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

Study Protocol

Study sponsor:

Mitsubishi Tanabe Pharma Corporation

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CONFIDENTIALITY

This study protocol contains information which should be viewed only by those directly involved with the study. The contents of this document should only be published or disclosed to third parties with the express written consent of Mitsubishi Tanabe Pharma Corporation.

The study will be performed in compliance with the Pharmaceutical Affairs Law, Ordinance on Good Clinical Practice (GCP), related regulations, and this study protocol.

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List of abbreviations

Abbreviation	Non-abbreviated term
ADR	Adverse Drug Reaction
AE	Adverse Event
BCRP	Breast cancer resistance protein
CKD	Chronic kidney disease
CYP	Cytochrome P450
EDC	Electronic data capture/ Systems for using electronic devices and software to collect data on clinical study subjects from study centers or contract testing laboratories
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
GCP	Good clinical practice
GFR	Glomerular filtration rate
HD-CKD	Hemodialysis dependent chronic kidney disease
HIF-PH	Hypoxia inducible factor prolyl hydroxylase
MRP	Multidrug resistance-associated protein
NDD-CKD	Nondialysis dependent chronic kidney disease
OATP	Organic anion transporting polypeptide
OAT	Organic anion transporter
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Preferred term
QOL	Quality of life
SOC	System organ class

List of abbreviations for pharmacokinetic parameters

Abbreviation	Non-abbreviated term
AUC	Area under the plasma concentration-time curve
C_{max}	Maximum plasma concentration
IC_{50}	Median inhibitory 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

Protocol Summary

1. Study title

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. Purpose of the study

To evaluate the pharmacokinetics and safety of MT-6548 when MT-6548 and oral iron or iron-containing phosphate binders are coadministered.

3. Subjects

3.1 Subjects

Healthy adult male volunteers

3.2 Inclusion criteria

Subjects must meet all inclusion criteria below and have capacity to grant informed consent.

(1) Men aged no younger than 20 years and no older than 45 years at the time of informed consent
(2) Japanese (both parents and both grandparents must be Japanese)
(3) Persons whom the investigator/subinvestigator deem to be suitable as a subject via the screening tests, and the interview and examinations on Day -1 (day before administration of the study drug) and Day 1 (day of administration of the study drug).

3.3 Exclusion criteria

Persons who meet any of the following exclusion criteria at the informed consent procedure, screening, Day -1 (day before administration of the study drug), and before administration of the study drug on Day 1 (day of administration of the study drug) will be excluded from consideration as subjects.

(1) Persons with a current medical history or treatment history (drug treatment, in-patient treatment, etc.) as follows.
    1) Heart: Angina pectoris, arrhythmia, myocardial infarction, heart failure, or other heart disease
    2) Liver: Liver disease with decreased liver function
    3) Kidney: Kidney disease with decreased kidney function
    4) Gastrointestinal system: Gastric ulcer, pancreatitis, or other gastrointestinal disease (excluding, however, persons with no recurrence for at least 5 years on drug therapy alone)
    5) Respiratory system: Pulmonary tuberculosis, obstructive pulmonary disease, or other respiratory disease
    6) Nervous system: Diseases accompanied by sensory disorder or other neurological disorder

7) Hematopoietic function: Blood disease accompanies by findings of anaemia with pronounced deviations from reference values
8) Endocrine function: Endocrine disease that is deemed to have a pronounced effect on endocrine function such as thyroid, parathyroid, or pituitary function
9) Other: Malignant tumor

(2) Persons with signs of heart disease at screening (for example, QTcF interval of 450 msec or greater in 12-lead ECG findings).
(3) Persons with a history or current symptoms of drug or alcohol dependence.
(4) Persons who the investigator/subinvestigator believe cannot adhere to the prohibitions during the confinement period.
(5) Persons who have previously used MT-6548.
(6) Persons with a history or current symptoms of drug or food allergy
(7) Persons with, at screening, BMI less than 18.5 kg/m^2 or greater than 25.0 kg/m^2. Alternatively, persons with body weight less than 50.0 kg (in BMI calculations, the second decimal place is rounded off).
(8) Persons who have donated blood components with 2 weeks before informed consent. Alternatively, persons who have donated blood or had blood drawn in an amount of 400 mL or more within 12 weeks or 200 mL or more within 4 weeks before informed consent.
(9) Persons who have donated or had blood drawn in an amount of 800 mL or more within 1 year before informed consent.
(10) Persons with a history of surgical procedures that are known to have an effect on gastrointestinal drug absorption (excluding appendicectomy and hernia operations).
(11) Persons with a positive result for HBs antigen, serological test for syphilis, HCV antibody, or HIV antigen or antibody at screening.
(12) Persons who are unwilling to consent to use contraception from the beginning of the study period to 90 days following the final dose of the study drug.
(13) Persons who have participated in another clinical study and received study drugs within 12 weeks prior to informed consent, or within 5 times the half-life of the study drug (whichever is longer).
(14) Persons who used any medications other than the study drug to be administered in this study or other therapies within 7 days before the start of administration of the study drug.
(15) Persons who consumed any supplements within 7 days before the start of administration of the study drug.
(16) Persons who consumed grapefruit or other citrus fruits, apples, or processed foods containing any of these within 7 days before the start of administration of the study drug.
(17) Persons who consumed health foods containing St. John's wort (Japanese name, seiyo-otogiri-so) within 2 weeks before the start of administration of the study drug.

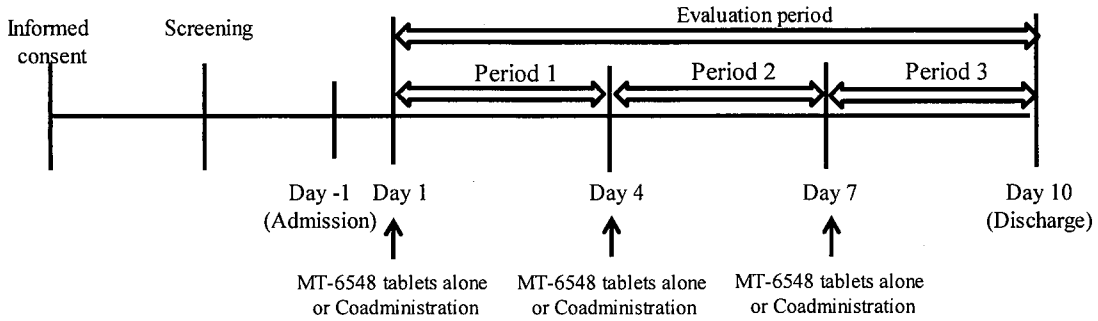
(18) Other persons judged by investigators/subinvestigators to be inappropriate as a subject in this study.

4. Study design

Single dose, open-label, randomized, crossover study

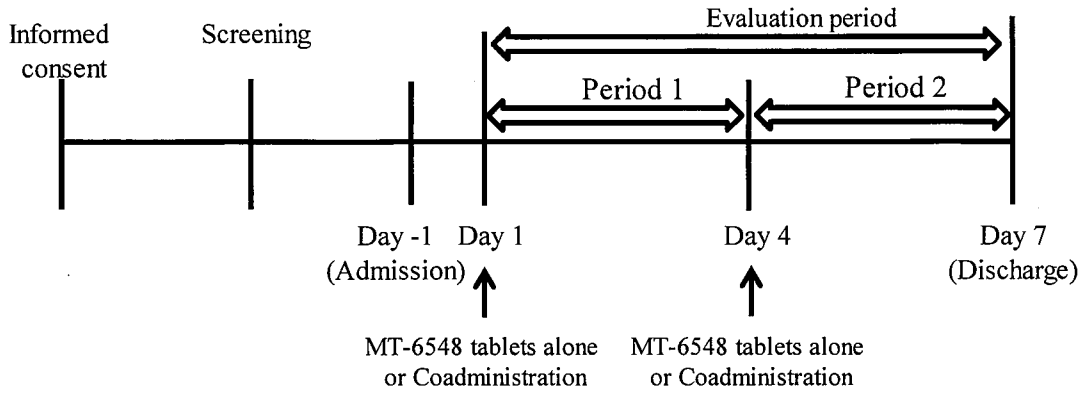
Number of subjects: 61 (Cohort 1 (administration after meal): 21 subjects; Cohort 2 (administration before meal): 20 subjects; Cohort 3 (administration in fasting): 20 subjects)

Cohort 1 (Administration after meal)



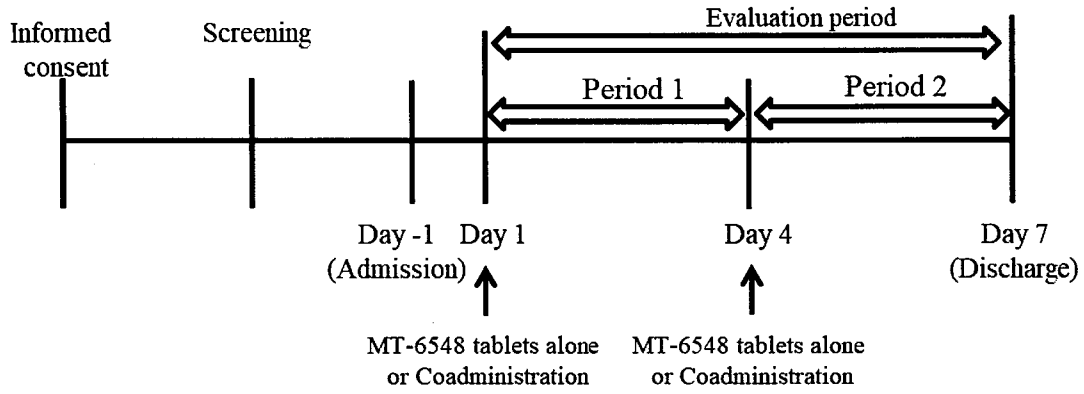
	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
Group 1	MT-6548 Tablets	MT-6548 Tablets and Sodium Ferrous Citrate	MT-6548 Tablets and Ferric Citrate Hydrate
Group 2	MT-6548 Tablets and Ferric Citrate Hydrate	MT-6548 Tablets	MT-6548 Tablets and Sodium Ferrous Citrate
Group 3	MT-6548 Tablets and Sodium Ferrous Citrate	MT-6548 Tablets and Ferric Citrate Hydrate	MT-6548 Tablets

Cohort 2 (Administration before meal)



	Period 1 (Day 1)	Period 2 (Day 4)
Group 4	MT-6548 Tablets	MT-6548 Tablets and Sucroferric oxyhydroxide
Group 5	MT-6548 Tablets and Sucroferric oxyhydroxide	MT-6548 Tablets

Cohort 3 (Administration in fasting)



	Period 1 (Day 1)	Period 2 (Day 4)
Group 6	MT-6548 Tablets	MT-6548 Tablets and Dried Ferrous Sulfate
Group 7	MT-6548 Tablets and Dried Ferrous Sulfate	MT-6548 Tablets

Study period: From the day consent is obtained until the end of the post-administration tests.

