Errata

A Phase III, Open-label Study of MT-6548 in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

Study Protocol Number	MT-6548-J04

Date of Errata preparation	March 26, 2019
Errata prepared by	[redacted]

Object document	Statistical Analysis Plan
Object document version number	Version 2
Signature date	January 29, 2019

NCT number: NCT03461146
Note; This document was translated into English from the Japanese original version.

The Statistical Analysis Plan (Version 2) in "A Phase III, Open-label Study of MT-6548 in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan" is corrected as follows:

Applicable part	Correct
7.2.2. Subjects who discontinued or interrupted their treatment	(Error) Item: Number and proportion of cases of interruption in subjects who enrolled in the treatment period (Correct) Item: Number of cases of interruption in subjects who enrolled in the treatment period
	(Reason) Unnecessary description remained.

Applicable part	Correct
7.5.2 Analysis of other endpoints (5) Total number of dosage adjustments	(Error) , and the number, proportion, and 95% CI (Clopper–Pearson [Exact] method) of the proportion of subjects are shown. The number and proportion of subjects by total number of dose adjustments for each scheduled study visit period should be shown. (Correct) , and the number, proportion, and 95% CI (Clopper–Pearson [Exact] method) of the proportion of subjects 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
Table 7.5.4 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
7.6.1.2. Individual adverse events	(Error) For adverse events, adverse drug reactions, serious adverse events, non-serious adverse events, serious adverse drug reactions, adverse events leading to discontinuation of study drug, 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 version: 2x.x (hereinafter the same). (Correct) For adverse events, adverse drug reactions, serious adverse events, non-serious adverse events, serious adverse drug reactions, adverse events leading to discontinuation of study drug, 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).
	(Reason) Due to typographical error.

Applicable part	Correct
7.6.4. Kt/V, Body weight after dialysis and dry weight	(Error) Descriptive statistics (except 2-sided 95% CIs of the mean) should be calculated by evaluation time point. Changes in post-dialysis body weight and dry weight from the first day of the treatment period to each evaluation time point should also be summarized. (Correct) Descriptive statistics (except 2-sided 95% CIs of the mean) are calculated by evaluation time point. They are also summarized for changes from the first day of the treatment period to each evaluation time point in the same manner.
	(Reason) Unnecessary description remained.

Applicable part	Correct
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	(Reason) Added because there was description omission in the underlined part.

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

End

Statistical Analysis Plan

A Phase III, Open-label Study of MT-6548 in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan

Mitsubishi Tanabe Pharma Corporation

Preparation date	January 28, 2019
Study protocol number	MT-6548-J04
Version number	Version 2

Revision History

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

Statistical Analysis Plan

A Phase III, Open-label Study of MT-6548 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
BCRP	Breast cancer resistance protein
CKD	Chronic kidney disease
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
EDC	Electronic data capture
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
FAS	Full analysis set
GFR	Glomerular filtration rate
GCP	Good clinical practice
HD-CKD	Hemodialysis dependent chronic kidney disease
HIF-PH	Hypoxia inducible factor prolyl hydroxylase
IC_{50}	Median inhibitory concentration
JSDT	The Japanese society for dialysis therapy
LOCF	Last observation carried forward
MMRM	Mixed model repeated measures
MRP	Multidrug resistance-associated protein
NDD-CKD	Nondialysis dependent chronic kidney disease
OATP	Organic anion transporting polypeptide
OAT	Organic anion transporter
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Preferred term
PPS	Per protocol set
QOL	Quality of life
SOC	System organ class
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach maximum plasma concentration
TIBC	Total iron binding capacity
TSAT	Transferrin saturation

Definitions of terms

Term	Definitions
Study period	From the day of informed consent to the final day of the follow-up observation period
Treatment period	From the first day of the treatment period to the final day of the treatment period
Day of completion of treatment period	Week 52 of the treatment period or the day of discontinuation during the treatment period
X weeks prior to the first day of the screening period	Same day of the week X weeks prior to the first day of the screening period
MT-6548 tablets	Each film-coated tablet contains 150 mg vadadustat

1. Introduction

This is a document that shows more detailed contents in addition to those of the study plan on the statistical analysis plan for the efficacy and safety in the fixed data of "A Phase III, Open-label Study of MT-6548 in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease in Japan."

