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Statistical Analysis Plan

A Clinical Pharmacological Study to Evaluate the Effects of Oral Irons and Iron-containing Phosphate Binders on the Pharmacokinetics of MT-6548 in Healthy Male Volunteers

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Version 2	
final edition	

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Approval Column

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List of Abbreviations

Abbreviation	Full term
BMI	Body mass index
PKP	Population for pharmacokinetic analysis
SAF	Population for safety analysis
BCRP	Breast cancer resistance protein
PK	Pharmacokinetics
PT	Preferred term
SOC	System organ class

List of Abbreviations for Pharmacokinetic Parameters

Abbreviation	Full term
AUC	Area under the plasma concentration-time curve
C_{max}	Maximum plasma concentration
Kel	Apparent terminal elimination rate constant
MRT	Mean residence time
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach maximum plasma concentration
R^2	Adjusted R^2
R	Correlation coefficient

Definitions of terms

Term	Definitions
Study phase	Cohort 1: Period 1 is defined as the period from the time of administration of the study drug on Day 1 to before administration of the study drug on Day 4. Period 2 is defined as the period from the time of administration of the study drug on Day 4 to before administration of the study drug on Day 7. Period 3 is defined as the period from the time of administration of the study drug on Day 7 to the end of the prescribed tests on Day 10. Cohorts 2 and 3: Period 1 is defined as the period from the time of administration of the study drug on Day 1 to before administration of the study drug on Day 4. Period 2 is defined as the period from the time of administration of the study drug on Day 4 to the end of the prescribed tests on Day 7.
Conditions of administration	Cohort 1: Administration of MT-6548 tablets alone, coadministration of MT-6548 tablets and sodium ferrous citrate formulation, or coadministration of MT-6548 tablets and ferric citrate hydrate tablets Cohort 2: Administration of MT-6548 tablets alone or coadministration of MT-6548 tablets and sucroferric oxyhydroxide chewable tablets Cohort 3: Administration of MT-6548 tablets alone or coadministration of MT-6548 tablets and ferrous sulfate sustained-release tablets

1. Introduction

This is a document that shows more detailed contents in addition to the study protocol on the statistical analysis plan of "A Clinical Pharmacological Study to Evaluate the Effects of Oral Irons and Iron-containing Phosphate Binders on the Pharmacokinetics of MT-6548 in Healthy Male Volunteers."

2. Study Objectives and Design

2.1 Study objectives

This study evaluates the pharmacokinetics and safety of MT-6548 in healthy male subjects following coadministration of MT-6548 and oral iron or iron-containing phosphate binders.