Screening: Screening tests to verify eligibility will be performed after informed consent is obtained, after which eligible subjects will be selected. Screening will take place within 4 weeks before the day of administration of the study drug in Period 1 (Day 1). After all the prescribed screening test results are available, subjects will be admitted to the study site. Day -1 (the day before administration of the study drug) will be defined as the day of admission.

Evaluation period: For Cohort 1, the 10-night, 11-day period of confinement. 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.

Cohort 2 and Cohort 3 will be confined to the study site 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: These will be performed 3 days after administration of the last dose of the study drug.

5. Study drug, dosage, and administration

5.1 Study drug name

Name: MT-6548 Tablets 150 mg

Nonproprietary name: vadadustat (INN)

Vadadustat (JAN) (English name)

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

The following commercially-available products will be used in addition to the study drug in this study.

<u>Iron supplements</u>

- Sodium ferrous citrate (Ferromia® Tablets 50mg)
- Dried ferrous sulfate (Fero-Gradumet® Tablets 105mg)

<u>Iron-containing phosphate binders</u>

- Ferric citrate hydrate (Riona® Tablets 250mg)
- Sucroferric oxyhydroxide (P-TOL® Chewable Tablets 500mg)

5.2 Dosage and administration

Cohort 1 (Administration after meal)

(1) Administration of MT-6548 tablets alone

After fasting for at least 10 hours, subjects will eat breakfast over a period of 10 minutes, then immediately after finishing the meal (5 minutes after finishing the meal), 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(2) Administration of MT-6548 tablets and sodium ferrous citrate

After fasting for at least 10 hours, subjects will eat breakfast over a period of 10 minutes, then immediately after finishing the meal (5 minutes after finishing the meal), 1 MT-6548 tablet (150 mg) and 4 tablets of sodium ferrous citrate (containing 200 mg of iron) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(3) Administration of MT-6548 tablets and ferric citrate hydrate

After fasting for at least 10 hours, subjects will eat breakfast over a period of 10 minutes, then immediately after finishing the meal (5 minutes after finishing the meal), 1 MT-6548 tablet (150 mg) and 8 tablets of ferric citrate hydrate (containing 2000 mg of ferric citrate) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. After collection of blood samples at 4 hours after administration of the study drug, subjects will eat lunch over a period of 20 minutes, then immediately after finishing the meal, 8 tablets of ferric citrate hydrate (containing 2000 mg of ferric citrate) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). Subjects will fast from lunch to before dinner, and at 10 hours after administration of the study drug, subjects will eat dinner over a period of 20 minutes, then immediately after finishing the meal, 8 tablets of ferric citrate hydrate (containing 2000 mg of ferric citrate) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the

extra volume will be recorded). Subjects will fast from dinner until breakfast the next morning.

Cohort 2 (Administration before meal)

(1) Administration of MT-6548 tablets alone

After fasting for at least 10 hours and immediately before eating breakfast (5 minutes before starting the meal), 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water, then breakfast will be eaten over a period of 10 minutes (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(2) Administration of MT-6548 tablets and sucroferric oxyhydroxide

After fasting for at least 10 hours and immediately before eating breakfast (5 minutes before starting the meal), subjects will chew and swallow 2 tablets of sucroferric oxyhydroxide (containing 1000 mg of iron), then 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water, then breakfast will be eaten over a period of 10 minutes (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. After blood samples are collected at 4 hours after administration of the study drug and immediately before lunch, subjects will chew and swallow 2 tablets of sucroferric oxyhydroxide (containing 1000 mg of iron), then eat lunch over a period of 20 minutes. After lunch, subjects will fast until dinner, and immediately before dinner at 10 hours after administration of the study drug, chew and swallow 2 tablets of sucroferric oxyhydroxide (containing 1000 mg of iron), then eat dinner over a period of 20 minutes. Subjects will fast from dinner until breakfast the next morning.

Cohort 3 (Administration in fasting)

(1) Administration of MT-6548 tablets alone

After fasting for at least 10 hours, 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). Subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(2) Administration of MT-6548 tablets and dried ferrous sulfate

After fasting for at least 10 hours, 1 MT-6548 tablet (150 mg) and 2 tablets of dried ferrous sulfate (containing 210 mg of iron) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). Subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

5.3 Duration of treatment

Cohort 1

(1) MT-6548 tablets: Single dose administered alone, 3 times
(2) Sodium ferrous citrate: Single dose, administered once
(3) Ferric citrate hydrate: Three times a day, administered once on 1 day

Cohort 2

(1) MT-6548 tablets: Single dose administered alone, twice
(2) Sucroferric oxyhydroxide: Three times a day, administered once on 1 day

Cohort 3

(1) MT-6548 tablets: Single dose administered alone, twice
(2) Dried ferrous sulfate: Single dose, administered once

6. Endpoints

6.1 Pharmacokinetic endpoints

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

6.2 Safety endpoints

(1) Adverse events (AEs) and adverse drug reactions (ADRs) (refer to "9.2.4.2 Adverse events" for details)
(2) General laboratory tests
(3) Vital signs
(4) Standard 12-lead ECG

7. Target sample size

Cohort 1: 21 subjects

Cohort 2: 20 subjects

Cohort 3: 20 subjects

8. Study period

[redacted]

9. Test and observation schedule

Cohort 1 (Administration after meal)

	Informed consent	Screening	Day -1	Evaluation period																																											Discontinuations only	
				Period 1														Period 2														Period 3															At discontinuation [d]	Post-administration tests [e]
				Day 1												Day 2	Day 3	Day 4												Day 5	Day 6	Day 7												Day 8	Day 9	Day 10 (Post-administration tests) [c]		
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 [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 will be administered after food, depending on the allocated group.

[c] Completed subjects will undergo post-administration tests on Day 10.

[d] Performed on discontinuation after administration of the study drug.

[e] 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 (Administration before meal)

	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 test(s)) [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 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 will be administered before food, depending on the allocated group.

[c] Completed subjects will undergo post-administration tests on Day 7.

[d] Performed on discontinuation after administration of the study drug.

[e] 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 (Administration in fasting)

	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 [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 will be administered depending on the allocated group.

[c] Completed subjects will undergo post-administration tests on Day 7.

[d] Performed on discontinuation after administration of the study drug.

[e] 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, current medical condition
Interview/examination		Interview/examination
Vital signs		Blood pressure (supine position), pulse rate (supine position), body temperature (axillary)
Resting standard 12-lead ECG		Findings
Laboratory tests	Hematology tests	RBC count, haemoglobin, hematocrit, WBC count, platelet count, WBC fraction (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, ketones, bilirubin
Immunology tests (only at screening)		Serologic reaction for syphilis, HBs antigen, HCV antibody, HIV antigen/antibody

1. Protocol history and background information

(1) Target disease and treatment methods

Chronic kidney disease (CKD) is defined in Japanese Society of Nephrology's "Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012"[1] as renal disorders (e.g., proteinuria) or renal impairment with glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for 3 or more months.

CKD is a significant public health problem throughout the world, and in Japan alone 20% of adults are estimated[2] to have GFR of <60 mL/min/1.73 m^2. In Japan there are more than 300,000 CKD patients requiring dialysis, a number which has increased in the past 30 years[3]. Anaemia is a well-known complication of renal disease, and occurs early after onset of CKD[4]. Prevalence of anaemia increases as CKD progresses, with 53% to 89% of dialysis patients affected by the disease[5, 6]. Causes of anaemia in CKD patients include exsanguination, reduced RBC (red blood cell) lifespan, iron deficiency, erythropoietin (EPO) deficiency, [redacted] The primary cause of nephrogenic anaemia is EPO deficiency, which results from hypoxic disorders or cells surrounding renal tubules or cell decrease in cells surrounding renal tubules[4, 7]. [redacted] Further, iron loss due to dialysis is an extremely important cause of anaemia in CKD and requires iron supplementation[7]. Anaemia significantly affects organ function by decreasing oxygen transport to tissue, resulting in various symptoms such as fatigue, shortness of breath, and exercise intolerance[6]. Compensatory changes occur in the structure and function of the heart in these anaemia patients, including increased cardiac output and left ventricular hypertrophy, which can ultimately result in cardiac failure[8]. Other anaemia-related disorders observed in CKD patients include cognitive function disorders, sleep disorders, and impaired immune function, sometimes resulting in reduced quality of life (QOL)[4, 9]. Anaemia is also a factor related to poor prognosis in CKD patients[4, 7]. Improving anaemia results particularly in markedly improved QOL in terms of energy, fatigue, and physical function[4, 7, 10].

Erythropoiesis-stimulating agents (ESAs), which include recombinant epoetin alfa, recombinant epoetin beta, recombinant darbepoetin alfa, and recombinant epoetin beta pegol, are the standard of care for the treatment of anaemia in patients with CKD, but they must be given intravenously or subcutaneously.

(2) Study drug names and explanations

MT-6548 is a hypoxia-inducible factor prolyl hydroxylase enzyme (HIF-PH) inhibitor currently under development for treatment of anaemia in CKD patients either using or not using dialysis. It is a novel small-molecule compound which can be taken orally. HIF-PH causes hydroxylation of HIF-α in normoxic conditions, reducing HIF-α levels with von Hippel-Lindau

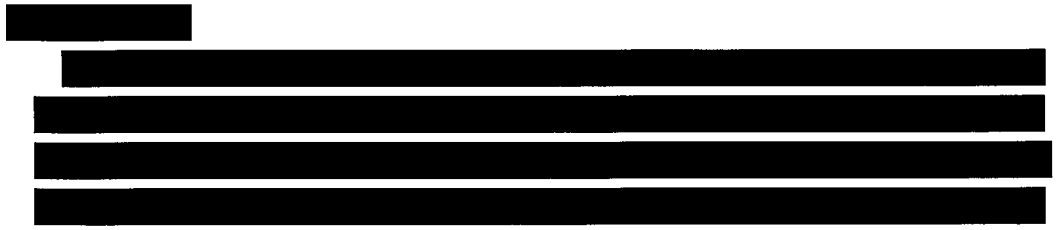
(VHL)-dependent breakdown of HIF-α. However, in hypoxic conditions HIF-PH activity is reduced, causing stabilized HIF-α to be transported to the cellular nucleus, where it forms a dimer with HIF-β and binds with hypoxia response elements to control various target genes, such as activation of EPO genes which increase EPO protein production. By inhibiting HIF-PH activity, MT-6548 creates a physiological response similar to that of hypoxic conditions, thereby increasing EPO protein production and [redacted] resulting in increased Hb and RBC production11).