2. Study Objectives and Design

2.1 Study objectives

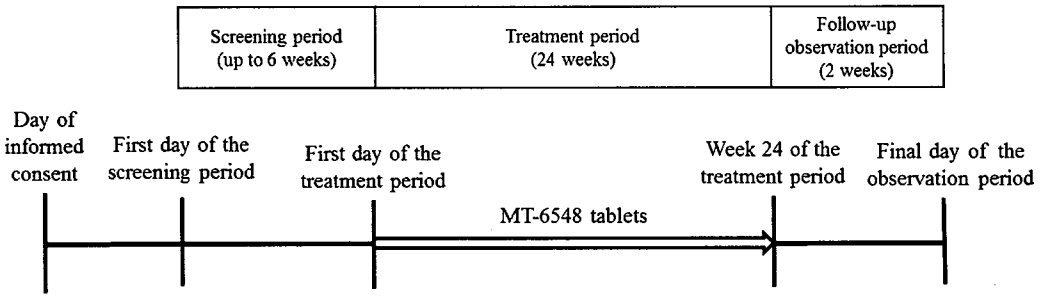
The study evaluates the effects of MT-6548 on improvement and maintenance in hemoglobin levels and safety in patients with anemia associated with hemodialysis-dependent chronic kidney disease (HD-CKD) who are not treated with any erythropoiesis-stimulating agent (ESA).

2.2 Study design

Study phase: Phase III

Study type: Confirmatory study

Multicenter, uncontrolled, open-label study



Evaluation time point

Item \ Visit	Informed consent	Screening period [a]		Treatment period [b]											Final day of the follow-up observation [c]
		First day	Visit 2	First day [b]	W2	W4	W6	W8	W10	W12	W16	W20	W24	Day of discontinuation	
Visit number	IC	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9	TV10	TV11	FU
Permitted range (days)	-	-	-	-	±3	±3	±3	±3	±3	±3	±7	±7	±7	+7 or +14 [e]	+7
Procedure/evaluation															
Informed consent	X														
Inclusion/exclusion criteria	X	X	X	X											
Patient backgroud and history	X			X											
Height				X											
Dry weight, body weight [f]				X						X			X	X	
Folic acid and vitamin B_{12} [g]		X													
Pregnancy tests [i]		X											X	X	
Hematology tests [g], [h], [j]		X	X [k]	X	X	X	X	X	X	X	X	X	X	X	
Blood biochemistry tests [g], [h], [l]		X		X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein [g], [h]		X		X									X	X	
Ion-related measures [g], [h]		X		X	X	X	X	X	X	X	X	X	X	X	
Hepcidin [h]				X	X	X	X			X			X	X	
EPO [h]				X	X	X	X			X			X	X	
VEGF[h]				X						X			X	X	
Vital signs [g], [h], [m]		X		X	X	X	X	X	X	X	X	X	X	X	
Resting standard 12-lead ECG [h], [n]				X									X	X	
Fundoscopy [e]		X										X		X	
Chest X-ray [e]		X										X		X	
Duration of hemodialysis				X									X	X	
QOL measures (EQ-5D-5L, KDQOL)				X						X			X	X	
AE investigation				X	X	X	X	X	X	X	X	X	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										
Product evaluation/procedure															
Investigation of concomitant medications/therapies				X	X	X	X	X	X	X	X	X	X	X	X
MT-6548 tablets [p], [q]				Administered according to the dosage adjustment guidelines											
Iron supplements		Iron supplements administered to maintain serum ferritin values of ≥100 ng/mL or 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] Should be performed before study drug administration (AE investigations begin after study drug administration).

[e] Fundoscopy and chest X-ray should be performed once during the screening period. Should be performed once during Week 20 to Week 24 of the treatment period. Should be performed within 14 days after discontinuation whenever possible if discontinued during the treatment period.

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

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

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

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

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

[k] Only Hb values should be measured.