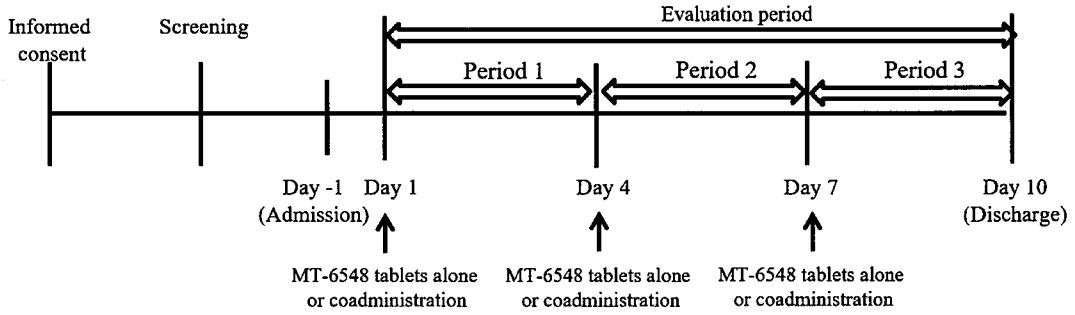
2.2 Study design

Study phase: Phase III

Study type: Clinical pharmacology study

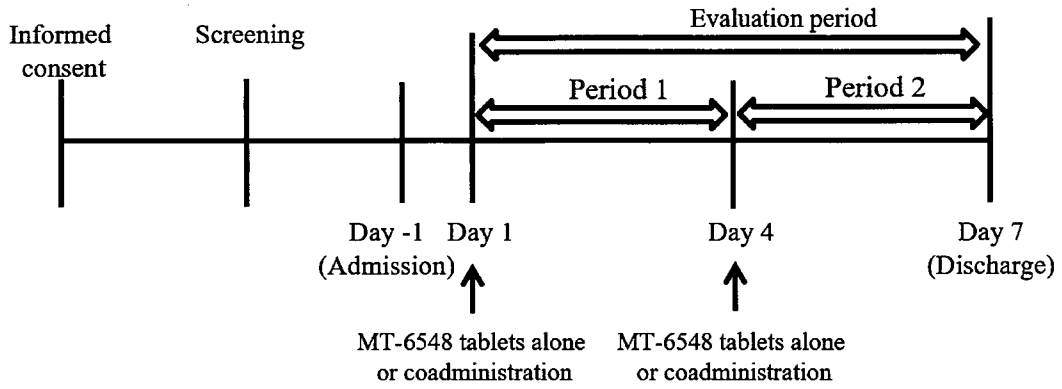
Single dose, open-label, randomized, crossover study

Cohort 1 (postprandial cohort)



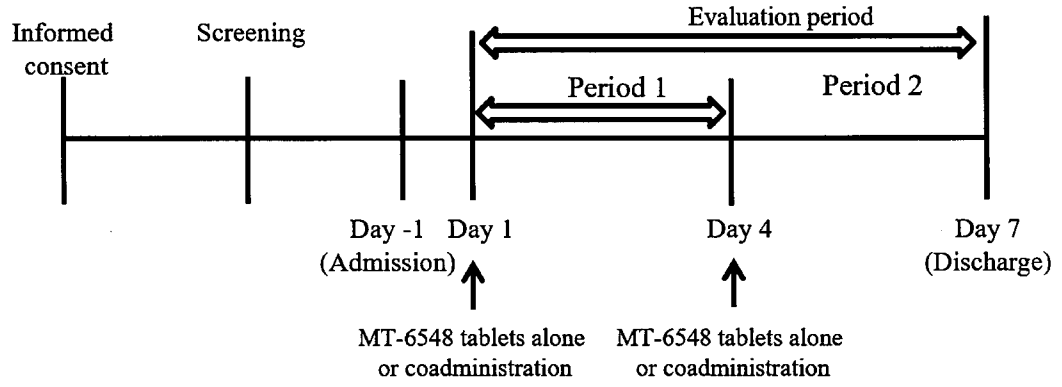
	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
Group 1	MT-6548 tablets	MT-6548 tablets and sodium ferrous citrate formulation	MT-6548 tablets and ferric citrate hydrate tablets
Group 2	MT-6548 tablets and ferric citrate hydrate tablets	MT-6548 tablets	MT-6548 tablets and sodium ferrous citrate formulation
Group 3	MT-6548 tablets and sodium ferrous citrate formulation	MT-6548 tablets and ferric citrate hydrate tablets	MT-6548 tablets

Cohort 2 (preprandial cohort)



	Period 1 (Day 1)	Period 2 (Day 4)
Group 4	MT-6548 tablets	MT-6548 tablets and sucroferric oxyhydroxide chewable tablets
Group 5	MT-6548 tablets and sucroferric oxyhydroxide chewable tablets	MT-6548 tablets

Cohort 3 (fasting cohort)



	Period 1 (Day 1)	Period 2 (Day 4)
Group 6	MT-6548 tablets	MT-6548 tablets and ferrous sulfate sustained-release tablets
Group 7	MT-6548 tablets and ferrous sulfate sustained-release tablets	MT-6548 tablets

Study period: The study period is defined as the period from the date of informed consent to the completion of follow-up examinations.

Screening tests: After obtaining consent, screening tests should be performed to confirm eligibility and eligible subjects will be selected. Screening tests should be performed within 4 weeks before the day of study drug administration in Period 1 (Day 1). Subjects should be admitted after obtaining the results of all tests specified in the screening tests. Day −1 (the day before study drug administration) is the admission date.

Evaluation period: Cohort 1 should be admitted for 10 nights and 11 days. Period 1 is defined as the period from the time of administration of the study drug on Day 1 to before administration of the study drug on Day 4. Period 2 is defined as the period from the time of administration of the study drug on Day 4 to before administration of the study drug on Day 7. Period 3 is defined as the period from the time of administration of the study drug on Day 7 to the end of the prescribed tests on Day 10.

Cohorts 2 and 3 should be admitted for 7 nights and 8 days. Period 1 is defined as the period from the time of administration of the study drug on Day 1 to before administration of the study drug on Day 4. Period 2 is defined as the period from the time of administration of the study drug on Day 4 to the end of the prescribed tests on Day 7.