(3) Nonclinical and clinical study results

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

[redacted]

[redacted]



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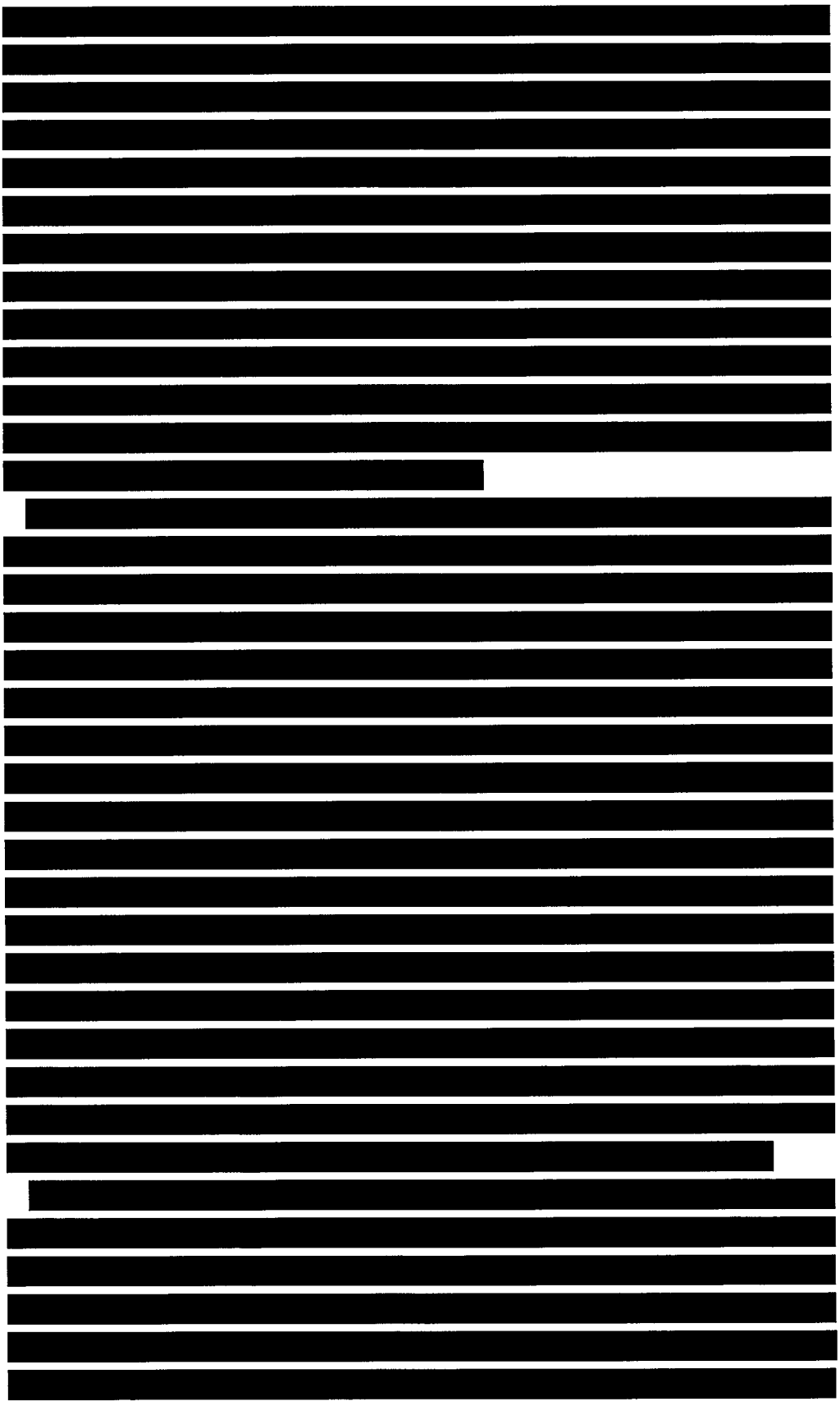


[redacted]

(4) Investigational plan

From the results of a clinical study in which MT-6548 and the oral iron ferrous sulfate were coadministered under fasting conditions that showed reduced bioavailability of MT-6548 (Study CI-0012), it was decided that the oral iron or iron-containing phosphate binder would be taken at least 2 hours before or after administration of MT-6548 in the Japanese Phase III study that is currently in progress. Iron supplementation for patients with renal anaemia in Japan is provided whenever iron deficiency is seen without the use of ESA preparations, or in circumstances in which iron consumption due to ESA preparations or low responsiveness is evident during treatment with an ESA preparation, and phosphate binders are used to address deficient phosphate removal due to dialysis therapy in the dialysis phase. The current study was planned with the objective of evaluating the PK and safety of MT-6548 when MT-6548 and oral iron or iron-containing phosphate binders are coadministered in Japanese clinical practice

The conduct of this study was planned in accordance with Methods of Investigating Drug Interactions (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001), Clinical Pharmacokinetic Studies on Drugs (Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001), Guideline for Bioequivalence Studies of Generic Products (Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012), and the draft Guideline on Drug Interactions for Drug Development and Labeling (September 4, 2017 edition). Oral iron is widely used in the Japanese health-care sector, and sodium ferrous citrate and dried ferrous sulfate, for which efficacy and safety evaluations have been established, were selected for the study. For iron-containing phosphate binders, ferric citrate hydrate and sucroferric oxyhydroxide, which are marketed in Japan, were selected.

2. Study objectives

To evaluate the pharmacokinetics and safety of MT-6548 when MT-6548 and oral iron or iron-containing phosphate binders are coadministered.

3. Subjects

3.1 Subjects

Healthy adult male volunteers

3.2 Inclusion criteria

Subjects must meet all inclusion criteria below and have capacity to grant informed consent.

(1) Men aged no younger than 20 years and no older than 45 years at the time of informed consent
(2) Japanese (both parents and both grandparents must be Japanese)
(3) Persons whom the investigator/subinvestigator deem to be suitable as a subject via the screening tests, and the interview and examinations on Day -1 (day before administration of the study drug) and Day 1 (day of administration of the study drug).

Rationale

Healthy volunteers were chosen as the population for this study with reference to Methods of Investigating Drug Interactions (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001) and the draft Guideline on Drug Interactions for Drug Development and Labeling (September 4, 2017 edition). With the aim of standardizing the subjects' characteristics as much as possible, restrictions were placed on age, sex, and ethnicity.

3.3 Exclusion criteria

Persons who meet any of the following exclusion criteria at the informed consent procedure, screening, Day -1 (day before administration of the study drug), and before administration of the study drug on Day 1 (day of administration of the study drug) will be excluded from consideration as subjects.

(1) Persons with a current medical history or treatment history (drug treatment, in-patient treatment, etc.) as follows.
    1) Heart: Angina pectoris, arrhythmia, myocardial infarction, heart failure, or other heart disease
    2) Liver: Liver disease with decreased liver function
    3) Kidney: Kidney disease with decreased kidney function
    4) Gastrointestinal system: Gastric ulcer, pancreatitis, or other gastrointestinal disease (excluding, however, persons with no recurrence for at least 5 years on drug therapy alone)
    5) Respiratory system: Pulmonary tuberculosis, obstructive pulmonary disease, or other respiratory disease
    6) Nervous system: Diseases accompanied by sensory disorder or other neurological disorder

7) Hematopoietic function: Blood disease accompanies by findings of anaemia with pronounced deviations from reference values
8) Endocrine function: Endocrine disease that is deemed to have a pronounced effect on endocrine function such as thyroid, parathyroid, or pituitary function
9) Other: Malignant tumor

(2) Persons with signs of heart disease at screening (for example, QTcF interval of 450 msec or greater in 12-lead ECG findings).
(3) Persons with a history or current symptoms of drug or alcohol dependence.
(4) Persons who the investigator/subinvestigator believe cannot adhere to the prohibitions during the confinement period.
(5) Persons who have previously used MT-6548.
(6) Persons with a history or current symptoms of drug or food allergy.
(7) Persons with, at screening, BMI less than 18.5 kg/m^2 or greater than 25.0 kg/m^2. Alternatively, persons with body weight less than 50.0 kg (in BMI calculations, the second decimal place is rounded off).
(8) Persons who have donated blood components with 2 weeks before informed consent. Alternatively, persons who have donated blood or had blood drawn in an amount of 400 mL or more within 12 weeks or 200 mL or more within 4 weeks before informed consent.
(9) Persons who have donated or had blood drawn in an amount of 800 mL or more within 1 year before informed consent.
(10) Persons with a history of surgical procedures that are known to have an effect on gastrointestinal drug absorption (excluding appendicectomy and hernia operations).
(11) Persons with a positive result for HBs antigen, serological test for syphilis, HCV antibody, or HIV antigen or antibody at screening.
(12) Persons who are unwilling to consent to use contraception from the beginning of the study period to 90 days following the final dose of the study drug.
(13) Persons who have participated in another clinical study and received study drugs within 12 weeks prior to informed consent, or within 5 times the half-life of the study drug (whichever is longer).
(14) Persons who used any medications other than the study drug to be administered in this study or other therapies within 7 days before the start of administration of the study drug.
(15) Persons who consumed any supplements within 7 days before the start of administration of the study drug.
(16) Persons who consumed grapefruit or other citrus fruits, apples, or processed foods containing any of these within 7 days before the start of administration of the study drug.
(17) Persons who consumed health foods containing St. John's wort (Japanese name, seiyo-otogiri-so) within 2 weeks before the start of administration of the study drug.

(18) Other persons judged by investigators/subinvestigators to be inappropriate as a subject in this study.

Note: Calculation of time periods is as follows.

- Twelve weeks before informed consent is defined as the same week day, 12 weeks before.
- One year before informed consent is defined as the same date in the previous year.
- Seven days before the start of treatment is defined as the same week day of the previous week.
- Two weeks before the start of treatment is defined as the same week day, 2 weeks before.

Rationale

(1), (2), (3), (6), (11), (18) Set in regard to safe and ethical performance of study.

(4) To conduct the study in accordance with the protocol.

(5) The safety evaluation may be biased if the response to MT-6548 is obvious

(7) To exclude obese or underweight persons.

(8), (9) The blood sample volumes and intervals were instituted for subject safety reasons, and decided with reference to the Law on Securing a Stable Supply of Safe Blood Products.

(10), (14), (15), (16), and (17) Set because of their likely effects on the PK of MT-6548.

(12) Reproductive and developmental toxicity safety has not been established in humans, and the possibility that the study drug may transfer to human sperm cannot be ruled out.

(13) Set in regard to ethical performance of study. Also, unevaluated drugs may affect pharmacokinetics or safety in unpredictable ways.

4. Explanations to subjects and consent

4.1 Informed consent forms and written information

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

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

4.2 Content of written information

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

(1) The study is for research purposes.

(2) Study objectives

(3) Names, titles, and addresses of investigators and subinvestigators

(4) The study methods (including the experimental nature of the study, the subject inclusion and exclusion criteria, and, if the study will be randomized, the probability of being assigned to each cohort.)

(5) The fact that the study drug is not expected to confer any benefit for the subject's physical or mental health, and the foreseeable disadvantages for the subject

(6) Expected period of study participation for the subject.

(7) Participation in the study is purely voluntary, and the subject may rescind agreement to participate at any time. If the subject determines not to participate in the study or withdraws consent, he/she will not be disadvantaged in anyway, and will not forego any benefits from not participating.

(8) Study monitors, auditors, IRB members, and regulatory authorities may view source documents from the study. In this event, subject confidentiality will be preserved. The subject consents to this viewing of source documents by signing (or printing name and affixing personal seal) the consent form.

(9) Subject confidentiality will be preserved even if study results are published.

