [q], [r], [s]				Administered according to the dosage adjustment guidelines																		
Darbepoetin alfa injection [r], [t]				Administered according to the dosage adjustment guidelines																		
Iron supplements		Iron supplements administered to maintain a serum ferritin level of ≥100 ng/mL or a TSAT of ≥20%																				

[a] 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] The scheduled study visit during the treatment period shall be the dialysis day 2 days after the previous dialysis, and if it is difficult, the dialysis day 1 day after the previous dialysis.

[c] Should not be performed if discontinued before the treatment period.

[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 after discontinuation whenever possible if discontinued during the treatment period.

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

[f] Measurements on the day of dialysis should be performed before dialysis during the screening period.

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

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

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

[j] Only Hb values should be measured.

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

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

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

[n] AE investigation should begin after study drug administration.

[o] 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.

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

[q] 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.

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

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

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

2.4 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.

[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 11.0 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 1.73 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 (10.0–12.0 g/dL) and non-inferiority could be established.
The assumed standard deviation was set at 1.73 g/dL based on the upper limit of the two-sided 95% confidence interval of the standard deviation in the MT-6548 300 mg group at Week 6 in study CI-0022.

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 (10.0 to <12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each evaluation time point in the treatment period

3.1.2 Other endpoints

(1) Number of days to maintain target Hb values

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

(3) Study drug dosage

(4) MT-6548 group only: total number of MT-6548 tablet dosage adjustments

(5) Iron supplement dosage

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

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

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

(9) Changes in hematocrit, red blood cell count, reticulocytes (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and erythropoietin from the first day of the treatment period

(10) 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

(11) 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 corpuscular hemoglobin, mean cell 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, uric acid, CPK, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, Na, K, Cl, Ca, P, Mg, bicarbonate, total cholesterol, LDL-C, HDL-C, triglycerides

3) C-reactive protein
4) Vascular endothelial growth factor (hereinafter, VEGF)
5) Dehydroepiandrosterone sulfate (hereinafter, DHEA-S)

(3) Resting standard 12-lead ECG

(4) Dry weight

(5) Body weight

(6) Vital signs

(7) Fundoscopy

(8) Chest X-ray

(9) Proportion of subjects with documented Hb values of ≥12.0 g/dL or ≥13.0 g/dL

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

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

(12) Hb value after dose reduction or interruption of the study drug

(13) Kt/V

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 acquisition [month] < Date of birth [month]) or (Date of consent acquisition [month] = Date of birth [month] and Date of consent acquisition [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 (year) = (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 Period from the first day of hemodialysis

The period from the start of hemodialysis (year) should be the period from the start of hemodialysis (time of first hemodialysis or hemodiafiltration) to the month of consent acquisition and should be the integer part + 1 digit (rounded). The period from the start of hemodialysis should be calculated as follows:

Period from the start of hemodialysis (year) = (Date of consent acquisition [year] − Start of hemodialysis [year]) + (Date of consent acquisition [month] − Start of hemodialysis [month])/12

If the month of the start of hemodialysis is unknown, the month should be calculated as 1.

4.4 BMI

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

Should be rounded and displayed to one decimal place.

4.5 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.

4.6 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) = Day of resumption of study drug administration − First day of study drug interruption

If there are multiple interruptions, the sum of them should be used.
Resumption date of study drug administration: 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 should be administered 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 52 for hematology tests or the day before the day of treatment discontinuation should be used.
First day of study drug interruption: The day of administration when "Daily Dose" = 0 mg or 0 μg is first entered in the CRF.

4.7 Study drug administration/treatment duration

For subjects who completed treatment period:

Study drug administration/treatment 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/treatment duration (days) = Day of discontinuation − First day of the treatment period

4.8 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

4.9 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%.

4.10 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 scheduled 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 14 days

- ✓ 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 hematology 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 period between scheduled study visits

4.11 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.

4.12 Adverse drug reactions

In the MT-6548 group, adverse events for which a causal relationship to MT-6548 tablets is evaluated as "reasonably possible" are defined as adverse drug reactions associated with MT-6548 tablets, and in the darbepoetin group, adverse events for which a causal relationship to darbepoetin alfa injection is evaluated as "reasonably possible" are defined as adverse drug reactions associated with darbepoetin alfa injection.

4.13 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 (Day 1) to Day 14
- ✓ Week 2 of the treatment period to Week 4 of the treatment period: Days 15 to 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 hematology 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).

4.14 Kt/V

Kt/V is defined by the following equation. It should be calculated based on the first day of treatment period, Week 24, Week 52, and the day of discontinuation. All items used for the calculation of Kt/V should be those measured on the same day.

$Kt/V = -\ln(Ct/C0 - 0.008 \times t) + (4 - 3.5 \times Ct/C0) \times (BW0 - BWt)/(BWt)$

t: Dialysis time, C0: BUN concentration before dialysis, Ct: BUN concentration after dialysis, BW0: Body weight before dialysis, BWt: Body weight after dialysis

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

Responses to 5 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 4.15.1).[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 4.15.1 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 4.15.1 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

4.16 QOL (KDQOL) scoring

Step 1 (See Table 4.16.1): The appropriate score is converted from the response choices for each item number in Table 4.16.1 for each subject.

Table 4.16.1 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 4.16.2): The mean of the scores calculated at Step 1 in the item numbers in the right column of Table 4.16.2 should be 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 4.16.2 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, E
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

5. Analysis Sets

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

The analysis sets are defined below. Details of treatment of subjects regarding the final fixed data will be decided by the sponsor before fixing the data.

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 HD-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:

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

6. Patient Cohort

The patient cohort is defined as follows:

Conversion cohort: A group of patients who have received ESA formulations from 8 weeks prior to the first day of the screening period.

7. Data Handling

Final fixed data should be handled as follows: The handling of data other than the following 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 a single 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 ranges for study visits" section of the study 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 model repeated measures (hereinafter, MMRM) should not use data imputing missing data.

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) (hereinafter, 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, values imputed by the LOCF method at Week 52 of the treatment period should also be derived for clinical laboratory value, vital sign, QOL indices among the efficacy endpoints.

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 quantification limit 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: < 3 Significant figures of the measuring facility: up to ones digit
→ Tabulation handling: 2.9

Report: <500 Significant figures 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 quantification 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

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%. Confidence interval will be 2-sided with a confidence coefficient of 95%.

8.1.2 Descriptive statistics to calculate

Types of descriptive statistics items to be calculated for each continuous variable 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 is 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.

Items: Number of subjects enrolled in treatment period, number of subjects completed the treatment period phase 2, number of subjects discontinued the study, number of subjects who received rescue therapy, number of subjects in the FAS and its proportion, number of subjects not included in the FAS and its proportion, number of subjects and its proportion in the safety analysis set, number of subjects not included in the safety analysis set 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 tabulated 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 subjects who discontinued in each treatment group among those enrolled in the treatment period; number and proportion subjects who discontinued by reasons

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

Item: Number and proportion of subjects who discontinued in each treatment group among those enrolled in the treatment period

For subjects enrolled in the treatment period, the number of cases of interruption of MT-6548 tablets 150 mg in the MT-6548 group and darbepoetin alfa injection (recombinant) in the darbepoetin group should be tabulated by reasons for drug interruptions. The denominator of the proportion should be the sum of the number of drug interruptions. If there are multiple reasons for a single interruption, it should be counted for each reason and tabulated as the total 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 tabulated.