[l] Urea nitrogen levels should be measured only before and after dialysis on the first day, Week 24 of the treatment period, and on the day of treatment discontinuation.

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

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

[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] 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.

[q] In principle, dosage adjustments should be performed at scheduled study visits; however, an unscheduled 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 value time course.

2.3 Rationale for sample size

Twenty subjects enrolled in the treatment period

[Rationale]

The proportion of patients who are not treated with any ESA formulation is as small as approximately 10% of the total number of dialysis patients in Japan. Patients receiving any ESA formulation are allowed to register after undergoing a washout; however, the target sample size was set at 20 after consideration of the feasibility as the number of eligible patients was thought to be very limited when considering the inclusion/exclusion criteria.

3. Endpoints

3.1 Efficacy endpoints

3.1.1 Primary endpoint

(1) Mean Hb values at Week 20 and Week 24 of the treatment period

(2) Hb value at each timepoint in the treatment period

(3) Proportion of subjects with mean Hb values within the target range (10.0 to12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each time point in the treatment period

(4) Number of days from the first day of the treatment period required to reach the target Hb range (10.0 to <12.0 g/dL)

(5) Hb value increase rate

3.1.2 Other endpoints

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

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

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

(4) Study drug dosage

(5) Total number of study drug dosage adjustments

(6) Iron supplement dosage

(7) Proportion of subjects receiving iron supplements via oral, intravenous, or any route.

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

(9) 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

(10) 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

(11) 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

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

3.2 Safety endpoints

(1) Adverse events and adverse drug reactions

(2) Laboratory test values

1) Hematology tests:

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

2) Blood biochemistry tests:

Total protein, albumin, blood glucose, urea nitrogen, creatinine, 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 (VEGF)

(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 value 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 day of study drug administration: Defined as "Scheduled first day of the modified dose administration" when a value of >0 mg is entered for the first time after the entry of "Changed Dose" = 0 mg in the CRF. 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: Defined as "Scheduled first day of the modified dose administration" when "Changed Dose" = 0 mg is entered in the CRF.

4.7 Duration of study drug administration

For subjects who completed treatment period:

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

For subjects who discontinued:

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

4.8 Number of study drug administration days

The number of days of study drug administration 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

4.9 Study drug compliance rate

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

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

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

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

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

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

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.

4.12 Hb value increase rate

The Hb value increase rate (g/dL/week) is defined as the rate calculated using the following method.

- Hb value increase rate (g/dL/week):
  (Hb value at Week 4 of the treatment period − Hb value at the first day of the treatment period)/([Hb value measurement day at Week 4 of the treatment period − Hb value measurement day at the first day of the treatment period]/7)
- Hb value increase rate (regression) (g/dL/week):
  The slope of the regression line calculated based on the Hb values measured from the first day of the treatment period to Week 6 of the treatment period and the measurement day (number of weeks from the first day of the treatment period) is defined as the Hb value increase rate (regression). Subjects without data at the first day and Week 6 of the treatment period should be excluded from the tabulation. The number of weeks from the first day of the treatment period used to obtain the regression line is defined by the following formula.

  First day of the treatment period: 0
  Treatment period of Week 2: (Measurement day at Week 2 of the treatment period − First day of the treatment period)/7
  Treatment period of Week 4: (Measurement day at Week 4 of the treatment period − First day of the treatment period)/7
  Treatment period of Week 6: (Measurement day at Week 6 of the treatment period − First day of the treatment period)/7

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

4.13 Iron supplement dosage

The dose of iron supplements is defined by the following formula.

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

*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 five questions (mobility [Mo], self care [Sc], usual activities [Ua], pain/discomfort [Pd], anxiety/depression [Ad] in 5 levels (level 1 is healthy and the level goes up to 5, and the health status decreases with increases in level) are converted into index values. The index value is calculated using the Japanese EQ-5D-5L conversion table (Table 4.15.1) [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

4.16QOL (KDQOL) scoring

Step 1 (See Table 4.16.1[2]): The appropriate score is converted from the response choices for each item number in Table 4.16.1 [2] (See Listing 16.2.4.9 for questions) for each subject.