(10) Contact information for consultations with the study center for when subjects wish to learn more information about the study or their rights, or for when study-related damage to health occurs

(11) Financial reimbursements or treatments available to subjects in the event of damage to health resulting from the study

(12) Types of IRBs that will investigate and determine issues related to appropriate performance of the study, types of issues which fall under IRB purview, and other study-related issues concerning the IRB

(13) Planned number of subjects in the study

(14) If any information comes to light which may affect the willingness of the subject to continue

study participation, that information will be rapidly shared with the subject.

(15) Conditions and reasons leading to study withdrawal

(16) Details of any costs to be borne by the subject, if applicable

(17) Details of any money to be paid to the subject, if applicable (agreements for determining amounts, etc.)

(18) Behaviors or rules to be followed by the subject

4.3 Method of obtaining consent

(1) Prior to initiating study, the investigator/subinvestigator will hand the informed consent forms and written information approved by the IRB to each potential subject in person, and conduct a full explanation. Clinical coordinators may also perform supplementary explanations. Explanations will be based on written information for the study and use as simple language as possible to ensure potential subject understanding. All questions from each potential subject will be answered fully. After confirming that the potential subject understands fully, he/she may freely grant informed consent for participation in the study in writing.

(2) The informed consent form will be signed (or names printed and personal seals affixed) and dated by both the potential subject and the investigator/subinvestigator who performed the explanation. If clinical coordinators performed supplementary explanations, he/she will also sign (or print name and affix personal seal) and date the form.

(3) Before each subject begins participation in the study (at screening), the investigator/subinvestigator will issue hand him or her a signed (or names printed and personal seals affixed) and dated copy of the informed consent forms and written information. Originals of the consent forms will be stored at each study center in accordance with that center's regulations.

(4) The date of informed consent will be recorded on each case report form (CRF).

4.4 Revision of informed consent forms and written information

(1) If new significant information is obtained which may impact a subject's consent, investigators/subinvestigators will verbally convey this information to each subject participating in the study in a timely manner, confirm whether the subject wishes to continue participation, and record these actions in the medical records.

(2) In this event, investigators will determine in a timely manner whether this new information requires revision of informed consent forms and written information.

(3) If it is determined that informed consent forms and written information must be revised, investigators must make said revisions in a timely manner and obtain approval from the IRB.

(4) The investigator/subinvestigator must explain relevant information to subjects already participating in the study using revised informed consent forms and written information newly approved by the IRB, and obtain freely-given consent in writing.

(5) As with the initial informed consent, the revised informed consent form will be signed (or names printed and personal seals affixed) and dated by both the subject and the investigator/subinvestigator who performed the explanation. If clinical coordinators performed supplementary explanations, he/she will also sign (or print name and affix personal seal) and date the form.

(6) Investigators/subinvestigators will give subjects a signed (or names printed and personal seals affixed) and dated copy of the informed consent forms and written information. Originals of the consent forms will be stored at each study center in accordance with that center's regulations.

5. Study Design

5.1 Study phase and type

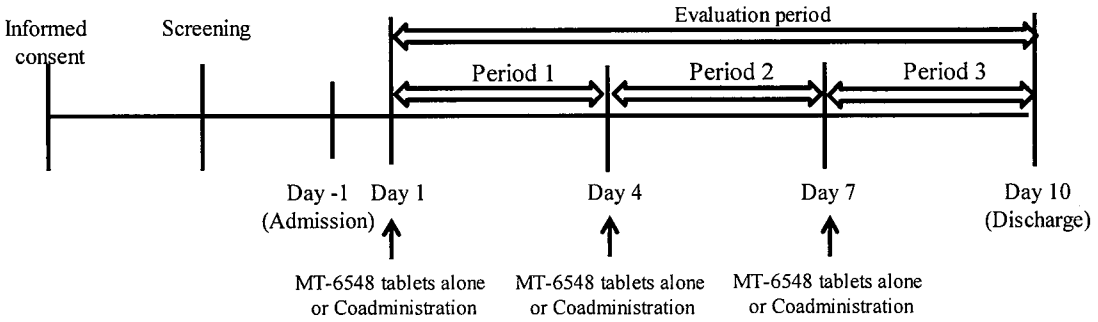
Study phase: Phase 3

Study type: Clinical pharmacology

5.2 Study design

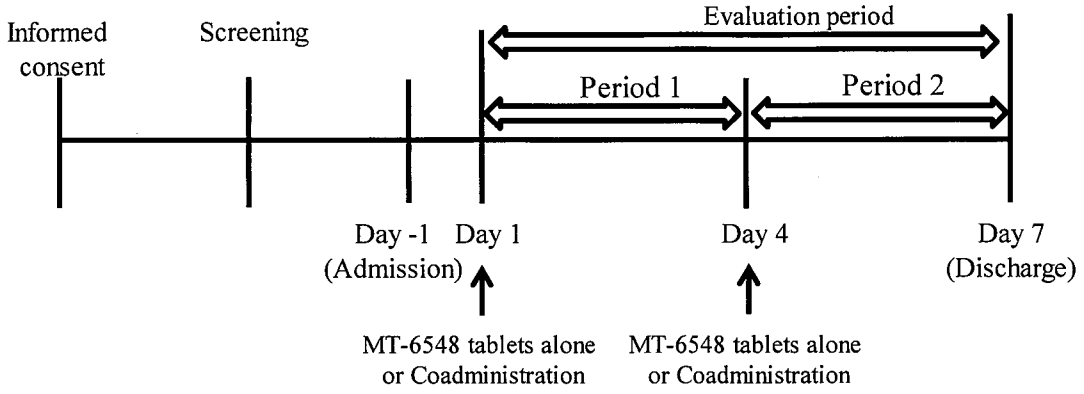
Single dose, open-label, randomized, crossover study

Cohort 1 (Administration after meal)



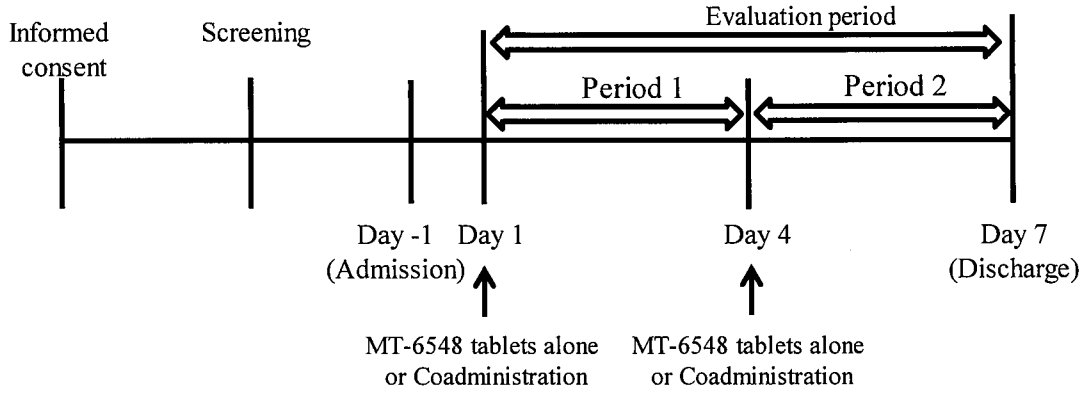
	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
Group 1	MT-6548 Tablets	MT-6548 Tablets and Sodium Ferrous Citrate	MT-6548 Tablets and Ferric Citrate Hydrate
Group 2	MT-6548 Tablets and Ferric Citrate Hydrate	MT-6548 Tablets	MT-6548 Tablets and Sodium Ferrous Citrate
Group 3	MT-6548 Tablets and Sodium Ferrous Citrate	MT-6548 Tablets and Ferric Citrate Hydrate	MT-6548 Tablets

Cohort 2 (Administration before meal)



	Period 1 (Day 1)	Period 2 (Day 4)
Group 4	MT-6548 Tablets	MT-6548 Tablets and Sucroferric oxyhydroxide
Group 5	MT-6548 Tablets and Sucroferric oxyhydroxide	MT-6548 Tablets

Cohort 3 (Administration in fasting)



	Period 1 (Day 1)	Period 2 (Day 4)
Group 6	MT-6548 Tablets	MT-6548 Tablets and Dried Ferrous Sulfate
Group 7	MT-6548 Tablets and Dried Ferrous Sulfate	MT-6548 Tablets

Study period: From the day consent is obtained until the end of the post-administration tests.

Screening: Screening tests to verify eligibility will be performed after informed consent is obtained, after which eligible subjects will be selected. Screening will take place within 4 weeks before the day of administration of the study drug in Period 1 (Day 1). After all the prescribed screening test results are available, subjects will be admitted to the study site. Day -1 (the day before administration of the study drug) will be defined as the day of admission.

Evaluation period: For Cohort 1, the 10-night, 11-day period of confinement. 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.

Cohort 2 and Cohort 3 will be confined to the study site 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: These will be performed 3 days after administration of the last dose of the study drug.

Rationale

To evaluate the PK and safety of MT-6548 when MT-6548 and oral iron or iron-containing phosphate binders are coadministered in accordance with the methods of administration described in their respective package inserts, three cohorts were established: one to receive the study drug after a meal, one to receive it before a meal, and one to receive it under fasting conditions.

With reference to the draft Guideline on Drug Interactions for Drug Development and Labeling (September 4, 2017 edition), a crossover design was adopted for this study to achieve an evaluation with a high degree of accuracy in a small number of subjects. An open-label design was adopted for this study because the effects of evaluation bias are minor and PD will not be evaluated.

[redacted]

5.3 Randomization methods

5.3.1 Randomization and allocation methods

The person responsible for preparing the randomized keycode table will prepare a randomized keycode table for each cohort in accordance with the predetermined procedures on study drug assignment, and submit these in the sealed state for each cohort to the investigator. The investigator/subinvestigator will assign subject IC numbers to all subjects in each cohort, and after specifying the subjects and reserve subjects (reserve subjects will be determined in advance, also in order of enrollment), unseal the randomized keycode table, and assign subjects to each group in ascending order of subject IC number, and assign them with subject ID. If a subject is to be substituted in the final selection process, they will be substituted by matching their subject IC number to the predetermined order of enrollment for reserve subjects, in ascending order. The investigator/subinvestigator, or clinical coordinator will submit a copy of the randomized keycode table to the sponsor. The investigator/subinvestigator will prescribe the study drug and/or the oral iron or iron-containing phosphate binder to the group to which the subject is assigned. Specifics of randomization will be defined in the study drug allocation specifications.

5.4 Endpoints

5.4.1 Pharmacokinetic endpoints

(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

Rationale

In accordance with Methods of Investigating Drug Interactions (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001), and with reference to Clinical Pharmacokinetic Studies on Drugs (Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001) and the Guideline for Bioequivalence Studies of Generic Products (Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012), the following PK parameters were selected for the PK evaluation of unchanged MT-6548: $AUC_{0-\infty}$,C_{max}, t_{max}, AUC_{0-last}, $MRT_{0-\infty}$, Kel, and $t_{1/2}$.