Items: Number of cases of interruption of MT-6548 tablets 150 mg/darbepoetin alfa injection in each treatment group among subjects enrolled in the treatment group; number and proportion of cases of interruptions by reasons

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).

Table 8.3.1 Items relating to 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
	Dry weight (kg)	Continuous
	BMI (kg/m^2)	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	Type of previous ESA formulation 4 categories: epoetin (epoetin alfa, epoetin beta, or epoetin kappa), 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 a week, every 2 weeks, every 3 weeks, every 4 weeks, other	Polytomous
	Weekly dose of epoetin alfa, epoetin beta, or epoetin kappa (IU)	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: <10, 10 to <11, ≥11	Tricotomous
	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	Tricotomous
	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
Hemodialysis	Types of hemodialysis (2 categories: hemodialysis, hemodiafiltration)	Dichotomous
	Duration of hemodialysis (years)	Continuous
	Frequency of dialysis (2 categories: 3x per week, other)	Dichotomous

8.4 Study drug administration/treatment period and compliance status

For FAS and safety analysis set, the descriptive statistics of administration/compliance rate (no calculation of 95% CI of the mean) of MT-6548 tablets 150 mg/darbepoetin alfa injection (recombinant) should be calculated by treatment group to provide the number and proportion of subjects with administration/compliance rate of MT-6548 tablets 150 mg/darbepoetin alfa injection (recombinant) of ≥80% and <80%.

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

For FAS and safety analysis set, the descriptive statistics of the cumulative dosage of MT-6548 tablets 150 mg/darbepoetin alfa injection (recombinant) should be calculated by treatment group (no calculation of 95% CI of the mean).

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. 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 Week 48 and Week 52 of the treatment period

Descriptive statistics for changes in Hb values from the first day of the treatment period to mean Hb values at Week 48 and Week 52 in the treatment period should be calculated for each 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 (hereinafter, 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% confidence intervals should be calculated.

[MMRM Model]

- Covariate: response variable value of the first day of the treatment period
- Fixed effects: treatment group, evaluation time point, interaction of evaluation time point × treatment group
- Degrees of freedom adjustment: Kenward-Roger method
- Covariance matrix within subject for each subject: unstructured (type = UN; unstructured)
  If the within-subject variance–covariance matrix is not converged using unstructured data, the within-subject variance–covariance matrix should be changed in the following order, and the analysis should be performed using the within-subject variance–covariance matrix that is 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 values and changes in Hb values from the first day of the treatment period at each evaluation time point of the treatment period will be obtained, and their descriptive statistics should be calculated for each treatment group. Before and after comparison should be conducted for changes in Hb values from the first day of the treatment period to each evaluation time point using the paired t-test in the MT-6548 group only.

LSMean, its standard errors, and 2-sided 95% CI for mean Hb values should be calculated in each treatment group using the MMRM (with compound symmetry [CS] for a covariance matrix within subject variance) similar to the analysis used in "(1) mean Hb levels at Week 48 and Week 52 of the treatment period".

Furthermore, LSMean, its standard errors, and 2-sided 95% CI of the change from the first day of the treatment period should be calculated at each evaluation time point of the treatment period in each treatment group using the MMRM.

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

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

An analysis similar to "1) Hb values 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.

3) Analysis by previous ESA formulation type

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be conducted by the type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). A time course diagram for the mean value is created separately for each treatment group. However, this analysis is only for the MT-6548 group; neither tabulation in the darbepoetin group nor comparison with the darbepoetin group is performed.

4) Analysis by dose of previous ESA formulation types

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be conducted for weekly dose of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa: ≥4500 IU, <4500 IU; other: ≥ 15 μg, <15 μg; 2 categories) by type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). The number of patients classified by dose was set to be almost equal. The time course diagram of the means should be prepared separately by treatment group. However, this analysis is only for the MT-6548 group; neither tabulation in the darbepoetin group nor comparison with the darbepoetin group is performed.

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

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be conducted by Hb value on the first day of the treatment period (subjects are divided into 3 categories with equal population). A time course diagram for the mean value is created separately for each treatment group. However, no comparison with baseline of the darbepoetin group or comparison with the darbepoetin group will be conducted.

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

An analysis similar to "1) Hb values 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. However, subjects who uses intravenous iron at least once should be excluded from the tabulation. Only the MT-6548 group is analyzed.
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) Hb values at each evaluation time point in the treatment period" should be conducted for subjects continuously using iron supplements or iron-containing phosphate binders during the treatment period. However, subjects who uses intravenous iron at least once should be excluded from the tabulation. Only the MT-6548 group is analyzed.

8) Analysis by Hb value at Week 52 of the treatment period and CRP levels 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: Hb value at Week 52 of the treatment period

(3) Proportion of subjects whose Hb level during the treatment period is within the target range (10.0 to <12.0 g/dL) or outside the target range (<10.0 g/dL or ≥12.0 g/dL)

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of subjects with Hb value within the target range (10.0 to <12.0 g/dL, within), <10.0 g/dL (below), and ≥12.0 g/dL (above) at each time point of the treatment period should be provided by treatment group. For the MT-6548 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. The proportion of subjects with Hb value within the target range at each evaluation time point of the treatment period should be provided as a stacked bar chart with the number of subjects in each treatment group as 100%. Stacked bar charts should be generated separately for each treatment group.

8.5.2 Analysis of other endpoints

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

The total number of maintenance days from the state meeting the target Hb range to leaving the target Hb range 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 52 weeks, the maintenance days should be until Week 52 of the treatment period.

(2) Proportion of subjects who received rescue therapy with ESA, blood transfusion, or phlebotomy

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of 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.

(3) Study drug dosage

1) Study drug dosage

Descriptive statistics of the mean daily dose of MT-6548 tablets 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 tablets 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 study visit and the day before the next scheduled study visit.

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

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the 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 chart 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 time point of the treatment period, the dose should be based on the immediately before prescription.

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

An analysis similar to "1) Study drug dosage" should be conducted by the timing of administration of MT-6548 tablets (before meal, after meal, other). Only the MT-6548 group is analyzed.

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, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). Only the MT-6548 group is analyzed.

5) Analysis by dose of previous ESA formulation types

An analysis similar to "1) Study drug dosage" should be conducted for weekly dose (epoetin alfa, epoetin beta or epoetin kappa: ≥4500 IU, <4500 IU; other: ≥ 15 μg, <15 μg; 2 categories) by type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). Only the MT-6548 group is analyzed.

6) Analysis by 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 (subjects are divided into 3 categories with equal population).

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. However, subjects who uses intravenous iron at least once should be excluded from the tabulation. Only the MT-6548 group is analyzed.

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. However, subjects who uses intravenous iron at least once should be excluded from the tabulation. Only the MT-6548 group is analyzed.

9) Analysis of the mean dose of the study drug at Week 48 and Week 52 of the treatment period and CRP levels 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: Mean dose of study drug at Week 48 to Week 52 of the treatment period

(4) Total number of dosage adjustments

The cumulative total number of dose adjustments during the entire treatment period from the first day of the treatment period to Week 52 of the treatment period should be calculated, and the number and proportion of subjects per cumulative number of adjustments and the 95% CI (Clopper-Pearson [Exact] method) of the proportion should be provided.

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 and during the entire period from the first day to Week 52 of the treatment period. 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), 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.

(5) 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 2-sided 95% CI, 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.

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

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion of subjects treated with oral, intravenous, or oral iron supplement (any route) should be provided by treatment group 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. A McNemar tests should be used for before and after comparison between baseline (ratio of subjects receiving iron supplements by the aforementioned route in the 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.