Post-administration tests: Post-administration tests should be performed 3 days after the last dose of the study drug.

Randomization methods

The person responsible for preparing the randomization keycode table should prepare a randomization keycode table for each cohort in accordance with the predetermined study drug allocation procedures and provide it in a sealed state for each cohort to the investigator. The investigator/coinvestigator should assign subject identification codes to all subjects in each cohort, and after identifying the subjects and reserve subjects (reserve subjects should be determined in advance, also in order of enrollment), unseal the randomization keycode table, and assign subjects to each group in ascending order of subject identification codes, and assign subject numbers. If subjects are to be substituted in the final selection process, they should be substituted by matching their subject identification codes to the predetermined order of enrollment for reserve subjects in ascending order. The investigator/coinvestigator, or clinical coordinator should submit a copy of the randomization keycode table to the sponsor. The investigator/coinvestigator should prescribe the study drug and/or the oral iron or iron-containing phosphate binder assigned to the group. Details of randomization should be defined in the study drug allocation procedures.

2.3 Test and observation schedule

Cohort 1 (Postprandial cohort)

	Informed consent	Screening	Day -1	Evaluation period																																						Discontinuations only	
				Period 1															Period 2														Period 3											
				Day 1												Day 2	Day 3		Day 4											Day 5	Day 6		Day 7								Day 8	Day 9	Day 10 (Post-administration tests) [c]	At discontinuation [d]	Post-administration tests [e]
Time (h) [a]				0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48		0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48		0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72		
Informed consent	●																																											
Administration of MT-6548 tablets				●															●														●														
Administration of oral iron preparations [b]				●															●														●														
Administration of iron-containing phosphate binders [b]				●						●			●						●						●			●					●						●			●						
Meals on the day of administration of the study drug				●						●			●						●						●			●					●						●			●						
Subject baseline characteristics	●	●	●	●																																								
Interview/examination		●	●	●					●							●	●		●					●						●	●		●					●						●	●	●	●	●
Vital signs		●	●	●												●	●		●												●	●		●					●						●	●		●	
12-lead ECG		●		●												●			●												●			●					●						●			●	
Laboratory tests		●		●												●			●												●			●					●						●			●	
Immunology tests		●																																											
Blood sampling for pharmacokinetics analysis				●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●	●	●	●	●	●	●	●				●	●	●	●	●	●	●	●	●	●	●	●					
Check for adverse events				←																																									→	●	●
Check for use of concomitant drugs				←																																									→	●	●

[a] The time of administration of the study drug in each evaluation period is designated as 0 h.
[b] On one of Day 1, Day 4, or Day 7, the study drug should be administered immediately after meal, depending on the allocated group.
[c] Completed subjects should undergo post-administration tests on Day 10.
[d] Should be performed on discontinuation after administration of the study drug.
[e] Should be performed 3 days after administration of the last dose of the study drug. However, the post-administration tests may be omitted if the tests on discontinuation occur 3 days or later after administration of the last dose of the study drug.

Cohort 2 (Preprandial cohort)

	Informed consent	Screening	Day -1	Evaluation period																												Discontinuations only	
				Period 1															Period 2															
				Day 1												Day 2	Day 3		Day 4											Day 5	Day 6	Day 7 (Post-administration tests) [c]	At discontinuation [d]	Post-administration tests [e]
Time (h) [a]				0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48		0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72		
Informed consent	●																																	
Administration of MT-6548 tablets				●															●															
Administration of iron-containing phosphate binders [b]				●						●			●						●						●			●						
Meals on the day of administration of the study drug				●						●			●						●						●			●						
Subject background	●	●	●	●																														
Interview/examination		●	●	●					●							●	●		●					●							●	●	●	●	●
Vital signs		●	●	●												●	●		●												●	●		●	
12-lead ECG		●		●												●			●												●			●	
Laboratory tests		●		●												●			●												●			●	
Immunology tests		●																																
Blood sampling for pharmacokinetics analysis				●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●	●	●	●	●	●	●	●				
Check for adverse events				←																											→		●	●
Check for use of concomitant drugs				←																											→		●	●

[a] The time of administration of the study drug in each evaluation period is designated as 0 h.
[b] On one of Day 1 or Day 4, the study drug should be administered before food, depending on the allocated group.
[c] Completed subjects should undergo post-administration tests on Day 7.
[d] Should be performed on discontinuation after administration of the study drug.
[e] Should be performed 3 days after administration of the last dose of the study drug. However, the post-administration tests may be omitted if the tests on discontinuation occur 3 days or later after administration of the last dose of the study drug.