Table 4.16.1 Step 1 in KDQOL scoring [2]

Item number	Response choices	Score
Question 4 A–D	1	0
Question 5 A–C, Question 21	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	1	0
Question 5 A, C	2	25
Question 12 A–D	3	50
	4	75
	5	100
Question 9 B, C, F, G, I	1	0
Question 18 B	2	20
	3	40
	4	60
	5	80
	6	100
Question 20	1	100
	2	0
Question 1, Question 2, Question 6,	1	100
Question 8	2	75
Question 11 B, D, Question 14 A–M	3	50
Question 15 A–H, Question 16 A, B	4	25
Question 24 A, B	5	0
Question 7	1	100
Question 9 A, D, E, H	2	80
Question 13 A–F	3	60
Question 18 A, C	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[2]): The mean of the scores calculated at Step 1 in the item numbers in the right column of Table 4.16.2[2] is calculated for each subject by subscale. For questions 17 and 22, the scores obtained are multiplied by 10 to convert the values from 0 to 100. The mean value should be the score for each subject by subscale. If at least one question constituting the subscale is answered,

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

Table 4.16.2 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

4.17 Adverse drug reaction

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

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; however, details of the handling of subjects should be determined by the sponsor by the time the data are fixed.

5.1 Efficacy analysis set

The analysis set consisting of all subjects transitioned to the treatment period excluding the following subjects is the FAS.

- Subjects who did not have anemia associated with HD-CKD
- Subjects who have never received a dose of study drug
- Subjects with no efficacy data after the first day of study drug administration

5.2 Safety analysis set

The analysis set consisting of all subjects transitioned to the treatment period excluding the following subjects is the safety analysis set.

- Subjects who have never received a dose of study drug
- Subjects with no safety data after the first of study drug administration

6. Data Handling

Data should be handled as follows:

6.1 Handling of missing data

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

6.2 Handing of data for tabulation at each evaluation time point

Data that meet the permitted range specified in the "Table 9.1-1 Permitted range of study visits" section of the protocol should be used for the tabulation at each evaluation time point and should not be imputed with those outside the permitted range.
If there are multiple data within the permitted range, then the one closer to the reference date should be adopted. If the deviations from the reference date are the same, data for the efficacy and safety evaluations should be adopted before and after the reference date, respectively.

6.3 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.

6.4 Imputation of missing values

The mixed repeated-measures model (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.

For the primary endpoint, the mean Hb levels at Weeks 20 and 24 of the treatment period, missing data are imputed with data from the evaluation period immediately before the missing evaluation period (excluding the first day of the treatment period) (LOCF method). When any one evaluation time points has missing values, the data at the evaluation time point closest to the missing evaluation time point is adopted, and when two evaluation time points have missing values, the data in the two different evaluation time points closest to and before the missing evaluation time points should be adopted to calculate the mean Hb value. However, Hb values at the same evaluation time point should not be used.

In addition, clinical laboratory values, vital signs, and QOL indices among the efficacy endpoints, values imputed by the LOCF method at Week 24 of the treatment period should also be output. Data of Week 24 of the treatment period imputed with missing values will be used as data from the completion of treatment period.

6.5 Handling of clinical laboratory test values not more than the limit of quantification, etc

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

[Handling of quantification limit values]

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

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

1) After checking the number of significant figures of the applicable item, 1 should be subtracted from the lowest significant figure of the 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 figure from the measuring facility: up to ones digit
→ Tabulation handling: 2.9

Report: <500 Significant figure from the measuring facility: up to tens digit
→ Tabulation handling: 499

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

Example) Not more than the limit of quantification

Report: ≤10 → Tabulation handling: 10

Not less than the limit of quantification

Report: ≥20 → Tabulation handling: 20

7. Statistical Method

7.1 Basic Matters

7.1.1 Level of significance and confidence coefficient

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

7.1.2 Descriptive statistics to calculate

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

7.1.3 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 three decimal places.

7.2 Breakdown of subjects

7.2.1 Disposition

For subjects enrolled in the treatment period, the breakdown of each analysis set should be provided.