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

The number, proportion, and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with serum ferritin levels of ≥100 ng/mL or TSAT levels of ≥20% should be provided at each evaluation time point of the treatment period for each treatment group. A McNemar tests should be used for before and after comparison between baseline (ratio of subjects receiving iron supplements by the aforementioned route in the 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 with serum ferritin ≥100 ng/mL or TSAT ≥20%.

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

Iron-related indices (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin should be measured at each evaluation time point of the treatment period, and their changes and rate of changes should be calculated from the first day of the treatment period to each evaluation time point of the treatment period. Descriptive statistics of the measurements, changes, and rate of changes should be calculated for each treatment group. 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 indices (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 within-subject variance–covariance matrix). 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 indices (serum iron, TIBC, TSAT, and serum ferritin levels) 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 similar time course diagram should be prepared for 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 ferritin should be conducted by baseline value (subjects are divided into 3 categories with equal population). The time course diagram of LSMean 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

(9) Changes in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period

Descriptive statistics of hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO at each evaluation time point should be calculated for each treatment group. The change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each treatment group.
A group comparison should be conducted for the change in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period to each evaluation time point. MMRM (with compound symmetry [CS] for within-subject variance–covariance matrix) is used to calculate LSMean and its standard error and 2-sided 95% CI for each treatment group, and the point estimate, its standard error, the 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin groups) of LSMean are shown.
For hematocrit, red blood cell count, and reticulocyte (count and rate), neither comparison of before and after changes in the darbepoetin group nor comparison with the darbepoetin group was performed.
A histogram of EPO measurements should be prepared for evaluation time point at Week 52 of the treatment period.

(10) Changes in systolic blood pressure, diastolic blood pressure, and blood glucose from the first day of the treatment period, changes and rate of changes in lipid (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides) from the first day 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 52 of the treatment period should be calculated for each treatment group by baseline value (subjects are divided into 3 categories with equal population). The change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each 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 within-subject variance–covariance matrix). The LSMean for each treatment group is calculated, and the point estimate of the between-group difference (MT-6548 − darbepoetin) of LSMean, its standard error, 2-sided 95% CI, and p-value were shown.

Descriptive statistics should be similarly calculated for each treatment 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 within-subject variance–covariance matrix).

(11) 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, its 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 within-subject variance–covariance matrix). 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.

[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, VAS score, or change in index value or VAS score from the first day of the treatment period
- ✓ Estimated item (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 in each treatment group by subscale (Section 4 [Table 4.16.2] "subscale") for measured values and changes from the first day of the treatment period at each evaluation time point. Scores by subscale should be calculated using a scoring method 2) (Section 4.16).

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. 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 using the MMRM (with compound symmetry [CS] for within-subject variance–covariance matrix).

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 by the MMRM model 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. This statistical analysis plan was prepared to analyze the final fixed data.

8.5.4.4 Multicenter trial

For FAS, the following analysis should be conducted for each following endpoint for each facility.
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 Week 48 to Week 52 of the treatment period for each treatment group.

8.5.4.5 Subgroup analyses

For the FAS, the following analyses should be performed for subgroups based on stratification factors (Table 8.5.4.5.1) for each of the following endpoints.

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

(2) Study drug mean dose at Week 48 to Week 52 of the treatment period

Descriptive statistics should be calculated for each treatment group.

(3) 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 (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 8.5.4.5.1 Subgroup analysis of efficacy

Endpoints	**Stratification factor**	**Stratified category**
1. Hb at Week 52 of the treatment period 2. Study drug mean dose at Week 48 to Week 52 of the treatment period 3. Target Hb achievement rate at Week 52 of the treatment period	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65
		<75, ≥75
	Dry 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	<10, ≥10 to <11, ≥11
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both not more than 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
	Ferritin (ng/mL) 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 supplement on the first day of the treatment period	Yes or No
	Treatment with oral iron supplement at Week 52 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 52 of the treatment period	Yes or No
	Previous ESA formulation	Epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol, other
	Dosage of epoetin alfa, epoetin beta, or epoetin kappa	Divide the number of subjects into three categories based on the tertile
	Dosage of darbepoetin alfa	Divide the number of subjects into three categories based on the tertile
	Dosage of epoetin beta pegol	Divide the number of subjects into three categories based on the tertile
	CYP2B6 substrate*	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

The mean Hb values at Week 20 and Week 24 of the treatment period, the primary endpoints of this study, are 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.

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.

- 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 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, non-serious adverse events, serious adverse drug reactions, 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 of subjects and incidence rate should be calculated for each adverse event classified by SOC and PT in MedDRA/J 20.1. (hereinafter, the same).
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 of the same severity occur in the same subject, the same severity should be counted as 1 subject.

(3) 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 event 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.

* The tabulation unit by time of onset should be 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.
(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)

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 events and adverse drug reactions 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 the maximum 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 * Maximum Cumulative dosage", the number of days until the subject concerned reaches x/4 * maximum cumulative dosage should be calculated for each subject. In the case of ≥3/4 * 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 (tabulation unit: 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).

8.6.1.7 Adverse events before and after drug interruption

For adverse events and adverse drug reactions, the number of subjects in the overall and in individual events classified by SOC and PT and the incidence rate to subjects with drug interruption should be calculated in before and after interruption of the active drug. It is 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 has had multiple interruptions, a second interruption within 4 weeks of the first interruption is counted both 4 weeks before and 4 weeks after the first interruption.

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, and dehydroepiandrosterone sulfate (hereinafter, DHEA-S). Changes from the first day of the treatment period at each evaluation time point should also be summarized.

8.6.3 Number and proportion of subjects whose liver function values meet interruption/discontinuation criteria of the study drug

For AST and ALT, the number and proportion of subjects who meet the following conditions should be provided in each period between scheduled hospital 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 Kt/V, Body weight after dialysis and dry weight

Descriptive statistics (except for 2-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 2-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 edema]) 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 ≥12.0 g/dL or ≥13.0 g/dL

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of subjects with confirmed Hb ≥12.0 g/dL or ≥13.0 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 >12.0 g/dL or 13.0 g/dL in the same subject, the subject should be counted in both categories.

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 8.6.8.

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

The number, proportion, and 2-sided 95% CI (Clopper-Pearson [Exact] method) of subjects with confirmed Hb increase rate of≥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 48 of the treatment period should be provided for each treatment group. The Hb increase rate in this tabulation should be calculated based on the difference in Hb values in each period between scheduled study visits in every 4 weeks and the treatment interval obtained from the actual study visit date.

8.6.12 Summary statistics of Hb values before and after dose reduction or drug interruption

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

For the Hb value after dose reduction/drug interruption of the study drug (active 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 (active 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.

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 8.6.12.1 and 8.6.12.2).

Table 8.6.13.1 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
	Dry weight (kg) on the first day of the treatment period	<60, ≥60
	Hb value (g/dL) on the first day of the treatment period	<10, ≥10 to <11, ≥11
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both not more than 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.

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 hospital 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 hospital 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, 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.

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

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 hospital 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.

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.

(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 of the between-group difference (MT-6548 − darbepoetin) of LSMean, its standard errors, 2-sided 95% CI, and p-value should be calculated.