Cohort 3 (Fasting cohort)

	Informed consent	Screening	Day -1	Evaluation period																													Discontinuations only	Post-administration tests
				Period 1																	Period 2														
				Day 1													Day 2	Day 3		Day 4												Day 5	Day 6	Day 7 (Post-administration tests) [c]	At discontinuation [d]	[e]
Time (h) [a]				0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72		
Informed consent	●																																	
Administration of MT-6548 tablets				●														●																
Administration of oral iron preparations [b]				●														●																
Meals on the day of administration of the study drug										●			●											●			●							
Subject background	●	●	●	●																														
Interview/examination		●	●	●					●							●	●	●					●							●	●	●	●	●
Vital signs		●	●	●												●	●	●												●	●		●	
12-lead ECG		●		●												●		●												●			●	
Laboratory tests		●		●												●		●												●			●	
Immunology tests		●																																
Blood sampling for pharmacokinetics analysis				●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●				
Check for adverse events				←																												→	●	●
Check for use of concomitant drugs				←																												→	●	●

[a] The time of administration of the study drug in each evaluation period is designated as 0 h.
[b] On one of Day 1 or Day 4, the study drug should be administered depending on the allocated group.
[c] Completed subjects should undergo post-administration tests on Day 7.
[d] Should be performed on discontinuation after administration of the study drug.
[e] Should be performed 3 days after administration of the last dose of the study drug. However, the post-administration tests may be omitted if the tests on discontinuation occur 3 days or later after administration of the last dose of the study drug.

Variable

Variable		Details
Subject background		Sex, ethnicity, birth date, age, height, body weight, BMI, concomitant disease
Interview/examination		Interview/examination
Vital signs		Blood pressure (supine position), pulse rate (supine position), body temperature (axillary)
Standard 12-lead ECG		Findings
Laboratory tests	Hematology tests	RBC count, hemoglobin value, hematocrit, WBC count, platelet count, WBC fractions (neutrophils, eosinophils, monocytes, lymphocytes, basophils)
	Blood biochemistry tests	Total protein, albumin, blood glucose, urea nitrogen, serum creatinine, uric acid, CPK, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, Na, K, Cl, Ca, P, Mg, total cholesterol, LDL-C, HDL-C, triglycerides, C-reactive protein, serum iron, ferritin, TSAT
	Urinalysis (qualitative)	Glucose, protein, urobilinogen, occult blood, specific gravity, pH, ketone bodies, bilirubin
Immunology tests (only at screening)		Serologic reaction for syphilis, HBs antigen, HCV antibody, HIV antigen/antibody

2.4 Rationale for sample size

Cohort 1: 21 subjects

Cohort 2: 20 subjects

Cohort 3: 20 subjects

[Rationale]

[redacted]

3. Endpoints

3.1 Pharmacokinetics

(1) Plasma concentration

Plasma concentration of unchanged MT-6548

(2) Pharmacokinetic parameters

$AUC_{0-\infty}$, C_{max}, t_{max}, AUC_{0-last}, $MRT_{0-\infty}$, Kel, and $t_{1/2}$ of unchanged MT-6548

3.2 Safety endpoints

The following endpoints should be evaluated.

(1) Adverse events and adverse drug reactions

(2) General laboratory tests

(3) Vital signs

(4) Standard 12-lead ECG

4. Calculation of Pharmacokinetic Parameters

For each evaluation period, plasma concentrations of unchanged MT-6548 should be measured, and pharmacokinetic parameters should be calculated by noncompartmental analysis. The time used for calculation of pharmacokinetic parameters should be the actual elapsed time with the time of administration of the study drug at 0.00 hours for each study period (round to two decimal places). If observed and predicted values exist for the same parameter, the observed value should be adopted.

4.1 Area under the plasma concentration-time curve extrapolated to infinity: $AUC_{0-\infty}$

Unit: μg·h/mL

Number of display digits: Should be rounded and displayed to one decimal place.