Items: Number of subjects enrolled in the treatment period, number and proportion of subjects in the FAS, number and proportion of subjects not included in the FAS, number and proportion of subjects in the safety analysis set, number and proportion of subjects not included in the safety analysis set

7.2.2 Subjects who discontinued or interrupted their treatment

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

Item: Number and proportion of discontinued subjects who enrolled in the treatment period and the number and proportion of subjects who discontinued by reasons of discontinuation.

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

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

7.3 Demographic and other baseline characteristics

For each analysis set, key demographic and other baseline characteristics are 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 safety analysis set is the same as the FAS, the results for the former will not be presented.

Table 7.3 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 nor Latino, Hispanic or Latino, Unknown	Polytomous
	Ethnicity 3 Categories: Asian (Japanese), Asian (Other), Other	Polytomous

Evaluation data	Hb value (g/dL) on the first day of the treatment period	Continuous
	3 Categories: <9, 9 to <10, ≥10	Trichotomous
	Liver function test (U/L) on the first day of the treatment period	
	3 Categories: AST and ALT both not more than 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	Trichotomous
	CRP (mg/dL) on the first day of the treatment period	Continuous
	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
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
Iron supplement	With or without iron supplements on the first day of the treatment period	Dichotomous
	2 Categories: oral, intravenous	Dichotomous
Iron-containing phosphate binders	With or without iron-containing phosphate binders on the first day of the treatment period	Dichotomous
Previous ESA formulation	ESA formulation washout (yes/no)	Dichotomous
Hemodialysis	Types of hemodialysis 2 Categories: hemodialysis, hemodiafiltration	Dichotomous
	Duration of hemodialysis (years)	Continuous
	Frequency of dialysis 2 Categories: 3 × per week, other	Dichotomous

7.4 Duration of study drug administration and treatment compliance

For the FAS and safety analysis set, descriptive statistics of the compliance rate of the study drug (no calculation of 95% CI of the mean) should be calculated to provide the number and proportion of subjects with a compliance rate of ≥80% and <80%.

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

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

7.5 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.

7.5.1 Analysis of primary endpoint

(1) Mean Hb values at Week 20 and Week 24 of the treatment period

Descriptive statistics should be calculated for the primary efficacy endpoint of the mean Hb values at Week 20 and Week 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 for Week 20 and Week 24 of the treatment period should be obtained, and the least squares mean (LSMean), its standard error, and 2-sided 95% CIs for the mean Hb values should be calculated.

[MMRM Model]

- Covariate: Response variable value of the first day of the treatment period
- Fixed effects: Evaluation time point
- Degrees of freedom adjustment: Kenward-Roger method
- Covariance matrix within subject for each subject: Unstructured (type = UN; unstructured)

If the variance-covariance matrix within subjects is not converged using unstructured data, the variance-covariance matrix within subjects should be changed in the following order, and the analysis should be performed using the variance-covariance matrix within subjects that converges 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

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

LSMean, its standard errors, and 2-sided 95% CI of mean Hb values at each evaluation time point of the treatment period should be calculated using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects) similar to that used in "mean Hb values at Week 20 and Week 24 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 using the MMRM (with compound symmetry [CS] for a variance-covariance matrix within subjects).

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

(3) Proportion of subjects with mean Hb levels within the target range (10.0–12.0 g/dL), <10.0 g/dL, and ≥12.0 g/dL at each 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. Before and after comparison should be conducted for changes from the first day of the treatment period to each evaluation time point using the McNemar test.

The proportion of subjects in each Hb category (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 should be provided as a stacked bar graph assuming that the number of subjects at each evaluation time point is 100%. Stacked bar charts should be separately prepared.

(4) Number of days from the first day of the treatment period required to reach the target Hb range (10.0 g/dL to <12.0 g/dL)

Descriptive statistics should be calculated for number of days required from the first day of the treatment period to reach target Hb range (10.0 g/dL to <12.0 g/dL). The number of days should be calculated as the first evaluation date reached target Hb range − first date of the treatment period

+ 1. If target Hb range is not reached, the final date of evaluations − first date of the treatment period + 1 should be assumed.