(2) Study drug mean dose at Week 20 to Week 24 of the treatment period

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 8.7.3.1 Subgroup analyses of 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 value 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

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, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

Study protocol number	MT-6548-J03

Date of errata preparation	May 10, 2019
Errata prepared by	[redacted]

Object document	Statistical Analysis Plan
Object document version number	Version 2
Signature date	January 31, 2019

The Statistical Analysis Plan (Version 2) in "A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan" is corrected as follows:

Applicable part	Correct
8.5.3 Analysis of other endpoints (9) Changes in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period	MMRM (within-subject variance–covariance matrix using the compound symmetry [CS]) is used to calculate LSMean and its standard error and 2-sided 95% CI for each treatment group, and the point estimate, its standard error, the 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin groups) of LSMean are shown. For hematocrit, red blood cell count, and reticulocyte (count and rate), neither comparison of before and after changes in the darbepoetin group nor comparison with the darbepoetin group was performed.
	(Reason) The underlined part has been added because it was not included in the description.

End

Errata

A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

Study protocol number	MT-6548-J03

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

Object document	Statistical Analysis Plan
Object document version number	Version 2
Signature date	January 31, 2019

The Statistical Analysis Plan (Version 2) in "A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan" is corrected as follows:

Applicable part	Correct
8.5.2 Analysis of secondary endpoints 1) Hb values at each evaluation time point in the treatment period	(Correct) In addition, an MMRM model similar to the one used in the analysis of the primary endpoints (within-subject variance–covariance matrix using the compound symmetry [CS]) is used to ~~compare Hb values between groups.~~calculate LSMean and its standard error and two-sided 95% CI for the mean Hb values at each evaluation time point in the treatment period for each treatment group ~~should be calculated~~.
	(Reason) Due to typographical error.

Applicable part	Correct
8.5.2 Analysis of secondary endpoints 2) Analysis by previous ESA formulations type	(Correct) A time course diagram for the mean value is created separately for each treatment group. However, this analysis is only for the MT-6548 group; neither tabulation in the darbepoetin group nor comparison with the darbepoetin group is performed.
	(Reason) The underlined part has been added because it was not included in the description.

Applicable part	Correct
8.5.2 Analysis of secondary endpoints (2) Proportion of subjects with Hb value within the target range (10.0 to <12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each evaluation time point of the treatment period	(Correct) The proportion of subjects with Hb value within the target range at each evaluation time point of the treatment period should be provided as a stacked bar chart with the number of subjects in each treatment group as 100%. Stacked bar charts should be generated separately for each treatment group. ~~For proportion of subjects within the target range at each evaluation time point of the treatment period, the point estimate, its 95% CI (exact method), and p-value (Fisher's exact test) of the between-group difference (MT-6548 – darbepoetin) will be calculated.~~
	(Reason) Unnecessary description remained.

Applicable part	Correct
8.5.3 Analysis of other endpoints 4) Analysis by previous ESA formulation type	(Correct) An analysis similar to "1) Study drug dosage" should be conducted by the type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). Only the MT-6548 group is analyzed.
	(Reason) The underlined part was added because it was not included in the description.

Applicable part	Correct
8.5.3 Analysis of other endpoints 5) Analysis by dose of previous ESA formulation types	(Correct) An analysis similar to "1) Study drug dosage" should be conducted for weekly dose (epoetin alfa, epoetin beta or epoetin kappa: ≥4500 IU, <4500 IU; other: ≥ 15 μg, <15 μg; 2 categories) by type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). Only the MT-6548 group is analyzed.
	(Reason) The underlined part was added because it was not included in the description.

Applicable part	Correct
8.5.3 Analysis of other endpoints (4) MT-6548 group only: cumulative number of dose adjustments	(Correct) The total number of dose adjustments over the scheduled study visit period from the first day of the treatment period to Week 24 and over the entire period from the first day of the treatment period to Week 24 is calculated, and the number of subjects for each total number and its proportion with a 95% confidence interval (Clopper-Pearson [exact] method) are shown. ~~The number and proportion of subjects by total number of dose adjustments for each scheduled study visit period should be shown.~~
	(Reason) Unnecessary description remained.

Applicable part	Correct
8.5.3 Analysis of other endpoints (9) Changes in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period	(Correct) Descriptive statistics of hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO at each evaluation time point should be calculated for each treatment group.
	(Reason) The underlined part was added because it was not included in the description.

Applicable part	Correct
Table 8.5.4.6.1 Subgroup analysis of efficacy	(Error) CYP2B6 inducer combination * 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
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, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

Mitsubishi Tanabe Pharma Corporation

Preparation date	January 31, 2019
Study protocol number	MT-6548-J03
Version number	Version 2

Revision History

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

For Fixed Data Analysis of Treatment Period Phase 1

Statistical Analysis Plan

A Phase III, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

Approval Column

[redacted]

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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
HD-CKD	Hemodialysis 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	Film-coated tablets containing 150 mg of vadadustat per tablet
Darbepoetin alfa injection	Plastic syringe containing darbepoetin alfa (recombinant) in 1 syringe (0.5 mL)
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, Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan."

2. Study Objectives and Design

2.1 Study objectives

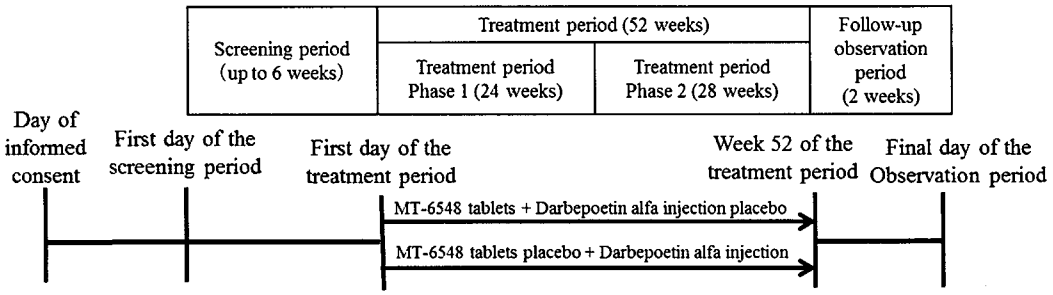
The study evaluates the non-inferiority of MT-6548 in patients with anemia associated with hemodialysis-dependent chronic kidney disease (HD-CKD) who are currently treated with an erythropoiesis-stimulating agent (ESA) using hemoglobin (Hb) levels as a measure and darbepoetin alfa (recombinant) as a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

2.2 Study design

Study phase: Phase III

Study type: Confirmatory study

Multicenter, randomized, double-blind, active-controlled, double-dummy, parallel group comparative study.



2.3 Randomization methods

2.3.1 Blinding methods

The treatment period Phase I in this study should be conducted in a double-blind manner. Blinding of this study should be achieved by not providing information to persons involved in the study as to which study drug is being administered and by using a placebo that is indistinguishable from the active

drug. Data up to Week 24 of the treatment period phase 1 should be fixed and the key code should be opened; however, the blinding of subjects, healthcare providers, and monitoring staff should be maintained until the final data fixation at the end of the study is completed. Details of the procedure of maintaining the blindness should be separately defined before opening of the key code.

The randomization business contract organization should prepare the main part and the sub part of the material list, the main part of the randomization key code table, and the allocation number list and strictly stores and manages the main part of the material list, the randomization key code table, and the allocation number list until the key code is opened so that the key code information does not leak outside. The main part of the material list, randomization key code table, and allocation number list should be opened after all case report forms for the treatment period phase 1 have been completed, data have been fixed, and their handling has been determined.