Calculation method: $AUC_{0-\infty} = AUC_{0-t} + C_{obs}/Kel$

Where AUC_{0-t} is the area under the plasma concentration-time curve from before administration to the last observation point, which is not below the lower limit of quantification (Linear Trapezoid [Linear Interpolation]), C_{obs} is the concentration at the last observation point, and Kel is the elimination rate constant of the terminal elimination phase in the elimination phase. If Kel is not calculated, it should be regarded as a missing value and displayed as "–".

4.2 Maximum plasma concentration: C_{max}

Unit: μg/mL

Number of display digits: Same as the measured value (however, the units should be converted from ng/mL to μg/mL).

Calculation method: The measured value showing the highest plasma concentration in each subject should be used. If the concentrations are below the lower limit of quantification at all time points, the concentration should be 0.000 μg/mL. If the values measured at all time points are not adopted, they are regarded as missing values and displayed as "–".

4.3 Time to reach maximum plasma concentration: T_{max}

Unit: h

Number of display digits: Should be displayed to two decimal places.

Calculation method: The time point showing the highest plasma concentration in each subject is used. If the C_{max} value is at least two time points, the first time point should be taken as t_{max}. If the plasma

concentrations are below the lower limit of quantification at all time points, they should be regarded as missing values and displayed as "–".

4.4 Area under the plasma concentration-time curve up to the last measurement time point: AUC_{0-last}

Unit: μg·h/mL

Number of display digits: Should be rounded and displayed to one decimal place.

Calculation method: The area under the plasma concentration-time curve from baseline to the last measurement time point is calculated using the trapezoidal method (Linear Trapezoid [Linear Interpolation]).

If the concentrations are below the lower limit of quantification at all time points, the concentration should be 0.0 μg/mL.

4.5 Mean residence time extrapolated to infinity: $MRT_{0-\infty}$

Unit: h

Number of display digits: Should be rounded and displayed to two decimal places.

Calculation method: $MRT_{0-\infty} = AUMC_{0-\infty}/AUC_{0-\infty}$

However, $AUMC_{0-\infty}$ is the first moment of $AUC_{0-\infty}$; and if Kel is not calculated, it should be regarded as missing value and displayed as "–".

4.6 Elimination rate constant of the terminal elimination phase: Kel

Unit: /h

Number of display digits: Should be rounded and displayed to four decimal places.

Calculation method: This is the slope of the regression line when the linear regression of logarithmic concentration against time is performed for the terminal elimination phase of the concentration curve. However, it should be calculated only if there are ≥3 points traced back from the last time point when plasma concentrations are detectable without including C_{max}, and the number of trace points with the highest R^2 of linear regression should be adopted. It should be regarded as missing and "–" is displayed if ≤2 points.

4.7 Terminal elimination half-life: $t_{1/2}$

Unit: h

Number of display digits: Should be rounded and displayed to two decimal places.

Calculation method: $t_{1/2} = \ln(2)/Kel$

It should be calculated for only subjects with a calculated Kel. If Kel is not calculated, it should be regarded as a missing value and displayed as "–".

4.8 Degree-of-freedom adjusted coefficient of determination R^2

Unit: –

Number of display digits: Should be rounded and displayed to three decimal places.

Calculation method: This is the degree-of-freedom adjusted coefficient of determination when Kel is calculated. If Kel is not calculated, it should be regarded as a missing value and displayed as "–".

4.9 Correlation coefficient: r

Unit: –

Number of display digits: Should be rounded and displayed to three decimal places. Calculation method: This is the correlation coefficient between logarithmic concentration and time at the time of Kel calculation. If Kel is not calculated, it should be regarded as a missing value and displayed as "–".

4.10 Time range of the regression line used to calculate Kel: Lambda_z_lower and Lambda_z_upper

Unit: h

Number of display digits: Should be displayed to two decimal places.

Calculation method: This is the lower (Lambda_z_lower) and upper (Lambda_z_upper) time limits of the regression line used to calculate Kel.

If Kel is not calculated, it should be regarded as a missing value and displayed as "–".

4.11 Ratio of pharmacokinetic parameters between treatment conditions (t_{max} is the difference between the treatment conditions)

Number of display digits: Should be rounded and displayed to three decimal places. T_{max} should be rounded and displayed to two decimal places.

Calculation method: It is defined as the ratio of pharmacokinetic parameters between treatment conditions = concomitant administration / single administration (for t_{max}, difference between treatment conditions = concomitant administration − single administration). If any of the pharmacokinetic parameters is missing or has a denominator of 0, it should be regarded as missing and displayed as "–".