A Kaplan-Meier plot should be shown for days from the first day of the treatment period required to reach the target Hb range.

No subjects with an Hb value of≥10.0 g/dL on the first day of the treatment period will be included in the calculation.

(5) Hb value increase rate

Descriptive statistics should be calculated for the Hb value increase rate (g/dL/week).

The Hb value increase rate should be analyzed by 2 methods defined in the "Hb value increase rate".

7.5.2 Analysis of other endpoints

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

Descriptive statistics for change from Hb value on the first day of the treatment period to mean Hb values at Week 20 and Week 24 in the treatment period should be calculated. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period. The analysis should be conducted using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects). LSMean, its standard errors, and 2-sided 95% CI for change from Hb value on the first day of the treatment period to mean Hb values at Week 20 and Week 24 of the treatment period should be calculated.

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

The number, proportion, and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with a mean Hb increase of≥1.0 g/dL from the first day to each evaluation time point of the treatment period should be provided.

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

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

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.

(4) Study drug dosage

1) Study drug dosage

Descriptive statics of mean daily dose should be calculated for each scheduled study visit from the first day of the treatment period up to treatment period Week 24. The time course diagram for mean daily dose should be separately prepared. 95% CI of the mean will be represented by an error bar. Each period between scheduled study visits is defined as the period between the scheduled visit and the day before the next scheduled study visit.

2) Distribution of dose of MT-6548 tablets

The number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion of subjects per daily dose based on the prescription should be provided at each evaluation time point.

The proportion of subjects per daily dose based on the prescription at each evaluation time point of the treatment period should be provided as a stacked bar graph with the number of subjects in each treatment group as 100%. Stacked bar charts should be separately prepared.

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

(5) Total number of dosage adjustments

The cumulative total number of dose adjustments from the first day of the treatment period to Week 24 of the treatment period should be calculated, and the number, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion of subjects 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 the 95% CI (Clopper-Pearson [Exact] method) of the proportion of subjects should be provided for 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 increase (Increase), dose decrease (Decrease), drug interruption (Interrupt)

Dose adjustment should include the number of times of increase, decrease, and interruption, and should not count as the increase when it is resumed after interruption.

(6) 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 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. Descriptive statistics should be calculated for the changes.

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.

(7) 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 iron supplement via oral, intravenous, or any route should be provided for screening period, and after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period. Before and after comparison should be conducted for changes between baseline (proportion of subjects receiving iron supplements by the aforementioned route in screening period) and each period between scheduled study visits using the McNemar test.

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 iron supplement via oral, intravenous, or any route are to be subjects who have received an iron supplement at least once during the relevant period.

(8) Proportion of subjects with serum ferritin $\geq$ 100 ng/mL or TSAT $\geq$ 20%.

The number, proportion, and 95% CI (Clopper-Pearson [exact] method) of the proportion of subjects with serum ferritin levels of $\geq$100 ng/mL or TSAT levels of $\geq$20% should be provided at each evaluation time point of the treatment period. Before and after comparison should be conducted for changes between baseline and each period between scheduled study visits using the McNemar test.

(9) 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

Descriptive statistics should be prepared for measured values of iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin at each evaluation time point of the treatment period and their change and change rates from the first day of the treatment period. A paired t-test should be performed for before and after comparison of changes and change rates from the first day of the treatment period.

LSMean, its standard errors, and 2-sided 95% CI should be calculated for the change in iron-related measures (serum iron, TIBC, TSAT, and serum ferritin) and hepcidin from the first day of the treatment period to each evaluation time point using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects). Only the serum ferritin value at each evaluation time point of the treatment period should be analyzed similarly.

The time course diagram of changes in the iron-related measures (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. The 95% CI of LSMean will be represented by an error bar. For only the serum ferritin value, a time course diagram should also be prepared for mean ferritin value at each evaluation time point of the treatment period. 95% CI of the mean will be represented by an error bar.

The serum ferritin values are shown as follows.

- 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 values at baseline

  y: Serum ferritin values at Week 24 of the treatment period

(10) 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 (number and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO should be calculated at each evaluation time point. And, the change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period.