The randomization business contract organization should submit the sub part of the material list to the study drug QA director of the sponsor for the study drug allocation work after receiving the sending request from the sponsor. The study drug manufacturing management supervisor of the sponsor should prepare the study drug to which the kit code is affixed based on the material list. MT-6548 tablets should be produced so that placebo and active drug cannot be distinguished in appearance. Darbepoetin alfa Injection should be prepared so that the placebo, the active drug, and the content are visually indistinguishable. The study drug QA manager of the sponsor should strictly store and manage the sub part of the material list until the key code is opened so that the key code information does not leak to parties other than those involved in the study drug assignment work.

The randomization service contract organization should prepare emergency keys for emergency response and should provide them to the emergency contact center. The emergency contact center should strictly store and manage emergency keys until the end of the clinical trial so that the key code information does not leak outside. For reporting suspected unexpected serious adverse reactions (SUSAR) of Akebia Therapeutics Inc. which is conducting clinical studies of MT-6548 outside Japan, the randomization service contract organization should prepare key codes for SUSAR open key report of overseas regulatory authorities, and should provide them to the emergency contact center. The emergency contact center should strictly store and manage the key code for the overseas regulatory authority SUSAR open key report until the key code is opened so that the key code information does not leak outside.

The randomization service contract organization should provide key code information to the contract testing laboratory. The contract testing laboratory should use this information to send only specimen from the MT-6548 group to the drug concentration measurement laboratory. The contract testing laboratory should strictly store and manage the key code information until the key code is opened so that the key code information does not leak outside. The drug concentration measurement laboratory should strictly store and manage the plasma drug concentration measurement results until the key code

is opened so that the plasma drug concentration measurement results do not leak outside. The results of plasma drug concentration measurements shall not be disclosed to subjects, study center staff, or monitoring staff until the final data fixation at the end of the study has been completed.
The contract testing laboratory should store and control the measurement result of erythropoietin (hereinafter, EPO) strictly until the key code is opened so that the measurement result of EPO does not leak outside. The results of EPO measurements shall not be disclosed to subjects, study center staff, or monitoring staff until completion of the final data lock at the end of the study. The measurement of EPO in the study centers should be prohibited for blind maintenance during the treatment period.

2.3.2 Randomization and allocation methods

The randomization service contract organization should prepare randomization key code tables in accordance with predefined procedures for creation and storage of randomization key code tables. Subjects who are judged to be eligible for transition to the treatment period will be assigned to treatment groups based on the randomization key code table in the Web registration system, and the assignment number should be notified on the Web registration system. Details of the randomization shall be specified in the enrollment center subject allocation specifications. Subjects should be randomly assigned in a 1:1 ratio to MT-6548 and darbepoetin groups.

Evaluation time point

Item \ Visit	Informed consent	Screening period [a]		Treatment period [b]																		Final day of the follow-up observation [c]
				Treatment period Phase 1										Treatment period Phase 2								
		First day	Visit 2	First day	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	Day of discontinuation	
Visit number	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	TV12	TV13	TV14	TV15	TV16	TV17	TV18	FU
Permitted range (days)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+ 7 or + 14 [d]	+7
Procedure/evaluation																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X	X	X																		
Allocation				X																		
Patient background and history	X			X																		
Height				X																		
Dry weight, body weight [e]				X						X			X			X				X	X	
Forlic acid and vitamin B_{12} [f]		X																				
Pregnancy test [h]		X											X							X	X	
Hematology tests [f], [g], [i]		X	X [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry test [f], [g], [k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein [f], [g]		X		X									X							X	X	
Iron-related measures [f], [g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepcidin [g]				X	X	X	X			X			X			X				X	X	
EPO [g]				X	X	X	X			X			X			X				X	X	
VEGF [g]				X						X			X			X				X	X	
DHEA-S [g]				X						X			X			X				X	X	
Vital signs [f], [g], [l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Resting standard 12-lead ECG [g], [m]				X									X							X	X	
Fundoscopy [d]		X										X							X		X	
Chest X-ray [d]		X										X							X		X	
Duration of hemodialysis				X									X							X	X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X							X	X	
AE investigation [n]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK testing						X				X			X									
Blood sampling for genetic analysis [o]					Blood sampling for genetic analysis performed once as early as possible after Week 2 of treatment period																	
Blood sampling for plasma protein binding test [p]		X																				
Product evaluatio/procedure																						
Investigation of concomitant medications/therapies				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MT-6548 tablets [q], [r], [s]				Administered according to the dosage adjustment guidelines																		
Darbepoetin alfa injection [r], [t]				Administered according to the dosage adjustment guidelines																		
Iron supplements		Iron supplements administered to maintain a serum ferritin level of ≥100 ng/mL or a TSAT of ≥20%																				

[a] 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] The scheduled study visit during the treatment period shall be the dialysis day 2 days after the previous dialysis, and if it is difficult, the dialysis day 1 day after the previous dialysis.

[c] Should not be performed if discontinued before the treatment period.

[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 after discontinuation whenever possible if discontinued during the treatment period.

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

[f] Measurements on the day of dialysis should be performed before dialysis during the screening period.

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

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

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

[j] Only Hb values should be measured.

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

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

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

[n] AE investigation should begin after study drug administration.

[o] 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.

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

[q] 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.

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

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

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

2.4 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.

[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 11.0 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 1.73 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 (10.0–12.0 g/dL) and non-inferiority could be established.
The assumed standard deviation was set at 1.73 g/dL based on the upper limit of the two-sided 95% confidence interval of the standard deviation in the MT-6548 300 mg group at Week 6 in study CI-0022.

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

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

(2) Proportion of subjects with mean Hb values within the target range (10.0 to <12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each evaluation time point in the treatment period

3.1.3 Other endpoints

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

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

(3) Study drug dosage

(4) MT-6548 group only: total number of MT-6548 tablet dosage adjustments

(5) Iron supplement dosage

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

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

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

(9) Changes in hematocrit, red blood cell count, reticulocytes (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and erythropoietin from the first day of the treatment period

(10) 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

(11) 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 corpuscular hemoglobin, mean cell 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, uric acid, CPK, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, Na, K, Cl, Ca, P, Mg, bicarbonate, total cholesterol, LDL-C, HDL-C, triglycerides

3) C-reactive protein
4) Folic acid and vitamin B_{12}
5) Vascular endothelial growth factor (hereinafter, VEGF)
6) Dehydroepiandrosterone sulfate (hereinafter, DHEA-S)

(3) Resting standard 12-lead ECG

(4) Dry weight

(5) Body weight

(6) Vital signs

(7) Fundoscopy

(8) Chest X-ray

(9) Proportion of subjects with documented Hb values of ≥12.0 g/dL or ≥13.0 g/dL

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

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

(12) Hb value after dose reduction or interruption of the study drug

(13) Kt/V

3.3 Pharmacokinetic endpoints

Plasma concentrations 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 acquisition [month] < Date of birth [month]) or (Date of consent acquisition [month] = Date of birth [month] and Date of consent acquisition [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 (year) = (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 Period from the first day of hemodialysis

The period from the start of hemodialysis (year) should be the period from the start of hemodialysis (time of first hemodialysis or hemodiafiltration) to the month of consent acquisition and should be the integer part + 1 digit (rounded). The period from the start of hemodialysis should be calculated as follows:

Period from the start of hemodialysis (year) = (Date of consent acquisition [year] − Start of hemodialysis [year]) + (Date of consent acquisition [month] − Start of hemodialysis [month])/12

If the month of the start of hemodialysis is unknown, the month should be calculated as 1.