5. Definition of Derived Variables

5.1 Age at consent acquisition

Age (year) = Date of consent acquisition (year) − Date of birth (year)

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

5.2 BMI

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

6. Analysis sets

Pharmacokinetic analysis will be performed in the pharmacokinetics analysis set. Safety analysis will be performed in the safety analysis set. The analysis sets are defined below; however, details of the treatment of subjects should be determined by the sponsor by the time the data are fixed.

6.1 Pharmacokinetics analysis set

Among subjects who received at least one dose of the study drug, a population of subjects whose pharmacokinetics can be evaluated is the pharmacokinetics analysis set.

6.2 Safety analysis set

The population of subjects who received the study drug at least once is the safety analysis set.

7. Data handling

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 Definition of missing values

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.

7.2 Definition of logarithmic transformation

The logarithmic transformation uses natural logarithm.

7.3 Handling of PK-related data

The permitted range of blood sampling for plasma concentration measurement is set as shown below, in consideration of the range of working hours for puncture, etc. Data outside the permitted ranges should not be imputed. Details of the acceptance or rejection of drug concentration data used for the

tabulation of drug concentration data and the calculation of pharmacokinetic parameters and the handling of other drug concentration data should be decided in the review of handling of drug concentration data and described in the final version of the statistical analysis plan.

- Immediately before study drug administration: Within 30 minutes before the specified time
- 0.5 to 16 hours after study drug administration: Within ±5 minutes of the specified time
- 24 hours after study drug administration: Within ±15 minutes of the specified time

(1) Rejected data

They will not be included in the calculation of summary statistics or pharmacokinetic parameters at each time point of blood sampling.

(2) Plasma MT-6548 concentrations (units should be converted from ng/mL to μg/mL)

1) "NS": No data

Should be treated as a missing value.

2) "<LLOQ": Below the lower limit of quantification (0.1 μg/mL)

Should be treated as 0.000 μg/mL.

7.4 Handling of data at 72 hours after study drug administration

PK data, the results of measurement of general laboratory tests and vital signs, and the results of evaluations of standard 12-lead ECGs obtained immediately before administration of the study drug in Period 2 and Period 3 should not be tabulated as results obtained at 72 hours after administration of study drug in Period 1 and Period 2, respectively, but should instead be handled as data obtained immediately before administration of the study drug (i.e., baseline data) in Period 2 and Period 3, respectively. However, if data obtained immediately before administration of the study drug in Period 2 and Period 3 are judged to be adverse events compared with the baseline data in Period 1 and Period 2, respectively, they should be handled as adverse events occurring in Period 1 and Period 2.

8. Statistical Method

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 (CI) will be 2-sided with a confidence coefficient of 95%.

8.1.2 Descriptive statistics to calculate

Unless otherwise specified, the following descriptive statistics should be calculated for each continuous variable item (excluding pharmacokinetic analysis).
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

(1) The number of digits to be displayed in the analysis results of demographic and other baseline characteristics (subject background), vital signs, and laboratory test should 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

(2) Pharmacokinetics analysis

1) Number of digits to be displayed for mean, SD, median, geometric mean:

- Plasma MT-6548 concentrations (μg/mL) should be provided as 3 significant figures. Rounding to round down at 4 and up at 5.
- The pharmacokinetics parameters should be as follows.
  The number of digits should be displayed as specified in "4. Calculation of Pharmacokinetics Parameters".

2) Number of subjects and number of subjects with events:

- Should be displayed as an integer.

3) Minimum, maximum:

- Pharmacokinetic parameters should be displayed in the number of digits specified in "4. Calculation of pharmacokinetic parameters". Plasma concentrations should be expressed in the same number of digits as measured (μg/mL, 3 significant digits).

4) Geometric coefficient of variation (%) (pharmacokinetic parameters other than t_{max}):

- Should be rounded and displayed to one decimal place.

Should be calculated using the following formula.

Geometric coefficient of variation (%) = $[\exp(SD^2) - 1]^{1/2} \times 100$

where SD is the standard deviation after logarithmic conversion of the data.

5) Coefficient of variation (%):

- Should be rounded and displayed to one decimal place.

Should be calculated using the following formula.

Coefficient of variation (%) = SD/Mean × 100

SD is standard deviation and Mean is the mean.

6) Pharmacokinetic parameter (except for t_{max}) ratios and CI:

- Will be rounded and displayed to three decimal places.