LSMean, its standard errors, and 2-sided 95% CI should be calculated for the change in hematocrit, red blood cell count, reticulocyte (number and rate), mean corpuscular volume, mean corpuscular hemoglobin, and EPO from the first day of the treatment period to each evaluation time point using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects).

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

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

The change from the first day of the treatment period should be obtained, and the descriptive statistics should be calculated. A paired t-test should be performed for before and after comparison of changes from the first day of the treatment period. LSMean, standard error, and 2-sided 95% CI should be calculated for the change from the first day of the treatment period using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects).

The descriptive statistics should be similarly calculated for the change rate 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 LSMean, standard error, and 2-sided 95% CI should be calculated using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects).

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

1) EQ-5D-5L

The number, proportion, and 2-sided 95% CI (Clopper-Pearson [Exact] method) of the proportion 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 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.

The change in Index value and VAS score from the first day of the treatment period at each evaluation time point should be compared between groups using the MMRM model (with compound symmetry [CS] for a covariance matrix within subject variance), and LSMean, its standard errors, and 2-sided 95% CI should be calculated.

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 (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.

LSMean, its standard errors, and 2-sided 95% CI should be calculated for the change in KDQOL from the first day of the treatment period to each evaluation time point using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects).

7.5.3 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, the analysis using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects) 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.

7.5.4 Handling of dropout or missing data

Provided in 6. Data handling.

7.5.5 Multicenter trial

For FAS, the following analysis should be conducted for each following endpoint for each site. Descriptive statistics of Hb values should be calculated at Week 24 of the treatment period (imputed by the LOCF method).

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

7.5.6 Subgroup analyses

The following analyses should be conducted for subpopulations based on the stratification factor for each endpoint in the table below in the FAS.

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

LSMean, standard error, and 2-sided 95% CI should be calculated using the MMRM model (with compound symmetry [CS] for a variance-covariance matrix within subjects).

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

Descriptive statistics should be calculated.

(3) Responder rates at Week 24 of the treatment period

With respect to the responder rate at Week 24 of the treatment period (proportion of subjects with increased Hb value by ≥1.0 g/dL from the first day of the treatment period), the number of responders, proportion, and 95% CI (Clopper-Pearson [Exact] method) of the proportion should be provided.

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

The number, proportion, and 95% CI (Clopper-Pearson [Exact)] method) of the proportion of subjects with Hb levels within the target range (10.0 g/dL to <12.0 g/dL) should be provided.

Table 7.5.4 Subgroup analysis 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. Responder rates at Week 24 of the treatment period 4. Target Hb achievement rate at Week 24 of the treatment period	Sex	Male, Female
	Age at time of consent (years)	<65, ≥65
		<75, ≥75
	Dry weight (kg) on the first day of the treatment period	<60, ≥60
	BMI (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	Presence or absence of hypertension, diabetes, dyslipidemia
	Hb value (g/dL) on the first day of the treatment period	<9, 9 to <10, ≥10
	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
	Serum ferritin (ng/dL) on the first day of the treatment period	Divide the number of subjects into three categories based on the tertile
	TSAT (%) on the first day of the treatment period	Divide the number of subjects into three categories based on the tertile
	Smoking status	3 Categories: Never smoked, ex-smoker, current smoker
	Administration of oral iron on the first day of the treatment period	Yes or No
	Treatment with oral iron supplement at Week 24 of the treatment period	Yes or No
	Iron-containing phosphate binders on the first day of the treatment period	Yes or No
	Iron-containing phosphate binders at Week 24 of the treatment period	Yes or No
	Wash-out of prior treatment ESAs	Yes or No
	CYP2B6 inducer combination *	Yes or No

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

7.5.7 Multiple comparison and multiplicity

In this study, no multiplicity problem occurs.

7.6 Safety analysis

The safety analysis population should be analyzed. When necessary, frequency and proportion should be calculated for discrete variables and descriptive statistics for continuous variables.

7.6.1 Adverse events and adverse drug reactions

7.6.1.1 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.