4.4 BMI

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

Should be rounded and displayed to one decimal place.

4.5 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.

4.6 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) = Day of resumption of study drug administration − First day of study drug interruption

If there are multiple interruptions, the sum of them should be used.
Resumption date of study drug administration: 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 should be administered 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.
First day of study drug interruption: The day of administration when "Daily Dose" = 0 mg or 0 μg is first entered in the CRF.

4.7 Study drug administration/treatment duration

For subjects who completed treatment period phase I:

Study drug administration/treatment 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/treatment duration (days) = Day of discontinuation − First day of the treatment period

4.8 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

4.9 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%.

4.10 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 scheduled 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: Days 15 to 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 hematology 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 period between scheduled study visits

4.11 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.

4.12 Adverse drug reactions

In the MT-6548 group, adverse events for which a causal relationship to MT-6548 tablets is evaluated as "reasonably possible" are defined as adverse drug reactions associated with MT-6548 tablets, and in the darbepoetin group, adverse events for which a causal relationship to darbepoetin alfa injection is evaluated as "reasonably possible" are defined as adverse drug reactions associated with darbepoetin alfa injection.

4.13 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 (Day 1) to Day 14
- ✓ Week 2 of the treatment period to Week 4 of the treatment period: Days 15 to 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 hematology

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 is counted as 30.4375 days (365.25/12 = 30.4375).

4.14 Kt/V

Kt/V is defined by the following equation. It is calculated based on the first day of treatment period, Week 24, and the day of discontinuation. All items used for the calculation of Kt/V should be those measured on the same day.

$Kt/V = -\ln(Ct/C0 - 0.008 \times t) + (4 - 3.5 \times Ct/C0) \times (BW0 - BWt)/(BWt)$

t: Dialysis time, C0: BUN concentration before dialysis, Ct: BUN concentration after dialysis, BW0: Body weight before dialysis, BWt: Body weight after dialysis

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

Responses to 5 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 4.14.1).[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 4.14.1 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 4.14.1 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

4.16 QOL (KDQOL) scoring

Step 1 (See Table 4.15.1): The appropriate score is converted from the response choices for each item number in Table 4.15.1 for each subject.

Table 4.15.1 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 4.15.2): The mean of the scores calculated at Step 1 in the item numbers in the right column of Table 4.15.2 should be 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 4.15.2 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, E
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

5. Analysis Sets

Efficacy analysis will be performed in the full analysis set (hereinafter, FAS). Primary endpoint analysis will also be performed with the set of subjects conforming to the study protocol, or the per-protocol set (hereinafter, 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 of subjects regarding treatment period phase 1 fixed data and 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 HD-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 from the FAS excluding the following subjects:

- ✓ 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 150 mg tablets or darbepoetin alfa injection

5.2 Safety analysis set

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

- ✓ 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 150 mg tablets
- ✓ Subjects with no post-randomization plasma drug concentration data

6. Patient Cohort

The patient cohort is defined as follows:

Conversion cohort: A group of patients who have received ESA formulations from 8 weeks prior to the first day of the screening period.

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 a single 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 ranges for study visits" section of the study 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 model repeated measures (hereinafter, MMRM) used to analyze the primary efficacy endpoint should not use data imputing missing data. 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 (hereinafter, 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) (hereinafter, 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, values imputed by the LOCF method at Week 24 of the treatment period should also be derived for clinical laboratory value, vital sign, QOL indices among the efficacy endpoints. 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 quantification limit 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: <3 Significant figures of the measuring facility: up to ones digit
→ Tabulation handling: 2.9

Report: <500 Significant figures 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 quantification 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

7.6 Handling of PK-related data

The permitted range of 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 descriptive statistics items to be calculated for each continuous variable 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 should be displayed 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 in the original variable
Descriptive statistics (mean, SD, median)	Number of digits of the original variable + 1 digit
Hb value 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.

Items: Number of subjects enrolled in treatment period, number of FAS subjects and its proportion, number of subjects excluded from FAS and its proportion, number of PPS subjects and its proportion, number of subjects excluded from PPS and its proportion, number of subjects in the safety analysis set and its proportion, number of subjects excluded from the safety analysis set and its proportion, number of subjects in the drug concentration analysis set and its proportion, and number of subjects excluded from the drug concentration analysis set 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 tabulated in each treatment group and by reasons for discontinuation.

Items: Number and proportion of subjects who discontinued in each treatment group among those enrolled in the treatment period; number and proportion subjects who discontinued by reasons.

For subjects enrolled in the treatment period, the number of cases of interruption of MT-6548 tablets 150 mg in the MT-6548 group and darbepoetin alfa injection in the darbepoetin group should be tabulated by reasons for drug interruptions. The denominator of the proportion should be the sum of the number of drug interruptions. If there are multiple reasons for a single interruption, it should be counted for each reason and tabulated as the total number of interruption cases.

Items: Number of cases of interruption of MT-6548 tablets 150 mg/darbepoetin alfa injection in each treatment group among subjects enrolled in the treatment group; number and proportion of cases of interruptions by reasons.

8.3 Demographic and other baseline characteristics

The key demographic and other baseline characteristics for each analysis set (excluding the PK analysis set) 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) . If the PPS or safety analysis set is the same as the FAS, the results for the analysis sets will not be presented.

Table 8.3.1 Items relating to 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
	Dry weight (kg)	Continuous
	BMI (kg/m^2)	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	Type of previous ESA formulation 4 categories: epoetin (epoetin alfa, epoetin beta, or epoetin kappa), 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 a week, every 2 weeks, every 3 weeks, every 4 weeks, other	Polytomous
	Weekly dose of epoetin alfa, epoetin beta, or epoetin kappa (IU)	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: <10, 10 to <11, ≥11	Trichotomous
	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
Hemodialysis	Types of hemodialysis (2 categories: hemodialysis, hemodiafiltration)	Dichotomous
	Duration of hemodialysis (years)	Continuous
	Frequency of dialysis (2 categories: 3x per week, other)	Dichotomous

8.4 Study drug administration/treatment period and compliance status

For FAS and safety analysis set, the descriptive statistics of administration/compliance rate (no calculation of 95% CI of the mean) of MT-6548 tablets 150 mg/darbepoetin alfa injection should be calculated by treatment group to provide the number and proportion of subjects with administration/compliance rate of MT-6548 tablets 150 mg/darbepoetin alfa injection of ≥80% and <80%.

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

For FAS and safety analysis set, the descriptive statistics of the cumulative dosage of MT-6548 tablets 150 mg/darbepoetin alfa injection (no calculation of 95% CI of the mean) should 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. 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 value at Week 20 and 24 of the treatment period. 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 20 and Week 24 of the treatment period for each treatment group should be obtained. The least squares mean (hereinafter, 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% confidence intervals should be calculated. When the lower limit of 95% CI of the difference between the groups is no less than −0.75 g/dL, MT-6548 will be considered noninferior to darbepoetin alfa (recombinant).