5.4.2 Safety endpoints

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

(2) General laboratory tests

(3) Vital signs

(4) Resting standard 12-lead ECG

6. Target sample size and study period

6.1 Target sample size

Cohort 1: 21 subjects

Cohort 2: 20 subjects

Cohort 3: 20 subjects

Rationale

[redacted]

6.2 Study period

[redacted]

7. Study drug

7.1 Study drug names

Name: MT-6548 Tablets 150 mg

Nonproprietary name: vadadustat

Vadadustat (JAN) (English name)

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

The following commercially-available products to be used in addition to the study drug in this study will be purchased by the study site: sodium ferrous citrate (Ferromia® Tablets 50 mg), ferric citrate hydrate (Riona® Tablets 250 mg), sucroferric oxyhydroxide (P-Tol Chewable® Tablets 500 mg), and dried ferrous sulfate (Fero-Gradumet® 105 mg).

7.2 Study drug packaging and labelling

(1) Packaging

Each bottle contains 100 tablets of MT-6548 tablet.

(2) Labelling

MT-6548 Tablets 150 mg for clinical study, 100 tablets
Study type: Clinical pharmacology study, Lot no. XXXXXX
Storage method: Store at 1–30°C.
Dosage and administration: Please follow your doctor's instructions.
*Please return unused study drug.
*Those not participating in the MT-6548 study must not take the study drug.
Mitsubishi Tanabe Pharma Corporation, 3-2-10 Dosho-machi, Chuo-ku, Osaka

7.3 Storage method

Store at 1–30°C.

7.4 Study drug handling, storage, and management methods

The study monitor will supply study drugs to each study center after conclusion of the study agreement. Study drug managers will follow the Procedures for Management of Study Drug provided by the study sponsor in storage and management of the study drugs, then return all unused study drugs to the monitor.

Investigators/subinvestigators and study drug managers will notify the study sponsor immediately if any abnormalities in study drug quality are discovered. Any such study drug will be returned to the study sponsor as necessary in accordance with the Procedures for Management of Study Drug. Study drugs must not be used for any other purpose than those described in this protocol (other clinical studies, animal

experiments, basic research experiments, etc.).

8. Subject-related test methods

8.1 Lists of screened subjects, enrolled subjects, and identification codes

The investigator will prepare a list of all screened potential subjects who received an explanation of the study. All subjects on this list who have granted consent will be assigned an identification code, and a subject IC number list prepared. Key information for comparisons with source documents will be included. A record that enables identification of subjects and reserve subjects will also be prepared.

The investigator will also prepare a list of enrolled subjects (including those who withdrew or reserved), including date of consent, subject IC number, and other information.

On demand, the investigator will submit the screening register to the sponsor. In submitting the register, thoroughgoing care will be taken to protect the subjects' privacy and personal information.

8.2 Subject enrollment

8.2.1 Subject selection

(1) Screening

The investigator/subinvestigator will conduct screening tests (for the test items, see Section 9.2 Tests and observation timepoints) within 4 weeks before administration of the study drug in Period 1.

If the investigator/subinvestigator notes any test value that is outside the reference range and considers it likely to be a deviation due to the degree of the variation being within the daily range of variation or an incidental reason, etc., and therefore concludes that a repeat test is required, they will repeat the test at a suitable interval after obtaining the subject's consent. However, if the investigator/subinvestigator concludes that the nature and degree of the deviation from the reference range are medically acceptable and it does not pose any problems in evaluating the safety of the study drug[*1], the person may be selected as a subject or a reserve subject.

The investigator/subinvestigator will confirm eligibility (including the results of repeat tests), and select those persons who meet the inclusion criteria in Section 3.2 and do not meet the exclusion criteria in Section 3.3 as subjects or reserve subjects.

*1: If it is concluded to be medically acceptable

If the repeat test results and previous test results show that the deviation from the reference range is attributable to factors specific to the subject.

(2) Day before administration of the study drug in Period 1

The investigator/subinvestigator will interview and examine candidates and measure their vital signs on the day before administration of the study drug in Period 1 to confirm the eligibility of

repeat subjects and reserve subjects.

(3) Day of administration of study drug (Period 1)

The investigator/subinvestigator will interview and examine subjects, measure their vital signs, and perform a standard 12-lead ECG examination before administration on the day of administration of the study drug (Period 1), to confirm that there are no abnormal findings, and make the final assessment of the subject's eligibility. If there are any abnormal findings, the person will be excluded from consideration as a subject. However, if the investigator concludes that the nature and degree of the abnormal finding are medically acceptable and it does not pose any problems in evaluating the safety of the study drug*2, the person may be selected as a subject.

*2: If it is concluded to be medically acceptable

A symptom that is commonly seen and mild in severity, and which is not likely to affect the evaluation of the study drug in this study

8.2.2 Substitution of subjects

If the selection process results in exclusion of a potential subject, the investigator/subinvestigator may replace the excluded candidate with a substitute. A person substituted before administration of the study drug in Period 1 will not be handled as a discontinued subject.

8.2.3 Study drug dosage

(1) The investigator/subinvestigator will prescribe the study drug and/or the oral iron or iron-containing phosphate binder to the group to which the subject is assigned, in accordance with Section 5.3.1 Randomization and allocation methods.

(2) The subject IC number, subject ID, cohort number, and group number will be recorded in the CRF.

8.3 Dosage and administration

8.3.1 Cohort 1 (Administration after meal)

(1) Administration of MT-6548 tablets alone

After fasting for at least 10 hours, subjects will eat breakfast over a period of 10 minutes, then immediately after finishing the meal (5 minutes after finishing the meal), 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug.

Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(2) Administration of MT-6548 tablets and sodium ferrous citrate

After fasting for at least 10 hours, subjects will eat breakfast over a period of 10 minutes, then immediately after finishing the meal (5 minutes after finishing the meal), 1 MT-6548 tablet (150 mg) and 4 tablets of sodium ferrous citrate (containing 200 mg of iron) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(3) Administration of MT-6548 tablets and ferric citrate hydrate

After fasting for at least 10 hours, subjects will eat breakfast over a period of 10 minutes, then immediately after finishing the meal (5 minutes after finishing the meal), 1 MT-6548 tablet (150 mg) and 8 tablets of ferric citrate hydrate (containing 2000 mg of ferric citrate) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. After collection of blood samples at 4 hours after administration of the study drug, subjects will eat lunch over a period of 20 minutes, then immediately after finishing the meal, 8 tablets of ferric citrate hydrate (containing 2000 mg of ferric citrate) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). Subjects will fast from lunch to before dinner, and at 10 hours after administration of the study drug, subjects will eat dinner over a period of 20 minutes, then immediately after finishing the meal, 8 tablets of ferric citrate hydrate (containing 2000 mg of ferric citrate) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). Subjects will fast from dinner until breakfast the next morning.

8.3.2 Cohort 2 (Administration before meal)

(1) Administration of MT-6548 tablets alone

After fasting for at least 10 hours and immediately before eating breakfast (5 minutes before

starting the meal), 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water, then breakfast will be eaten over a period of 10 minutes (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(2) Administration of MT-6548 tablets and sucroferric oxyhydroxide

After fasting for at least 10 hours and immediately before eating breakfast (5 minutes before starting the meal), subjects will chew and swallow 2 tablets of sucroferric oxyhydroxide (containing 1000 mg of iron), then 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water, then breakfast will be eaten over a period of 10 minutes (extra water may be drunk if more is needed when taking the tablets, and the extra volume will be recorded). After breakfast, subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. After blood samples are collected at 4 hours after administration of the study drug and immediately before lunch, subjects will chew and swallow 2 tablets of sucroferric oxyhydroxide (containing 1000 mg of iron), then eat lunch over a period of 20 minutes. After lunch, subjects will fast until dinner, and immediately before dinner at 10 hours after administration of the study drug, chew and swallow 2 tablets of sucroferric oxyhydroxide (containing 1000 mg of iron), then eat dinner over a period of 20 minutes. Subjects will fast from dinner until breakfast the next morning.

8.3.3 Cohort 3 (Administration in fasting)

(1) Administration of MT-6548 tablets alone

After fasting for at least 10 hours, 1 MT-6548 tablet (150 mg) will be taken orally with 200 mL of water (extra water may be drunk if more is needed when taking the tablet, and the extra volume will be recorded). Subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

(2) Administration of MT-6548 tablets and dried ferrous sulfate

After fasting for at least 10 hours, 1 MT-6548 tablet (150 mg) and 2 tablets of dried ferrous sulfate (containing 210 mg of iron) will be taken orally with 200 mL of water (extra water may be

drunk if more is needed when taking the tablets, and the extra volume will be recorded). Subjects will fast until the end of the collection of blood samples at 4 hours after administration of the study drug. Subjects will eat lunch over a period of 20 minutes after blood samples are collected at 4 hours after administration of the study drug. After lunch, subjects will fast until dinner, when they will eat dinner over a period of 20 minutes at 10 hours after administration of the study drug. Subjects will fast from dinner until breakfast the next morning.

Rationale

To evaluate the effects of iron on the absorption of MT-6548 in the gastrointestinal tract under maximal conditions, the dose selected for MT-6548 was the minimum proposed clinical dose, and those selected for the oral iron and iron-containing phosphate binders were the maximum clinical doses.

Oral iron and iron-containing phosphate binders are to be administered before or after meals, or under fasting conditions, with reference to the methods of administration noted in their respective package inserts. As MT-6548 tablets are to be administered at the same time, the timing of administration was matched to those of the oral and iron-containing phosphate binders.

8.4 Treatment period

Cohort 1

(1) MT-6548 tablets: Single dose administered alone, 3 times
(2) Sodium ferrous citrate: Single dose, administered once
(3) Ferric citrate hydrate: Three times a day, administered once on 1 day

Cohort 2

(1) MT-6548 tablets: Single dose administered alone, twice
(2) Sucroferric oxyhydroxide: Three times a day, administered once on 1 day

Cohort 3

(1) MT-6548 tablets: Single dose administered alone, twice
(2) Dried ferrous sulfate: Single dose, administered once

Rationale

As MT-6548 appears to structurally form a chelate complex with iron atoms in the gastrointestinal tract, thereby changing the amount and rate of absorption of MT-6548, a single dose was selected for MT-6548 to evaluate the time course of plasma concentration and PK parameters. For the same reason, the dosing frequency for the oral iron and iron-containing phosphate binders was established with reference to the once-daily frequency noted in the package inserts, because it is unnecessary for the blood

concentration to reach steady state in repeated administration.

8.5 Prohibitions before and during the study period

8.5.1 Prohibitions

From 7 days before the start of administration of the study drug until the end of the evaluation period, the use of any medications other than the study drug to be administered in this study and other therapies is not permitted. This will not apply, however, if the investigator/subinvestigator concludes that it is necessary for the treatment of an adverse event.

Consumption of the following is not permitted during the specified periods.