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

7.6.1.2 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 of study drug, 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 2x.x (hereinafter the same). The SOC is shown in the order of international consensus, and the PT is shown in descending order of the number of subjects with events (if the number is the same, ascending order of PT Code).

7.6.1.3 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 one 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.

7.6.1.4 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)

7.6.1.5 Adverse events by dose immediately before onset

The number and incidence rate to total exposure period of adverse events and adverse drug reactions in overall and individual events classified by SOC and PT should be calculated 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)

7.6.1.6 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.)

7.6.1.7 Adverse events before and after drug interruption

The number of subjects and incidence rate should be calculated for adverse event and adverse drug reaction by before and after drug interruption for the overall and for individual events classified by SOC and PT. It 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 had multiple drug interruptions and the adverse event occurred within 4 weeks after the drug interruption and within 4 weeks before the drug interruption, the subject should be counted as 1 subject for both periods.
Drug interruption period is defined as the "Planned start date of the modified dose" when "Yes" was selected in the question of "Did you choose the dosage according to the dosage adjustment algorithm?" and "Changed dose" = 0 mg in the question of "Whether the dose was changed" in the "Administration status of MT-6548" 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.

7.6.2 Laboratory test values

Descriptive statistics (except 2-sided 95% CI of the mean) should be calculated by treatment group in each evaluation time point for hematology tests, blood biochemistry tests, C-reactive protein, and VEGF. Changes from the first day of the treatment period at each evaluation time point should also be summarized.

7.6.3 Resting standard 12-lead ECG

The frequency of each decision result (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be calculated at the 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.

7.6.4 Kt/V, Body weight after dialysis and dry weight

Descriptive statistics (except 2-sided 95% CIs of the mean) should be calculated by evaluation time point. Changes in post-dialysis body weight and dry weight from the first day of the treatment period to each evaluation time point should also be summarized.

7.6.5 Vital signs

Descriptive statistics (except for 2-sided 95% CIs of the mean) should be calculated by evaluation time point for the items of blood pressure and pulse rate. Changes from the first day of the treatment period to each evaluation time point should also be summarized.

7.6.6 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.

7.6.7 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.

7.6.8 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 values ≥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 24 of the treatment period should be provided. If Hb value is >12.0 g/dL or 13.0 g/dL in the same subject, the subject should be counted as 1 in both categories.

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

Subjects with confirmed Hb <9.0 g/dL or <8.0 g/dL should be analyzed in the same manner as in Section 7.6.8.

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

The number and proportion of subjects in whom the Hb value increase rate is confirmed to be >0.5 g/dL/week, after the first day of the treatment period, in each period between scheduled study visits and during the entire treatment period from the first day to Week 24 of the treatment period should be provided. The Hb value increase rate in this tabulation should be calculated based on the difference in Hb values between the 2 time points measured on the scheduled study visit day in every 4 weeks (first day of the treatment period, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 of the treatment period) and the Hb value measurement interval obtained from the actual study visit date.

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

Descriptive statistics of Hb values at dose reduction/interruption and after dose reduction/interruption of the study drug should be calculated. In addition, the change in Hb value after dose reduction/interruption of the study drug should be determined, and descriptive statistics should be calculated.

For the Hb value after dose reduction/drug interruption of the study drug, the data of the day closest to 4 weeks (28 days) after the Hb measurement day at dose reduction/drug interruption should be adopted. If no study drug data at the time of dose reduction/drug interruption are available, subjects

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

7.6.12 Subgroup analyses

In the safety analysis set, the number and incidence ratio of subjects with adverse events and/or adverse drug reactions should be calculated for each subgroup based on the stratification factors for each endpoint in the table below.

Table 7.6.10.1 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	<9, 9 to <10, ≥10
	Liver function value	AST or ALT ≤ upper limit of normal, either > 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	Dose timing	Before meal, after meal, other

8. Software to Use

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

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

(1) Mean corpuscular volume and mean corpuscular hemoglobin were added to the other efficacy endpoints.

Reason: Because the importance of mean corpuscular volume and mean corpuscular hemoglobin has increased in the efficacy evaluation from a clinical point of view.

10. References

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

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