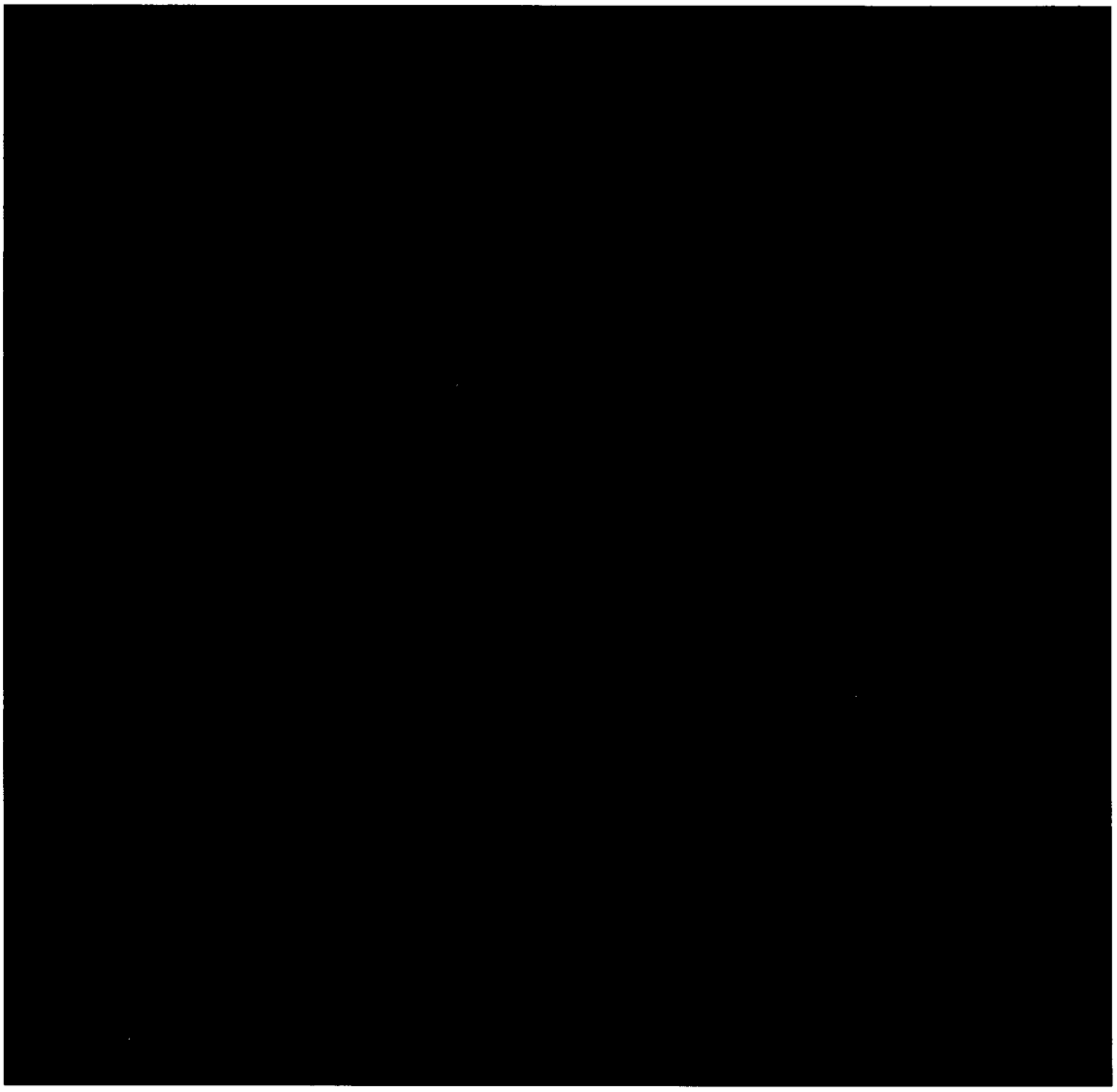
The robustness of the results will be examined by the same analysis for PPS.

[MMRM Model]

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

- Fixed effects: treatment group, evaluation time point, interaction of evaluation time point × treatment group
- Degrees of freedom adjustment: Kenward-Roger method
- Covariance matrix within subject for each subject: unstructured (type = UN; unstructured)
  If the within-subject variance–covariance matrix is not converged using unstructured data, the within-subject variance–covariance matrix should be changed in the following order, and the analysis should be performed using the within-subject variance–covariance matrix that is 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 values and its 95% CI of MT-6548 cohort at Weeks 20 and 24 of the treatment period are included within the target range (≥10.0 g/dL and <12.0 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 values 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 values 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% CI 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 LSMean of between-group differences (MT-6548 – darbepoetin). 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 values and changes in Hb values from the first day of the treatment period at each evaluation time point of the treatment period will be obtained, and their descriptive statistics should be calculated for each treatment group. Before and after comparison should be conducted for changes in Hb values from the first day of the treatment period to each evaluation time point using the paired t-test in the MT-6548 group only.

In addition, an MMRM model similar to the one used in the analysis of the primary endpoints (within-subject variance–covariance matrix using the compound symmetry [CS]) is used to compare Hb values between groups. LSMean and its standard error and two-sided 95% CI for the mean Hb values at each evaluation time point in the treatment period for each treatment group should be calculated.

A group comparison should be conducted for the change from the first day of the treatment period using the MMRM model. LSMean of changes in Hb values from the first day of the treatment period at each evaluation time point should calculated for each treatment group.

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

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

An analysis similar to "1) Hb values 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.

3) Analysis by previous ESA formulation type

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be conducted by the type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). A time course diagram for the mean value is created separately for each treatment group.

4) Analysis by dose of previous ESA formulation types

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be conducted for weekly dose of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa: ≥4500 IU, <4500 IU; other: ≥ 15 μg, <15 μg; 2 categories) by type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol). The number of patients classified by dose was set to be almost equal.
A time course diagram for the mean value is created separately for each treatment group.

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

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be conducted by Hb value on the first day of the treatment period (subjects are divided into 3 categories with equal population). A time course diagram for the mean value is created separately for each treatment group.

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

An analysis similar to "1) Hb values at each evaluation time point in the treatment period" should be performed for subjects who continuously used iron supplements or iron-containing phosphate binders during the treatment period and for subjects who have never used iron supplements or iron-containing phosphate binders during the treatment period.

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

An analysis similar to "1) Hb values 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 by formulation using the MMRM model.

8) Analysis by Hb value at Week 24 of the treatment period and CRP levels 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: Hb value at Week 24 of the treatment period

(2) Proportion of subjects with Hb value within the target range (10.0 to <12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each time point of the treatment period

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion of subjects with Hb value within the target range (10.0 to <12.0 g/dL, within), <10.0 g/dL (below), and ≥12.0 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. The proportion of subjects with Hb value within the target range at each evaluation time point of the treatment period should be provided as a stacked bar chart with the number of subjects in each treatment group as 100%. Stacked bar charts should be generated separately for each treatment group.

For proportion of subjects within the target range at each evaluation time point of the treatment period, the point estimate, its 95% CI (exact method), and p-value (Fisher's exact test) of the between-group difference (MT-6548 − darbepoetin) will be calculated.

8.5.3 Analysis of other endpoints

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

The number of maintenance days from the state meeting the target Hb range to leaving the target Hb range should be calculated 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.

(2) Proportion of subjects who received rescue therapy with ESA, blood transfusion, or phlebotomy

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of 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.

(3) Study drug dosage

1) Study drug dosage

Descriptive statistics of the mean 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 study visit and the day before the next scheduled study visit.

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

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of 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 chart 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 time point of the treatment period, the dose should be based on the immediately before prescription.

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

An analysis similar to "1) Study drug dosage" should be conducted by the timing of administration of MT-6548 tablets (before meal, after meal, other). Only the MT-6548 group is analyzed.

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, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol).