7) Difference and CI of t_{max}:

- Should be rounded and displayed to two decimal places.

8) Test statistics:

- Should be rounded and displayed to two decimal places.

9) P value:

- Will be rounded and displayed to three decimal places.

When the p-value is less than 0.001, "< 0.001" is displayed.

8.2 Breakdown of subjects

8.2.1 Disposition

Analysis set: Subjects who received the study drug

Analysis methods: The breakdown by group in each analysis set should be displayed.

Items: Number of subjects treated with study drug, pharmacokinetics analysis set and its proportion, number and its proportion of subjects excluded from pharmacokinetics analysis set, number and its proportion of subjects included in safety analysis set, number and its proportion of subjects excluded from safety analysis set

8.2.2 Discontinued subjects

Analysis set: Subjects who received the study drug
Analysis method: The number and proportion of discontinued subjects should be tabulated by group. The number and proportion of subjects should be tabulated by reasons of discontinuation.

Item: Number and proportion of subjects who completed the study by group in subjects treated with the study drug, number and proportion of subjects who discontinued the study by group in subjects treated with the study drug, number and proportion of subjects who discontinued the study by reasons of discontinuation

8.3 Demographic and other baseline characteristics

Analysis set: Pharmacokinetics analysis set If pharmacokinetics analysis set and safety analysis set are different, the same analysis should be performed in the safety analysis set.
Analysis method: Key demographic and other baseline characteristics should be summarized for each group. Frequency and proportion should be provided for discrete variables and descriptive statistics for continuous variables (no calculation of 95% CI of the mean).

Table 8.3 Demographic and other baseline characteristics

Category	Item	Type of variables
Subject background	Sex (male, female)	Dichotomous
	Age (years) as of informed consent	Continuous
	Height (cm)	Continuous
	Body weight (kg)	Continuous
	BMI (kg/m^2)	Continuous
	Presence of complications 2 categories: Yes, No	Dichotomous
	Ethnicity 2 categories: Japanese, Other	Dichotomous

8.4 Pharmacokinetics analysis

As a general rule, pharmacokinetic analysis should be performed on the pharmacokinetics analysis set. When necessary, descriptive statistics for continuous variables should be calculated and frequency and proportion will be calculated for discrete variables.

8.4.1 Tabulation of plasma concentrations of unchanged MT-6548

Analysis set: Pharmacokinetics analysis set

Analysis method: Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) for each cohort at each time point of blood collection should be calculated by treatment condition.

8.4.2 Tabulation of pharmacokinetic parameters of unchanged MT-6548

(1) Calculation of summary statistics for pharmacokinetic parameters

Analysis set: Pharmacokinetics analysis set

Analysis method: Summary statistics (number of subjects, mean, SD, coefficient of variation, median, minimum, maximum, geometric mean and, geometric coefficient of variation) should be calculated for pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, t_{max}, AUC_{0-last}, $MRT_{0-\infty}$, Kel, and $t_{1/2}$) for each cohort by treatment condition. If the individual values of C_{max}, AUC_{0-last}, or $AUC_{0-\infty}$ become 0.000 μg/mL or 0.0 μg·h/mL, respectively, no geometric mean or geometric coefficient of variation will be calculated but "–" will be provided. No geometric mean or geometric coefficient of variation will be calculated but "–" will be provided for t_{max}.

(2) Calculation of summary statistics of ratios of pharmacokinetic parameters between treatment conditions

Analysis set: Pharmacokinetics analysis set

Subject item: Summary statistics (number of subjects, mean, SD, coefficient of variation, median, minimum, maximum, geometric mean and, geometric coefficient of variation) should be calculated for pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, t_{max}, AUC_{0-last}, $MRT_{0-\infty}$, Kel, and $t_{1/2}$) by treatment condition. T_{max} is calculated using differences between treatment conditions.