- Smoking: From the day of admission to the study site to the day of discharge
- Alcohol, xanthine, or caffeine-containing foods and beverages: From the day of admission to the study site to the day of discharge
- Grapefruit or other citrus fruits, apples, or processed foods containing any of these: From 7 days before the start of administration of the study drug until discharge from the study site
- Health foods containing St. John's wort (Japanese name, seiyo-otogiri-so): From 2 weeks before the start of administration of the study drug until discharge from the study site

Rationale

The use of medications other than the study drug, smoking, and the consumption of alcohol and certain other foodstuffs was prohibited for the purpose of appropriately carrying out the PK and safety evaluations. However, for safety and ethical considerations when conducting this study, it was determined that this would not apply in circumstances when the investigator/subinvestigator recognized that the use of other medications was necessary.

8.5.2 Recording of concomitant drugs and therapies

The investigators/subinvestigators, or clinical coordinators will record the following information on concomitant drugs, therapies, or interventions used after the start of administration of the study drug, in the Concomitant Drugs, Therapies, and Interventions section of the CRF. However, physiological saline or other solvents used to dissolve injectable preparations will not be recorded.

(1) Concomitant drugs: Drug name, daily dosage, frequency, administration route, start date, completion date, purpose

(2) Concomitant therapies and interventions: Name of therapy or intervention, start date, completion date, purpose

8.6 Subject oversight

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

8.6.1 Confinement and site visits

(1) Screening will take place within 4 weeks before the start of administration of the study drug in Period 1.

(2) On the day designated for screening, subjects will be required to attend the study site having fasted at least 10 hours before blood samples are to be drawn.

(3) On the day of admission to the study site, subjects will be asked to come to the study site without eating dinner, and to eat dinner at the site.

(4) For the interview and examinations 3 days after taking the study drug in the final evaluation period, subjects will only be allowed to leave the study site after confirmation from their signs, symptoms, and other findings that there are no safety (health) concerns. However, if the investigator/subinvestigator deems that it is necessary to ensure subject safety, the subject will be followed up by extending the duration of confinement and performing a reexamination or additional tests after their informed consent is obtained, and the date of the tests and details of the tests will be recorded in the CRF.

8.6.2 Lifestyle guidance

(1) Unless otherwise instructed, subjects should remain at rest, either seated or standing, for 4 hours after administration of the study drug, and should walk when moving from place to place. However, this does not apply when adverse events occur.

(2) During the confinement period, adequate exercise is permitted, but subjects should rest unless otherwise instructed.

(3) Subjects should rest for 5 minutes before the tests are performed.

(4) From 7 days before the start of administration of the study drug until the end of the post-administration tests, subjects should abstain from vigorous exercise and binge eating and drinking.

(5) Subjects should contact investigators/subinvestigators or clinical coordinators in a timely manner if they experience abnormal symptoms.

(6) Subjects should be instructed to use the contraception methods described below during the study period and up to 90 days following the final dose of the study drug. Calendar, anovulation, ovulation detection through body temperature, post-ovulation, and withdrawal do not constitute appropriate forms of contraception.

1) Abstain from intercourse
2) Use two effective types of contraception. Joint use of a barrier method (latex condoms for men or diaphragm) in conjunction with a highly effective method such as oral contraceptives, intrauterine device, tubal ligation, or vasectomy is recommended.

8.6.3 Meals

(1) The foods and beverages listed in Section 8.5.1 Prohibitions may not be consumed during the specified periods.
(2) On the day before administration of the study drug, subjects will fast for at least 10 hours before the scheduled administration of the study drug on the following day.
(3) From 1 hour before until 1 hour after administration of the study drug, subjects may not consume anything other than the water and food and beverages designated for consumption at the time of administration of study drug.
(4) Subjects will be instructed to eat all the designated food on the day of administration of the study drug. During the confinement period, the consumption of any food other than the specified meals is prohibited. The breakfast start time, finishing time, and conditions on the day of administration of the study drug will be recorded in the CRF. The content of the meals eaten during the confinement period will be reported to the sponsor.
(5) The meals to be eaten for breakfast, lunch, and dinner on the day of administration of the study drug will be identical in all groups and evaluation periods for each cohort. Normal meals will be eaten during the confinement period.
(6) The calorific values of the meals on the days of administration of the study drug will be 2100–2300 kcal (carbohydrates, 55% to 65%; fats, 20% to 30%; protein, 13% to 16%) for Cohorts 1 and 2, and 1600–1800 kcal (carbohydrates, 55% to 65%; fats, 20% to 30%; protein, 13% to 16%) for Cohort 3.
(7) Meal starting times on the days of administration of the study drug
Breakfast: From 08: 30 am to 10: 00 am (Cohort 3 will not have breakfast)
Lunch: From 4 to 5 hours after administration of the study drug
Dinner: From 10 to 11 hours after administration of the study drug

9. Tests and observations

9.1 Test and observation schedule

Cohort 1 (Administration after meal)

	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 [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 will be administered after food, depending on the allocated group.

[c] Completed subjects will undergo post-administration tests on Day 10.

[d] Performed on discontinuation after administration of the study drug.

[e] 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 (Administration before meal)

	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]		
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	At discontinuation [d]	
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 will be administered before food, depending on the allocated group.

[c] Completed subjects will undergo post-administration tests on Day 7.

[d] Performed on discontinuation after administration of the study drug.

[e] 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 (Administration in fasting)

	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 oral iron [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 will be administered under fasting conditions, depending on the allocated group.

[c] Completed subjects will undergo post-administration tests on Day 7.

[d] Performed on discontinuation after administration of the study drug.

[e] 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, current medical condition
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, haemoglobin, hematocrit, WBC count, platelet count, WBC fraction (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, ketones, bilirubin
Immunology tests (only at screening)		Serologic reaction for syphilis, HBs antigen, HCV antibody, HIV antigen/antibody

9.2 Test and observation timepoints

9.2.1 Subject background

The following subject background factors will be determined and recorded in the CRF.

(1) Sex
(2) Ethnicity
(3) Date of birth (western calendar)
(4) Age (as it will be calculated from the date of birth, it will not be recorded in the CRF)
(5) Height (in integers)
(6) Body weight (to the first decimal place)
(7) BMI (as it will be calculated from the height and body weight, it will not be recorded in the CRF)
(8) Current medical condition (medical condition on the first day of the treatment period)

9.2.2 Study drug adherence

The time and conditions when the study drug, oral iron, and iron-containing phosphate binders are

taken will be recorded in the CRF.

9.2.3 Pharmacokinetic-related endpoints

Blood samples will be collected for measurement of the plasma concentration of unchanged MT-6548. Date and time of blood sampling will be recorded in CRFs.

(1) Measuring plasma concentration of unchanged MT-6548.

1) Blood sampling timing and volume for cohort 1

a) Timing of blood collection: Immediately before administration of the study drug, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours after administration of the study drug (similarly for all periods)

b) Number of times blood is sampled: 39

c) Blood sampling volume: About 6 mL each time, for a total of about 234 mL (per subject)

2) Blood sampling timing and volume for cohort 2 and cohort 3

a) Timing of blood sample collection: Immediately before administration of the study drug, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours after administration of the study drug (similarly for all periods)

b) Number of times blood is sampled: 26

c) Blood sampling volume: About 6 mL each time, for a total of about 156 mL (per subject)

(2) Blood processing

[redacted]

(3) Sample transport and storage

Plasma samples for measurement of drug concentration will be packed [redacted] for transport to the drug concentration assay laboratory.

Rationale

The sample collection times were selected with reference to an ethnobridging study in Japanese and white healthy subjects (Study CI-0020), Clinical Pharmacokinetic Studies on Drugs (Notification

No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001), Guideline for Bioequivalence Studies of Generic Products (Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012), and the draft Guideline on Drug Interactions for Drug Development and Labeling (September 4, 2017 edition).

9.2.4 Safety endpoints

The safety evaluation period is defined as the time from the start of administration of the study drug until the end of the post-administration tests. Adverse events that occur in each evaluation period will be tabulated for the following time periods.

Period 1: From the time of administration of the study drug on Day 1 to before administration of the study drug on Day 4.

Period 2: From the time of administration of the study drug on Day 4 to before administration of the study drug on Day 7.

Period 3: From the time of administration of the study drug on Day 7 to before administration of the study drug on Day 10.

9.2.4.1 Objective findings

Investigators/subinvestigators will promptly check the results and record day of confirmation and confirmation results (clinical significance) for all the following tests.

(1) General laboratory tests

The following laboratory tests will be performed on the day of screening (any time), in the evaluation period (immediately before administration of the study drug, and 24 hours after administration of the study drug in each period), and at discontinuation (only for subjects withdrawn from the study after the start of administration of the study drug; any time). The target volume of blood collected each time is approximately 2 mL for 1), 11 mL for 2), and 11 mL for 4) below, and the amount of urine to be collected is approximately 10 mL. The collection date and purpose of the blood sample will be recorded in the CRF. The study site will report the test results (excluding 4)) to the sponsor only for subjects who receive the study drug.

1) Hematology tests:
RBC count, haemoglobin, hematocrit, WBC count, platelet count, WBC fraction (neutrophils, eosinophils, monocytes, lymphocytes, basophils)

2) Blood biochemistry tests:
AST (GOT), ALT (GPT), ALP, LDH, γ-GTP, total protein, albumin, blood glucose, total cholesterol, LDL-C, HDL-C, triglycerides, total bilirubin, urea nitrogen (BUN), serum creatinine, uric acid, CPK, Na, K, Cl, Ca, P, Mg, C-reactive protein, serum iron, ferritin, TSAT

3) Urinalysis (qualitative)
Glucose, protein, urobilinogen, occult blood, specific gravity, pH, ketones, bilirubin

4) Immunology tests: Only at screening
HBs antigen, serological test for syphilis, HCV antibody, HIV antigen or antibody

(2) Vital signs (blood pressure, pulse rate, body temperature)

Blood pressure (systolic and diastolic blood pressure), pulse rate, and axillary body temperature (ascertained to the first decimal place) will be measured for subjects in the seated position on the day of screening (any time), Day -1 (day before administration of the study drug), in the evaluation period (immediately before administration of the study drug, 24 hours after administration of the study drug, and 48 hours after administration of the study drug in each period), and at discontinuation (only for subjects withdrawn from the study after the start of administration of the study drug; any time). Date and results will be recorded in CRFs.

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

(3) Standard 12-lead ECG

Resting 12-lead ECGs will be obtained for subjects in the supine position on the day of screening (any time), in the evaluation period (immediately before administration of the study drug, 24 hours after administration of the study drug, and 48 hours after administration of the study drug in each period), and at discontinuation (only for subjects withdrawn from the study after the start of administration of the study drug; any time). From the ECG findings, the results of arrhythmia diagnosis, waveform diagnosis, and other procedures will be evaluated globally and assessed according to the following 3-point scale, and the date of measurement and results of evaluation will be recorded in CRFs.

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

1) Normal
2) Abnormal, Not Clinically Significant
3) Abnormal, Clinically Significant

9.2.4.2 Adverse events

AEs are all clinically problematic or unplanned signs (including clinically significant abnormal laboratory values), symptoms, or illnesses occurring after administration of the study drug during the safety evaluation period, regardless of causal relationship with the study drug.

(1) Symptoms and diseases

Investigators/subinvestigators will confirm AEs through interviews and examinations.