5) Analysis by dose of previous ESA formulation types

An analysis similar to "1) Study drug dosage" should be conducted for weekly dose (epoetin alfa, epoetin beta or epoetin kappa: ≥4500 IU, <4500 IU; other: ≥ 15 μg, <15 μg; 2 categories) by type of previous ESA formulation (epoetin alfa, epoetin beta or epoetin kappa, darbepoetin alfa, epoetin beta pegol).

6) Analysis by 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 (subjects are divided into 3 categories with equal population).

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 and Week 24 of the treatment period and CRP levels 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: Mean dose of study drug at Week 20 to Week 24 of the treatment period

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

The total number of dose adjustments over the scheduled study visit period from the first day of the treatment period to Week 24 and over the entire period from the first day of the treatment period to Week 24 is calculated, and the number of subjects for each total number and its proportion with a 95% confidence interval (Clopper-Pearson [exact] method) are shown. The number and

proportion of subjects by total number of dose adjustments for each scheduled study visit period should be shown.

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion should be provided for the subjects defined below in each period between scheduled study visits and during the entire period from the first day to Week 24 of the treatment period. 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), 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.

(5) 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 2-sided 95% CI, 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.

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

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion of subjects treated with oral, intravenous, or oral iron supplement (any route) should be provided by treatment group 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. A McNemar tests should be used for before and after comparison between baseline (ratio of subjects receiving iron supplements by the aforementioned route in the 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.

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

The number, proportion, and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with serum ferritin levels of ≥100 ng/mL or TSAT levels of ≥20% should be provided at each evaluation time point of the treatment period for each treatment group. A McNemar tests should be used for before and after comparison between baseline (ratio of subjects receiving iron supplements by the aforementioned route in the 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 with serum ferritin ≥100 ng/mL or TSAT ≥20%.

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

Iron-related indices (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin should be measured at each evaluation time point of the treatment period, and their changes and rate of changes should be calculated from the first day of the treatment period to each evaluation time point of the treatment period. Descriptive statistics of the measurements, changes, and rate of changes should be calculated for each treatment group. 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 indices (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 within-subject variance–covariance matrix). 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 indices (serum iron, TIBC, TSAT, and serum ferritin levels) 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 similar time course diagram should be prepared for 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 ferritin should be conducted by baseline value (subjects are divided into 3 categories with equal population). The time course diagram of LSMean 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

(9) Changes in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period

Descriptive statistics of hematocrit, red blood cell count, reticulocyte (count and rate), and EPO at each evaluation time point should be calculated for each treatment group. The change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each 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 in hematocrit, red blood cell count, reticulocyte (count and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period to each evaluation time point. MMRM (within-subject variance–covariance matrix using the compound symmetry [CS]) is used to calculate LSMean and its standard error and 2-sided 95% CI for each treatment group, and the point estimate, its standard error, the 2-sided 95% CI, and p-value of the between-group difference (MT-6548 − darbepoetin groups) of LSMean are shown.

A histogram of EPO measurements should be prepared for evaluation time point at Week 24 of the treatment period.

(10) Changes in systolic blood pressure, diastolic blood pressure, and blood glucose from the first day of the treatment period, changes and rate of changes in lipid (total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, triglycerides) from the first day 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 (subjects are divided into 3 categories with equal population). The change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated for each 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 within-subject variance–covariance matrix). The LSMean for each treatment group is calculated, and the point estimate of the between-group difference (MT-6548 − darbepoetin) of LSMean, its standard error, 2-sided 95% CI, and p-value were shown.

Descriptive statistics should be similarly calculated for each treatment 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 within-subject variance–covariance matrix).

(11) 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, its 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 within-subject variance–covariance matrix). 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.

[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, VAS score, or change in index value or VAS score from the first day of the treatment period
- ✓ Estimated item (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 [Table 4.16.2] "subscale") for measured values and changes from the first day of the treatment period at each evaluation time point. Scores by subscale should be calculated using a scoring method 2) (Section 4.15).

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. 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 using the MMRM (with compound symmetry [CS] for within-subject variance–covariance matrix).

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 by the MMRM model 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.

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

The primary analysis for the primary endpoint should also be performed similarly 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 Week 20 to Week 24 of the treatment period for each treatment group.

8.5.4.6 Subgroup analyses

For the FAS, the following analyses should be performed for subgroups based on stratification factors (Table 8.5.4.6.1) for each of the following endpoints.

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

(2) Study drug mean dose at Week 20 to Week 24 of the treatment period

Descriptive statistics should be calculated for each treatment group.

(3) Target Hb 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 8.5.4.6.1 Subgroup analyses of efficacy

Endpoints	**Stratification factor**	**Stratified category**
1. Hb 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	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65
		<75, ≥75
	Dry 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	<10, ≥10 to <11, ≥11
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both not more than 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
	Ferritin (ng/mL) 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 supplement 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	Epoetin alfa or epoetin beta, darbepoetin alfa, epoetin beta pegol, other
	Dosage of epoetin alfa, epoetin beta, or epoetin kappa	Divide the number of subjects into three categories based on the tertile
	Dosage of darbepoetin alfa	Divide the number of subjects into three categories based on the tertile
	Dosage of epoetin beta pegol	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.

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 rate 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 the study drug (active 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, 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 should be calculated for each adverse event classified by SOC and PT in MedDRA/J 20.1. (hereinafter, the same). 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 of the same severity occur in the same subject, the same severity should be counted as 1 subject.

(3) 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 event 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 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 days (days) each dose has been administered during the study period.

* The tabulation unit by dose immediately before onset is 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, 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 to 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

For adverse events and adverse drug reactions, the number of subjects in the overall and in individual events classified by SOC and PT and the incidence rate to subjects with drug interruption should be calculated in before and after interruption of the active drug. It is 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 has had multiple interruptions, a second interruption within 4 weeks of the first interruption is counted both 4 weeks before and 4 weeks after the first interruption.

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, and dehydroepiandrosterone sulfate (hereinafter, DHEA-S). Changes from the first day of the treatment period at each evaluation time point should also be summarized.

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 Kt/V, Body weight after dialysis and dry weight

Descriptive statistics (except for 2-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 2-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 edema]) 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 ≥12.0 g/dL or ≥13.0 g/dL

The number and proportion of subjects with confirmed Hb ≥12.0 g/dL or ≥13.0 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 >12.0 g/dL or 13.0 g/dL in the same subject, the subject should be counted in both categories.

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 with confirmed Hb increase rate of ≥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 for each treatment group. The Hb increase rate in this tabulation should be calculated based on the difference in Hb values in each period between scheduled study visits in every 4 weeks and the treatment interval obtained from the actual study visit date.

8.6.11 Summary statistics of Hb values before and after dose reduction or drug interruption

Descriptive statistics of Hb values at dose reduction/drug interruption and after dose reduction/drug interruption of the study drug (active drug) should be calculated for each treatment group. In addition, the change of Hb after dose reduction/drug interruption of the study drug (active 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 (active 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 (active drug) to the Hb measurement after dose reduction/drug interruption should be calculated, and the descriptive statistics should be provided in each treatment group.

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
	Dry weight (kg) on the first day of the treatment period	<60, ≥60
	Hb value (g/dL) on the first day of the treatment period	<10, ≥10 to <11, ≥11
	Liver function test (U/L) on the first day of the treatment period	AST and ALT both not more than 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
Adverse events and adverse drug reactions	Timing of taking (MT-6548 group only)	Before meal, after meal, other

8.7 Pharmacokinetics analysis

[redacted]

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.