8.4.3 Evaluation of tabulation of pharmacokinetics after administration of MT-6548 tablets alone or in combination with oral iron supplements or iron-containing phosphate binders

Analysis set: Pharmacokinetics analysis set

Analysis methods: For each cohort, pharmacokinetic parameters, $AUC_{0-\infty}$, C_{max}, and AUC_{0-last}, are logarithmically transformed, and the least squares mean (LSMean), standard errors, and the difference of LSMean (each combination therapy − monotherapy) should be calculated by analysis of variance

using a linear mixed effects model with treatment condition (monotherapy or combination therapy), treatment period, and group as fixed effects and subject as random effects.
The ratio of geometric mean (for each combination/monotherapy) and its 90% CI should be calculated by inverse logarithmic transformation of the difference of LSMean of the above obtained logarithmic values. Geometric mean ratios (for each combination/monotherapy) and their 90% CIs will be converted to % and displayed to 2 decimal places.
In addition, within-individual CV should be calculated using intra-individual variance (SD^2_{wthin}) of analysis of variance using a linear mixed effects model.

$$\text{Intra individual CV (\%)} = [\exp (SD^2_{wthin}) - 1]^{1/2} \times 100$$

[MMRM Model]

- Fixed effects: administration condition, study period, group
- Methods of freedom adjustment: Kenward-Roger method
- Random effects: subjects

8.4.4 Scatter plot chart of plasma concentration of unchanged drug

Analysis set: Pharmacokinetics analysis set
Subject item: Plasma concentrations of unchanged MT-6548 by subject
Drawing method: A time-course chart (linear and semilogarithmic plots) for plasma concentrations of unchanged drug over time following MT-6548 tablet administration should be prepared for each cohort by administration condition.

Analysis set: Pharmacokinetics analysis set
Subject item: Mean and SD of plasma concentrations of unchanged MT-6548 by administration condition
Drawing method: Time course diagram (linear plot) of the mean + SD and time course diagram (semilogarithmic plot) of the mean of plasma concentration of unchanged drug versus time after administration of MT-6548 tablets by treatment condition for each cohort.

8.4.5 Time course diagram of pharmacokinetic parameters after administration of MT-6548 tablets alone or in combination with oral iron supplements or iron-containing phosphate binders

Analysis set: Pharmacokinetics analysis set

Subject item: Individual values and mean ± SD of pharmacokinetic parameters of unchanged MT-6548

Drawing method: Spaghetti plots should be prepared for each cohort regarding changes over time in pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, and AUC_{0-last}) from monotherapy to each combination therapy in each subject. The mean ± SD for each treatment condition should also be plotted.

8.5 Safety analysis

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

8.5.1 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 should be calculated in each cohort.

- Adverse event
- Adverse drug reaction
- Serious adverse event
- Serious adverse drug reaction
- Adverse event leading to discontinuation
- Adverse event leading to death (adverse event of fatal outcome)

8.5.2 Summary of adverse events and adverse drug reactions

The number of subjects and the incidence rate of individual adverse events and adverse drug reactions classified by SOC and PT in MedDRA/J Version 21.0 (hereinafter the same) should be calculated. The SOC will be sorted by order of international consensus, the PT by descending order of the number of subjects in monotherapy and by descending order of the number of subjects in combination therapy (PT code by ascending order when the number is equal).

8.5.3 Summary of adverse events and adverse drug reactions 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 for each treatment condition in each cohort.

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

(1) When adverse events of different severity occur in the same subject

The most severe adverse event should be counted as 1 subject.

(2) When multiple adverse events with the same degree occur in the same subject

The same severity should be counted as 1 subject.

(3) When multiple same adverse events occur in the same subject

The most severe adverse event should be counted as 1 subject.

8.5.4 Laboratory test values

For hematology, blood biochemistry, and urinalysis (specific gravity, pH), descriptive statistics should be calculated for each treatment condition in each cohort at each evaluation time point. The changes from baseline at each evaluation time point should be summarized in the same manner.
Concerning qualitative urinalysis (glucose, protein, urobilinogen, occult blood, ketone bodies, bilirubin), a shift table composed of frequency tabulation by category at each evaluation time point and decision results at baseline and each evaluation time point in each evaluation period should be provided for each administration condition in each cohort.

8.5.5 Resting standard 12-lead ECG

The frequency of decision results (normal, clinically nonsignificant abnormal, or clinically significant abnormal) should be tabulated at the evaluation time point by administration condition in each cohort, and a shift table composed of the decision results at baseline and each evaluation time point should be provided.

8.5.6 Vital signs

For blood pressure and pulse rate, descriptive statistics should be calculated for each treatment condition in each cohort at each evaluation time point. The changes from baseline at each evaluation time point in each evaluation period should be summarized in the same manner.

7. Software to Use

The applications to be used and their versions will be as follows.

SAS for Windows (Release 9.4)
Phoenix® WinNonlin® Ver.6.3

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

9. References