(2) Objective findings

Objective findings determined clinically significant abnormalities* by

investigators/subinvestigators are treated as AEs.

*Clinically significant abnormalities are determined according to the following criteria.

- If related to clinical signs or symptoms.
  However, if the sign or symptom has already been separately reported as an AE, the relevant laboratory test abnormality does not require treatment as adverse event.
- If the relevant laboratory test abnormality was treated medically or surgically.
- If investigators/subinvestigators otherwise determine the abnormality to be clinically significant.

(3) Adverse event evaluation and standards

1) Date of onset

Date the symptom or laboratory test abnormality was observed.

2) Severity

Adverse event severity is classified as follows:

1. Mild: No effect on activities of daily life
2. Moderate: Moderate impairment of activities of daily life caused by event
3. Severe: Event prevents performing activities of daily life

3) Seriousness

AE seriousness is classified as follows:

1. Not serious: Any events other than 2 below.
2. Serious: Any events (a) to (f):
   (a) Results in Death
   (b) Life-threatening
   (c) Inpatient hospitalization/Prolongation of existing hospitalization
   (d) Persistent or significant disability / Incapacity
   (e) Other medically important condition
   (f) Congenital anomaly / Birth defect

4) Causal relationship with the study drug

The investigator/subinvestigator will assess whether or not there is a reasonable possibility that the study drug caused the AE. This assessment will take into account factors not related to the study drug, including risk factors such as natural course and concurrent treatments for concomitant diseases, as well as the temporal relationship between the study drugs and the event (elimination after discontinuation, etc.). AEs for which a reasonable possibility of a causal relationship with the study drug exists will be treated as ADRs.

1. Reasonable possibility

2. No reasonable possibility

5) Outcome

AE outcomes are classified as follows:

1. Recovered
2. Recovering
3. Not recovered
4. Recovered with sequelae
5. Fatal
6. Unknown

6) Date of outcome

Date of outcome is determined according to the following criteria:

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

Recovering: Date on which recovering was confirmed or determined.

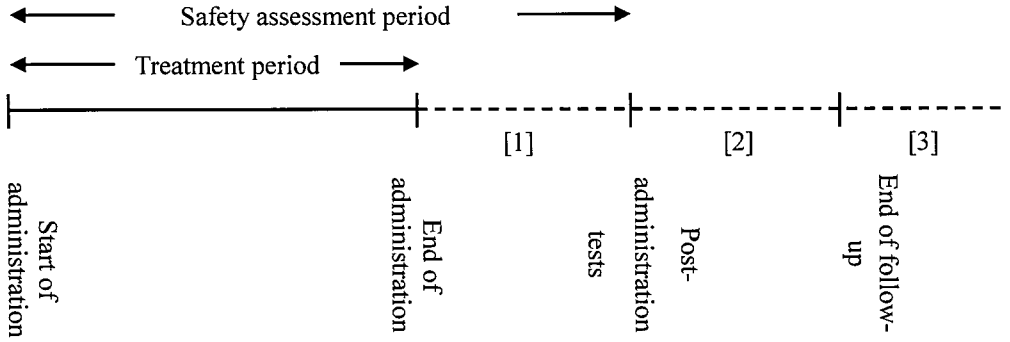
Not recovered: Date on which "not recovered" was confirmed or determined.

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

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

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

7) Follow-up investigation



- Period [1] above is the 3 days during which any AEs will be investigated.
- Period [2] above is the 28 days; it is the period for follow-up investigations of AEs occurring during the safety evaluation period (treatment period + Period [1]).
- Course of AEs subject to follow-up investigation during Period [2] are recorded in the subject's CRF. The date of outcome written in the CRF for AEs with outcomes of relief or not recovered

is the day of observation after completion of Period [2], during Period [3].

- Further investigations (Period [3]) will be performed for the course of ADRs with outcomes of relief or not recovered as of the end of Period [2].
- If there is a valid reason to halt investigations mid-way after completion of the safety evaluation period (after completion of Period [1]), record reasons for this and conclude the follow-up investigation.

(4) Recording information in CRFs

If an AE is observed, investigators/subinvestigators will record the following information in the subject's CRF: name of AE*, date of onset, category for the time of onset, severity, seriousness, actions taken to the study drug, causal relationship with study drug, details of any actions taken (drug names, treatment methods, etc.), outcome, and date of outcome.

*AE names are handled in the following manner:

- Fundamentally, the name of diagnosis is used.
- The symptom name is used if a clear diagnosis has not been made.
- If there are multiple symptoms which can be expressed by a one diagnosis, that diagnosis name is used.
- Medical treatments etc. are not considered AEs; rather the disease or symptom requiring surgical treatment is considered the AE.

10. Evaluation methods and standards

10.1 Pharmacokinetics

For each evaluation period, the plasma concentration of unchanged MT-6548 will be assayed, and the following parameters calculated by noncompartmental analysis: $AUC_{0-\infty}$, C_{max}, t_{max}, $AUC_{0\text{-last}}$, $MRT_{0-\infty}$, Kel, and $t_{1/2}$. Details of the calculation methods for each parameter will be included in the statistical analysis protocol.

The PK measurement center will create separate testing plans for plasma concentration measurements prior to initiating measurements, and create reports of measurement results. See Section 13.3.1 Pharmacokinetics for details of the PK analysis.

10.2 Safety

The following endpoints will also be studied.

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

(2) General laboratory tests

(3) Vital signs

(4) Standard 12-lead ECG

11. Ensuring subject safety

11.1 Responses to serious adverse events

If an SAE occurs after start of study drug administration and before post-administration tests, investigators/subinvestigators will immediately take appropriate actions toward the subject regardless of causal relationship with the study drug.

Investigators/subinvestigators will immediately notify monitors once an SAE has occurred (fundamentally in writing), and make a detailed written report to the study sponsor within 7 days of this report. Investigators/subinvestigators will also report the SAE to the director of the applicable study center.

[Definition of serious adverse events]

(1) Results in Death
(2) Life-threatening
(3) Inpatient hospitalization/Prolongation of existing hospitalization
(4) Persistent or significant disability / Incapacity
(5) Other medically important condition
(6) Congenital anomaly or Birth defect

11.2 Significant adverse events

There are no significant AEs which should be defined with regard to studying the safety profile of the drug.

11.3 Pregnancy reporting

If investigators/subinvestigators learn that the female partner of a male subject may have exposed an embryo or fetus to the study drug before the end of the contraception period, they will immediately inform the study sponsor using Pregnancy Reports (Appendix 1). If the female partner of a male subject wishes to deliver the baby, investigators/subinvestigators will to the extent possible perform follow-up investigation up to birth in order to investigate effects of the study drug on the newborn. Results of the investigation will be reported to the study sponsor using Pregnancy Reports (Appendix 1).

11.4 Contacting subjects' other doctors

Investigators/subinvestigators will confirm whether or not each subject is receiving medical care other than as part of the current study during the study period. If a subject is receiving such care, the other doctor will be contacted with the consent of the subject and informed of the subject's participation in the

study.

12. Withdrawal criteria and procedures

12.1 Withdrawal criteria

Subjects will be withdrawn from the study if the following criteria are met:

(1) If the subject expresses a desire to withdraw from the study.

(2) If it is discovered that the subject is clearly ineligible for study participation.

(3) If investigators/subinvestigators determine that AEs make continued participation in the study difficult.

(4) If the investigator/subinvestigator determines a subject should withdraw from the study for any other reason.

Rationale

For ethical conduct of the study, and taking the subject's safety in consideration.

12.2 Procedures for withdrawal

When withdrawing a subject from the study following the start of study drug administration through the end of evaluation period, investigators/subinvestigators will take appropriate measures with that subject, promptly notify the monitor of the withdrawal. Investigators/subinvestigators will also perform designated tests and observations required at discontinuation.

Investigators/subinvestigators will record date of withdrawal and reasons for withdrawal in the CRF. If the reason for withdrawal is an AE, the name of the event will be recorded in the CRF. The date of evaluations performed upon withdrawal is used as the date of withdrawal, but if these evaluations could not be performed, the date of determination of withdrawal may be used instead.

If observations and tests required at withdrawal cannot be performed for a given subject, or the subject does not make any post-withdrawal visits, follow-up investigation will be performed through correspondence (sealed letters) or telephone to ascertain reasons for this and subsequent course, and the information obtained recorded.

13. Statistical analysis

13.1 Analysis sets

The analysis sets are defined as follows. However, details regarding subjects handling will be determined by the sponsor before data lock.

(1) Pharmacokinetics analysis set

The pharmacokinetics analysis set is defined as the population of subjects who received the study drug at least once for whom PK is evaluable.

(2) Safety analysis set

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

13.2 Data handling

Excluding those matters determined in the sponsor's Case Review Meeting and the Review of the Handling of Drug Concentration Data, the handling of data will be as follows.

(1) Definition of missing values

If test measurements are missing or if problems with samples etc. result in invalid measurements, these are handled as missing values.

(2) Pharmacokinetics data handling

For blood samples collected for the measurement of plasma concentration, the following time windows will be established in light of the variance in the times of venipuncture and other considerations. Data outside the allowable ranges will not be imputed. Whether or not tabulations of drug concentration data or drug concentration data used to calculate PK parameters will be included in analysis, and details of the handling of other drug concentration data will be determined in the Review of the Handling of Drug Concentration Data, and included in the Statistical Analysis Protocol.

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

(3) Handling of data at 72 hours after administration of the study drug

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 will not be tabulated as results obtained at 72 hours after administration of

study drug in Period 1 and Period 2, respectively, but will 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 it is concluded that data obtained immediately before administration of the study drug in Periods 2 and 3 are adverse events relative to baseline in Periods 1 and 2, they will be handled as adverse events that occurred in Periods 1 and 2, respectively.

13.3 Statistical analysis protocol

For the following statistical methods, a statistical analysis protocol (including evaluations of PK etc.) that includes more detailed information will be separately prepared before data locking.

13.3.1 Pharmacokinetics

For PK evaluations after administration of MT-6548 tablets alone and in coadministration of MT-6548 tablets and oral iron or iron-containing phosphate binders, the PK parameters $AUC_{0-\infty}$ and C_{max} for each individual cohort will be transformed to logarithmic values, and from the difference in the mean logarithmic values obtained from a linear mixed-effects model with the subject designated as the random effect and the administration conditions (monotherapy or coadministration), evaluation period, and group as the fixed effect, the ratios of the geometric means (coadministration/monotherapy) obtained by inverse log-transformation, and their 90% confidence intervals will be calculated.

For the plasma concentration of unchanged MT-6548, summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be calculated and displayed for each time point under each set of administration conditions.

For the PK parameters of unchanged MT-6548($AUC_{0-\infty}$, C_{max}, t_{max}, AUC_{0-last}, $MRT_{0-\infty}$, Kel, and $t_{1/2}$), summary statistics (number of subjects, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and 95% confidence intervals, etc.) will be calculated and displayed for each set of administration conditions.

The plasma concentration-time graph for unchanged MT-6548 will also be plotted.

13.3.2 Safety

Adverse events and adverse drug reactions will be compiled for each set of administration conditions, and the frequencies of occurrence will be calculated for each. For the results of general laboratory tests and vital signs measurements, summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be calculated and displayed for each measurement time under each set of administration conditions. Changes from baseline to each measurement time in 12-lead ECG data will be displayed in shift tables for each set of administration conditions.

13.4 Changes in statistical analysis protocol

If any portion of the statistical analysis plan stated above is modified prior to data lock, reasons for change will be described in the statistical analysis protocol and the clinical study report. If the analysis plan is modified or analyses added after data lock, reasons for modification will be described in the statistical analysis protocol and the clinical study report, and analytical results will be distinguished from the original plan.

14. Study protocol compliance, deviation, and modification

14.1 Study protocol agreement and compliance

Before each investigator agrees with the study sponsor about the study protocol, he or she will discuss it with the study sponsor based on the protocol, newest investigator's Brochure (IB), and other materials provided. The investigator must fully study the ethical and scientific validity of the study prior to agreement.

In order to demonstrate agreement with the study sponsor on the study protocol and intent to comply with it based on these considerations, the investigator will sign (or print name and affix personal seal) the Agreement and enter the date with the study sponsor.

14.2 Study protocol deviations and modifications

Investigators/subinvestigators may not deviate from or modify the study protocol without previous written permission from the study sponsor and IRB. However, if there are circumstances in which such a deviation or modification is medically necessary on an emergency basis to avoid placing subjects in danger, investigators/subinvestigators may perform such actions without prior permission from the study sponsor and IRB.

In such cases, investigators must submit and receive approval for said deviations or modifications, reasons for these, and if appropriate revisions to the study protocol as rapidly as possible from the study sponsor, study center director, and the IRB. Approval from the study center director and agreement from the study sponsor must be obtained in writing.

Investigators/subinvestigators shall fully record all actions deviating from the study protocol. Investigators shall also draft a report detailing all medically required emergency deviations from or modifications to the study protocol for the purpose of avoiding placing subjects in danger, including the reasons why they were necessary. Investigators will keep a copy of this report and send it to the study sponsor and study center director.

Investigators must immediately submit a report to the study sponsor, study center director, and IRB about all modifications which may significantly influence the study or increase risk to subjects.

15. Revisions to the study protocol

The study sponsor may revise the study protocol during the study if modifications are required. The study sponsor will discuss the revisions with investigators and come to agreement about them, then immediately notify the study center director in writing and obtain approval from the IRB through the study center director.

If the study center director requests modification of the protocol based on the opinion of the IRB, the study sponsor will determine whether the modification is warranted and revise the protocol as necessary. The study sponsor will discuss the revisions with investigators and come to agreement about them, then immediately notify the study center director in writing and obtain approval from the IRB through the study center director.

If investigators request modification of the protocol, the study sponsor will determine whether the modification is warranted and revise the protocol as necessary. The study sponsor will discuss the revisions with investigators and come to agreement about them, then immediately notify the study center director in writing and obtain approval from the IRB through the study center director.

16. Termination or suspension of the entire study

(1) Standards for termination or suspension of the study

In the following circumstances, the study sponsor will determine whether or not continuation of the study is warranted.

1) If significant information is learned about study drug quality, efficacy, or safety, or if other information about appropriate conduct of the study comes to light.
2) If modifications to the study protocol are required which study centers cannot adopt.
3) If a study center director requests modifications to the study protocol based on the opinion of the IRB, but the study sponsor cannot accept these changes.
4) If a study center director orders termination of the study based on the judgment of the IRB.
5) If a study center makes significant or continued deviations from GCP, the current study protocol, or the study contract.

(2) Termination or suspension of the entire study by the study sponsor

If the study sponsor determines to terminate or suspend the entire study, study center directors and regulatory authorities will be notified immediately in writing of this decision and reasons for it. If a study center director receives notification of termination or suspension of the study from the study sponsor, they will immediately notify in writing the investigator and IRB of this fact, including detailed reasons.

If an investigator receives notification of the termination or suspension of the study from the study center director, he or she will immediately inform subjects and ensure the safety of the subject afterwards.

See "12.2 Procedures for Withdrawal" for actions taken related to subjects upon study termination.

(3) Termination or suspension of study at a study center by investigator or IRB

If an investigator determines on his or her own judgment to terminate or suspend the study, he or she will immediately inform the study center director in writing of the details regarding this decision. The study center director will then immediately inform the study sponsor and IRB in writing.

If the IRB determines to terminate or suspend the study, it will immediately inform the study center director in writing of the details regarding this decision. The study center director will then immediately inform the investigator and study sponsor in writing.

(4) Termination due to dissolution of contract with study center

The study sponsor will immediately inform the regulatory authorities if it terminates the study at a study center due to serious or continued violations of GCP or the study protocol during the

study period.

17. Case report forms

17.1 Case report form (CRF) format

This study will use electronic CRFs using an EDC system. Electronic CRFs reviewed and digitally signed by investigators will be considered originals. In addition, the study site will report the general laboratory test results (excluding immunology tests) to the sponsor, which will not be recorded in CRFs. For the results obtained for drug concentration, the reports issued by the analytical laboratory measuring drug concentration will be designated as source documents, and not recorded in CRFs.

17.2 Direct recording of information in the CRF and CRF as source documents

There is no item or category in the current study for which the electronic CRF is considered the source document. If data from an electronic CRF is to be considered the source document, this will be agreed upon separately in writing by the study sponsor and investigator prior to initiation of the study.

17.3 Notes on making CRF entries

Investigators/subinvestigators or clinical coordinators will make CRF entries according to the following stipulations. CRFs will be created according to "Procedures for CRF modifications or revisions,"* to be supplied separately by the study sponsor.

*"Procedures for CRF modifications or revisions": EDC operation manual and eCRF input manual

(1) The study sponsor will perform user management duties, such as giving user names and passwords to investigators/subinvestigators and clinical coordinator, which will not be shared beyond the person to which they were originally assigned. Data entry will be performed only by those with authority to do so (investigators/subinvestigators and clinical coordinator).

(2) CRFs will be created for all subjects who received the study drug.

(3) Investigators may record any information in CRFs. Subinvestigators may record any information in CRFs excluding digital signatures. Clinical coordinator may transfer information from source documents to the CRF which do not require medical judgment, such as treatment records.

(4) When information recorded in CRFs is modified or revised, the reason for this will be recorded electronically in the CRF.

(5) Investigators will electronically sign the CRF on the EDC system after reviewing it and confirming accuracy and completeness, and that audit trails and electronic signature information are viewable.

(6) Investigators will retain copies of CRFs on recording media such as CDRs (stored as PDF copies of the electronic CRF after review by the investigator). Granting electronic access to

CRFs (permission to view on the EDC system) may serve in lieu of submitting copies in the period from electronic signing until submission of the CDRs or other storage media.

(7) If there is conflicting data between data in the CRF and source documents, the investigator will submit a document containing the reason for this discrepancy to the study sponsor, and retain a copy.

17.4 CRF submission timepoints

Investigators/subinvestigators will immediately make CRF entries and submit these to the study sponsor.

18. Direct access to source documents

Investigators and study center directors shall grant direct access to all source documents related to the study in response to monitoring or auditing by the study sponsor, or in response to investigations by the IRB or regulatory authorities.

19. Study quality control and quality assurance

In order to ensure a high level of quality for the study, the study sponsor must perform study quality control and quality assurance based on Mitsubishi Tanabe Pharma Corporation's GCP procedures. Meanwhile, study centers and investigators will grant their cooperation in sponsor's performance of study quality control and quality assurance.

As a part of quality control efforts, study monitors will directly observe activities as appropriate to ensure that the study is compliant with related procedures, the latest version of the study protocol, and GCP. Monitors will also confirm that information recorded in CRFs by investigators/subinvestigators can be compared with source documents and other related materials in order to verify accuracy and completeness.

The study auditor will audit the study in accordance with the GCP Standard Operating Procedure to ensure compliance with the study protocol and GCP, and otherwise confirm appropriate implementation of quality control measures.

20. Ethics

20.1 Ethical conduct of the study

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki, and in compliance with the Pharmaceutical Affairs Law, GCP, and the study protocol.

20.2 Institutional Review Board

The Institutional Review Board (IRB) of each study center will review the study (including its continuation) based on IB, study protocol, and informed consent forms and written information for subjects from ethical, scientific, medical, and pharmaceutical perspectives.

20.3 Subject confidentiality

Identification of each subject through enrollment and CRFs shall be possible only with the subject IC number. All personnel involved with the current study shall endeavor to preserve subject confidentiality during direct access to source documents, publishing in academic journals, and submissions to regulatory authorities.

21. Record storage

(1) Records stored by study centers

The records storage manager appointed by each study center director shall store all study-related documents and other records to be stored at each study center until 1) or 2) below, whichever comes later. However, if the study sponsor requests that these materials be stored for a longer period, each study center will discuss storage methods and periods with the study sponsor.

If the study sponsor determines not to include materials related to results from the clinical study in the application, it will notify study center directors of this fact and the reasons for it in writing.

Further, the study sponsor will notify study center directors in writing if marketing approval is granted for the study drug, or if approval is not granted and development is canceled.

1) Day of marketing approval for the study drug (or 3 years from receipt of notification if notified of cancelation of development, or that study results will not be included in application)
2) Three years from the day of termination or completion of the study

(2) Records stored by the study sponsor

The study sponsor shall store all study-related documents and other records to be stored by the study sponsor until 1) or 2) below, whichever comes later.

1) Five years from the day of marketing approval for the study drug , or day of completion of re-review (or 3 years from the date of cancellation of development)
2) Three years from the day of termination or completion of the study

22. Monetary compensation

Monetary compensation made to study subjects and study centers will be paid in accordance with contracts and agreements between the study centers and the study sponsor.

23. Compensation for health damage and insurance

23.1 Compensation for health damage

In the event that a subject experiences damage to health related to the study, the study sponsor shall provide compensation according to determined standards, excluding instances in which causal relationship with the study has been denied. (Forms of said compensation may include the medical coverage, treatment allowances, or financial compensation.) In these events, it shall not be the burden of the subject to prove causal relationship with the study.

23.2 Insurance

The study sponsor shall procure health insurance and take other measures to ensure fulfillment of liability and compensatory responsibilities to subjects related to damage to health arising from the study.

24. Publication policy

Information contained within this study protocol is the property of the study sponsor. Although it is provided to investigators/subinvestigators, others involved with the study, and IRBs, information contained herein shall not be disclosed to third parties without express written consent of the study sponsor, save when doing so is required for the study itself.

Information obtained through the study may be published (to academic societies, journals, etc.) by investigators/subinvestigators, or others involved with the study at study centers, only after obtaining prior consent from the study sponsor.

Finally, the study sponsor reserves the right to freely use information obtained through the study for any purpose, including reports to regulatory authorities, appropriate drug use, and sales promotions.

25. Administrative structure

See Appendix 1.

26. References

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Contact Information

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[redacted]

[redacted]

Night/Holiday Contact Information

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

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

[redacted]

[redacted]

[redacted]

[redacted]